The University of Nottingham

Synthesis of Drug Intermediates in Carbon Dioxide

By

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Acknowledgments

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Abstract

The application of supercritical CO_2 ($scCO_2$) as a solvent for the synthesis of fine and bulk chemicals has been well documented; however its application as a solvent for the synthesis of pharmaceuticals is yet to be exploited fully. To address this issue, two synthetically important reactions have been investigated in $scCO_2$; chemoselective *N*-debenzylation and diastereoselective hydrogenation.

Chapter 3 details the study of catalytic *N*-debenzylation in the presence of sensitive functional groups (COMe and Cl). It has been shown that selective *N*-debenzylation in the presence of a carbonyl (COMe) is difficult to achieve due to the high operating temperatures that are required to facilitate continuous flow debenzylation. *N*-debenzylation in the presence of chloro- substituents was also investigated. Dechlorination can be a major problem during this reaction however several different strategies were developed to suppress dechlorination including: (i) the correct selection of catalyst support; (ii) selective poisoning of a Pd catalyst; (iii) the addition of acids, such as H_2SO_4 to the reactant stream; (iv) the use of an aprotic co-solvent, such as THF.

Chapter 4 covers progress made on the diastereoselective hydrogenation of the pharmaceutical intermediate, *rac*-sertraline imine. It has been shown that the hydrogenation reaction can be performed with excellent levels of chemo- and diastereoselectivity (*cis*:*trans* ratio of 97:3, 0.7 % by-product formation) by performing the reaction as a continuous flow process in the presence of $scCO_2$.

All details of the apparatus, experimental and synthetic procedures are reported in Chapter 2.

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Abbreviations

API	-	Active pharmaceutical ingredient
Ar	-	Aromatic
ASES	-	Aerosol spray extraction system
Bn	-	Benzyl
BPR	-	Back pressure regulator
CAN	-	Ceric ammonium nitrate
°C	-	Degrees Celsius
CI	-	Chemical ionisation
DDQ	-	2,3-Dichloro-4,5-dicyanobenzoquinone
DMF	-	Dimethylformamide
DMSO	-	Dimethylsulfoxide
d. r.	-	Diastereomeric ratio
e. e.	-	Enantiomeric excess
EI	-	Electron impact
Ether	-	Diethyl ether
FDA	-	Food and drug administration
F. G	-	Functional group
FID	-	Flame ionisation detector
g	-	Gramme(s)
GAS	-	Gas antisolvent precipitation
GC-MS	-	Gas liquid chromatography - mass spectrometry
GLC	-	Gas liquid chromatography
h	-	Hour(s)
HPLC	-	High performance liquid chromatography
IL	-	Ionic liquid
IPA	-	Isopropyl alcohol
JM	-	Johnson Matthey
M	-	Mole(s) per litre of solvent
mg	-	Milligramme(s)
min	-	Minute(s)
μm	-	Micrometer
mL	-	Millilitre(s)

mmol	-	Millimole(s)
mp	-	Melting point
NIST	-	National institute of science and technology
nm	-	Nanometer
NMR	-	Nuclear magnetic resonance
OD	-	Outer diameter
PCA	-	Precipitation with compressed antisolvents
ppm	-	parts per million
PVP	-	Poly-(*N*)-vinyl-2-pyrrolidone
R	-	general substituent e.g. alkyl, aryl, allyl
Rac	-	Racemic
RESOLV	-	Rapid expansion of a supercritical solution into a liquid solvent
RESS	-	Rapid expansion of a supercritical solution
RTIL	-	Room temperature ionic liquid
SAS	-	Supercritical antisolvent
$scCO_2$	-	Supercritical carbon dioxide
SCF	-	Supercritical fluid
SEM	-	Scanning electron microscope
SFC	-	Supercritical fluid chromatography
SFE	-	Supercritical fluid extraction
SMB	-	Simulated moving bed chromatography
SOP	-	Standard operating procedure
SSRI	-	Selective serotonin reuptake inhibitor
TBACl	-	Tetrabutylammonium chloride
TFA	-	Trifluoroacetic acid
THF	-	Tetrahydrofuran
VOC	-	Volatile organic compound

Chapter 1

Introduction

1 Introduction

This Thesis describes the application of heterogeneous catalysis and continuous flow supercritical CO_2 ($scCO_2$) as an alternative to batch processing in the pharmaceutical industry. Two reactions in particular have been studied: *N*-debenzylation and diastereoselective hydrogenation, both of which are important synthetic transformations within the pharmaceutical industry. The research described in this Thesis was performed at the University of Nottingham, in collaboration with AstraZeneca (Charnwood) and with the support of Thomas Swan & Co. Ltd. of Consett, County Durham.

The aim of this Chapter is first to provide an introduction to Green Chemistry and its role within the pharmaceutical industry. The application of alternative solvents, in particular supercritical fluids (SCFs) and supercritical CO_2 ($scCO_2$) will then be discussed with the focus directed toward their application in the pharmaceutical industry. The last section of this Chapter will describe the scope of this Thesis and its relevance to both Green Chemistry and the pharmaceutical industry.

1.1 Green Chemistry

It is vital that countries continue to develop manufacturing and chemical processes to support population growth and help provide a better standard of living for their inhabitants. However, in the past, these developments have been at a great cost to the environment. Global climate change and depletion of the ozone layer were some of the earliest signs of the damage which has been caused to our environment.[1-3]

The chemical industry is the single biggest producer of hazardous waste in the world. Previously, governments have dealt with waste production by increasing the volume of environmental legislation (Figure 1-1).[4,5] Although these

regulations encourage less waste production, they do not address the intrinsic factors associated with its production.

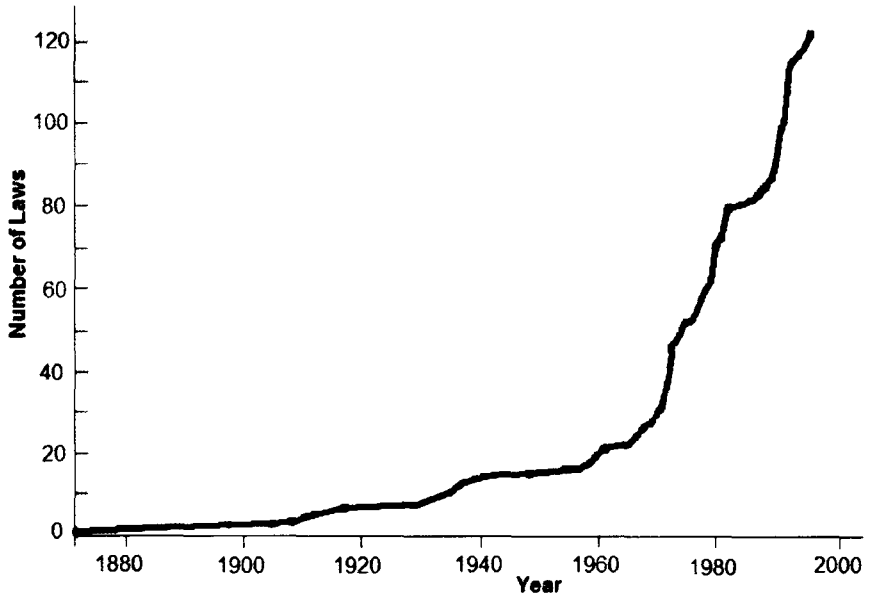


Figure 1-1: Increase in environmental legislation in the USA from 1970 until 2000.[4]

One of the main reasons that the chemical industry creates such a large amount of waste is that historically, synthetic chemists have only been interested in the beginning of the chemical process, i.e. identifying a high yielding method to make a certain chemical. However, the environmental problems associated with a chemical process have traditionally been identified at the end of the process when it is too late. Consequently, "end-of-pipe" solutions to waste management were provided which address the symptoms but not the cause of the problem.

Instead of treating waste at the end of the process, it would be much better to avoid formation of hazardous compounds altogether. This involves chemists developing new chemical processes and reactions that are sustainable. Sustainability in this context is about 'preserving the things you cannot live without and preserving them forever.' [4] It is hoped that Green Chemistry will provide the solutions to sustainable process design.

The term 'Green Chemistry' was first introduced by Anastas and Warner in the 1990s and has since become associated with all areas of chemical research.[6] It should be noted that Green Chemistry is not a *new* type of chemistry or an environmental movement, nor is it "what we do already". Green Chemistry is simply a new environmental priority for the design of chemical processes.[7]

Green Chemistry can defined on the basis of the 12 Principles[8]:

1. ***Prevention***: It is better to prevent waste than to treat or clean up waste after it has been created.
2. ***Atom Efficiency***: Synthetic methods should be designed to maximise the incorporation of all materials used in the chemical process.
3. ***Less Hazardous Chemical Syntheses***: Wherever practicable, synthetic methodologies should be developed to use and generate substances that possess little or no toxicity to human health and the environment.
4. ***Designing Safer Chemicals***: Chemical products should be designed to preserve their efficacy of function while reducing toxicity.
5. ***Safer Solvents and Auxiliaries***: The use of auxiliary substances (e.g. solvents, separation agents, etc) should be made unnecessary wherever possible and, innocuous when used.
6. ***Design for Energy Efficiency***: Energy requirements should be recognised for their environmental and economic impacts and should be minimised. If possible, synthetic methods should be conducted at ambient temperature and pressure.
7. ***Use of Renewable Feedstocks***: A raw material or feedstock should be renewable rather than depleting wherever technically and economically practicable.
8. ***Minimise Derivatisation***: Unnecessary derivatisation (blocking group, protection/ deprotection, temporary modification of physical/ chemical processes) should be avoided whenever possible.

9. ***Catalysis***: Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.
10. ***Design for Degradation***: Chemical products should be designed so that at the end of their function they do not persist in the environment and break down into innocuous degradation products.
11. ***Real-time Analysis***: Analytical methods should be developed to allow real-time *in situ* monitoring and control prior to the formation of hazardous substances.
12. ***Safer Chemical Processes for Accident Prevention***: Substances and the form of a substance used in a chemical process should be chosen so as to minimise the potential for chemical accidents, including releases, explosions and fires.

Green Chemistry can also address the issues of sustainability by educating the future generation of scientists. [9-12] To make the 12 Principles easier to remember and understand, the mnemonic PRODUCTIVELY can be used as a teaching aid that conveniently summarises the main points of Green Chemistry: Prevent waste – Renewable materials – Omit derivatisation steps – Degradable chemical product – Use safe synthetic methods – Catalytic reagents – Temperature and pressure ambient – In-process monitoring – Very few auxiliary substances – E-factor, maximise feed in products – Low toxicity of chemical products – Yes, it is safe.[13]

Green Chemistry takes on different forms in each sector of the chemical industry. Consequently, there are many variations of the 12 Principles of Green Chemistry, although they all have same unifying theme of sustainability.[14-16] The focus of this Thesis will be on the application of Green Chemistry in the pharmaceutical industry.

1.2 Green Chemistry in the Pharmaceutical Industry

Not all of the 12 Principles are applicable in the pharmaceutical industry. For example, Principle 10, designing for degradation can be inappropriate for the design of an Active Pharmaceutical Ingredient (API). This is because an API relies upon its precise chemical structure for the desired biological activity and it must also demonstrate adequate stability and acceptable shelf life.[7]

Traditionally, the measure of process efficiency within the pharmaceutical industry was calculated by combining the yield of each chemical transformation in the process. However, this measurement of process efficiency is no-longer acceptable since it does not take into account the amount of waste that is generated during synthesis. Since the introduction of Green Chemistry, several other metrics have been designed to measure process efficiency, such as; Life Cycle Assessment (LCA), atom economy, and carbon efficiency.[17-19] One of the most relevant measures of process efficiency is called the E-factor and was designed by Sheldon in 1997.[20] The E-factor can be calculated by dividing the mass of waste produced by the total mass of product. When comparing the E-factor of each sector of the chemical industry Sheldon found the pharmaceutical industry to be the biggest producer of waste per kg of product.

Table 1-1: E-factor for each sector of the chemical industry.[20]

Industry sector	Product tonnage	Kg by-product per kg product
Bulk chemicals	10^4-10^6	< 1-5
Fine chemicals	10^2-10^4	5-50
Pharmaceuticals	10-10^3	25 > 100

It is not surprising that the pharmaceutical industry has the largest E-factor compared to the other sectors of the chemical industry given the molecular complexity of the products. Bulk chemicals are often relatively simple organic molecules, in contrast to pharmaceuticals that are often very complex organic

molecules that contain multiple functional groups (Figure 1-2). As the complexity of the product increases, so too does the number of synthetic steps. This together with an increase in the number of separation and purification steps contributes to a high E-factor.

