

Carbon Dioxide as a Reagent and Solvent

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"Your enthusiasm is not enough"
-12th Principle of CO₂ Chemistry

Abstract

The work described in this Thesis has been carried out within the Erasmus Mundus framework for Sustainable Industrial Chemistry (SINCHEM). The work concentrates on the possible utilisation of carbon dioxide as a solvent and as a starting material.

Chapter 1 introduces carbon dioxide and its utilisation. In addition, the 12 Principles of CO₂ Chemistry are presented, as well as continuous flow chemistry and self-optimising reactors. The relevant aspects of these reactors are discussed further in Chapter 2.

The results of the research are presented in Chapters 3-6. A self-optimising reactor with FT-IR analysis was employed for the methylation of alcohols as explained in Chapter 3.

Chapters 4-6 concentrate on *N*-alkylation reactions. In Chapter 4, the reactivity between aniline, tetrahydrofuran and dimethyl carbonate in supercritical carbon dioxide is discussed. This research led to the discovery of novel transformations.

In Chapters 5 and 6, methanol was employed to methylate amines. A ruthenium triphosphate catalyst, which can produce methanol from carbon dioxide and hydrogen, was used to catalyse the reactions between methanol and aliphatic amines, as described in Chapter 5. Also the cyclisation and subsequent methylation of amino alcohols was studied. This reactivity is also the topic of

Chapter 6, where γ -alumina was used as catalyst and supercritical carbon dioxide as solvent.

Finally, Chapter 7 summarises the work described in this Thesis and evaluates the progress made towards achieving the aims that are introduced at the end of Chapter 1. One of these aims is to evaluate the work carried out in this Thesis according to the 12 principles of CO₂ Chemistry. This evaluation is shown in Chapter 7.

German Abstract

Die dieser Dissertation zugrunde liegende Arbeit wurde im Rahmen des Erasmus-Mundus-Projekts SINCHEM durchgeführt. Die Arbeit konzentriert sich auf die mögliche Benutzung von Kohlendioxid als Lösungsmittel und als Reagenz.

Kapitel 1 behandelt Kohlendioxid und dessen Nutzung. Darüber hinaus werden die 12 Prinzipien der Chemie von CO₂ sowie kontinuierliche Strömungschemie und selbstoptimierende Reaktoren dargestellt. Die relevanten Aspekte dieser Reaktoren werden in Kapitel 2 genauer diskutiert.

Die Ergebnisse der Forschung werden in den Kapiteln 3-6 dargelegt. Ein selbstoptimierender Reaktor mit FT-IR Analyse wurde für die Methylierung von Alkoholen benutzt, wie in Kapitel 3 beschrieben ist.

Die Kapitel 4-6 konzentrieren sich auf *N*-Alkylierungsreaktionen. In Kapitel 4 wird die Reaktivität zwischen Anilin, Tetrahydrofuran und Dimethylcarbonat in überkritischem Kohlendioxid behandelt. Diese Forschung führte zur Entdeckung neuer Transformationen.

In den Kapiteln 5 und 6 wird der Einsatz von Methanol zur Methylierung von Aminen diskutiert. Ein Rutheniumkatalysator, der Methanol aus Kohlendioxid und Wasserstoff produzieren kann, wurde verwendet, um die Reaktionen zwischen Methanol und aliphatischen Aminen zu katalysieren, wie in Kapitel 5 beschrieben wird. Auch die Zyklisierung und anschließende Methylierung der Aminoalkohole wurde untersucht. Diese Reaktivität wird auch in Kapitel 6 thematisiert, γ -

Alumina wurde hier als Katalysator mit überkritischem Kohlendioxid als Lösungsmittel verwendet.

In Kapitel 7 ist die Arbeit dieser Dissertation zusammengefasst. Es umfasst eine Bewertung der Fortschritte hinsichtlich der Verwirklichung der Ziele, die am Ende des Kapitels 1 eingeführt worden sind.

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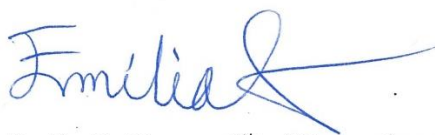
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Finally, I would like to apologise for any confusion or anger reading my Finnish-English may cause.

Declaration

I declare that the work presented in this Thesis is a record of my own work for the period of September 2013 to September 2016. 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.



Emilia S. Streng, 9th of December 2016



PROFESSOR SIR MARTYN POLIAKOFF
PLD Supervisor.

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Abbreviations

Al(OTf) ₃	Aluminium trifluoromethanesulfonate (triflate)
APT	Attached Proton Test (NMR)
ATR	Attenuated Total Reflection (FT-IR)
BME	Butyl methyl ether
BPR	Back pressure regulator
Bu-	Butyl-
COD	1,5-Cyclo-octadiene
CCS	Carbon capture and storage
CDU	Carbon dioxide utilisation
CRI	Carbon Recycling International
CV	Covariance
DMC	Dimethyl carbonate
DME	Dimethyl ether
DMSO	Dimethyl sulfoxide
DoE	Design of Experiment
DTGS	Deuterated triglycine sulfate
Et-	Ethyl-

EtOAc	Ethyl acetate
EtOH	Ethanol
FID	Flame ionisation detector
FT	Film thickness
FT-IR	Fourier transform infrared spectroscopy
GLC, GC	Gas liquid chromatography
GUI	Graphical user interface
HPLC	High-performance liquid chromatography
ID	Inner diameter
IL	Ionic liquid
<i>i</i> -PrOH	Isopropyl alcohol, 2-propanol
LCA	Life cycle assessment
MCT	Mercury cadmium telluride (detector)
Me-	Methyl-
MEA	Monoethanolamine
MeOH	Methanol
MOF	Metal-organic framework
N.O.	Not observed
NHTf ₂	Trifluoromethanesulfonimide
NMSIM	Normal mode Simplex algorithm
P _c	Critical pressure
PME	Pentyl methyl ether
PPh ₃	Triphenyl phosphine

Ppm	Parts per million
Rig	The entire high pressure continuous flow apparatus
scCO ₂	Supercritical carbon dioxide
Sel.	Selectivity
SL	Sample loop
SMSIM	Super-modified Simplex algorithm
SNOBFIT	Stable Noisy Optimisation by Branch and Fit –algorithm
nreq	Requested amount of points to be generated by SNOBFIT
p	Percentage of nreq that are requested as global points
dx	Resolution vector
T _c	Critical temperature
THF	Tetrahydrofuran
TMM	Trimethylenemethane
TON	Turn over number
Triphos	1,1,1-tris(triphenylphosphinomethyl)ethane
Vopt	Ratio of the IR-absorptions of the product to the reference peak

Compounds

For convenience, a key for all the numbered compounds in Chapters 4-6 can be found in the Appendix on page 253.

Chapter 1. Introduction

In recent years, there has been growing scientific interest towards developing processes, and discovering reactions, in which carbon dioxide can be utilised. In this Thesis, some potential applications of carbon dioxide as a solvent, and as a starting material, will be discussed. The work was carried out within the European Doctoral Programme on Sustainable Industrial Chemistry (SINCHEM), at two different locations: the University of Nottingham, and the ITMC, RWTH Aachen. At Nottingham, several different reactions were carried out in supercritical carbon dioxide and were studied with the help of a self-optimising reactor. Such technologies can be employed to locate the optimal reaction conditions, within a set parameter space, relatively effortlessly. In Aachen the focus of the research was aimed at the possible utilisation of carbon dioxide in chemical reactions, building upon the expertise on such reactivity within the group.

A common theme throughout the work presented in this Thesis, is the alkylation of heteroatoms via halogen free routes. Initially, the etherification of alcohols with dimethyl carbonate was studied, after which the focus was aimed at *N*-alkylations of both aromatic and aliphatic amines with alcohols. In this Chapter a general introduction to CO₂, continuous flow systems and self-optimisation is given. Each of the studied reactions is described in more detail in the subsequent Chapters.

1.1 Carbon Dioxide

In the last few decades, the concentration of carbon dioxide in the atmosphere has rapidly increased due to anthropogenic emissions.¹⁻³ It has been shown that the CO₂ concentration stayed nearly constant for 900 years, as it only increased from 280 ppm to 295 ppm between the years of 1000 and 1900. Since then, mainly due to industrialisation, the increase in the amount of CO₂ in the atmosphere has accelerated. By 1958 the atmospheric CO₂ concentration was already 315 ppm, and in August of 2016 it reached 402 ppm (October 3rd approximately 400 ppm).^{3, 4} Despite the fact that carbon dioxide plays a vital role in sustaining life on earth, and belongs in the atmosphere, the uncontrollable emissions caused by human activities are considered to be one of the main contributors to global warming and climate change, making the increase in CO₂ concentration extremely worrying.^{2, 3, 5} The main problem is that each year more CO₂ is being produced than can be captured by the natural carbon cycle. These emissions then lead to an increasing excess of CO₂ in the atmosphere, which is slowly approaching a magnitude of a teraton (10¹² tons).⁵ The main sources of the anthropogenic CO₂ emissions include fossil fuel combustion for power generation of industrial and residential purposes, as well as combustion by the transport sector.² Additional emissions are produced in the fermentation of biomass (sugars to alcohols), in the production of metals from ores (carbon as a reducing agent), and the thermal decomposition (calcination) of limestone and dolomite when producing cement.

Energy production is still heavily dependent on the burning of fossil fuels, and as the energy demand keeps growing with the growing global population, so too will the amount of emissions released from processes linked to energy production.^{2, 3, 6-8} It has been estimated that in the year 2020 over 2000 GW of energy⁹ will be produced by burning fossil fuels. This amount of combustion is predicted to lead

to CO₂ emissions reaching levels of 29-44 Gt/year by year 2020, and up to 84 Gt/year in 2050.^{2, 3} Even though the energy demand keeps rising, the need to decrease emissions is becoming urgent.

The main routes by which CO₂ emissions could be decreased include; switching to less carbon intensive fuels (e.g. from coal to natural gas), and increasing the use of renewable energy resources; transforming current processes to be more energy efficient; chemically or physically utilising CO₂; and carbon capture and storage (CCS).^{1-3, 10} In coal-burning power plants, it has been estimated that by increasing the efficiency of the process, one third of the CO₂ emissions could be avoided (ca. 1.8 Gt CO₂ yearly).⁹ Another suggestion concerns the utilisation of CO₂ in chemical processes: due to the vast amount of available CO₂ in the atmosphere, only 0.1 % of the free CO₂ could be utilised.^{5, 11} However, the production of, for instance, high value products could be used to improve the feasibility of the other carbon mitigation processes.^{10, 12} Currently, CCS is the most promising short term option, when striving to diminish carbon dioxide emissions, especially when combined with the other strategies.^{1-3, 9}

1.1.1 Carbon Capture and Storage

In CCS, the principal goal is to produce a concentrated, high pressure stream of CO₂, which can then be transported to a storage site, and stored underground.¹³ As explained below, the technologies with the highest potential of being implemented for CO₂ capture include post-combustion, oxy-fuel (or oxy-combustion) and pre-combustion procedures.^{2, 3, 13} In the post-combustion method, the CO₂ is captured by washing the flue gas with, for example, amine solutions, such as monoethanolamine (MEA in aqueous solutions, e.g. 0.3 g MEA per 1.0 g of water). In the oxy-fuel technology, oxygen is first separated from air, and then the pure oxygen is used to combust the fuel. This method leads to

a much higher CO₂ concentration in the flue gas, because N₂ is absent. CO₂ can thereafter be purified simply by demineralising the gas. In the pre-combustion method the CO₂ is captured from the fuel gas before the combustion of hydrogen. Firstly, the fossil fuel (e.g. coal) is gasified to syngas (mixture of H₂, CO₂, CO, H₂O, N₂ etc.) and after purification the CO is reacted with steam to form hydrogen and CO₂ (water-gas-shift). The CO₂ can then be separated from the hydrogen gas. All of these capture technologies have both advantages and also disadvantages, which makes it important to keep developing the capture methods, by finding new materials to perform the separation of CO₂ from the other gases.^{2, 10, 13} Such technologies include; using metal organic frameworks (MOFs), carbon-based adsorbents, or membranes in the separation.¹⁴⁻²⁰ An interesting alternative is to produce biomass, such as microalgae, by mitigating CO₂, either by directly or indirectly capturing the CO₂ straight at the source.²¹

After the capture and transportation, the CO₂ needs to be stored in very large amounts for a long period of time, in order to achieve an actual impact on the atmospheric CO₂ levels.^{13, 22} The most promising storage options include; geological storage in saline aquifers, in depleted oil and natural gas supplies, and in coal mines.^{2, 23, 24} The storage is based on a number of physical and geochemical trapping mechanisms (e.g. carbonate formation), and because the CO₂ will be stored at depths of over 800 m, the stored CO₂ will be in the supercritical phase, which will improve the storage safety and the utilisation of the available storage space.

When CCS processes become viable, the captured CO₂ will be available at a high pressure, but it will still contain some impurities, and depending on the end use, it might need further purification (e.g. for the food industry).^{10, 25} However, if the goal is to utilise the captured CO₂ as e.g. a solvent in reactions, it is important to make sure the impurities do not detrimentally affect the reaction outcome. If the

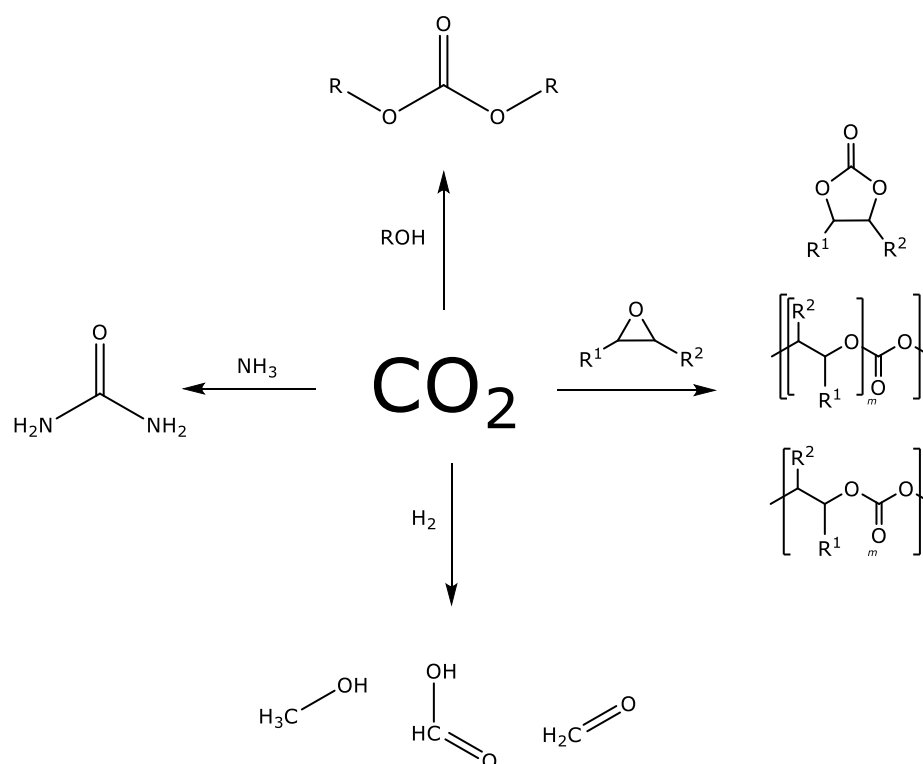
CO₂ needs to be purified in order to be used as a solvent, the cost of utilising CO₂ is once again increased. It is therefore important to make sure that the purity, which is sufficient for transport and storage, is also high enough for utilisation. Stevens *et al.*²⁶ studied the effect of different amounts of the most common impurities (N₂, CO and H₂O), present in the captured CO₂, on the hydrogenation of isophorone to 3,3,5-trimethylcyclohexanone using supercritical CO₂ as a solvent. They found that the impurities did not greatly affect the reaction outcome and that, in the case of the studied hydrogenation, CO₂ originating from carbon capture could have been used without further purification.

1.1.2 Carbon Dioxide Utilisation

One potential way of bringing value to captured CO₂ is to use it in chemical reactions, either as a starting material, or as a solvent (a.k.a. Carbon Dioxide Utilisation, CDU).^{5, 27} Using CO₂ as a carbon source in chemical reactions is also important, when trying to replace the use of petrochemical substances in the chemical industry. In addition, alternative solvents, including scCO₂, have received much attention recently, as they have the potential to help replace traditionally used, often toxic and flammable organic solvents. There is, however, a scale mismatch with the emissions of CO₂ and the amount that can be utilised: yearly global CO₂ emissions are in the order of 10¹⁰ tons whereas the maximum amount of CO₂ that can be utilised in chemical and industrial processes is estimated at 10⁸ tons p.a.¹² However, by bringing value to CO₂ by utilisation, the CCS process could possibly be made more cost effective, and hence help with CO₂ mitigation.

Carbon Dioxide as a Starting Material

The high oxidation state of carbon in CO_2 (+IV) makes the molecule very stable.²⁸ In order for CO_2 to be utilised in chemical reactions, energy needs to be added to the system, as either by reactions with energy-rich reaction partners, or by adding heat, light or electricity. Carbon dioxide can be used as a starting material in the production of many different types of chemicals with the help of a variety of catalysts (Scheme 1.1).^{5, 12, 27, 29-39} CO_2 can be transformed to, for example, lactones, esters, carboxylic acids, methanol and organic carbonates. Thermal processes include the production of urea, salicylic acid and inorganic carbonates.⁴⁰ In addition, carbon dioxide can be made to react photochemically,^{41, 42} electrochemically^{20, 43} or by using bio-catalysts.⁴⁴



Scheme 1.1. Some of the products that can be produced from CO_2 . For example reactions with epoxides, alcohols and hydrogen, produce organic carbonates, methanol and carboxylic acids respectively. In addition, urea can be formed in reactions with ammonia.

Chapter 1

In reactions with high energy hydrogen molecules, for example methanol, formic acid and dimethyl ether can be produced from carbon dioxide.⁴⁵⁻⁵⁰ These substances can be used as fuels or as starting materials in chemical processes. Both heterogeneous and homogeneous catalysts have been studied for these hydrogenation reactions. The advantage of homogenous catalysts is the efficiency of the catalytic system. Heterogeneous catalysts, on the other hand, are easier to recycle. More details on the formation of methanol, and using CO₂ together with H₂ as a methylating agent for the *N*-methylation of amines, are given in Chapter 5.⁴⁷⁻⁴⁹

In addition to hydrogenation, the production of organic carbonates has been extensively studied.⁵¹⁻⁵⁶ The so called linear carbonates (e.g. dimethyl carbonate, DMC) and cyclic carbonates (e.g. propylene carbonate) can be used as green solvents or starting materials in organic synthesis. Furthermore, DMC can be used as a green methylating or carbonylating agent, in a number of different reactions. These reactions are especially green, when DMC is produced from e.g. CO₂ or via other routes that avoid the implementation of the highly toxic phosgene.^{57, 58} In this Thesis, the reactivity of DMC was studied and it is described further in Chapters 3 and 4. In addition to DMC, polycarbonates, such as polypropylene carbonate, have very useful properties including durability and biodegradability. Therefore, polycarbonates produced from CO₂, have the potential of becoming useful materials, if industrially viable synthesis methods are developed.

In 1969 Inoue *et al.*^{59, 60} were the first to produce polypropylene carbonate and cyclic propylene carbonate from propylene oxide and carbon dioxide, using a heterogeneous diethyl zinc complex together with water as the catalytic system. Since then reactions where CO₂ is inserted into epoxides have been widely studied.^{51-54, 56} Depending on the temperature, the CO₂ pressure, the employed

catalyst system and the epoxide, the synthesis will yield either a cyclic carbonate or a polycarbonate as the main product. Cyclic carbonates are often easier to produce than the corresponding polycarbonates, due to the thermodynamic stability of the cyclic carbonate molecule. Also, the fact that cyclic carbonates are occasionally generated as side products in the copolymerisation of epoxides and CO₂, due to depolymerisation caused by back-biting reactions, makes cyclic carbonates the more likely product. Hence, a wider range of different catalytic systems have been studied to produce cyclic carbonates compared to the synthesis of polycarbonates. The most efficient copolymerisation catalysts include different types of zinc, cobalt and chromium complexes. These reactions will often also produce cyclic carbonates, if the reaction conditions are altered.

The 12 Principles of CO₂ Chemistry

In order to develop viable systems that can incorporate CO₂ into chemical reactions, several different aspects need to be taken into account. Hence, during the project described in this Thesis, the 12 Principles of CO₂ Chemistry¹¹ were developed together with Professors Poliakoff and Leitner. These principles give, in a similar manner to the well-established 12 Principles of Green Chemistry,⁶¹ guidelines for reactions utilising CO₂ (Figure 1.1) to help assess a process and its viability. All of these principles should be considered, when aiming for a process with the true potential of utilising CO₂.¹¹ They concentrate on how the transformation is achieved (chemically and process wise), the source of CO₂, the type of product that is synthesised, and other factors such as the energy input and the required realism, when the aim is to discover industrially applicable processes.

C	Catalysis is crucial
O	Origin of the CO ₂ ?
2	Tomorrow's world may be different
C	Cleaner than existing process?
H	High volume or high value products?
E	E-factor must be low
M	Maximise integration
I	Innovative process technology
S	Sustainability is essential
T	Thermodynamics cannot be beaten
R	Renewable (& reasonable) energy input
Y	Your enthusiasm is not enough

Figure 1.1. The 12 Principles of CO₂ Chemistry, as presented by Poliakoff *et al.*¹¹
The purpose of these guidelines is to help scientists and engineers to develop viable processes that utilise CO₂. The details of each principle are given in the text.

The details on each principle shown in Figure 1.1, and as presented in the publication,¹¹ are given below. After this introduction, the Principles are used to evaluate a process which utilises CO₂ on a commercial scale.

Catalysis is crucial: CO₂ is notoriously unreactive in organic synthesis and in reductive processes. It can be considered a thermodynamic minimum with only highly energy rich compounds being able to react with it. Such reactions do not necessarily require a catalyst. For example, once heated, magnesium metal reacts with CO₂ in a highly exothermic reaction⁶² ($2\text{Mg} + \text{CO}_2 \rightarrow 2\text{MgO} + \text{C}$) but the reaction yields elemental carbon which is not necessarily a useful starting point for making chemicals, especially given the financial and energy costs of obtaining metallic magnesium. Thus, nearly all reactions for making chemicals from CO₂ really need to use catalysts.^{29, 49} Heterogeneous catalysts are able to promote important transformations of carbon dioxide such as the famous Sabatier reaction $\text{CO}_2 + 4\text{H}_2 \rightarrow \text{CH}_4 + 2\text{H}_2\text{O}$.³² Homogeneous catalysts are very

selective for many synthetically useful C-C and C-X bond formation processes.^{28,}
³⁰ Electro- and photochemical transformations of CO₂ also require suitable catalyst materials or molecular catalysts due to the large over-potential for CO₂ reduction to its radical anion.⁴⁶ Nature's ingenious catalytic processes for construction of its entire material basis from CO₂ can serve as motivation to develop man-made catalysts for industrial implementation.

Origin of the CO₂? : CO₂ can be sequestered from many industrial processes and other sources.⁶³ The need for catalysis may well place quite severe restrictions on the purity of the CO₂. Trace impurities could easily poison catalysts or oxidise expensive ligands. Fortunately, the large disparity between global CO₂ production and the possible consumption by the chemical industry means that operators of chemical processes can afford to be quite choosy about the source of their CO₂. For example, some processes may require relatively dry CO₂ and could benefit from fears of pipeline corrosion in CCS that are leading to relatively stringent proposals for acceptable levels of H₂O currently for any captured CO₂ to be transported by pipeline.²⁵ At the same time, using atmospheric CO₂ will always carry a large energy cost because of the need to move very large masses of air to obtain a sufficient flux of CO₂ through one's chemical process. It may well be hard to beat photosynthesis by plants/trees/algae as a means of deriving carbon compounds from the atmosphere, even though such photosynthesis often requires very large amounts of fresh water, a commodity that may well be in short supply in the future. Furthermore if a process is based on sequestration of CO₂ by formation of biomass, one needs to consider questions of land usage, of "food versus chemicals" as well as water usage, all of which impact on the overall sustainability.⁶⁴

Tomorrow's world may be different: Unlike academic research, commercial chemical manufacture has to face economic reality. This means that any CO₂-based process will be fully exposed to changes in the financial environment. Government subsidies can change rapidly with changes of government or policy. In this context it is important to remember that, although CO₂-based chemistry cannot make a significant impact on overall anthropogenic CO₂ emissions, it could reduce the emissions from a particular plant or company; such a reduction could give significant fiscal advantage to that company. Also, the global oil price which is a key parameter in determining the commercial viability of any CO₂-based process can fluctuate widely; for example the price of Brent Crude has dropped by nearly 50% over the last 12 months (23/09/2014-22/09/2015),⁶⁵ gravely affecting the economics of otherwise attractive processes using alternative carbon sources. On the other hand, the possibility of providing an outlet for fluctuating "excess" renewable energy could constitute a novel, quite unexpected business opportunity in the future.^{34, 48} Hence, the distinction between economically "useful" or "useless" processes is likely to depend on time and place, leading to different strategies when devising short-term and long-term goals in science.

Cleaner than existing process?: Just like in any chemical process, "greenness" should be an a priori criterion for CO₂ Chemistry: it seems only sensible that any new process should be cleaner (or at least not dirtier) than any existing process that it replaces. This is more than a mere gesture towards environmentalism. Disposal of waste has become a significant and increasing cost for chemical producers and the more toxic the waste, the more expensive is its disposal. Importantly, CO₂ holds great potential also in this context; it is a non-toxic, safe reagent as compared to many other C1-building blocks, often producing water as the only by-product. Ideally, the energetic and material aspects of the "green" approach work together to minimise both energy

requirements and the waste produced, and it can be a very difficult task to balance the benefits and drawbacks if this is not the case.⁶⁶

High volume or high value products?: This is an absolutely key question. If one is aiming to make high volume/low value products, any CO₂-based process must necessarily be low cost, thereby removing the option of using expensive catalysts or other costly processing options. Such processes will also be particularly vulnerable to fluctuations in the price of oil because feedstock price will be a large proportion of the cost of the final product. Conversely, if one is making low volume/high value products, the price of the feedstock will be only a small component in the overall cost and so any cost advantage of CO₂ as a feedstock may only be marginal. An attractive option, therefore, may be to aim for medium volume/medium value products where the cost of feedstock is significant but low enough to dampen out effects of temporary swings in the oil price. A good example described below is the CO₂-based production of polyols for the manufacture of polyurethane polymers, which is currently being implemented on industrial scale in Germany.^{67, 68}

E-factor must be low: One of the key concepts of Green Chemistry is the E-factor, originally proposed by Sheldon.⁶⁹ The factor is the weight of waste generated per unit weight of the product. Its use has had real impact on chemical production, for example resulting in huge reductions in solvent usage in the production of Viagra.⁷⁰ However, it has even more importance in CO₂-based chemistry. This is because conversion of CO₂ into organic compounds is energy intensive and therefore waste organic compounds will also represent a waste of energy. To highlight the importance of the E-factor, the Braskem process for making poly-ethene from cane sugar, hence using CO₂ via photosynthesis, is an interesting example.^{71, 72} The subsequent chemistry is simple: sucrose is fermented to ethanol, which is dehydrated to ethene that is then polymerised.

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The advantage is that the product slots into existing supply chains without the need to create new commercial infrastructure. As regards the E-factor, 33% of the carbon fixed by photosynthesis is released as CO₂ during the fermentation. (And, like all CO₂ utilisation processes, it is vulnerable to falling oil prices which can render the cost of the product uncompetitive).

Maximise integration: *Although research in CCS and research in CDU have often been carried out separately, it clearly makes sense to integrate carbon capture and its subsequent use. Such integration might be achieved, if the captured CO₂ was exploited as a solvent for reactions in supercritical CO₂.²⁶ The rationale is that the energy costs of compressing CO₂ represent a substantial fraction of the cost of supercritical processing; however, compression of CO₂ is an integral part of the capture and transport technology. Consequently, power plants or industrial processes equipped with capture units could provide high pressure CO₂ at no or moderate additional cost. Although a supercritical CO₂ solvent is not strictly "utilised", because the CO₂ is still there at the end of the process, it could represent a substantial reduction in usage of petroleum-based material as solvents. A more chemically elegant example of integration is the process developed jointly by Bayer together with the CAT Catalytic Center at RWTH Aachen, which is now being commercialised by the company Covestro.⁶⁷ The catalytic transformation has been demonstrated to be compatible with captured CO₂ even from coal fired power plants and other processes; the process is now being industrialised with production using the CO₂ by-product from an ammonia synthesis plant located on the same industrial site.*

Innovative process technology: *Many proposed CO₂-based processes will require new chemical plants to implement them, immediately adding capital expenditure to other start-up costs. Therefore, the introduction of innovative process technology, particularly continuous processing could have a significant*

impact on the economics of the process. The synthesis of formic acid from CO₂ and H₂ provides an illustrative example, where the thermodynamics of the reaction require additional stabilisation of the product in the reaction stage that needs to be overcome during the downstream product separation.^{73, 74}

Sustainability is essential: *Long term sustainability is a major reason, if not the major reason, for developing CO₂-based chemistry. Therefore, it has to be a criterion for judging the viability of any proposed process. However elegant the catalysis, one must always look at the whole life cycle; the energy and/or chemical resources needed to make the catalyst may well reveal that an otherwise attractive process is totally unsustainable. Furthermore, it is important to stress that sustainability involves more than demonstrating that a particular catalyst is based on abundant and easily obtained elements. Although the sustainability of a process can only be reasonably established by Life Cycle⁷⁵ or similar assessments,⁷⁶ which are quite lengthy procedures, it may often be easier and quicker to recognise processes that are obviously unsustainable.*

Thermodynamics cannot be beaten: *As in other areas of chemistry, the thermodynamics of CO₂-based processes depend on where one draws the system boundary. For example, the hydrogenation of CO₂ mentioned above, $\text{CO}_2 + 4\text{H}_2 \rightarrow \text{CH}_4 + 2\text{H}_2\text{O}$, is exothermic, provided that one does not consider the energy involved in generating the hydrogen. Thermodynamics assume that systems are in equilibrium. Therefore, although thermodynamics cannot be beaten, it may be possible to side-step thermodynamic barriers by deliberately avoiding equilibrium situations, for example in plasma processing.^{77, 78} Furthermore, even an endothermic process using CO₂ can be advantageous, if the alternative routes consume even more energy to arrive at the same product or function. This emphasises again that one must consider the whole system*

with clearly defined boundary conditions in making an evaluation, and most evaluations are only valid in comparison, rather than as absolute values.

Renewable (& reasonable) energy input: *Since the aim of CO₂ Chemistry is to avoid use of fossil carbon in the manufacture of chemicals, it is clearly not sensible to incorporate less CO₂ into the chemicals than one creates by burning fossil carbon to generate the energy needed to make those chemicals. Otherwise, one might as well start with the fossil carbon as the feedstock. Therefore, renewable energy might seem to be the panacea for CO₂-based chemistry. If renewable energy sources are coupled with CO₂ as carbon source, this could decouple the carbon emission from the energy sector and the feedstock.^{34, 48} Of course, this does not eliminate the challenge of devising energy efficient processes. Also renewable energy will not be "for free", either economically or environmentally. Furthermore, if renewable energy does become available on large scale, the chemical industry will not be the only potential outlet and its use may have an even larger impact on our carbon emissions in other sectors. Hence, the goal of minimising the energy requirements of chemical production remains a core issue in CO₂ chemistry, regardless of the primary energy source.*

Your enthusiasm is not enough: *In the context of this Discussion, the purpose of CDU is to devise processes that can lead to viable methods of using CO₂ as a chemical feedstock. Therefore, one needs to apply a certain degree of realism to any proposed CDU process whatever its intellectual and academic fascination. This is not to say that successful CDU processes will be mundane or boring. Merely, it means that processes will have the best chance of success if they arouse widespread interest, not only in academia but amongst those who make chemicals to sell. Even so, it must be stressed that society is wider than either academia or industry. Ethical issues and environmental consequences as*

well as aesthetic impact on the landscape are also important, if not paramount issues. These are also issues that are strongly championed by non-governmental organizations (NGOs) and other lobby groups. Therefore, it is salutary to remember that no process, however elegant and potentially profitable, will be genuinely sustainable without the positive support from the wider community.

Implementing the 12 Principles of CO₂ Chemistry to Evaluate a Commercial Process Utilising CO₂

To demonstrate the implementation of the principles introduced above, a large scale commercial processes that utilises CO₂ is evaluated. The chosen example is the production of methanol from CO₂ by Carbon Recycling International (CRI) in Iceland (Figure 1.2), which produces yearly up to 5 million litres of methanol.⁷⁹
⁸⁰ This facility is located close to the Svartsengi Power Station, which is a geothermal power plant, and also provides the required energy for the process. The utilised CO₂ is obtained from the emissions of this plant. Geothermal systems are one of the main CO₂ sources in Iceland. This CO₂ is not considered anthropogenic, as it is released from steam originating from deep in the earth and contains CO₂ as a result of degassing magma in the mantle.⁸¹

In the CRI methanol process, CO₂ is captured from flue gas from the power plant, and purified before it is reacted with hydrogen gas produced from the electrolysis of water. The different reaction steps are catalysed by several catalysts and the required electricity is provided by renewable sources making the produced hydrogen carbon neutral. The synthesised methanol is then used in the production of biofuel (a mixture of MeOH and gasoline).

This methanol production system was chosen as the example to illustrate the use of the 12 Principles, because in Chapter 5, methanol (possibly derived from CO₂) is used as a reagent.

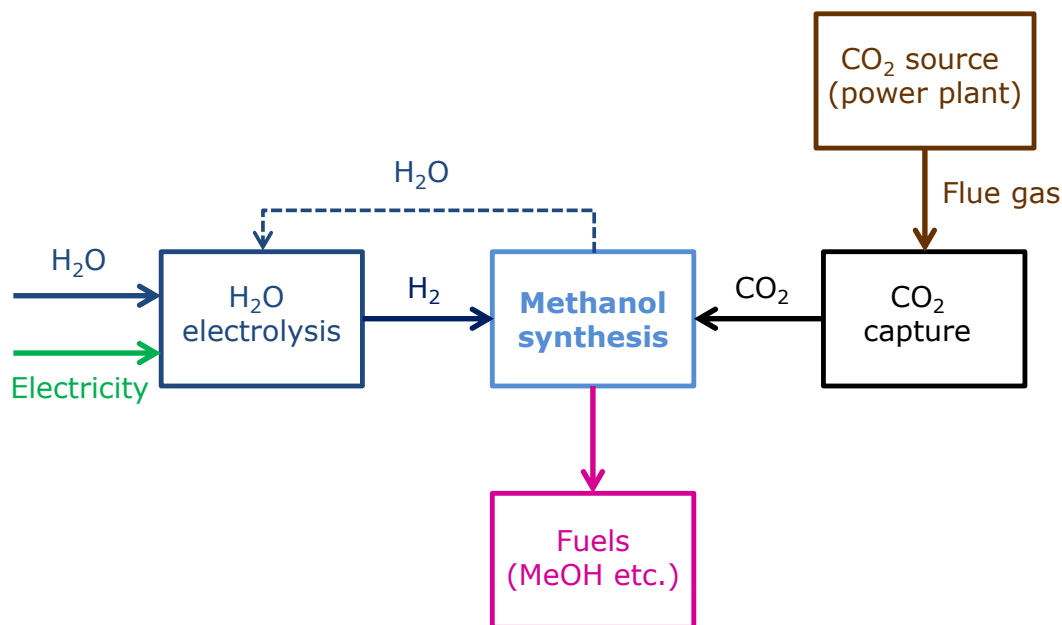


Figure 1.2. A simplified flow chart for the CRI process of synthesising methanol from CO₂ and H₂. The CO₂ is captured from the exhaust gas of a geothermal power plant and purified before it is introduced to the methanol synthesis step. The hydrogen is obtained from water electrolysis and the input electricity is obtained from a renewable source (geothermal or hydro power). Initially CO₂ reacts with H₂ forming CO and H₂O, after which more H₂ is added to form methanol from CO and H₂. The different reaction steps are catalysed by proprietary catalysts. This process is used to illustrate the implementation of the 12 Principles of CO₂ Chemistry.

In fact, the CRI process is very elegant, and it fulfils nearly all of the 12 Principles of CO₂ Chemistry, at least to some extent:

Principle 1. Catalysis is crucial: All the reaction steps in this system are catalysed by different catalysts, the specific identity of which have not been disclosed.⁷⁹ According to the patent the catalyst for the methanol synthesis step seems to be Cu/γ-alumina. The other steps involve other commercially available catalysts, indicating they are economically viable, and hence relatively sustainable.

Principle 2. Origin of the CO₂?: The CO₂, in this example, is captured from flue gas released by a geothermal power plant located close to the CRI factory, and it is subsequently purified.⁸⁰ These types of CO₂ sources are mainly limited to volcanic areas such as Iceland, but if a similar facility was built elsewhere, it could be combined with a different source of CO₂ relatively easily.

Principle 3. Tomorrow's world may be different: This process can be incorporated with a further reactor which allows the produced methanol to be transformed into different hydrocarbons (e.g. by methanol-to-fuel processes).⁷⁹ This ability to add reaction steps, is important as it offers the possibility to change the final product according to e.g. the market pull, and therefore retain a viable process.

Principle 4. Cleaner than existing processes?: Most of the methanol currently produced originates from fossil resources, making the CRI process inevitable cleaner than the existing ones. In the current system, the captured CO₂ is firstly reacted with H₂ to produce CO, which then reacts with more H₂ to form the target product.⁷⁹ The methanol is then distilled to separate it from the water and any possible unreacted starting materials. The substrates can then be recycled back through the system to produce more methanol.

Principle 5. High volume or high value products?: Methanol is considered a low value product, and hence the production volume needs to be significant to retain the viability of the process. Currently five million litres of MeOH can be produced yearly by utilising up to 5500 tonnes of CO₂.⁸⁰

Principle 6. E-factor must be low: The process is solvent-free and molecular oxygen is the only side product. O₂ is in itself valuable, and can help make the process more economically viable.⁸⁰

Principle 7. Maximise integration and **Principle 8. Innovative process technology**: In the established process the capture and purification of CO₂ is combined with a water electrolysis unit, which produces H₂ for the synthesis of methanol, and a renewable energy power plant. The electrolysis unit can also be equipped with a water purification system, making it possible to use a similar process starting from e.g. seawater. To showcase that such facilities could be built elsewhere (outside Iceland in places with no geothermal energy), the plant also has a H₂ storage tank, which makes it possible to produce an excess of the required H₂ utilising other renewable energy sources e.g. solar or wind power, whenever they are available (irregular supply). This stored H₂ can then be added to the main reaction whenever needed, and ensures continuous production of methanol independent of the origin of the electricity.

Principle 9. Sustainability is essential: According to a full life-cycle assessment, using this renewable methanol releases 90 % less CO₂ compared to when fossil fuels are used.⁸⁰ In addition, as mentioned above, the catalysts used are probably not based on noble metals, and are hence unlikely to diminish the sustainability of the process.

Principle 10. Thermodynamics cannot be beaten: The overall reaction producing methanol from CO₂ and H₂ is thermodynamically favourable. The exact reaction conditions have not been detailed, in the current case, but several reaction steps require high pressures and/or high temperatures.⁷⁹ However, the energy for these steps, is provided by either heat recovered from the exothermic reaction steps (e.g. CO + H₂ → MeOH), or from renewable energy sources.

Principle 11. Renewable (& reasonable) energy input: As mentioned above, in the example process the energy for the electrolysis (and for other steps as required) is provided by renewable sources (geothermal or hydroelectric in the case of Iceland), and does hence not contribute to further CO₂ emissions.

Principle 12. Your enthusiasm is not enough: The example process has been found to be competitive, when optimised and combined with the right catalysts.⁸⁰ In addition, the process is even more attractive due to incentives from regulations by e.g. the EU, as well as a market pull for renewable methanol. Another advantage is that this bio-fuel is based on waste CO₂ and not biomass, removing all ethical issues combined with land use for growing feedstocks for fuels.

This example produces a large scale relatively low value product, but also other types of processes have been commercialised with the potential of bringing value to CO₂. An example of synthesising a medium value product from CO₂, is the formation of polyurethane to produce e.g. foams used as fillings for mattresses.^{67, 68} Slightly more expensive catalysts and starting materials can be used in this case, compared to the methanol synthesis, in order for the system to still be viable, as was briefly mentioned in the 12 principles of CO₂ Chemistry.¹¹

Inspired by these examples, the work described in this Thesis will also be judged according to these 12 principles in Chapter 7. As mentioned above, the principles were initially designed for reactions incorporating CO₂ into molecules, but they will also be used to assess the work concentrating on the second method of bringing value to CO₂: carrying out reactions in scCO₂. A short introduction to this strategy is given below.

Supercritical Carbon Dioxide as a Solvent

Two of the goals of Green Chemistry are to prevent the generation of waste and to avoid the use of harmful substances in chemical processes.^{61, 82-85} Therefore, a fair amount of research has concentrated on the replacement of traditional organic solvents, which constitute one of the main sources of waste generated by the chemical industry.⁸⁶ Organic solvents are also often toxic, and disposing of them properly can be expensive. Alternatives that have been studied, as replacements for organic solvents, include water, ionic liquids, solvents produced from renewable resources and supercritical fluids.⁸⁷ The use of supercritical carbon dioxide (scCO₂) has been extensively studied due to its potential advantages: CO₂ is non-flammable, nontoxic and "chemically inert".^{83, 86, 88, 89} Also, when using scCO₂ as a solvent, releasing the system pressure separates the products from the solvent, and hence further purification steps might be avoided. The supercritical state of CO₂ is quite easy to achieve as the critical temperature (31.1 °C) and pressure (73.8 bar) are relatively low (Figure 1.3). scCO₂ has liquid like densities combined with low viscosity and high diffusion rates, which are properties linked to gases. The supercritical phase is highly compressible, which means that the solvent properties can be varied by slight changes in the temperature and pressure.

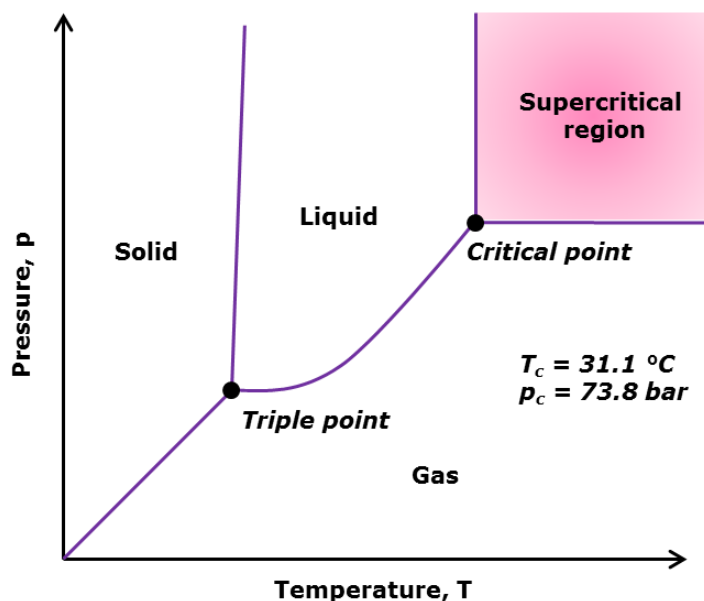


Figure 1.3. Phase diagram for pure carbon dioxide.⁸⁸ Above the critical point ($T > T_c$, and $p > p_c$), carbon dioxide exists as a supercritical fluid, which has properties of both the liquid and the gas phase. When other components are added, such as co-solvents or reagents, the phase diagram becomes much more complicated.

Initially scCO_2 was used mainly in extraction processes, and material sciences, but in the last few decades carrying out chemical reactions in scCO_2 has received more attention.^{83, 86, 88-99} As a solvent, pure scCO_2 is similar to *n*-hexane,⁹⁶ but several ways of altering the solvation properties, have been demonstrated, for example, by modifying the solute (especially relevant for metal complexes),^{88, 94, 95} or adding a more polar co-solvent, such as methanol, to the system.⁹⁶ Both homogeneous^{89, 99} and heterogeneous^{86, 90, 93, 96} metal catalysts have been studied for reactions carried out in scCO_2 . In addition, even asymmetric transformations have been shown to be possible.⁹⁴ Also, by combining scCO_2 with different ionic liquids (ILs), interesting biphasic systems can be achieved.^{91, 97, 98} In these systems, the substrates, and possibly also the catalyst, are dissolved in the IL, and scCO_2 is used to extract and remove the product.

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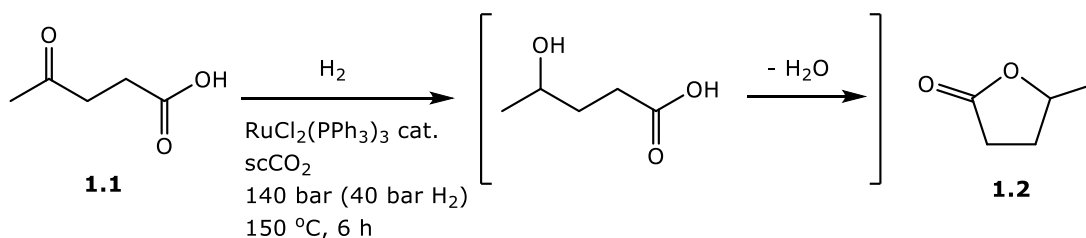
In addition to the above mentioned benefits scCO₂ can make a process safer and it can also help to improve reaction rates.^{83, 86, 88-99} Particularly in reactions involving highly reactive reagents (e.g. molecular hydrogen and oxygen), the use of non-flammable and non-explosive scCO₂ as the reaction medium reduces the potential hazards of the process.^{92, 93} Due to the dilution effects using CO₂ has on gaseous reagents, higher amounts of these may be added to a reaction safely, which can then lead to higher reaction rates. Higher rates can also be achieved owing to an increased mass transfer that takes place between scCO₂ and the gaseous reagents or the organic compounds that are miscible with CO₂, as there are no phase boundaries.

As a result of all these beneficial properties of supercritical carbon dioxide, many different kinds of catalytic reactions have been studied using scCO₂ as the reaction medium.^{83, 86, 88-99} These include many important transformations such as; hydrogenation, hydroformylation, oxidation, Friedel-Crafts alkylation and etherification. Examples of some of these reactions can be seen in Scheme 1.2.

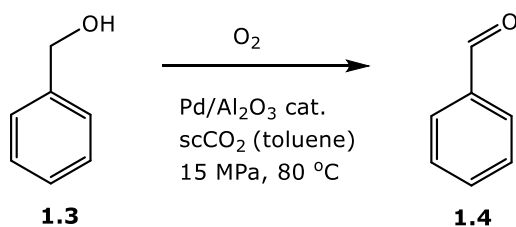
For instance, two industrially useful molecules γ -valerolactone (**1.2**)¹⁰⁰ and benzaldehyde (**1.4**)¹⁰¹ can be synthesised in scCO₂. In the shown example for the hydrogenation of levulinic acid (**1.1**), the presence of CO₂ was shown to be beneficial, as it formed an active species with the catalyst, and the conversion of **1.1** increased, when increasing the pressure of CO₂.¹⁰⁰ The catalyst RuCl₂(PPh₃)₃ formed RuHCl(CO)(PPh₃)₃ in scCO₂, and this species was shown to enhance the rate of the hydrogenation. Also in the oxidation of benzyl alcohol (**1.3**), choosing the right system pressure was important in order to obtain high conversions and selectivity of the desired product.¹⁰¹ When all the reagents were dissolved in the scCO₂, the reaction rates were increased. An additional improvement was discovered, when small amounts of a co-solvent (1 mol-% toluene) was added to the system as this addition helped to dissolve the alcohol, and a single phase

could be achieved at a lower pressure (130 bar compared to 150 bar without toluene).

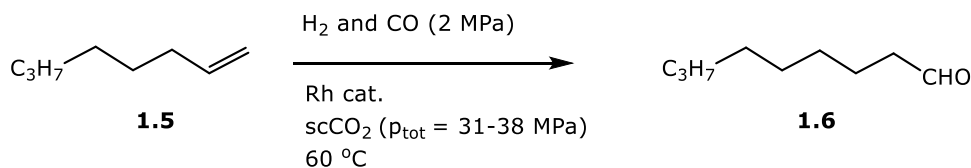
Hydrogenation



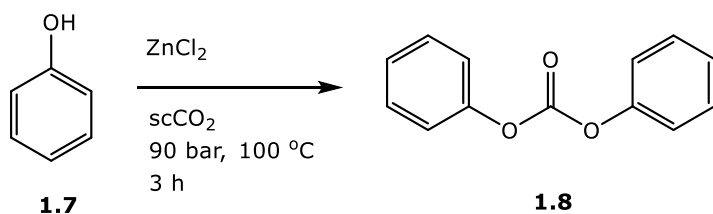
Oxidation



Hydroformylation



Carboxylation



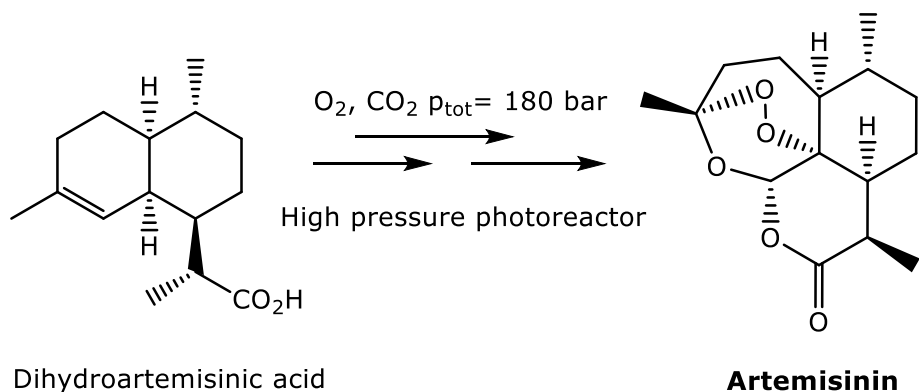
Scheme 1.2. Examples of reactions carried out in scCO₂: hydrogenation of levulinic acid (1.1) to produce γ-valerolactone (1.2);¹⁰⁰ oxidation of benzyl alcohol (1.3) with molecular oxygen to give benzaldehyde (1.4);¹⁰¹ hydroformylation of octene (1.5) resulting in nonanal (1.6);¹⁰² and the carbonylation of phenol (1.7) with CO₂ to give diphenyl carbonate (1.8).¹⁰³

In hydroformylation reactions, a carbonyl group, originating from syngas (H₂ and CO), is added to an olefin to produce aldehydes, which are important intermediates in producing alcohols or carboxylic acids amongst other species.⁹⁶

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Propene is the most common substrate, but also other olefins, such as 1-octene to produce nonanal with a rhodium catalysts (**1.5** to **1.6**, Scheme 1.2), have been studied.¹⁰² In this system all components, including the rhodium catalyst, were in the same phase, and it was found that, when ligands that increased the solubility of the catalyst in scCO₂ were used, the conversion of the reaction increased. The ligands were different triarylphosphines with and without *tert*-butyl substituents on the phenyl rings. Furthermore, an interesting example was presented by the system, where CO₂ can be used both as solvent and a starting material (Scheme 1.2, **1.7** to **1.8**).¹⁰³ Diphenyl carbonate (**1.8**) is an important starting material for polycarbonates, and it is traditionally synthesised with highly toxic phosgene and phenol as starting materials. In this case, where CO₂ was used as both the carbonylation agent and solvent, yields of up to 31.7 % of **1.8** were achieved at 90 bar, 100 °C after 3 h, using a ZnCl₂ catalyst (**1.7**:ZnCl₂ molar ratio 1:0.5).

Over the past decade, the research in the Poliakoff group, at the University of Nottingham, has concentrated on transformations carried out in supercritical fluids, and also in high temperature, near critical, water. An especially successful topic has been the implementation of scCO₂ as solvent for organic reactions, where commercially important molecules are produced either catalytically or photochemically.^{26, 104-130} These transformations include photo-oxidations,¹⁰⁴⁻¹¹⁰ which led to the synthesis of antimalarial trioxanes¹⁰⁹ and finally pure artemisinin¹¹⁰ (Scheme 1.3) in liquid CO₂ and also H₂O/ethanol or H₂O/THF mixtures. The advantage of CO₂, regarding photo-oxidations, is that the reactive singlet oxygen (¹O₂) species has a longer lifetime in scCO₂ than in e.g. pure water, which is one of the relatively few non-chlorinated solvents which displays this behaviour towards ¹O₂.



Scheme 1.3. The antimalarial artemisinin, which can be produced via photo-oxidations of dihydroartemisinic acid with singlet-oxygen in e.g. liquid CO₂ in a high pressure photoreactor.¹¹⁰

In addition to oxidations, also hydrogenations have been studied^{26, 111-113} due to the advantages of carrying out these kinds of reactions in scCO₂ mentioned above. For example, the hydrogenation of isophrone to trimethyl cyclohexanone,^{26, 111} and the hydrogenation of furfural to different products, the selectivity of which was shown to depend on the conditions,¹¹³ have been studied. Also the above mentioned formation of **1.2** from **1.1** was investigated with a system that provided pure **1.2** via an in-line separation process.¹¹² Furthermore, the formation of different ethers in scCO₂ has also been a popular topic in the group.¹¹⁴⁻¹²² Reactions including cyclocondensations of diols,¹¹⁴ the formation of symmetrical ethers,^{114, 115} and the methylation of alcohols with either methanol,¹¹⁶ dimethyl ether¹¹⁶ or dimethyl carbonate,¹¹⁶⁻¹²² have been studied over solid acid catalysts, such as γ -alumina. Such halogen free etherification reactions of alcohols, are important as they allow for e.g. methyl ethers to be formed with water (and CO₂) as the only side products.¹³¹ All of these reactions have been carried out in continuous flow reactors, as is the preferred way, when reactions involving high pressure, high temperature and supercritical fluids, are being studied.^{86, 89, 96}

1.2 Continuous Flow Processes

Additional benefits of carrying out reactions in scCO_2 are seen when they are performed in continuous flow reactors.^{89, 96} These systems allow high throughput chemistry to be achieved relatively simply, and also for the properties of the fluid to be tuned easily, by increased control over the reaction conditions.¹³²⁻¹³⁶ Continuous flow set-ups can be used to maximise efficiency, and they can help increase the greenness of a process, by minimising waste. Such procedures, are considered to be an effective and economical way of making large amounts of chemicals within a short time frame.¹³³ Also, as when employing supercritical fluids, non-conventional reaction conditions can be reached relatively easily; high temperatures (for gas phase reactions), and high pressures (e.g. for supercritical fluids).¹³⁷ Such conditions can be used to discover new reactivities and chemistries, which might not be possible with more traditional equipment, and have hence been overlooked by synthetic chemists.^{138, 139} Flash chemistry, as introduced by Yoshida's group,¹³⁹ is an example on such behaviour; using continuous flow microreactors, which offer very precise control of the reaction time, to carry out extremely fast reactions with high selectivity for the target product. These reactions include protecting-group-free syntheses, multi-step transformations, asymmetric syntheses and others. Most of these examples cannot be carried out in batch processes, where heating and cooling the system can affect the outcome, as precise control of the reaction time is not possible. In continuous flow this feature is avoided as the starting and stopping point of the reaction can be easily determined (Figure 1.4).

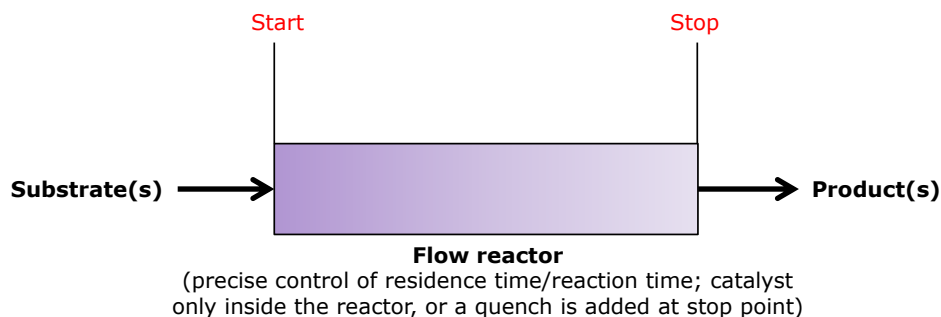


Figure 1.4. Figure illustrating the enhanced control of reaction times in a continuous flow reactor compared to a batch system. The flow reactor, in this case, can be filled with catalyst, and hence the reaction will stop, once the mixture flows out of the reactor. Another option is that the reactor is heated, and at the stop position a quench flow is added, which stops the reaction immediately (similarly in situations, where the reaction starts, when two substrate flows meet, and stops by the addition of a quench). By controlling the volume of the reactor, and the flow rate of the substrates, the residence time, and therefore the reaction time, can be controlled. Such restraint is not possible under batch conditions, where all reagents are constantly present (after they have been added, and the reaction has started), and heating and cooling periods require additional time, which might change the end point of a reaction.

Choosing between batch or continuous flow for a particular reaction depends on many factors.^{133-136, 140} Usually reactions aimed at discovering new chemistry are carried out in batch. On the other hand, in process chemistry where the aim is to optimise the conditions, or to study the kinetics of a reaction, flow systems are often more attractive. Especially in reactions where efficient heat transfer is required, or the reaction rates are controlled by mass transport, the use of a flow reactor is beneficial as a better control over mixing and heating is achieved in flow compared to batch processes. However, the initial investment linked to the equipment can be much higher for a flow reactor, which consists of several components, compared to a simple glass flask that is traditionally used for batch synthesis.¹⁴⁰

Another interesting aspect of flow chemistry is the implementation of in-line or on-line analysis, as it offers the possibility for real time monitoring of reaction streams.^{133, 141, 142} This feature is especially important when carrying out

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reactions on a large scale, as continuous monitoring of the output can help identify problems the instant that they occur. Therefore, any encountered issues can be fixed immediately, and thus avoid mixing 'valuable products' with streams that are producing lower quality outputs due to a failure in one part of the system.¹³³ In a batch process, this procedure is normally not possible, and hence the success of a reaction can only be evaluated once it has finished. In the event where a problem has occurred, large amounts of waste might be produced by having to discard entire batches of substandard product mixtures.