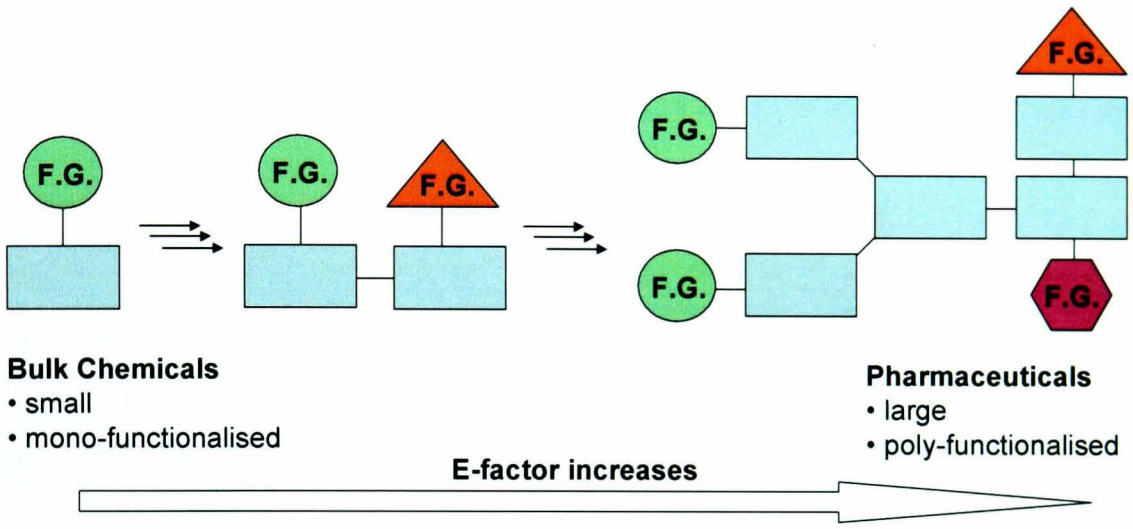


Figure 1-2: Complexity of target molecules increases across chemical industry from the synthesis of bulk chemicals to pharmaceuticals. (FG = Functional Group)

Chemists working in the bulk chemicals industry have always collaborated with engineers to design unique facilities that provide specific engineering solutions for large-scale manufacture and address the physical properties of relatively simple molecules. In contrast, pharmaceutical scientists have traditionally worked with little or no specialised engineering solutions to generate a diverse array of exceptionally complex target molecules. Chemists and engineers must collaborate together in all sectors of the chemical industry to fully realise sustainable process design.[21]

The pharmaceutical industry has always been much slower at adapting to changes in technology and process design compared with the other sectors of the chemical industry. For example, catalysis is a well developed field for the synthesis of many bulk and fine chemicals; whereas the pharmaceuticals industry still relies heavily on the use of stoichiometric reagents to make drug targets.[22] So why is this?

Figure 1-3 shows a standard timeline for development of a drug molecule.[23] It takes an average of eleven years of R&D before a drug goes to market. The implications of this long process are that pharmaceutical companies must get their drugs to clinical trials as quickly as possible. This, together with pressures of IP protection has meant that the pharmaceutical industry opts for established methodology and technology that minimises timeline and regulatory risk.

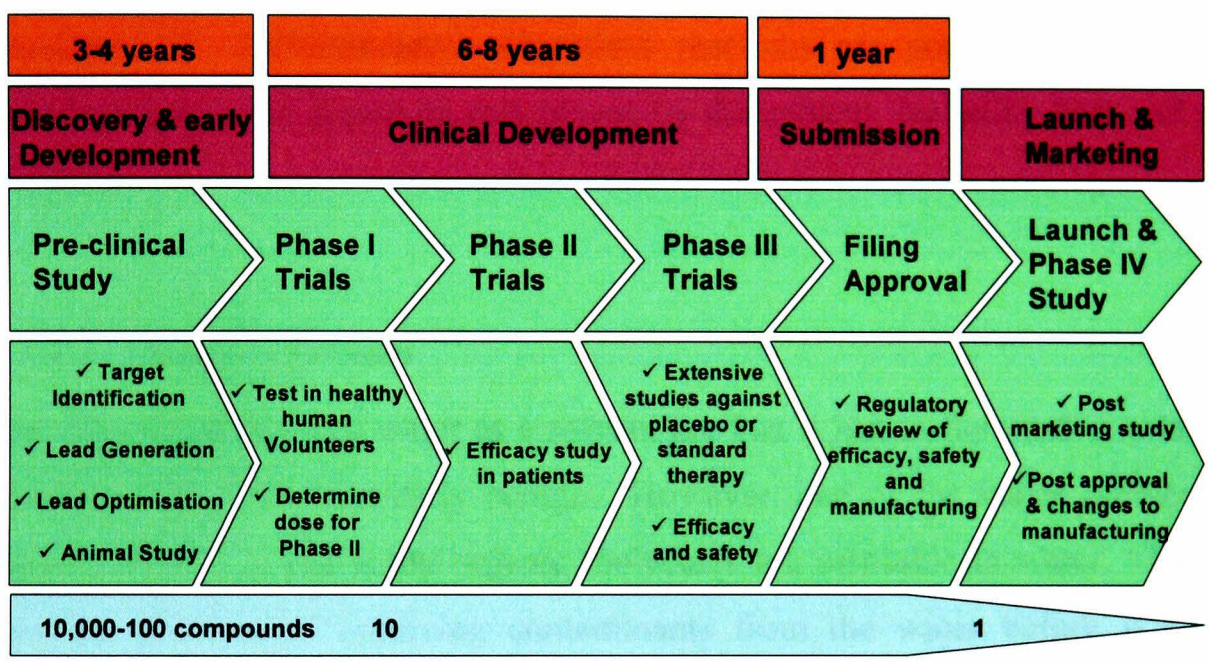


Figure 1-3: Development of a pharmaceutical process.[23]

There are many green alternative technologies that are under development for use within the pharmaceutical industry.[24,25] These include; rapid-optimisation and high-throughput screening;[26] micro-reactor and spinning disk technologies;[27] continuous flow techniques;[28-30] microwave reactions;[31,32] and more efficient separation techniques.[33] Many of these technologies are close to being commercially viable.

It has been approximated that 80 % of waste generated during manufacture of a typical API is related to solvent use.[34] Therefore in terms of helping the pharmaceutical industry reduce its E-factor, the most important technologies are those that eliminate (or reduce) the need for organic solvents.

1.3 Alternative Solvents

There are a number of alternative solvents that are currently being developed that avoid the environmental issues typically associated with the use of traditional volatile organic solvents (VOCs).[35,36] The alternative solvents can be divided into four main categories: (i) Aqueous solvents; (ii) Fluorinated solvents; (iii) Ionic liquids; (iv) Supercritical fluids. Ideally, solvents would not be required at all in a chemical reaction and indeed there are efforts directed at developing solventless reactions.[37,38] Unfortunately, solventless reactions are not practical for most reactions due to the important role played by the solvent, including heat and mass transport.

1.3.1 Aqueous Solvents

The main advantages of water as a solvent are that it is non-flammable, relatively abundant and environmentally benign. However, one of the major problems of aqueous media is that many organic molecules are insoluble in water. There is also the problem of removing contaminants from the water before it can be released back into the environment. Various strategies have been developed to make organic molecules soluble in aqueous solutions including:

Heating water to > 200 °C: Inside a sealed vessel at temperatures > 200 °C the hydrogen bonds of the water molecules are partially broken and therefore the solubility of organics increases.[39,40] This method may not always be suitable due to degradation of the starting materials or products at high temperature.

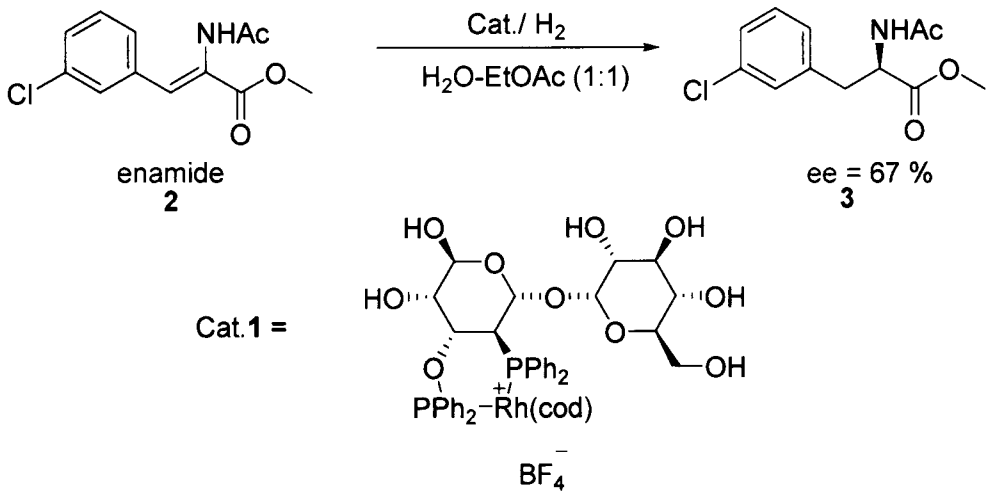
Use of co-solvents: A co-solvent reduces the degree of hydrogen bonding of the aqueous system, making it more effective at dissolving non-polar molecules. Some of the more common co-solvents are the lower alcohols, acetone and acetonitrile.[41,42]

pH control: If the solute is ionisable, it is possible to enhance solubility by adjusting pH. At the end of the reaction, the product can then be recovered by adjusting the pH to afford precipitation.[41]

Use of surfactants: By using amphiphilic molecules (molecules that contain polar and non-polar sections) it is possible to minimise contact between the solute (non-polar) and the water molecules (polar).[43]

Hydrophilic auxiliaries: This involves incorporating hydrophilic groups onto insoluble reactants. This is a strategy of major importance in the synthesis of drug molecules that rely on high water solubility for their therapeutic efficacy.

A good example of using water as a solvent is the asymmetric hydrogenation of enamides using a water-soluble chiral rhodium catalyst **(1)**.[44] The catalyst contains carbohydrate groups to enhance solubility in aqueous media. This has proven to be an effective route to many different amino acids (Scheme 1-1).



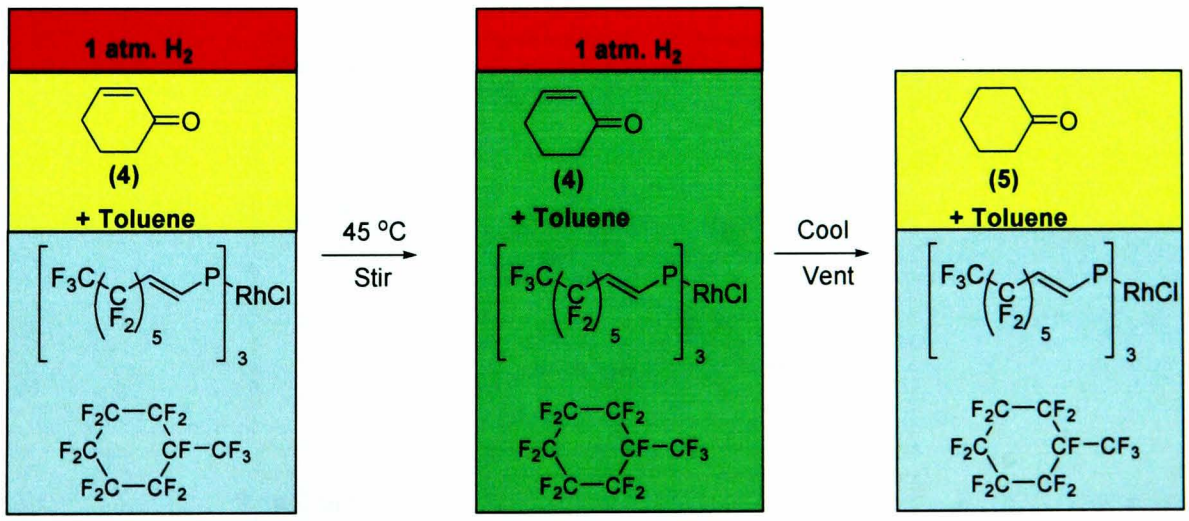
Scheme 1-1: The enantioselective hydrogenation of enamide (2) conducted in aqueous media using a water soluble rhodium catalyst.[44]

1.3.2 Fluorinated Solvents

Fluorinated solvents are environmentally benign and can be used in fluorous biphasic catalysis.[45-48] The field of fluorous phase catalysis was pioneered by

Horvàth and Rabai who also coined the phrase 'fluorous' (analogous to aqueous) which is used to describe highly fluorinated, alkane, ether, and tertiary amine solvents.[49] Under ambient conditions, fluorous solvents are not normally miscible with organic solvents. However, when heat or pressure is applied, a homogeneous phase can be formed. If the reactants and products are soluble in the organic phase and a catalyst is soluble in the fluorous phase then separation of the catalyst from the products can be achieved by lowering the temperature or pressure to afford phase separation. This method of biphasic catalysis avoids one of the major problems typically associated with homogeneous catalysis that is catalyst/ product separation.