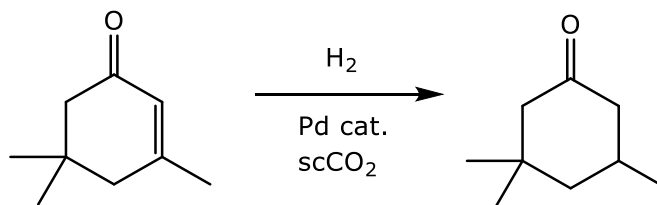
Continuous flow operation also allows for safer use of gases, as lower quantities are needed, at one single moment, because the reaction volumes can be much smaller than in batch processes, especially after scale up of the reaction has been performed.^{133, 143} Furthermore, safer access to extremely toxic or explosive reagents becomes possible, as these can often be produced and reacted *in situ* in a continuous process, and therefore the need to store large quantities of such reagents becomes unnecessary, which again improves the safety of large scale production.

Further advantage of continuous flow processes is the ability to make a process more sustainable, by improving the scalability.^{133-136, 140} There are three main ways in which a continuous process can be scaled up; running a process for a longer period of time ("scaling out"), increasing the number of reactors carrying out the process simultaneously ("numbering up"), or by developing a larger, continuous reactor and then scaling up.¹³³ In the last case, re-optimising the conditions after scale-up might be required, as the properties within a larger reactor can be different compared to a smaller one. As most reactions on a large scale are carried out in a continuous manner, performing discovery chemistry in similar systems could be beneficial, as it could help bridge the gap between industry and academia, as viable technologies would be utilised from the very

beginning.¹³⁴ Thus, the time and effort required, later on in the process to switch to continuous systems, could be saved.

Along with all the benefits of continuous processes, there are also some limitations in utilising flow systems, which include the possible precipitation of intermediates or products causing blockages, and the issues linked to using highly corrosive substances as reagents, as additional attention needs to be paid, when choosing the suitable reactor set-ups.¹³³ Moreover, reactions such as crystallisations or fermentation processes might not benefit from continuous operations, and hence the development of such transformations in flow might not be useful.

As mentioned in the previous section, reactions in continuous flow have been extensively studied by the Poliakoff group. As reported in 2003,¹¹¹ the research even led to the scale up of a reactor system, and the launch of a commercial plant by Thomas Swan & Co. Ltd. for the hydrogenation of isophorone in scCO₂ (Scheme 1.4); up to 1000 tons/year. However, it turned out that the energy required to compress the CO₂ made the process economically unviable, because the price of energy increased sharply around the time the plant started operation.²⁶ Nevertheless, the concept of using scCO₂ in flow reactions on a large scale was realised, and all that would be required to make the process profitable, is a cheaper source of compressed CO₂. A highly probable solution to this problem will, in the near future, be provided by the carbon capture and storage process, which will produce large amounts of high pressure CO₂, as described above. The pressure of the CCS CO₂ stream is expected to be over 100 bar, which would be high enough to remove the need to compress the CO₂ further in the plant, and therefore diminish the amount of required energy for the whole process.



Scheme 1.4. Hydrogenation of isophorone over a supported (SiO₂/Al₂O₃) palladium catalyst to yield 3,3,5-trimethylcyclohexanone.¹¹¹ This reaction was scaled up by Thomas Swan & Co. Ltd.

When continuous processes are combined with reactions carried out over heterogeneous catalysts, advantages, such as easy separation and recycling of the catalyst become evident, as the catalyst is confined within a set reactor volume.¹³⁴ Therefore, when the reagents flow over the catalyst, the contact time with the surface is higher for each molecule compared to when carrying out heterogeneous batch reactions, where all the reagents are present during the entire reaction. On the other hand, the main difficulty when employing homogeneous catalysis in flow is the recycling and the recovery of the catalyst. However, several solutions have been suggested including the immobilisation of the catalyst on solid supports, biphasic systems, and using supercritical fluids to recover the catalyst.¹⁴⁴ Supercritical fluids, especially scCO₂, have also been shown to be particularly useful, when combined with heterogeneous catalysts, as several advantages can be achieved.^{86, 90, 96} These benefits, when combined with continuous operation, include possible enhancement of the reaction rate, control over the selectivity, improved mass and heat transfer (as phase boundaries are eliminated), increased catalyst lifetime and regeneration (by dissolution of inactive particles deposited on the catalyst surface), easier separation and process intensification, as well as tunability of the solvent properties by changing the pressure or adding a co-solvent.⁹⁰

The implementation of enabling technologies¹⁴² such as the previously mentioned in-line or on-line analysis, can allow for automation of continuous

processes. These methods make it possible to perform labour intensive repetitive tasks, such as optimisation of reaction conditions automatically, and can hence be used to save time and thus also money. Such technologies also include in-line processing tools and telescoping reactions, where all steps of a synthesis can be carried out subsequently without intervention from the operator.^{134, 142, 145} These approaches also open up the possibility to produce more complicated molecules, and even the synthesis of natural products via multi-step flow processes have been established.¹⁴⁶ An elegant example of a telescoped synthesis procedure, was reported by the Ley group,¹⁴⁷ where a multi-step synthesis was achieved in one integrated process with seven different operations including purification and solvent switch steps in order to achieve the target transformation.

1.3 Self-optimisation in Continuous Flow

Optimising the reaction conditions of different transformations already at the discovery level is important in order to make scale-up and large scale processes more efficient.¹⁴⁸ These procedures can help to save money and reduce waste, as higher throughput of the target products are obtained at the optimal conditions compared to when carrying out a reaction under unoptimised conditions. However, such processes when performed correctly can be very labour intensive and tedious, as well as time consuming. Traditionally, optimisations have been carried out one variable at a time, resulting in conditions that may well not be the global optimum of the parameter space for a particular reaction. These situations showcase the relevance of chemometrics; obtaining useful information from chemical data by the means of statistics.¹⁴⁹⁻¹⁵¹ One such approach is called Design of Experiment (DoE), where a predefined number of reactions are carried out, in order to gain maximal knowledge of the global parameter space, in as few experiments as possible.^{152, 153} Another way to achieve this goal, is the implementation of evolutionary search algorithms.

Particularly, when conducting reactions with several variables, the importance of optimisation increases, but the optimisation process becomes more complicated, because varying one parameter might affect the impact of another parameter in an unexpected way.¹³⁴ In addition, it is often impractical to explore the entire parameter space in order to find the best reaction conditions. One way of finding the optimised conditions, in a certain parameter space, is to use an optimising search algorithm that varies the parameters (e.g. temperature, pressure, flow rates) and tries to maximise the function value (e.g. yield).¹⁴² The function to be optimised can be chosen as desired and in case the aim is to, for example, find the most sustainable reaction conditions the algorithm can be set accordingly. Such approaches might help make optimisation processes more accurate, but they can still be very time consuming, if performed manually. Hence, the true benefits of using algorithms of this kind are seen when linking them to an automated reactor.

When combining on-line or in-line analysis and automated continuous systems with the optimising algorithms (enabling technologies), reactions can be optimised much faster and with less input from the researcher.^{142, 154-157} Such systems are called self-optimising (Figure 1.5), and most examples are linked to organic reactions carried out in microreactors, as demonstrated especially by the Jensen group.¹⁵⁸⁻¹⁶¹ The first example of such technologies was introduced by DeMello and co-workers,¹⁶² who used different algorithms to optimise the automated continuous synthesis of CdSe nanoparticles using fluorescence spectroscopy as the analysis method. Later on the Poliakoff group introduced a self-optimising system, which could be used to optimise reactions on a larger scale.^{118, 119}

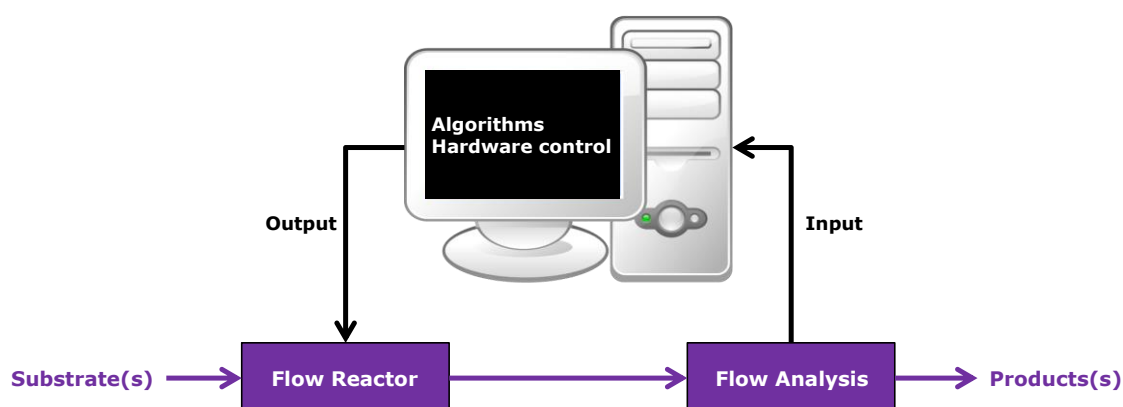
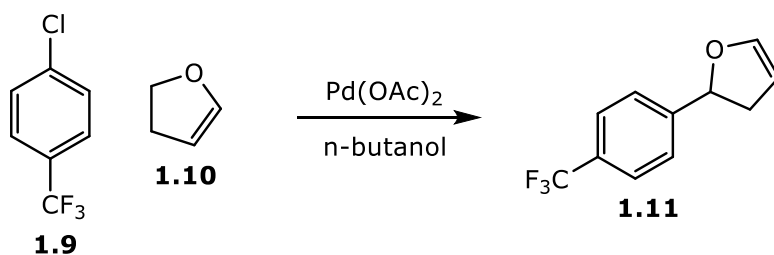


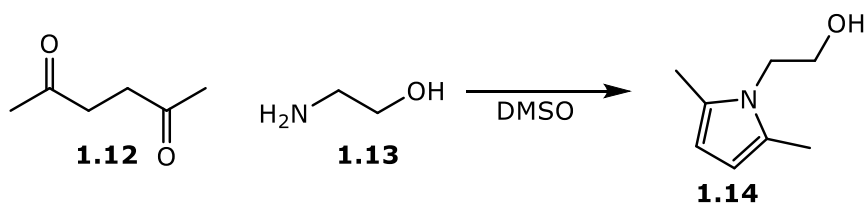
Figure 1.5. The basic principle of a self-optimising (micro)reactor. The system is autonomous, and all the components are controlled by the computer with control software. The new conditions for a reaction are determined by optimising algorithms, which evaluate the data they receive from the analysis of the reaction stream, and calculate further conditions in order to increase the function value. The analysis methods that have been used include fluorescence spectroscopy, HPLC, FT-IR, NMR and GLC.

The advantage of microreactors in such processes is that very small amounts of reagents are required during the search for the optimal conditions, and hence the entire optimisation can be relatively fast, and does not produce large amounts of waste. Several different in-line or on-line analysis methods have been linked to self-optimising reactors; HPLC^{158, 160}, FT-IR^{121, 159}, NMR¹⁶³ and GLC^{118-121, 164} (Scheme 1.5). The only requirement for the analysis is that it produces a numerical value, which corresponds, in some manner, with the function that is being optimised (either minimised or maximised).

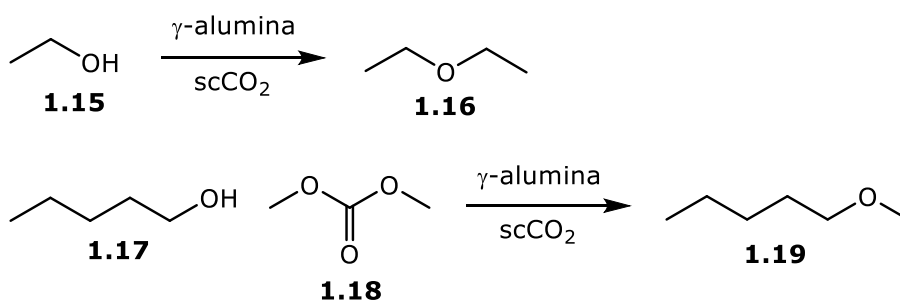
HPLC - Heck-type coupling reaction



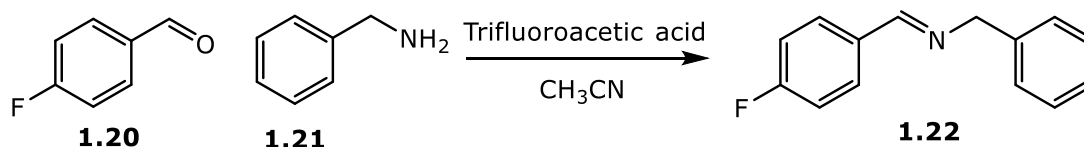
FT-IR - Paal-Knorr reaction



GLC - Etherification



NMR - Imine formation



Scheme 1.5. Examples of reactions that have been optimised using self-optimising reactors. HPLC-analysis was used to optimise the reaction conditions of a Heck-type coupling, where **1.9** reacts with **1.10** forming **1.11** over a palladium catalyst.¹⁵⁸ FT-IR analysis was used to study a Paal-Knorr reaction between **1.12** and **1.13** forming **1.14**.¹⁶¹ In addition, etherification reactions were optimised with the help of GLC-analysis (**1.15** to **1.16**, as well as **1.17** together with **1.18** forming **1.19**).¹¹⁸⁻¹²⁰ The last example is the formation of **1.22** from **1.20** and **1.21**, which was optimised using flow-NMR analysis.¹⁶³

HPLC analysis was used to optimise the yield of **1.11** formed in a Heck-type coupling reaction from **1.9** and **1.10** with a palladium catalyst (Scheme 1.5).¹⁵⁸

With HPLC, a number linked to the yield of the target product can be obtained

directly from the analysis, whereas with FT-IR analysis the direct determination of yields is not possible, and hence some form of calibration to determine product yields is required.¹⁵⁴ Such calibration was carried out, when optimising the Paal-Knorr reaction between **1.12** and **1.13** producing **1.14**.¹⁶¹ In this case, the decrease of the carbonyl peak, in the analysis, was observed. GLC analysis has mainly been used by the Poliakoff group for the optimisation of etherification reactions of alcohols with either other alcohols or dimethyl carbonate (**1.15** to **1.16**, or **1.17** and **1.18** forming **1.19**).¹¹⁸⁻¹²⁰ Furthermore, the acid catalysed formation of **1.22** from **1.20** and **1.21** was monitored and optimised with the help of in-line ¹H NMR.¹⁶³ When carrying out optimisations, the most commonly used algorithms are based on different simplex methods.^{165, 166} Also, the SNOBFIT algorithm¹⁶⁷ has been used in several reported optimisations. These algorithms will be introduced in more detail in Chapter 2.

Additionally, as described recently, one interesting aspect of self-optimising systems is that they allow for reactions to be carried out from remote locations, giving researchers from different backgrounds the opportunity to carry out continuous flow reactions without having to acquire the equipment themselves. This concept was initially demonstrated by Skilton *et al.*¹²² through Cloud Chemistry; where chemists from different locations, who had no prior experience of the equipment, were allowed to control and run self-optimisations with reactors located in a laboratory at the University of Nottingham. Such concepts could possibly help to equalise chemists, all over the world, as they would be able to remotely provide valuable information, such as kinetic data, or the optimal conditions of a reaction. This data would then be processed by the researcher to extract the relevant information. The lack of obtaining the physical product would not be a problem, as normally the aim of the majority of experiments is to only collect the significant information, and not the material itself. If such technologies became more common, each research group would

not necessarily have to acquire and set up expensive reactors, but rather the only requirement would be to have access to the internet, in order to be able to connect to facilities with such equipment. A similar example, but mainly aimed at in-house reaction monitoring, was given by the Ley group,¹⁶⁸ whose internet based LeyLab platform provides the possibility to start and monitor automated experiments across the internet.

As mentioned above, the self-optimisation research branch in the Poliakoff group has mainly focused on the important halogen-free etherification reactions shown in Scheme 1.5.^{118, 120, 121, 164} The aim of some of the work described in this Thesis is to attempt to expand the Nottingham self-optimising chemistry to include other reactions in addition to the well-established methyl ether formations. Such reactions include *N*-alkylations via halogen-free routes, which have similar benefits as the alcohol etherifications with methanol or dimethyl carbonyl, as they avoid the usage of halogenated methylating agents. When these halogenated molecules are synthesised, extensive amounts of waste can be produced. In addition, avoiding their usage can help to avoid the formation of unwanted side products. When an alcohol or dimethyl carbonate is employed, water and possibly CO₂ are the only side-products produced, which makes the process more benign compared to when halogenated waste is formed. As further motivation, the alkylation of heteroatoms, especially nitrogen, is a very important and interesting research strand, because these molecules make up some of the most common motifs in drug candidates in the pharmaceutical industry.¹⁶⁹ More details on the studied reactions will be given in Chapter 4 and Chapter 6.

Thesis Aims

The overall aim of this Erasmus Mundus SINCHEM project is to find ways to add chemical value to carbon dioxide. As outlined in the Introduction, there are two main strategies by which this can be achieved; utilising CO₂ as a reagent in chemical reactions, and exploring the potential of using scCO₂ as a solvent in chemical processes. In order to study this utilisation, the main aims of the work described in Chapters 3-6 were:

1. To optimise the conditions for the solvent-less methylation of alcohols with dimethyl carbonate using FT-IR analysis, and to thereafter transfer this analytic method to reactions carried out in scCO₂.
2. To expand the scope of reactions that can be studied and optimised with the self-optimising reactor in scCO₂ and with γ -alumina as the catalyst.
3. To study reactions, where CO₂ can be incorporated into molecules, either directly or indirectly.
4. To evaluate to what extent the 12 Principles of CO₂ Chemistry are fulfilled in the work described in this Thesis.

Chapter 2. Experimental

The work described in this Thesis was carried out at 2 different universities; the University of Nottingham, and the ITMC, RWTH Aachen. In this Chapter the experimental methods used in Nottingham are described. In section 2.1 the self-optimising reactor is introduced, whereas the implemented optimisation algorithms are discussed in section 2.2. Section 2.3 concentrates on the analytical methods implemented in the optimisations (FT-IR and GC). A standard operating procedure is given in section 2.5. The reactor and procedures for the work, carried out at the ITMC, RWTH Aachen, are detailed in Chapter 5.

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2.1 Description of the Apparatus

The focus of the work described in this Thesis, was predominantly aimed at expanding the chemistry studied with the previously developed self-optimising reactor.^{170, 171} Only slight changes to the set-up were made throughout the work. As described in the Introduction, when carrying out a self-optimisation, the conditions of the reaction (temperature, flow rates, pressure) are controlled by a computer that determines the value of the different parameters according to the feedback it gets from the analysis as shown in Figure 2.1.

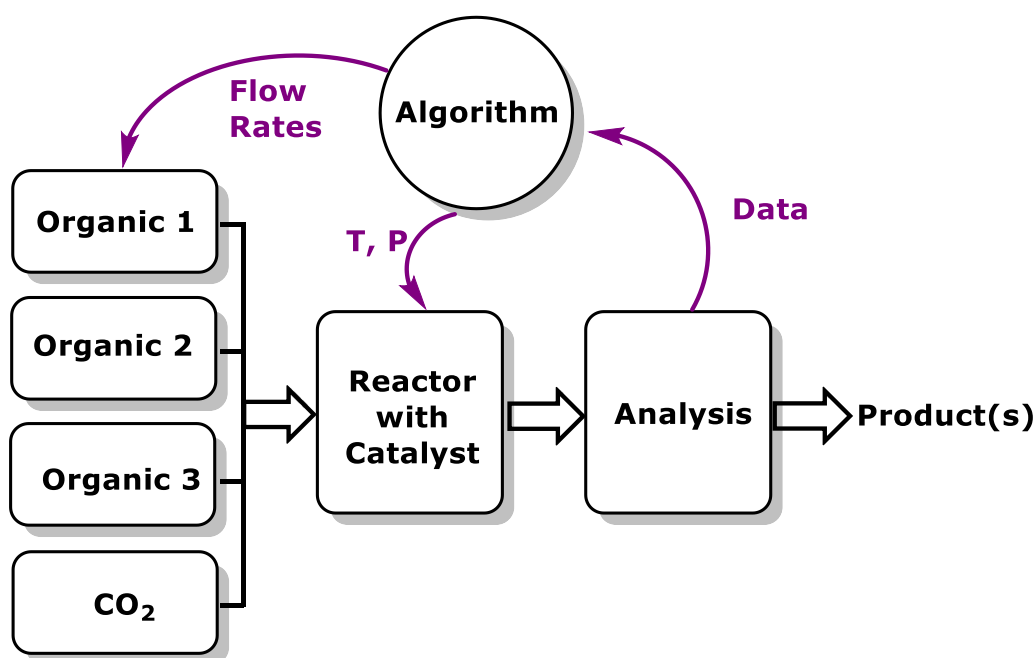


Figure 2.1. Schematic picture of an automated self-optimising reactor. The conditions (e.g. temperature, pressure and flow rates) are controlled by the computer (Algorithm) that changes the conditions according to the feedback it receives from the analysis (Data) in order to maximise the function value (yield).

In this Thesis the analysis was performed by either an on-line GC (Chapters 4 and 6) or in-line ATR FT-IR (Chapter 3). FT-IR is a much faster analysis method, and allows for optimisations to be finished up to 10 times faster compared to when the same optimisation algorithm is used with GC analysis.¹²¹ Because of

this rapidness, the FT-IR analysis was combined also with a global search algorithm (SNOBFIT¹⁶⁷ Stable Noisy Optimisation by Branch and FIT). Such algorithms measure more points than linear algorithms in order to find the optimum within the search space, and hence the speed of the analysis determines how long an optimisation experiment lasts. Using an algorithm such as SNOBFIT gives a higher confidence that the located optimum is the global optimum of the search space, which justifies its implementation, even though the experiment might take longer to finish.

The other algorithm that was used is the SMSIM algorithm (Super-Modified Simplex),¹⁶⁶ which is a linear method and was used for the preliminary development of the set-up, but later also for all the optimisations involving GC analysis. However, due to limitations linked both to the ATR FT-IR analysis and the SMSIM algorithm, the software was modified to allow global optimisations to be carried out also with the GC as the analysis method, as shown later in this Chapter.

2.1.1 Detailed Description of the Self-optimising Reactor

The equipment was designed to withstand high temperatures and pressures. The two different set-ups used for the work presented in this Thesis, are depicted in Figure 2.2 (FT-IR experiments) and Figure 2.3 (GC-analysis). The connections between the different parts, in the systems, were made with 1/16" (outer diameter) stainless steel piping by using the appropriate Swagelok fittings. The reactor (R) and premixer (M) were ¼" stainless steel tubes, likewise connected to the system by appropriate Swagelok fittings. The reactor and mixer were heated by Eurotherm 2616 heaters, connected to heating cartridges, inside aluminium heating blocks. The temperature of the heating blocks, and the inside temperature of the reactor and premixer, were monitored by a Picologger that

logged the data. Overheating was controlled by temperature trips (Eurotherm 2122). The liquid reagents were pumped to the system by using JASCO PU-980 HPLC pumps (Figure 2.2: Organic 1, Organic 2 and Organic 3; Figure 2.3: Org 1, Org 2 and Org 3), and each pump was separated from the system by either an SSI- or an HIP-valve (V-3, V-4 and V-5, SSI: Scientific Systems, Inc; HIP: High Pressure Equipment Company). The carbon dioxide was pumped to the system with a chilled JASCO PU-1580-CO₂ pump (CO₂ pump). The pump was connected to the CO₂ cylinder and the system by two SSI-valves (V-1 and V-2). The system pressure was controlled by a Jasco BP-1580-81 back pressure regulator (BPR), and monitored by placing a pressure transducer, linked to a pressure trip, before the premixer.

In the FT-IR experiments (Figure 2.2), the reaction outcome was analysed by a Bruker ALPHA FT-IR spectrometer equipped with a Platinum ATR single reflection diamond ATR module (ALPHA P). The spectrometer was placed downstream of the BPR due to pressure limitations of the apparatus. The connections to the flow cell, placed on top of the diamond, were made by using plastic pipes with Omnifit-fittings. These fittings would disconnect at a pressure of approximately 10 bar, which helps to prevent breakage of the spectrometer, in case over-pressure starts forming, due to blockages in the piping after the flow cell. The reactions were simultaneously analysed by a Shimadzu GC-2014 gas chromatograph. The sampling to the GC was done by a high pressure sample loop (SL), which allowed a sample to be taken from the reaction stream at regular intervals. The experiments with only GC-analysis (Figure 2.3) were analysed with an on-line Shimadzu GC-2014 or 2010 gas chromatograph (GLC), with a high pressure sample loop. The analysing apparatus were controlled by software: OPUSTM for the FT-IR, and GCsolutionTM or LabSolutionsTM for the GC.

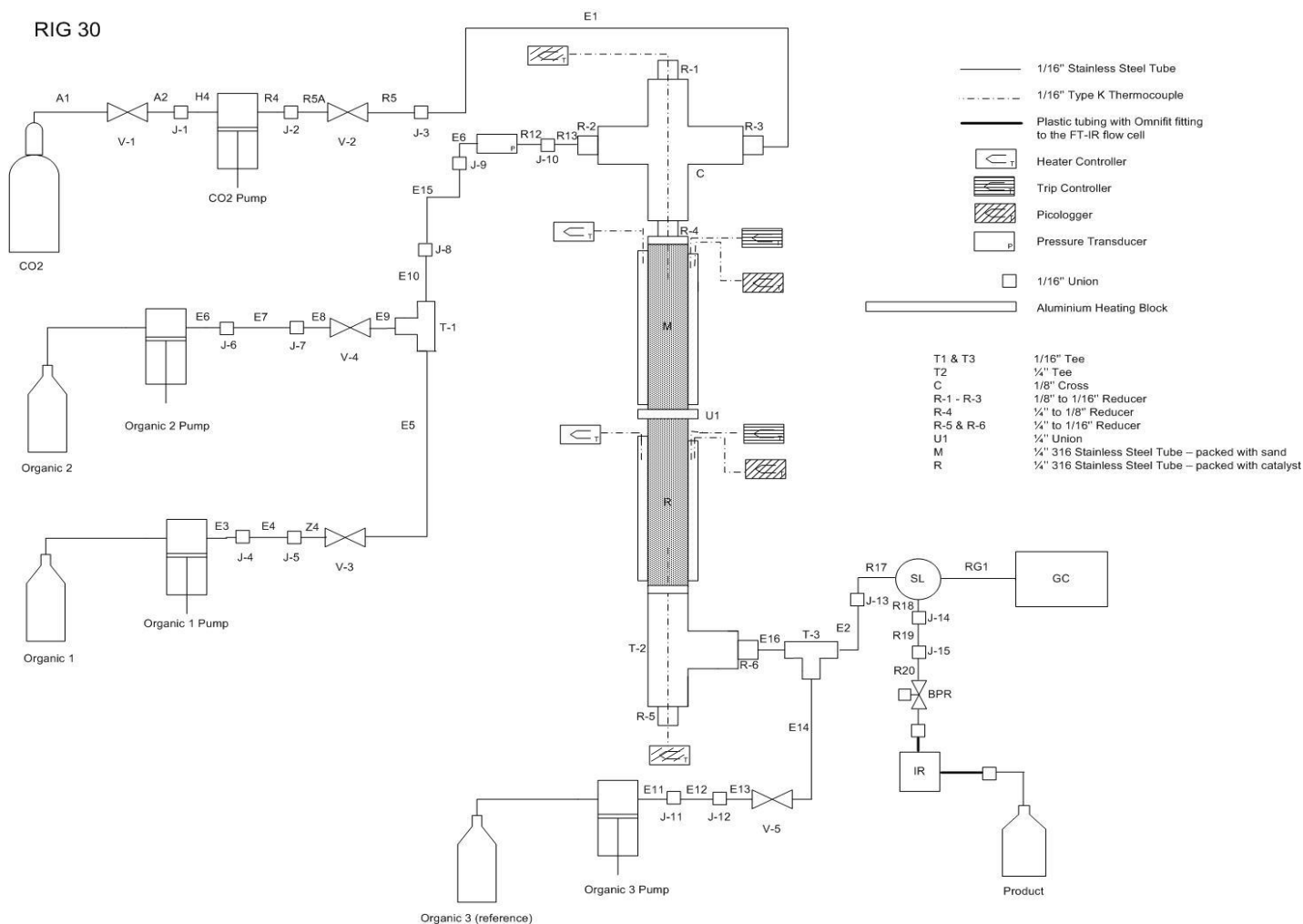


Figure 2.2. Diagram of the equipment used in Chapter 3; with experiments utilising FT-IR analysis. The system consists of 3 liquid pumps and a CO₂-pump, which deliver the substrates, solvent and reference material through the reactor. The IR is placed after the back pressure regulator (BPR), which controls the pressure of the system. The reactor and preheater are heated by aluminium heating blocks.

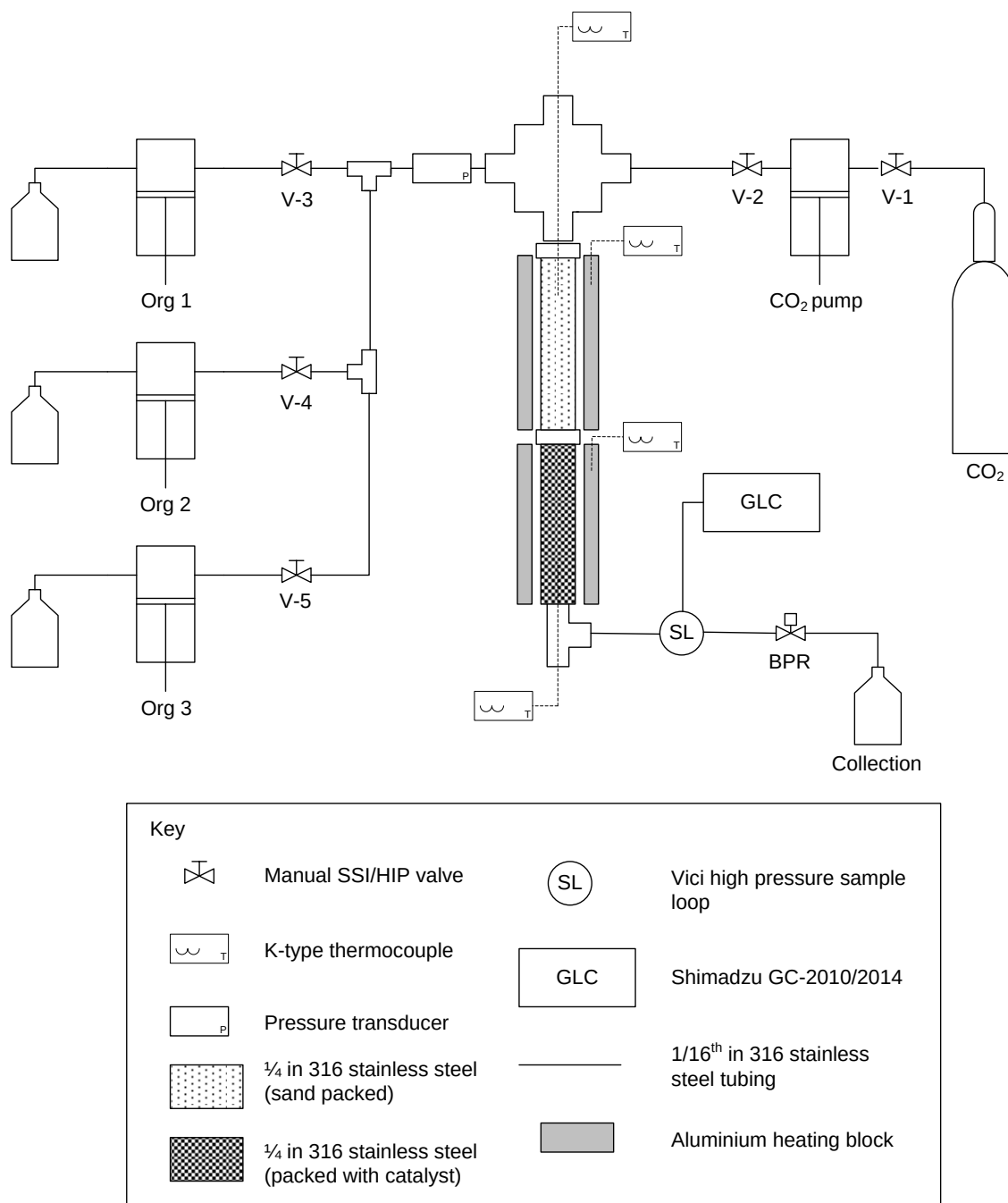


Figure 2.3. Schematic diagram for the equipment used for self-optimisations with GC-analysis (Chapter 4 and 6). The substrates and solvents are delivered through the system with high pressure pumps. The pressure of the system is controlled by a BPR, and the temperature with aluminium heating blocks. On-line sampling is carried out by a high pressure sample loop, which passes a sample of the reaction stream onto the GC-column for analysis. Even though only one thermocouple per heating block is displayed, there were, in fact, 3 placed in both of them: 1 to the heater, 1 to the trip, and 1 to the Picologger.

For convenience, more details on the operation of some of the components in the reactor set-ups shown in Figure 2.2 and Figure 2.3 are given below:

CO₂ pump: The CO₂ was delivered to the system as a liquid (at -10 °C) with a Jasco™ PU-1580-CO₂ pump. Before starting an experiment, the CO₂ pump was pressurised against a closed tap to more than the desired reaction pressure (e.g. 100 bar), to ensure it was working correctly. The pump remained on, and under the CO₂-cylinder pressure at all times, as the pump check valves are sensitive to changes in their environment and do not cope well with repeated heating and cooling. The efficiency of the CO₂ pump was tested regularly using a bubble flowmeter. The main issue encountered with the pump was linked to the efficiency of pumping, which was fixed by checking and occasionally replacing the check valves or piston seals.

HPLC-pumps: The organic materials were pumped to the system using Jasco™ PU-980 high performance liquid chromatography (HPLC) pumps. The efficiency of the HPLC pumps were tested regularly by measuring, how long it took for a known volume to be filled, under a constant flow rate. Before starting an experiment, the pumps were primed with the desired solution, and each pump was pressurised against a closed tap to higher than the system pressure, to ensure that they could deliver liquids properly to the system.

Pre-mixer and Reactor: The pre-mixer and reactor were made up of stainless steel tubes (1/4" outer diameter, 0.049" wall thickness, 15.6 cm in length, 1.83 ml volume) with appropriate Swagelok® fittings at each end. The pre-heater was packed with sand, and the reactor with approximately 2 g of γ -alumina (125 μm < size < 170 μm). The temperature of these were controlled via heated aluminium blocks, which again were controlled by temperature controllers (Eurotherm 2616), which monitor the temperature via K-type thermocouples.

Back Pressure Regulator (BPR): The system pressure was controlled by a Jasco™ BP-1580-81 BPR. The BPR was heated at the point of depressurisation to prevent the formation of blockages inside or after the BPR. The BPR was cleaned regularly by flushing it with a solvent, e.g. *i*-PrOH, to prevent materials accumulating around the needle, and hence allowing it to move freely, and the BPR to operate correctly.

RS-232 serial connections to the computer: The temperature controllers, HPLC pumps (including the chilled CO₂ pump) and the GC were connected to a single PC via RS-232 serial ports. These connections allowed for commands to be sent to the equipment, and real-time monitoring signals to be received by software that has been developed by a number of previous students and postdoctoral researchers in the group (CO₂ GUI).^{116, 118-121, 170, 171} Data logging was performed by the GUI using a TC-08 PicoLogger™ unit. The reactor and pre-heater temperatures, (internal and external), were recorded.

Safety features: Prior to starting an experiment all the connection points were leak tested with a liquid leak detector (Snoop™), whilst the system was pressurised with CO₂ at the operating pressure. To ensure safe operation, all heating block thermocouples were checked before the start of each experiment, to insure they were working correctly, and thereafter positioned securely in the heating blocks. The over-temperature trips were tested prior to starting an experiment, and set to the desired value (normally 15-20 °C above the maximum temperature). The system over-pressure trip was typically set to ca. 20 bar over the desired operating pressure, and it was tested before each experiment. Each trip was set up in such a way that if initiated, would lead to the temperature controllers and all the organic pumps being shut down. The CO₂ pump remained on, in order to try and clear possible blockages. The rig was also

equipped with an emergency stop button, which when pressed switched off all equipment connected to the trip system (HPLC pumps and heaters).

2.2 Self-optimisation – The Algorithms and the Software

As mentioned briefly in section 2.1, the search algorithms that were used for the optimisations presented in this Thesis, and in previous work by the group, are the SMSIM (super modified simplex) algorithm¹¹⁸⁻¹²¹ and the SNOBFIT (stable noisy optimization by branch and fit) algorithm.¹²¹ Here the generation of new measurement points by both algorithms is explained briefly. Further details on these algorithms can be found in the appropriate references.

2.2.1 SMSIM

The SMSIM algorithm, developed by Routh *et al.*¹⁶⁶ is an improved version of the NMSIM (modified simplex) algorithm, by Nelder and Mead,¹⁶⁵ which is based on the simplex optimisation method introduced by Spendley *et al.*¹⁷² in 1962. A simplex is an n -dimensional geometrical figure with $n+1$ vertices (in optimisations n equals the number of parameters).¹⁶⁶ In the two dimensional case, shown in Figure 2.4, the simplex formed from three vertices, ($n=2$, $n+1=3$), is a triangle. During an optimisation, the initial simplex is determined by evaluating the function (carrying out the reaction) at $n+1$ vertices pre-set by the operator. Once the reaction has been carried out at all of these points, each vertex is labelled according to its function value (e.g. the yield of the target).^{119,}
¹⁶⁶ The worst vertex gets the label W, the next worst is labelled N, and finally the best point gets the label B. After this, the location of the new vertex is determined in the following way: after the worst vertex has been identified, the responses at the midpoint (P; between N and B), and the reflected vertex (R),

are measured, and a second-order polynomial curve is fitted to the responses at W, P and R (Figure 2.4).¹⁶⁶ The curve is also extrapolated beyond W and R, and the function is evaluated at the predicted optimum (O). If the response at O is a maximum, the new vertex is set at this point, and the optimisation continues, by forming a simplex from vertices N, B and O. However, if O is not the maximum, and the function value at, for instance, R is higher than at O, the new simplex is formed with R as the new vertex instead.

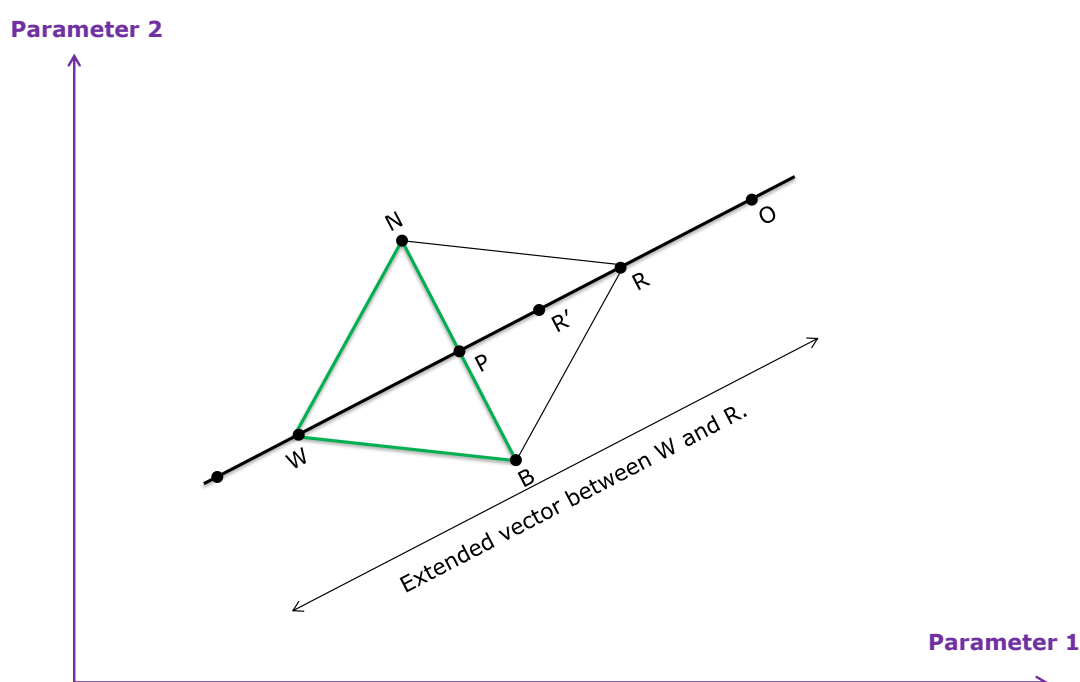


Figure 2.4. Scheme showing the different types of points produced by the SMSIM algorithm, demonstrated by a two dimensional case with 2 different parameters. The green triangle is made up of the vertices W, N and B, and forms the original simplex. P is the midpoint between N and B, and R is the reflection of W through P. The estimated optimal point (O) is determined by fitting a second-order polynomial to the responses of W, P and R. R' is a contraction of R, and the function is evaluated here in case of boundary violations.

The SMSIM algorithm allows the new vertex to be located at almost an infinite number of points along the vector joining W and R, and also the extension of this vector determined by the extension coefficient (γ).¹⁶⁶ To prevent the new vertex (O) from being too close to the already measured midpoint, or the worst point, a safety limit is set, which ensures that the number of dimensions in the simplex is

retained throughout the optimisation. This limit has been set to ± 0.3 in the optimisations carried out with the SMSIM algorithm.¹¹⁹ In case a measurement point is placed beyond the limits of the variables, a boundary violation occurs. These are handled by contracting the reflection vertex that violates the boundaries to be inside the limits, and the function is evaluated at this point (R').¹⁶⁶ Then a second-order polynomial is fitted similarly to a non-violation case, to find the optimum point. New vertices are produced until a pre-set stopping criterion is met (covariance between the responses for the last simplex is below a predetermined value, normally set to 0.5).

As the SMSIM algorithm is a linear method, only the responses linked to the last constructed simplex are taken into account and the previous measurements are ignored, when determining the new optimum point. This means that the located optimum is not necessarily the global optimum of the search space. In addition, as shown in Chapters 3 and 4, the simplex can lose dimensions, in case no or very similar responses are obtained at one or more measurement points, as this retards the optimisation process. Moreover, prior knowledge of the optimised reaction needs to be obtained before starting an optimisation, in order for the operator to be able to define a starting simplex, which gives non-zero responses at all vertices, and hence allows for the optimisation to get going. These reasons, lead to the implementation of a global search algorithm in combination with the self-optimising reactor.

2.2.2 SNOBFIT

As mentioned above, the search carried out by the SMSIM algorithm does not necessarily cover the entire parameter space. SNOBFIT, on the other hand, is a search algorithm with both local and global search aspects.¹⁶⁷ This means that the maximum value, which the SNOBFIT algorithm finds is more likely to be the global maximum of the search space.¹²¹ The SNOBFIT algorithm does not require any pre-defined conditions, and all that is needed for an optimisation are the physical limits of the reaction (e.g. max and min temperature).¹⁶⁷

During optimisations a file with all the required data is sent to the separate SNOBFIT package (a 'call' to SNOBFIT), which then generates the new points as output.¹⁶⁷ The input points (the measured data) are assessed by the algorithm using local models (quadratic for the current best-point and linear for all other points), and new evaluation points are generated accordingly. The reaction is then carried out at these points to determine their function value (the yield of the target).

Each call to SNOBFIT will generate a certain amount (nreq) of evaluation points.¹⁶⁷ The global aspect of the algorithm is fulfilled by a pre-defined percentage (p) of the generated n points being global. These global points are generated in unexplored regions, in order to get a broader picture of the search space. Due to the global aspect of the algorithm, evaluation points might be further apart, and the difference in conditions especially temperature is greater between evaluation points with SNOBFIT than with the SMSIM algorithm.¹²¹ This difference means that with the SNOBFIT algorithm the time to reach steady state, in between measurements during an optimisation, can be longer than with the SMSIM algorithm. A simplified feedback loop for an optimisation carried out with SNOBFIT is shown in Figure 2.5. As of yet, the software does not have a stopping criterion, and hence the operator needs to stop the optimisation.

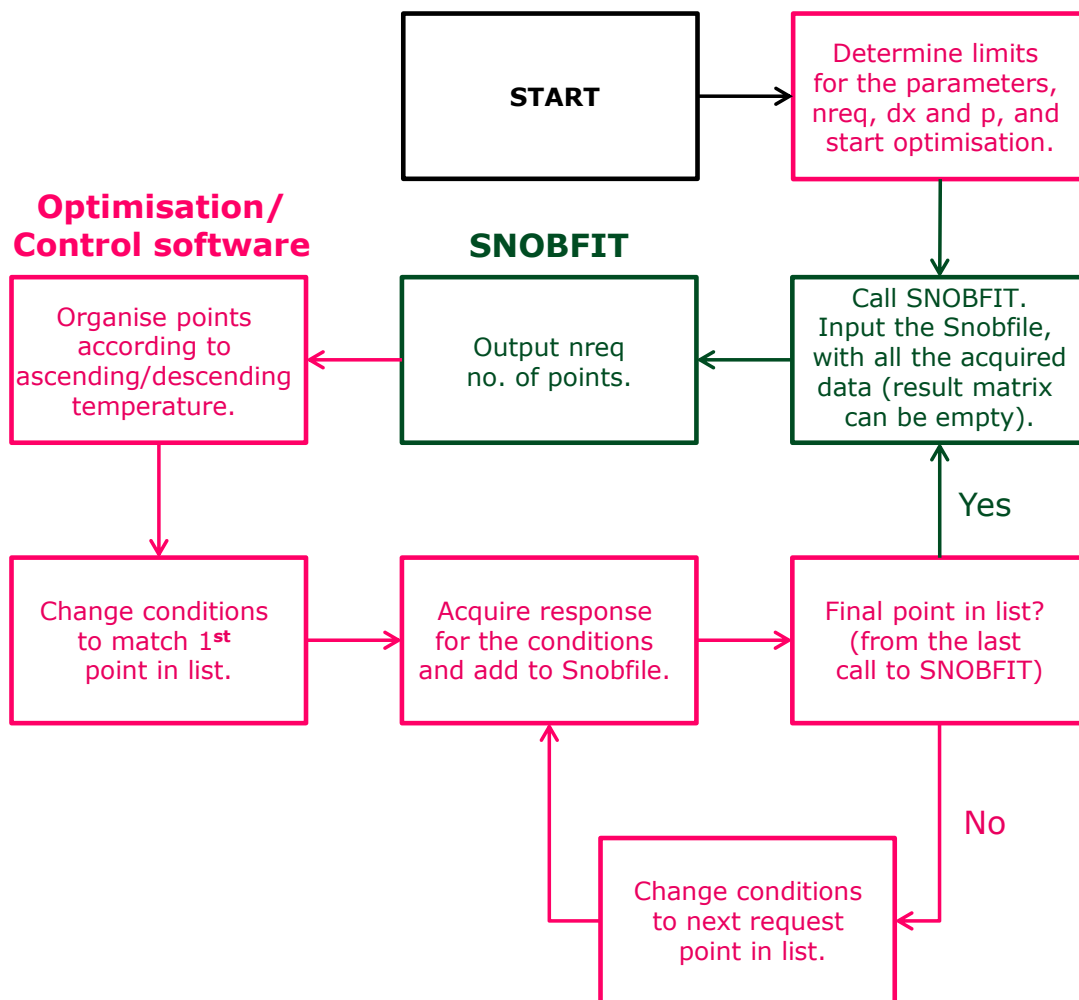


Figure 2.5. Schematic of the relevant parts of the feedback loop for optimisations carried out with the SNOBFIT algorithm. To start with, the physical limits of the parameters, as well as, the requested number of points (nreq), the percentage of global points (p), and the resolution vector (dx) are determined before the optimisation is started and SNOBFIT is called for the first time. SNOBFIT then outputs nreq number of points, which indicate the conditions the reaction should be evaluated at. To minimise the time required for an optimisation, the points outputted by SNOBFIT are arrange according to temperature; either descending or ascending depending on, which way the previous set of conditions were organised. The optimisation software then ensures that all the points requested by SNOBFIT are measured and a response from the analysis is obtained. Once this has been achieved, a new call to SNOBFIT is done, giving the next set of conditions where the reaction should be evaluated at. Additional commands and responses, which are not shown in this loop, are sent to and from the equipment.

As shown in Figure 2.5 the new evaluation points are generated when the optimisation software calls SNOBFIT. One call to SNOBFIT is roughly made up of the following steps:¹⁶⁷

- A list of points, and the measured function values (e.g. yields), corresponding to these points, together with other parameters, such as the limits of the search region, the requested number of points (nreq), the percentage of points that should be global (p) and dx, the resolution vector that indicates, how far away two points have to be from each other, to be considered to be two different points, are inputted to SNOBFIT as a matrix. The list of inputted points might be empty, which is the case during the initial (first) call to SNOBFIT.
- The algorithm then generates the requested number of points (nreq) at which the function should be evaluated.
- The requested measurement points belong to one of five classes. The class is outputted together with the points, and it indicates, how each point has been generated, especially, if they have been produced by the global or local aspect of the algorithm:
 - Points in classes 1-3 represent the local aspect of the algorithm, and they are produced by local linear or quadratic models in regions, where the function is expected to reach high values (already known regions of the search space). A point belongs to class 1, only if it is estimated to be a new global optimum. Class 2 is for possible local optimums, and class 3 for points that are produced close to already measured points, but are not expected to be an optimum.
 - Points in classes 4 and 5, on the other hand, are generated by the global aspects of the algorithm. They are produced in regions that have not yet been extensively studied by the search. Points in

class 5 are only produced during the initial call to SNOBFIT, and are randomly spread throughout the search space, until enough information is gained, for it to be possible to also produce points in other classes. Points in class 4 are produced by dividing the search space into boxes, with each box containing 1 point. Thereafter, the largest box is determined (represents the region that has been studied the least), and it is then divided into 2 boxes and the new class 4 point is produced into the empty box.

- All the points are outputted together with their class, and an estimation of their function value, which has been produced by using local models for each generated point.
- The function is then measured at the outputted points, and the responses are added to the input matrix for a continuation call to SNOBFIT.

Initially SNOBFIT was only combined with the FT-IR analysis,¹²¹ as it is a fast method and allows for optimisations to finish rapidly, even when a large number of conditions are investigated. However, due to the limitations of the FT-IR analysis (as shown in Chapter 3) and the SMSIM algorithm (discussed in Chapter 4), it became clear that SNOBFIT would be an interesting algorithm to utilise also when combined with GC-analysis. Then it could be implemented to optimise the conditions of reactions when targeting more complicated products in more diluted solutions.

The change in the software was relatively simple, as it was achieved by combining the two sets of existing code; SNOBFIT with IR-analysis, and SIMSIM with GC-analysis. As shown in this section the main difference between the two algorithms is in the way the new conditions are determined. In the software linked to the SMSIM every new point is calculated by equations written within the script. Whereas, the points for SNOBFIT are generated in a separate script,

and they are then sent back to the main program where the points are ordered according to temperature and then measured, before a new 'call' to SNOBFIT. For both the GC and IR analysis, the data used in the calculations, is recovered from text-files. In the case of the IR-analysis, these files are constantly checked, whereas for the GC long enough waiting periods need to be implemented, so that the acquisition has finished before the file is read. In addition, with the GC-analysis there needs to be a notification, which identifies when the GC is ready for a sample to be injected (and when a sample has already been taken) to make it possible for the optimisation to proceed.

Through trial and error a program, which could run optimisations with GC-analysis and the SNOBFIT algorithm, was developed. This version of the software was implemented in experiments described in section 4.2.3 and Chapter 6.

2.3 Analytical Techniques

A brief introduction to the main analytical techniques, used in the work presented in this Thesis, is provided in this section. A more detailed description is beyond the scope of this Thesis, but can be found in the literature.¹⁷³⁻¹⁷⁵

2.3.1 Gas Chromatography

With gas chromatography compounds can be separated, and identified, by the differences in retention times; how long it takes to elute a compound through the column.¹⁷³ The length of this time is determined by, to which extent, a substance is retarded by the stationary phase in the column. This phase is coated on the column wall, and the retention time depends on the polarity of the phase and also the substance. When the molecule leaves the column together with the carrier gas, it passes on to the detector. In all cases, described in this Thesis, a flame ionisation detector (FID) has been used. The FID consists of a

base, where the output of the column is mixed with H_2 , a jet, and an electrode.¹⁷⁴ Air is supplied to the FID in order to enhance combustion of the substances. Once in the FID, the molecules burn in the flame, and form positive ions (and electrons) in the process. The ions are then moved to the collector electrode, due to a potential difference between the jet and the electrode (the jet is ground and the electrode is negatively charged). The resulting ionisation current is then amplified and recorded, which gives rise to a chromatogram.

High Pressure Sample Loop

When a GC is combined with a high pressure sample loop, samples can be taken directly from a high pressure reaction stream, as is the case for most of the work described in this Thesis. By implementing this on-line GC system, samples can be taken without depressurisation, and hence the loss of potentially volatile compounds, present in the stream, is avoided. The sample loop delivers the sample to the injector port of the GC, where the sample is diluted according to the set split ratio, in order to avoid overloading the column. The principle of operation of a sample loop, connected to a GC, is shown in Figure 2.6. The sample loop consists of 4 small internal volumes (A-D, either 0.06 μl or 0.5 μl , depending on the size of the sample loop). It is connected to the system via one of these ports (A), and to the GC via another (B). During normal procedure (not sampling), the reaction stream flows via port A, from the reactor to the BPR, and the carrier gas is delivered to the GC injector via B. Then, when a sample is taken, the sample loop turns 90° clockwise, which results in port A being located in the carrier gas stream, and so the sample filling volume A, is delivered to the GC injector. Once sampling is finished, the sample loop returns to the original position to await the next sampling.

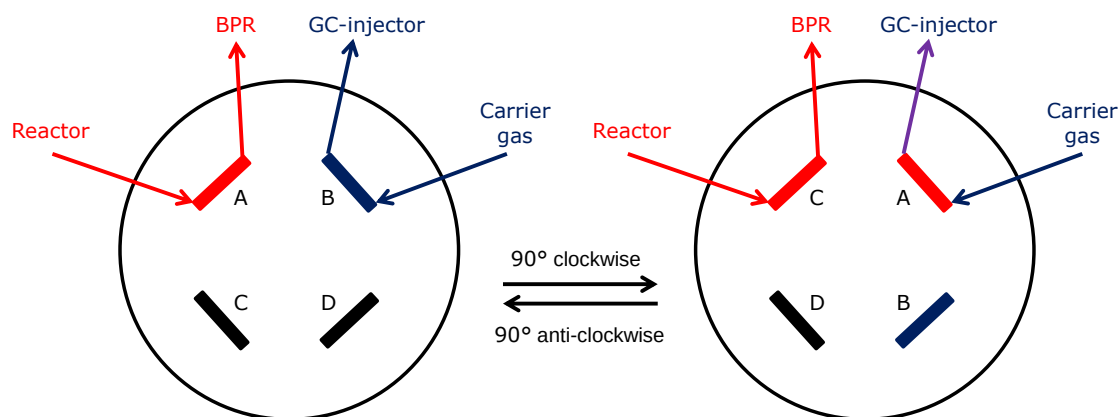


Figure 2.6. Schematic of how a high pressure sample loop connected to a gas chromatogram works. Most of the time the sample loop will be in the position shown on the left, where a continuous flow from the reactor to the BPR goes through slot A, and the carrier gas (He) is flushed through slot B. During sampling the sample loop turns in such a way that slot A moves to replace slot B. Then the sample inside A (0.06 or 0.5 μl) is flushed by the carrier gas flow into the injector where it is gasified before entering the column (depending on the split ratio, only a small part of the sample will be injected). After sampling, the sample loop returns to the original position (sampling time is normally 0.05-0.5 s).

In GC-analysis the same amount of different organic compounds can give rise to different responses from the FID, and these differences are normally overcome by determining response factors for all the related substances. However, in the work described here, not all products were known from the beginning, and therefore the response factors could not be calculated, and were assumed to be equal to 1. Hence, most of the obtained results, which are based on GC-analysis, are semi-quantitative.

2.3.1 ATR FT-IR

In this Thesis, attenuated total reflection FT-IR spectroscopy (ATR FT-IR) was used as the analysis method, as described in Chapter 3. The mid-infrared region of the electromagnetic spectrum ($400\text{-}4000\text{ cm}^{-1}$), can be used to identify some functional groups in a molecule, and to monitor the changes in the concentration. In FT-IR spectroscopy, a beam of a broadband IR radiation is

passed through a sample, and the total absorption in the sample at each wavelength, is measured as an interferogram. A Fourier transform is then performed on this data, in order to obtain an absorption spectrum. Different functional groups absorb IR at different wavenumbers, depending on the vibration of the group.

In attenuated total reflection FT-IR (ATR FT-IR), the sample is placed on top of a crystal (Figure 2.7).¹⁷⁵ When the IR-beam enters the crystal, it undergoes total internal reflection at the interface to the sample, when the angle θ is larger than the critical angle θ_c (defined by the refractive indices of the crystal and the sample: $\theta_c = \sin^{-1}(n_1/n_2)$, n_1 for the crystal, n_2 for the sample). However, the beam also penetrates the sample, by a half of a wavelength, resulting in an evanescent wave. When the surface is in close contact with a substance that selectively absorbs radiation, the beam loses energy at that specific wavelength. This absorption leads to attenuated radiation, the magnitude of which is measured at the detector and plotted as a function of the wavelength, showing the characteristic absorptions of the sample. As the pathlength of the evanescent wave depends on the wavelength of the light beam, the depth of penetration, into the sample, decreases with increasing wavenumber. Therefore, also the relative band intensities decrease with increasing wavenumber, and ATR exaggerates lower wavenumbers over higher ones. In transmission spectroscopy this behaviour is avoided, as the pathlength is the same at all wavelengths (the beam penetrates the entire sample).

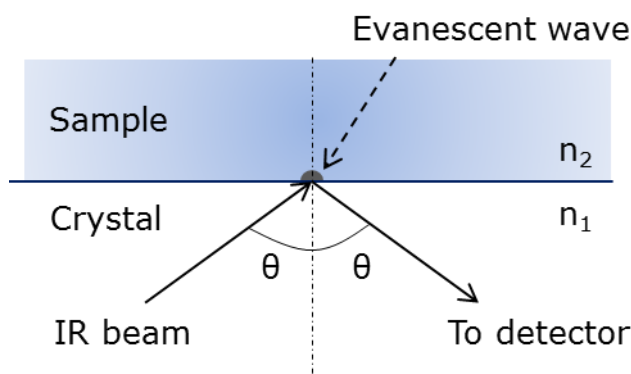


Figure 2.7. Basic principle of attenuated total reflection (ATR) FT-IR. The IR beam from the light source enters the crystal, and total reflection occurs at the interface to the sample. Parts of the beam penetrates the interface into the sample leading to the evanescent wave, which loses energy at any wavelength that the sample absorbs IR radiation. The resulting attenuated beam is measured and as a result the absorption spectrum of the sample can be plotted.

2.4 Materials and Methods

All liquid reagents and solvents were purchased from commercial sources and used as received. The CO_2 was supplied by BOC Gases (99.8 %, food grade). The γ -alumina (Puralox NWA 155) was supplied by the SI Group (initially in 2008) and later on by SASOL (Puralox NWA155). It was filtered before use, to obtain the desired particle size (125-170 μm), which was used as catalyst. Also the larger particles (>170 μm) were used in some experiments in Chapter 4, and showed similar activity compared to the smaller particles.

2.4.1 GC Methods

Most of the results described in this Thesis were based on semi-quantitative GC-yields and selectivities. When available standards were used to verify the retention times of the products formed. Different GC-methods were used for the different reactions in order to maximise the separation of the studied mixtures.

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Chapter 3: On-line Shimadzu GC-2014 with a high pressure sample loop (0.06 μ l) and an RTX-1 column (30 m, 0.32 mm ID, 0.25 μ m FT): hold 40 $^{\circ}$ C 1 min, ramp to 90 $^{\circ}$ C at 10 $^{\circ}$ C/min, ramp to 240 $^{\circ}$ C at 25 $^{\circ}$ C/min, hold for 1 min, pressure 78.5 kPa, purge 3.0 ml/min, split ratio 80.

Chapter 4: On-line Shimadzu GC-2010 with a high pressure sample loop (0.06 μ l) and an SE-30 column (30 m, 0.32 mm ID, 1.0 μ m FT): hold 50 $^{\circ}$ C 2 min, ramp to 100 $^{\circ}$ C at 30 $^{\circ}$ C/min, ramp to 135 $^{\circ}$ C at 10 $^{\circ}$ C/min, ramp to 175 $^{\circ}$ C at 25 $^{\circ}$ C/min, ramp to 200 $^{\circ}$ C at 10 $^{\circ}$ C/min, ramp to 240 $^{\circ}$ C at 25 $^{\circ}$ C/min, hold for 2.25 min, pressure 125.8 kPa, purge 3.0 ml/min, split ratio 100.

On-line Shimadzu GC-2014 with a high pressure sample loop (0.06 μ l) and an RTX-1 column (30 m, 0.32 mm ID, 0.25 μ m FT): hold 40 $^{\circ}$ C 1 min, ramp to 90 $^{\circ}$ C at 10 $^{\circ}$ C/min, ramp to 240 $^{\circ}$ C at 25 $^{\circ}$ C/min, hold for 4 min, pressure 132.1 kPa, purge 3.0 mL/min, split ratio 100.

Chapter 6: On-line Shimadzu GC-2014 with a high pressure sample loop (0.5 μ l) and an OPTIMA delta-3 column (30 m, 0.25 mm ID, 0.25 μ m FT): hold 50 $^{\circ}$ C 4 min, ramp to 100 $^{\circ}$ C at 25 $^{\circ}$ C/min, ramp to 250 $^{\circ}$ C at 10 $^{\circ}$ C/min, hold for 2 min, pressure 132.1 kPa, purge 3.0 mL/min split ratio 40.

When required, NMR-spectra were acquired on Bruker AV(III)-400, AV400 or DPX300 instruments by using CDCl_3 (reference δ 7.270 in ^1H NMR and 77.000 ppm in ^{13}C NMR) or CD_3OD (reference δ 3.35 and 4.78 in ^1H NMR, and 49.3 (septet) in ^{13}C NMR) as the solvent.

2.5 Standard Operating Procedures

2.5.1 Carrying Out a Self-optimisation Experiment

The standard operating procedure for the preparation of the continuous flow self-optimisation equipment was carried out before each experiment as detailed below:

1. The reactor tube was filled with catalyst (e.g. approximately 2 g of γ -alumina), and a frit (2 μm) was placed at the bottom of the reactor to ensure that the catalyst was contained within the reactor during operation.
2. The reactor was resealed to the system, and the valve to the CO_2 pump (V-2) was opened to allow all the fittings to be leak tested with liquid leak detector SnoopTM.
3. The heating blocks containing the heating cartridges were attached to the reactor and the pre-heater. It was ensured that the thermocouples connected to the temperature trip box and Picologger, were appropriately inserted into the heating blocks.
4. The BPR was set to the required pressure.
5. The system trips were tested and set to the appropriate values for the experiment; temperature 15 °C above the maximum allowed temperature and pressure at 20 bar above the maximum pressure.
6. The CO_2 pump over-pressure trip was set at a higher pressure than the system pressure trip, so that CO_2 was pumped through the system, even if all other trips were initiated. This feature ensured that all the organic material was pumped away from the catalyst, and any reactions taking place in the reactor were terminated.
7. The CO_2 pump was set at the desired flow rate and started.

8. The pre-heater and reactor heating controllers were turned on and set to the desired starting temperatures.
9. The organic pump (Organic/Org 1, 2 or 3) trip pressures were set below that of the CO₂ pump trip level.
10. The organic pumps were primed with the desired organic material. The liquid was then pumped against a closed tap (V-3, V-4 or V-5 depending on which organic pump was in use) to ensure that the pump was able to deliver the liquid.
11. The appropriate tap was opened to allow the organic material to be pumped into the system, and the flow rate of the pump was set at the desired speed.
12. The system was left to equilibrate before proceeding (approximately 10-20 min).
13. For the FT-IR experiments: The OPUSTM software was opened and the appropriate instrument tests for the FT-IR spectrometer were carried out. A background spectrum was then measured with an empty flow cell. The output files for the OPUS macro were emptied, before the appropriate macro was started (long running experiment). The macro was programmed to measure one spectrum every 15 seconds. The number of measurements was usually set to a total of 5 000 or 10 000 spectra, to make sure the IR kept measuring spectra through the whole experiment.
14. The GCsolutionTM or LabSolutionTM software was opened. The appropriate method file was chosen, and a batch file, which collected multiple chromatograms, was created. The results of the GC, were set to be outputted as a text file (ASCII format), and named appropriately. The GC batch file was started along with the data logging software (Picolog Recorder).

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15. The organic pumps, CO₂ pump, the heaters and BPR were programmed to change at various times through the experiment, exploring different reaction conditions. This was done by using an in-house developed graphical user interface (CO₂ GUI and supermodgui) in MATLAB.¹⁷⁰ For optimisations, the appropriate optimisation code was opened (either SMSIM or SNOBFIT with GC- or IR-analysis), and the optimisation was started.
16. The system was now running an automated experiment or a self-optimisation. The progress and the conditions of the system were automatically logged to a text file.

After the experiment has finished:

1. The system was flushed with an appropriate solvent, e.g. toluene, MeOH or *i*-PrOH.
2. After 30-60 min, the organic pumps (Organic/Org 1, 2 and 3) were turned off and taps V-3, V-4 and V-5 were closed.
3. After 20-30 minutes, the heaters were turned off and the reactor was left to cool, with CO₂ flowing through the system.
4. The CO₂ pump was stopped and tap V-2 was closed.
5. The equipment was depressurised by gradually decreasing the pressure at the BPR.

General notes:

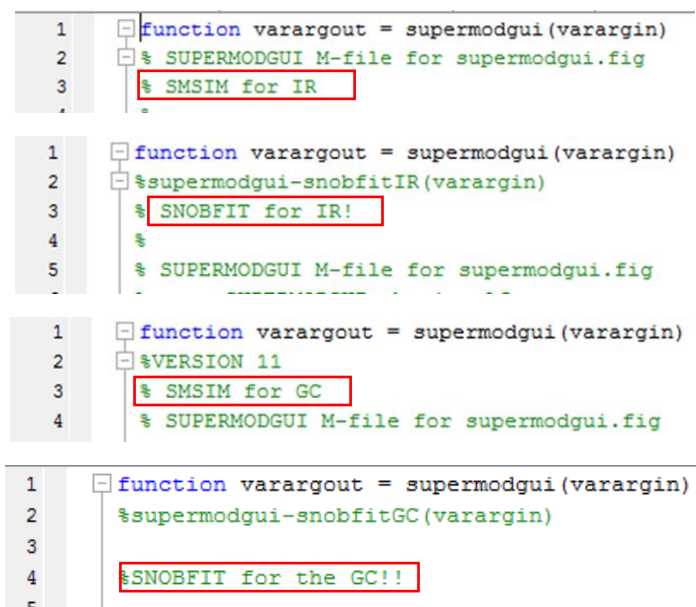
- From the outputted IR-data, the average of the normalised product peak height, for 5 or 10 spectra, can be calculated as explained in Chapter 3. This value was maximised in an optimisation.

- The FT-IR spectrometer was not turned off between experiments, as it is very sensitive to changes in its environment (e.g. temperature and moisture).
- After the reactor had been allowed to reach a steady state, samples were taken using the on-line GC. The sample loop was turned, when instructed by the GUI, which started the GC method, and the chromatogram was recorded.
- For optimisations with GC-analysis, the GC-yield of the target product was calculated from the outputted ASCII file, after each analysis. Internal normalisation was used to determine the yield, and hence no internal standards were required: 1. All the peaks related to the starting material were identified; 2. The ratio of the peak area of the desired product peak, to the peak areas of all the related peaks, was calculated giving the GC-yield of the product. If desired, the different response factors of the different substances could be taken into account, by changing the RF-matrix code in MATLAB (also used to ignore e.g. solvent peaks during the calculation of the GC-yield).

2.5.2 Carrying Out an Optimisation with SNOBFIT

The user interface in MATLAB for carrying out optimisations with the SNOBFIT algorithm is currently under development. Therefore, prior to starting an optimisation, all the relevant manipulations (e.g. defining the input matrix) are performed directly in the MATLAB code for the optimisation software. Currently, all different versions of the optimisation program are called `supermodgui.m`, and presently four versions exist: 1. SMSIM with FT-IR analysis; 2. SNOBFIT with FT-IR analysis; 3. SMSIM with GC analysis; 4. SNOBFIT with GC analysis. The

version of the program in use is indicated at the beginning of the code (Figure 2.8).



```

1 function varargout = supermodgui(varargin)
2 % SUPERMODGUI M-file for supermodgui.fig
3 % SMSIM for IR
4
5
1 function varargout = supermodgui(varargin)
2 %supermodgui-snobfitIR(varargin)
3 % SNOBFIT for IR!
4 %
5 % SUPERMODGUI M-file for supermodgui.fig
6
7
1 function varargout = supermodgui(varargin)
2 %VERSION 11
3 % SMSIM for GC
4 % SUPERMODGUI M-file for supermodgui.fig
5
6
1 function varargout = supermodgui(varargin)
2 %supermodgui-snobfitGC(varargin)
3
4 % SNOBFIT for the GC!!
5

```

Figure 2.8. The identifications of the 4 different versions of the supermodgui.m code (optimisation program). Before starting an optimisation the desired code needs to be located in the appropriate file, and the others moved to a different folder.

Prior to starting an optimisation with SNOBFIT, the required values are changed directly in the code. The limits of the reaction, the number of variables and dx , are determined. The number of variables needs to be changed at 3 different locations, for the software to operate properly. Throughout the optimisations with SNOBFIT, n_{req} was kept constant at 6, and p at 0.1 (6 points are generated by each call, and 10 % of these points are global points). Outlined below is a list of changes that were made to the code, prior to carrying out an optimisation with SNOBFIT. The list assumes the operator to be somewhat familiar with the software in order to be able to carry out the changes.

1. The 'Go To'-button is used to find `start_callback`. This is the function, where the input file for SNOBFIT is formed, at the beginning of an optimisation.

```

2917
2918 % --- Executes on button press in start.
2919 function start_Callback(hObject, eventdata, handles)
2920 % hObject    handle to start (see GCBO)
2921 % eventdata  reserved - to be defined in a future version of MATLAB
2922 % handles    structure with handles and user data (see GUIDATA)
2923
2924 button = get(hObject, 'Value'); %is this a button down or button up
2925
2926 if button==1 %if button down
2927

```

2. The section of code shown below was found, and the limits of the reaction (red box), the dx vector (green box), and the number of parameters (blue box) were defined. The variables in the red and green box are listed in the order they appear in, in the CO2 GUI (first temperature, followed by flow rates of different pumps).

```

3261 %get and store the list of conditions generated from ResGen
3262 %function
3263 handles.GC_method_time = 23;
3264 global GLOBALGCTIME
3265 GLOBALGCTIME = 0.1;
3266 handles.params = struct('bounds', {[300,0.1],[380,1.0]}, 'nreq', 6, 'p', 0.1);
3267 handles.file = 'snob_file';
3268
3269 [conditions, xbest, fbest] = snobfit(handles.file, [], [], handles.params, [5 0.05]);
3270 conditions = sortrows(conditions(:,1:end));
3271 snobfit_data = struct('conditions', zeros(6,2), 'snob_count', 1, 'response', ...
3272     zeros(6,1), 'cycle', 1, 'stableTime', [], 'startTime', [], 'fullconditions', []);
3273
3274 snobfit_data.conditions(1:size(conditions,1), 1:size(conditions,2)-2) = conditions(:,1:2);
3275

```

3. As a comparison to the initial call to SNOBFIT, ResGentimcallback is the section of code where the continuation calls are made (new set of conditions are acquired and recorded).

```

3376
3377 function ResGentimcallback(obj, event, handles)
3378     %try
3379     %get current snobfit data from the snobfit_data structure.
3380     snobfit_data = get(obj, 'UserData');
3381     %set the current ExpNo
3382     expNo = snobfit_data.snob_count;
3383     %set sampling to 0 (no sample is being measured)
3384     %snobfit_data.sampling = 0;
3385     %is the cycle (which determines where you are in the conditions list)
3386     %smaller than the number of conditions (meaning that the list hasn't been
3387     %completed)
3388     if snobfit_data.cycle > size(snobfit_data.conditions,1)
3389
3390         %get the conditions that have just been run
3391         runconds = snobfit_data.conditions;
3392
3393         f = zeros(size(snobfit_data.conditions, 1),2);
3394         f(:,1) = snobfit_data.response;
3395

```

4. The new conditions are sorted by temperature, to make the heating or cooling period as short as possible (temperature was always the first variable in the list of variables and boundaries). The number of parameters was also changed here (blue box).

```

3396
3397 % call to snobfit again
3398 [conditions,xbest,fbest] = snobfit(handles.file,runconds,-f,handles.params);
3399 snobfit_data.snob_count = snobfit_data.snob_count + 1;
3400 if iseven(snobfit_data.snob_count)%if snob count is 2 or multiples thereof
3401     conditions = sortrows(conditions(:,1:end));%sort the conditions into ascending order (default)
3402     conditions = flipdim(conditions,1); %flip them the other way, so they are descending
3403 else
3404     conditions = sortrows(conditions(:,1:end));%sort the conditions into ascending order
3405 end
3406
3407 %update the ResGentim userdata for the next runs
3408 snobfit_data.conditions = conditions(:,1:2);
3409 %snobfit_data.fullconds(snobfit_data.snob_count) = conditions
3410 snobfit_data.cycle = 1;
3411 end
3412
3413 %update status fields
3414 set(handles.status1, 'String', sprintf...

```

5. The determination of the GC-method time, and the retention time of the desired peak, as well as, the linking of the variables (reactor and pre-heater temperature), were made in the optimisation GUI (SuperMod), in a similar manner to when the SMSIM algorithm was used. Pressing start

in the SuperMod GUI, and selecting the appropriate file, initiated an optimisation with the SNOBFIT algorithm.

6. Currently this version of the software does not have a stopping criterion, and therefore the optimisation was run continually until stopped by the operator. The optimisation was stopped, when it was believed the optimum had been reached (the optimal point had not improved during several calls to SNOBFIT), or the optimisation had measured more than 100 different conditions (if more variables were optimised this number would be higher).

Chapter 3. Self-optimisation with FT-IR Analysis in Practice

3.1 Introduction

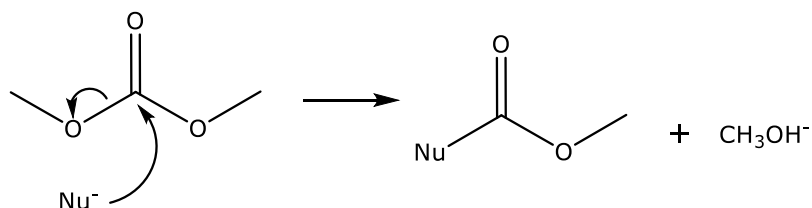
In this Chapter, the use of the automated self-optimising reactor combined with FT-IR analysis is reported. The system was employed to optimise the reaction conditions for the acid catalysed methylation of different alcohols (section 3.2.1 for 1-pentanol, and 3.2.2 for 1-butanol). Two different optimisation algorithms (SMSIM and SNOBFIT) were used, and the reactions were successfully optimised with both search algorithms resulting in similar optimal conditions. It was also found that despite pressure limitations of the in-line ATR FT-IR spectrometer, the system could be used to investigate reactions, where supercritical carbon dioxide was used as the solvent (latter part of section 3.2.2).

Dimethyl carbonate (DMC) was used as the methylating agent. DMC can react in two different ways depending on which carbon atom reacts with the nucleophile (Scheme 3.1).^{57, 176} Methoxycarbonylation (the nucleophile attacks the carbonyl carbon on DMC) produces the transesterification product, whereas methylation (the nucleophile attacks one of the methyl carbons) gives the methylated product and $\text{CH}_3\text{OCO}_2\text{H}$, which decomposes to methanol and CO_2 . It has been shown that the reactivity of DMC depends mainly on the temperature of the reaction, as at lower temperatures the methoxycarbonylation is predominant and

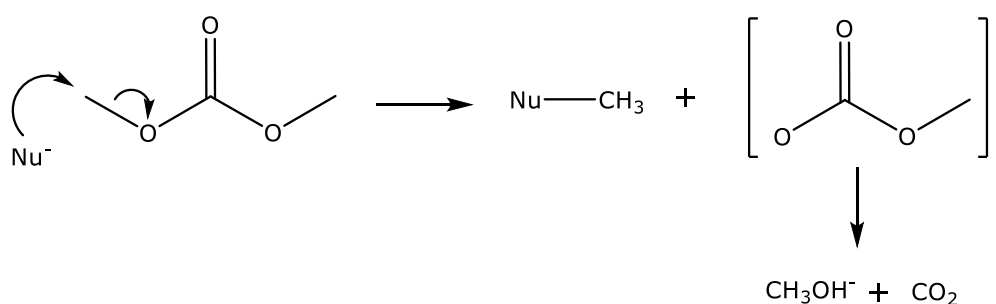
Chapter 3

at higher temperatures ($T > 160\text{ }^{\circ}\text{C}$) the methylation is the main reaction occurring.¹⁷⁶

Methoxycarbonylation



Methylation



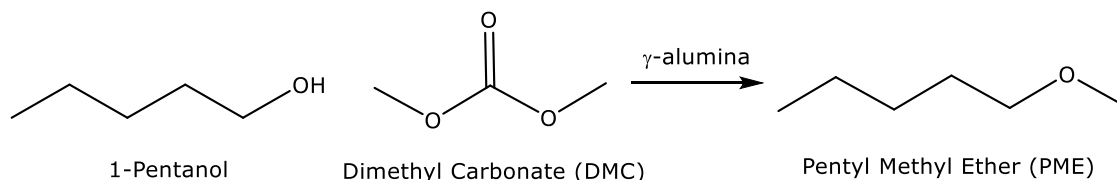
Scheme 3.1. The reactivity of DMC in the presence of a nucleophile. The nucleophile can attack either the carbonyl carbon resulting in methoxycarbonylation, or one of the methyl carbons yielding the methylated product.¹⁷⁶ In this Chapter the methylation route is studied.

In this Chapter the methylation of alcohols with DMC is studied. The carbonylation route will be discussed in Chapter 4, where reactions between aniline and DMC are studied.

3.2 Results and Discussion

3.2.1 Methylation of 1-Pentanol

The work began by building a reactor with an ATR FT-IR spectrometer as the analysis tool. A similar set-up had been used in a previous study,¹²¹ but in that case a different spectrometer had been employed. Previously the analysis was carried out by an apparatus equipped with a React-IR flow cell, and a MCT-detector (mercury cadmium telluride). Whereas, the current device had a DTGS-detector (deuterated triglycine sulfate), which did not require cooling with liquid nitrogen, which was the case for the MCT-detector. This feature, however, makes the DTGS detector less sensitive. Nevertheless, the current spectrometer was easier to handle, and to transport, if necessary. Therefore, to confirm similar results could be obtained with both set-ups, the same reaction was studied, as in the previous case: the acid catalysed reaction between 1-pentanol and dimethyl carbonate (DMC) (Scheme 3.2). The desired product was pentyl methyl ether (PME). As mentioned in Chapter 1, such etherification reactions, which avoid the use of halogenated reagents, are of great importance, as the only side-products that are formed are water and CO₂, and possibly methanol or dimethyl ether from the decomposition of DMC.



Scheme 3.2. The methylation of 1-pentanol with dimethyl carbonate (DMC) over γ -alumina to produce pentyl methyl ether (PME). The conditions of the reaction were studied with the self-optimising reactor and are discussed further in this Chapter.

Calibration

As described in the previous research,¹²¹ utilising the FT-IR-analysis in optimisations, requires a calibration, which makes it possible to correlate IR-absorptions with product yields. To achieve comparable values, relating to the yield of the product, a reference material, ethyl acetate (EtOAc), was pumped through the system at the same flow rate as 1-pentanol, to allow for normalisation of the product peak. The EtOAc pump was connected to the system after the reactor, and therefore EtOAc did not participate in the occurring reactions, and could be used as a reference material. Normalisation of the product peak was required, because when the flow rates of the starting materials were changed, the concentration of the formed product also changed, and as the flow rates varied, similar absorptions may have been achieved at different conditions with different dilutions, and with different conversions. Hence, if only the product peak absorption would have been monitored, no representative value for the yield would have been obtained. Distinct peaks for both the product and the reference were identified (Figure 3.1), which meant that when EtOAc was pumped at the same flow rate as 1-pentanol, a value relating to the yield of the product, independent of the concentration of the product, could be obtained by calculating the ratio between the absorptions for the product and the reference. The same wavenumbers, as indicated in Figure 3.1, were also used in the previous study, which again allowed for a comparison to be made between the current system and the previous one.¹²¹

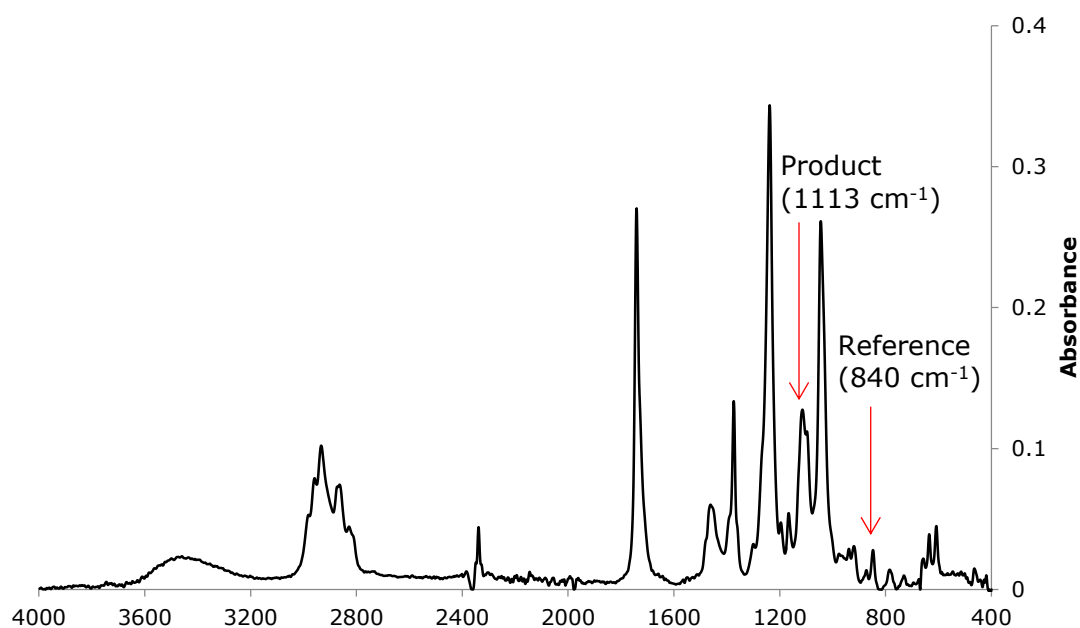


Figure 3.1. The IR-spectrum of the reaction mixture for the methylation of 1-pentanol with DMC showing the unique peaks for the product (PME) and the reference (EtOAc).

To be able to determine the yield of the reaction, using IR-absorptions, a correlation model, relating the normalised absorptions (V_{opt} , in equation 1) to the GC-yield of the product, had to be constructed. Initially, a temperature ramp reaction at constant flow rates was carried out to make sure the GC-yield of PME correlated with the normalised absorption of the product (V_{opt} , Figure 3.2). The reaction was monitored by both GC and FT-IR. The IR-data were matched to the GC-chromatograms by checking the acquisition times of all the chromatograms. Then the IR-spectrum measured at the same moment as the GC-acquisition started, and the four consecutive spectra, were used to calculate the V_{opt} -values. First the peak heights (absorptions) for all five product peaks, and separately the five reference peaks, were added together, and then their ratio was calculated:

$$V_{opt} = \frac{\sum_{i=1}^5 Abs(product)_i}{\sum_{i=1}^5 Abs(reference)_i} \quad (1)$$

The GC-yields for PME were calculated by internal normalisation: the 1-pentanol related peaks in the chromatogram were identified, and then the percentage of the area for the desired product compared to the area of all the 1-pentanol related peaks, was calculated. In Figure 3.2, both the GC-yields and Vopt-values have been drawn as a function of the reaction temperature. As both analysis methods produce a curve with similar shapes, it can be concluded that there is a correlation between the GC-yields of PME and the Vopt-values. However, at temperatures above 250 °C, the correlation diminishes, and currently the reason for this behaviour is unclear.

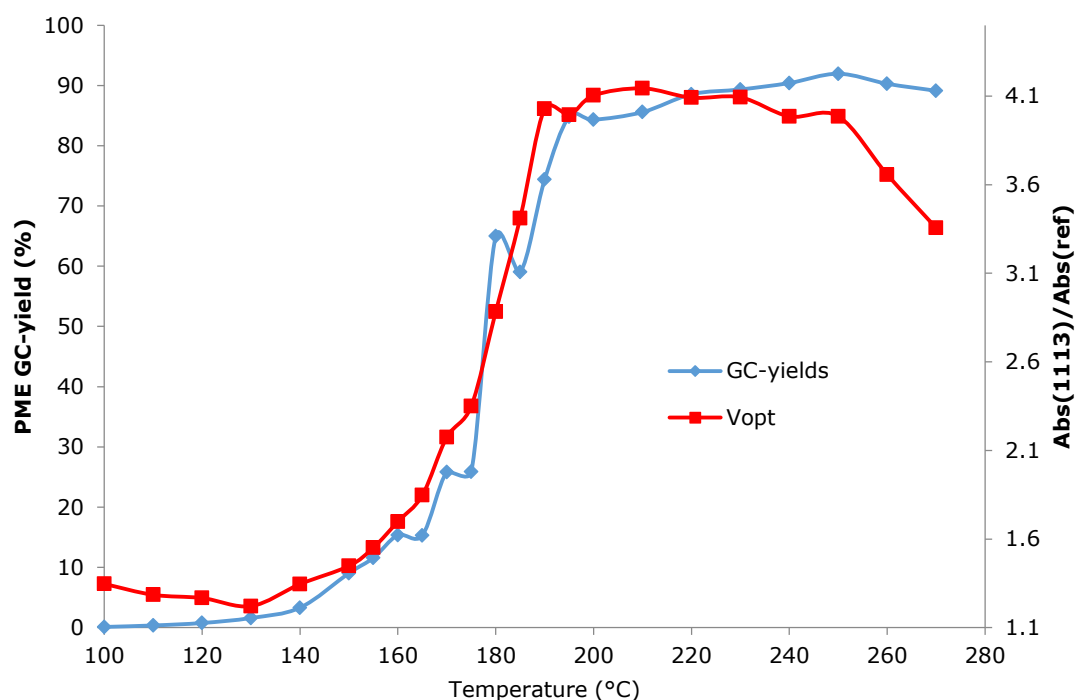


Figure 3.2. The changes in the PME GC-yield and the Vopt-values as a function of temperature. It can be seen that as the shapes of the figures are similar, there is a correlation between the two values. At high temperatures (>250 °C) the Vopt-value decreases, even though the GC-yield does not. The reason for this is currently unknown. Conditions: 0.2 ml/min (1-pentanol, EtOAc and DMC), 100-270 °C (step size: 10 °C between 100-150 °C and 200-270 °C, and 5 °C between 150-200 °C), atm.

Figure 3.2 shows a clear correlation between the GC-yields of PME and the Vopt-values, and so a more elaborated correlation model was constructed by carrying out the reaction at 27 different conditions, and again following the progress of the reaction with both FT-IR and GC. The conditions under which the reaction was carried out are listed in Table 3.1. All the variables (temperature, 1-pentanol flow rate and DMC flow rate) had 3 different values, and these varied in such a way that resulted in 27 different combinations: at each reaction temperature 9 different conditions were measured. These were achieved by keeping the 1-pentanol flow rate constant during three of the conditions, and varying the DMC flow rate each time.

Table 3.1. Conditions for the experiment for constructing the correlation model. The variables were varied separately, which resulted in 27 different conditions, for instance at 150 °C 9 different conditions were tested; the 1-pentanol flow rate changed after 3 conditions while the DMC flow rate varied every time.

Variable	Value 1	Value 2	Value 3
Temperature (°C)	150	200	250
1-Pentanol (and EtOAc) flow rate (ml/min)	0.48	0.86	1.24
DMC flow rate (ml/min)	0.48	0.86	1.24

At each condition listed in Table 3.1, 3 GC-chromatograms were acquired and the average GC-yield was calculated. Also, the average for the three corresponding Vopt-values was determined. In Figure 3.3, the GC-yields are presented as a function of the Vopt-values. By fitting a quadratic trendline to these points, a correlation model that converts IR-absorptions to GC-yields can be obtained. The equation for the model is also shown in Figure 3.3.

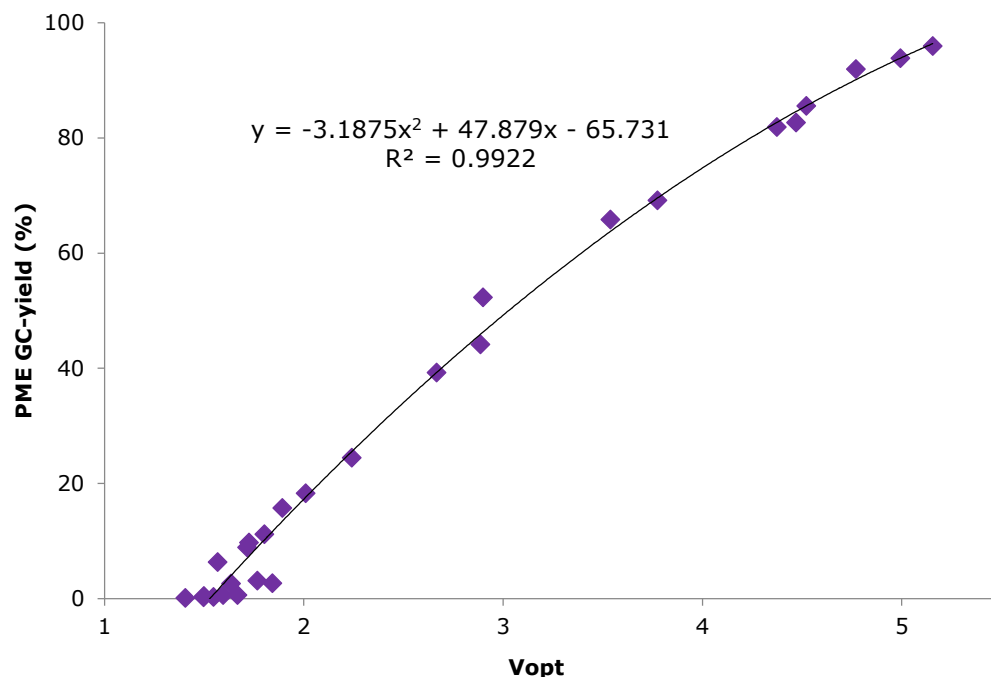


Figure 3.3. The GC-yields of PME as a function of the Vopt-values. The displayed equation is the result of a quadratic fitting to the data, and it can be used to transform infrared absorptions to yields of the product.

To evaluate the accuracy of the Vopt-values, the coefficient of variation (CV) was used. It was defined as the ratio of the standard deviation of the five separately normalised peak heights ($\sigma(Vopt)$), and the average height of these five normalised peaks ($\mu(Vopt)$, equation 2):

$$CV = \frac{\sigma(Vopt)}{\mu(Vopt)} \quad (2)$$

The CV-values during the experiment leading to the correlation model were calculated, in order to determine a suitable value for it, for carrying out the optimisation. As each condition had at least a 20 min equilibration time, before the GC acquisition started, and hence before the IR-data used for the calculation was measured, it was clear that steady state had been reached, at each condition, and so an accurate CV-value could be obtained. During optimisations, the CV-value was used to determine, when the system had reached steady

state. This feature made the waiting time shorter, as the moment stable conditions had been reached could be determined in real-time, instead of it being a pre-set length of time defined by the operator. The latter was the case in optimisations carried out using GC-analysis, where the time had to be set to be long enough to make sure a stable state had been reached; normally 10 min.

SMSIM Optimisation

After the correlation model had been constructed, it was time to carry out an optimisation with the aim to maximise the V_{opt} -values and thus the yield of PME. Based on the data for the calibration reactions, the CV-value was fixed at 0.02. During the optimisation the time to reach steady state was set at a minimum of 2 minutes. However, in case the CV-value for the five most recently measured IR-spectra was above 0.02 after 2 minutes, the program was made to wait another 20 seconds before proceeding, to see if the data would improve. The waiting period did not exceed 5 minutes, and in case the CV-value was still above the threshold value after this time a larger set of data (10 spectra) was used to determine the V_{opt} -value instead of the normally used 5 spectra.

The moment five consecutive spectra gave similar V_{opt} -values that led to the CV-value being less than the threshold, steady state had been reached. Then the V_{opt} -value could be recorded and the conditions could be changed further. This feature of the IR-monitoring that verifies, when steady state has been reached, is the main reason for why optimisations carried out using IR-analysis are significantly faster than the ones monitored with GC. When using GC-analysis, the time between each measurement is approximately 30 min, but with the IR this time can be up to ten times shorter.

The result of the optimisation carried out with the SMSIM-algorithm can be seen in Figure 3.4. During the experiment 44 simplexes, with a total of 162 vertices

(different reaction conditions), were constructed, before the optimisation reached a pre-set stopping criterion. The conditions did not change significantly after the first 50 vertices by which point the Vopt-value had already become large enough to suggest 100 % yields according to the correlation model. The optimal point (with the highest Vopt-value) was at 242 °C, 0.103 ml/min (0.95 mmol/min) 1-pentanol and 0.77 ml/min (9.16 mmol/min) DMC. Also the simultaneously measured GC-chromatograms showed high PME yields (98 %), and helped to validate the fact that a region with high yields had been located. This result is comparable to the research done previously,¹²¹ where the optimum point with the SNOBFIT algorithm was found to be 246 °C, 0.2 ml/min (1.85 mmol/min) 1-pentanol and 1.44 ml/min (17.2 mmol/min) DMC, as the temperature and the molar ratios of the reagents were similar (DMC:pentanol = 9.6:1 and 9.2:1 respectively).

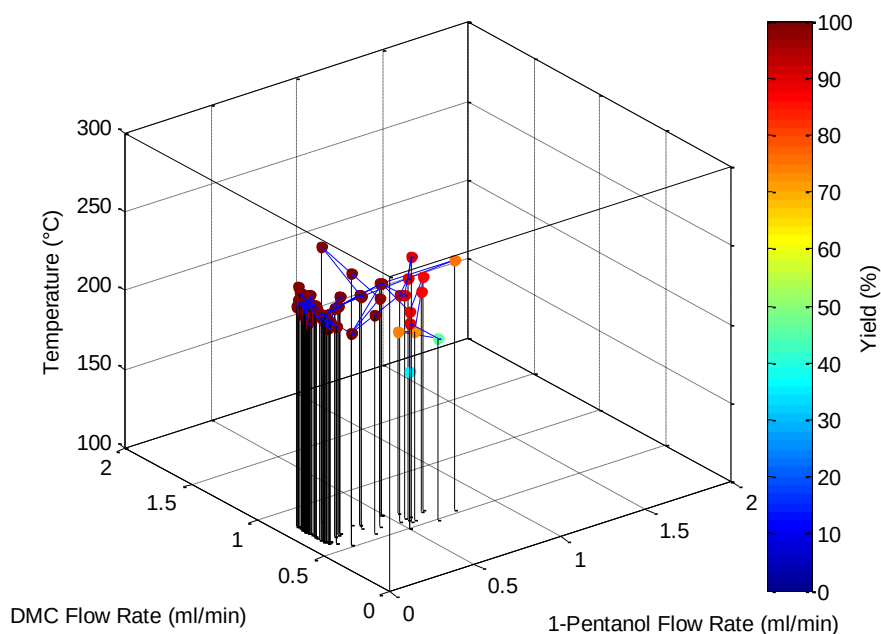


Figure 3.4. The result of the SMSIM optimisation to maximise the yield of pentyl methyl ether. The colour of the dots represents the calculated yield of PME. The highest yields were achieved with 0.1 ml/min 1-pentanol, 0.6-0.9 ml/min DMC and a temperature of 235-245 °C.

The changes in the substrate flow rates, as the experiment proceeded, can be seen in Figure 3.5. A problem linked to the SMSIM algorithm, was that the variation of the different parameters was not always significant, and thus the search for the maximum value was confined within a relatively small volume of the search space.

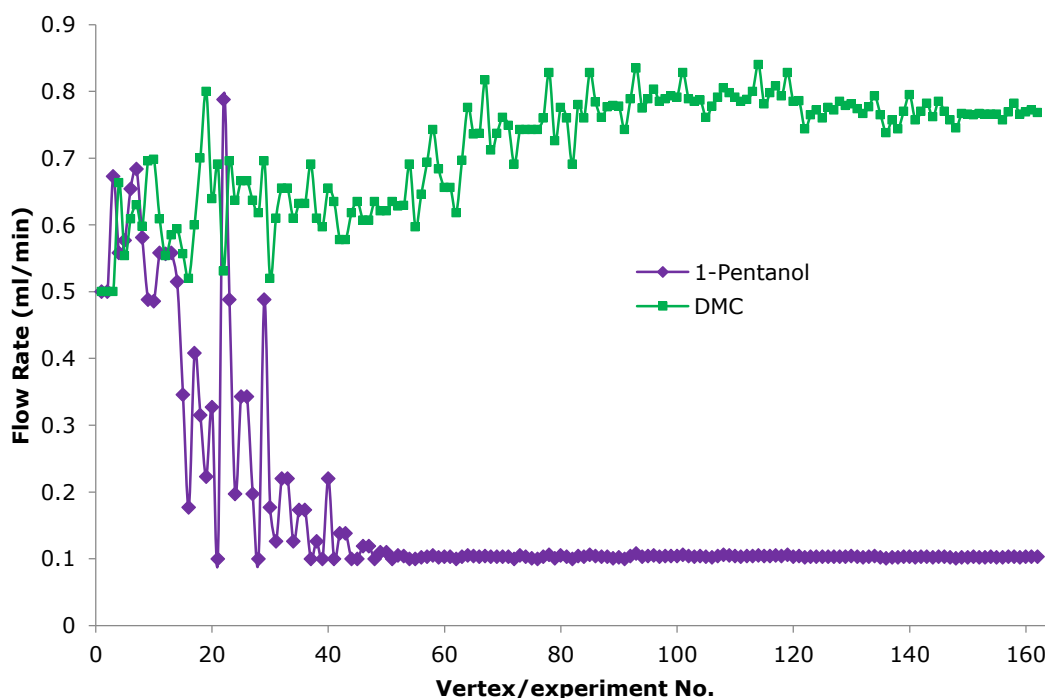


Figure 3.5. The changes in the flow rates as a function of the vertex number for the optimisation experiment. It can be seen that especially the 1-pentanol flow rate did not change significantly after the 50th vertex.

As mentioned earlier, V_{opt} reached values which, according to the correlation model, suggest yields of over 100 % for the target product. The evolution of the V_{opt} -values, during the optimisation, can be seen in Figure 3.6. A closer examination of the reference peak helped to identify, why the optimisation did not finish sooner. The reason was that the intensity of the absorption for the chosen reference peak did not vary, when the conditions were changed. This feature meant that with increased absorptions of the product peak (change in concentration), the V_{opt} -value increased, not solely due to increased yields of

the product, which again resulted in the correlation model giving yields of over 100 %. As the algorithm kept trying to get Vopt-values that gave more than a 100 % yield, the optimisation went on for a longer time than was actually necessary. As demonstrated in the next section, this problem could have been avoided with a more careful selection of the reference peak. This result also suggests that there are slight differences between the 2 IR-detectors (the current and the previously¹²¹ used one), and the fact that similar issues were not encountered with the MCT-detector, might suggest the current problems were related to the lower sensitivity of the employed DTGS-detector.

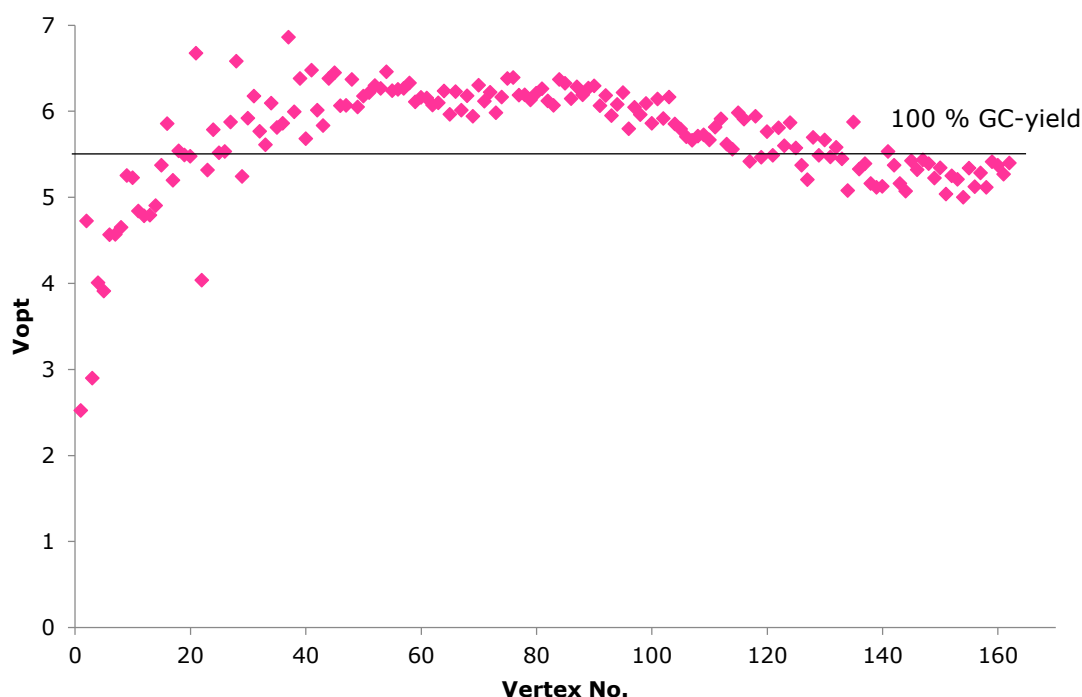
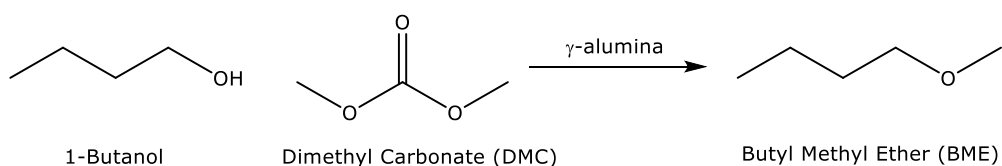


Figure 3.6. A representation of the changes in the Vopt-values as a function of the vertex number in the SMSIM optimisation for PME. The line at 5.5 represents the Vopt-value above which the correlation model gives GC-yields of over 100 %. This had to do with a poorly chosen reference peak, as the intensity did not vary significantly at different EtOAc concentrations.

3.2.2 1-Butanol Methylation

In order to try to fix the problem linked to the reference peak, encountered during the pentanol methylations, a different alcohol, 1-butanol, was studied (Scheme 3.3). The reference material was still ethyl acetate, and in this case the target product, when 1-butanol reacted with DMC, was butyl methyl ether (BME). The formation of BME has been previously studied in scCO_2 by using DELOXAN ASP as the acid catalyst and methanol as the methylating agent, leading to relatively low yields (27 %), and therefore it was of additional interest to see, if an improvement, in the yields, could be reached.¹¹⁴ The same reaction, as shown in Scheme 3.3, was later studied in research involving Cloud Chemistry; carrying out self-optimisations from remote locations, and so a comparison to optimisations carried out with GC-analysis could be achieved.¹²²



Scheme 3.3. The acid catalysed methylation of 1-butanol with dimethyl carbonate to produce butyl methyl ether. The reaction was carried out with and without supercritical carbon dioxide as the solvent utilising both the SMSIM and SNOBFIT algorithm.

Calibration

Because of the difficulties linked to the calibration model for the 1-pentanol methylation, a closer look at the spectra for the methylation of 1-butanol was required. The aim was to find a reference peak, with an intensity that would vary, in a reproducible way, when the conditions were changed. Two peaks for both the product (1115 cm^{-1} and 830 cm^{-1}) and reference (1370 cm^{-1} and 840 cm^{-1}) were identified (Figure 3.7), and a temperature ramp reaction at constant flow rates was carried out to determine which combination of these peaks would give the best correlation to the GC-yields of BME (Figure 3.8). The shapes of the curves in Figure 3.8 suggested that the V_{opt} -value calculated for the product peak at approximately 1115 cm^{-1} and the reference peak at 1370 cm^{-1} gave the best correlation.

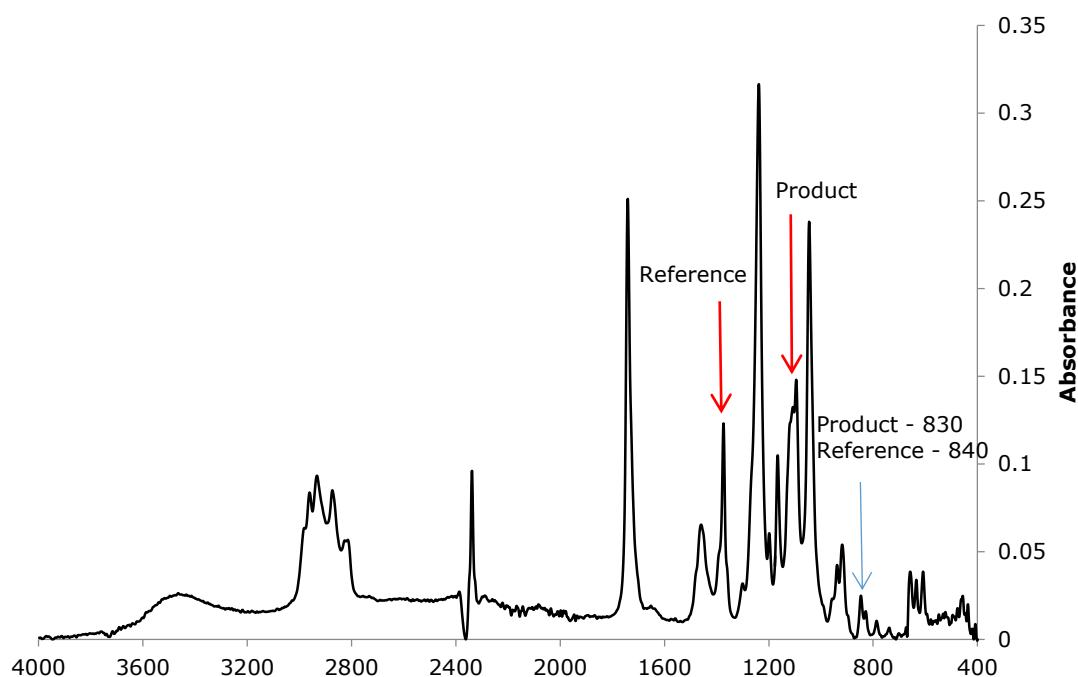


Figure 3.7. An IR-spectrum of the reaction mixture during the methylation of 1-butanol with DMC. The reference (1370 cm^{-1}) and product (1115 cm^{-1}) peaks that were chosen for the calculations are indicated in with red arrows. The two other candidates (Product at 830 cm^{-1} , and Reference at 840 cm^{-1}) are marked by the blue arrow.

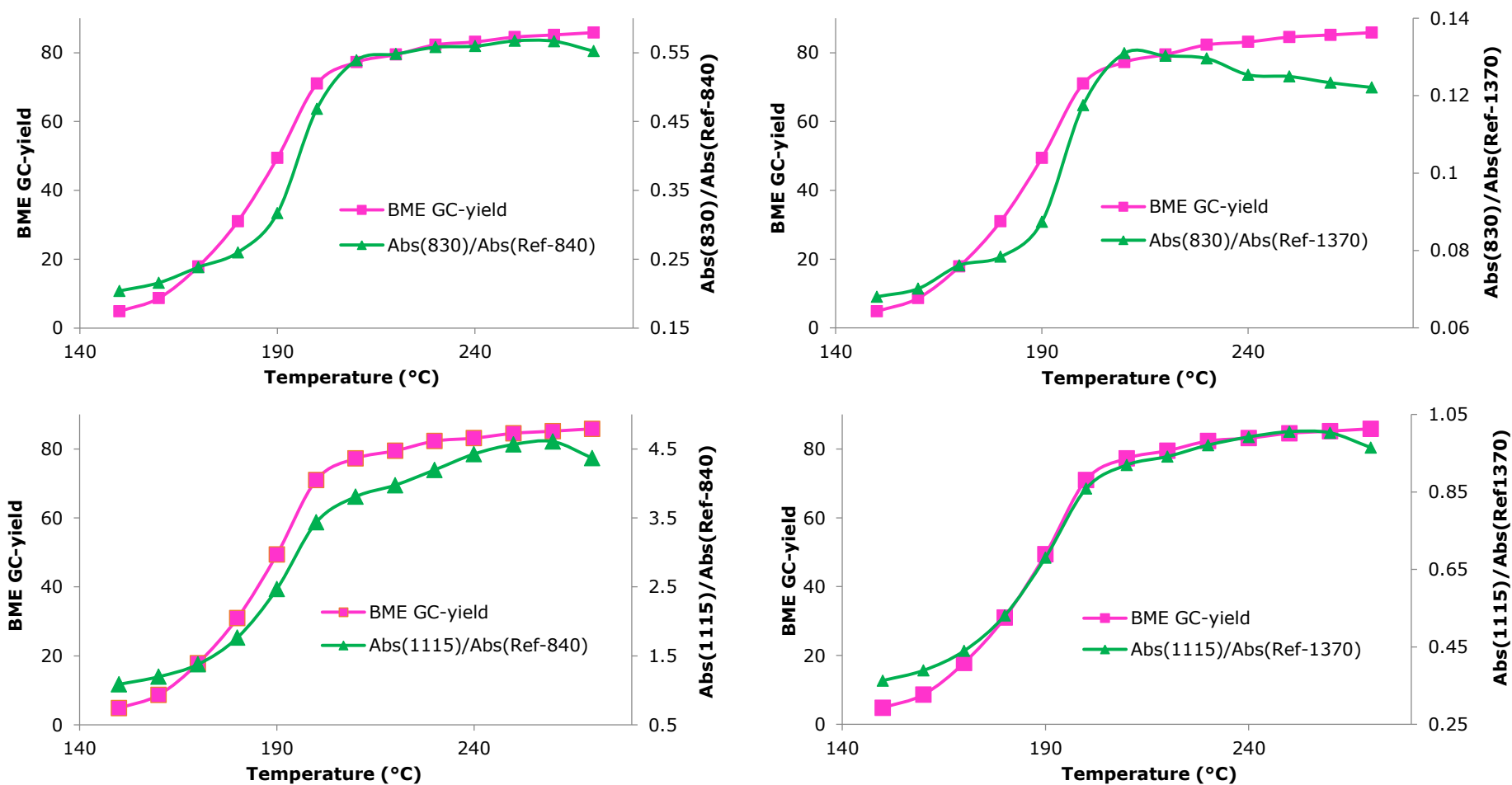


Figure 3.8. The correlations between the GC-yields of BME at different temperatures and the 4 corresponding Vopt-values (derived from different peaks). The Vopt from Abs(1115)/Abs(Ref-1370) correlates best with the GC-yields of BME (overlapping curves). Conditions: 0.2 ml/min (1-butanol, EtOAc and DMC), 150-270 °C (step size: 10 °C), atm.

The V_{opt} -values used for determining the BME yield were calculated differently compared to the ones calculated for the 1-pentanol reactions (equation 1), because the “real” average of the five normalised peak heights was the desired value. First, the V_{opt} (normalised absorption) for each of the five consecutive spectra were calculated separately, and then the average of these values was determined:

$$V_{opt} = \frac{\sum_{i=1}^5 \left(\frac{Abs(product)_i}{Abs(reference)_i} \right)}{5} \quad (3)$$

The CV-value (coefficient of covariance) was calculated similarly as for the 1-pentanol methylation (equation 2), but because of the more accurate reference peak, and less noise in the spectra, a CV-value of 0.010 was used in the optimisations for the methylation of 1-butanol.

The correlation model, to determine the GC-yields of BME, was constructed in a similar way as the one for the yields for PME: the reaction was carried out at 27 different conditions (see Table 3.1, where the 1-pentanol flow rate corresponds to the 1-butanol flow rate), and 3 GC measurements were taken at each condition. The average GC-yields and the corresponding V_{opt} -values were calculated. The correlation model together with the equation to transform IR-absorptions to GC-yields can be seen in Figure 3.9.

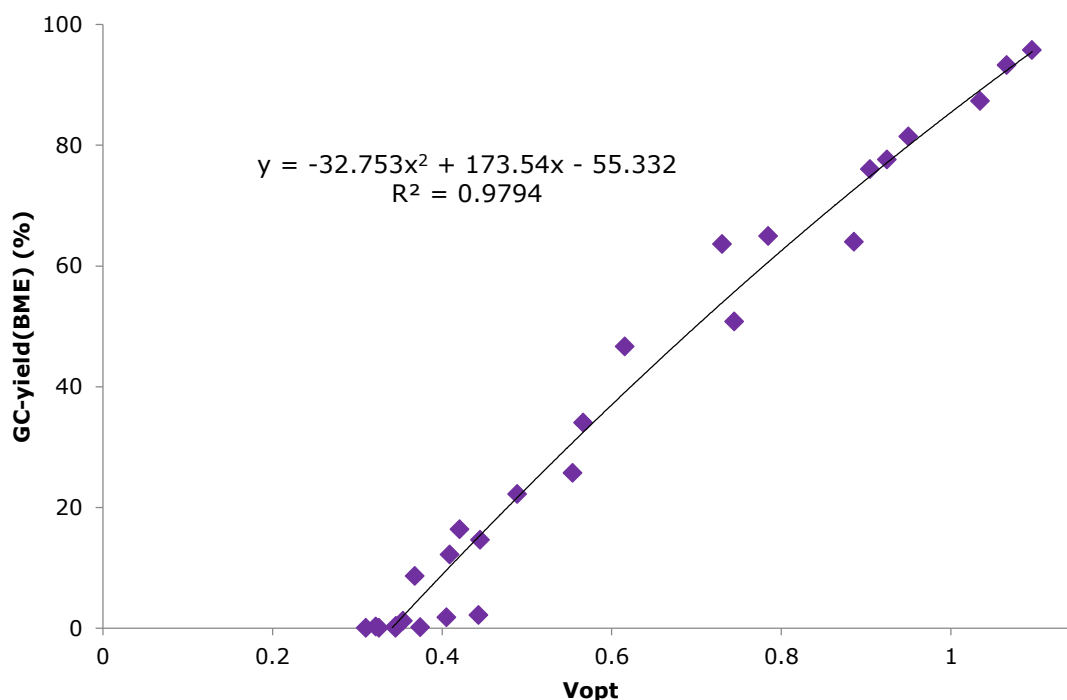


Figure 3.9. The calibration model that correlates the GC-yields of BME to IR-absorptions (Vopt-values), and the equation used in the calculations. It can be seen that at low BME yields (< 10 %) the Vopt-values vary quite drastically, and hence the model does not predict low yields very accurately, which is, however, not a major problem, as the aim is to maximise the yield of BME.