An example of biphasic catalysis using fluorous solvents is displayed in Scheme 1-2. In this example, Horvàth and co-workers demonstrated the successful hydrogenation of cyclohexene-1-one **(4)** using a Rh catalyst which was rendered soluble in the fluorinated solvent by attaching fluorinated "ponytail" ligands. The fluorinated catalytic phase was recycled three times with only a very slight decrease in yield which was always > 90 %.



Scheme 1-2: Hydrogenation of 2-cyclohexene-1-one (4), using a Rh catalyst with fluorinated ponytail ligands, immobilised in a fluorinated solvent. The fluorinated catalyst and solvent can be recycled.[49]

The disadvantages of fluorous biphasic catalysis are that conventional solvents must still be used and that the products have to be separated from them. Also, fluorinated ligands and solvents are relatively expensive in comparison to water and other conventional reaction media. There are also environmental concerns regarding the widespread use of fluorinated organics.[50]

1.3.3 Ionic Liquids

Ionic liquids (ILs) are generally salts of organic cations that are molten at temperatures below 100 °C. Room Temperature ILs (RTILs) are molten salts at around ambient temperature. ILs are interesting as reaction media because they exhibit no measurable vapour pressure and remain in liquid phase over a wide range of temperatures. Solvent properties such as polarity and hydrophilicity can be tuned by varying the combination of cations and anions; this has led to ILs being labelled 'designer solvents'. Their solvent power is very high and they are able to dissolve organic and inorganic compounds as well as gases such as H_2, CO_2 and CO. This makes them widely applicable as solvents for a range of different reactions. Some of the more common ILs are displayed in Figure 1-4.

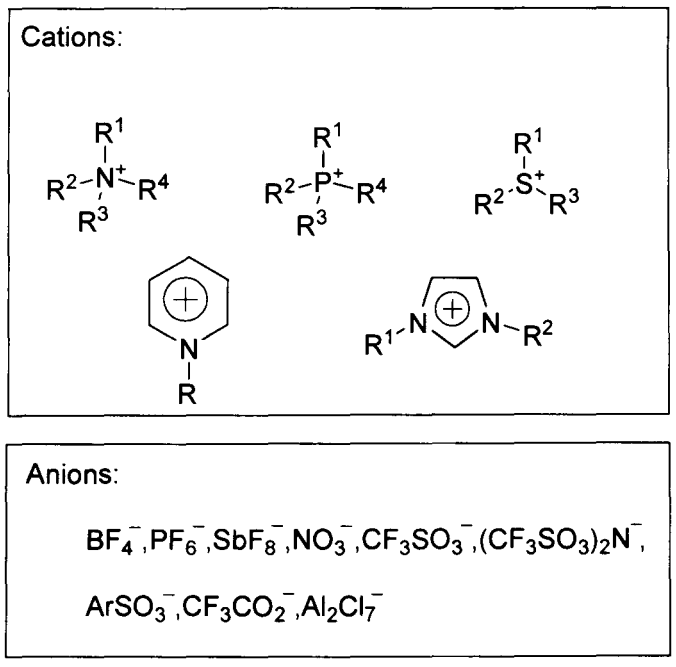
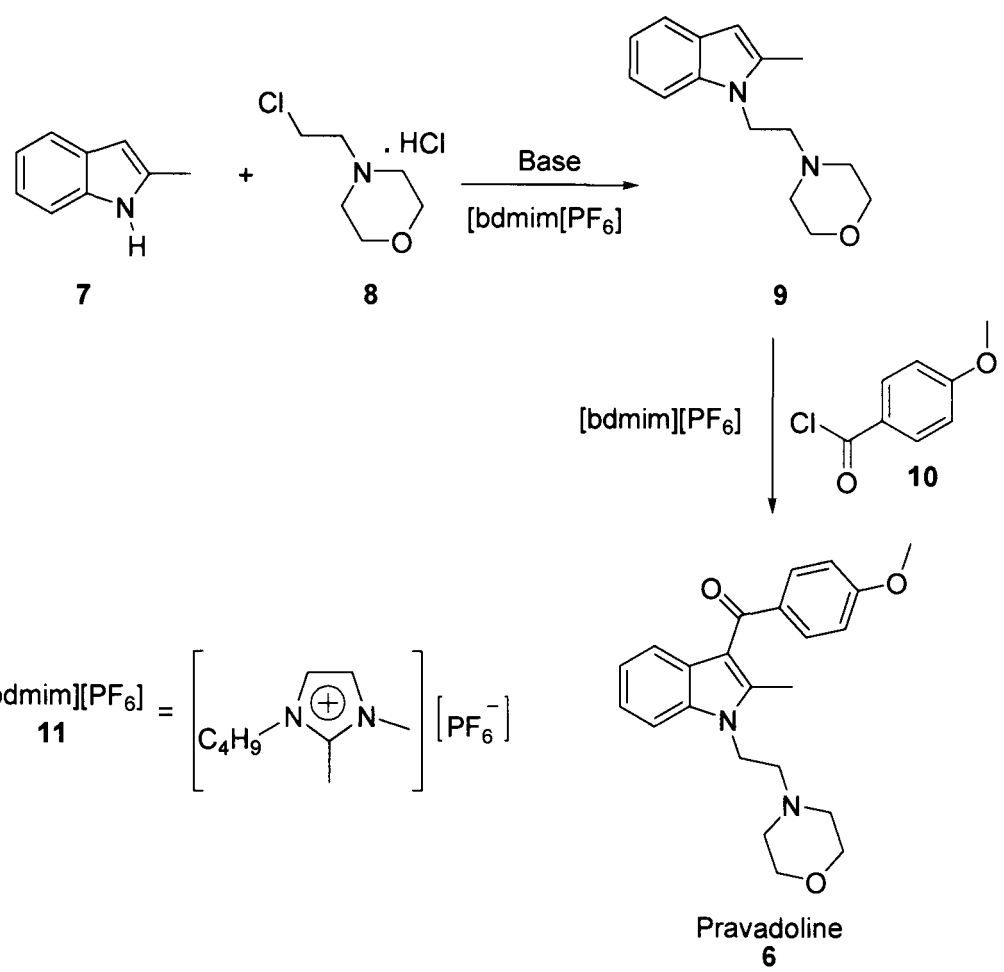


Figure 1-4: A selection of the most common cation and anions used in the synthesis of ILs.[51]

ILs and RTILs have been used as solvents for a variety of catalytic reactions[52,53] including hydrogenation[54-56], hydroformylation[57,58], acid-catalysed reactions [59,60] and various C-C bond forming reactions.[61,62]

Seddon and co-workers were able to synthesise a pharmaceutical, Pravadoline **(6)**, a non-steroidal anti-inflammatory drug using ILs as solvent (Scheme 1-3).[63]



Scheme 1-3: Synthesis of the pharmaceutical Pravadoline (6) performed in two steps in the ionic liquid [bdmim][PF_6] (11).[63]

In the conventional synthesis, the solvent (DMF or DMSO) was difficult to separate from the product, leading to a reduction in yield. Seddon was able to synthesise Pravadoline in two steps and high yield (90-94 %) by performing an *N*-alkylation followed by Friedel-Crafts acylation. Both steps were performed using the same ionic liquid, 1-butyl-2,3-dimethyl-2,3-dimethylimidazolium hexafluoro-phosphate ([bdmim][PF_6]) **(11)**. No Lewis Acid catalyst was required in the

Friedel-Crafts step and therefore all associated aluminium waste disposal of traditional Friedel-Crafts chemistry was avoided.

Although ILs are excellent solvents they are also very expensive. This problem can be reduced if ILs can be effectively recycled. There is also little information on the environmental impact of their production, toxicity and disposal which may be preventing them from being used on a commercial scale.[64]

1.3.4 Supercritical Fluids

A supercritical fluid (SCF) is defined as a substance above it critical pressure (p_c) and critical temperature (T_c), but below the pressure required to condense it into a solid (Figure 1-5).[65] However, for many SCFs the pressure required to form a solid is impractically high and therefore the last part of this definition is often omitted.

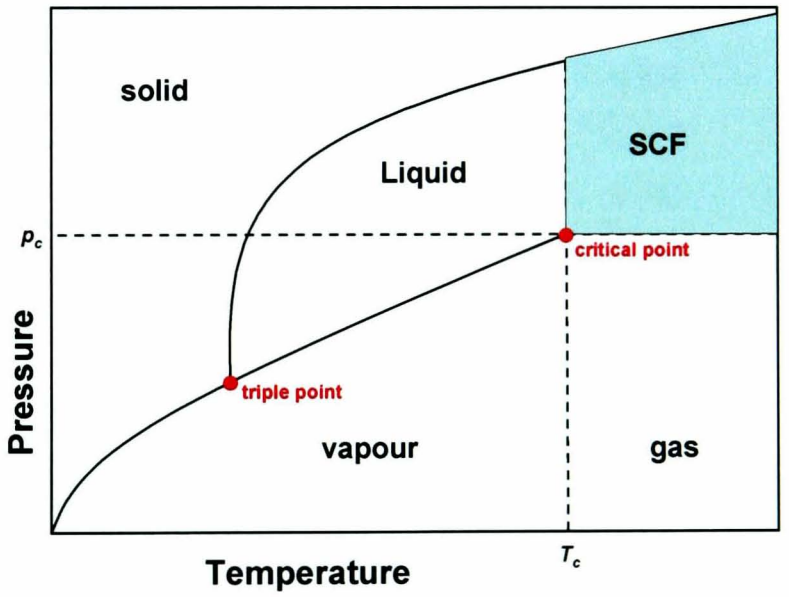


Figure 1-5: Phase diagram of a pure substance showing the critical temperature (T_c) and critical pressure (p_c). The critical point is located at the intersection of T_c and p_c.[66]

The critical density (ρ_c) can also be used to define a SCF; that is the average density of the gas phase at T_c and p_c. The physical properties of a SCF are intermediate of a liquid and gas. This is because the liquid and gas phases merge at the critical point and become indistinguishable. The fact that SCFs possess high

diffusivity and low viscosity but can also display liquid like densities makes them interesting as a alternative reaction media.

SCFs have several potential advantages as alternative solvents. For example, changing the temperature and/ or pressure can alter the density and therefore solvent power of the SCF. Also, gases are completely miscible in SCFs, thus any reactions involving gaseous reactants (such as hydrogenation and hydroformylation) are not restricted by mass transport.[66] A range of SCFs and their critical parameters are displayed in Table 1-2. Compared with the other SCFs, the critical parameters of CO_2 are relatively mild. This makes it an attractive solvent since less energy is required to pressurise and depressurise the system.

Table 1-2: Supercritical parameters for several compounds and elements.[67]

SCF	T_c / °C	p_c / bar	ρ_c / g mL^{-1}
Ar	-122.5	48.6	0.531
Xe	16.6	58.3	1.099
CO_2	31.1	73.8	0.047
SF_6	45.5	37.6	0.737
HCl	52.5	82.6	0.420
H_2O	374.0	220.6	0.322

In this Chapter, discussions will focus on $scCO_2$ and its application as an alternative solvent in different areas of the pharmaceutical industry.