SMSIM Optimisation

The search for the optimal conditions for the methylation of 1-butanol was started with an optimisation using the SMSIM algorithm. The result of the optimisation can be seen in Figure 3.10. The optimal point was found after only 12 simplexes and 44 vertices. The total time for the optimisation was 197.4 min (3.3 h), which means that the time between two measurements at different conditions was approximately 4.4 min. The highest Vopt-value was 1.1023, which corresponds to a 96 % yield of BME, when calculated with the correlation model. This result was in good accordance with the simultaneously measured GC-yields, where the highest yield was found to also be 96 %. The average error between the measured GC-yields compared to the calculated yields, based on

the Vopt-values, was approximately 2 %, which is already in the same region as the error of the GC-results alone.

The starting conditions (the four first vertices) for the optimisation are listed in Table 3.2. The 1-butanol flow rate was set to be quite high, in the beginning, to help the search algorithm to look at a broader set of conditions compared to the optimisation for the methylation of 1-pentanol. At the optimal point, 1-butanol was flowing at 0.77 ml/min, and still giving high yields (optimal for 1-pentanol was 0.1 ml/min).

Table 3.2. The initial vertices (starting Simplex) for the SMSIM optimisation for the methylation of 1-butanol with DMC. These values were pre-set by the operator, and the following vertices were determined by the algorithm as seen in Figure 3.10.

Vertex	Temperature (°C)	1-butanol flow rate (ml/min)	DMC flow rate (ml/min)
1	200	1	1.5
2	230	1	1.5
3	215	1.43	1.5
4	215	1.144	1.908

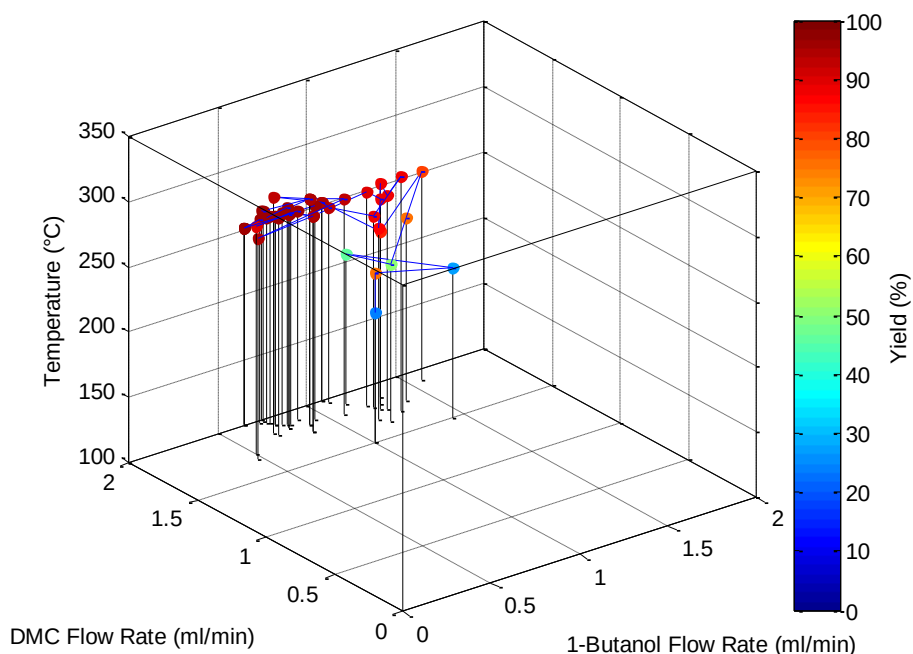


Figure 3.10. The result of the SMSIM optimisation to maximise the yield of butyl methyl ether. The colour of the dots represents the calculated yield of BME. The optimisation finished after 44 measurements with a 96 % yield of BME. The optimum point was found at 260 °C, 0.77 ml/min 1-butanol and 1.93 ml/min DMC.

SNOBFIT Optimisation

After the SMSIM optimisation, the SNOBFIT algorithm was employed to determine the optimal conditions for the studied reaction. As detailed in Chapter 2, SNOBFIT does not require the operator to choose the starting conditions for the experiment. The only parameters that are required are the boundaries of the variables (temperature and flow rates), the number of points to be generated by each call to SNOBFIT ($n_{req} = 6$), and the ratio for how many percentages of all the generated points should be global points ($p = 0.1$).

Through trial and error, it was found that the reaction temperature limits for the SNOBFIT optimisation needed to be set higher than the boundaries for the SMSIM optimisations. If the lower limit was too low, a large quantity of dibutyl ether (up to 56 % yields) was produced at lower temperatures (below 200 °C). This reactivity was a problem, because the chosen product peak, in the IR, was not unique for butyl methyl ether, as also the other ether product produced a peak at the same wavenumber. Hence, the measured V_{opt} -values, at these temperatures, did not correlate only with the BME-yield.

The lower temperature limit was set to 200 °C, as above this temperature butyl methyl ether was the major product, and only small quantities of the other ether product were observed. These problems were avoided with the SMSIM optimisations, because the search did not vary the temperature to reach values below 200 °C, and hence the methylation reaction was the only observed reaction taking place. However, in the case of SNOBFIT, due to the global aspect of the algorithm, the search covered the whole parameter space, and hence reactions were carried out also in the regions producing dibutyl ether.

The SNOBFIT algorithm did not have a stopping criterion, and hence it tried to increase the Vopt-value until the optimisation was stopped by the operator. In Figure 3.11, the evolution of the SNOBFIT optimisation can be seen. The figures depict how the search proceeds by displaying 25, 50, 75 and 100 points. It can be seen that already after 75 measurements the optimal region for the reaction conditions had been located, and stopping the optimisation after 100 measurements was justifiable, as the yield was not increasing. It took 515 minutes (8.6 hours) to measure 100 points, which meant that the average time between the points, in this case, was 5.15 minutes.

The highest Vopt-value achieved was 1.1645, which correlated to an over 100 % GC-yield (102 %) at 236 °C, 2 ml/min DMC and 0.57 ml/min 1-butanol. In fact, the SNOBFIT algorithm located a region of conditions giving similar results (yield above 98 %): Temperature 230-275 °C, 1-butanol flow rate 0.4-0.8 ml/min and DMC flow rate 1.6-2 ml/min.

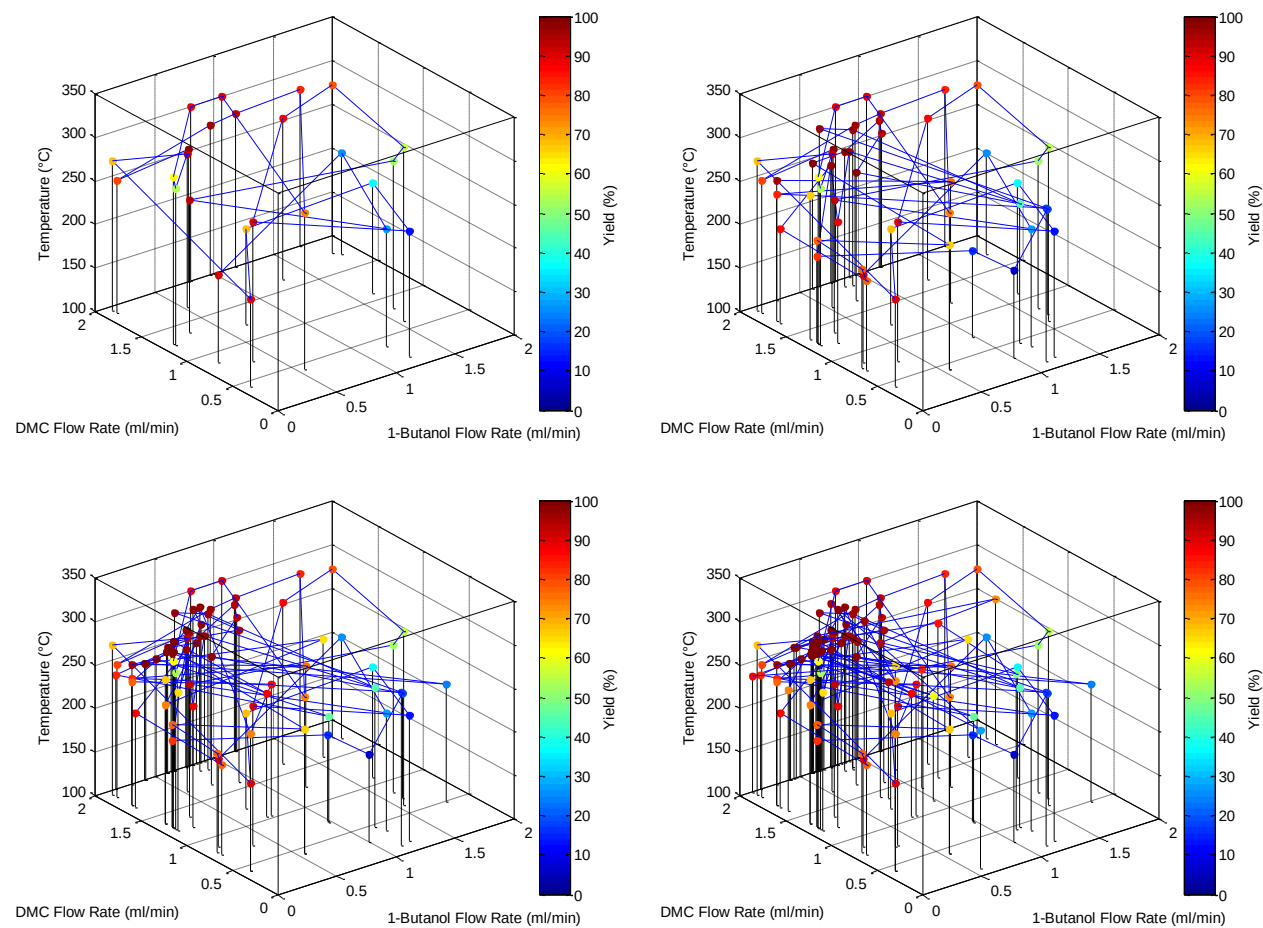
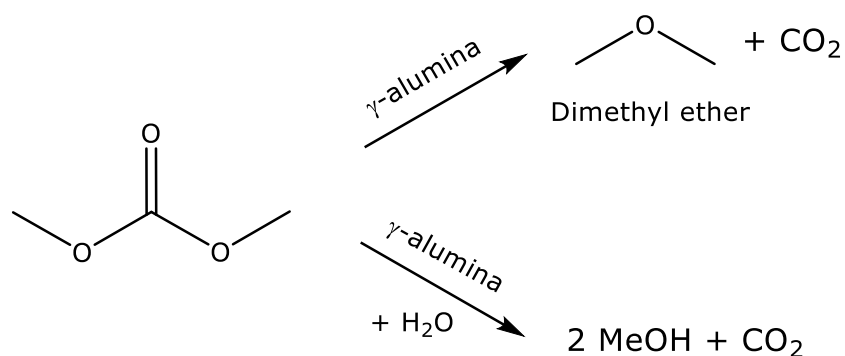


Figure 3.11. The evolution of the optimisation with the SNOBFIT algorithm. 25, 50, 75 and 100 points are shown. It is clear that SNOBFIT is a more global algorithm than SIMPLEX, and so a more comprehensive view of the parameter space is achieved.

The results of the optimisation were validated by simultaneous GC-measurements that gave similar errors as in the SMSIM optimisation, when the yields were high (error < 2 %). However, when the yields of the desired product were low, the correlation model was not very accurate, which was already determined, when it was constructed. In addition, when the 1-butanol flow rate was close to 0.1 ml/min, and the DMC flow rate near 2 ml/min, the FT-IR was not able to produce a representative spectrum of the mixture flowing through the flow cell. This behaviour was believed to be a result of the thermal decomposition of DMC over γ -alumina at elevated temperatures (over 200 °C), which possibly resulted in the formation of dimethyl ether (DME), methanol and CO_2 (Scheme 3.4).^{170, 177}



Scheme 3.4. The thermal decomposition of DMC over γ -alumina giving dimethyl ether and CO_2 or, in the presence of H_2O , MeOH and CO_2 .¹⁷⁷

As DME is a gas at room temperature (and at 50 °C, which was the temperature of the heater at the BPR), and the concentration of butanol (and the reference) was low, meant that the entire sample might have been in the gas phase when flowing through the IR flow cell. This phase change would have prevented the FT-IR from measuring a spectrum, as there would not have been a liquid film in the cell, and hence not enough attenuation of the formed evanescent waves would have occurred, as the gas would not have absorbed enough energy.

Optimisations with scCO₂ as the Solvent

With the issues encountered at low 1-butanol flow rates without a solvent, it was hypothesised that the use of a solvent, namely scCO₂, would help get the product and reference to separate from the DME that was potentially present after pressure release. This separation would then give rise to a liquid phase in the mixture flowing through the IR flow cell, and a valid spectrum could thus be produced also at low flow rates.

In all the experiments carried out with scCO₂, the CO₂ flow rate and pressure of the system were kept constant at 1.0 ml/min and 100 bar respectively. Firstly, it was investigated, whether the spectra for the reactions carried out with scCO₂ contained the same peaks, with similar absorptions, as the ones for reactions carried out without a solvent. As this was the case, it was concluded that the same correlation model that was used for reactions without scCO₂, could be used to transform the measured Vopt-values to GC-yields also when scCO₂ was used.

Two optimisations with the SMSIM algorithm were carried out to determine how changing the starting vertices affected the outcome (Table 3.3, Figure 3.12). The first optimisation was carried out by using the same boundaries, as in the experiment without scCO₂, and it resulted in a maximum yield of 91 %. The reason the yields were not higher, was that the algorithm hit the upper temperature boundary, and instead of decreasing the reagent flow rates, to increase the residence time in the reactor, the optimisation tried to maximise the yield of BME with high flow rates. The optimal point was reached after 44 vertices with a Vopt-value of 1.062: temperature 288 °C, 0.62 ml/min 1-butanol and 2.0 ml/min DMC. The four starting vertices are shown in Table 3.3 (prefix 1).

For the second optimisation the upper temperature limit was increased to 350 °C (instead of 300 °C). The starting temperature was increased to 285 °C, and also the starting 1-butanol flow rate was reduced to 0.5 ml/min (Table 3.3). This change gave an optimum point with a Vopt-value of 1.0909, which corresponds to a GC-yield of 95 %. The optimal conditions were reached after 26 measurements at 306 °C, 0.672 ml/min 1-butanol and 2 ml/min DMC. It is noteworthy that the optimal 1-butanol flow rate ended up being quite high, and close to the optimum for the first optimisation, even though, the starting flow was significantly different in the two cases.

Table 3.3. The initial conditions (4 first vertices) for the SMSIM optimisation carried out with scCO₂ as a solvent. The four first conditions are for the first optimisation (upper limit 300 °C, prefix 1), and the rest are for the second optimisation (upper limit 350 °C, prefix 2)

Vertex	Temperature (°C)	1-Butanol flow (ml/min)	DMC flow (ml/min)
1-1	200	1	1.5
1-2	230	1	1.5
1-3	215	1.17	1.5
1-4	215	1.06	1.66
2-1	285	0.5	1.5
2-2	315	0.3	1.5
2-3	300	0.5	1.8
2-4	300	0.64	1.75

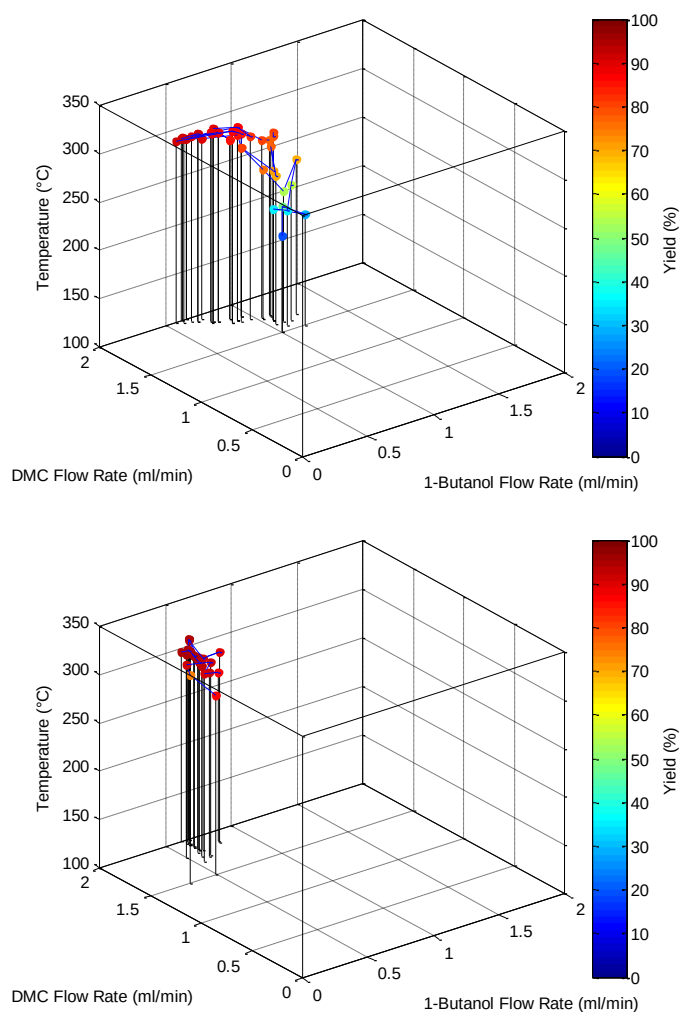


Figure 3.12. The results for the SMSIM optimisations for the methylation of 1-butanol with DMC in scCO_2 . The upper picture shows an optimisation that finished with only 91 % yield, because the upper temperature limit was set too low. In the lower optimisation, a 95 % yield was reached because the upper limit was increased (300 vs 350 °C).

As a comparison, also the SNOBFIT algorithm was used to optimise the methylation reaction with scCO_2 as the solvent. The result can be seen in Figure 3.13, where the progress of the search can be observed. Also, here figures for 25, 50, 75 and 100 points are displayed. The upper limit for this optimisation was 300 °C, so the system was not able to test higher temperatures. The optimum point was found to be at 299.5 °C, 0.46 ml/min

1-butanol and 2 ml/min DMC, with a Vopt-value of 1.1387 which corresponds to nearly 100 % yield (99.8 %).

The problem encountered with the SNOBFIT optimisation was that the data seemed to be very noisy, which meant that the Vopt-values were calculated from 10 spectra instead of the normally used 5 (equation 3). This also meant that the time between the different conditions was longer compared to when the data was less noisy. The 100th point was measured 590 minutes (9.8 hours) after the experiment had started, which meant that the average time between measurements was 5.9 minutes. This time is approximately 13 % longer compared to the SNOBFIT optimisation carried out without CO₂, which also indicates that the data was more noisy than without a solvent. To overcome the noisiness problem, and allow for the data to be calculated from 5 spectra, a higher CV-value could have been used (it was kept at 0.01 throughout the 1-butanol experiments).

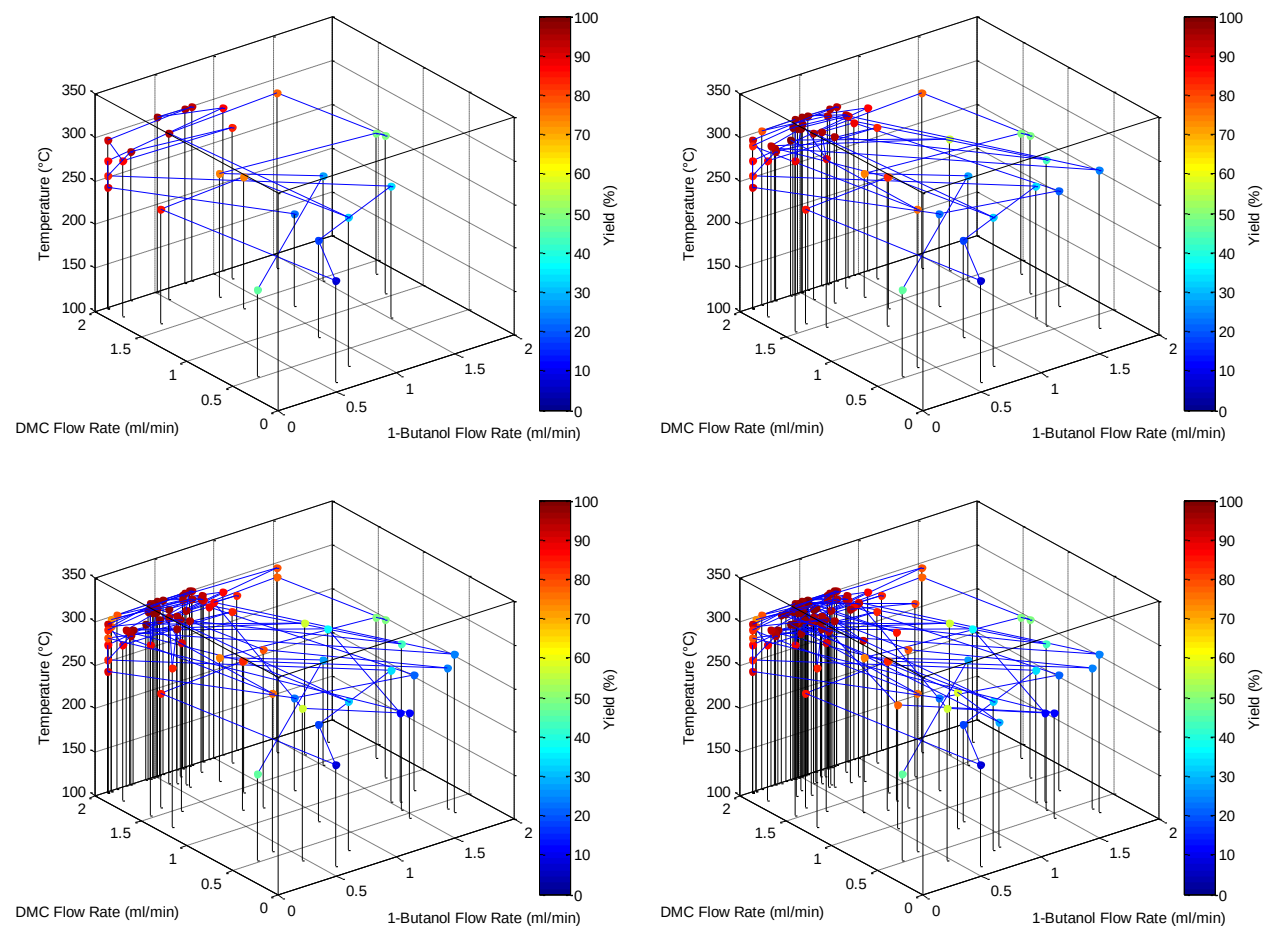


Figure 3.13. The evolution of the SNOBFIT algorithm, with scCO_2 as the solvent. 25, 50, 75 and 100 points are shown. When using scCO_2 a higher temperature is required to reach high yields compared to when the optimisation was carried out without CO_2 .

In addition, to the problems, also the expected advantage at low 1-butanol flow rates was discovered. When 1-butanol (and the reference) flowed through the system at 0.1 ml/min, it was possible to measure a spectrum independent of the temperature and the DMC flow rate. The peak intensities were however quite low, but even so this result meant that the V_{opt} -values calculated at these conditions were more accurate and dependable, when $scCO_2$ was used as the solvent compared to when it was not. In reactions without $scCO_2$, the spectra at low 1-butanol flow rates were only noise, as there was no liquid film present in the flow cell.

All of the optimisation experiments were simultaneously monitored with the GC (sample every 22.5 min). In the SMSIM optimisations, the errors between the measured GC-yields and the yields calculated from the V_{opt} -values, with the correlation model, were quite small (< 5 %). For the SNOBFIT optimisations, on the other hand, the errors between the measured and the calculated GC-yields reached quite high values, which led to an average error of approximately 12.5 %. The reason for this was that most of the GC-samples were taken under conditions that were not a steady state, but rather under conditions that were constantly changing, and so a valid V_{opt} -value from 5 spectra that correspond to exactly the conditions the GC-sample was taken at, could not be calculated. As the SNOBFIT algorithm has a global aspect, the differences between the conditions are larger, and the different evaluation points are further apart than with the SMSIM algorithm. This feature means that it takes a longer time to change the conditions, and therefore the probability of a GC-sample being measured, while the conditions are changing is higher, which again leads to greater error compared to the SMSIM optimisation. However, it would seem that the results from both SNOBFIT optimisations were valid, as optimal regions in the parameter space were located, and they corresponded well to the results obtained with the SMSIM optimisations.

Chapter 3

In

Table 3.4, a summary of the results of all the different optimisations for the methylation of 1-butanol with DMC are shown. To help compare the results, also the molar flow rates of the reagents and the resulting molar ratios are shown. In addition, conditions relating to the stoichiometric ratio of 1-butanol and DMC are reported, to help compare the obtained optimal points to conditions a researcher would be most prone to study (DMC:1-butanol 1:1; Table 3.4 S1-S2 and S3-S4). These points were measured during the SNOBFIT optimisations, and therefore the temperatures do not necessarily correspond to the optimal temperatures located by the algorithms. These points give a maximum yield of 80 % BME without CO₂ (S2 at 296 °C) and 65 % in the presence of scCO₂ (S4 at 261 °C). Both of these yields are lower than the ones discovered with the algorithms. However, studying such stoichiometric conditions further (under different flow rates and temperatures) could be of interest in order to compare the results obtained by the algorithms to results a human investigator would be most likely to locate. A further comparison, and some insight to the mechanism, is provided by point S3, which was carried out with a 0.5:1 molar ratio of DMC:butanol. This ratio could be considered the stoichiometric ratio, if the methanol formed from the DMC during a methylation (Scheme 3.1) would react with another 1-butanol molecule producing two BME molecules from one DMC molecule. However, the yield of the product is relatively low at these conditions, suggesting that this is not the case, but rather that a 1:1 reaction occurs.

Table 3.4. The optimal point or region determined by the different algorithms with and without scCO₂ as a solvent as well as conditions relating to stoichiometric amounts of the reagents (S1-S5, chosen from the SNOBFIT experiments).^a To compare also results from the Cloud Chemistry (CC) research¹²² are listed.^b

Experiment	T (°C)	1-butanol (ml/min)	1-butanol (mmol/min)	DMC (ml/min)	DMC (mmol/min)	Molar ratio ^c	GC-yield (%)
SMSIM	260	0.77	8.4	1.93	23	2.7:1	96 ^d
SMSIM with scCO ₂	306	0.66	7.2	2.0	24	3.3:1	95 ^d
SNOBFIT	230-275	0.4-0.8	4.4-8.7	1.6-2.0	19-24	2.2-5.5:1	>98 ^d
SNOBFIT with scCO ₂	275-300	0.4-0.6	4.4-6.6	1.8-2.0	21-24	3.2-5.5:1	>95 ^d
S1 (no scCO ₂)	217	1.85	20	1.7	20	1:1	25
S2 (no scCO ₂)	296	1.64	18	1.49	18	1:1	80
S3 (no scCO ₂)	244	1.61	18	0.78	9.3	0.53:1	46
S4 (with scCO ₂)	256	0.84	9.2	0.71	8.4	0.91:1	58
S5 (with scCO ₂)	261	1.33	15	1.35	16	1.1:1	65
Nb ₂ O ₅ (CC) ¹²²	350	0.09	0.98	0.39	4.6	4.7:1	97
NbOPO ₄ (CC) ¹²²	335	0.05	0.55	0.19	2.3	4.2:1	>90
γ-alumina (CC) ¹²²	236	0.05	0.55	0.63	7.5	12:1	>99

a) Conditions: 150-350 °C (SMSIM), 200-300 °C (SNOBFIT), 0.1-2.0 ml/min (butanol, reference and DMC), 1.0 ml/min CO₂ at 100 bar when applicable; b) Conditions: 150-350 °C, 0.05-2.0 ml/min (1-butanol and DMC), 1.0 ml/min CO₂ at 100 bar; c) DMC:1-butanol; d) Determined from the measured V_{opt}-values.

All the optimisations lead to conditions with an excess of DMC (2.2-5.5:1), which is in accordance with previous research on the etherification of alcohols with DMC.¹¹⁹⁻¹²¹ The optimisations carried out with scCO₂ required a higher temperature mainly because of the shorter residence time inside the reactor, due to an increased total flow and higher pressure. In addition, increasing the temperature increased the rate of the reaction, which counteracted the lower conversion caused by an increase in the total flow rate. However, accounting for the above mentioned advantages resulting from the presence of scCO₂, its use as a solvent in this reaction might be justifiable especially, if studying the reaction at different conditions is desired. Also, the results for the experiments carried out during the Cloud Chemistry research are shown in

Table 3.4.¹²² The optimisations, in this case, were carried out with the SMSIM algorithm, GC-analysis, with scCO₂ as the solvent, and with 3 different catalysts; Nb₂O₅, NbOPO₄ and γ -alumina. High yields were obtained with all three catalysts, but with γ -alumina the required temperature was much lower (236 °C vs 335-350 °C), but in this case the excess of DMC was much higher (12:1 vs 4.2-4.7:1), hence possibly resulting in more waste. However, the optimal flow rate of 1-butanol was relatively low after all the optimisations (< 0.1 ml/min), and hence the results obtained in the current research, with the FT-IR optimisations, could afford a much higher throughput of the product.

3.3 Chapter Conclusions

The conditions for the methylation of 1-butanol with dimethyl carbonate over γ -alumina to produce butyl methyl ether was successfully optimised with two different optimisation algorithms by using an automated self-optimising reactor with FT-IR analysis. It was also shown that the system could be implemented for reactions using scCO₂ as the solvent, despite the pressure limitations of the FT-IR apparatus.

Chapter 4. Discovering New Reactions in Flow

4.1 Introduction

One of the benefits of the self-optimising system is that the identities of all products formed need not be known prior to carrying out an optimisation. Not even the identity of the target product is required, as long as adequate separation of all the components in the mixture is provided by the on-line analysis, in this case, gas chromatography. Then the GC-yield of the target product, determined by internal normalisation, can be optimised before identifying the reaction occurring. This research approach is not common for reactions carried out in continuous flow, as normally these processes are employed to optimise known reactions, as then transformations giving, for example, insoluble side-products, leading to possible blockages of the system, can be avoided. However, by diluting the mixture with a co-solvent (in addition to CO₂), this problem can be avoided in most cases. This interesting feature of the self-optimising system is the topic of the current Chapter, where the conditions for the formation of several different products synthesised in the same reaction mixture are optimised. Some of these molecules have been reported in the literature, and some lead to the discovery of novel transformations.

The work was started by Dr Ryan Skilton prior to the start of this SINCEM project, and his work is described separately. The original aim of the work had been to expand the self-optimising chemistry by optimising the synthesis of *N,N*-dimethyl aniline starting from aniline and dimethyl carbonate (DMC).¹⁷¹ However, when these reagents were delivered as pure substances through the system, several blockages appeared, and hence a co-solvent, THF, was added. This addition lead to the formation of several products, as shown in Figure 4.1, where a GC for the reaction mixture formed between aniline, THF and DMC over γ -alumina in scCO_2 is shown. The presence of all these peaks in the chromatogram suggested that THF was acting as a reagent, and also inspired the use of the self-optimising reactor to help increase the selectivity (and yield) for each product. Identifying these products, as shown in this Chapter, offered some insight into the mechanistic aspects of the reactions taking place.

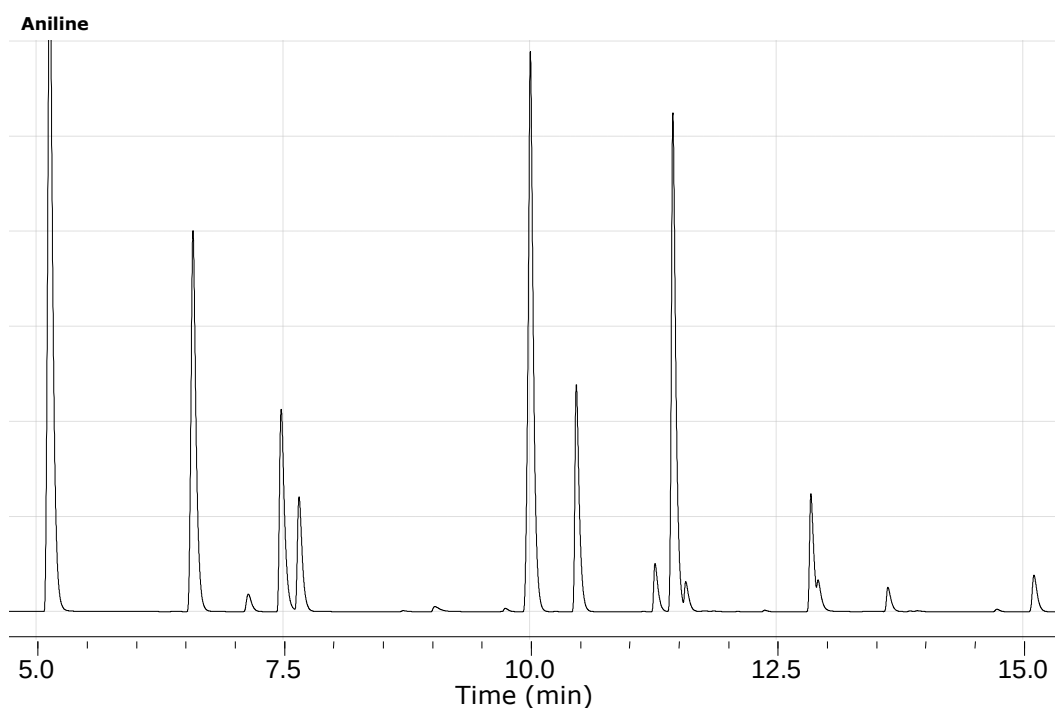


Figure 4.1. A GC chromatogram measured for the unknown mixture of products obtained after the reaction of aniline, THF and DMC. The aniline peak is shown. Several of these peaks (products) were targeted by the optimisation as explained in this Chapter. The THF and DMC peaks are not shown (retention time < 5min).

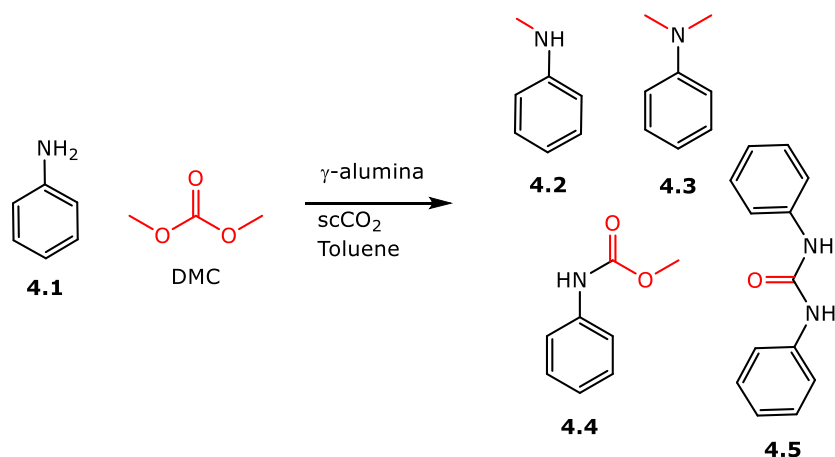
As mentioned above, not all the products formed in the reaction between aniline, THF and DMC were known, and therefore toluene was used as co-solvent instead of THF, and initially the two component reactions between aniline and dimethyl carbonate, as well as aniline and tetrahydrofuran over γ -alumina were studied. These are known transformations, and the optimisations of the conditions for these reactions are described in section 4.2.1, and partially 4.2.2. The remainder of 4.2.2 concentrates on new multi-component reactions that were discovered in flow.

In addition, the optimisation software was later developed to allow for the SNOBFIT algorithm to be used in conjunction with GC analysis, and some of the previous reactions were repeated in order to compare the two algorithms, as shown in the first part of section 4.2.3. In the latter part of section 4.2.3, another multicomponent reaction was studied, as aniline was reacted with both methanol and ethanol, and the yield for the mixed dialkyl product (*N*-methyl-*N*-ethyl-aniline) was increased via optimisation. Some of the results, and all the characterisations of the new compounds described were published in the European Journal of Organic Chemistry.¹⁶⁴ These are also listed in section 4.4 (Chapter Appendix).

4.2 Results and Discussion

4.2.1 Reactions between Aniline and Dimethyl Carbonate

The work began by studying the known transformations between aniline and dimethyl carbonate (DMC) over γ -alumina catalyst (Scheme 4.1). When DMC is used as the reaction partner with aniline (**4.1**) either methylation or carbonylation can take place. The plausible products include *N*-monomethyl aniline (**4.2**), *N,N*-dimethyl aniline (**4.3**), methyl phenylcarbamate (**4.4**) and *N,N'*-diphenyl urea (**4.5**). On some occasions, also *C*-alkylation products can be formed, but these were not observed in this work. In previous studies, depending on the reaction outcome, one of products **4.2-4.5** has been targeted and the others have been considered to be side products or impurities in the reaction.^{116, 178-192} In alkylation reactions with either MeOH or DMC, the outcome has been shown to depend on the acidity and surface structure of the catalyst,^{178, 193} the temperature,^{182, 194-197} the methanol (or DMC) to aniline molar ratio,^{182, 194, 196, 198-200} and the degree of substrate conversion.^{182, 195, 198-200}



Scheme 4.1. Reactions between aniline (**4.1**) and dimethyl carbonate (DMC) producing products **4.2-4.5**. The yield of products **4.2-4.4** were optimised, **4.5** was identified as it precipitated out of the reaction solution.

As mentioned in Chapter 1, DMC can be produced starting from CO₂ and methanol.^{5, 12, 32, 55} Therefore, reversing this reactivity and using DMC as a methylating agent has become more attractive over the last few decades. However, only a few continuous flow systems have been developed for the *N*-methylation of aniline with DMC.^{116, 180, 201} On the other hand, *N*-methylations with methanol have been widely studied in continuous flow systems; mainly in the gas phase.^{194-196, 198, 202-208} In previous work by the Poliakoff group,¹¹⁶ the formation of **4.3**, but also **4.2** and some *C*-alkylation products were observed, when studying the reaction between aniline and DMC at different temperatures, with γ -alumina as catalyst in scCO₂. In the current study, it was found that the same system could produce products **4.2-4.5**; with the selectivity of the reaction depending on the conditions. Hence, the aim of the work presented here was to employ the self-optimising reactor to maximise the yield of products **4.2-4.5** individually. The SMSIM-algorithm was used to vary the flow rates and temperature in order to increase the yield. The optimisation experiments were carried out by using toluene as a co-solvent in addition to scCO₂, mostly to try and prevent blockages in most of the experiments involving aniline.

When studying the *N*-methylation reactions, both aniline and DMC were used as 0.275 M solutions in toluene, and were pumped separately into the system to permit the algorithm to vary the reaction stoichiometry. The flow rates were allowed to change between 0.05 ml/min and 2 ml/min. The pressure and CO₂ flow rate were the only parameters that remained constant, at 100 bar and 1 ml/min respectively. Thus, the three variables for these experiments were the temperature (150-350 °C) and the flow rates of the aniline and DMC solutions.

As mentioned above, the SMSIM algorithm was used to optimise the conditions of these transformations, and as described in Chapter 2 this algorithm requires the operator to determine the starting simplex in order for an optimisation to be

performed. Hence, when targeting *N*-monomethyl aniline (**4.2**), it was of interest to see whether the selection of the starting conditions would affect the outcome of the optimisation, and therefore two different optimisations were carried out (Table 4.1). The first experiment was started at a lower temperature (4 first vertices 250-290 °C) and it resulted in a 60 % yield of **4.2** (255 °C, 0.05 ml/min aniline and 0.48 ml/min DMC). High selectivity was achieved, when the aniline conversion was lower (35 % conversion, 100 % selectivity; reaction conditions: 260 °C, 0.11 ml/min aniline and 0.44 ml/min DMC). This observation was in accordance with previous studies, where it had been shown that, when the conversion of aniline increases the selectivity for **4.2** decreases.^{182, 195, 198-200} The second optimisation was started at a higher temperature (4 first vertices at 250-314 °C) and it found relatively high yielding regions at much higher temperatures than the first optimisation (65 % yield at 340-350 °C, aniline flow rate 0.22 ml/min and DMC 0.46 ml/min). The reaction was less selective in this region, but on the other hand the throughput of the reaction was much higher in the latter case (2.4 mmol/h vs. 0.50 mmol/h).

Table 4.1. The starting vertices for the two different SMSIM optimisations for product 4.2 and the resulting optimal point. The five first conditions are for the first optimisation (prefix 1), and the rest are for the second optimisation (prefix 2).^a

Vertex	Temp. (°C)	4.1 Flow (ml/min)	DMC Flow (ml/min)	DMC/4.1 mol-ratio	GC-yield ^b (%)	Sel. (%)	Throughput ^c (mmol/h)
1-1	250	0.1	0.3	3	60	69	1.0
1-2	290	0.1	0.3	3	6	5.6	0.10
1-3	270	0.36	0.3	3	37	86	2.2
1-4	270	0.19	0.55	2.9	60	78	1.9
1-opt	255	0.05	0.48	9.6	60	87	0.50
2-1	250	0.1	0.3	3	64	74	1.1
2-2	270	0.18	0.36	2	60	75	1.8
2-3	300	0.2	0.4	2	42	42	1.4
2-4	314	0.15	0.4	2.6	11	11	0.27
2-opt	340-350	0.22	0.46	2.1	65	69-72	2.4

a) Conditions: 0.05-2 ml/min (**4.1** and DMC 0.275 M solutions in toluene), 150-350 °C, 1 ml/min CO₂, 100 bar; b) based on GLC-analysis of the reaction mixture; c) based on **4.1** flow (mol(aniline)*yield*60min).

The reason the two experiments lead to different optimal points, was linked to the linear character of the algorithm. In the first case, the search did not exceed 290 °C whereas in the latter case most of the studied conditions were located above 300 °C. If this search would have been carried out with a global algorithm (e.g. SNOBFIT), the entire variable space would have been studied in one experiment and the global optimum could have been found more easily. Therefore, this reaction was later on also studied with the SNOBFIT algorithm as detailed in section 4.2.3.

Selective *N*-monomethylation is traditionally a challenging reaction, but a number of systems capable of high yielding, and highly selective transformations between aniline and either methanol or DMC, have been reported. Especially with methanol, several examples of the selective *N*-monomethylation of aniline have been described; affording up to 98 % yields of **4.2**.^{194, 196, 203-207, 209-211} Also with DMC, a few examples of this selectivity have been presented previously, some of which are only highly selective at low aniline conversions, which is also the case in the current study.^{180, 199-201, 212-216} This result is believed to be linked with the slightly increased nucleophilic nature of **4.2** compared to **4.1** and hence the formation of **4.3** might be favoured once **4.2** has been formed, especially with high conversion of **4.1**.

The advantage of the system discussed here over previously studied ones, is that the same catalyst (and solvents) can be used to produce different products by controlling the reaction conditions; hence *N,N*-dimethyl aniline (**4.3**) was also synthesised selectively. The progress for the SMSIM optimisation for **4.3** can be seen in Figure 4.2.

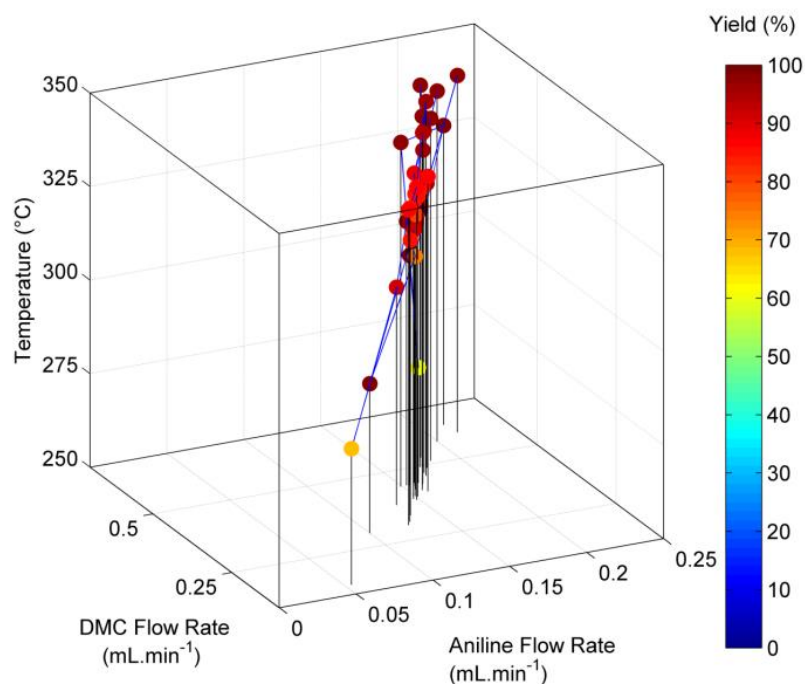


Figure 4.2. The SMSIM optimisation for product **4.3**, which is formed in reactions between DMC and aniline. The colour of the dots represent the yields of the reaction at different conditions. It can be seen that high yields were obtained at several different conditions (dark red dots), and the optimal range was 340-350 °C, 0.14-0.2 ml/min **4.1**, 0.4-0.6 ml/min DMC (DMC/**4.1** ratio >2.5). Conditions: 150-350 °C, 0.1-2 ml/min (**4.1** and DMC 0.275 M in toluene), 100 bar, 1 ml/min CO₂.

High yields (>97 %, 100 % conversion) of **4.3** were reached at a number of different conditions. The optimal temperature turned out to be very similar to the one found for **4.2** (340-350 °C). This observation can be explained by taking a closer look at the results: as DMC and aniline were used at the same concentration, comparing the flow rates is also a comparison of the molar amounts of the reagents. For the monomethylation experiments the optimal DMC to aniline ratio at temperatures above 300 °C was between 2.0-2.5:1 (DMC:**4.1**), and for product **4.3** between 2.5-3.3:1 (DMC:**4.1**). This result is in agreement with previous research, where increasing the amount of the methylating agent has been shown to result in an increase in the selectivity for

4.3.^{182, 194, 196, 198-200} Also, when DMC was used in large excess, the selectivity of the *N*-methylation reaction was, quite expectedly, determined by the temperature, as above 245 °C **4.2** was not observed. These results show, how by slightly adjusting one parameter (e.g. the flow rate), the selectivity of the reaction can be altered.

During the methylation experiments, it was noticed that the catalyst activity seemed to change over time. To examine the deactivation of γ -alumina, the reaction was carried out at set conditions for 18 h (Figure 4.3). During this experiment, aniline was pumped as a 4 M solution in toluene and DMC was pumped separately (0.3 and 0.4 ml/min respectively). The reason for this change in concentration was that the ultimate aim was to follow the reaction with FT-IR, which required a higher concentration of **4.1**, to assure that the aniline related stretches would be detectable in the measured spectra.

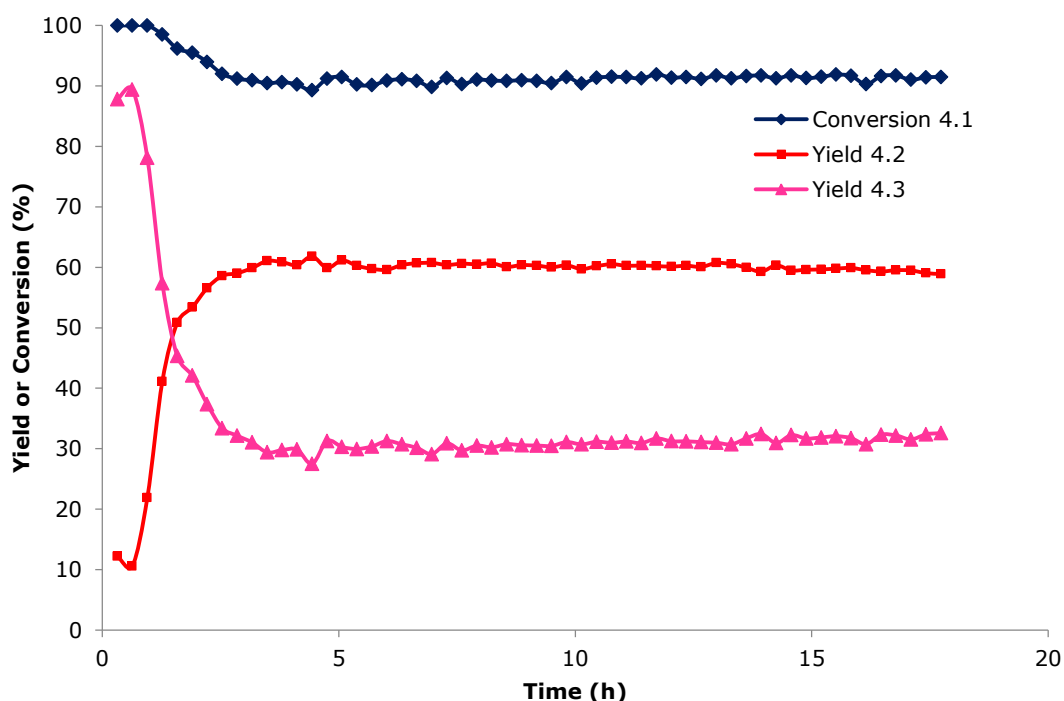


Figure 4.3. Experiment showing the deactivation of the γ -alumina catalyst. After approximately 2 h the catalyst becomes stable. Reaction conditions: 320 °C, 0.3 ml/min **4.1** (4 M solution in toluene, 1.2 mmol/ml), 0.4 ml/min DMC (pure, 4.8 mmol/ml), 1 ml/min CO₂ and 100 bar.

The results in Figure 4.3 show that there is a clear deactivation period, as the main product is switched from **4.3** to **4.2** after 2 h of reaction. However, after this initial deactivation the catalyst seems stable. The activity is thought to change, as aniline or one of the formed products adsorbs on the surface of the catalyst, and possibly changes the active sites on the surface. Similar behaviour was reported by Horváth *et al.*²¹⁷ who studied the oxidation of cyclohexylamine over γ -alumina, and found that some of the formed products accumulated on the surface of the catalyst hence changing its activity.

In the current study with aniline, the catalyst was observed to change colour during the experiments (from white to brown or even black), which also indicated a change was taking place. Further studies into this deactivation were not carried out, but due to this switch in activity, all the other optimisations (with pure DMC and THF) were started after a deactivation period of 1-2 h, during which the reagents flowed over the catalyst with constant flow rates at 250 °C, to ensure the catalyst had reached stable activity.

The next step in this research was to study the formation of *N*-methylphenyl carbamate (**4.4**) and diphenyl urea (**4.5**) starting from aniline and DMC. The benefit of using DMC is highlighted, when it is used as a carbonylation reagent, as it has the potential of replacing phosgene, which is traditionally used to form these compounds, even though it is highly toxic.¹⁷⁶ However, some difficulties were encountered, when trying to make **4.5**, but also **4.4**, as both of these molecules are solids at room temperature, which could lead to potential blockages in the system. Due to this problem, **4.5** was never the target of an optimisation, and it was identified as it crystallised out of the reaction mixtures after other optimisations. While the *N*-methylation of aniline with either MeOH or DMC as the methylating agent is well-studied in continuous flow systems (usually gas-phase), the carbamates from aniline and DMC are mainly produced

in batch processes.^{183-189, 191, 192, 218-223} This fact is partially explained by the realisation that to obtain high selectivity for **4.4**, longer reaction times at lower temperatures are required. Another reason, which favours batch processes are the above mentioned insolubility issues. The target transformation has been achieved previously with a variety of different catalysts, both homogeneous and heterogeneous. Recent studies have focused on different Zn-catalysts, which have been shown to be highly active in this reaction.^{189, 190, 192, 220, 222, 223} One of these (basic ZnCO₃) was utilised in continuous flow by Grego *et al.*¹⁹⁰ The catalyst was shown to be active for over 180 h, and high yields of **4.4** were obtained (90-99 % conversion, 88-96 % selectivity for **4.4**). Iron based catalysts have also been employed in continuous flow to produce carbamates from different amines, however this system suffered from very low conversions when aniline was used as the substrate.²²⁴

In addition to the low solubility of carbamate **4.4**, another potential challenge with the carbonylation of aniline in scCO₂, is the possible decomposition of DMC. This behaviour of DMC, was observed also during the work outlined in Chapter 3, where it was found that DMC decomposed over the γ -alumina catalyst to produce methanol and dimethyl ether, as reported previously.^{170, 177} In the current study, it was found that DMC was fully decomposed at temperatures above 200 °C, independent of the flow rate (max 2 ml/min), or whether it was pure or in a solution. Due to this reactivity, it is unlikely that products related to the carbonate (e.g. **4.4**) will be produced at higher temperatures, as little to no DMC will be present.

To maximise the possibility of making **4.4**, and to avoid the insolubility problems, pure DMC was used instead of a solution of it in toluene. It was believed that the formed product would be more soluble in DMC (or if DMC was decomposed; in MeOH). Aniline was still delivered as a 0.275 M solution in

toluene, due to the inert nature of this solvent. In Figure 4.4 and Figure 4.5, the variation of the conditions, and the results of the optimisation can be seen. The selectivity for **4.4** was mainly between 50-60 % (Figure 4.5), under all the studied conditions. The other product that was produced, during the experiment, was **4.2**, which suggests that the methylation of aniline was competing with the carbonylation.

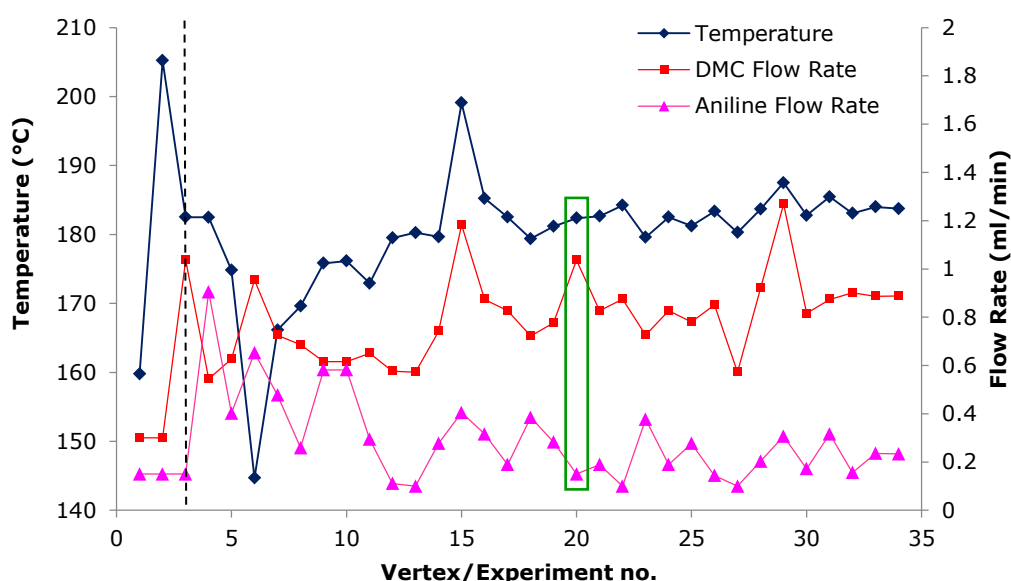


Figure 4.4. The variation in reaction conditions during the optimisation for **4.4**. Each horizontal set of 3 points represent the conditions of one experiment during the optimisation (e.g. vertex 5, indicated by the dotted line, at 182.5 °C, 1.036 ml/min DMC and 0.15 ml/min aniline); the green box highlights the optimal conditions. The optimal temperature was 180-185 °C, as the majority of the measurements were carried out between these temperatures. This might be because, it represents a compromise region, where the catalyst was active enough to form **4.4**, but not too active for DMC to be entirely decomposed. The optimisation was stopped after the 34th vertex. Conditions: 150-300 °C, 0.1-2 ml/min (0.275 M **4.1** in toluene, pure DMC), 200 bar, 1 ml/min CO₂.

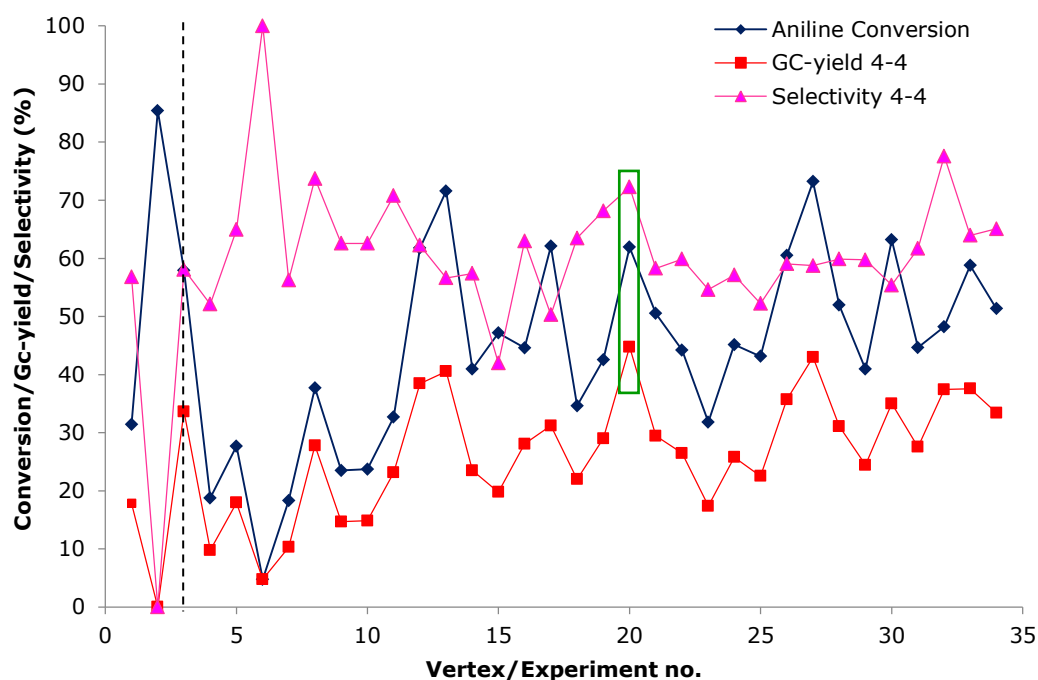


Figure 4.5. The results of the optimisation for 4.4. Each horizontal set of points represent the conversion of 4.1, and the yield and selectivity for 4.4 after one experiment during the optimisation (e.g. Vertex 5: 58 % conversion, 58 % selectivity and 34 % GC-yield). The optimal point is indicated by the green box: the highest yield was nearly 45 %, which was achieved with approximately 60-70 % conversion. *N*-methylation of 4.1 forming 4.2 was the second reaction taking place, decreasing the selectivity for 4.4.

Figure 4.4 shows that the temperature did not change significantly during the optimisation, and that 180-185 °C seemed to be the optimal temperature in terms of the yield of carbamate **4.4** and the degree of DMC decomposition. At this temperature, the catalyst was active enough to achieve the formation of **4.4**, but not too active for DMC to be fully decomposed (over 50 % of the DMC remained in the mixture at this temperature). The optimisation was stopped after 34 measurements, and the optimal conditions were found to be: 0.15 ml/min aniline (0.275 M), 1.0 ml/min DMC at 183 °C (1 ml/min CO₂, 200 bar). This point gave a 61 % conversion of aniline, with 72 % selectivity for **4.4**.

In Figure 4.6 the identities of some of the GC peaks for the reaction mixture formed in reactions between aniline, DMC and THF are shown (compare with Figure 4.1). It can be seen that several of the occurring transformations are not formed in reactions between just DMC and aniline (yielding compounds **4.1-4.5**) and hence also THF is participating in the reactions as is discussed in the next section.

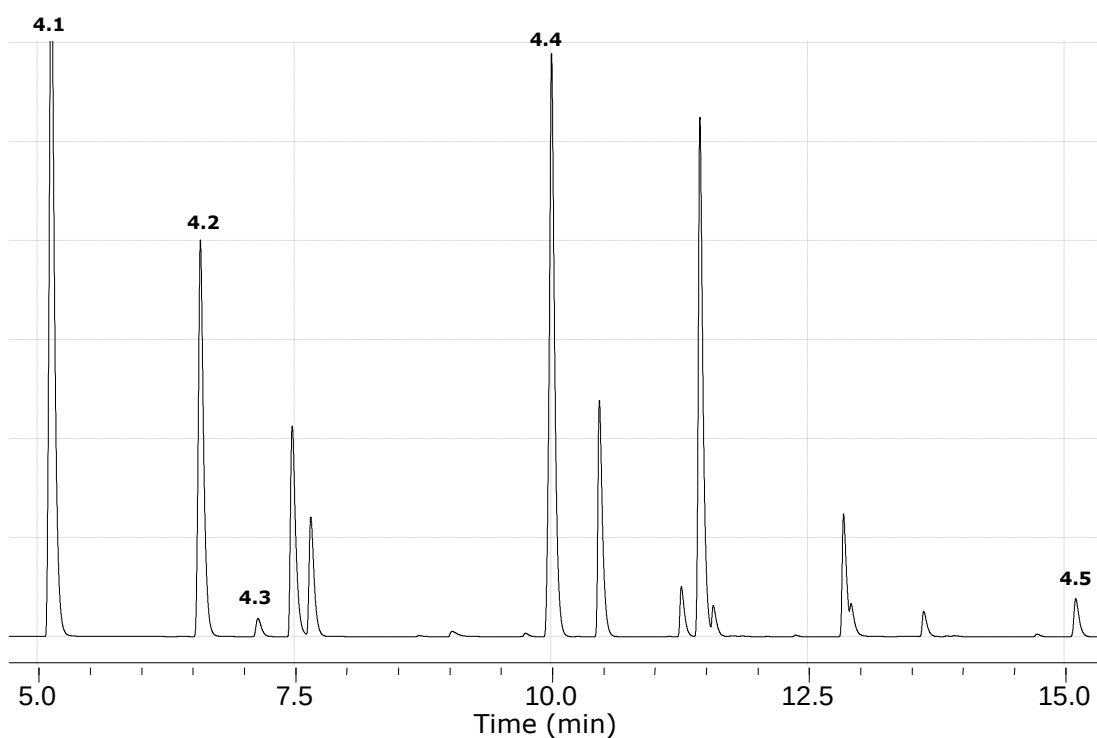
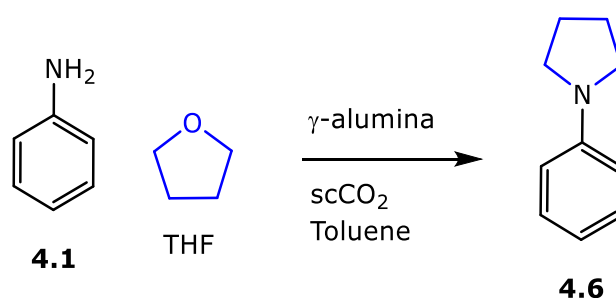


Figure 4.6. The GC for the mixture formed in the reactions between aniline, THF and DMC as also shown in Figure 4.1. The peaks obtained when aniline is allowed to react with DMC (compounds **4.1-4.5**) are identified. However, still several peaks originating from unknown compounds are present, suggesting reactions occurring between all three of these compounds.

4.2.2 Reactions between Aniline, THF and DMC

In addition to *N*-methylation and carbonylation, the production of *N*-phenyl pyrrolidine (**4.6**), formed in the simple alkylation of aniline by THF (Scheme 4.2), was found to be one of the reactions occurring in the mixture of aniline, THF and DMC (peak at approx. 11 min in Figure 4.6). This reaction route to form **4.6** was first proposed in 1937,²²⁵ but has received quite little attention since. Hargis and Shubkin²²⁶ studied the reaction in flow, and recently the reaction between several different aniline and THF derivatives were carried out with AlMe₃ in toluene.²²⁷ When aniline was reacted with THF, pyrrolidine was obtained in 72 % yield. The reaction between sterically hindered anilines and THF over γ -alumina has also been studied before in the gas phase.²²⁸



Scheme 4.2. Reaction between **4.1** and THF making pyrrolidine **4.6** over γ -alumina in scCO₂. This reaction was initially studied by Dr R. Skilton.

The optimisation for **4.6** was carried out by Dr R. Skilton (0.275 M solutions in toluene of both reagents), locating a high yielding optimal region (100 % conversion, >99 % selectivity, 260-290 °C, 0.05-0.25 ml/min aniline, 0.2-0.4 ml/min THF, 100-120 bar, 1.0-1.2 ml/min CO₂).¹⁷¹

As this reaction seemed to be highly favourable within the system, it was used to test the strength of the self-optimising reactor by carrying out the optimisation for **4.6** in the presence of DMC (DMC and THF pure, aniline 0.275 M in toluene).

The aim of this experiment was to see, if high yields of the pyrrolidine **4.6** could be obtained also in the presence of a second alkylating agent; DMC, and if the DMC flow rate would be minimised in order to maximise the yield of **4.6**. The competing reactions in this case were the *N*-methylations of aniline as well as other alkylation reactions described later in this section. The power of the system was shown, as the algorithm decreased the DMC/THF ratio to increase the yield of the product (Figure 4.7). Unfortunately, the minimum DMC flow rate was set to 0.2 ml/min (to avoid blockages), and hence there was a limit to how low the DMC/THF ratio could go. Had this not been the case, even higher yields (>80 %) than the ones obtained in the experiment shown in Figure 4.7, could probably have been achieved. This result suggests that the formation of **4.6** is highly favourable, as it was the major product even in the presence of DMC at all the conditions studied (Figure 4.7).

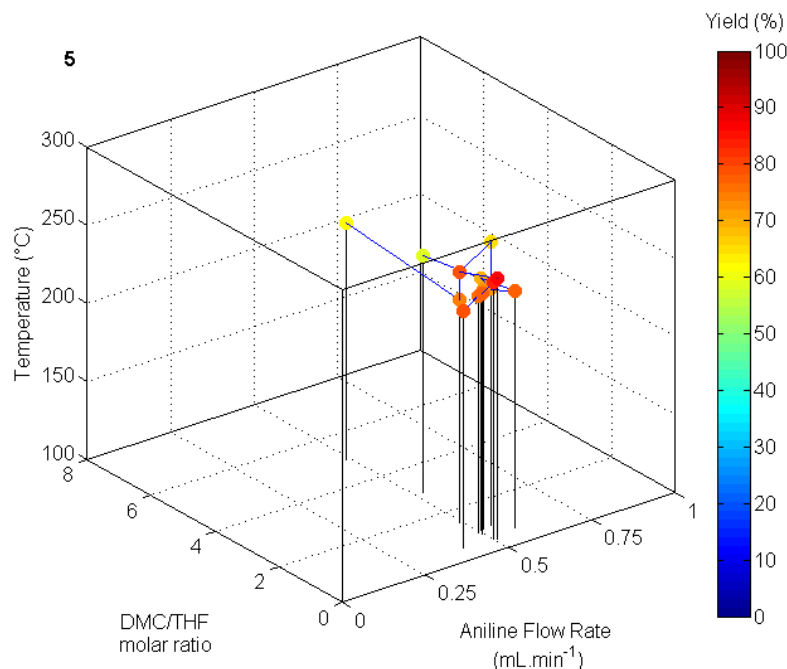
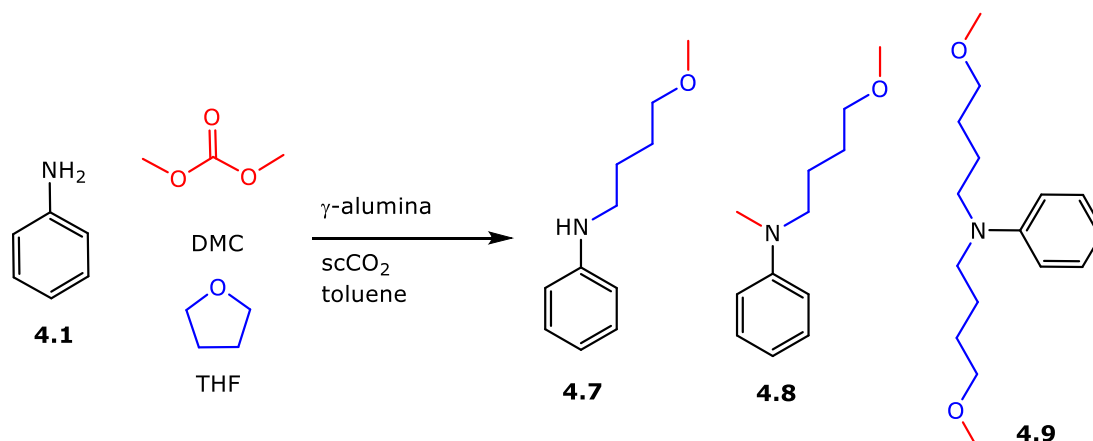


Figure 4.7. SMSIM optimisation for product 4.6 in the presence of DMC. The Figure shows how the algorithm diminished the DMC/THF molar ratio to increase the yield of the target. The experiment was stopped after 24 measurements. Conditions: 150-300 °C, 0.1-2 ml/min (0.275 M **4.1 in toluene, pure THF and DMC), 200 bar, 1 ml/min CO₂.**

To gain further insight into which reactions were occurring in the three component reaction between aniline, THF and DMC, some of the unknown peaks in the GC shown in Figure 4.6 were targeted separately by the optimisation in order to increase the yields and selectivities for these molecules. As a result products **4.7-4.9** (Scheme 4.3) were identified.



Scheme 4.3. Reactions between aniline, DMC and THF forming products 4.7-4.9. Product 4.7 was introduced in Dr Skilton's thesis,¹⁷¹ but products 4.8 and 4.9 have not been reported before. Also products 4.2-4.6 can be formed in these reactions but are omitted for clarity.

These types of 4-*N*-arylamino-1-butanols have only been presented twice in the literature: 4-(phenylamino)-butan-1-ol has been produced by the reduction of *N*-phenyl lactones with Li-aminoborohydrides ($\text{LiH}_3\text{BNR}'_2$) in THF,²²⁹ and more recently by the hydrogenation reaction between peroxidic THF and aniline over a Pd/C catalyst.²³⁰ This particular product was not obtained in the current system, but instead, among other things, its methylated derivatives were. None of products **4.7-4.9** have been reported previously (product **4.7** is described in Dr R. Skilton's Thesis¹⁷¹).

In the previous work carried out by Dr Skilton, the discovery of **4.7** was achieved.¹⁷¹ Product **4.7** was produced in 37 % yields, but with a very low flow rate of aniline, hence leading to low throughput of the product. The optimal

conditions that were located were: 229 °C, 1 ml/min CO₂, 100 bar, 0.011 ml/min aniline, 0.204 ml/min THF and 0.739 ml/min DMC. During this experiment all the reagents were fed into the system as 0.275 M solutions in toluene.

In order to increase the throughput of **4.7**, a new optimisation was carried out; this time with pure DMC and THF, to maximise the probability of the *N*-alkylation of aniline and hence the formation of product **4.7**. The conditions for the starting simplex and the optimal point achieved during this optimisation are shown in Table 4.2. Also the selectivities for the main side products formed under these conditions are listed.

Table 4.2. The starting vertices for SMSIM optimisation for product 4.7 and the resulting optimal point.^a

Vertex	T (°C)	DMC (ml/min)	THF (ml/min)	4.1 (ml/min)	Conv. ^b (%)	4.7	Sel. ^c (%)			
							4.2	4.4	4.6	
1	203	0.38	0.61	0.195	89	20	29	5.4	39	
2	210	0.38	0.61	0.195	95	21	23	0	50	
3	190	0.8	0.61	0.195	49	33	32	35	0	
4	190	0.52	0.61	0.64	27	19	31	39	11	
5	190	0.52	0.94	0.31	49	32	18	29	19	
30-41	205	0.48	0.6	0.12	~85	25-30	35	0	30-35	

a) Conditions: 0.05-2 ml/min (**4-1** 0.275 M solutions in toluene, DMC and THF pure), 150-300 °C, 1 ml/min CO₂, 200 bar; b) Conversion of **4.1**; c) Based on GC analysis of the reaction mixture.

A detailed figure on the progress and results of this optimisation can be found in section 4.4 (Chapter Appendix). The highest yield, in the optimisation for **4.7** was approximately 25 %, which was achieved at aniline flow rates of 0.1-0.15 ml/min (0.275 M in toluene). Hence, the throughput at these conditions was 6 to 9 times higher than the previously reported, and therefore it was decided that pure THF and DMC would be used also, when trying to increase the yields of **4.8** and **4.9**. This selection aimed to increase the concentration of the alkylating agents (both THF and DMC), and hence the probability of an alkylation occurring. When all the reagents were present as 0.275 M solutions, the main part of the reaction volume was made up of the co-solvent hence decreasing the opportunity for intermolecular reactions (e.g. alkylations). In addition, the only

way to change the reaction stoichiometry, in this case, was by increasing the flow rate, but the resulting concentrations were still very low, which made the consecutive alkylations required to synthesise **4.7-4.9** relatively unlikely. Also, in this case when the flow rates increased, the residence time decreased possibly limiting the formation of **4.7-4.9**. In hindsight, it might have been worth studying different molarities of DMC and THF in order to increase the production of products **4.7-4.9**.

When maximising the yield of **4.8** was targeted by the optimisation, full conversion of aniline was observed at all the studied conditions, as the temperature was constantly above 220 °C, and the aniline flow rate did not exceed 0.4 ml/min. Yields of up to 25 % of **4.8** were found, but mainly 15-20 % yields were observed (Table 4.3, see also section 4.4 for more information).

Table 4.3. The starting vertices for SMSIM optimisation for product 4.8 and the resulting optimal point.^a In addition the optimal point for 4.9 is shown.

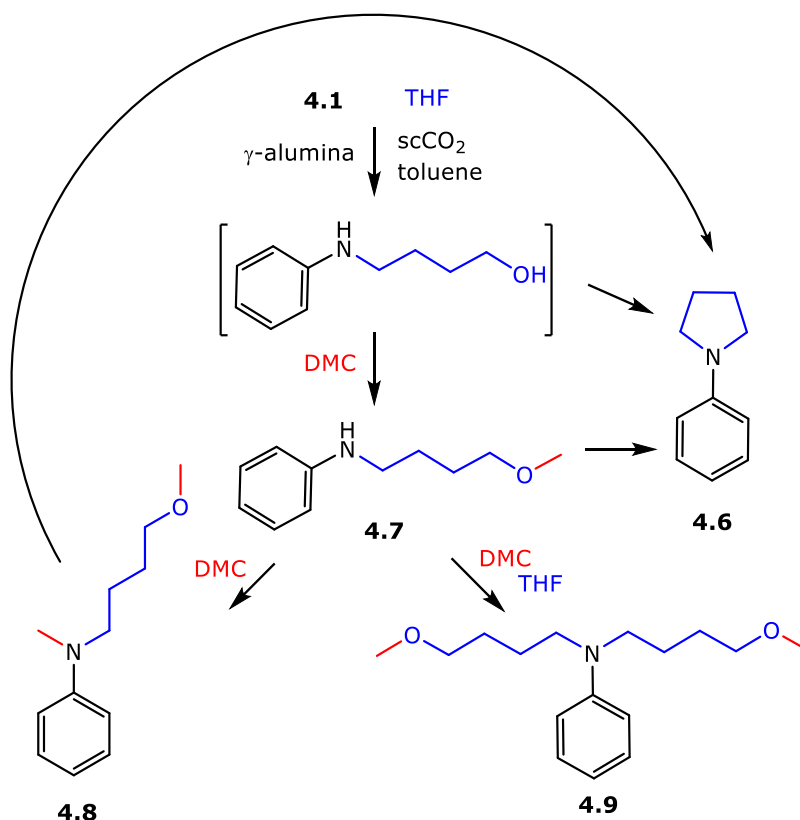
Vertex	T (°C)	DMC (ml/min)	THF (ml/min)	4.1 (ml/min)	Conv. ^b (%)	Sel. ^c (%)				
						4.8	4.2	4.3	4.6	4.9
1	225	0.3	0.2	0.2	100	16	10	15	56	0
2	248	0.3	0.2	0.2	100	11	14	14	58	2
3	236	0.74	0.2	0.2	100	12	17	11	58	1
4	236	0.45	0.2	0.64	100	16	7	10	62	2
5	236	0.45	0.63	0.31	100	26	0	11	49	6
28	233	0.51	0.42	0.14	100	25	0	11	52	5
Opt-4.9 ^d	196	1.05	0.46	0.16	72	0	16	0	15	8

a) Conditions: 0.05-2 ml/min (**4-1** 0.275 M solutions in toluene, DMC and THF pure), 150-300 °C, 1 ml/min CO₂, 200 bar; b) Conversion of **4.1**; c) Based on GC analysis of the reaction mixture.

d) In this case also 17 % of **4.7** and 22 % of **4.4** were observed.

As mentioned above, pure THF and DMC were used in the optimisations for **4.7** and **4.8**. Unsurprisingly, this choice led to increased selectivity for the pyrrolidine **4.6** and also *N,N*-dimethyl aniline **4.3**, as both alkylating agents were present in huge excess (50-100 times more DMC and THF compared to aniline). In the case of both **4.7** and **4.8**, the molecules can possibly be considered as methylated intermediates when forming pyrrolidine **4.6** (Scheme 4.4). This is because, as was explained in the paper published on the basis of this work:¹⁶⁴ the formation

of **4.7-4.9** can be rationalised by an unusual sequence of nucleophilic substitutions (Scheme 4.4). The intermediate, obtained from the first alkylation of THF, is inclined to both *N*- and *O*-methylation to produce **4.7** or **4.8**. The isolation of **4.7** suggests that *O*-alkylation is kinetically favoured. In addition, **4.7** can react with an additional molecule of THF to produce **4.9**. All of these reactions are likely to be nearly simultaneous and they take place under similar conditions. The main limitation in achieving higher selectivity for **4.7-4.9** is the fact that ring closure is always predominant and pyrrolidine **4.6** is obtained as a major product. Alkylation is also in competition with the methylation and carbamoylation processes and **4.2**, **4.3** and **4.4** are observed as well.



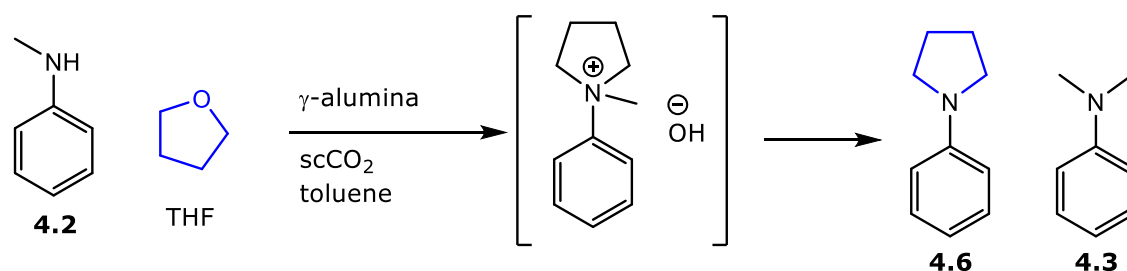
Scheme 4.4. The reaction sequences taking place within the aniline (**4.1**), DMC and THF system for the production of **4.7-4.9**. **4.7** has been shown to form **4.6**,¹⁶⁴ and in addition **4.6** can possibly also be formed from **4.8**, but this was not confirmed.

The competing reactions are listed in Table 4.2 and Table 4.3, and for product **4.8** the optimum conditions are in regions that are high yielding in pyrrolidine **4.6**, but also **4.3** is formed (230-240 °C). Product **4.7** is produced at slightly lower temperatures (180-200 °C) with 20-30 % selectivities. In this region, the main competing reactions include *N*-monomethylation and carbamylation of aniline, but also the pyrrolidine formation.

When **4.9** was targeted with the optimisation, very low yields were achieved (<10 %, Table 4.3), which can be explained by the fact that it is formed in a sequence of intermolecular reactions, whereas for instance the formation of **4.6** only requires one intermolecular reaction before the intramolecular ring-closure, which may well be a faster reaction step. Therefore the formation of **4.9** is disfavoured in comparison to e.g. the *N,N*-dimethylation, or the reaction forming pyrrolidine **4.6**.

After these results, attempts were made to selectively produce the ring-opened products (**4.7-4.9**), by using *N*-monomethyl aniline (**4.2**) as the starting material together with THF. It was thought that this reaction would produce 4-(methyl-(phenyl)-amino)-butan-1-ol (Scheme 4.5) that could then react further with DMC to yield compound **4.8**. The expected product was not formed, but instead demethylation of **4.2** forming pyrrolidine **4.6** together with methanol took place under the studied conditions (Scheme 4.5). The formed methanol could then react with **4.2** to produce **4.3**. In addition, small amounts of compound **4.8** were observed in this reaction, which probably resulted from the methylation of an intermediate alcohol, before the demethylating ring closure took place forming **4.6**. This result was unexpected, but not surprising, as undried reagents that had been stored under air were used, and hence water and oxygen could have been present in the system. The observation also offers insight into why products **4.7-4.9** are difficult to synthesise, as they might, once

formed, react further by the demethylation path to form mainly **4.6**, but also **4.3** as a side product. However, a reaction where either H₂O or O₂ was removed (or deliberately added) was not carried out.



Scheme 4.5. When monomethyl aniline **4.2** was allowed to react with THF, demethylation occurred forming **4.6** and MeOH, which could then give **4.3** in reactions with **4.2**. Reproduced from reference 164.

In addition to the competing reactions limiting the formation of products **4.7-4.9**, also some problems linked to the GC-analysis were noticed, as during some of the optimisations, not very representative results were obtained. Moreover the lack of response factors might have exacerbated the low yields and difficulty of targeting all these products. This challenging analysis was possibly also linked to sampling issues, which might have been caused by the presence of different phases in the sample loop, when the sample was taken, and therefore not enough of the reaction mixture was injected to the column. Nevertheless, the values obtained during optimisations were comparable, and suggested that the yield for each product was improved by the optimisation, but as was mentioned in Chapter 2, the results obtained in this Thesis are mainly semi-quantitative, and the reported yields might differ slightly from the real values.

Figure 4.8 shows all the assignments for the molecules that have been identified to be formed in the reaction between aniline, DMC and THF over γ -alumina in scCO_2 (and toluene). It has been shown that by separately targeting each of

these products (**4.2-4.9**) the selectivity can be increased, thus showing that even by small changes in the conditions the selectivity of the reaction can be altered.

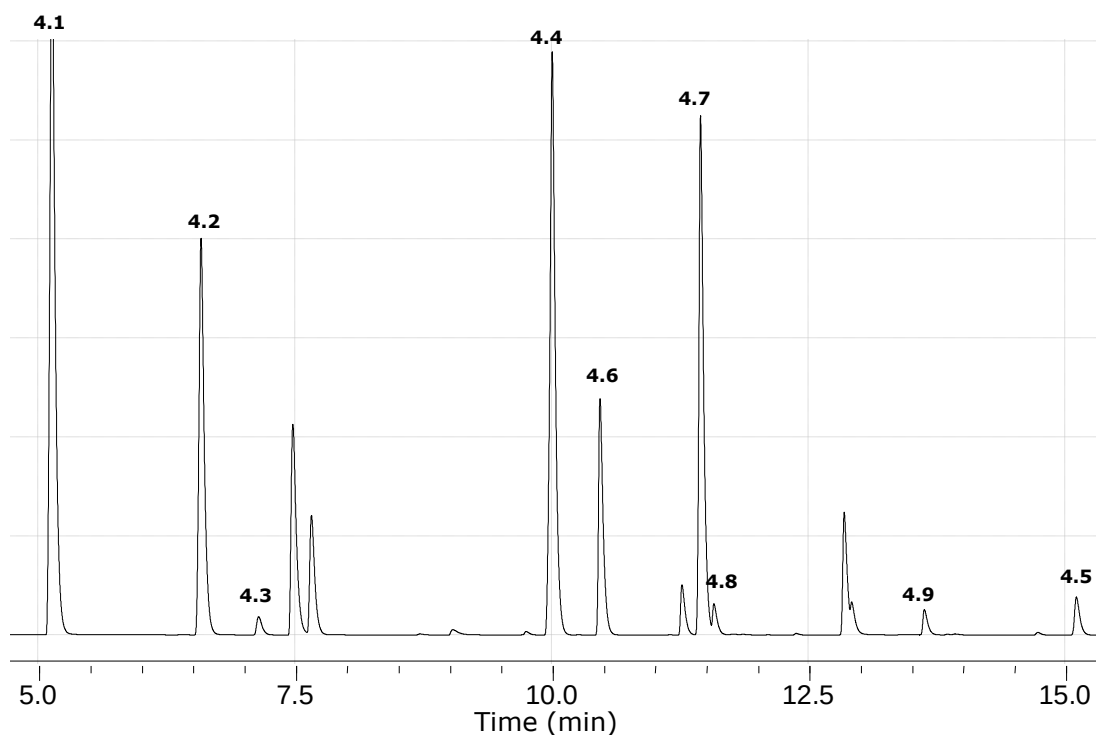


Figure 4.8. A chromatogram showing the assignments for some of the products that can be synthesised in the relatively complicated series of reactions taking place between aniline, THF and DMC. Most of these molecules were used as targets in optimisations in order to increase their yield and selectivity. The peaks at 7.68 min and 11.28 min are believed to originate from reactions between THF and DMC. The peak at 12.6-12.7 min might be another carbonate product. The key on page 253 can help to remind the reader which structures are shown.

In the optimisations for both **4.7** and **4.8**, the conditions did not vary significantly during the experiment, as the starting 5 vertices gave similar results, and did not allow for the SMSIM-algorithm to change the conditions in a meaningful manner. This observation was especially highlighted in the optimisation for **4.8**, which was carried out for nearly 90 experiments, but in the

end only very small variations in the conditions occurred (see section 4.4). This behaviour is due to the nature of the SMSIM-algorithm, where the contraction of the simplex can hinder a broad study of the parameter space. The results of these experiments motivated the development of the system to allow a global search algorithm (SNOBFIT) to be used together with GC-analysis. This change enabled a broader range of conditions to be studied during optimisations, and thus improved the opportunity for locating a global optimum within the studied limits (as described in Chapter 2).

4.2.3 Optimisations of Multicomponent Reactions Using the SNOBFIT Algorithm

Revisiting the Reactions between Aniline, THF and DMC

As was explained in the previous section, the problems encountered with the SMSIM algorithm lead to the development of the self-optimising software to allow the SNOBFIT algorithm to be used in conjunction with GC-analysis. Once this system had been developed it was tested for some of the reactions introduced previously in this Chapter: the formation of *N*-monomethyl aniline (**4.2**) from aniline (**4.1**) and DMC; and the synthesis of one of the previously unknown molecules, **4.7**, formed in the reaction between **4.1**, DMC and THF. It was of interest to see, if the yields of these targets could be increased by using a global search algorithm (SNOBFIT) instead of the previously used linear simplex method (SMSIM).

The highest yielding points for the first example (**4.2**) are shown in Table 4.4. The optimisation was carried out for 100 measurements before it was stopped. It can be seen that the SNOBIT algorithm located conditions under which the yield of **4.2** was above 70 %, which is the highest yield found for **4.2** so far.

Table 4.4. The highest yielding points located by the SNOBFIT algorithm for the synthesis of **4.2** starting from aniline and DMC.^a

Measurement no.	T (°C)	4.1 (ml/min)	DMC (ml/min)	DMC/ 4.1 mol-ratio	Yield ^b (%)	
					4.2	4.3
49	305	0.55	1.0	1.81	76	22
64	295	0.1	0.25	2.5	75	25
75	313	0.1	0.2	2.0	77	22
87	316	0.1	0.25	2.5	72	28
89	312	0.1	0.1	1.0	73	7
96	312	0.1	0.45	4.5	74	26
98	316	0.15	0.25	1.6	73	17
Opt-1 ^c	255	0.05	0.48	9.6	60	9
Opt-2 ^c	340-350	0.22	0.46	2.1	65	35

a) Conditions: 150-350 °C, 0.1-1.0 ml/min (**4.1** and DMC 0.275 M solutions in toluene), 1 ml/min CO₂, 100 bar, (nreq=6 and p=0.1); b) Yields determined according to GC-analysis, the only formed products at these conditions were **4.2** and **4.3**. c) The optimal results located by the SMSIM algorithm as shown in section 4.2.1.

The optimal temperature for **4.2** was approximately 305-315 °C, which was between the two optimums located previously by the SMSIM algorithm (Table 4.4). Interestingly at a 0.55 ml/min flow of **4.1** and 1.0 flow of DMC, a 76 % yield of *N*-monomethyl aniline was reached. This yield is around 10 % higher than the highest yield obtained by the SMSIM algorithm. The other high yielding points located by the SNOBFIT algorithm were achieved with a lower flow rate of aniline (0.1-0.15 ml/min) at slightly higher temperatures. These results suggest that there are several local optimums within the reaction space giving high yields under a number of different conditions. As the experiment described here was mainly carried out to test the software combining the SNOBFIT algorithm with GC analysis, this interesting aspect of the reactivity was not studied further.

The highest yielding points for the SNOBFIT optimisation of **4.7** are shown in Table 4.5. Also in this case the optimisation was allowed to run for 100 measurements. The SNOBFIT optimisation for **4.7** obtained quite different results compared to the SMSIM optimisation carried out in section 4.2.2. High flow rates of all the reagents were found to give the highest yield of **4.7**, verifying the intermediate nature of product **4.7**, as lower residence times gave higher yields. For the optimisation shown in Table 4.5, the highest flow rates

were set to 1.0 ml/min, but an even higher yield could possibly have been obtained with higher maximum flow rates. The optimal temperature was similar with both the SMSIM and SNOBFIT algorithms.

Table 4.5. The highest yielding points located by the SNOBFIT algorithm for the synthesis of **4.7 starting from aniline and DMC and THF.^a**

Measurement no.	T (°C)	4.1 (ml/min)	DMC (ml/min)	THF (ml/min)	Yield ^b (%)	Conv. ^b (%)	Sel. ^b (%)		
							4.7	4.2	4.6
47	217	1.0	0.7	1.0	21	78	27	25	35
49	196	0.4	0.45	0.4	21	70	30	33	28
64	219	1.0	0.85	1.0	23	79	29	26	32
75	199	0.1	0.15	0.65	21	100	21	0	58
87	219	1.0	0.75	1.0	21	82	25	28	36
89	211	0.6	0.6	1.0	27	100	27	20	33
96	200	0.55	0.35	1.0	27	100	27	19	36
Opt-SMSIM ^c	205	0.12	0.48	0.6	23	85	27	35	32

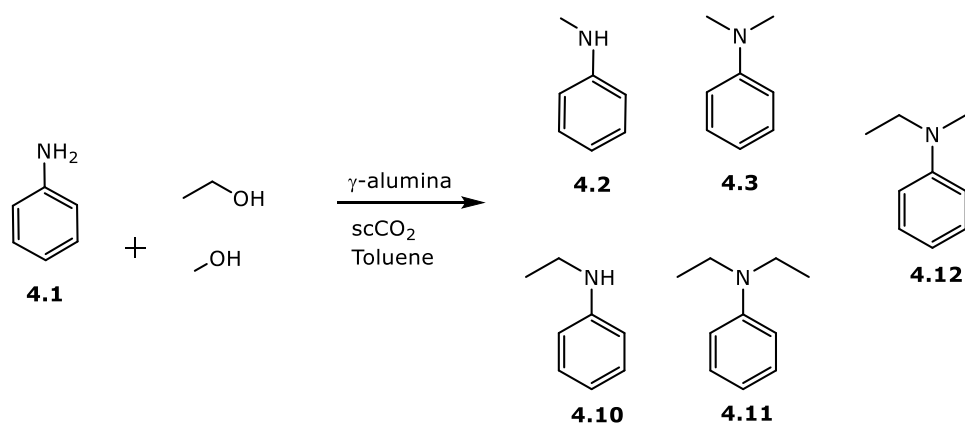
a) Conditions: 150-300 °C, 0.1-1.0 ml/min (**4.1** 0.275 M solution in toluene, THF and DMC pure), 1 ml/min CO₂, 200 bar, (nreq=6 and p=0.1); b) Determined according to GC-analysis, yield of **4.7**, conversion of **4.1**. The main side products are shown, even though others were also formed. c) The optimal results located by the SMSIM algorithm as shown in section 4.2.2.

While, the results for both these SNOBFIT optimisations suggested that higher yields were obtained with this global algorithm, it needs to be noted that these optimisations were carried out with a different batch of the catalyst than the SMSIM optimisations. Even though preliminary experiments showed similar activity for both batches of catalyst, the SMSIM optimisations should be rerun with the new catalyst batch to be able to more reliably compare the results obtained by the two algorithms.

The advantage of the SNOBFIT algorithm is highlighted in both of the above examples (the optimisation for **4.2** and **4.7** respectively), as a broader view on the entire reaction space was gained. In both cases, high yielding previously unexplored parts of the variable space were located, suggesting SNOBFIT to be more suitable for the optimisations of the synthesis of intermediate products such as **4.2** and **4.7** than the SMSIM algorithm, which seems to work best when combined with well-known transformations.

Formation of *N*-methyl-*N*-ethyl Aniline from Aniline, Ethanol and Methanol

As producing unsymmetrical amines is an interesting transformation, and as one of the aims of this Thesis was to expand the self-optimisation chemistry, also the reactivity within another multicomponent system; this time between aniline, methanol and ethanol (Scheme 4.6) was investigated. The possible products in this case include *N*-monoalkylated anilines (**4.2** and **4.10**), as well as *N,N*-dimethyl or *N,N*-diethyl aniline (**4.3** and **4.11**). The target product in this study was *N*-methyl-*N*-ethyl aniline (**4.12**), and it was of interest to see, if by utilising the SNOBFIT algorithm with GC-analysis, it would be possible to increase the yield for **4.12**. This product has been reported before, but it has not previously been synthesised via the direct alkylation of aniline with ethanol and methanol.



Scheme 4.6. The reactions taking place when aniline (**4.1**) is allowed to react with methanol and/or ethanol forming products **4.2-4.3** and **4.10-4.12**.

First, the retention time for the target product was determined, which was achieved by allowing aniline to react separately with each alcohol, in order to identify products **4.2**, **4.3**, **4.10** and **4.11**. Then both ethanol and methanol were added simultaneously into the system, and a new peak was discovered (Figure 4.9), which was then targeted by the optimisation as shown in Figure 4.10 and Figure 4.11. The product was later confirmed to be **4.12** by NMR data (section 4.4 Chapter Appendix).

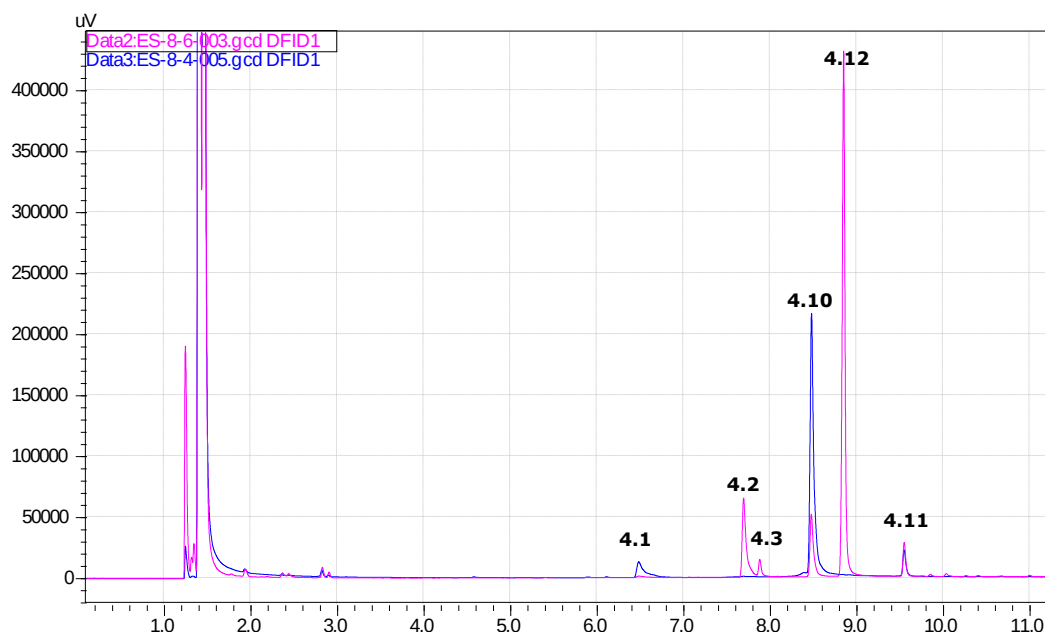


Figure 4.9. GC showing the different peaks for the products produced in reactions between aniline (**4.1**), MeOH and EtOH. The blue chromatogram was obtained, when aniline was allowed to react with EtOH forming mainly **4.10** but also **4.11** (overlap with pink). The pink chromatogram was obtained in a reaction starting from **4.2** when striving to selectively produce **4.12** in order to obtain a standard for it. However, it seems that in this case demethylation also took place as can be seen from the presence of the dialkylated products **4.3** and **4.11**. The key on page 253 can help to remind the reader which structures are shown.

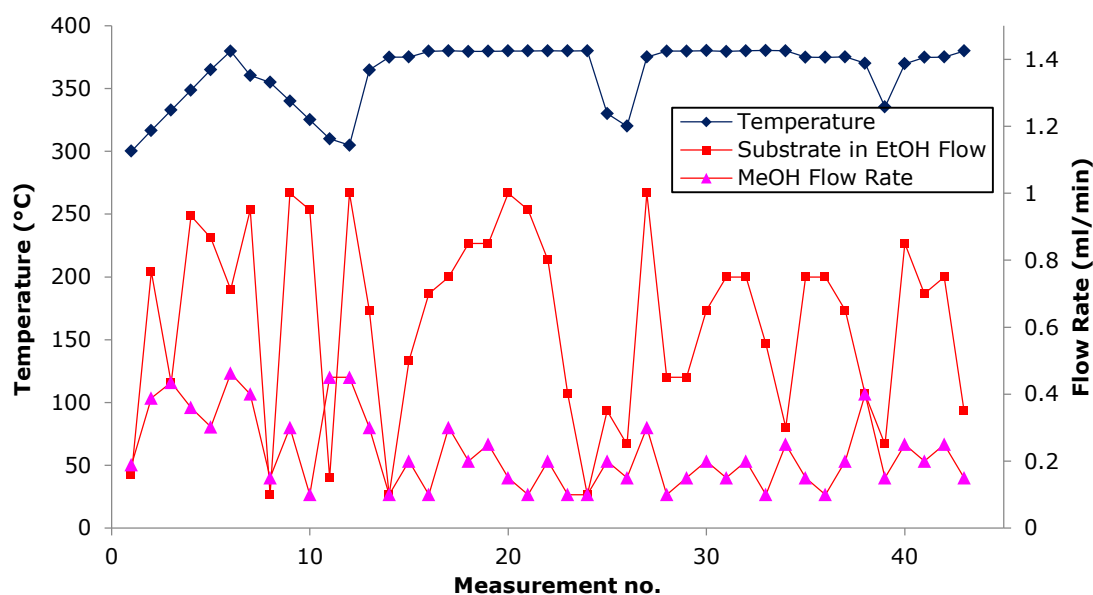


Figure 4.10. The progress of the SNOBFIT optimisation for 4.12 produced in reactions between aniline, methanol and ethanol (43 sets of conditions were studied). Aniline was pumped together with ethanol as a 0.5 M solution, and methanol was added separately. It can be seen that the SNOBFIT algorithm varies the conditions more than the SMSIM algorithm does, and hence a broader view of the parameter space is achieved. Conditions: 300–380 °C, 0.1–2 ml/min (0.5 M aniline in EtOH, pure MeOH), 100 bar, 0.5 ml/min CO₂.

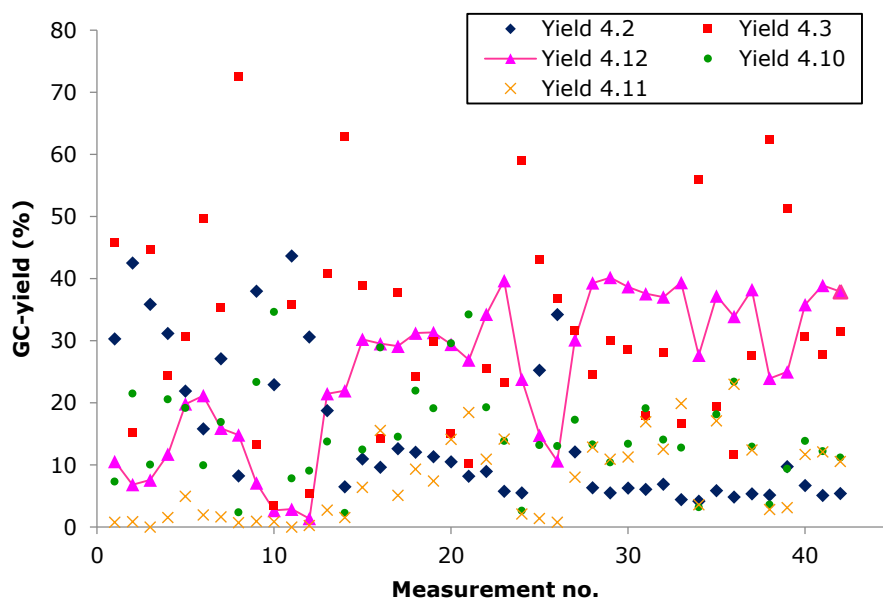


Figure 4.11. The results of the optimisation, the progress of which is shown in Figure 4.10 (4.12 in pink). Aniline was fully converted throughout the experiment. The yields of all the known products are shown, to illustrate the difference in selectivities at different conditions. The high yielding points of 4.12 are listed in Table 4.6 for convenience.

The highest yield of **4.12** was 40 %, which was reached at several different conditions. The temperature was 375-380 °C in the high yielding region. During the optimisation aniline was delivered as a 0.5 M solution in ethanol, and methanol was pumped in by a separate pump. This set-up meant that a huge excess of the alkylation agents compared to aniline were present, regardless of the flow rates. In addition, ethanol was mostly in excess compared to methanol (MeOH flow rate 0.1-0.2 ml/min, 2.5-4.9 mmol/min; EtOH flow rate 0.6-0.8 ml/min, 10-13.7 mmol/min). It is however not clear, which route for producing **4.12** is favourable; via *N*-monomethyl aniline (**4.2**) or *N*-monoethyl aniline (**4.10**).

From Table 4.6, it can be seen that **4.2** seems to be more reactive than **4.10**, as the yield for *N,N*-dimethyl aniline, **4.3**, is mostly significantly higher than the yield of **4.2**, whereas **4.10** is often in excess compared to the diethylated product, **4.11**. Hence, it could be possible that the ethylation of **4.2** is preferred over the methylation of **4.10**, when forming **4.12**.

Table 4.6. Comparison of some of the conditions measured during the SNOBFIT optimisation for 4.12 (Figures 10 and 11).^a The key on page 253 can help to remind the reader which structures are shown.

No. ^b	T (°C)	4.1 in EtOH (ml/min)	MeOH (ml/min)	EtOH/MeOH mol-ratio ^c	Yield ^d (%)					mmol/h of 4.12 ^e
					4.12	4.2	4.3	4.10	4.11	
8	355	0.1	0.15	0.46	15	8	72	2	0.7	0.45
20	380	1.0	0.15	4.6	29	11	15	30	14	8.7
21	380	0.95	0.1	6.5	27	8	10	34	18	7.7
29	380	0.45	0.15	2.1	40	5.5	30	10	11	5.4
33	380	0.55	0.1	3.8	39	4	17	13	20	6.4
36	375	0.75	0.1	5.2	34	5	12	23	23	7.7
37	375	0.65	0.2	2.2	38	5	28	13	12	7.4
38	370	0.4	0.4	0.69	24	5	62	4	2.8	2.9

a) Conditions: 300-380 °C, 0.1-1 ml/min (0.5 M aniline in EtOH, pure MeOH), 100 bar, 0.5 ml/min CO₂; b) measurement number in the optimisation; c) calculated based on pure EtOH; d) determined by GLC analysis; e) Throughput based on aniline flow (mol(aniline)*yield(**4.12**)*60min).

Similar behaviour has also been observed in the literature, where during the methylation of aniline with methanol, the second methylation (**4.2** → **4.3**) has been shown to be faster than the first methylation, due to a higher rate constant

and a lower activation energy of the second step.^{194, 195} However, it is possible that when **4.10** is formed, which is mainly at high flow rates, the residence time in the reactor is not long enough to allow the subsequent methylation, and hence **4.10** is the main product under such conditions (EtOH 0.95-1 ml/min). In addition, the throughput of the product is the highest at high ethanol flow rates, mainly because aniline was a solution in ethanol. An experiment, where all the components were pumped in separately (all reagents 0.5 M solutions in toluene) was carried out, but no improvement to the selectivity was gained, due to the favoured formation of the methylation products. Hence, the first system (aniline in EtOH, and pure MeOH) seems to be the best found so far for the production of **4.12** starting from aniline, EtOH and MeOH. However, studying the effect of the concentrations of the alkylating agents on the yield of **4.12** could perhaps help improve the yield further.

4.3. Chapter Conclusions

The reaction system between aniline, THF and DMC was studied. The reaction conditions for several of the products, including monomethyl aniline, dimethyl aniline, methyl phenyl carbamate, and three previously unknown molecules, were optimised with moderate to high yields using the SMSIM algorithm.

An issue encountered during these optimisations, especially for the more complicated transformations, was the lack of alteration in reaction conditions with the SMSIM algorithm. Therefore, the software was developed to use a global search algorithm together with GC-analysis, and this system was then shown to give similar or better results for some of the products. In addition, the system was employed also for the synthesis of *N*-methyl-*N*-ethyl aniline directly from aniline, ethanol and methanol. In this case, up to 40 % yields of the target were obtained.

4.4 Chapter Appendix

The evolution of the SMSIM optimisations for products **4.7** and **4.8** are shown in Figures SI-4.1-4.4, to demonstrate the limited variation of the reaction conditions offered by the SMSIM algorithm. In addition the characterisations of some of the products described in this Chapter are shown.

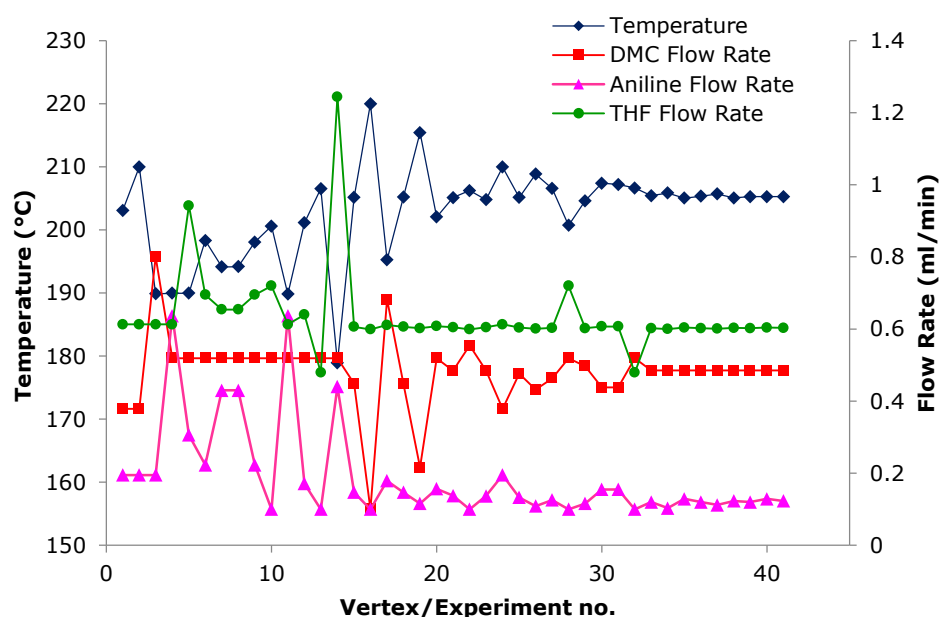


Figure SI-4.1. The variation in reaction conditions during the SMSIM optimisation for 4.7. The experiment was carried out under 42 sets of different conditions, and it can be seen that there is not a great amount of variation in the conditions during the experiment, and hence the yield did not improve greatly during the optimisation. Limits: 150-300 °C, 0.1-2 ml/min (0.275 M 4.1 in toluene, pure DMC and THF), 200 bar, 1 ml/min CO₂.

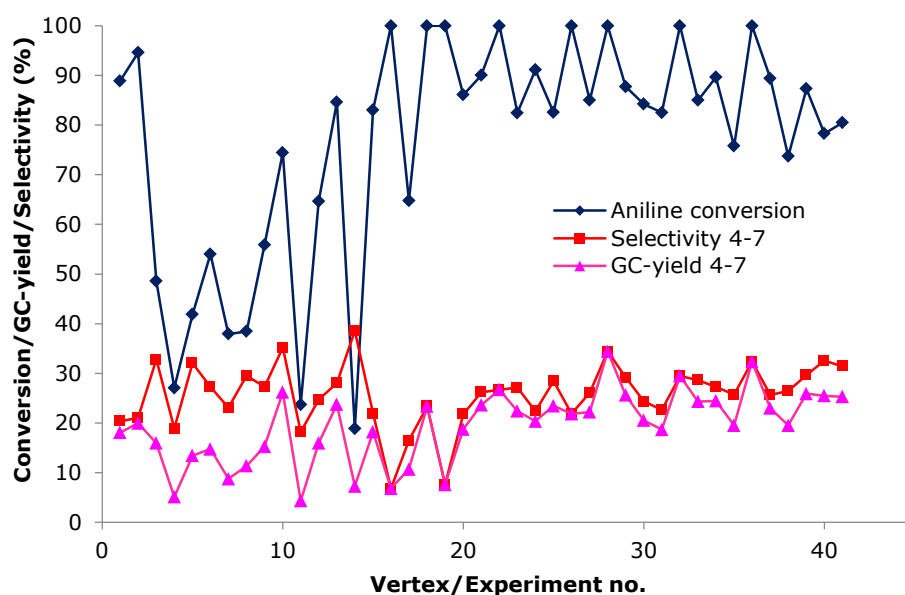


Figure SI-4.2. The changes in the aniline conversion, and the selectivity and yield of 4.7 during the SMSIM optimisation the conditions of which are shown in Figure SI-4.1 (42 sets of results). Due to only minor changes in the conditions, there is not a lot of variation in these values either. The highest yield and selectivity for 4.7 located by the SMSIM algorithm were 20-25 % and 25-30 % respectively.

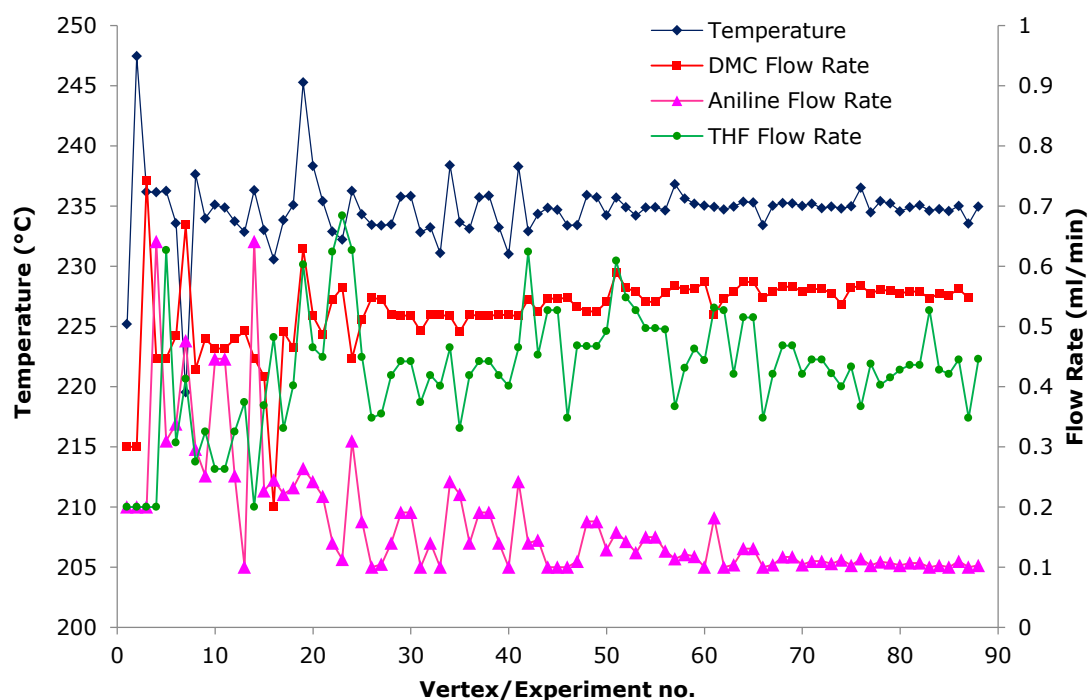


Figure SI-4.3. The variation in the conditions during the SMSIM optimisation for 4.8. The experiment was run for nearly 90 vertices (90 different measurements), and it can be seen that the conditions did not vary significantly during the experiment. Most of the studied conditions gave similar responses (15-25 % yield) as shown in Figure SI-4.4. Conditions: 150-300 °C, 0.1-2 ml/min (0.275 M 4.1 in toluene, pure DMC and THF), 200 bar, 1 ml/min CO₂.

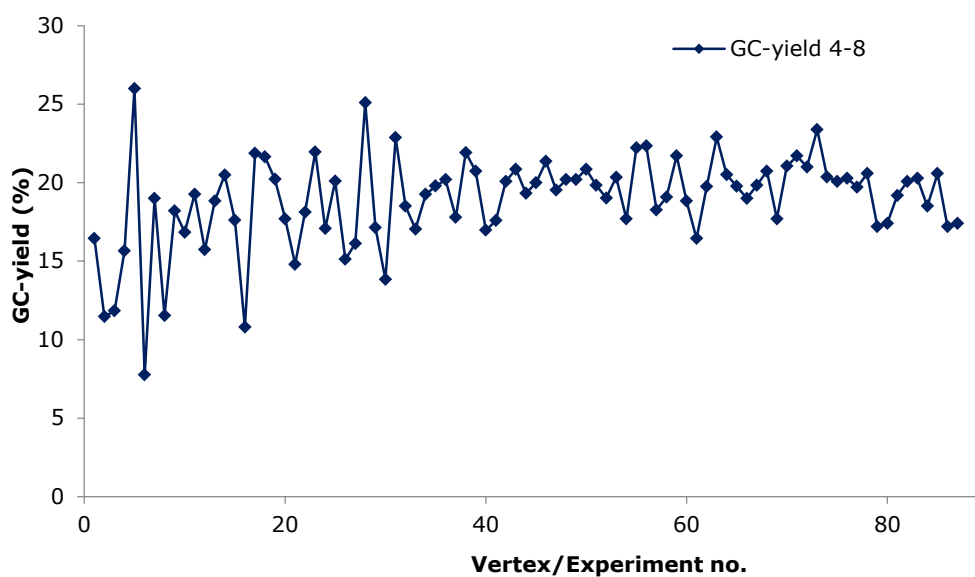
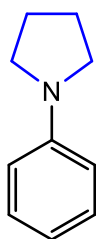


Figure SI-4.4. The GC-yields of 4.8 during the SMSIM optimisation (result of the nearly 90 different measurements). The conditions are represented in Figure SI-4.3, and as they did not change considerably, neither did the responses shown here. Full conversion of 4.1 was reached throughout the experiment, and the average yield of the target was 15-20 %.