1.4 $scCO_2$ in the Pharmaceutical Industry

A number of different applications have been developed for the pharmaceutical industry that involve the use of SCFs, particularly $scCO_2$.[68-70] Regardless of its application, the major advantage of $scCO_2$ in all of these applications is the potential for eliminating, or at least reducing, the amount of organic solvent used in the process. $scCO_2$ is an ideal processing medium for all pharmaceutical

applications because it is in plentiful supply, non-flammable, cheap, leaves no toxic residues, and has been approved for use by the FDA. Compared to other SCFs, $scCO_2$ is ideal because of its relatively mild critical parameters. This means that the advantages of near-critical and supercritical CO_2 can be applied, but it is still possible to operate at low temperature where the degradation of sensitive pharmaceutical molecules should be minimised.

Pure CO_2 has a solvent power similar to that of *n*-hexane and so is a poor solvent for most pharmaceutical molecules, which are often very polar, high molecular weight compounds. However, there are several factors that can be exploited to increase solubility:

1. Variation in Pressure and Temperature

Over the last ten years there has been a huge increase in the number of applications of $scCO_2$ as a solvent, or anti-solvent within the pharmaceutical industry, particularly in the field of extraction. Therefore, a large number of publications on the phase behaviour and solubility of pharmaceutical compounds in $scCO_2$ has been published.[71-81] Most pharmaceuticals are complex, high molecular weight molecules that have high melting points. It has been shown that solubility of solid organic molecules can be correlated with their melting point; the higher melting point, the lower the solubility in CO_2.[65]

This was evident when studying the relative solubility of the drugs benzocaine **(12)**, metronidazole benzoate **(13)** and naproxen **(14)** (Figure 1-6).[82] The order of solubility correlates with the melting point of the molecule. Increasing the pressure of $scCO_2$ at a constant temperature results in increasing its density and thereby its solvent strength.

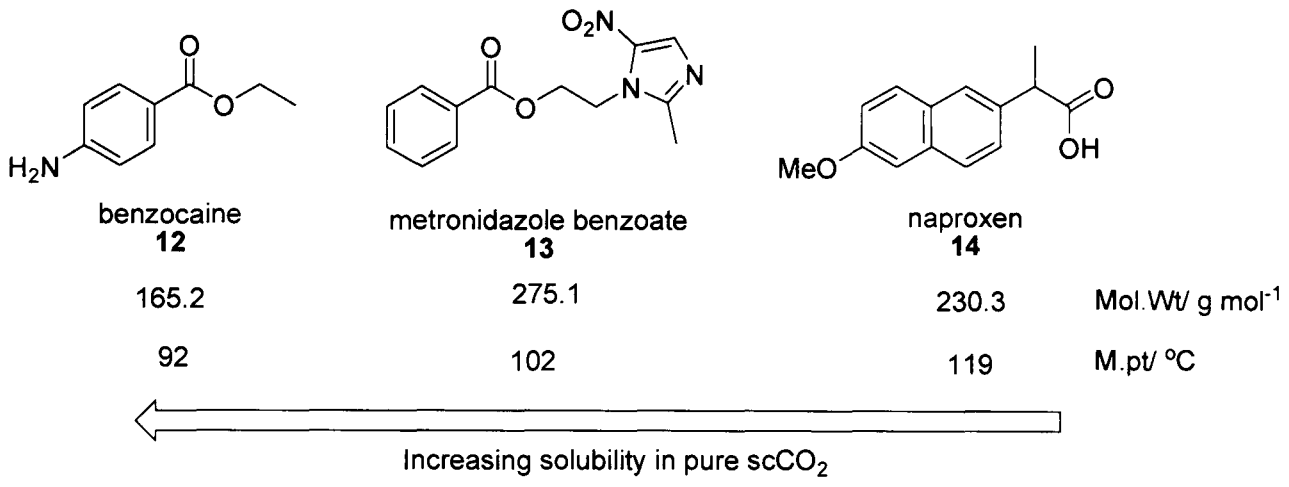


Figure 1-6: Solubility of solids in pure $scCO_2$ is correlated with the melting point of the substrate. For example the order of solubility of the three drugs above is, benzocaine (12) > metronidazole benzoate (13) > naproxen (14).[82]

Temperature also influences the solute vapour pressure and solvent density, and hence can also be used to affect changes in solubility. When the pressure of $scCO_2$ is constant, and temperature is increased, the effect on solvent strength depends on the density. If the pressure is below the single phase region, increasing temperature leads to lowering the solvent strength of the CO_2 due to a decrease in fluid density. However, in the single phase region, an increase in temperature usually improves solvent strength despite the decrease in fluid density since the vapour pressure of the analyte is increased.[82,83]

2. Addition of a Co-solvent

Changing the pressure and/ or temperature of the system may not always be suitable. Instead, solubility can be enhanced by the addition of a small amount of a co-solvent. This can be a solvent such as MeOH or EtOH which is added to the solute/ CO_2 mixture. [84-86] The choice of co-solvent (in terms of polarity) can also have a major effect on solute-solute interactions (hydrogen-bonding, etc) and therefore also effects solubility in $scCO_2$.[87,88] Increasing the mole fraction of co-solvent present in the CO_2 mixture often leads to an exponential increase in solubility.[88,89]

One of the major disadvantages of adding even small amounts of organic solvent to increase solubility is that an extra separation step will be required to remove the co-solvent from the solute. This detracts from the overall 'greenness' of the process and therefore the amount of co-solvent added should always be kept to a minimum.

3. Fluorination

Fluorinated compounds exhibit significantly higher levels of solubility in $scCO_2$ than their non-fluorinated analogues.[90-92] For example the solubility of benzoic acid **(15)** and its fluorinated analogues [**(16)-(18)**] were studied in dense phase CO_2 (Figure 1-7).[93] It was found that benzoic acid **(15)** is only sparingly soluble in $scCO_2$ (always < 1.0 wt. % under all conditions) due to the presence of the carboxylic acid group. Adding only one fluorine led to only a moderate increase in solubility with 3-fluorobenzoic acid **(16)** soluble at only 1.8 wt. % at 35 °C and 290 bar. However, the addition of a trifluromethyl group showed a significant improvement in solubility. The solubility of 3-(trifluoromethyl)benzoic acid **(18)** in $scCO_2$ at 35 °C and 100 bar was 7 wt. %, which was almost 40 times higher than the solubility of benzoic acid **(15)** under the same conditions.

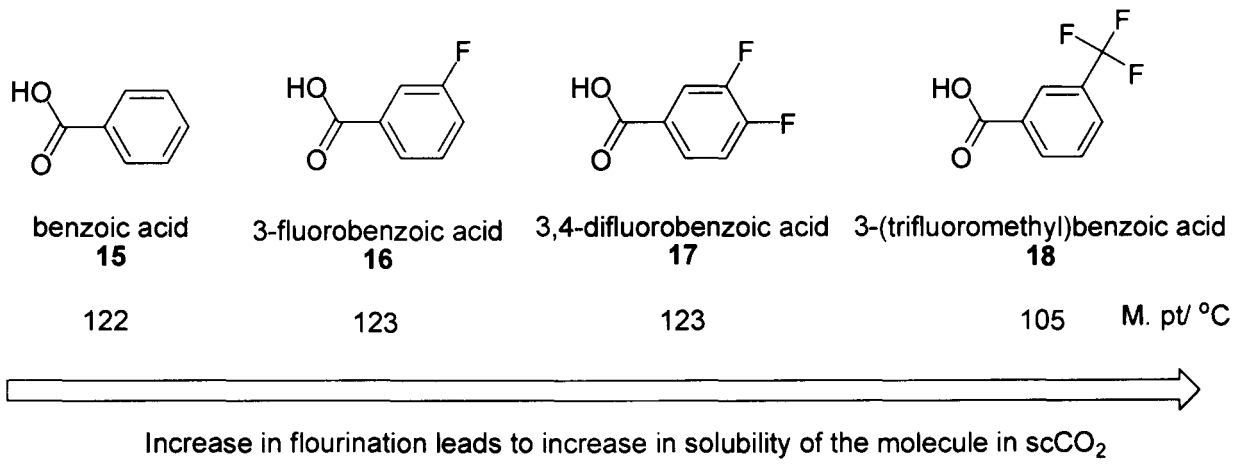


Figure 1-7: Increasing the fluorine content increases the solubility of molecules in $scCO_2$.[93]

It has already been mentioned that as a general rule, the higher the melting point, the lower the solubility in $scCO_2$. However, the order of solubility for fluorinated molecules does not follow that order (Figure 1-7). Instead, the order of increasing solubility is a factor of the increased degree of fluorination.

Fluorine is attached to many pharmaceutical molecules to control their transport and metabolic rates.[93] Therefore, there may be cases were it is possible to take advantage of the enhanced solubility of fluorine in $scCO_2$ by designing pharmaceutical molecules with fluorine atoms present.

The enhanced solubility of fluorinated compounds has been taken advantage of in other areas of SCF chemistry, particularly in the field of polymer synthesis where a surfactant containing a CO_2-philic tail, consisting of fluorine substituents, can help to control the solubility of polymers.[94-96] It has also been applied more directly to the synthesis of fluorinated polymers in $scCO_2$.[95,97,98]

Now that the factors affecting solubility have been discussed, it is important to address the various applications of $scCO_2$ within the pharmaceutical industry.

1.4.1 Drug Particle Formation

It is vital that the API of a drug can be efficiently delivered to the area of the body for which is intended. The effectiveness of an API can be significantly affected by changes in physical properties such as morphology and particle size distribution. Fine particles with a narrow particle size distribution are essential for the development of inhalation aerosols, injectable suspensions and controlled release drugs. Particle size can also be critical when determining the rate of dissolution of a drug in a biological fluid, and hence can have a significant effect on the bioavailability of poorly water-soluble drugs for which dissolution is the rate-determining step to absorption. It is estimated that 40 % of new drug development has failed because of poor biopharmaceutical properties.[99]

Conventional techniques for adjusting the particle size of a drug molecule include mechanical techniques (crushing, grinding, and milling), recrystallisation of the solute particles from solution using a liquid anti-solvent, freeze-dying, and spray drying. Some of the limitations of these conventional techniques include: excessive use of organic solvent; solvent disposal; thermal and physical degradation of products; potentially toxic trace residues; lack of control of particle size distribution. Therefore, the production of contaminant-free drug particles with controlled particle size and desired product qualities in an environmentally responsible manner is a major challenge in the pharmaceutical industry.

Several techniques have been developed for drug particle formation that take advantage of the tunable solvent properties of $scCO_2$. The ability to vary the solvent strength rapidly and thereby the rate of supersaturation and nucleation of dissolved compounds is a unique aspect of drug particle formation in $scCO_2$. Drug particle formation techniques in $scCO_2$ can broadly be divided into two groups: those that use CO_2 as a solvent, for example the rapid expansion of supercritical solutions (RESS); and those that use CO_2 as an antisolvent in techniques such as gas antisolvent precipitation (GAS) and precipitation with compressed antisolvents (PCA). Each of these techniques will now be discussed in detail.

Rapid Expansion of Supercritical Solutions (RESS)

In this process, the solute is first solubilised in the SCF. The SCF solution is then expanded across a nozzle, or capillary at high velocity. The rapid expansion leads to supersaturation of the solute and subsequent precipitation of virtually contaminant-free particles (Figure 1-8).