Characterisation:

Molecules **4.6** and **4.7-4.9** were characterised in a recent publication based on the work presented in this Chapter:¹⁶⁴



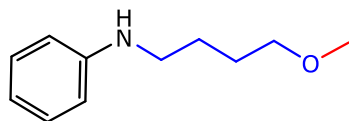
4.6:

¹H NMR (CDCl₃, 400MHz): δ 7.37 (2H_m, t, J= 7.0 Hz), 6.81 (1H_p, t, J= 6.9 Hz), 6.71 (2H_o, d, J= 7.8 Hz), 3.41 (4H, t, J= 5.5 Hz), 2.12 (4H, t, J= 5.5 Hz)

¹³C NMR (CDCl₃): δ 147.88 (C_{ar}), 129.00 (CH_{ar}), 115.27 (CH_{ar}), 111.55 (CH_{ar}), 47.44 (CH₂), 25.35 (CH₂)

HRMS calculated for C₁₀H₁₃N₁ ([M+H]⁺) 148.1121, found 148.1110

Chapter 4

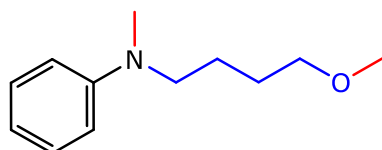


4.7:

^1H NMR (CDCl_3 , 400MHz): δ 7.19 (2H_m, m), 6.71 (1H_p, tt, J = 7.3, 1.0 Hz), 6.62 (2H_o, dd, J = 7.7, 1.0 Hz), 3.71 (br s, NH), 3.44 (2H, m), 3.37 (3H, s), 3.16 (2H, m), 1.71 (4H, m)

^{13}C NMR (CDCl_3): δ 148.38 (C_{ar}), 129.17 (CH_{ar}), 117.06 (CH_{ar}), 112.65 (CH_{ar}), 72.40 (CH₂), 58.55 (CH₃), 43.69 (CH₂), 27.24 (CH₂), 26.22 (CH₂)

HRMS calculated for C₁₁H₁₇NO ($[\text{M}+\text{H}]^+$), 180.1383, found 180.1385

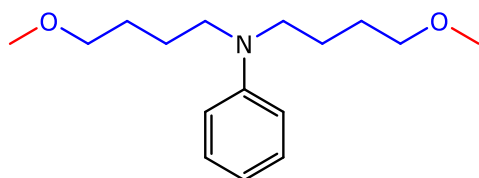


4.8:

^1H NMR (CDCl_3 , 400MHz): δ 7.25 (2H_m, m), 6.64-6.60 (3H, m), 3.42 (2H, t, J = 6.1 Hz), 3.36 (5H, m), 2.95 (3H, s), 1.66-1.64 (4H, m)

^{13}C NMR (CDCl_3): δ 149.28 (C_{ar}), 129.10 (CH_{ar}), 115.90 (CH_{ar}), 112.11 (CH_{ar}), 72.61 (CH₂), 58.56 (CH₃), 52.57 (CH₃), 38.25 (CH₂), 27.26 (CH₂), 23.48 (CH₂).

HRMS calculated for C₁₂H₂₀NO ($[\text{M}+\text{H}]^+$), 194.1539 found 194.1541



4.9:

^1H NMR (CDCl_3 , 400MHz): δ 7.20 (2H_m, m), 6.67-6.61 (3H, m), 3.43-3.41 (4H, t, J = 6.0 Hz), 3.35 (6H, s), 3.30-3.27 (4H, t, J = 7.1 Hz), 1.70-1.62 (8H, m)

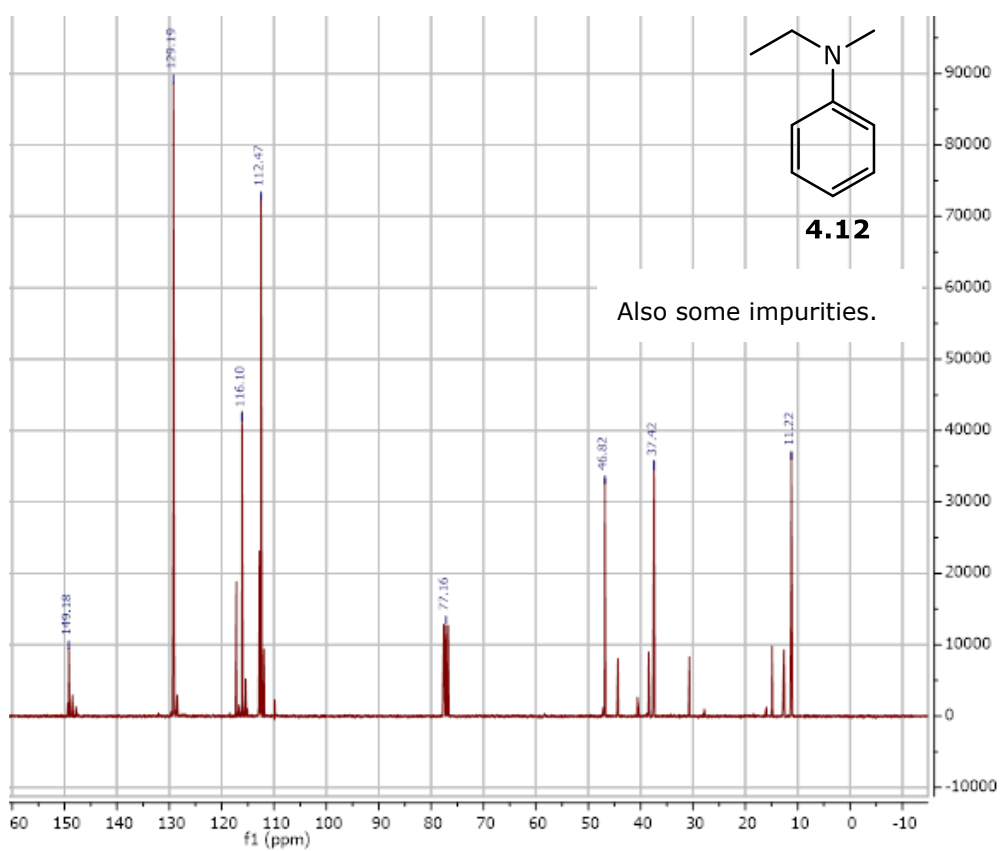
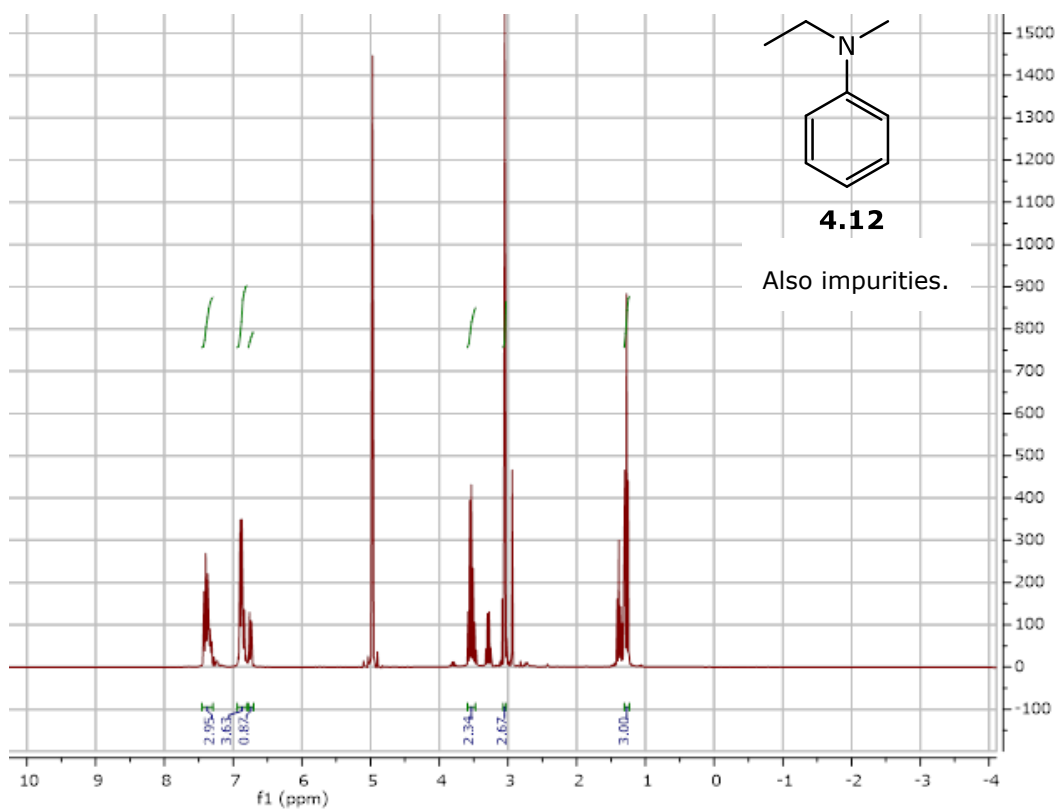
^{13}C NMR (CDCl_3): δ 148.01 (C_{ar}), 129.20 (CH_{ar}), 115.38 (CH_{ar}), 111.89 (CH_{ar}), 72.62 (CH₂), 58.59 (CH₃), 50.82 (CH₂), 27.24 (CH₂), 24.00 (CH₂).

HRMS calculated for C₁₆H₂₈NO₂ ($[\text{M}+\text{H}]^+$), 266.2115 found 266.2115

4.12 (mixture with **4.2** (used as starting material in this experiment) and other side products), measured spectra (below) in agreement with previously published data:²³¹

^1H NMR (300 MHz, CDCl_3) δ 7.23 (m, 2H), 6.76-6.66 (m, 3H), 3.39 (m, 2H), 2.90 (s, 3H), 1.11 (m, 3H).

^{13}C NMR (300 MHz) δ 149.06 (quat), 129.21 (Ar), 116.19 (Ar), 112.52 (Ar), 46.92 (N-CH₂-), 37.55 (N-CH₃), 11.22 (-CH₂-CH₃).



Chapter 5. [Ru(Triphos)(TMM)]

Catalysed Methylations of Amines with Methanol – an Indirect Way of Utilising Carbon Dioxide

5.1 Introduction

In this Chapter work carried out at the ITMC, RWTH Aachen (host-university of this SINCHEM project) will be presented. The research was undertaken during a period of 9 months in 2015 under the supervision of Professors Jürgen Klankermayer and Walter Leitner. The original topic of this work, was intended to cover utilising carbon dioxide as a substrate in chemical reactions, but as interesting results in the methylation of amines using methanol (possibly derived from CO₂) were achieved with the Ru(Triphos)(TMM) catalyst, the perspective of the research changed slightly.

First, a brief review on the previous research on the relevant topics is presented, including the catalyst and its many uses (section 5.1.1). More details are given on CO₂ activation reactions forming methanol and methylated amines (sections 5.1.2 and 5.1.3), before going through previous research on amine methylations with methanol using ruthenium catalysts in section 5.1.4. In many cases the

reactions occur via a 'hydrogen borrowing' mechanism, which is described later. After this introduction, the experimental methods implemented throughout this Chapter are introduced in section 5.2, before the results for the work carried out on the topic are discussed, including reactions with both octylamine and butylamine as substrates (sections 5.3.1 and 5.3.2). Finally, 5-amino-1-pentanol was used as a substrate to form *N*-methyl piperidine. This reaction is briefly introduced in section 5.3.3 together with results obtained from the studied experiments. More details on previous work on this reactivity is given in Chapter 6. The data shown in Figures throughout this Chapter will be listed in separate tables in section 5.5 (Chapter Appendix).

5.1.1 [Ru(Triphos)(TMM)]

The work presented in this Chapter was carried out by using Ru(II)(Triphos)(TMM) (TMM=trimethylenemethane, Triphos=1,1,1-tris(triphenylphosphinomethyl)ethane) as catalyst. This well-defined homogeneous catalyst was developed in the Klankermayer/Leitner group,²³² and has been shown to be active in a number of important transformations. These include cleavage of C-O-bonds²³² and C-C-bonds²³³ in lignin model compounds, CO₂ activation reactions,²³⁴⁻²³⁹ and hydrogenations of carboxylic acids to alcohols,²⁴⁰ as well as, lactams to cyclic amines.²⁴¹ In the last case, the aromatic rings on the Triphos moiety were *meta*-substituted to afford enough steric bulk around the Ru-centre to inhibit dimerisation of the catalyst and hence deactivation of the system.

The most relevant application of the Ru(Triphos)(TMM)-catalyst system for the work presented here is the activation of CO₂, forming both methanol^{234, 235} and in separate studies methyl groups for amine or imine methylations.²³⁶⁻²³⁸ In addition, very recently, dialkoxymethane ethers were synthesised from CO₂, H₂ and the corresponding alcohol.²³⁹

5.1.2 Methanol from CO₂ and H₂

The hydrogenation of CO₂ to methanol has the potential of providing a route to produce a CO₂-neutral liquid fuel and starting material. This transformation has been achieved with both heterogeneous^{32, 49} and homogeneous catalysts. Here the recent advances made in the latter case are presented. The Ru(Triphos)(TMM) complex together with an acid (1 eq. HNTf₂, trifluoromethanesulfonimide) and EtOH additive (10 mmol) was the first single organometallic catalyst able to catalyse this transformation.²³⁴ TONs (Turn Over Number; moles of product per moles of catalyst) of up to 221 were achieved after 24 h, at 140 °C, 60 bar H₂ and 20 bar CO₂. Later this system was further improved and the transformation was realised without any additives and with a total TON of 769 after 4 cycles of recycling the catalyst system.²³⁵ The mechanism was studied closer, and it was revealed that CO₂ could be directly transformed to methanol on the Ru-Triphos centre, instead of a previously reported 3 step process. In the previous systems, formic acid would initially be formed from CO₂ and H₂, and it would then react further to methyl formate by esterification. The final step, in these examples, is the hydrogenation of methyl formate to methanol. Prior to the Ru-Triphos results the highest TON for the CO₂ hydrogenation with H₂ using a homogeneous catalyst was 40, which was achieved by a cascade catalyst system where 3 different homogeneous catalysts were used to achieve the 3 transformations describe above.²⁴²

As this reaction is considerably difficult to achieve, recent work has been focused on systems where CO₂ is simultaneously captured by amines and these products are then transformed to MeOH.²⁴³⁻²⁴⁵ In the first example, a Ru(Triphos)-complex was used together with dimethylamine, a CO₂ capture agent, under basic conditions.²⁴³ This system resulted in a 95 % conversion of CO₂ to MeOH, dimethylformamide and dimethylammonium formate. In the second case, the

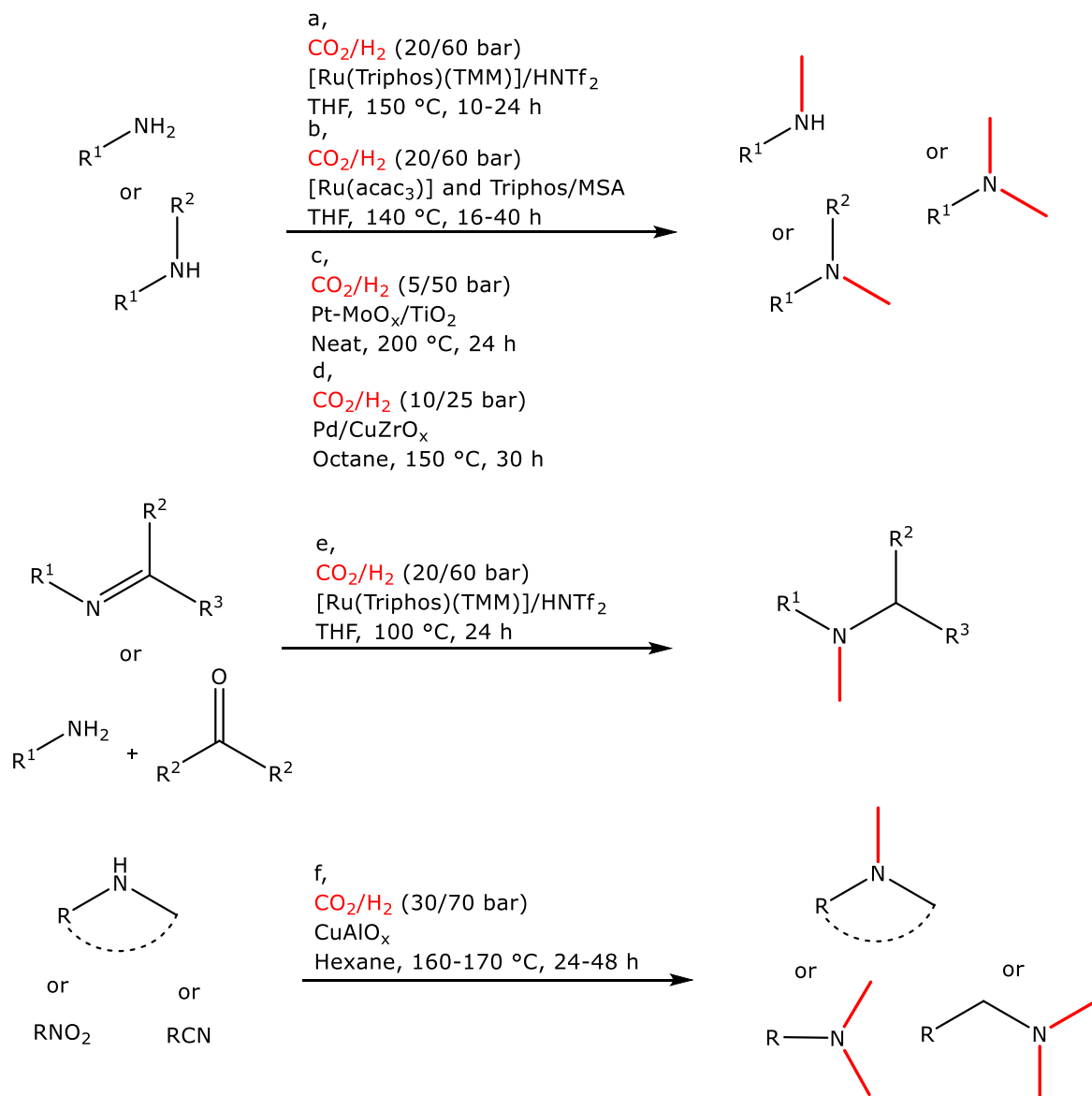
CO₂ was captured with aminoethanols at 1-3 bar CO₂ catalysed by CsCO₃.²⁴⁴ This led to the formation of oxazolidinone, which could be directly hydrogenated with a Ru-pincer complex and H₂ to give the starting aminoethanol and MeOH. When the reactions were carried out without the separation of the intermediate, a 50 % yield of MeOH was reached. In the final example, a polyamine base was used to capture CO₂, even directly from air, by forming carbamate adducts. These could then be converted to methanol with a homogeneous Ru-catalyst reaching CO₂ conversions of up to 79 %.²⁴⁵

5.1.3 Amine Methylations with CO₂ and H₂

The second way Ru(Triphos)(TMM) has been utilised in CO₂ activation reactions, is by directly methylating amines with CO₂ and H₂ forming the methylated products in high yields and selectivities.²³⁶⁻²³⁸ The first report on this reactivity was presented by Klankermayer, Leitner and co-workers, who found that primary and secondary aromatic amines could be *N*-methylated with high yields of the dimethyl products (20 examples, up to 94 % yield).²³⁶ This reactivity was simultaneously discovered by the Beller group, who used [Ru(acac)₃] together with a triphos ligand reaching up to 99 % yields of methylated aromatic and aliphatic secondary and primary amines (33 examples).²⁴⁶ Methylated amines are pharmaceutically and industrially important functionalities, and they also play a central role in biological processes.^{47, 49, 247-250} Traditionally the methylation reaction has been carried out using hazardous methylating agents in basic media with low selectivities. Hence, it is important to develop new methylating methods to improve the synthesis, which the presented systems are good examples of.

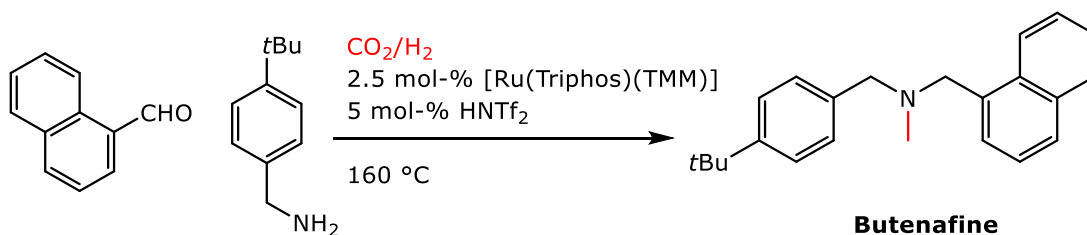
Since the preliminary results, also heterogeneous catalysts (CuAlO_x,²⁵¹ Pt-MoO_x/TiO₂²⁵² and Pd/CuZrO_x²⁵³ and Au/Al₂O₃²⁵⁴) have been utilised for the

transformation. Also here high yields with several substrates can be achieved, but the real advantage in these cases is the recyclability of the catalyst systems (See Scheme 5.1 for details).



Scheme 5.1. Some of the different catalyst systems capable of amine methylations with CO_2 and H_2 . In some cases a variety of starting materials are tolerated. The systems in a,²³⁶ b²⁴⁶ and e²³⁷ are homogeneous whereas c,²⁵² d²⁵³ and f²⁵¹ are heterogeneous.

As shown in Scheme 5.1, the Ru(Triphos)(TMM)-system was later developed to include imines as substrates,²³⁷ as well as ammonia, or ammonium chloride to make trimethylamines.²³⁸ In the first case,²³⁷ the reaction could be carried out with isolated imines, and also the direct coupling of primary amines, aldehydes and CO₂ were shown to be possible. This protocol was also implemented for an improved synthesis of butenafine starting from 1-naphtalene aldehyde and 4-*tert*-butylbenzyl amine (Scheme 5.2). The preparation of this pharmaceutical compound was accomplished in 60 % yields in one step, which is a great improvement to the previously established 4-step method, which was linked to high E-factors, because of salts that were produced as side products, and solvent changes that occurred after each step.



Scheme 5.2. The direct synthesis of butenafine, starting from 1-naphtalene aldehyde, 4-*tert*-butylbenzyl amine, CO₂ and H₂, using Ru(Triphos)(TMM) as the catalyst.²³⁷

The selective triple *N*-methylation of ammonia and its hydrochloride salt was also achieved.²³⁸ In this case, it was shown that also the Lewis acid Al(OTf)₃ (aluminium trifluoromethanesulfonate) could be used as the co-catalyst resulting in yields of up to 77 % of the product. When NH₄Cl_{aq} was used as the substrate, no co-catalyst was required, and furthermore the reaction could be carried out in a biphasic system (dioxane/water). However, despite all the advancement presented here, one downside of this catalytic entity is that it has not, to date, been applicable to aliphatic amines. Hence MeOH, which could, in theory, be derived from CO₂ and H₂, as described in the previous section, was employed as

the methylating agent in reactions with aliphatic amines as described in this Chapter.

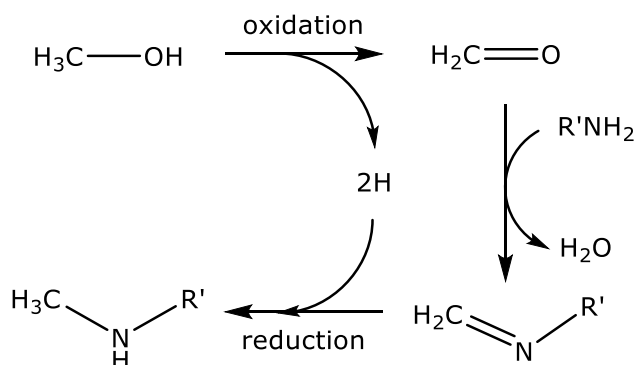
5.1.4 Amine Methylations with Methanol Using Ru-catalysts

The methylation of amines using methanol as the methylating agent and ruthenium as a catalyst has been known since the early 1980s.²⁵⁵⁻²⁵⁹ This route is attractive, as it offers an alternative to the traditional synthesis, and also avoids the use of hydrogen, which presents potential safety problems. Initially, active Ru-catalysts for the methylation of aliphatic amines were discovered and later also aromatic amines were successfully methylated. $\text{RuCl}_2(\text{Ph}_3\text{P})_3$ was the first Ru-catalyst to achieve the methylation of several aliphatic amines with high conversions at 180 °C after 7 h.²⁵⁶ It was found that the outcome of the reaction depended on the conditions particularly the amount of methanol; with a 15 fold excess of methanol *N,N*-dimethyl alkylamine was produced selectively, whereas with less methanol (2.5 eq.) mainly *N,N*-dialkyl methylamine was produced. The same catalyst was also employed in the methylation of aminoarenes, but low reactivity was found.^{257, 258}

The first efficient system for aminoarene methylations turned out to be $\text{RuCl}_3 \cdot n\text{H}_2\text{O} \cdot \text{P}(\text{OBu})_3$ at 180 °C and 15 h reaction times.²⁵⁹ Several different substrates were methylated with high conversions (>90 %) and high selectivity for the *N,N*-dimethyl product. Later examples show other Ru-complexes achieving the methylation of alkyl amines²⁶⁰ or monomethylation of arylamines.²⁶¹ In a recent communication the system of $[\text{RuCp}^*\text{Cl}_2]_2/\text{dpePhos}$ with a basic co-catalyst (LiOt-Bu) at 100 °C and 24 h, was shown to selectively monomethylate arylamines, but dimethylate aliphatic amines.²⁶² It was also revealed that when the reaction was carried out in the presence of both ethanol and methanol mainly *N*-methylation took place (83 % selectivity).

Hydrogen Borrowing Mechanism

Most of the examples above have been suggested to proceed via a hydrogen transfer or hydrogen borrowing mechanism (Scheme 5.3).²⁶³⁻²⁶⁶ In most of these processes there is no net reduction or oxidation, but instead hydrogen is transferred from the substrate to the final product, utilising a hydrogenation catalyst. In the methylation of amines with methanol this means that first the alcohol is activated by the removal of hydrogen to form formaldehyde, which in turn reacts with the amine forming an imine by removal of water. Then the borrowed hydrogen is returned and the *N*-methylated amine is formed. Water is the only by-product in this reaction, and therefore methylations using methanol are considered greener options to traditional approaches, where alkyl halides have been used resulting in halogenated side products.



Scheme 5.3. The concept of hydrogen borrowing for producing methylated amines with MeOH.²⁶⁴ First the methanol is activated by removal of hydrogen forming formaldehyde, which reacts with the amine producing an intermediate imine, which is then reduced to the *N*-methylated amine.

5.2 Experimental Procedure

As the work presented in this Chapter was carried out at a different university, slightly different procedures were implemented compared to the ones presented in Chapter 2. The reactions were performed in high pressure autoclaves, under inert atmosphere, as depicted below.

5.2.1 Materials and Methods

All starting materials were purchased from commercial suppliers and used as received. The solvents were distilled and dried over 3 or 4 Å molecular sieves, and degassed with argon. Unless otherwise stated, all reactions and preparations were carried out under an argon atmosphere.

NMR-spectra were recorded on Bruker AV400 and AV300 instruments in CDCl₃ (reference δ 7.270 and 77.000 ppm). GLC-chromatography was carried out on a Trace-1 (butylamine) and Focus2 chromatograph (amino alcohol) using an Rtx-1-PonaII column (50 m, FT 0.5 μ m, ID 0.25 mm) and FID detector.

For the butylamine reactions: hold at 50 °C for 10 min, ramp to 250 °C at 8 °C/min, hold for 15 min. Injector at 250 °C and FID at 280 °C.

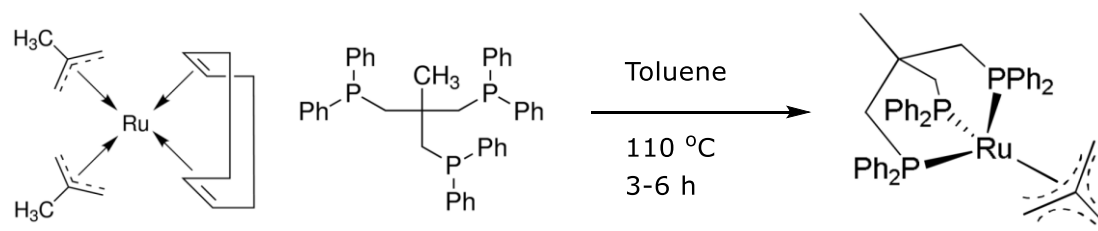
For reactions starting from 1-amino-5-pentanol: hold at 50 °C for 8 min, ramp to 250°C at 12°C/min hold for 15 min. Injector and FID at 250 °C.

Examples of the GCs for the butylamine and the 1-amino-5-pentanol reaction mixtures are shown in section 5.5 (Chapter Appendix).

GC-MS was carried out with the same column and methods as the GLC-chromatography to help identify some of the unknown products formed in the reactions.

5.2.2 Catalyst Synthesis

The catalyst was prepared via a previously developed route (Scheme 5.4).²³² In a 35 ml Schlenk tube, 159 mg (0.5 mmol) of $[\text{Ru}(\text{COD})(\text{methallyl})_2]$ (COD is 1,5-cyclooctadiene) and 312 mg (0.5 mmol) of 1,1,1-tris(diphenylphosphino)methylethane (triphos), were weighed, and 10-15 ml of dry and degassed toluene was added. The mixture was stirred for 3-6 h at 110 °C and left to cool. To help precipitation 10-20 ml of *n*-pentane was added before the solvent was removed. The formed solid was washed 3 times with 10 ml of *n*-pentane and dried under vacuum for at least 12 h. After drying, the complex was obtained as a pale yellow powder in 43-61 % yields and stored under argon in a glove box.



Scheme 5.4. The formation of $\text{Ru}(\text{Triphos})(\text{TMM})$, when starting from Triphos and $[\text{Ru}(\text{COD})(\text{methallyl})_2]$. This compound was used as catalyst in the reactions described in this Chapter.

5.2.3 General Procedure

All the methylation reactions described in this Chapter were carried out in 10 ml finger autoclaves, which had been built in-house (Figure 5.1). A 10 ml test tube, with a magnet, was put in the autoclave. All solid substrates were weighed into the test tube, before the reactor was closed. The autoclave was dried for 3 h under vacuum. A Schlenk tube, with a magnet was dried for 1 h, before the catalyst (2.5 mol-% compared to amine) and acid (5 mol-% compared to amine, NHTf_2 or $\text{Al}(\text{OTf})_3$) were weighed into the tube. After this, the solvent (2 mL), the

substrate (1 mmol) and when applicable the methanol was added to the Schlenk, and the obtained mixture was transferred to the dry autoclave, under a flow of argon. Most of the reactions were carried out under an argon atmosphere, without added pressure. The autoclave was put in a preheated aluminium heating block, which was shaped as a cone and placed on top of a heating plate, for the appropriate reaction time. When the reaction had finished, the autoclave was cooled in a water-ice bath for at least 30 min, and then the autoclave was depressurised, and the reaction mixture was analysed using ^1H - and ^{13}C -NMR, and APT-NMR (Attached Proton Test; 1D ^{13}C NMR experiment, which gives positive signals for CH and CH_3 carbons, and negative signals for CH_2 or quaternary carbons) spectroscopy. The conversions and selectivities were determined by GLC-chromatography.

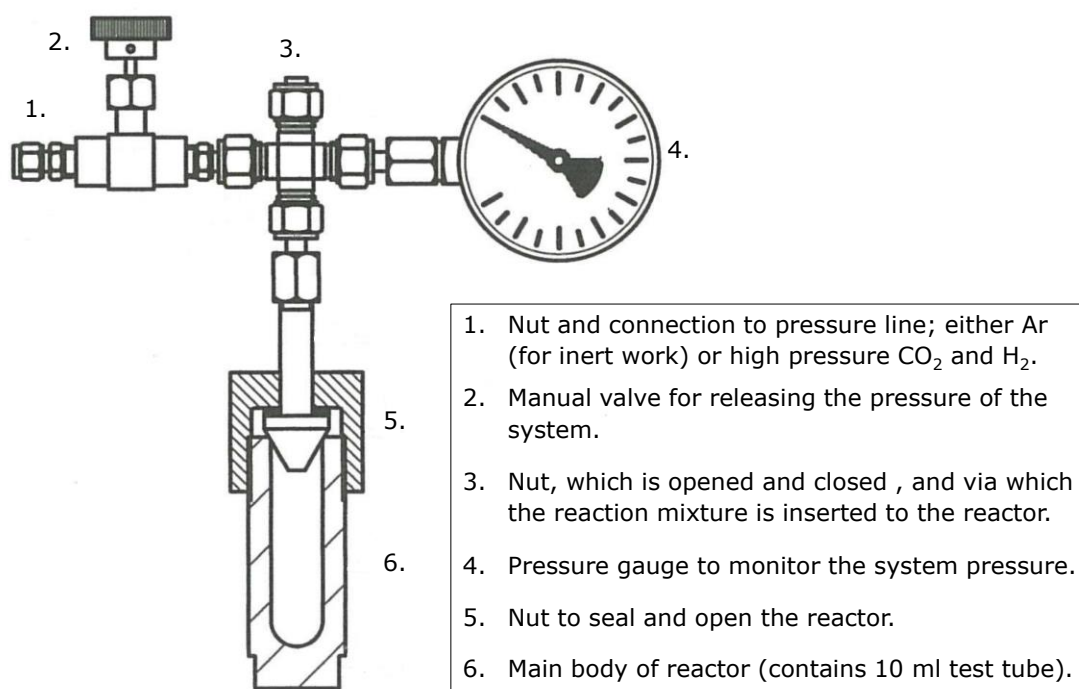


Figure 5.1. Schematic diagram, including an explanation of the different parts, of the autoclave used for reactions carried out in Aachen. The picture is reproduced from an instruction sheet provided by the workshop at ITMC, RWTH Aachen.

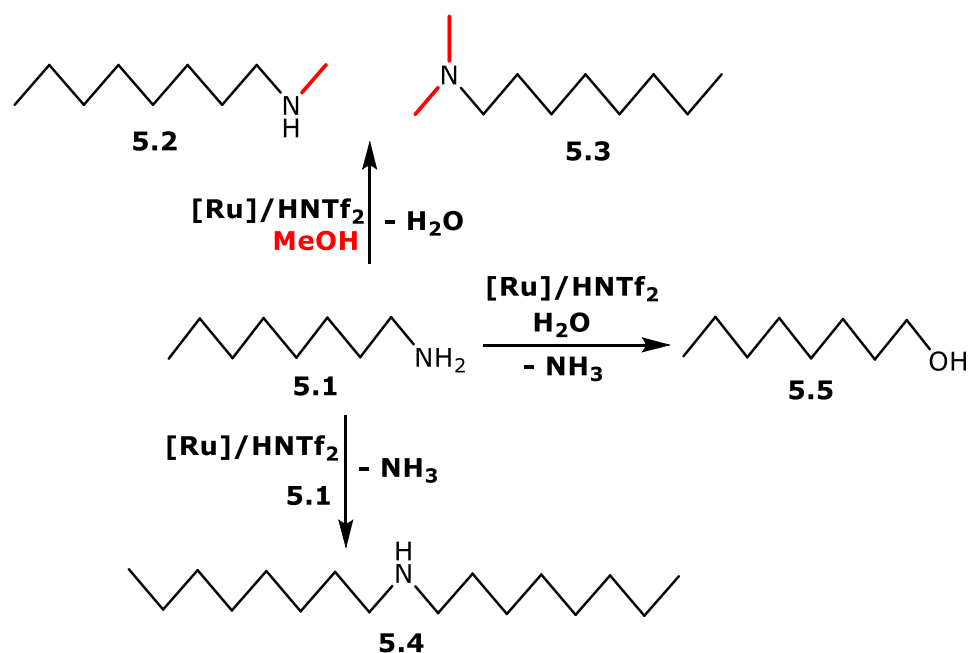
5.3 Results and Discussion

Preliminary work was carried out by using 3,5-dimethylaniline as the starting material. The reason was that this substrate had been used in previous research, where the aim had been to study the possible immobilisation of the catalyst system in amine methylation reactions starting from CO₂ and H₂ by using ionic liquids as solvents.²⁶⁷ In the current case, during these experiments, methanol was found to be capable of producing *N*-mono- and *N,N*-dimethylated products, when the system was not pressurised. In fact, running the reaction under either hydrogen or CO₂ pressure, in the presence of methanol, retarded the catalytic system and only very low conversions (<10 %) were found. This finding suggests that the reaction proceeds via the hydrogen borrowing mechanism described previously, and hence all consecutive reactions with MeOH were carried out without H₂ or CO₂.

5.3.1 Reactions between Octylamine and Methanol

Octylamine (**5.1**) was chosen as the substrate, as it had been used previously in the group in similar reactions, and hence some of the possible intermediates were already available and this simplified the analysis of the reaction mixtures. It was found that the methylation of **5.1** with methanol occurs without any added pressure in both THF and pure methanol (Scheme 5.5, Figure 5.2). The main product in all cases was *N,N*-dimethyl octylamine (**5.3**), and depending on the conditions also other products e.g. *N*-methyl octylamine (**5.2**), dioctylamine (**5.4**) and octanol (**5.5**) were formed. In THF, the selectivity of the reaction depended on the temperature as at 130 °C the selectivity for the methylation products **5.2** and **5.3** was higher than at 150 °C (at 130 °C 23 % **5.2** and 58 % **5.3**, at 150 °C 10 % **5.2** and 50 % **5.3**). This was due to the increased formation of side products at higher temperatures as deamination to **5.5** and its

further reactions became possible. When the reaction was carried out in methanol, full conversion of **5.1**, with high selectivity (nearly 65 %) to **5.3**, was achieved. Also the amount of **5.5** increased in this case, as the deamination reaction became more likely.



Scheme 5.5. Reactions of octylamine (**5.1**) in the presence of methanol catalysed by Ru(Triphos)(TMM) (2.5 mol-%) and a co-catalytic acid (5 mol-%) producing **5.2-5.5**.

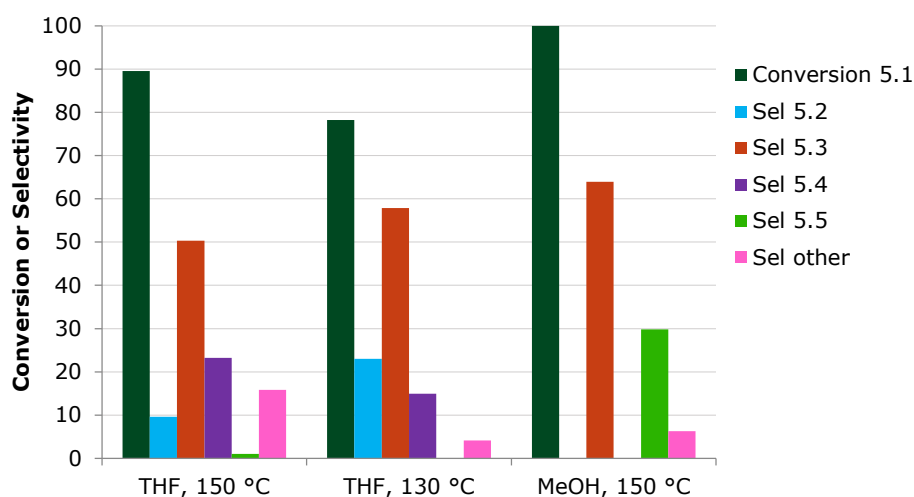


Figure 5.2. Methylation of 5.1 with MeOH – effect of temperature and solvent. It can be seen that when the reaction was carried out in THF, decreasing the temperature from 150 °C to 130 °C decreases the conversion, with a slight change in selectivity. When the reaction was carried out in MeOH, neither 5.2 nor 5.4 were observed. Moreover, the selectivity for 5.5 increased in this case. Conditions: 1 mmol substrate, 2.5 mol-% catalyst, 5 mol-% acid (HNTf₂), 2 mL solvent and 3.3 mmol MeOH (in THF). The reactions were carried out for 16 h in all cases. The conversions and selectivities were determined by GC-analysis. The reader is referred to the key for the structures on page 253 for convenience.

The side reactions were interesting as they took place via deamination of the substrate. Such reactivity has been reported previously, in systems utilising hydrogen borrowing Ru-catalysts, and in the case of synthesising alcohols from amines in the presence of water, as reported by Milstein and co-workers.^{268–269} ²⁷⁰ As the methylation of **5.1** with MeOH produces H₂O, it opens the pathway for forming octanol **5.5** by the cleavage of ammonia or possibly methylamines. The other pathway has been reported by, for instance, the Beller group,^{269, 270} and leads to the formation of dialkyl amines again via a hydrogen borrowing mechanism. As will be shown later, this reactivity takes place in the absence of water (butylamine without MeOH), and would possibly be the only side reaction in the system, if water had been removed as it was formed. The two pathways seem to be competing, and it is not yet clear, why or when one route is favoured over the other. Unfortunately, this side reactivity was not studied further, but it

opens up possibilities for future work to help gain a deeper understanding of the research described in this Chapter.

In order to check the reactivity within the system, *N*-methyl octylamine (**5.2**) and *N,N*-dimethyl octylamine (**5.3**) were used as substrates in the reaction (Figure 5.3). In the case of **5.3** no reaction took place, which meant that it was one of the final products in the mixture. However, **5.2** reacted further to **5.3**, as anticipated, but also a number of side products were formed. Both the conversion of **5.2** and the amount of the side products were higher, when the reaction was carried out in MeOH than when THF was used as the solvent. **5.4** seemed to be the predominant side product in both cases, which was unexpected as the starting material was already methylated. It is plausible that, in this case, the reaction produces dimethylamine or trimethylamine and leaves the dioctylamine unmethylated. In MeOH it would, however, be expected that **5.4** would react further to *N*-methyl dioctylamine, but this was not observed.

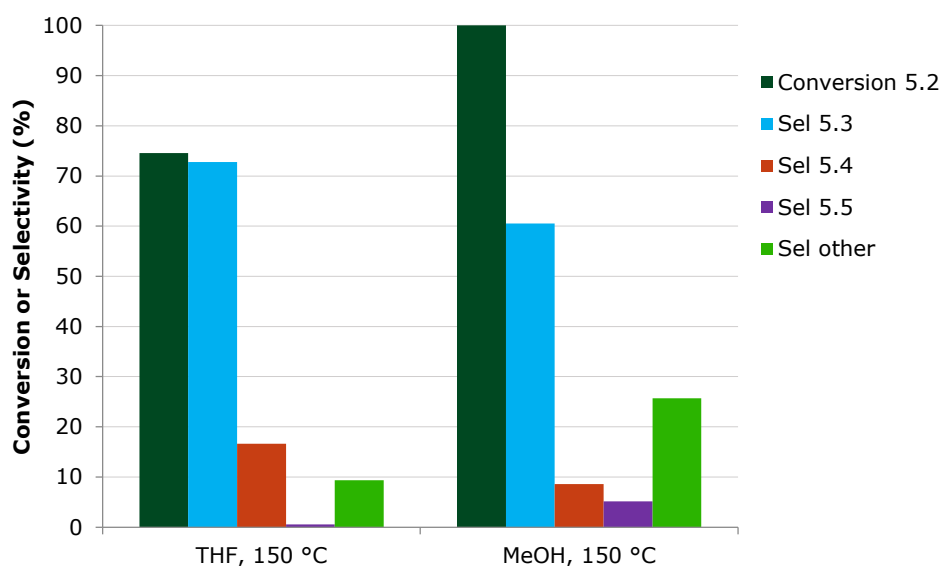
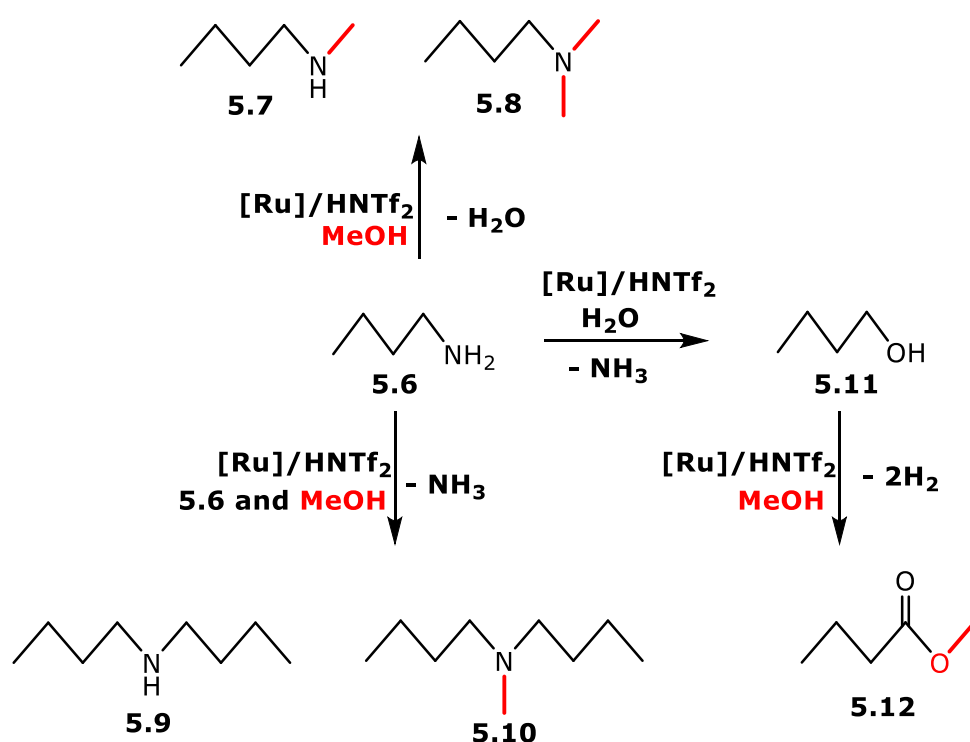


Figure 5.3. Results of reactions where 5.2 was used as starting material in reactions with methanol. The main product in both THF and MeOH is 5.3, which does not react further, when used as substrate. Also the amount of side products is higher in MeOH than in THF. Conditions: 1 mmol substrate, 2.5 mol-% catalyst, 5 mol % acid, 2 mL solvent and 3.3 mmol MeOH (in THF), 16 h. The conversions and selectivities were determined by GC-analysis.

5.3.2 Reactions between *N*-butylamine and Methanol

After the octylamine study another primary aliphatic amine, namely butylamine (**5.6**), was used as the substrate in the reaction with methanol (Scheme 5.6). The effect of solvent and temperature were studied as well as the reproducibility of the reactions. In general, reproducing the results turned out to be quite difficult and large errors were seen, especially when the reaction was carried out in pure methanol. This behaviour was most probably due to the high volatility of both the reagent and solvent, and the fact that the autoclaves were not pressurised during the reactions. This again meant that no leak detection was possible and also that while the autoclaves were opened (even after cooling to 0 °C), some of the more volatile products might have been lost. Also other

factors such as catalyst batch, exact amount of solvent etc. might have influenced the outcome of the reaction. As in the octylamine case, several different products could be formed here. These include the methylation products **5.7** and **5.8** (Scheme 5.6), as well as the alkylation products **5.9** and **5.10**. In addition, butanol (**5.11**) could also be formed, and it could then react further to methyl butyrate (**5.12**).



Scheme 5.6. The identified reactions taking place between *N*-butylamine (**5.6**) and **MeOH** in the presence of $Ru(Triphos)(TMM)$ (2.5 mol-%) and a co-catalytic acid (5 mol-%). The main products include **5.7**–**5.10**. In addition, **5.11** and **5.12** are formed, as well as small amines (NH_yMe_x , $y=0-3$, $x=3-y$) due to possible deamination reactions.

Figure 5.4 shows the solvent effect and the influence of the reaction temperature on the selectivity. In nearly all cases, where the temperature was above 120 °C, *N,N*-dimethyl butylamine (**5.8**) was produced with the highest selectivity. When the reaction was carried out in THF, the increase of temperature from 150 °C to 180 °C switched the selectivity of the side products from the dialkylated products to **5.11** and **5.12** (Figure 5.4, Table 5.1). At 200 °C, even more **5.12** was formed, even though full conversion was not reached, which may indicate a problem within the system during that specific experiment, which was not repeated due to shortage of time. The reaction was also carried out without MeOH, which led to the formation of dibutyl amine (**5.9**) with high selectivity (82 % conversion, 95 % selectivity). This result confirms that a hydrogen borrowing reaction resulting in the cleavage of ammonia was indeed occurring, and, when no H₂O was present, the other side reactions were avoided. The formation of ammonia (or in other instances methylamines) was not detected by analysis, but after the reactions had finished and the reactors were opened, there was a strong fishy odour indicating the formation of low molecular weight amines.

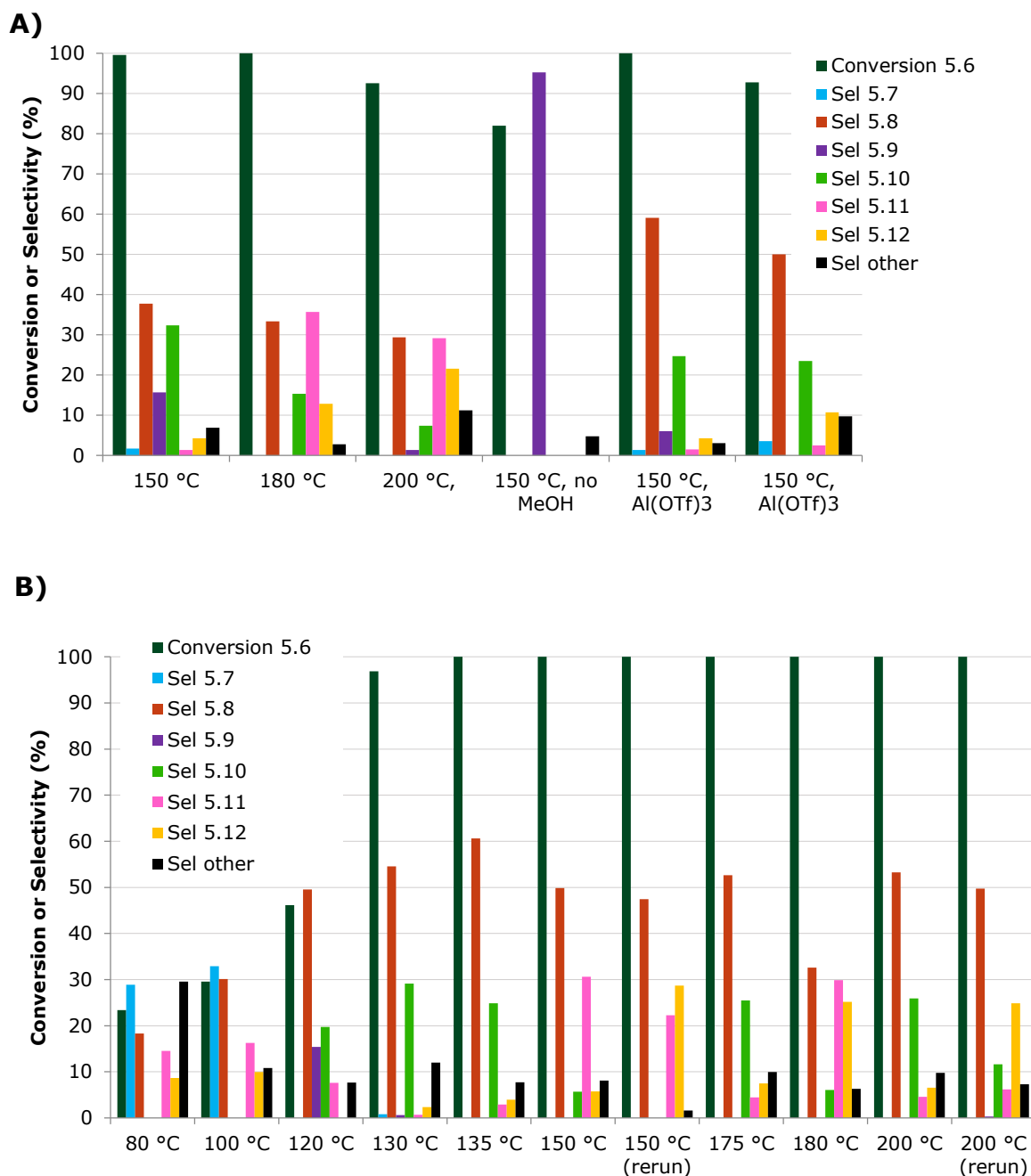
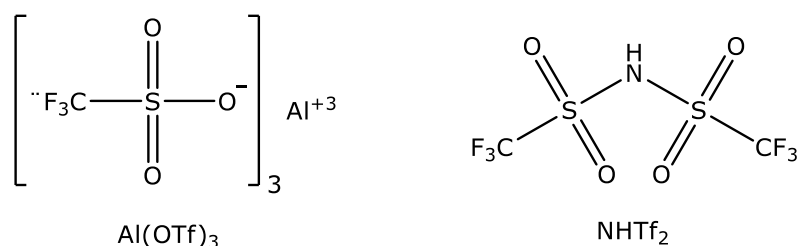


Figure 5.4. Result of the reactions of *N*-butylamine with MeOH in THF (A) and in MeOH (B) and the effect of temperature on the outcome of the reaction. In THF, the selectivity of the reaction was lower than in MeOH, but in both cases mixtures of products were obtained at most of the conditions. The highest selectivity for 5.8 was reached at 135 °C in MeOH. The results suggest that there are 2 competing pathways for the side reactions, one leading to the formation of 5.9 and 5.10, the other resulting in 5.11 and 5.12. Conditions: 1 mmol substrate, 2.5 mol-% catalyst, 5 mol-% acid, 2 mL solvent and 3.3 mmol MeOH (in THF), 16 h. The conversions and selectivities were determined by GC-analysis. The key on page 253 can help to remind the reader which structures are discussed.

In methanol, a wider temperature range was studied (Figure 5.4B) than in THF. The system was already active at 80 °C, when *N*-methyl butylamine (**5.7**) was observed. The highest selectivity for **5.7** was reached at 100 °C, but above 130 °C it was not observed, as a further methylation immediately occurred to yield **5.8** at conditions with high enough catalyst activity (long reaction time combined with higher temperatures). The dibutyl products were not formed below 120 °C and **5.9** was only observed at this temperature. Above 120 °C, the methylation of **5.9** to **5.10** was predominant; so only *N*-methyl dibutylamine (**5.10**) was present at higher temperatures. Full conversion was reached at and above 135 °C, which was also where **5.8** was produced with the highest selectivity (61 %, Table 5.1 entry 5). At higher temperatures **5.8** was formed with more than 50 % selectivity, except at 180 °C, where mainly butanol (**5.11**) and methyl butyrate (**5.12**) were observed. Interestingly these products were already detected at 80 °C, and only in low yields at 120-135 °C, above which they become the main side-products in addition to **5.10**.

The catalytic system was also tested with a different co-catalyst instead of HNTf₂, as aluminium triflate (Al(OTf)₃) was used in its place (Figure 5.4 for THF, and Figure 5.5 for MeOH, Scheme 5.7 for structures). Al(OTf)₃ is a Lewis acid whereas HNTf₂ is a Brønstedt acid, but since Al(OTf)₃ was successfully employed in a recent publication²³⁸ in reactions with ammonia, it was of interest to see whether the catalyst would be active in the absence of a strong protic acid also in the current case. It turned out that, when the reaction was carried out in THF, the selectivity for **5.8** actually increased to an average of 55 %, which is the highest selectivity for **5.8** in THF. On the other hand, in methanol, similar results were observed as with HNTf₂.



Scheme 5.7. Structures of the co-catalysts used in this Chapter. Al(OTf)_3 is a Lewis acid (can accept an electron pair) and NHTf_2 is a Brønstedt acid (proton donor), and hence they activate the catalyst in different ways.

As can be seen from Figure 5.4, for the experiments carried out in methanol, the variations of the results do not seem very consistent, which raised the question of the accuracy and reproducibility of the results obtained for this system. The problem can be seen for instance at 150 °C (Figure 5.5), where the selectivity varies quite drastically under the same conditions between the 3 experiments. As the reactions were carried out without any added pressure, the high volatility of both solvent and reagent increased the challenge of collecting the entire sample at the end of experiments. The reproducibility was investigated at 150 °C and also different methods for collecting the final mixture were tested. The results can be seen in Figure 5.5, where flush indicates that the autoclave was flushed with solvent before opening to ensure all materials were in the test tube, and collect means that while the autoclave tap was slowly being opened anything that came out was collected and added to the rest of the sample.

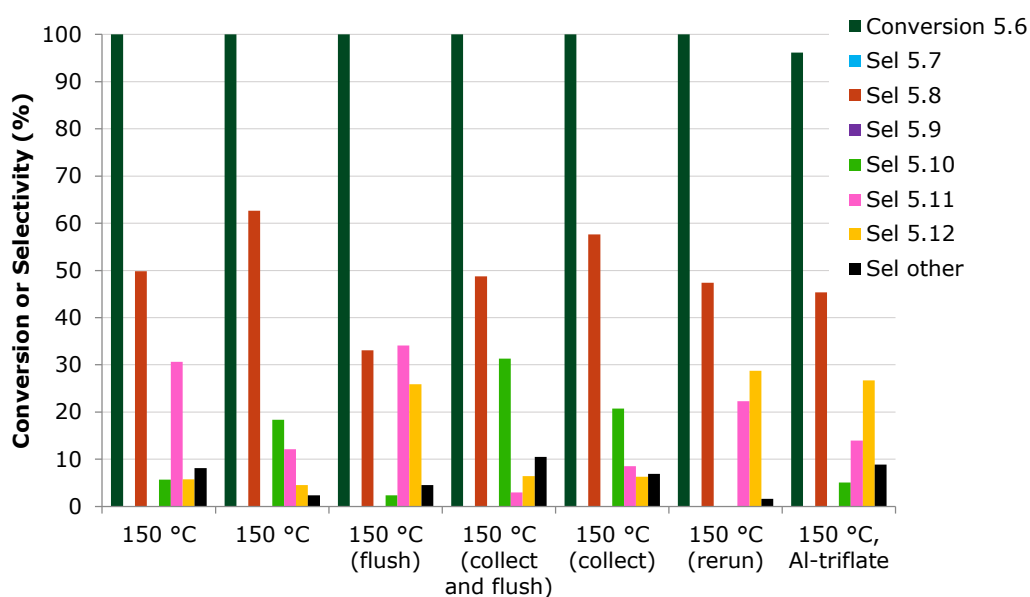


Figure 5.5. Determination of the influence of the collection method on the outcome of the reaction between butylamine and methanol. Flush = The reactor was flushed with solvent after opening the tap. Collect = Anything that came out of the reactor was collected while opening the tap. Conditions: 1 mmol substrate, 2.5 mol-% catalyst, 5 mol-% acid, 2 mL solvent. The conversions and selectivities were determined by GC-analysis. The key on page 253 can help to remind the reader which structures are discussed.

Figure 5.5 shows that full conversion of butylamine (**5.6**) was reached in all the experiments. The method of opening the autoclaves did not seem to have a great effect on the outcome, because large variations in the results were seen even between similar collections. Furthermore, comparison of the results is not straightforward as each experiment was done with a different starting solution of the substrate and catalyst system. The selectivity for **5.8** varied from 33-63 % and the selectivity for the different side products (**5.10**, **5.11** and **5.12**) changed from 2-30 %. This result is likely to be caused not merely by the difference in the collection method, as changing the starting solution and, in some cases, the catalyst batch might in itself cause much of the variation in the results, and shift the selectivity from the dibutylamine products to the butanol and methyl butyrate or vice versa. These two paths seemed to be competitive reactions in the system, as one of them was always the predominant side

reaction besides the main methylation. This side reactivity should be studied further.

The error seemed to be smaller when the reaction was carried out in THF (Figure 5.4A; at 150 °C, an average of 5 experiments with an error of $\pm 2\%$ in selectivities). This might be explained by the lower volatility of THF compared to methanol, and also by the higher solubility of the reaction mixture and catalyst system in THF. After these experiments, the method of opening the reactors was as follows: all the material that was released while opening the tap was collected and the autoclave was then flushed with Ar-gas to make sure all the mixture stuck on the walls and tubing of the autoclave would be recovered.

To study one of the side reactions in more detail, butanol (**5.11**) was used as the starting material instead of **5.6** in reactions with methanol (Figure 5.6). It was found that **5.11** mainly reacts to methyl butyrate (**5.12**) at both 150 °C and 180 °C (selectivity >90 %), which confirmed that in the reactions starting from butylamine (**5.6**), **5.12** could be formed as **5.11** is produced. The other products that were observed include presumably butyl methyl ether and possibly butyl butyrate. Also the conversion increased with increasing the temperature from 47 % to 58 %.

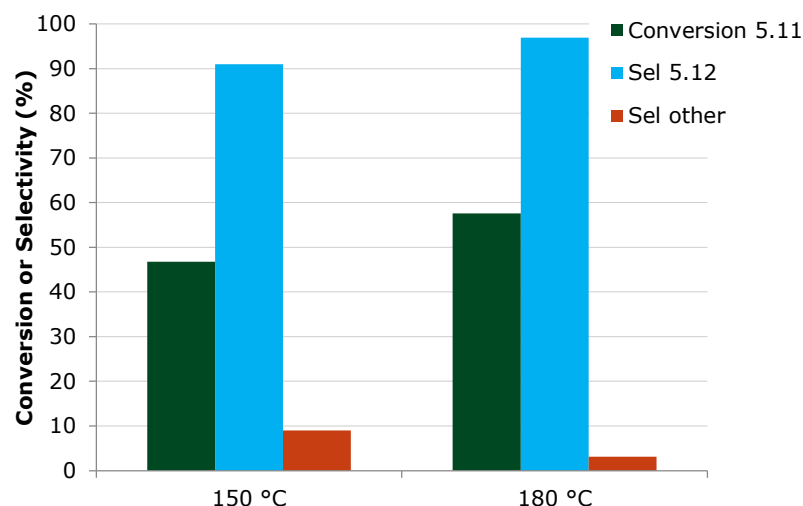


Figure 5.6. The result of the reaction between butanol (5.11) and methanol in methanol. The reaction was carried out at 150 and 180 °C and an increase in conversion as well as selectivity for 5.12 can be seen with an increase in the temperature. Conditions: 1 mmol substrate, 2.5 mol-% catalyst, 5 mol-% acid, 2 mL solvent. The conversions and selectivities were determined by GC-analysis.

This reactivity has previously been reported to proceed via a hydrogen transfer mechanism, which is similar to hydrogen borrowing, except that H_2 gas is liberated as a side product.²⁷¹⁻²⁷⁹ Most of this research has focused on Ru-catalysts, and some systems require hydrogen acceptors for the reaction to occur, whereas others have been shown to proceed via an acceptorless mechanism, which is also the case here. Furthermore, only recently has methanol been shown to be a suitable substrate for this transformation.^{275, 276} This method of producing esters directly from alcohols is potentially of great importance, as it avoids the use of stoichiometric oxidants, and more work should be done to study the scope of this reactivity in addition to work on the previously described side reactions.

In Table 5.1, are summarised the different conditions leading to the highest selectivities for the different products in both THF (entry 1-3) and MeOH (entry 4-7). The errors indicated are based on the average value of the

experiments carried out under each condition or, in the case, where only a single experiment was carried out, a 5 % error is assumed.

Table 5.1. The conditions with the highest selectivities for different products (in bold) in different solvents for the reaction between 5.6 and methanol.^a The key on page 253 can help to remind the reader which structures are discussed.

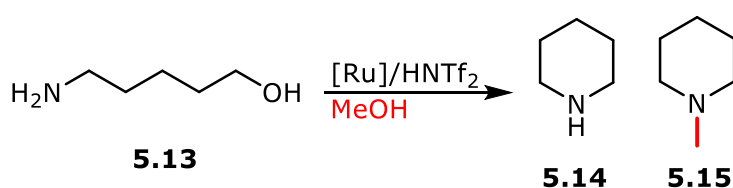
Entry	Solvent	Temp. (°C)	Conv. (%)	Selectivity (%)						
				5.7	5.8	5.9	5.10	5.11	5.12	Other
1	THF	150	100	2±2	38±4	16±2	32±2	1.4±1	4±2	7±2
2	THF	180	100	0	33±5	0	15±5	36±5	13±5	3±3
3 ^b	THF	150	97 ± 3	2±1	55±5	3±3	24±2	2±0.5	7±3	7±3
4	MeOH	100	30	33±5	31±5	0	0	16±5	10±5	11±5
5	MeOH	135	100	0	61±5	0	25±5	3±3	4±4	8±5
6	MeOH	180	100	0	32±5	0	6±5	30±5	25±5	6±5
7 ^b	MeOH	150	96 ± 2	0	45±5	0	5±5	14±5	27±5	9±5

a) Conditions: 1 mmol substrate, 2.5 mol-% catalyst, 5 mol-% acid, 2 mL solvent and 3.3 mmol MeOH (in THF), 16 h. The conversions and selectivities were determined by GC-analysis; b) 5 mol-% of Al(OTf)₃ was used as acid.

5.3.3 Cyclocondensation and Methylation of 5-amino-1-pentanol

The results obtained during the *N*-butylamine experiments and those reported in a recent publication²⁶² inspired the use of 5-amino-1-pentanol (**5.13**) as the substrate to establish the effect of using Ru(Triphos)(TMM) as a catalyst (Scheme 5.8). In reference 261, 6-amino-1-hexanol was used and the formation of *N,N*-dimethyl-6-amino-1-hexanol was observed in high yields. Here, the cyclisation of 5-amino-1-pentanol to piperidine (**5.14**) and *N*-methylpiperidine (**5.15**) was achieved. This intermolecular cyclocondensation of **5.13** has previously been studied with a number of different catalysts, including a couple of Ru-based systems.^{280, 281} In the first case, the coupling of amines to alcohols as well as the intermolecular reactions of amino alcohols were studied.²⁸⁰ When 5-amino-1-pentanol was used as substrate, piperidine was produced with 71 % conversion after 24 h at 155 °C. The mechanism of the cyclisation was later studied with another Ru-catalyst (*cis*-RuCl₂(dppb)(2-aminomethylpyridine))

using KOH as co-catalyst, identifying two reaction pathways by experimental results and DFT calculations.²⁸¹ One pathway led to the piperidine by a redox-neutral hydrogen borrowing route, and the second yielded a cyclic amide by a net oxidation involving the loss of H₂. The studied Ru-catalyst seemed to favour hydrogen formation, which meant that the lactam product was produced selectively (93 %). Other research on this reactivity will be discussed in more detail in Chapter 6.



Scheme 5.8. Reaction of 5-amino-1-pentanol (5.13) to produce piperidine (5.14) and *N*-methylpiperidine (5.15) in the presence of methanol.

In Table 5.2 the results of the cyclisation reaction are shown. The reaction was carried out in THF with and without methanol, and in pure methanol. In all cases full conversion of **5.13** was achieved. With THF as the solvent, and in the presence of methanol, a mixture of products was formed, but in the absence of methanol only **5.14** was observed (entries 1 and 3). When the reaction was carried out in pure methanol, the main product at 150 °C, 16 h, was **5.15**, which was formed with high selectivity (94 %, entry 2). The other product formed in methanol is still unidentified, but it is believed to be an intermediate with a carbonyl group. When the reaction was carried out without the catalyst (only acid) no product was formed, which showed that even the cyclisation step required the Ru-catalyst for it to be plausible.

Table 5.2. Result of the experiments for the reaction between 5.13 and MeOH in the presence of a Ru-catalyst and a co-catalytic acid.^a

Entry	Solvent	Temperature (°C)	Time (h)	Yield ^b (%)		
				5.14	5.15	other
1	THF	150	16	33	67	0
2	MeOH	150	16	0	94	6
3 ^c	THF	150	16	100	0	0
4	MeOH	100	24	84	11	4.6
5	MeOH	200	24	0	91	9
6	MeOH	200	8	0	87	13
7	MeOH	200	2	2	84	14
8	MeOH	150	8	8.4	81	10
9	MeOH	150	4	0	94	5.7

a) Conditions: 1 mmol substrate, 2.5 mol-% catalyst, 5 mol-% acid, 2 mL solvent and 3.3 mmol MeOH (in THF); b) The yields were determined by GC-analysis, and are based on the average of at least 2 experiments; c) Reaction in the absence of MeOH.

The effect of temperature and reaction time were studied in more detail with methanol as the solvent to see how the selectivity changed (entries 4-9). At 100 °C, **5.14** was the main product even after 24 h (entry 4). At 200 °C, shortening the reaction time, decreased the selectivity for **5.15** (entry 5-7). After only 2 h there was still some **5.14** left, which meant that the reaction time was not long enough to allow methylation of all the formed **5.14** to **5.15**. It is not yet clear, if the other product is an intermediate or a side product in the system. Decreasing the reaction time at 150 °C, gave interesting results (entry 2, 8-9), as after 8 h the selectivity for **5.15** was 81 %, but after 4 h already 94 %. This unexpected difference in the selectivities might be explained by differences in catalyst batches and their activity.

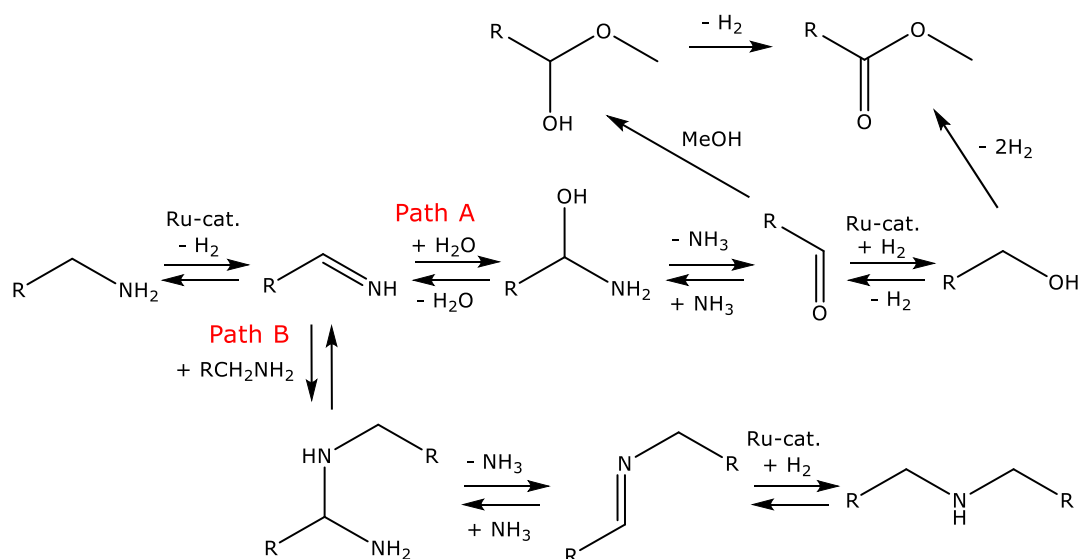
5.4. Chapter Conclusions and Future Work

The methylation of aliphatic amines with methanol catalysed by [Ru(Triphos)(TMM)] has been studied. The selectivities of the reactions were found to depend on the temperature, reaction time and solvent. Dimethylation of the amine was the main reaction, but also several other reactions took place producing for example monomethyl amines, dialkyl amines and the corresponding alcohol. When butylamine was used as the substrate and methanol as the solvent, full conversions were reached at and above 135 °C. The main challenge in this case was achieving reproducible results. Hence different methods of collecting the sample were tried, but no real improvement was achieved. This was probably due to the fact that the reactions were carried out at atmospheric pressure, so some of the final mixture was lost during workup of the reaction.

In addition, the reaction between an amino alcohol (5-amino-1-pentanol) and methanol was of interest. Full conversions to piperidine and *N*-methyl piperidine were achieved under all the studied conditions. Also in this case, the selectivities depended on the temperature, solvent and reaction time. In the presence of methanol and above 100 °C, the cyclisation to *N*-methyl piperidine was the predominant reaction (>80 % selectivity). It was found that the reaction was complete after only 2 h at 200 °C. The highest selectivity for the targeted *N*-methylation (94 %) was reached at 150 °C after both 4 h and 16 h.

As the work described here was carried out over a limited time period, the results raised several questions which would have required additional experiments to be answered properly. One of these questions regards the interesting side reactivity in the amine methylation reactions, which proceeds via deamination as well as the ester formation. One experiment that could shine

light on the reactivity is having an amine react together with water, in the absence of methanol, to see if the corresponding alcohol would be formed. After this the methylation reaction could be carried out in the presence of water scavengers to possibly hinder the alcohol formation and so increase the selectivity towards methylation. All of the side reactions could also be worthy of being studied on their own, to establish whether they are applicable to more substrates. Despite all the unanswered questions, it is quite clear that the methylation with MeOH using the studied catalyst system proceeds via a different mechanism to the previously reported amine methylation with CO₂ and H₂.²³⁶⁻²³⁸ The side products formed in the current case give evidence that the reactions with MeOH proceeds either via a hydrogen borrowing or hydrogen transfer mechanism depending on the product. In Scheme 5.9 are shown the two possible pathways that could lead to the formation of the different side products within the system.



Scheme 5.9. The possible pathways for side product formation within the amine methylation system. Path A leads to the formation of an alcohol, when H₂O is present, and in the presence of methanol also the ester can be formed. Path B on the other hand results in the formation of dialkylamines. Both pathways release ammonia (or possibly methylamines in the presence of methanol). Drawn on the basis of the Milstein group's work on alcohols being formed from amines.²⁶⁸

One benefit of the studied system compared to the previous one, is that it allows for aliphatic amines to be methylated even though the reactions are less selective due to the different pathways yielding the side products.

As mentioned above, another big challenge with the studied reactions was the irreproducibility of the results. Hence, efforts should be made to develop the current system. This improvement could, for instance, be achieved by running the reactions while pressurising the system with an inert gas such as argon or nitrogen. The mass balance of the reactions have not been discussed here, as the focus has been on conversions and selectivities, but in order to increase the accuracy of the system, the mass balances need to be improved. Preliminary experiments were carried out using 50 bar of Ar in the amino alcohol reaction, which led to a mass balance of 75 %. This result was much higher than the normally achieved 50-60 %. Hence, a clear indication that the pressure makes a difference for the results can be seen, and further improvements could possibly be achieved by optimising the work-up procedure.

Once the reproducibility issue is resolved, investigating the scope of the reaction, starting from a variety of amines and amino alcohols, could be of interest. In addition, as discussed earlier, starting from different alcohols to study the esterification reaction further could be useful. Furthermore, it would be interesting to study whether or not the catalyst system can also achieved hydrogenation of amino acids to amino alcohols, as this would make the system susceptible for cascade reactions starting from CO₂, H₂ and amino acids possibly leading to cyclic methylated amines. Also a closer look at different co-catalysts (e.g. Al(OTf)₃) could provide more information about the reactions.

Another solution to the encountered reproducibility issues could be to carry out the reaction in continuous flow, as this is normally the approach for gas phase reactions. This method could make the analysis more precise, especially if on-

line analysis would be implemented. Also, while designing the flow system a reactor with the possibility to perform a cascade reaction could be of interest. As the methylation of primary amines does not occur under H_2 and CO_2 pressure using the $[Ru(Triphos)(TMM)]$ complex, it would be required to design a system where first the hydrogenation of CO_2 produces methanol. Then, after depressurising, this methanol, would be made to react with the amine, which could possibly lead to a system where methylated amines can be produced starting directly from CO_2 , H_2 and the aliphatic amine. However, a challenge linked to developing a continuous system remains with the difficulty of achieving the immobilisation of the catalyst.

5.5 Chapter Appendix

The numerical values for the results shown in the Figures in this Chapter, are listed in Tables SI-5.1 to SI-5.6. Figure SI-5.1 shows examples for GCs of butylamine reactions carried out in MeOH (a) and THF (b), and Figure SI-5.2 for the 5-amino-1-pentanol reaction.

Table SI-5.1. Data for Figure 5.2 - The methylation of 5.1 with MeOH – effect of temperature and solvent.^a

Conditions	Conversion (%)	Selectivity (%)				
		5.2	5.3	5.4	5.5	Other ^b
THF, 150 °C	89.5	9.6	50.3	23.2	1.1	15.8
THF, 130 °C	78.3	23	57.9	15.0	N.O.	4.1
MeOH, 150 °C	100	N.O.	63.9	N.O.	29.8	6.2

a) Conditions: 1 mmol substrate, 2.5 mol-% catalyst, 5 mol-% acid, 2 mL solvent. 3.3 mmol MeOH (in THF), 16 h. The conversions and selectivities were determined by GC-analysis; b) A mixture of unidentified side products; N.O. Not observed.

Table SI-5.2. Data for Figure 5.3 – Results for, when 5.2 was used as starting material.^a

Conditions	Conversion (%)	Selectivity (%)			
		5.3	5.4	5.5	Other ^b
THF, 150 °C	74.6	72.8	16.6	0.6	9.4
MeOH, 150 °C	100	60.5	8.6	5.2	25.7

a) Conditions: 1 mmol substrate, 2.5 mol-% catalyst, 5 mol-% acid, 2 mL solvent. 3.3 mmol MeOH (in THF), 16 h. The conversions and selectivities were determined by GC-analysis; b) A mixture of unidentified side products; N.O. Not observed.

Table SI-5.3. Data for Figure 5.4A. Results for the reactions of *N*-butylamine (5.6) in THF.^a

Conditions	Conversion (%)	Selectivity (%)						
		5.7	5.8	5.9	5.10	5.11	5.12	Other ^b
150 °C	100	1.7	37.7	15.7	32.3	1.4	4.3	6.9
180 °C	100	N.O.	33.3	0.0	15.4	35.7	12.8	2.8
200 °C	92.5	N.O.	29.3	1.4	7.4	29.1	21.5	11.2
150 °C, no MeOH	81.9	N.O.	N.O.	95.2	N.O.	N.O.	N.O.	4.8
150 °C, Al(OTf) ₃	100	1.3	59.1	6.0	24.7	1.5	4.3	3.0
150 °C, Al(OTf) ₃	92.7	3.6	50.0	N.O.	23.5	2.5	10.7	9.7

a) Conditions: 1 mmol substrate, 2.5 mol-% catalyst, 5 mol-% acid, 2 mL solvent. 3.3 mmol MeOH (in THF), 16 h. The conversions and selectivities were determined by GC-analysis; b) A mixture of unidentified side products; N.O. Not observed.

Table SI-5.4. Data for Figure 5.4B. Results for the reactions of 5.6 carried out in MeOH.^a

Conditions	Conversion (%)	Selectivity (%)						
		5.7	5.8	5.9	5.10	5.11	5.12	Other ^b
80 °C	23.4	28.9	18.3	N.O.	N.O.	14.5	8.7	29.6
100 °C	29.6	32.9	30.1	N.O.	N.O.	16.3	9.9	10.8
120 °C	46.1	N.O.	49.6	15.4	19.7	7.6	N.O.	7.7
130 °C	96.9	N.O.	54.5	0.6	29.1	0.7	2.3	12.0
135 °C	100.0	N.O.	60.6	N.O.	24.8	2.9	3.9	7.7
150 °C	100.0	N.O.	49.9	N.O.	5.7	30.6	5.7	8.1
150 °C (rerun)	100.0	N.O.	47.4	N.O.	N.O.	22.3	28.7	1.6
175 °C	100.0	N.O.	52.7	N.O.	25.5	4.5	7.5	9.9
180 °C	100.0	N.O.	32.6	N.O.	6.1	29.9	25.2	6.3
200 °C	100.0	N.O.	53.3	N.O.	25.9	4.5	6.5	9.8
200 °C (rerun)	100.0	N.O.	49.8	0.3	11.7	6.2	24.9	7.3

a) Conditions: 1 mmol substrate, 2.5 mol-% catalyst, 5 mol-% acid, 2 mL solvent. 3.3 mmol MeOH (in THF), 16 h. The conversions and selectivities were determined by GC-analysis; b) A mixture of unidentified side products; N.O. Not observed.

Table SI-5.5. Data for Figure 5.5; Comparing collection methods of the sample.^a

Conditions	Conversion (%)	Selectivity (%)						
		5.7	5.8	5.9	5.10	5.11	5.12	Other ^b
150 °C	100.0	N.O.	49.9	N.O.	5.7	30.6	5.7	8.1
150 °C	100.0	N.O.	62.7	N.O.	18.4	12.1	4.5	2.3
150 °C (flush)	100.0	N.O.	33.1	N.O.	2.4	34.1	25.9	4.5
150 °C (collect and flush)	100.0	N.O.	48.8	N.O.	31.3	3.0	6.4	10.5
150 °C (collect)	100.0	N.O.	57.6	N.O.	20.7	8.5	6.3	6.9
150 °C (rerun)	100.0	N.O.	47.4	N.O.	N.O.	22.3	28.7	1.6
150 °C, Al-triplate	96.2	N.O.	45.4	N.O.	5.1	14.0	26.7	8.9

a) Conditions: 1 mmol substrate, 2.5 mol-% catalyst, 5 mol-% acid, 2 mL solvent. 3.3 mmol MeOH (in THF), 16 h. The conversions and selectivities were determined by GC-analysis; b) A mixture of unidentified side products; N.O. Not observed.

Table SI-5.6. Data for Figure 5.6 – Results for when 5.11 was used as starting material.^a

Conditions	Conversion (%)	Selectivity (%)	
		5.12	Other ^b
150 °C	46.8	91	9
180 °C	57.6	96.9	3.1

a) Conditions: 1 mmol substrate, 2.5 mol-% catalyst, 5 mol-% acid, 2 mL solvent. 3.3 mmol MeOH (in THF), 16 h. The conversions and selectivities were determined by GC-analysis; b) A mixture of unidentified side products; N.O. Not observed.

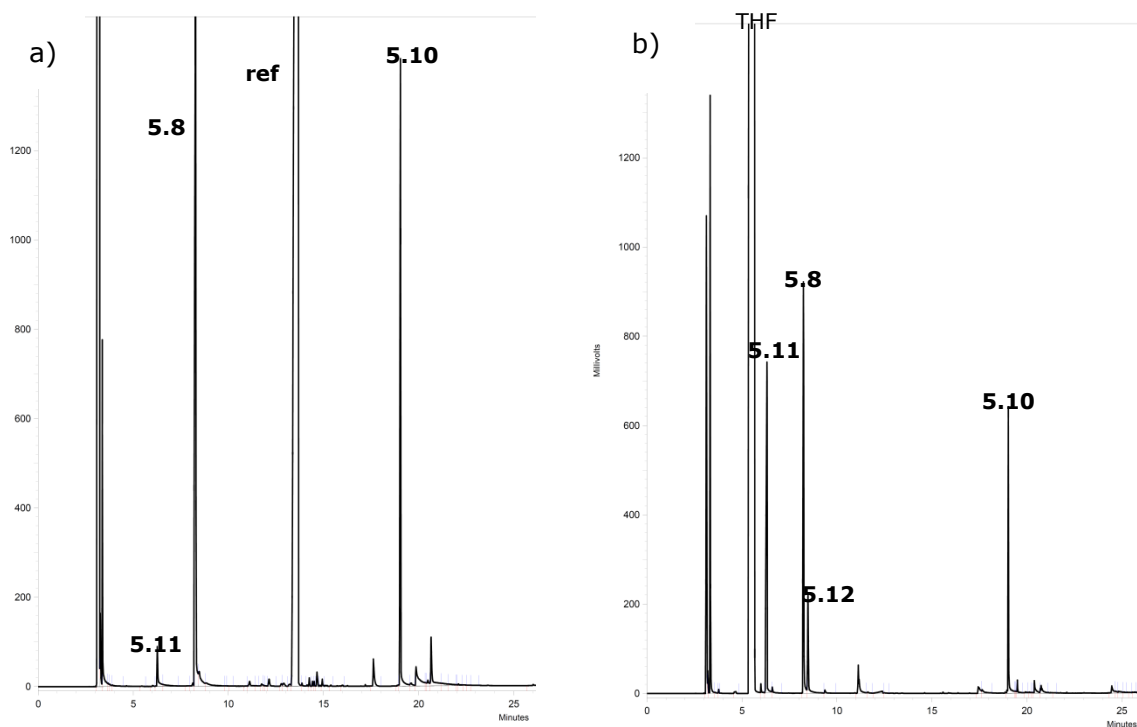


Figure SI-5.1. Examples of GCs after the reaction of *N*-butylamine with MeOH under different conditions, ref is *n*-octane and it was used as an internal standard. Peaks <5 min are MeOH and related peaks. Conditions: a) 1 mmol substrate, in MeOH, 135 °C, 16 h; b) 1 mmol substrate, 3.3 mmol MeOH in THF, 180 °C, 16 h. Entry 2 and 5 Table 5.1 are based on these results.

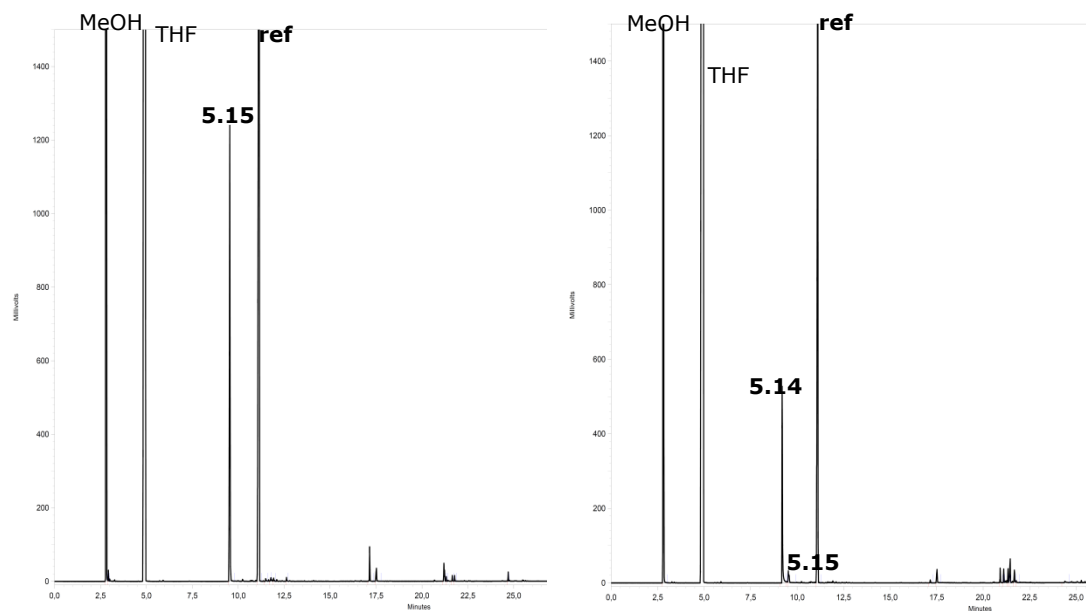


Figure SI-5.2. Examples of GCs after the reaction of 5.13 with MeOH under different conditions. Peaks below 3 min are for MeOH etc., THF was used as solvent for GC samples, ref is *n*-octane and it was used as an internal standard. Conditions: Right: 1 mmol substrate, in MeOH, 150 °C, 4 h under 50 bar of Ar; Left: 1 mmol substrate, in MeOH, 100 °C, 24 h.

Chapter 6. Reactions of Amino Alcohols over γ -Alumina Catalyst in scCO_2

6.1 Introduction

In this Chapter the syntheses of a number of different alkylated cyclic amines, starting from amino alcohols and alcohols, is described. The research discussed here was inspired by the work carried out in Aachen on similar reactivity (section 5.3.3), and hence initial experiments were carried out by using 5-amino-1-pentanol as the substrate (section 6.2.1). Methanol was used as the model alkylating agent, but also other alcohols were tested. The scope of the reaction was studied starting from a variety of different amino alcohols, and the conditions were optimised for each reaction (section 6.2.2). Finally, in section 6.2.3, interesting reactivity between CO_2 and some of the substrates, leading to the formation of cyclic ureas and urethanes, is presented. However, first, the previous research on the formation of alkylated cyclic amines from amino alcohols is summarised briefly in section 6.1.1. A paper based on the work described in this Chapter has been published in *the Beilstein Journal of Organic Chemistry*.²⁸²

6.1.1 Formation of Alkylated Cyclic Amines from Amino Alcohols

N-alkylated cyclic amines are important intermediates both in synthetically useful motifs, and in pharmaceuticals. These are traditionally produced using halogenated reagents, which afford stoichiometric amounts of waste, and are often toxic. When the *N*-alkylation is carried out using an alcohol, water is the only side product. The research presented in this Chapter focuses on forming *N*-alkylated cyclic amines starting from amino alcohols and alcohols. This reactivity is relatively widely studied, and the emphasis of the previous research has been on either the formation of cyclic amines from amino alcohols,^{281, 283-290} or on the cyclisation and subsequent *N*-methylation, leading to the target products.²⁹¹⁻²⁹⁷ In addition, research on the *N*-alkylation of cyclic amines has been carried out.^{193, 298-301} For instance, the *N*-methylation of morpholine was achieved in moderate yields by dimethyl carbonate even without catalyst (67 %),²⁹⁸ and with methanol over a CuO-NiO-catalyst in continuous flow (yield >90 %).²⁹⁹

Most of the previous work on the cyclisation reactivity has involved employing heterogeneous catalysts and continuous flow systems.^{284-286, 288, 290-297} However, on some occasions the presence of H₂, which has safety issues linked to it, is required, in order to avoid over-reacting the formed cyclic amine to aromatic compounds.^{284, 285, 291, 295-297} One example, where this was avoided, was reported by Oku *et al.*,^{293, 294} who studied the *N*-methylation of amino alcohols in supercritical methanol (scMeOH, T_c = 239.5 °C and P_c = 81 bar). Several substrates were reacted over different solid-acid catalyst, and it was found that the selectivity of the reaction could be tuned by varying the pressure and also the phase of the methanol. In the gas phase, mainly inter- and intramolecular dehydrations were observed, and in the supercritical phase selective *N*-methylation of the amino alcohols occurred. In the case of 5-amino-1-pentanol

at 300 °C, a 51 % conversion was obtained with 80 % selectivity to the *N*-methylated products, and 20 % selectivity to the cyclic products, using a heterogeneous Cs-P-Si catalyst.

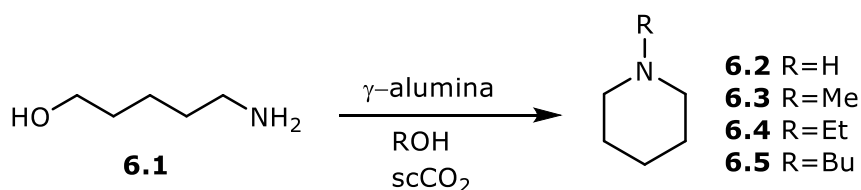
Another common feature in the previous work is that the focus has been on the development of new catalysts, and hence the substrate scope only includes a few molecules in order to prove the concept, and that the catalyst system is useful.^{281, 284-286, 288, 292, 295} Often γ -alumina has been overlooked as the catalyst, or found to be low in activity. Instead, zeolites,²⁹² supported metals^{284, 285, 290, 291, 295-297} and different Cs-catalysts^{286, 288, 293, 294} have been shown to be active as heterogeneous catalysts in the target transformation. Based on this information, and the previous work carried out with γ -alumina, the cyclisation of amino alcohols, followed by the *N*-methylation of the cycle were studied using the self-optimising reactor with scCO₂ as the solvent over γ -alumina. Unlike the reactions described in Chapter 5, which occurred via a hydrogen borrowing or hydrogen transfer mechanism, the reactions discussed in this Chapter are mainly simple dehydrations catalysed by a solid acid.

6.2 Results and Discussion

6.2.1 5-amino-1-pentanol

The work began after the discovery that 5-amino-1-pentanol (**6.1**, Scheme 6.1) can be methylated with MeOH using γ -alumina as catalyst. The conditions (temperature and flow rate) for this reaction were then optimised using the SNOBFIT algorithm, with the aim to maximise the yield for *N*-methyl piperidine (**6.3**). The optimisation was carried out with and without CO₂ and the results can be seen in Figure 6.1. In the presence of CO₂, high yields for **6.3** (93-94 %) were achieved (Table 6.1, entry 1-3, Figure 6.1A). When the optimisation was

carried out without CO₂, 10-15 % lower yields were obtained (highest yield <85% at 350 °C; Table 6.1, entry 5-8; Figure 6.1B). This result indicates that using scCO₂ as a solvent was beneficial for the reaction. In section 6.4 (Chapter Appendix), tables including all the measured points for the experiments described here, and for the other optimisations presented in this Chapter, can be found.



Scheme 6.1. The cyclisation and alkylation of 5-amino-1-pentanol (6.1) forming cyclic amines 6.2 to 6.5.

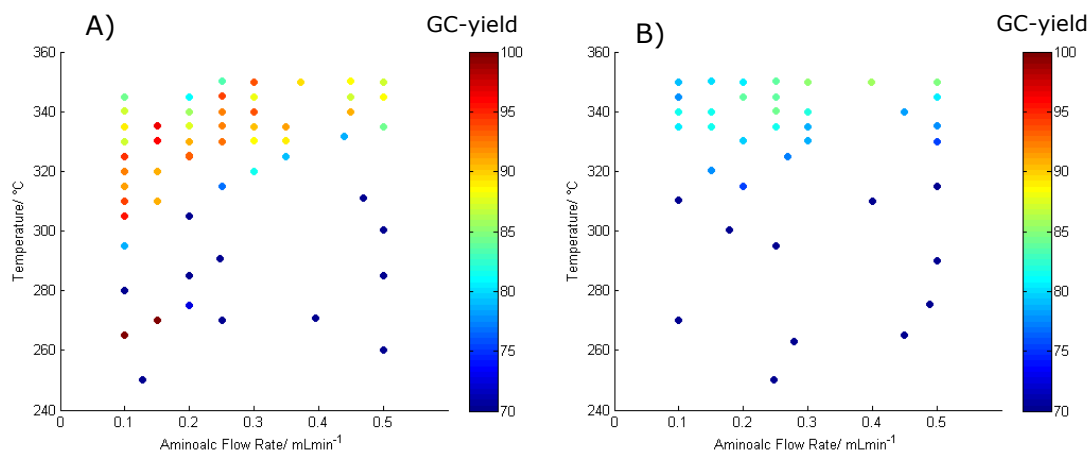


Figure 6.1. Result of the SNOBFIT optimisations for *N*-methyl piperidine (6.3) with CO₂ (A) and without CO₂ (B). The colour of the dots represents the yield of the reaction at each measured condition on a scale from 70-100 %. This scale makes it possible to identify the differences between the two experiments. It can be seen that higher yields of 6.3 were obtained when CO₂ was present in the system than when it was not. Conditions: 250-350 °C, 0.1-0.5 ml/min 6.1 (0.5 M solution in MeOH), 100 bar, 0.5 ml/min CO₂ when applicable.

The highest yielding points for the experiments shown in Figure 6.1 are listed in Table 6.1. In both cases, the optimal points or optimal regions were identified quite early on in the experiment. In the presence of scCO_2 , the optimisation was carried out for approximately 29 h during which 57 different conditions were tested. The optimisation was stopped by the operator at this stage (before a new 'call' to SNOBFIT was made), as the yield of the reaction had not increased since the 23rd measurement (entry 3), and it could be determined that the optimal conditions had been found. The first time high yields (>90 %) were located was at the 8th measured conditions. Without CO_2 , the highest yield was found already at the 6th point (entry 5), and hence the optimisation was stopped after 38 measurements (total time 19.5 h). During both experiments the parameter space was extensively studied (Figure 6.1), and high yields of the target were achieved at several different conditions (Table 6.1). This observation suggests that the located optimum regions correspond to the global optimum within the studied limits of the reaction.

Entry 1 in Table 6.1 was chosen as the optimal point, as it afforded the highest yield of **6.3** with an intermediate flow rate (94 %, 0.3 ml/min). The throughput was also calculated, and it was larger at higher flow rates than under the 'optimal conditions', even without CO_2 . However, as maximising the yield of **6.3** was the target of the optimisation, comparing the throughput of the reaction is not relevant. Had the optimisation been asked to target the throughput instead, quite different results could have been obtained. This behaviour was demonstrated by previous work in the group, where it was shown that depending on the target function of an optimisation, the outcome (the optimal conditions) can vary quite drastically.¹²⁰ Also it was thought that the chosen conditions would be suitable for studying the scope of the reaction and further alkylations of **6.1**. The optimal conditions: 0.3 ml/min at 340 °C were later confirmed by

carrying out the reaction at these conditions for 2 h, and reaching the same conversion and selectivity as during the optimisation.

Table 6.1. The highest yields of **6.3 found by the optimisations carried out with CO₂ (entries 1-3) and without CO₂ (entries 5-8).^a**

Entry	Temperature (°C)	Flow Rate (ml/min)	CO ₂	Yield of 6.3 ^b (%)	Throughput ^c (mmol/h)	Measurement no. ^d
1	340	0.3	Yes	94	8.46	44
2	310	0.1	Yes	94	2.82	27
3	330	0.15	Yes	96	4.32	23
4	350	0.5	Yes	87	13.05	20
5	350	0.4	No	86	10.32	6
6	350	0.3	No	85	7.65	19
7	350	0.5	No	83	12.45	32
8	340	0.3	No	82	7.38	29

a) Conditions: 250-350 °C, 0.1-0.5 ml/min **6.1** (0.5 M solution in MeOH), 0.5 ml/min CO₂, 100 bar; b) Based on GLC-analysis of the reaction mixture, the remaining material is a mixture of unidentified side products; c) Calculated from $c(\text{substrate}) \cdot \text{flow}(\text{substrate}) \cdot \text{yield} \cdot 60$; d) The experiment with CO₂ was stopped by the operator after 29 h and 57 measurements (optimal point 23rd measurement), and the one without CO₂ after 19.5 h and 38 measurements (highest yield at the 6th measurement point), as in either case the optimal point had not changed for a long enough time.

Entry 4 in Table 6.1 shows the result in scCO₂, for the point that afforded the highest throughput of **6.3** in the optimisation carried out without CO₂ (entry 7). Entry 8, on the other hand, was measured at the same conditions as entry 1 (optimal point), but without CO₂. Both of these results confirm that scCO₂ was useful for the reaction, as higher yields were obtained in the presence of CO₂ than in its absence.

After the optimisation, the scope of the reaction was studied using different alcohols as solvents (alkylating agents) and later by using different substrates. In most cases, a small temperature ramp was first carried out to investigate the reactivity and possible changes in selectivity. Also the effect of CO₂ on some of the reactions was studied. Optimisations were carried out when the selectivity for the target product was lower than expected.

In Table 6.2, the results for the alkylation of **6.1** with different alcohols are shown. It can be seen that when the reaction was carried out in ethanol or butanol, the targeted alkylated piperidines (**6.4** and **6.5**, Scheme 6.1) were

produced with high selectivity (>70 %) at 340 °C (entry 2 and 5 respectively). In both cases, using scCO₂ as a solvent increased the selectivity for the targets (entry 2 vs 3, and 5 vs 6). Also increasing the temperature from 300 °C to 340 °C increased the selectivity for the alkylated piperidines, which showed that the formation of the alkylated products were highly dependent on the temperature (entry 1 vs 2, and 4 vs 5). The reaction was also carried out in *i*-PrOH (entry 7 and 8), but mainly piperidine (**6.2**) was produced. In this case, the presence of scCO₂ did not affect the outcome of the reaction, as similar results were achieved both with and without CO₂ (80 % selectivity for **6.2**). This result might indicate that scCO₂ is beneficial for the alkylation reaction (alcohol activation), whereas the cyclisation occurs in either case. An optimisation was carried out to try and increase the selectivity for, what was assumed to be the target product, but no improvement was observed. This might suggest that γ -alumina is not active enough to activate the secondary *i*-PrOH, and hence the formation of the alkylated piperidine is hindered.

Table 6.2. Cyclisation and *N*-alkylation of **6.1 with different alcohols over γ -alumina in scCO₂ forming *N*-alkylated piperidines **6.4** and **6.5**.^a**

Entry	Alcohol	CO ₂	Temperature (°C)	Conversion ^b (%)	Selectivity ^b (%)		
					<i>N</i> -alkylated	6.2	Other ^c
1	EtOH	Yes	300	69	3.3	78	19
2	EtOH	Yes	340	100	82	10	8
3	EtOH	No	340	100	66	22	12
4	BuOH	Yes	300	100	36	N.O.	64
5	BuOH	Yes	340	100	73	N.O.	27
6	BuOH	No	340	100	60	3	37
7	<i>i</i> -PrOH	Yes	340	100	N.O.	80	13
8	<i>i</i> -PrOH	No	340	100	N.O.	79	15

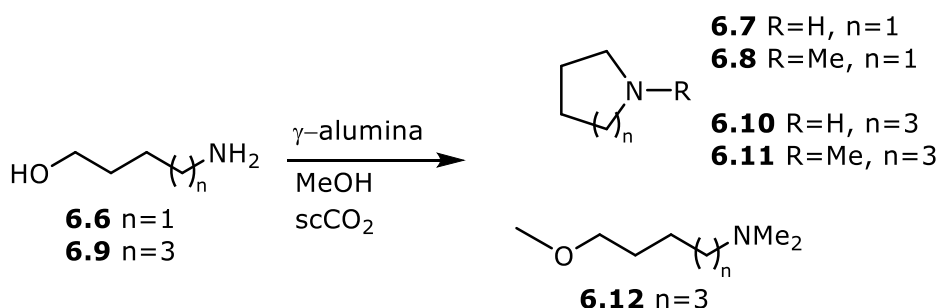
a) Conditions: 0.3 ml/min **6.1** (0.5 M solution in alcohol), 0.5 ml/min CO₂, 100 bar; b) Based on GLC-analysis of the reaction mixture; c) Unidentified side products; N.O. = Not Observed.

In addition to the alcohols mentioned in Table 6.2, also octanol and ethylene glycol were studied as alkylating agents. Octanol, which overlapped with the starting material in the GC, mainly formed dioctylether. Also another product was formed, which was detected at the same retention time as piperidine, and therefore no conversions or selectivities could be determined (NMR results

suggested that piperidine was not formed). Nevertheless, according to MS-results, the octyl alkylated piperidine was present, when the reaction was carried out at 340 °C. Ethylene glycol, on the other hand, formed several etherification products, when passed over the catalyst at 300-340 °C. The addition of the substrate to the reactor blocked the system, which indicated that a reaction took place between the two reagents. However, these products were not identified.

6.2.2 Substrate Scope

The next step, when investigating the scope of the reactivity, was to use different amino alcohols as substrates in reactions with MeOH. To start with, 4-amino-1-butanol (**6.6**, Scheme 6.2) and 6-amino-1-hexanol (**6.9**) were studied to see, if cyclic amines with different sizes could be produced. As expected, **6.6** was readily converted to the corresponding methylated pyrrolidine **6.8** at the optimal conditions for making **6.3** (94 % selectivity at 340 °C; Table 6.3, entry 3). It was also clear that by increasing the temperature the yield for **6.8** was increased (entry 1-3), and the unmethylated product **6.7** was only present at 300 °C.



Scheme 6.2. The products that are formed when 4-amino-1-butanol (**6.6**) or 6-amino-1-hexanol (**6.9**) cyclises and gets alkylated. **6.9** can, in addition to the cyclic products, form **6.12** at lower temperatures.

When **6.9** was used as the substrate, different reactivity was observed (Table 6.3, entry 4-6). The main reaction was the methylation of the amino alcohol instead of the cyclisation and subsequent methylation, hence forming **6.12** instead of **6.10** or **6.11**. The selectivity for **6.12** was highest, when the reaction was carried out without CO₂ at 340 °C (entry 7, 74 % selectivity for **6.12**, with 89 % conversion). The selectivity for 1-methylazepan (**6.11**) was only 20 % at the optimal conditions for producing **6.3** (entry 6), and hence an optimisation was carried out to try and increase this value (entry 8, Figure 6.2). The upper temperature limit was increased to 380 °C, which resulted in 50-55 % yields of the target.

Table 6.3. The results for the formation of 6.8 and 6.11 from 6.6 and 6.9 respectively.^a

Entry	Substrate	Flow Rate (ml/min)	Temp. (°C)	Conv. ^b (%)	Selectivity ^b (%)		
					6.7/6.10	6.8/6.11	6.12
1	6.6	0.3	300	100	30	65	
2	6.6	0.3	320	100	N.O.	87	
3	6.6	0.3	340	100	N.O.	94	
4	6.9	0.3	300	65	N.O.	N.O.	3
5	6.9	0.3	320	71	N.O.	12	69
6	6.9	0.3	340	93	N.O.	20	65
7 ^c	6.9	0.3	340	89	N.O.	12	74
8 ^d	6.9	0.25	370-380	100	N.O.	50-55	N.O.

a) Conditions: 0.3 ml/min substrate (0.5 M solution in alcohol), 0.5 ml/min CO₂, 100 bar; b) Based on GLC-analysis of the reaction mixture, the remaining material is a mixture of unidentified side products; c) The reaction was carried out without scCO₂; d) Results after optimisation for **6.11**, see Figure 6.2 for details; N.O. = Not Observed.

In addition to the observation that the formation of **6.11** was highly dependent on the temperature, it was also seen that as the temperature increased, the formation of the methylated amino alcohol **6.12** was hindered, and instead another unidentified side product was obtained. The optimisation was stopped only after 17 points as the software crashed (and the substrate ran out, Figure 6.2). The optimal conditions were confirmed by running the reaction at both 370 °C and 380 °C with 0.25 ml/min substrate flow, leading to 50-55 % selectivities for the cyclic products. This result was 30-35 %-units higher than that obtained before the optimisation.

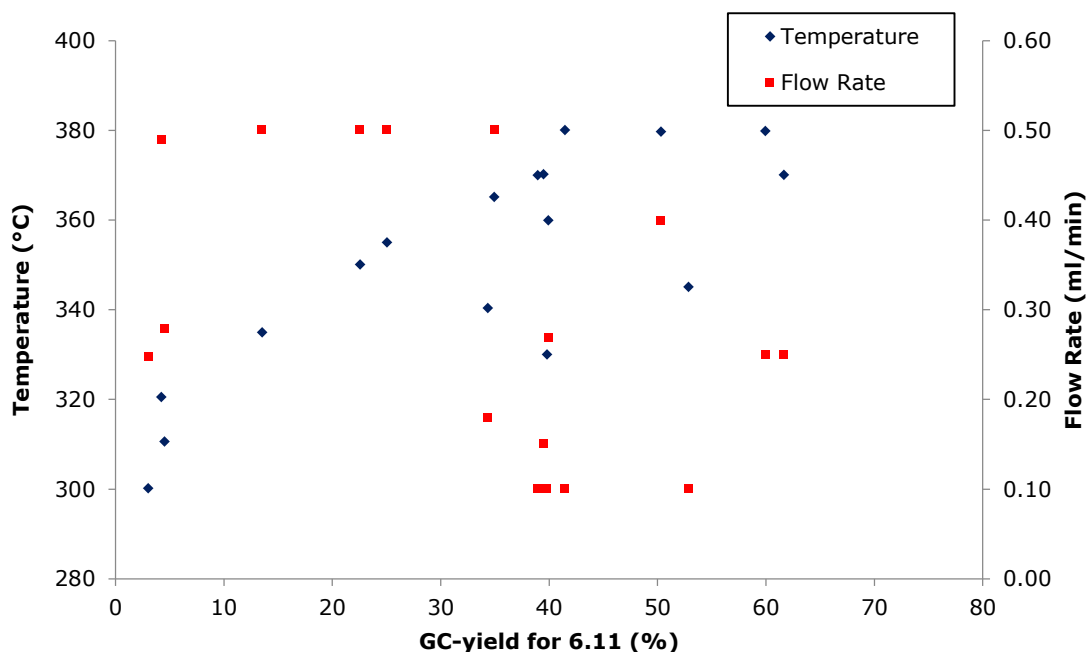
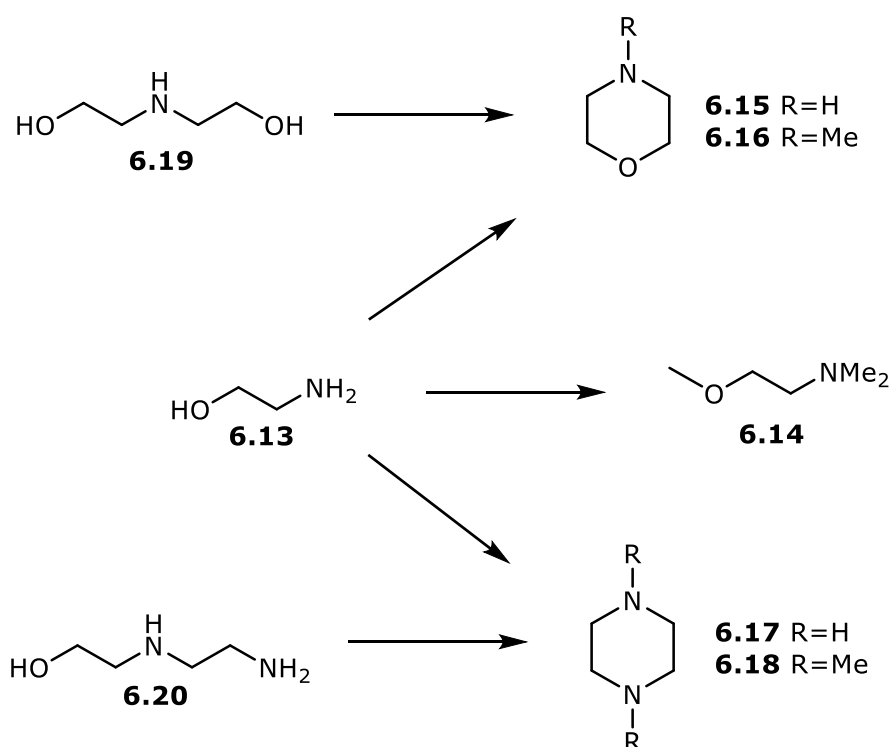


Figure 6.2. The SNOBFIT optimisation for *N*-methyl azepan (**6.11**). The optimisation was stopped already after 17 measurements, as the reagent ran out. The optimal region was determined to be 370-380 °C and 0.25 ml/min, as 50-55 % yields of **6.11** were obtained. Conditions: 0.1-0.5 ml/min (0.5 M of **6.9** in MeOH), 300-380 °C, 0.5 ml/min CO₂, 100 bar.

In order to try and avoid the methylation reactions of substrate **6.9**, other solvents, namely THF and *i*-PrOH, were also tried. These did not increase the selectivity for the azepan, but instead a similar reactivity to which was seen in the aniline study was observed. In section 4.2.1 the formation of *N*-phenyl pyrrolidine starting from aniline and THF occurred, and also in this case a pyrrolidine was produced, but this reactivity was not studied further.

Next the reactivity, when starting from ethanolamine (**6.13**, Scheme 6.3), was studied. In this case, similar activity to that of 6-amino-1-hexanol was found, as **6.14** was produced with high selectivity at the standard conditions (0.5 M solution, 0.3 ml/min, 340 °C; Table 6.4, entry 1, 72 % selectivity for **6.14**). Intra-molecular cyclisation of **6.13** was not observed, as at higher temperatures the cycles **6.16** or **6.18** were produced. To increase the selectivity for these, a

1 M solution of **6.13** in methanol was used, which gave 11 % and 63 % selectivities for **6.16** and **6.18** respectively, after optimisations (Table 6.4, entry 2 and 3). These results indicate that the favoured reactivity of **6.13**, is via the alcohol amination, which leads to the piperazine product (**6.18**), rather than the deamination pathway, which instead would results in the morpholine derivatives (**6.15** or **6.16**).



Scheme 6.3. Reactions that form cycles **6.15** to **6.18** starting from **6.13**. **6.15** and **6.16** can also be formed from **6.19**, whereas **6.20** produces **6.17** and **6.18**. **6.13** yields **6.14** with high selectivity under different conditions. All the reactions are carried out over γ -alumina catalyst, and with scCO_2 as solvent together with MeOH as co-solvent and reagent.

Table 6.4. Initial results, and optimal conditions, for the formation of 6.16 and 6.18 starting from 6.13, 6.19 or 6.20.^a

Entry	Reaction	Conc. (M)	Flow Rate (ml/min)	Temp. (°C)	Conv. ^b (%)	Selectivity ^b (%)	
						Cyclisation ^c	Other
1	6.13 → 6.16/18	0.5	0.3	340	100	13	6.14 , 72
2 ^d	6.13 → 6.16	1.0	0.1	370	100	11	6.18 , 48
3 ^d	6.13 → 6.18	1.0	0.1	360-365	100	57-63	
4	6.19 → 6.16	0.5	0.3	340	100	24	6.18 , 32
5 ^d	6.19 → 6.16	0.5	0.3	380	100	46	6.18 , 27
6	6.20 → 6.18	0.5	0.3	340	100	40	
7 ^d	6.20 → 6.18	0.5	1.0	380	100	68	

a) Conditions: Solutions in MeOH, 0.5 ml/min CO₂, 100 bar; b) Based on GLC-analysis of the reaction mixture, the remaining material is a mixture of unidentified side products; c) The product is the *N*-methylated cyclic product as indicated in the 'Reaction'-column; d) Results after optimisation, conditions: 300-380 °C, 0.1-1.0 ml/min substrate (in MeOH), 0.5 ml/min CO₂, 100 bar.

As low yields of *N*-methyl morpholine (**6.16**) were obtained when ethanolamine (**6.13**) was used as the substrate, diethanolamine (**6.19**) and also *N*-(2-hydroxyethyl)ethylenediamine (**6.20**) were tested as starting materials, in order to increase the selectivity for **6.16** and possibly **6.18** (Scheme 6.3). Again, high temperatures were required to reach moderate yields of **6.16** and **6.18** (Table 6.4, for **6.16** entry 4 and 5; for **6.18** entry 6 and 7).

The highest selectivity for dimethyl piperazine (**6.18**), 68 %, was obtained, when the temperature was 380 °C and the flow rate was 1.0 ml/min. This result implies that the formation of **6.18** is highly favourable in the system, and hence decreasing the residence time by increasing the flow rate will increase the yield of the target, as side reactions have less time to occur. The main side products in this case were **6.16** together with **6.14** or a derivative of **6.14**, which suggests decomposition of **6.20** as one pathway to forming side products.

Also, when starting from diethanolamine (**6.19**), the decomposition of the starting material led to interesting side reactions, where the main side product turned out to be **6.18** (entry 4 and 5). This product can possibly be formed via an ethanolamine intermediate. Ultimately, this side reactivity, currently limits the selectivity for **6.19** to 46 %, which is still an improvement compared to the starting conditions (from 24 % to 46 % selectivity). The formation of **6.18**

starting from **6.19** has previously been reported, when **6.19** has been allowed to react with methylamines over zeolite catalysts.^{302, 303}

The stability of the catalyst was studied with the reaction forming **6.18** from **6.20** by running a temperature ramp (Figure 6.3). The reason, why this reaction was chosen for the investigation of the catalyst activity was, because **6.20** is considerably cheaper than e.g. 5-amino-1-pentanol (**6.1**), and hence it was sensible to run a long stability test starting from **6.20** rather than **6.1** (**6.1** approx. £110/50g; **6.20** £48/1kg from Sigma-Aldrich, October 2016).