The RESS process can produce contaminant-free drug particles ranging from a few microns to several hundred microns in diameter. The factors that affect particle size and morphology include the length/ diameter of the expansion device, the time-scale for the solution to pass from the pre-heater to the expansion device, and the degree of particle agglomeration during free jet expansion.[99-101]

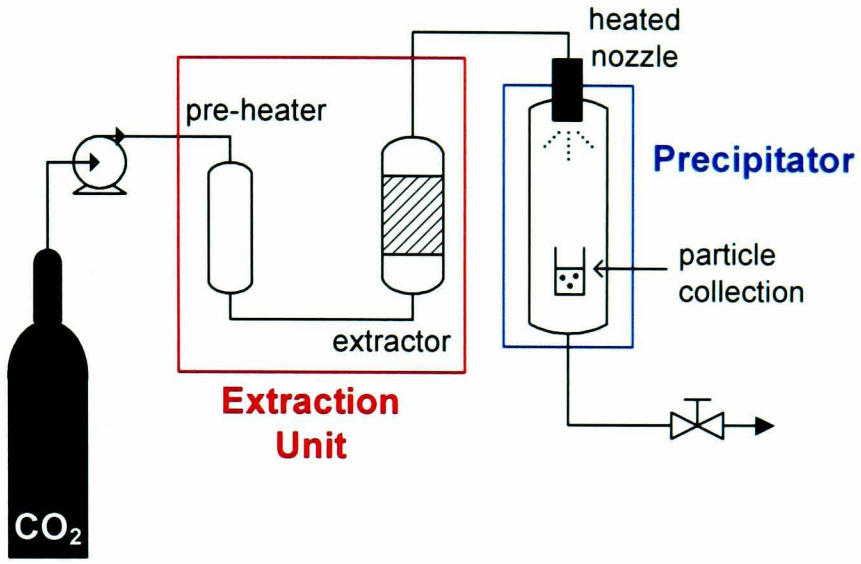


Figure 1-8: RESS technique for drug particle formation. [102]

The RESS process can be modified so that expansion of the supercritical solution takes place in a liquid solution (such as water) instead of ambient air; this is known as rapid expansion of a supercritical solution into a liquid solvent (RESOLV). This process has the advantage that nano-scale, rather than micron-scale particles can be produced since the liquid acts to suppress particle growth in the expansion jet.

Sun and co-workers studied ibuprofen and naproxen particle formation using the RESOLV process (Figure 1-9).[103,104] Particles of a narrow size distribution could be produced, however, particle agglomeration could be avoided by adding a stabilising agent, poly(*N*-vinyl-2-pyrrolidone) (PVP) to the aqueous suspension of nanoparticles.

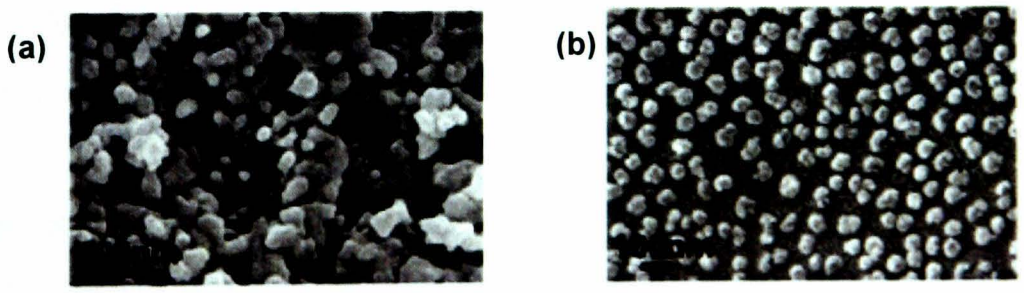


Figure 1-9: SEM images showing naproxen nanoparticles (average size of 64 nm and a size distribution of 10 nm) obtained from RESOLV process using neat water (a) and an aqueous PVP solution (b).[104]

There are many examples of RESS and RESOLV processes being applied, particularly for the production of controlled release drugs.[105,106] However, a major limitation of the RESS and RESOLV processes is that at moderate temperatures and pressures (< 60 °C and 300 bar), the solubility of pharmaceutical compounds in $scCO_2$ is of the order of 0.01 wt % or less.[102] Hence, relatively large amounts of CO_2 are required for increased product throughput. Co-solvents may be added to enhance solubility however this detracts from the 'greenness' of the process.

Gas Antisolvent Precipitation (GAS) and Precipitation with Compressed Antisolvents (PCA)

The RESS process involved using CO_2 as a solvent, however the GAS and PCA approaches utilise CO_2 as an anti-solvent. The relatively low solubilities of pharmaceutical compounds in unmodified CO_2 are exploited in these processes whereby the solute of interest (drug molecule, polymer or both) is dissolved in a conventional solvent to form a solution. The solute should be completely insoluble in CO_2, while the solvent should be completely miscible with dense CO_2 at the recrystallisation temperature and pressure. The solute can then be recrystallised from solution in one of two ways.

In the first method, a batch of the solution is expanded several-fold by mixing with dense CO_2 in a vessel [(a) from Figure 1-10]. Due to the fact that CO_2-expanded solvents have a lower solvent strength than pure CO_2, the mixture becomes supersaturated, forcing the solute to precipitate or crystallise as micro-particles. This process is gas antisolvent (GAS) precipitation.

The second method involves spraying the solution through a nozzle as fine droplets into compressed CO_2 [(b) from Figure 1-10]. This process has been termed precipitation with compressed antisolvents (PCA) and employs either liquid or $scCO_2$ as the anti-solvent. When using a supercritical antisolvent, the

spray process is often termed the supercritical antisolvent (SAS) process or aerosol spray extraction system (ASES).

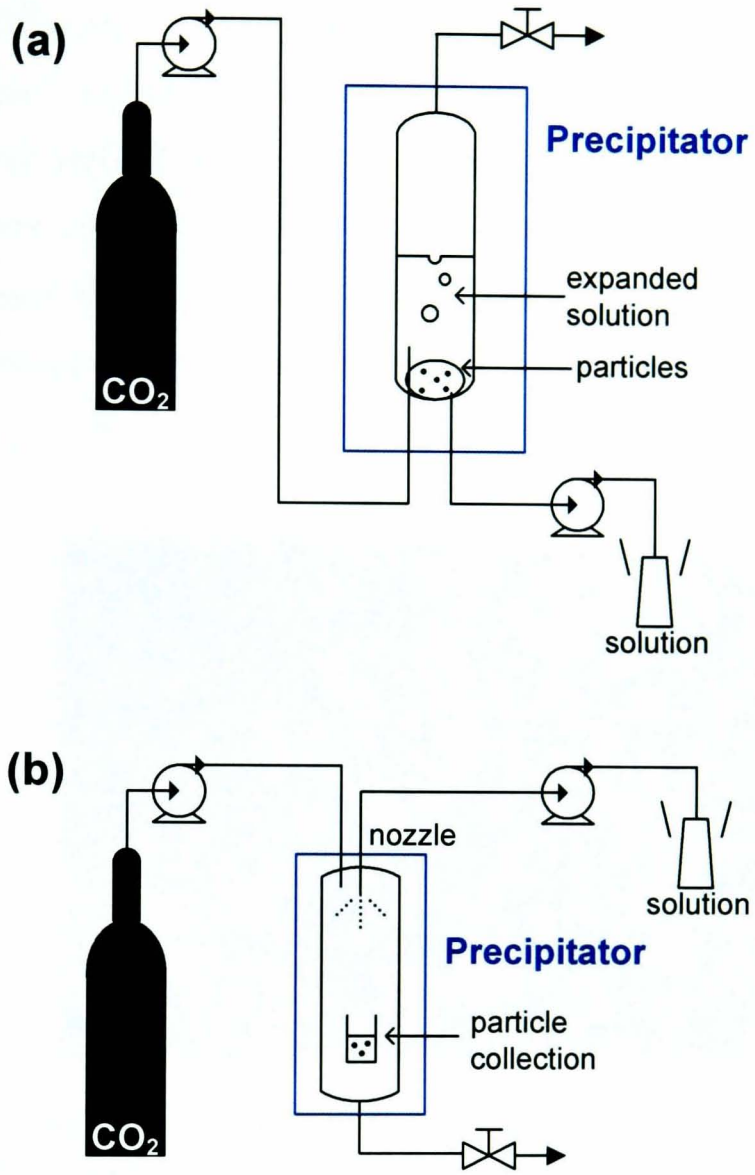


Figure 1-10: GAS (a) and PCA (b) techniques for drug particle formation utilise CO_2 as an antisolvent

In the spray processes, the particle size and morphology are dependent on several factors such as operating pressure, temperature, jet break-up, and mass transfer rates between the droplet and antisolvent phases. Jet break-up and droplet size is ultimately dependent on the nozzle configuration, spray velocity and the physical properties of the droplet and antisolvent phases.

The GAS and PCA processes are complementary to RESS, however, the advantages of the anti-solvent processes include higher solute throughput and flexibility of solvent choice. The PCA and GAS techniques have been used to micronise a wide variety of pharmaceutical compounds such as polymers used in controlled-release formulations, protein powders, and anti-inflammatory agents.[107-110] The reported particle sizes range from submicron to a few microns in a narrow size range which makes them suitable for either pulmonary delivery (1-3 μm) or for use in implantable devices (< 100 μm). For example, insulin was precipitated from a dimethylsulphoxide (DMSO) solution using the GAS process to produce spheres with a particle size distribution of 1.4 to 1.8 μm (Figure 1-11).[111]

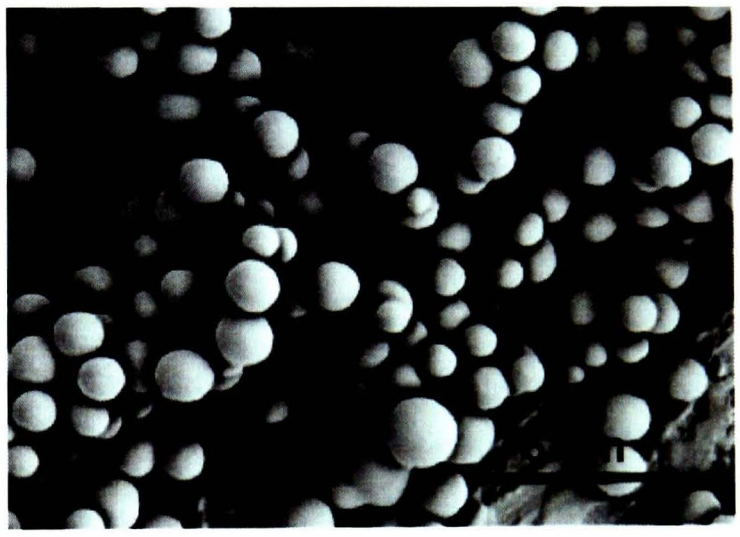


Figure 1-11: GAS process was used to precipitate insulin from a DMSO solution using the GAS process to produce particles with an average particle size of 1.4 to 1.8 μm. [111]

The spray-processes (PCA, SAS and ASES) permit faster depletion of the solvent, and hence greater production of particles, relative to the GAS process, and therefore have received increased attention in recent years. However, for these processes to be commercially viable it must be shown that particles can be produced with the desirable properties in high yielding, reproducible continuous flow processes which remains a major task for the future.[112]

1.4.2 SCF Chromatography (SFC)

The efficient separation of molecules, particularly enantiomers, is very important during the preparation of pharmaceuticals. Traditionally, separation may be carried out using preparative HPLC, however, this process involves the use of large amounts of organic solvent. The use of SCFs as a mobile phase for chromatography has been known since the 1960's,[113] however it has only been in the last ten years that the supercritical fluid chromatography (SFC) apparatus has been developed for commercial applications.[114,115]

The advantages of SFC over conventional techniques include faster resolution and higher selectivity due to the unique ability of SCFs to be able to vary solvent strength. SFC is also significantly more economical in terms of solvent use.[116,117] For preparative scale chromatography, another alternative to HPLC is simulated-moving bed (SMB) chromatography.[118] This process was originally developed for the separation of xylenes from C(8) aromatics, but has since been applied on a commercial scale to the synthesis of Zoloft®, a drug which is discussed later in Chapter 4.[119] The SMB approach is significantly more economical in terms of solvent use, however, it has also been shown that the use of organic solvent can be further reduced by using $scCO_2$ as a mobile phase for supercritical fluid simulated moving bed chromatography (SF-SMB).[120]

Supercritical Fluid Extraction (SFE)

The extraction of organic molecules from natural sources is the most widely studied application of SCFs.[121] The supercritical fluid extraction (SFE) apparatus is similar to that of the RESS apparatus (Figure 1-8). It consists of an extraction vessel charged with the raw matter to be extracted. As a rule, the starting material is dried and ground to favour the extraction process. It is loaded in a basket located inside the extractor that allows fast charge and discharge of the extraction vessel. The SCF at the exit of the extractor flows through a depressurisation valve to a separating unit, which is where the extracts are released and collected from the

gaseous medium. It is even possible to perform multi-step extraction processes. For example, it may be possible to perform the first expansion at low pressure, where the most soluble compounds are extracted (perhaps essential oils and other volatiles), and a second extraction at higher pressure to remove less soluble compounds (such as anti-oxidants for example).

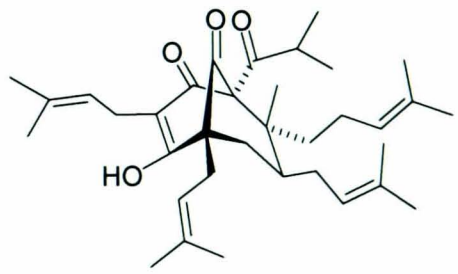
The selectivity of the extraction process can be varied according to the processing parameters (temperature, pressure, flow rates). A general rule for SFE is the higher the pressure, the larger the solvent power of the SCF and the smaller the extraction selectivity. Adding a co-solvent to increase solubility can have a similar effect and can lead to less control over selectivity.

Perhaps the most famous example of SFE is the commercial scale extraction of caffeine from coffee.[122,123] Since then, there has been a large number of publications on the extraction of various organic molecules, including the extraction of pharmaceuticals from natural sources using the SFE technique.[124-132]

One example is the extraction of Hyperforin **(19)** from *Hypericum perforatum L.*, or St. Johns Wort as it is commonly known.[133,134]

St. Johns Wort

SFE



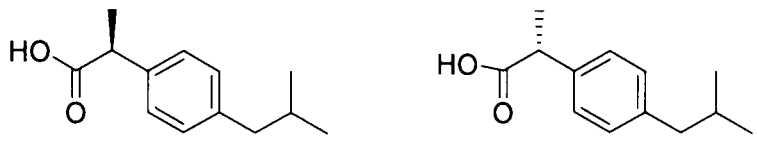
Hyperforin
19

Scheme 1-4: SFE can be used for the extraction of many natural products, including Hyperforin (19), which is extracted from St. Johns Wort [133,134]

St. Johns Wort is widely used as a herbal remedy for depression, but it is the extract, Hyperforin **(19)** that is believed to be the active ingredient. It was found

that Hyperforin **(19)** could be selectivity extracted from St. Johns Wort by performing the SFE in the presence $scCO_2$ at 120 bar for one hour.[133]

In terms of application within the pharmaceutical industry, it is also worth noting that SFE can be used for enantioseparations, such as for the enantioseparation of (±)-ibuprofen **(20)**. [135] Ibuprofen is a non-steroidal anti-inflammatory drug which can be administered in racemic form; however, the (*S*)-(+)-enantiomer **(20a)** is much more effective than (*R*)-(–)-enantiomer **(20b)**.



(S)-(+)-Ibuprofen
20a

R-(-)-Ibuprofen
20b

Figure 1-12: (±)-Ibuprofen (20) can be separated by combining classical resolution with SFE.[135]

SFE was used in combination with classical resolution (using (*R*)-phenylethylamine) to separate the diastereomeric salts of ibuprofen. The selection of co-solvent was found to have a significant effect on selectivity of the extraction process. Efficient separation was also possible in pure CO_2 without addition of a co-solvent when the process was performed above the melting point of ibuprofen.

In comparison with other extraction techniques, SFE has the advantage of potentially being able to eliminate the use of organic solvent completely from the extraction process.[136]

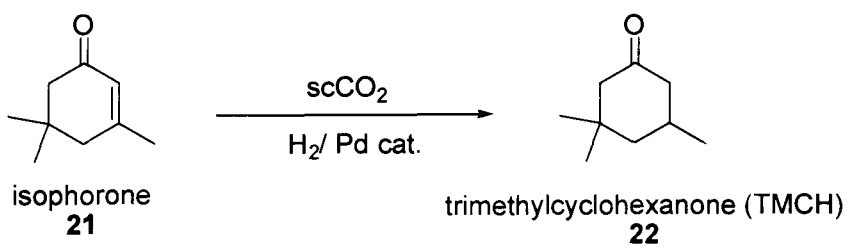
1.4.3 Synthesis

The application of SCFs as solvents for reactions is large and there are examples of many different SCFs being used as solvents including scEtOH,[137-140] scC_3H_8,[141,142] scH_2O and others.[143-148] However, in this Thesis it is the application of $scCO_2$ as solvent that is discussed in detail.

The number of reactions that can be performed in $scCO_2$ is forever expanding. Important C-C bond forming reactions such the Diels-Alder reaction [149-151] and Pd catalysed cross-coupling reactions can be performed.[152-154] Also acid catalysed reactions such as desymmetrisation[155] and Friedel-Crafts chemistry can be conducted efficiently as continuous flow processes.[156,157]

Perhaps the most studied of all reactions in $scCO_2$ are those of hydroformylation[158-160] and hydrogenation.[161-170] Both reactions take advantage of the enhanced solubility of the reagent gas (CO or H_2) in $scCO_2$ and can be performed using homogeneous[171] or heterogeneous catalysts.[67]

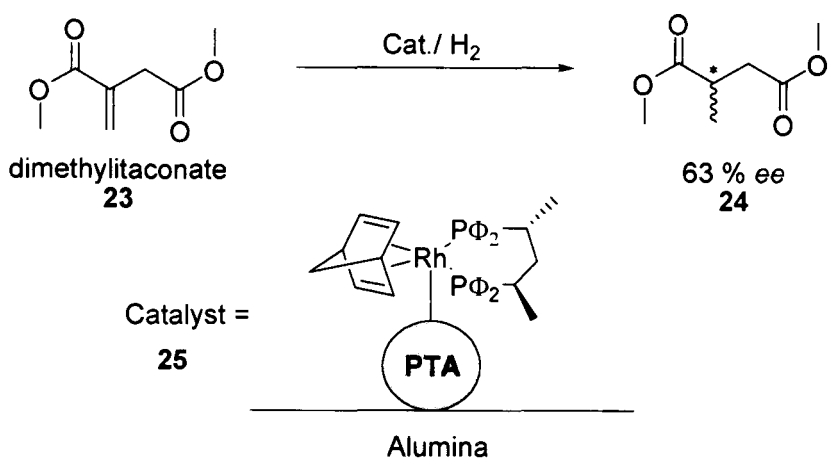
The application of heterogeneous catalysis for the hydrogenation of bulk and fine chemicals has been well studied in $scCO_2$ and as testament to this the first continuous $scCO_2$ hydrogenation plant was commissioned in 2002.[172] This plant is capable of producing 1000 tons *per annum* and has been used for the hydrogenation of molecules such as isophorone **(21)**.



Scheme 1-5: The continuous flow $scCO_2$ plant, opened in 2002, was developed for the hydrogenation of fine chemicals. Here, isophorone is selectively hydrogenated to the desired compound, TMCH (22).[172]

Particularly interesting for the synthesis of pharmaceuticals, is enantioselective hydrogenation. Enantioselective hydrogenation of model compounds can be performed in $scCO_2$ over modified heterogeneous,[173-175] or homogeneous catalysts.[176,177] A particularly interesting example is the enantioselective hydrogenation of **(23)** to produce **(24)** which can be performed using a supported

chiral Rh catalyst.[178] The chiral Rh catalyst **(25)** is anchored to the silica support by phosphotungstic acid (PTA) which acts as a 'magic glue', binding the metal to the support.



Scheme 1-6: Enantioselective hydrogenation using a supported homogeneous catalyst. (PTA is phosphotungstic acid [$H_3O_{40}PW_{12}$], $\Phi = C_6H_5$.[178]

In an effort to enhance the status of $scCO_2$ as a solvent for synthesis in the pharmaceutical industry, debenzylation and diastereoselective hydrogenation have been studied. Both are important reactions in the pharmaceutical industry.[179-181]

1.5 Scope of this Thesis

The aim of this Thesis is to investigate whether $scCO_2$ can used as an alternative solvent for the synthesis of pharmaceuticals. It is evident from this Chapter that the use of $scCO_2$ as an alternative solvent for the synthesis of bulk and fine chemicals is well established; however, little research has been focused on applying this technology to the pharmaceutical industry. To investigate the use of $scCO_2$ as an alternative reaction medium for synthesis within the pharmaceutical industry two different catalytic reactions have been studied; *N*-debenzylation and diastereoselective hydrogenation.

Chapter 3 describes the selective removal of the *N*-benzyl protecting group from a variety of model substrates. Interesting results were obtained during the chemoselective *N*-debenzylation of a chlorinated benzyl-protected aniline; various strategies were developed to avoid dechlorination.

Chapter 4 describes the diastereoselective hydrogenation of a pharmaceutical intermediate in $scCO_2$. Reactions have been performed over various heterogeneous catalysts to maximise the diastereo- and chemoselectivity of this reaction. Interesting observations were made when comparing the selectivity of reactions that were conducted in the presence, and absence of $scCO_2$.

The pharmaceutical industry has in the past performed hydrogenation and debenzylation reactions as batch processes. However reactions conducted in continuous flow are inherently safer than those conducted in batch. The ability to tune temperature and pressure independently in flow is also an advantage, particularly when using $scCO_2$. The work described in this Thesis aims to prove that debenzylation and diastereoselective hydrogenation reactions can be conducted efficiently in continuous flow. Chapter 2 provides details of all apparatus mentioned in this Thesis. Also included are details of the synthetic procedures and analytical methods.

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Chapter 2

Experimental

2 Experimental

This Chapter describes the experimental detail for all reactions and equipment reported in this Thesis. The majority of the experiments that have been reported were performed using the small-scale continuous flow apparatus; however, other high pressure apparatus has also been used. A description and Standard Operating Procedure (SOP) for all apparatus have been provided. Details of all analytical techniques that have been used are provided. Many of the substrates that have been studied in debenzylation and hydrogenation studies were synthesised according to literature procedures. Details of all experimental procedures and analytical data are provided at the end of this Chapter.

2.1 Equipment Description

Four different types of apparatus have been used throughout this Thesis. Both the large and small-scale continuous flow apparatus have been used for debenzylation and hydrogenation reactions in high pressure CO_2. Reactions have also been conducted inside an autoclave, as a batch process. These three pieces of apparatus were all built and designed in-house at the University of Nottingham. The fourth, the H-Cube, is a commercial piece of apparatus developed by Thales Nanotechnology.[1] The H-Cube was used to study the effects of continuous flow hydrogenation in the absence of CO_2.

It must be noted that the apparatus described in this Chapter has to be used at high pressure and therefore it is the responsibility of all researchers to verify that their equipment is fit-for-purpose and meets the necessary safety requirements.

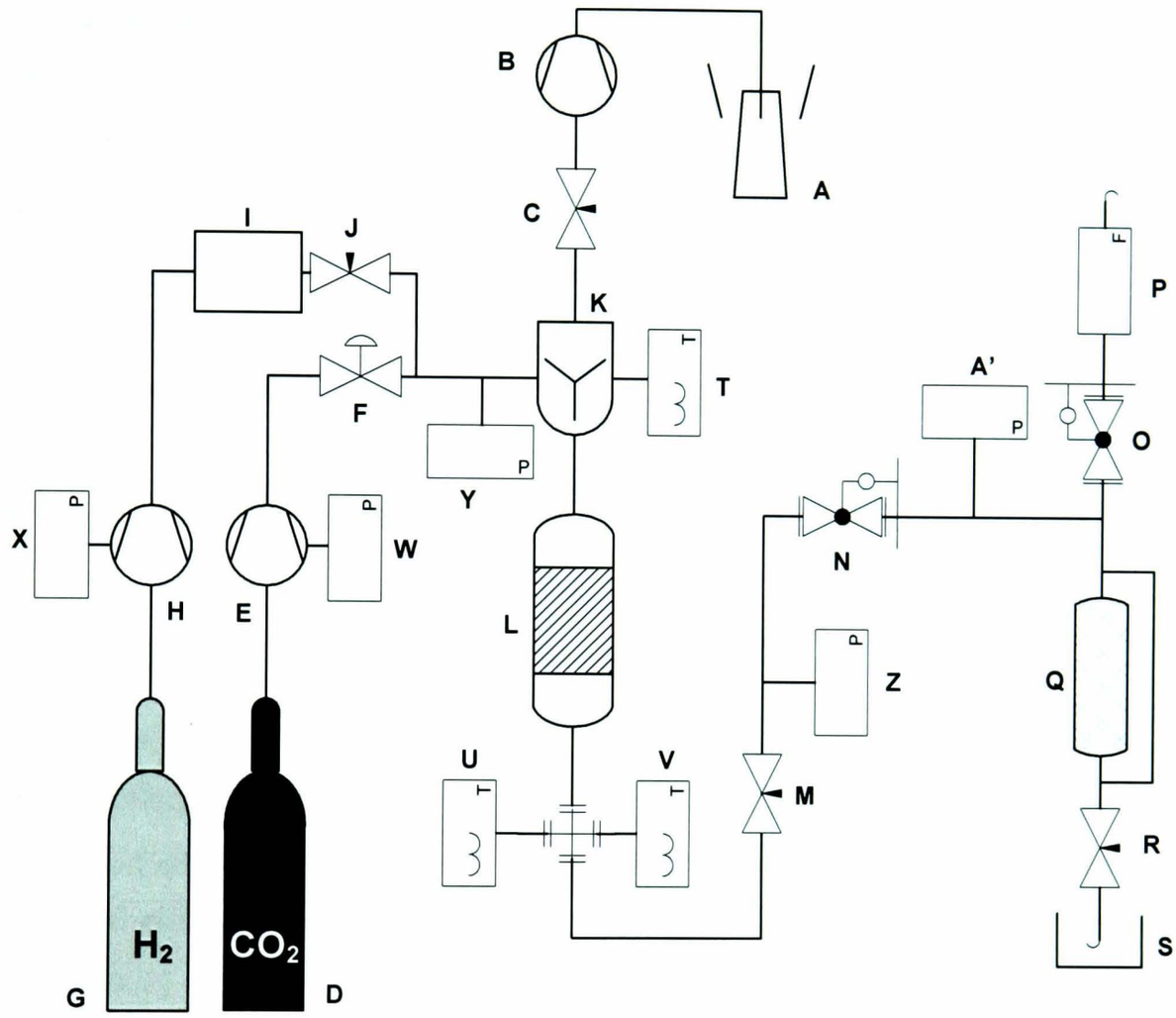


Figure 2-1: Schematic of large-scale continuous flow apparatus.