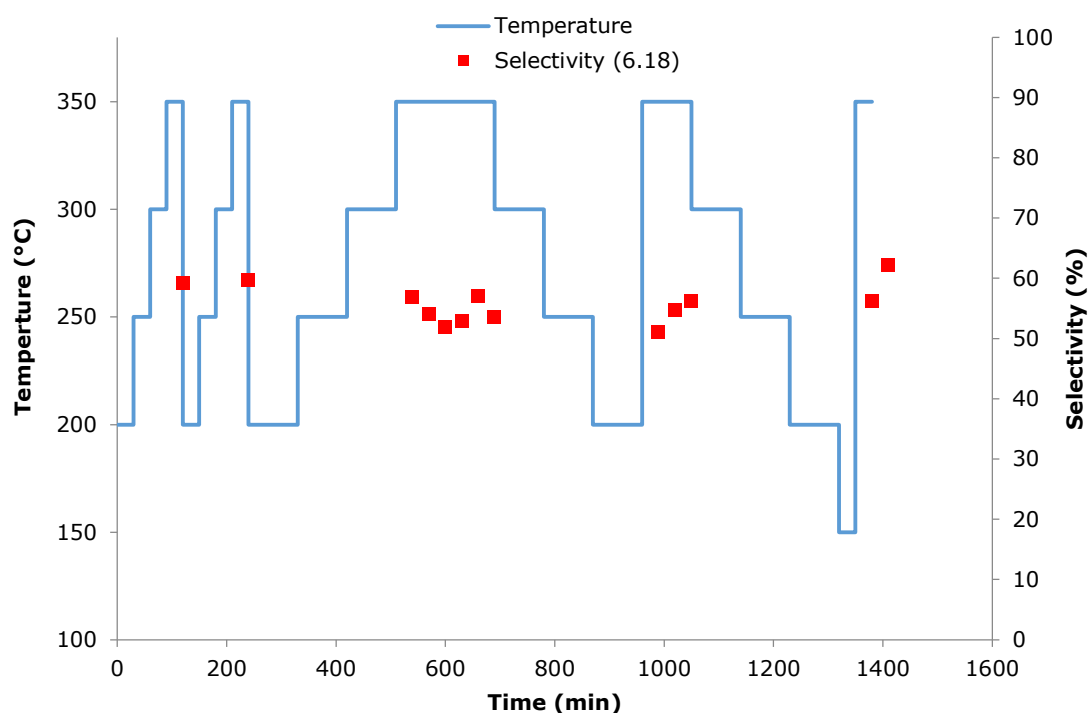


Figure 6.3. A temperature ramp to study the stability of the catalyst over a long period of time, and while changing the conditions. The step size was 50 °C, and during the 2 first ramps, 1 sample was taken at each temperature to see possible changes during the first few hours (sample every 30 min). Later on, 3 samples per temperature were taken before heating or cooling. As the sampling was done with the sample loop, only the results at 350 °C were representative. However the result shows that the catalyst was stable, which was the aim of the experiment. Conditions: 150-350 °C, step size 50 °C, 0.3 ml/min **6.18 (0.5 M in MeOH), 0.5 ml/min CO₂, 100 bar.**

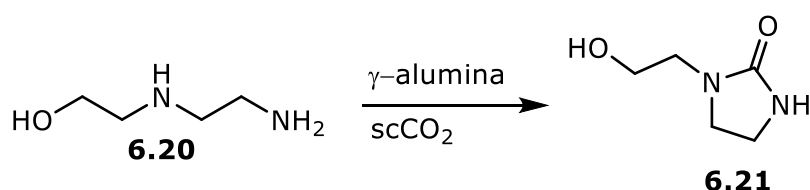
A temperature ramp (as shown in Figure 6.3) was carried out to see how well the catalyst withstands changes in the conditions, hence simulating an optimisation. By returning to the same conditions at set intervals, a comparison of the stability of the catalyst can be achieved by comparing the yields of the reaction. The sampling was done at 200 °C, 250 °C, 300 °C, 350 °C, and once at 150 °C. Unfortunately, due to the low sampling volume (sample diluted with CO₂), combined with the high response factors of the starting material and the formed products (except for **6.18**) representative results were only obtained at 350 °C. However, these results show that similar yields of **6.18** were achieved each time the ramp reached 350 °C, which indicated that the catalyst was, in fact, stable for at least 24 h.

6.2.3 Reactions between Amino Alcohols and CO₂

Throughout the work described so far in this Chapter, several side reactions were occurring, all of which were not identified. One interesting side reaction was the incorporation of CO₂ into some of the studied substrates (Scheme 6.4 and Scheme 6.5). These reactions were first identified, when investigating the formation of cycle **6.18** from **6.20**, and *N*-methyl morpholine (**6.16**) from **6.19**, as at lower temperatures (250 °C) other products; namely **6.21** and **6.22** were observed.

The formation of these kinds of cyclic ureas³⁰⁴⁻³¹² and urethanes^{306, 308, 313-324} from CO₂ and diamines or amino alcohols, have previously only been studied in batch processes. The reason for this might be that these materials are solids at room temperature, and also traditionally require long reaction times (over 8 h) to be formed. The importance of this reactivity is highlighted as it has been included in reviews concerning CO₂ utilisation, and the incorporation of CO₂ into cyclic compounds.^{33, 37} The formation of imidazolidones and oxazolidinones often

require catalysts; antimony^{304, 305, 313} or ceria^{309, 311, 323, 324} based systems have been most widely studied, but also tin,³¹⁹ tungsten,^{310, 312} and iron³¹⁴ have been used. A few examples, where no catalyst was necessary, have been reported.^{306, 307} Furthermore, on some occasions, especially when the chirality of the products have been studied, stoichiometric reagents such as phosphines, have been utilised to achieve the transformation.^{308, 315, 316, 321}



Scheme 6.4. The reaction between **6.20** and CO₂ forming imidazolium **6.21**.

Firstly, the synthesis of **6.21** from **6.20** was studied (Scheme 6.4, Table 6.5). The reaction was initially carried out without catalyst, but very low conversions were obtained, which proved that the reaction was, at least partly, a catalytic one. In the presence of catalyst, it was then studied, whether **6.21** was obtained from reactions between MeOH and the substrate, or CO₂ and the substrate. It can be seen from Table 6.5, that **6.21** is, in fact, formed in the latter case. When degassed MeOH was used as the solvent, no reaction took place (entry 2), and when the methanol was bubbled with CO₂, a nearly 15 % yield of urea **6.21** was obtained (entry 3). The highest selectivity for **6.21** was reached, when the reaction was carried out in ethanol together with scCO₂ (>85 % selectivity, 81 % conversion; entry 1).

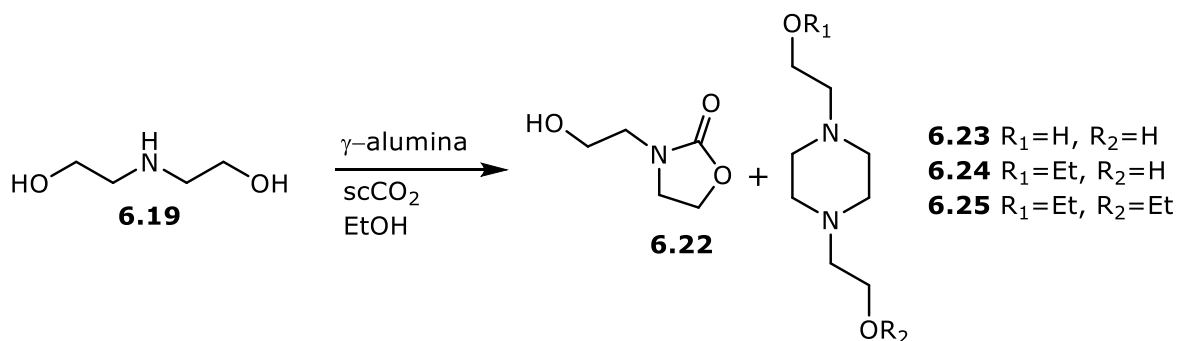
Table 6.5. Results for the formation of **6.21** from **6.20**.^a

Entry	Flow Rate (ml/min)	Temp. (°C)	Solvent	Conversion ^b (%)	Selectivity ^b (%)
1	0.3	250	CO ₂ , EtOH	81	>85
2	0.3	250	MeOH, degassed	-	-
3	0.3	250	MeOH (bubbled with CO ₂)	24	62

a) 100 bar, 0.5 ml/min CO₂ when applicable, 0.5 M **6.20** in MeOH; b) Based on GLC-analysis of the reaction mixture, the remaining material is a mixture of unidentified side products.

The stability of **6.21** was studied by flowing a 0.5 M solution of **6.21** in EtOH through the reactor at different temperatures. It was found that at 275 °C a new product started forming, and it became the major product at 325 °C. This substance was identified as the ethyl ether of **6.21**, which suggests that **6.21** was, indeed, stable over the catalyst. This result was confirmed, when the same experiment was carried out in *i*-PrOH in the presence of **6.20** (0.5 M solutions of both substrates), as **6.21** was identified as the only product at both 250 °C and 275 °C with 0.2-0.3 ml/min flow rates.

After these results, it was of interest to study the formation of **6.22** from **6.19** (Scheme 6.5). This reaction turned out to be less selective than the one above, as slight changes in the conditions resulted in the formation of dimers **6.23** to **6.25** instead of **6.22**.



Scheme 6.5. Diethanolamine (**6.19**) forms **6.22** in reactions with CO_2 . **6.19** can also dimerise to form products **6.23** to **6.25**, in the presence of ethanol.

The results for the experiments aiming at increasing the selectivity for **6.22** or **6.23** by changing the concentration, temperature, flow rate and pressure, are shown in Table 6.6. Unfortunately, optimisations could not be carried out for this reaction, as injections via the sample loop to the GC, did not afford representative results for the experiments under the studied conditions. Hence,

the conditions were changed manually, and then the collected sample was injected into the GC for analysis.

Table 6.6. Reactions between CO₂ and 6.19 forming 6.22 over γ -alumina in scCO₂. The formation of dimers 6.23 to 6.25 also takes place (6.24 and 6.25 are only formed in ethanol).^a

Entry	Substrate	Conc. (M)	Flow rate (ml/min)	P (bar)	T (°C)	Conv. ^b (%)	Selectivity ^b (%)
1	6.19	0.5	0.3	100	250	53	6.22 , 52; 6.23 42
2	6.19	0.5	0.2	100	250	98	6.22 , 20; 6.23 65
3	6.19	0.5	0.1	100	250	100	6.23 , 61; 6.24 12 ^c
4	6.19	0.5	0.3	100	240	48	6.22 , 69; 6.23 26
5	6.19	0.2	0.3	100	250	80	6.22 , 42; 6.23 38
6	6.19	0.2	0.3	150	250	73	6.22 , 65; 6.23 19
7	6.19	0.2	0.3	100	240	74	6.22 , 57; 6.23 31
8	6.19	0.2	0.3	150	240	53	6.22 , 72; 6.23 18
9	6.19	1.0	0.1	100	250	100	6.24 32 ^d
10	6.19	1.0	0.2	150	250	56	6.22 , 73; 6.23 22
11	6.19	1.0	0.2	150	275	100	6.22 , 12; 6.23 , 60 ^e
12	6.19	1.0	0.2	100	275	100	6.22 , 8; 6.23 63 ^e
13	6.13	2.0	0.3	100	250	100	6.22 , 15; 6.23 1.4 ^f
14	6.13	2.0	0.3	100	275	100	6.22 , 13.4; 6.23 35 ^f
15	6.13	2.0	0.3	100	300	100	6.22 , 6; 6.23 60 ^f

a) 0.5 ml/min CO₂; b) Based on GLC-analysis of the reaction mixture, the remaining material is a mixture of unidentified side products; c) Trace of **6.22** and its ethyl ether; d) Also forms the ethyl ether of **6.22**, and trace of **6.23** and **6.25**; e) Traces of **6.24**; f) **6.13** is fully converted to **6.19**, which reacts further.

The results in Table 6.6 suggest that the selectivity of the reaction depends on all of the studied variables. At 250 °C (0.5 M solution) the main product was either urethane **6.22** or dimer **6.23** depending on the flow rate of the substrate, and hence the residence time in the reactor. This observation implies that low flow rates favour the formation of **6.23** over **6.22** (entry 2 and 3). When the flow rate was only 0.1 ml/min, the ethylation of the dimer to form **6.24** was found as the major side reaction. **6.24** was seen as the main product at high substrate concentrations and low flow rates (entry 9), as the residence time was long enough for also ethylation of **6.23** to occur.

Lowering the temperature to 240 °C (entry 4) increased the selectivity for **6.22** but lowered the conversion of the starting material (69 % and 48 % respectively). The highest yield for **6.22** was reached by decreasing the concentration of the substrate to 0.2 M and increasing the pressure to 150 bar at

250 °C with a 0.3 ml/min flow rate; 65 % selectivity with 73 % conversion (entry 6). At 100 bar, under otherwise similar conditions, the conversion was 80 %, and the selectivity for **6.22** and dimer **6.23** were 42 % and 38 % respectively (entry 5). Interestingly, at 240 °C, only a 53 % conversion was obtained at 150 bar (72 % selectivity for **6.22**, entry 8), whereas lowering the pressure to 100 bar increased the conversion back to 74 %, but the selectivity for **6.22** was lower (entry 7). This change in selectivity due to the pressure change, might be caused by differences in the substrate concentration, as the density of the carbon dioxide in the system is lower at 100 bar than at 150 bar (250 °C pure CO₂; 2.4 mol/l at 100 bar vs 3.7 mol/l at 150 bar)³²⁵, and hence the relative concentration of the substrate is higher at lower than at higher pressures. This then meant that even though the residence time is shorter at lower pressures, the opportunity of forming the dimer is higher, whereas at higher pressures more CO₂ is present, which again increases the odds of forming **6.22**. The highest throughput of urethane **6.22** was, however, achieved by increasing the concentration to 1.0 M at 150 bar, as 73 % selectivity with a 56 % conversion was obtained (entry 10). Dimer **6.23** was the major product under conditions that provided full conversion of the substrate, but were not active enough to achieve the formation of ethers from **6.23**; low flow rate at 250 °C (entry 2 and 3) or 0.2 ml/min flow at higher temperature (entry 11 and 12).

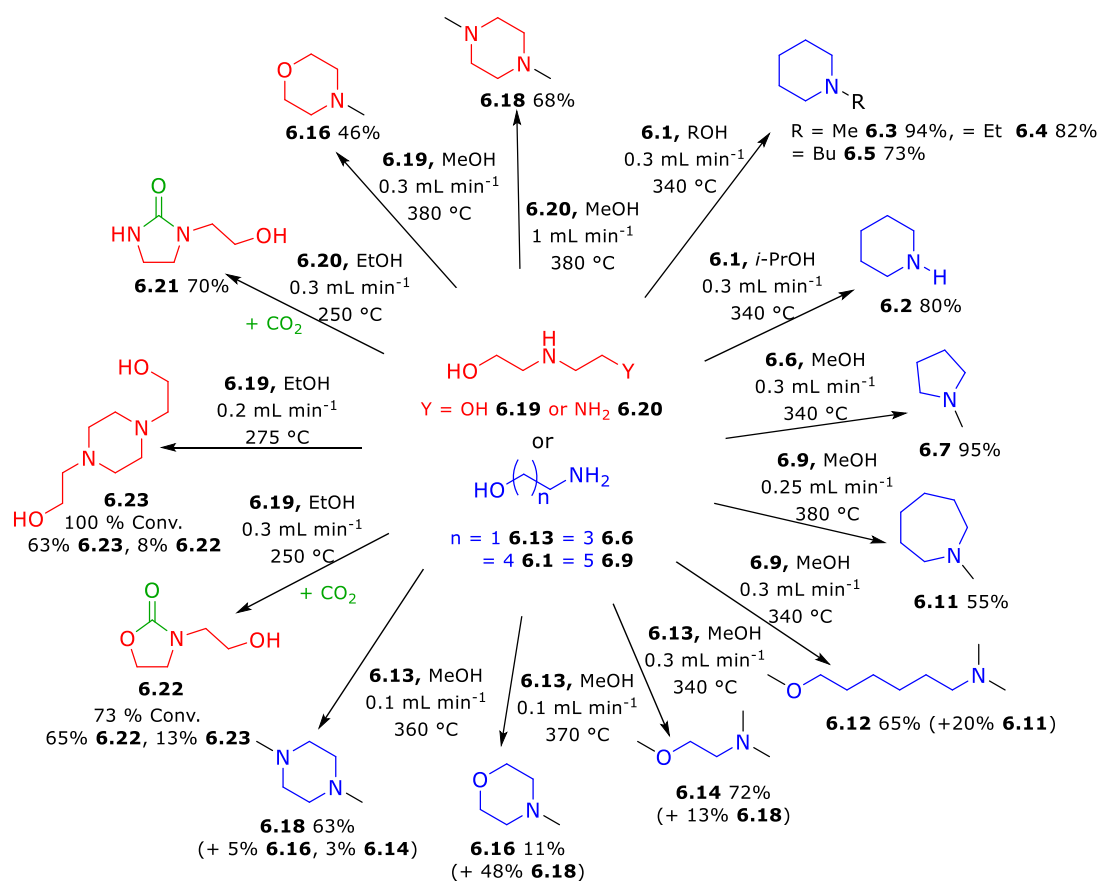
According to the literature dimer **6.23** can be formed from diamines reacting with diols,³²⁶ directly from diethanolamine³²⁷ or via the oxazolidinone intermediate.³²⁸ When a solution of **6.22** in *i*-PrOH was flowed over the catalyst at 250 °C, the formation of **6.23** was observed, which was expected from the results shown in Table 6.6. This observation indicates that the incorporation of CO₂ is reversible, and that once **6.22** is formed, it can react further to dimer

6.23, if the residence time is long enough, and the concentration of the substrate is high enough.

When ethanolamine (**6.13**) was used as the substrate, similar reactivity to diethanolamine (**6.19**) was observed. At all the studied conditions full conversion of the substrate was seen (entry 13-15). The main product at 250 °C (2 M solution in EtOH) was **6.19**, which then reacted further to form urethane **6.22**, and at higher temperatures mainly dimer **6.23**, but also ethers **6.24** and **6.25** were detected. The formation of diethanolamine (**6.19**) from **6.13**, suggests that unlike at higher temperatures and when MeOH was the co-solvent, deamination was favoured at the studied conditions over the alcohol amination, which would have led to the formation of **6.20** instead of **6.19**.

6.3 Chapter Conclusions

The formation of a number of alkylated cyclic amines from amino alcohols and alcohols in scCO₂ over γ -alumina has been presented (Scheme 6.6). In addition, reactions where CO₂ was inserted into the substrate, forming cyclic ureas or urethanes, were studied. This is the first account, where such molecules have been synthesised in continuous flow. In Scheme 6.6 the optimal conditions for the different products are shown.²⁸²



Scheme 6.6. Summary of the reactions studied in this Chapter using different amino-alcohols as substrates over γ -alumina. Reproduced from reference 282.

6.4 Chapter Appendix

All the optimisation experiments detailed in this Chapter were carried out using the SNOBFIT algorithm. The number of points produced by each call to SNOBFIT (nreq) was 6, and 10 % of the points were requested as global points ($p=0.1$). The results at each condition were determined by GLC-analysis. All the points produced during the optimisations are listed in Tables SI-6.1 through SI-6.7. The optimal point (region) was verified by repeating the reaction at those conditions, and injecting the resulting mixture into the GC. In some cases, the obtained values were lower than the yields measured during the optimisation, and so the reported optimal yields were the ones calculated from the injections.

Table SI-6.1. The conditions during the optimisation for 6.3 in the presence of CO₂.^a

Measurement no.	Temperature (°C)	Flow Rate (ml/min)	GC-yield of 6.3 (%)
1	250	0.13	0.0
2	270	0.40	29.9
3	291	0.25	40.2
4	331	0.44	33.8
5	271	0.40	78.5
6	350	0.37	89.4
7	311	0.47	86.9
8	340	0.1	92.5
9	320	0.1	24.1
10	300	0.5	6.0
11	285	0.5	58.2
12	280	0.1	0.0
13	260	0.5	78.6
14	295	0.1	64.6
15	305	0.2	90.9
16	310	0.15	94.4
17	325	0.1	90.8
18	340	0.45	84.4
19	345	0.1	83.2
20	350	0.25	87.3
21	350	0.5	88.3
22	350	0.45	92.7
23	330	0.25	96.2
24	330	0.15	91.2
25	315	0.1	72.8
26	275	0.2	29.7
27	270	0.25	94.3
28	310	0.1	93.8
29	325	0.2	87.0
30	330	0.1	96.3

31	335	0.15	85.9
32	340	0.2	92.1
33	340	0.25	88.6
34	345	0.5	87.0
35	345	0.45	92.1
36	335	0.25	88.9
37	335	0.1	81.4
38	320	0.3	76.6
39	315	0.25	95.8
40	305	0.1	91.0
41	320	0.15	78.9
42	325	0.35	87.8
43	335	0.2	84.2
44	335	0.5	93.4
45	340	0.3	93.7
46	350	0.3	88.0
47	345	0.3	94.0
48	345	0.25	89.1
49	330	0.35	88.6
50	330	0.3	93.1
51	270	0.15	0.0
52	265	0.1	0.0
53	285	0.2	49.7
54	330	0.2	90.9
55	335	0.3	90.6
56	335	0.35	91.1
57	345	0.2	80.9

a) Conditions: 250-350 °C and 0.1-0.5 ml/min (0.5 M of **6.1** in MeOH), 100 bar, 0.5 ml/min CO₂.

Table SI-6.2. The points measured during the optimisation for product 6.3 in the absence of CO₂.^a

Measurement no.	Temperature (°C)	Flow Rate (ml/min)	GC-yield of 6.3 (%)
1	250	0.25	0.0
2	263	0.28	0.0
3	275	0.49	2.3
4	300	0.18	62.7
5	325	0.27	77.1
6	350	0.40	85.7
7	340	0.10	81.3
8	335	0.50	77.8
9	315	0.50	54.5
10	310	0.10	69.8
11	290	0.50	10.3
12	270	0.10	25.7
13	315	0.20	75.5
14	335	0.25	81.5
15	340	0.15	81.6
16	340	0.45	78.0
17	350	0.10	79.1
18	350	0.25	83.7
19	350	0.30	85.2
20	345	0.25	83.6
21	345	0.20	83.6
22	335	0.10	80.7
23	330	0.30	78.6
24	330	0.20	79.6
25	295	0.25	47.9
26	310	0.40	58.0
27	330	0.50	75.5
28	340	0.25	84.1
29	340	0.30	82.0
30	345	0.10	77.9
31	350	0.15	80.0
32	350	0.50	84.7
33	350	0.20	80.4
34	345	0.50	80.4

35	335	0.30	78.9
36	335	0.15	81.3
37	320	0.15	77.7
38	265	0.45	0.0

a) Conditions: 250-350 °C and 0.1-0.5 ml/min (0.5 M of **6.1** in MeOH), 100 bar, 0.5 ml/min CO₂. The optimal conditions were verified, and an optimal yield of 86 % was found.

Table SI-6.3. The optimisation for product 6.11 starting from 6.9.^a

Measurement no.	Temperature (°C)	Flow Rate (ml/min)	GC-yield of 6.11 (%)
1	300	0.25	3.0
2	311	0.28	4.5
3	321	0.49	4.2
4	340	0.18	34.3
5	360	0.27	39.9
6	380	0.40	50.3
7	370	0.10	39.0
8	365	0.50	35.0
9	355	0.50	25.1
10	350	0.50	22.6
11	335	0.50	13.5
12	330	0.10	39.8
13	345	0.10	52.9
14	370	0.15	39.5
15	370	0.25	61.7
16	380	0.10	41.5
17	380	0.25	59.9

a) Conditions: 300-380 °C and 0.1-0.5 ml/min (0.5 M of **6.9** in MeOH), 100 bar, 0.5 ml/min CO₂. The optimal conditions were verified, and slightly lower yields were obtained: 50-55 %.

Table SI-6.4. The conditions during the optimisation for product 6.16 starting from 6.13.^a

Measurement no.	Temperature (°C)	Flow Rate (ml/min)	GC-yield of 6.16 (%)
1	300	0.16	0.6
2	317	0.77	1.2
3	332	0.43	2.6
4	349	0.93	9.0
5	365	0.87	6.7
6	380	0.71	11.0
7	360	1.00	6.4
8	355	0.10	13.4
9	340	0.95	7.6
10	325	1.00	10.7
11	310	0.10	3.1
12	305	1.00	6.6
13	330	1.00	7.1
14	350	0.80	7.0
15	360	0.50	3.6
16	370	0.10	15.3
17	380	0.10	8.7
18	380	0.50	10.8
19	375	1.00	2.8
20	375	0.85	4.3
21	375	0.45	11.0
22	360	0.10	12.5
23	345	0.35	2.5

a) Conditions: 300-380 °C and 0.1-1.0 ml/min (1 M of **6.13** in MeOH), 100 bar, 0.5 ml/min CO₂. This optimisation was troublesome as very low yields were seen throughout, and also at some instances false responses from the analysis. The 'optimal conditions' were verified to be 370 °C, 0.1 ml/min giving a 11 % yield.

Table SI-6.5. The conditions for the optimisation for 6.18 starting from 6.13.^a

Measurement no.	Temperature (°C)	Flow Rate (ml/min)	GC-yield of 6.18 (%)
1	300	0.16	0.0
2	317	0.77	0.0
3	333	0.43	10.5
4	349	0.93	5.0
5	365	0.87	12.7
6	380	0.71	33.4
7	360	1.00	6.3
8	355	0.10	38.2
9	340	0.95	5.5
10	325	1.00	4.2
11	310	0.10	26.0
12	305	1.00	7.5
13	330	0.10	26.2
14	345	0.20	19.9
15	360	0.50	16.1
16	370	0.10	30.0
17	380	0.10	18.0
18	380	0.40	34.9
19	380	0.65	22.6
20	380	0.85	18.9
21	375	0.60	21.5
22	370	0.35	42.6
23	365	0.15	48.3
24	350	0.10	31.8
25	345	0.35	11.2
26	325	0.10	19.5
27	340	0.10	26.9
28	350	0.45	11.0
29	360	0.10	57.1
30	360	0.25	24.2
31	370	0.25	40.0
32	375	0.35	34.4
33	380	0.25	50.7
34	370	1.00	10.4
35	365	0.50	19.1
36	365	0.40	23.0
37	360	0.30	26.6
38	360	0.15	51.9
39	325	0.35	9.6
40	315	0.35	0.0
41	335	0.10	25.7
42	355	0.15	44.8
43	365	0.10	70.8
44	365	0.30	24.3
45	380	0.30	35.9
46	380	0.80	19.8
47	380	0.50	34.7
48	375	0.20	57.6
49	370	0.50	19.0
50	360	0.45	16.7
51	345	0.10	38.2
52	315	0.10	20.2
53	305	0.80	9.0
54	305	0.10	36.0
55	305	0.70	11.4
56	350	0.20	24.9
57	350	0.30	18.1
58	360	0.75	10.2
59	375	0.45	33.1
60	380	0.15	50.3
61	380	0.25	43.3

a) Conditions: 300-380 °C and 0.1-1.0 ml/min (1 M of **6.13** in MeOH), 100 bar, 0.5 ml/min CO₂. The optimal conditions were verified, and slightly lower yields were obtained: 57-63 %.

Table SI-6.6. The conditions for the optimisation for 6.16 starting from 6.19.^a

Measurement no.	Temperature (°C)	Flow Rate (ml/min)	GC-yield of 6.16 (%)
1	300	0.16	14.0
2	317	0.77	10.9
3	333	0.43	18.7
4	348	0.93	19.3
5	365	0.87	31.1
6	379	0.71	41.5
7	360	1.00	25.7
8	355	0.10	43.1
9	340	0.95	16.7
10	325	1.00	13.8
11	310	0.10	13.7
12	305	1.00	13.7
13	345	0.20	24.8
14	360	0.50	31.7
15	370	0.10	51.5
16	380	0.10	68.2
17	380	0.40	57.3
18	380	0.50	44.7
19	380	0.80	38.8
20	380	0.30	63.3
21	380	0.15	59.0
22	375	0.40	51.7
23	365	0.10	58.6
24	360	0.65	28.2
25	345	0.35	23.4
26	335	0.15	29.7
27	360	0.10	30.6
28	365	0.20	36.8
29	375	0.10	53.6
30	375	0.45	37.9
31	380	0.25	46.6
32	375	0.45	36.5
33	376	0.30	46.0
34	374	0.15	48.3
35	360	0.35	34.9
36	350	0.45	29.7
37	350	0.10	42.4
38	325	0.35	20.9
39	365	0.30	42.2
40	370	0.15	55.1
41	375	0.45	42.4
42	380	0.35	50.8
43	380	0.55	45.1
44	380	0.45	51.0
45	375	0.65	37.9
46	375	0.25	39.5
47	370	0.35	44.9
48	360	0.75	27.1
49	330	0.10	48.9
50	325	0.10	36.3
51	345	0.50	23.8
52	370	0.45	40.6
53	375	0.20	53.6
54	375	0.35	51.9
55	380	0.60	43.4
56	380	0.20	53.2
57	375	0.55	39.1
58	370	0.70	39.5
59	370	0.25	55.6
60	365	0.40	41.0
61	335	0.10	49.0
62	325	0.45	21.7
63	340	0.10	38.5
64	355	0.75	0.0

a) Conditions: 300-380 °C and 0.1-1.0 ml/min (0.5 M of **6.19** in MeOH), 100 bar, 0.5 ml/min CO₂. During the verification experiment, 46 % of **6.16** was found at 0.3 ml/min, 380 °C .

Table SI-6.7. The conditions for the optimisation for 6.18 starting from 6.20.^a

Measurement no.	Temperature (°C)	Flow Rate (ml/min)	GC-yield of 6.18 (%)
1	300	0.16	59.6
2	317	0.77	30.3
3	333	0.43	47.0
4	349	0.93	58.9
5	365	0.87	64.3
6	379	0.71	72.8
7	360	1.00	64.8
8	355	0.10	52.8
9	340	0.95	49.6
10	325	1.00	27.7
11	310	0.10	63.5
12	305	1.00	24.1
13	330	0.10	54.1
14	355	0.90	62.8
15	360	0.50	67.1
16	371	0.10	30.8
17	375	0.50	68.4
18	380	0.10	32.9
19	380	1.00	67.9
20	380	0.65	70.5
21	375	0.90	63.8
22	370	1.00	63.2
23	370	0.45	64.2
24	365	0.55	64.9
25	350	0.30	66.1
26	345	0.35	58.9
27	325	0.35	50.0
28	355	0.40	64.0
29	370	0.55	64.0
30	375	0.65	64.8
31	380	0.50	64.7
32	380	0.80	62.8
33	375	0.55	65.6
34	375	0.40	69.5
35	355	1.00	58.9
36	355	0.50	62.2
37	355	0.25	67.3
38	340	0.45	63.8
39	320	0.10	49.3
40	350	0.55	59.0
41	359	0.25	65.8
42	361	0.65	64.6
43	360	0.75	64.5
44	365	0.45	68.3
45	365	0.80	66.7
46	380	0.55	72.0
47	380	0.15	46.2

a) Conditions: 300-380 °C and 0.1-1.0 ml/min (0.5 M of **6.20** in MeOH), 100 bar, 0.5 ml/min CO₂. During the verification experiment 68 % yields were found at 380 °C, 1 ml/min.

Chapter 7. Thesis Conclusions and Future Directions

The aims of this Thesis, as outlined at the end of Chapter 1, were:

1. To optimise the conditions for the solventless methylation of alcohols with dimethyl carbonate using FT-IR analysis, and to thereafter transfer this analytic method to reactions carried out in scCO_2 .
2. To expand the scope of reactions that can be studied and optimised with the self-optimising reactor in scCO_2 and with γ -alumina as the catalyst.
3. To study reactions, where CO_2 can be incorporated into molecules, either directly or indirectly.
4. To evaluate to what extent the 12 Principles of CO_2 Chemistry are fulfilled in the work described in this Thesis.

In this Chapter the progress towards meeting each of these aims is discussed. For each aim, the justification is reviewed together with a summary of the attempted work, followed by conclusions of the relevant results. In addition, possible directions for further work are proposed.

7.1 Aim 1

"To optimise the conditions for the solventless methylation of alcohols with dimethyl carbonate using FT-IR analysis, and to thereafter transfer this analytic method to reactions carried out in scCO₂."

7.1.1 Rationale

In previous work by the group, the optimal conditions for the methylation of 1-pentanol had been found by employing a self-optimising reactor with FT-IR analysis.¹²¹ However, only reactions carried out at atmospheric pressure were studied, due to pressure limitations of the spectrometer. It was therefore of interest to find out, if a similar set-up could be employed to study reactions in scCO₂. This expansion of reaction conditions could then allow for a broader range of reactions to be investigated with the fast analysis provided by FT-IR. In addition, a new spectrometer had been acquired, and initially its applicability to the reactor set-up needed to be ensured.

7.1.2 Progress

Chapter 3 describes the implementation of FT-IR analysis to the optimisation of the reaction conditions for the formation of butyl methyl ether and pentyl methyl ether starting from dimethyl carbonate and 1-butanol or 1-pentanol respectively. The pentanol reactions were carried out in order to compare the current system with the previously used set-up. As this initial optimisation was successful, 1-butanol was used as the starting material in a number of different optimisations implementing two different algorithms. It was also shown that this reactor set-up could be used for reactions where scCO₂ was used as solvent. All the different optimisations, with and without scCO₂, resulted in high yields of

butyl methyl ether, and the results obtained with the different algorithms were comparable. However, when using scCO_2 as the solvent, the optimal temperature was significantly higher than without scCO_2 . This result was possibly caused by the fact that the optimisations did not considerably vary the reagent flow rates, but instead increased production by increasing the temperature. When scCO_2 was present in the system, the total flow was higher, and hence the residence time within the reactor was shorter. By increasing the temperature to make the catalyst more active, the optimisation tried to counteract the effect of the increased flow rate.

During the work described in Chapter 3 some difficulties related to the FT-IR analysis were discovered: 1. In the test reaction (1-pentanol methylation), the reference peak absorption did not vary significantly; 2. In the SNOBFIT optimisation for the methylation of 1-butanol, overlap of peaks from different compounds became an issue at low temperatures; 3. Without a solvent, spectra could not be measured at certain conditions (low 1-butanol flow rate and high DMC flow rate). The first problem was solved by paying more attention to the choice of the reference peak in the 1-butanol case. The latter problem, on the other hand, was resolved by adding scCO_2 as the solvent, which made it possible to get results at the above mentioned conditions, as a liquid phase was present in the flow cell even at low butanol flow rates. With the current method of extracting information from the spectra, the second problem cannot be solved. However, by contracting the search space, by increasing the lower temperature limit, the production of the side product could be avoided, which also averted the challenge of overlapping peaks in the IR-spectrum.

7.1.3 Future Directions

The implementation of FT-IR analysis in combination with the self-optimising reactor was shown to be effective for the studied reactions. However, if the aim would be to broaden the reaction scope, the described method for the determination of product yields is not very robust, as most reactions will not afford distinct peaks for the product and a reference material in an FT-IR spectrum. This issue, in addition to the other problems encountered in the analysis, could possibly be resolved by developing the method of extracting information from the measured spectra. Methods that have the potential of making the analysis more accurate and versatile include principal component analysis³²⁹ and two-dimensional correlation spectroscopy.³³⁰⁻³³² These techniques could possibly provide information on which changes in the IR-absorptions are related to which changes in the conditions, and hence to the changes in product yields. Further details on these methods are beyond the scope of this Thesis. However, by improving the technique, more complicated reactions could possibly be studied with the fairly fast FT-IR analysis.

7.2 Aim 2

"To expand the scope of reactions that can be studied and optimised with the self-optimising reactor in scCO₂ and with γ -alumina as the catalyst."

7.2.1 Rationale

As mentioned in Chapter 1, the overall aim of this Thesis was to study systems with potential to add chemical value to CO₂. One way this can be achieved is by using scCO₂ as a solvent. Substituting traditionally used toxic and flammable organic solvents by alternative options is also important in order to decrease the

amount of waste that is produced by chemical processes. Previously in the group the chemistry studied with the self-optimisation set-up has been limited to well-established etherification reactions. Hence, it was of interest to study different transformations, mainly *N*-alkylations in scCO_2 , to find out whether or not the self-optimising reactor would be able to optimise the reaction conditions of slightly more complicated reactions. Acid-catalysed *N*-alkylations, were chosen as the target transformation, as synthesising the resulting molecules via halogen-free routes and with benign alkylation agents, such as alcohols, is of importance.

7.2.2 Progress

In Chapter 4 the reaction system between aniline (**4.1**), THF and DMC was studied over γ -alumina in scCO_2 . The reactivity within this mixture of starting materials turned out to be quite complicated, as several different products could be formed. However, by implementing the self-optimising reactor, the reaction conditions for several of the products, including monomethyl aniline (**4.2**), dimethyl aniline (**4.3**), methyl phenyl carbamate (**4.4**), and three previously unknown molecules (**4.7** to **4.9**), were optimised with moderate to high yields. During optimisations, the selectivity for several of the target products was increased. The ability to locate conditions with higher selectivities is important when trying to avoid unnecessary waste.

The results obtained suggested that under most reaction conditions, especially when pure DMC and THF were used, the outcome of the reaction was highly dependent on the reaction temperature. At lower temperatures monoalkylated products, such as *N*-monomethyl aniline (**4.2**), were formed, whereas dialkylation, producing for instance *N,N*-dimethyl aniline (**4.3**) or *N*-phenyl pyrrolidine (**4.6**), took place at higher temperatures. Due to this observation, it

could be of interest to study the formation of the so called open-ring products (**4.7** to **4.9**) with a lower THF concentration, to try to avoid the pyrrolidine formation. However, these products seem to be intermediates, in the formation of the pyrrolidine, and therefore decreasing the amount of THF in the system, might not affect the selectivity significantly.

An issue encountered during the optimisations, especially for the more complicated transformations, was the lack of alteration in reaction conditions with the SMSIM algorithm. Therefore, the software was developed to use a global search algorithm together with GC-analysis, and some of the SMSIM optimisations were repeated with the SNOBFIT algorithm. This allowed for a broader range of conditions to be explored offering higher yields of the targets. The results suggested that the SNOBFIT algorithm is particularly useful, when studying the formation of intermediate products such as *N*-methyl aniline (**4.2**) or product **4.7**.

This system was also employed for the optimisation of forming *N*-methyl-*N*-ethyl aniline (**4.12**) directly from aniline, ethanol and methanol. In this case, up to 40 % yields of the target were obtained. The moderate selectivity could be explained by the somewhat favourable formation of homo-*N*-dialkylation products (**4.3** and **4.11**). Though, under the optimised conditions, the target molecule was produced with the highest selectivity in the mixture.

The synthesis of **4.12** has been previously established, but not via the route described in this Thesis. Therefore, the transformation leading to **4.12** and also compounds **4.7** to **4.9** are novel, and their formation hence verifies that continuous flow reactors, especially when linked with self-optimisation, have the potential of providing means of discovering new chemistries. This approach is rather uncommon in flow, and opens up endless opportunities to discover unknown or unexpected transformations in continuous systems.

Further *N*-alkylation reactions were studied in Chapter 6, where the aim was to form alkylated cyclic amines from amino alcohols and alcohols in scCO₂ over γ -alumina. Initially, the conditions forming *N*-methyl piperidine (**6.3**) from 5-amino-1-pentanol (**6.1**) and methanol, were optimised. These conditions were then applied to other reactions; with different alkylating agents, or starting materials. Moderate to high yields of all the targeted methylated cyclic amines were reached after optimisations utilising the SNOBFIT-algorithm. The products include *N*-methyl pyrrolidine (**6.8**), *N*-methyl morpholine (**6.16**), 1,4-dimethyl piperazine (**6.18**) and *N*-methyl azepan (**6.9**).

7.2.3 Future Directions

The work in Chapters 4 and 6 showed that the same solvent and catalyst that had mainly been used for etherification reactions could be employed also for a variety of *N*-alkylations. Some of the synthesised products were not known prior to starting the relevant research, showcasing the vast potential of transformations that can be optimised with the self-optimising system. Hence, the only limitation for the scope of reactions that can be studied is mainly linked to the GC providing adequate separation of the substances in the formed reaction mixture.

As was briefly mentioned in section 6.2.1, it could be of interest to use the self-optimising reactor to target e.g. the throughput of a reaction, to see how the 'optimal conditions' change compared to when the yield of a product is maximised. This switch of the target function would be relatively simple, as in this case the value being maximised would still be a number which could be derived directly from the GC-analysis. Also, in some cases, targeting the selectivity of a product could be useful as in case highly selective regions, with

lower conversions, would be located, the starting solution could be recycled through the system to reach higher yields of the target.

Furthermore, the improvements made to the software allowing the SNOBFIT algorithm to be used in combination with GC-analysis, opens up new possibilities to get more comprehensive views on reactions in a reasonable time. The only requirements, in these cases, would be to find a stable catalyst for the studied reaction, and satisfactory separation of the products that are formed in the system.

7.3 Aim 3

"To study reactions, where CO₂ can be incorporated into molecules either directly or indirectly."

7.3.1 Rationale

The second way of bringing value to CO₂ is to use it as a starting material in chemical reactions. There is a large variety of useful molecules that can be synthesised using CO₂. By incorporating CO₂ into molecules, value can be added by forming valuable products from cheap starting materials (especially waste CO₂ is cheap). This incorporation can be done directly by inserting CO₂ into molecules, or indirectly by utilising compounds that are (or can be) formed from CO₂, without having to change the reaction system significantly (processes that use the same catalysts and solvents).

7.3.2 Progress

In Chapter 5 the methylation of aliphatic amines with methanol catalysed by [Ru(Triphos)(TMM)] was studied. The same catalyst has previously been used for

producing methanol from CO₂ and H₂,^{234, 235} and hence the current system offers an indirect method of utilising CO₂. The selectivities of the studied reactions were found to depend on the temperature, reaction time and solvent. The main reaction was the dimethylation of the amine (**5.1** yields **5.3**, and **5.6** gives **5.8**), but also several other reactions took place producing a number of side products. The different routes leading to these side products were analysed in more detail in section 5.4.

In addition to the methylations of aliphatic amines, the reaction between an amino alcohol (5-amino-1-pentanol, **5.13**) and methanol was studied. Full conversions to piperidine (**5.14**) and *N*-methyl piperidine (**5.15**) were achieved under all the studied conditions. Also in this case, the selectivities depended on the temperature, solvent and reaction time. In the presence of methanol and above 100 °C, the cyclisation to *N*-methyl piperidine was the predominant reaction (>80 % selectivity).

Furthermore, in Chapter 6 reactions where CO₂ was inserted into amino alcohols, forming a cyclic urea (**6.21**) or urethane (**6.22**), were studied. The reaction was catalysed by γ-alumina and scCO₂ was used as the reaction medium. Conditions under which high selectivity for the targets were reached, were located. As mentioned in Chapter 6, this account is the first time such molecules have been synthesised in continuous flow.

It was shown that these molecules were formed in reactions with CO₂ and the amino alcohol (**6.20** gives **6.21**, and **6.19** gives **6.22**) as no reaction was observed in the absence of scCO₂. In addition, **6.21** was shown to be relatively stable over the catalyst whereas **6.22** decomposed to dimer **6.23** and CO₂. Hence such compounds could possibly be used to capture CO₂, and then release it at higher temperatures when required.

7.3.3 Future Directions

Some suggestions for future work were given in the conclusions for Chapter 5 (section 5.4). Assuming all the issues encountered during the work could be resolved, several interesting reactions could be studied with the Ru(Triphos)(TMM) catalyst. One possibility, as was suggested in Chapter 5, would be to develop a continuous cascade reaction, where initially methanol would be formed from H₂ and CO₂. Then, in a next step after depressurisation, this methanol could be made to react with an aliphatic amine and hence allow for the synthesis of methylated aliphatic amines starting from H₂, CO₂ and the amine. However for this suggestion to be possible, the immobilisation of the catalyst would firstly have to be achieved.

As for the work described in Chapter 6, studying the scope of the reactions where the insertion of CO₂ into a molecule is catalysed by γ -alumina could be of interest (e.g. use epoxides as starting materials). Furthermore, it could be useful to study these transformations with the self-optimising reactor, and due to the possible presence of products with carbonyl groups, FT-IR-analysis could possibly be utilised.

7.4 Aim 4

"To evaluate to what extent the 12 Principles of CO₂ Chemistry are fulfilled in the work described in this Thesis."

7.4.1 Rationale

As was demonstrated in Chapter 1, the 12 Principles of CO₂ Chemistry,¹¹ which were established during this Project, can be used to evaluate reactions and processes that utilise CO₂. These principles demonstrate the possible viability of

a CO₂-utilising process by taking into account several different aspects of the system, including the reaction conditions, origin of the CO₂ and entire life cycle assessments etc. After the successful evaluation, performed in Chapter 1, of the CRI methanol synthesis process, it was of interest to judge the work described in this Thesis according to these 12 principles to find out to which extent they are fulfilled.

7.4.2 Progress – Evaluation of the Presented Work According to the 12 Principles of CO₂ Chemistry

In this Thesis, three different ways of utilising CO₂ have been described:

1. Indirect incorporation of CO₂, by carrying out methylations with MeOH potentially produced from CO₂ by utilising the Ru(Triphos)(TMM) catalyst system (Chapter 5); 2. Direct insertion of CO₂ by forming cyclic ureas and urethanes from amino alcohols and CO₂ (Chapter 6); 3. By using scCO₂ as solvent (Chapter 3, 4 and 6). These processes are each evaluated below either together or separately.

Principle 1. Catalysis is crucial:

All the processes studied in this Thesis were catalytic. This point is mainly relevant to the reactions incorporating CO₂:

Chapter 5: In this instance a catalyst (Ru(Triphos)(TMM)), which has been shown to form MeOH from CO₂ and H₂ was used to catalyse the methylation of aliphatic amines with MeOH. This catalyst is homogeneous and relatively expensive, as it is based on a transition metal and an expensive ligand, and hence in order to make this system more viable on a larger scale, the immobilisation of the catalyst system or improvement of the recovery of the catalyst would be essential.

Chapter 6 – Incorporation of CO₂: These reactions on the other hand were catalysed by γ -alumina, which is a relatively abundant and cheap solid Lewis acid. Furthermore, this catalyst was demonstrated to be stable towards the studied transformations, and hence it could be implemented, for such reactions, even on a larger scale.

Principle 2. Origin of the CO₂?:

Chapter 5: The CO₂ used for the methanol synthesis with the same catalyst was of high purity (99.9 %). Due to the sensitive nature of the catalyst, the effect of impurities on the catalytic activity might be drastic. This would however depend on which impurities are present, as H₂ is one of the reagents and its presence would not affect the activity.

scCO₂ as solvent: Also in this case, the CO₂ was of high purity (food grade, 99.8 %). However, considering that all the starting materials and co-solvents were used without purification, any possible additional impurities in the CO₂ would probably not affect the outcome of the studied reactions. Such behaviour was demonstrated by previous work, where different impurities were added to scCO₂, but still very similar outcomes of the studied reaction were obtained, as explained in Chapter 1.²⁶

Principle 3. Tomorrow's world may be different:

This guideline is not really relevant to the current work, but interestingly in all the examples one catalyst system, possibly developed for another reaction, could be employed to carry out several different transformations. Such versatility could be important, when considering larger scale production. However, as was demonstrated by the large scale scCO₂ plant,^{26, 111} it is not enough to be able to carry out a reaction utilising CO₂, the process also needs to be economically viable.

Principle 4. Cleaner than existing process?:

The work described in this Thesis has focused on alkylations of heteroatoms using benign alkylating agents. The ability of performing such transformations via halogen-free routes in greener solvents is of great importance, as a smaller amount of highly toxic waste is produced in the process. Hence, it may well be that the discussed reactions proceed via cleaner routes than would traditionally be used to synthesise these molecules. In addition, any reaction incorporating CO₂ into the molecule is highly likely to be cleaner than the alternative route, which often requires toxic reagents, such as phosgene, to be used.

Principle 5. High volume or high value products?:

Chapter 5: In this case the product directly formed from CO₂ would be MeOH, which was then used to methylated aliphatic amines. MeOH is considered a high volume product, as it is low in value. Therefore the ability to recycle or immobilise the catalyst would be important to justify for its high cost. Nevertheless, as was mentioned in section 5.1, the same catalyst has been shown to directly catalyse the formation of e.g. *N*-methylated aromatic amines starting from CO₂, H₂ and the amine. These or similar products could be of high enough value to allow for a more expensive catalyst to be used. Hence, a combination of different processes could be developed, where one catalyst is used to produce a number of different compounds starting from CO₂.

Chapter 6 – Incorporation of CO₂: In this example, a medium value product is produced in a relatively 'cheap' process, and could hence possibly be used as a value adding process.

scCO₂ as solvent: Utilising CO₂ as a solvent can, in the near future, become a very cheap option, as large amounts of CO₂ will be available from CCS processes. The systems introduced in this Thesis, where scCO₂ was used as

solvent, produced some interesting but often quite low value products. In addition, the requirement for co-solvents diminished the advantage, but these might not be required on larger scales, where the tolerance for solid products is higher. However, in order for such a process to help decrease CO₂ emissions, the CO₂ would need to be recaptured or recycled through the process, which would increase the cost and hence the possible implementation of such processes.

Principle 6. E-factor must be low:

As mentioned above, all the reactions carried out during this Project required organic solvents or co-solvents in order for them to be studied. Also, the concentrations were relatively low, in order to avoid blockages etc. In addition, the decomposition of DMC seen in Chapters 3 and 4 increased the amount of waste further, as it would not be possible to recycle the excess DMC required for the reactions due to the irreversible decomposition. Hence the E-factors for the processes may be quite high, though they were not determined in the work. However, due to a benign nature of the reagents, highly toxic (chlorinated) side products were avoided.

The magnitude of an acceptable value for the E-factor, depends on the product (and also the nature of the waste produced), as when more valuable products are formed, more money can be spent on waste treatment.⁶⁹ The molecules formed during this Project are either bulk chemicals (acceptable E-factor 1-5), or fine chemicals (acceptable E-factor 5-50). Obviously, independent of the target transformation, one of the aims of any research should be to minimise the formation of waste and hence strive to reach as low E-factors as possible (in oil-refining <0.1).

Principle 7. Maximise integration:

All the processes described here could possibly be integrated with CO₂ capturing facilities, and carried out potentially even without purification of the captured CO₂.

Principle 8. Innovative process technology:

For the work carried out in scCO₂, continuous flow processes were used, which can help to maximise production. In addition, the self-optimising reactor was used to locate the optimal conditions for a number of transformations, therefore increasing the selectivity and decreasing the amount of waste formed.

Principle 9. Sustainability is essential:

Carrying out full life cycle assessments (LCA) of these processes could be useful, in order to see the overall sustainability of each system.

Principle 10. Thermodynamics cannot be beaten:

All of the studied reactions were performed at high temperatures and for the scCO₂ work also at high pressures, therefore minimising any thermodynamic limitations of the reactions, because the effect of entropy will be maximised ($\Delta G = \Delta H - T\Delta S$).

Principle 11. Renewable (& reasonable) energy input:

The origin of the energy used to carry out the current investigations is unknown. However, as has been demonstrated by the recently opened Carbon Neutral Laboratory (CNL) at the University of Nottingham, installing e.g. solar panels on the roof of the building can provide sufficient energy for a laboratory to be fully operational.³³³

Principle 12. Your enthusiasm is not enough:

Currently, out of the research carried out for this Thesis, the processes involving scCO_2 have the highest potential of being implemented in practice. This is because they are performed in continuous flow reactors and they utilise a relatively benign catalyst. Furthermore, the production of oxazolidinones from diethanol amine (as described in Chapter 6) could possibly be used as a CO_2 capturing system, where the CO_2 could then be released, when needed, by the formation of the dimer. However, the dimer formation is irreversible, hence limiting its applicability for such processes.

Overall, according to the assessment above, the processes studied in this Thesis fulfil up to 10 of the principles depending on how strictly they are judged. By carrying out LCA:s and increasing the concentrations (or avoiding organic solvents altogether), these processes could be made even better, and allow for them to fulfil nearly all of the principles.

Currently the system introduced in Chapter 5, is mainly limited by the inability to recycle the catalyst. Once for instance an immobilisation technique is developed, the possibility of implementing this system on a larger scale becomes higher, and could also allow for continuous operation of different reactions. This would also help fulfil more of the principles, and hence increase the viability of such processes.

7.4.3 Future Directions

As these principles were developed during this project, they could not be used to evaluate the proposed systems, before the research started. Hence, in any future work concerning CO₂ the evaluation of the planned process should be carried out prior to starting, in order to ensure the studied system is as viable as it possibly can be. As these principles are quite broad, they do not limit the chemistry which can be studied, but instead help to identify possible hurdles within the process, which can hence be tackled early on in the development of a reaction system.

7.5 Outlook

During this project good progress has been made towards achieving the aims of the Thesis. This is especially true when considering the expansion of the self-optimisation chemistry at the University of Nottingham. The changes made to the software, will hopefully allow for an even broader range of reactions to be studied.

Some progress was also made towards the overall aim of adding chemical value to carbon dioxide, as several different transformations were studied in scCO₂ and also with CO₂ as a starting material. However, a lot of work still remains, when trying to increase the amount of viable CO₂ utilising processes, and hence several innovative discoveries should be expected in the near future. These will hopefully be achieved by taking into account the 12 Principles of CO₂ Chemistry, already starting at the discovery level.

8. References

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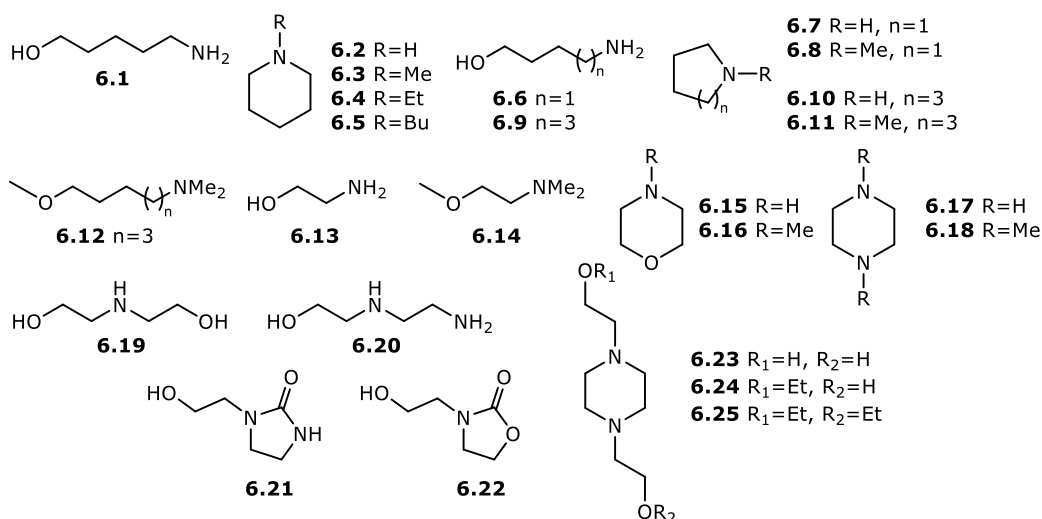
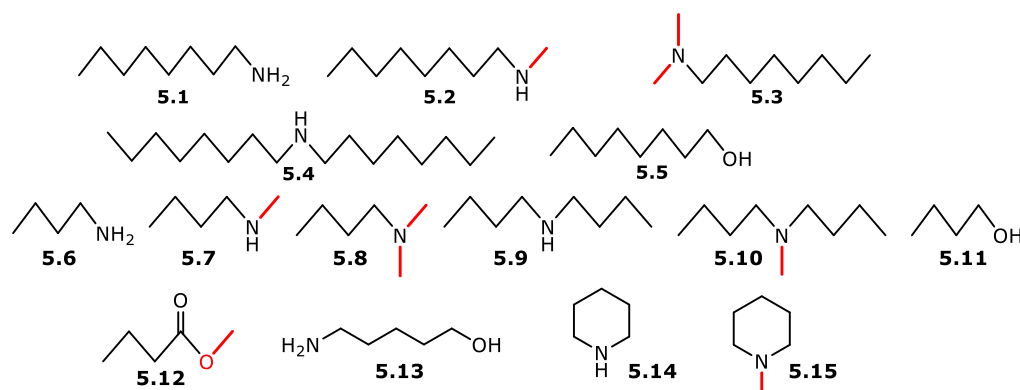
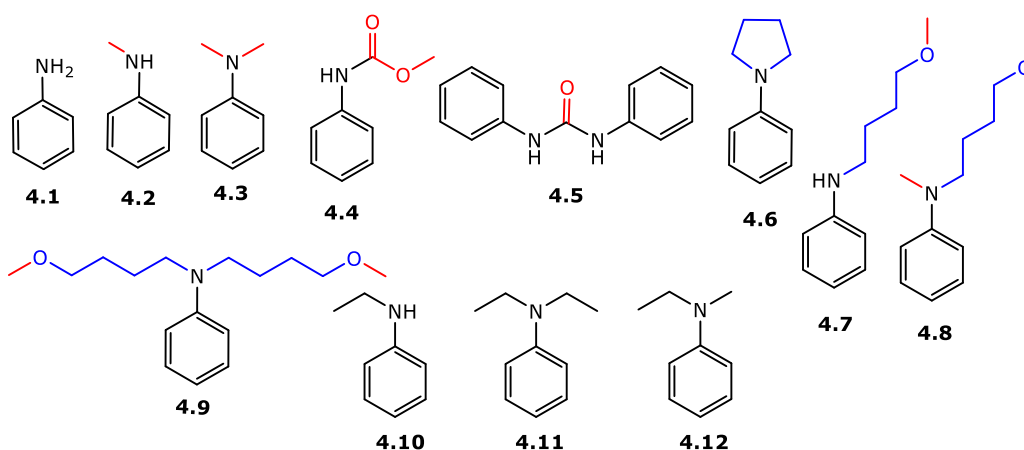
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Appendix

Key for Structures in Chapter 4-6



Publications

1. "Remote-controlled experiments with cloud chemistry", R. A. Skilton, R. A. Bourne, Z. Amara, R. Horvath, J. Jin, M. J. Scully, E. S. Streng, S. L. Y. Tang, P. A. Summers, J. Wang, E. Pérez, N. Asfaw, G. L. P. Aydos, J. Dupont, G. Comak, M. W. George and M. Poliakoff, *Nat. Chem.*, **7**, 1-5 (2015).
2. "Automated Serendipity with Self-Optimizing Continuous-Flow Reactors", Z. Amara, E. S. Streng, R. A. Skilton, J. Jin, M. W. George and M. Poliakoff, *Eur. J. Org. Chem.*, **2015**, 6141-6145.
3. "The Twelve Principles of CO₂ CHEMISTRY", M. Poliakoff, W. Leitner and E. S. Streng, *Faraday Discuss.*, 2015, **183**, 9-17.
4. "Selective Synthesis of Trimethylamine by Catalytic N-Methylation of Ammonia and Ammonium Chloride by utilizing Carbon Dioxide and Molecular Hydrogen", K. Beydoun, K. Thenert, E. S. Streng, S. Brosinski, W. Leitner and J. Klankermayer, *ChemCatChem*, 2016, **8**, 135-138.
5. "Continuous N-Alkylation Reactions of Amino Alcohols using γ -Al₂O₃ and supercritical CO₂; Unexpected Formation of Cyclic Ureas and Urethanes by Reaction with CO₂", E. S. Streng, D. S. Lee, M. W. George and M. Poliakoff, *Beilstein J. Org. Chem.*, **2017**, 329-337.