*(Key: **A** = Substrate reservoir; **B** = Gilson 305 HPLC pump; **C** = SSI tap; **D** = CO_2 dip tube cylinder; **E** = refrigerated reciprocating pump; **F** = diaphragm valve; **G** = H_2 cylinder; **H** = gas booster pump; **I** = Rheodyne gas dosage unit; **J** = SSI tap; **K** = static mixer; **L** = heated reactor; **M** = needle valve; **N** = 1st expansion valve; **O** = 2nd expansion valve; **P** = flow meter; **Q** = product isolation module; **R** = SSI tap; **S** = collection vial; **T** = temperature controller; **U** = temperature controller; **V** = temperature monitor; **W** = bourdon gauge; **X** = bourdon gauge; **Y** = pressure monitor; **Z** = pressure monitor; **A'** = pressure monitor.)*

2.2 Large-Scale Continuous Flow Apparatus

Large-scale reactors have been used for many years within the Clean Technology Group at Nottingham for the study of hydrogenation and hydroformylation reactions.[2-6] However, the large-scale reactors require a substantial amount of time to reach a steady state (up to 40 minutes) due to their large internal volume, therefore significant amounts of substrate are required to undertake detailed studies. Almost all of the substrates that have been studied in this Thesis had to be synthesised and therefore only the very early research, which was conducted using a commercially available substrate, was performed on the large-scale apparatus. The other studies were undertaken on the small-scale continuous flow apparatus which is described later in this Chapter.

2.2.1 Description of Large-Scale Apparatus (Figure 2-1)

CO_2 supplied *via* cylinder (**D**) equipped with a dip tube, was fed into refrigerated reciprocating pump (**E**) where it was cooled and compressed as liquid CO_2 (Figure 2-1). Compressed air was used to produce the pressure inside pump (**E**) through pressure multiplication, with the air being fed at low pressure (~6 bar) from a compressor. The CO_2 was then fed through 1/8" tubing up to system pressure valve (**F**). Diaphragm valve (**F**) was used to regulate system pressure; it also helps to dampen any pulsing produced by the pump (**E**). The system pressure was monitored throughout experiments using pressure transducer (**Y**) which was attached to a digital pressure monitor.

The reagent gas (H_2) was stored inside cylinder (**G**) and was fed through 1/8" tubing into gas booster pump (**H**) (NWA CU-105) which compresses the reagent gas to the desired pressure. A gas dosage unit (**I**), used a 6-port Rheodyne 7000L switching valve to dose the gas in a controlled manner (Figure 2-2). While one loop was open to the system, effectively being flushed, the other was being filled. The unit then switches at a pre-set rate based on calculations made to affect the appropriate H_2 to substrate ratio. The switching ratio was calculated based on the

concentration and flow rate of the substrate, and also the concentration of H_2 in each sample loop. It was important to use a high switch rate to avoid any pulsing effects caused by the dosage of reagent gas. A high rate can usually be achieved by using the smaller volume sample loops.

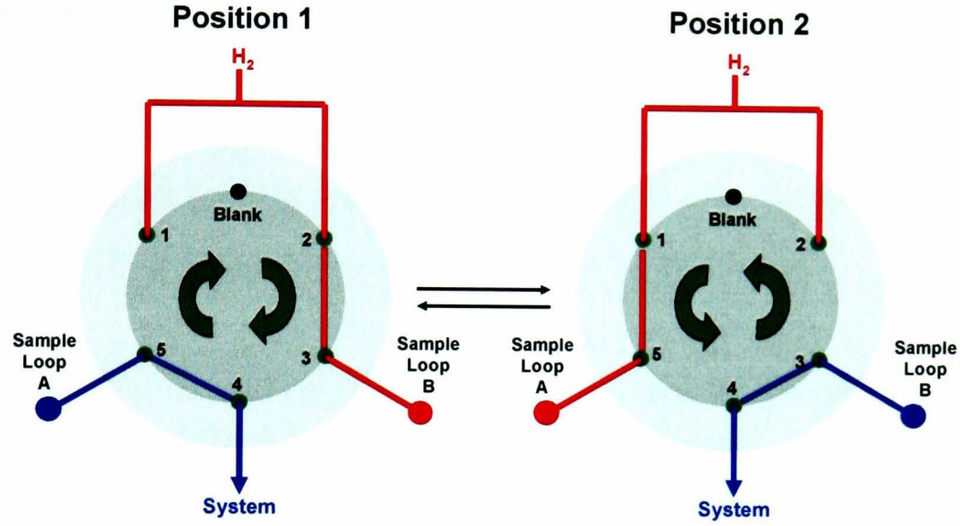


Figure 2-2: Schematic of gas dosage unit, Rheodyne 7000L. In position 1, ports 2 & 3 are linked by a channel, therefore sample loop B is filled. Ports 4 & 5 are also linked and therefore sample loop A is open to the system. After a specified time, the Rheodyne unit will rotate to position 2 where sample loop B is open to the system and sample loop A is being filled.

The organic substrate (**A**) was fed into the apparatus using a Gilson 305 HPLC pump (**B**) equipped with a 5 SC pump head, into a heated static mixer (**K**). The static mixer consists of a 1/4" NPT crosspiece filled with glass beads that help to maintain a consistent substrate flow and produce a homogeneous mixture. The mixer was surrounded by two machined aluminium blocks and inserted into these are two 240 V resistance heating cartridges. A Eurotherm™ 2216L heating controller and thermocouple were used to control the temperature of both cartridges, while a second thermocouple (**T**) was inserted into the aluminium blocks to monitor the temperature of the mixer throughout the experiment.

The reaction mixture was then passed over the reactor bed (**L**) containing a heterogeneous catalyst. The reactor consisted of a 12 mm (OD) stainless steel tube

with an internal volume of 5 ml. A frit, located at the bottom of the reactor, was small enough to make sure the catalyst remained inside, but large enough to allow passage of the reactant mixture. The reactor was heated using two aluminium blocks containing two 240 V resistance heating cartridges which were connected to a Eurotherm™ 2216L heating controller and monitor. Connected to the base of the reactor was a second 1/4" NPT crosspiece that contained two thermocouples. One thermocouple (**U**) sits half way up inside the reactor to monitor the temperature of the catalyst bed; the second thermocouple (**V**) sits in the middle of the crosspiece to monitor the temperature of the outflow. A control thermocouple was located in the aluminium block and connected to the trip circuit.

The organic/ H_2/ CO_2 mixture then passed to tap (**M**), before reaching pressure gauge (**Z**). Tap (**M**) allows isolation of the expansion system in case of emergencies while the pressure gauge (**Z**) allows the operator to decide if any blockages are present in the system between the reactor and the expansion system. The expansion system consisted of two membrane valves (DruVa®) (**N**) and (**O**), located in series, which were used to reduce sequentially the pressure from operating pressure down to atmospheric pressure in a safe and controlled manner. The 1st expansion valve (**N**) was heated to 60 °C to ensure that the CO_2 did not freeze upon expansion of the CO_2 and decreased the pressure of the system down to 10 - 20 bar. The second expansion valve (**O**) was designed to decrease the pressure of the system down to 0.5 - 6.0 bar. Between the two expansion valves the SCF/ organic mixture was separated from the organic liquid, which collected in the product isolation module (**Q**) and was siphoned off into collection vial (**S**) by opening the product collection tap (**R**). The flow of CO_2 was monitored using the Sho-rate™ flow meter (**P**) and controlled using the second expansion valve (**O**). The gaseous CO_2 was then vented to the back of the fume hood at atmospheric pressure.

2.2.2 SOP for Large-Scale Apparatus

Described below is a standard operating procedure for all continuous flow experiments conducted on the large-scale apparatus:

Start-up

1. System pressure valve (**F**), expansion system isolation tap (**M**) and product tap (**R**) were all closed.
2. Reactor (**L**) was loaded with a known amount of catalyst and swaged into position.
3. Gilson HPLC 305 pump (**B**) was primed with substrate solution.
4. Cylinders (**D**) and (**G**) were opened and the CO_2 pump allowed to cool.
5. The pressure of the reagent gas to be dosed into the system was set on pump (**H**) set at an over-pressure of ~50 bar.
6. The switch rate of the reagent gas dosing unit (**I**) was calculated (using data from NIST and an excel spreadsheet) and then set.
7. CO_2 pump (**E**) was pressurised to ~100 bar above the system pressure required.
8. System pressure valve (**F**) was slowly opened to pressurise the system up to the expansion system.
9. All joints and fittings were checked for leaks using leak detection fluid, Snoop®. If no leaks were detected then SOP continued. Otherwise the system was depressurized, the leaking fitting(s) tightened using a spanner and step 1 - 9 repeated.
10. Isolation tap (**M**) was opened and the 1st expansion valve (**N**) was set to 10 - 20 bar.
11. The bulk flow rate was monitored using flow meter (**P**) and controlled using the 2nd expansion valve (**O**).
12. All joints and fittings in the expansion system were then tested for leaks in the same manner as in step 8.
13. Heating blocks, complete with thermocouples, were assembled around the mixer (**K**) and also the reactor (**L**).

14. The heating controllers for the mixer (**K**) and catalyst bed (**L**) were turned on and set to the required temperature.
15. As the system was heated and began to equilibrate, the bulk flow rate, and therefore system pressure changed. Once the system reached a steady state the flow rate and system pressures were adjusted accordingly.
16. The reagent gas was dosed into the system by first opening tap (**J**) and then switching on the gas dosage unit (**I**). The system was then left for 20 minutes to ensure that the catalyst was fully reduced.
17. Once the system reached steady state (system temperature and pressure were constant), the organic isolation tap (**C**) was opened.
18. The pump rate was then set on the Gilson HPLC 305 pump **(B)** at the required flow rate and the pump switched on.

Reaction

19. The temperature, pressure and CO_2 flow were all carefully checked at this point and monitored throughout the experiment.
20. Samples were collected at regular intervals (5 - 10 minutes) in collection vials (**S**) by opening the product tap (**R**). Generally products were first detected after 10 - 30 minutes depending on flow rates.
21. If the reaction conditions needed changing (temperate, pressure, flow rates, etc.) then fractions would not be collected until the system had achieved a steady state (~40 minutes). Once this point was reached, steps 17 and 18 were repeated.

Shut-down

22. The Gilson HPLC pump (**B**) was shut down and tap (**C**) turned off.
23. The hydrogen dosage unit (**I**) was switched off and tap (**J**) turned off.
24. Gas booster pump (**H**) was depressurised and the H_2 cylinder (**G**) closed.
25. CO_2 flow was continued at constant flow for at least 40 minutes to remove any residual organic material. The system could also be flushed at this point with an organic solvent (e.g. MeOH) to help clean the system.

26. The heating controllers for the mixer (**K**) and reactor (**L**) were switched off.
27. Once the apparatus was cool the system pressure valve (**F**) was closed and the system slowly vented.
28. The refrigerated reciprocating pump (**E**) was decompressed and the CO_2 cylinder (**D**) isolated.

2.3 Small-Scale Continuous Flow Apparatus

Most of the continuous flow experiments that are discussed in this Thesis were performed on the small-scale apparatus. One of the major differences between the large and small-scale apparatus is that the small-scale apparatus does not require an expansion system since depressurisation is affected in a single step, which is controlled *via* the back-pressure regulator (BPR). The small-scale apparatus has a much smaller internal volume than the large-scale apparatus and therefore is more efficient in terms of amount of substrate used per experiment. The small-scale apparatus has been used within the Clean Technology Group for continuous flow oxidation and hydrogenation reactions under supercritical conditions.[7-9]

2.3.1 Description of small-scale apparatus (Figure 2-3)

CO_2 supplied *via* cylinder (**D**), equipped with a dip tube, was fed directly into the fume hood and into Jasco pump (PU-986) (**E**) (Figure 2-3). Jasco CO_2 pump (**E**) had an in-built pressure transducer (**Q**) which was connected to a trip circuit. If the reactor became blocked then pump (**E**) would register the over-pressure and stop pumping CO_2 until the blockage was removed and system pressure dropped to normal. The Jasco pump head was chilled using a recirculating pump filled with ethylene glycol to maintain a constant temperature (–10 °C). Liquid CO_2 was then fed into a cross-piece and through to static mixer (**K**).

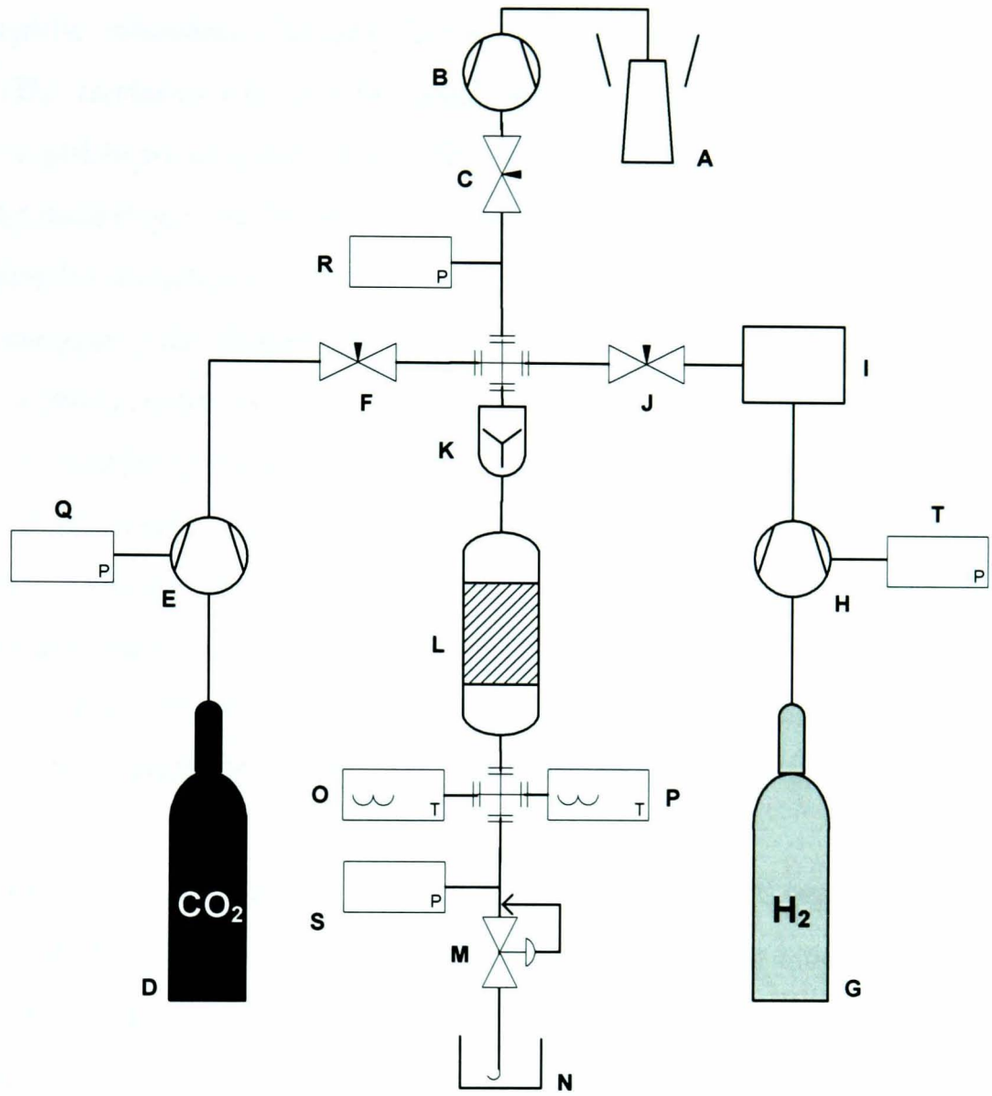


Figure 2-3: Schematic of small-scale continuous flow apparatus.

*(Key: **A** = Substrate reservoir; **B** = Gilson 305 HPLC pump; **C** = SSI tap; **D** = CO_2 dip tube cylinder; **E** = Jasco CO_2 pump fitted with chilled pump head; **F** = SSI tap; **G** = H_2 cylinder; **H** = NWA gas booster pump; **I** = Rheodyne gas dosage unit; **J** = SSI tap; **K** = static mixer; **L** = heated reactor; **M** = Jasco back pressure regulator; **N** = collection vial; **O** = temperature controller; **P** = temperature monitor; **Q** = pressure transducer; **R** = pressure transducer; **S** = pressure transducer; **T** = bourdon gauge.)*

The reagent gas (H_2) (**G**) was fed into mixer (**K**) at an over-pressure (~50 bar) *via* gas booster pump (**H**) (NWA CU-105) which compresses the reagent gas to the desired pressure. A gas dosage unit (**I**), used a 6-port Rheodyne 7000L switching valve to dose the gas in a controlled manner and works in the same manner as that described previously in the description of the large-scale apparatus.

The organic substrates (**A**) were fed into the apparatus *via* a Gilson 305 HPLC pump (**B**), equipped with a 5 SC pump head. The reagents and CO_2 were then mixed together inside static mixer (**K**) which was filled with glass beads, before entering reactor (**L**) which contained a known mass of catalyst. Reactor (**L**) could be heated by securing aluminium blocks around the outside of the reactor, which were equipped with thermocouples and 230 V heating cartridges. Eurotherm™ 2216L heating controllers were used to control the temperature of the heating blocks surrounding reactor (**L**) while the temperature was monitored at various points in the system using West 6700 temperature monitors. One thermocouple (**O**) was positioned half-way up inside the reactor to monitor internal reactor temperature, while another thermocouple (**P**) was situated in the reactor out-flow pipe. The temperature controllers were connected to a trip circuit which could cut power to the heaters if the maximum set temperature was breached.

The reaction mixture was then fed into the back-pressure regulator (Jasco BP-1580-81 BPR) (**M**) which was responsible for controlling system pressure The nozzle of the BPR was heated to ~50 °C to avoid freezing of the pipe work upon expansion of the CO_2. Samples of the reaction mixture were collected from the BPR nozzle in sample collection vials (**N**). All of the equipment was connected using 1/16" 316 stainless steel tubing with the appropriate size Swagelok or SSI fittings.

2.3.2 SOP for Small-Scale Apparatus

Described below is a standard operating procedure for all continuous flow experiments conducted on the large-scale apparatus:

Start-up

1. Reactor (**L**) was filled with the desired amount of catalyst and swaged to the apparatus.
2. Gilson 305 HPLC pump (**B**) was primed with substrate solution.

3. BPR (**M**) was set to the desired pressure for the experiment.
4. Recirculating pump filled with ethylene glycol was turned on to chill the Jasco CO_2 pump (**E**) and left to reach –10 °C.
5. CO_2 cylinder (**D**) was opened, as was tap (**F**) which allowed gaseous CO_2 to fill the system.
6. All joints and fittings were checked for leaks using a leak detecting solution, Snoop®.
7. A flow rate of 3 mL/ min was set on the Jasco CO_2 pump and the apparatus was allowed to fill with CO_2 until the BPR set pressure was reached and a flow of CO_2 was established.
8. Heating blocks, complete with thermocouples, were assembled around the reactor (**L**) and the heaters switched on at the required set temperature.
9. Once the system had equilibrated, H_2 cylinder (**G**) was opened and the overpressure on the gas booster pump (**E**) was set.
10. The pre-calculated switch rate for the gas-dosage unit was set and tap (**F**) opened.
11. The gas-dosage unit (**I**) was turned on and the system then left for 20 minutes to equilibrate and ensure that the catalyst is fully reduced.
12. Tap (**C**) was opened and the flow rate of substrate was entered on the Gilson HPLC pump.
13. The Gilson pump was turned on.

Reaction

14. The temperature, pressure and flow rates were all carefully checked at this point and monitored throughout the experiment.
15. Product fractions were collected in the sample collection vials (**N**) regularly (5-10 minutes) for analysis.
16. If the reactions conditions (pressure, temperature and flow rates, etc.) need to be changed, then the substrate flow was stopped and allowed to run dry. The conditions would then be changed and the system was allowed to

equilibrate before recommencing the substrate flow. Step 14 would then be repeated.

Shutdown

17. Gilson HPLC pump (**B**) was turned off and tap (**C**) closed.
18. The hydrogen dosage unit (**I**) was turned off and the H_2 cylinder (**G**) closed.
19. CO_2 flow was continued for a further 20 minutes to flush out any residual organic material.
20. The temperature controller for the reactor was turned off left to cool.
21. CO_2 pump (**E**) was turned off, tap (**F**) closed and the CO_2 cylinder (**D**) closed.

2.4 Reactor Design

Figure 2-4 shows the various types of reactor that have been used in continuous flow hydrogenation and debenzylation reactions described in this Thesis. Reactors (i) and (ii) were cut from 12mm 316 stainless steel and were compatible with the large-scale continuous flow apparatus. Reactors (iii) and (iv) were cut from 1/4" 316 stainless steel pipe and are much smaller volume reactors compatible with the small-scale continuous flow apparatus (Table 2-1).

Table 2-1: Compatibility and dimensions of each different reactor used in continuous flow experiments.

Reactor Type	Compatible with	Length (inches)	OD	Volume (mL)
(i)	Large-scale	6.0	12mm	9.9
(ii)	Large-scale	3.0	12mm	4.9
(iii)	Small-scale	6.0	1/4"	1.2
(iv)	Small-scale	3.0	1/4"	0.6
(v)*	Small-scale	N.A.	N.A.	0.2

** also known as the 'pot reactor'*

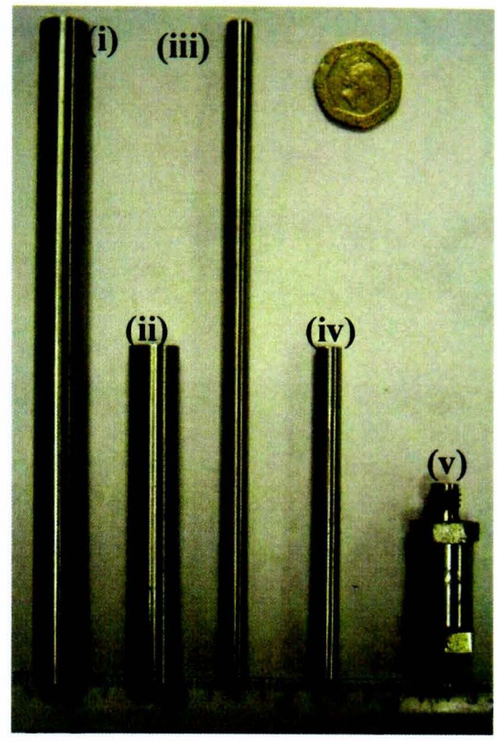


Figure 2-4: Each size and type of reactor that has been used in this Thesis, (The numbers (i)-(v) refer to Table 2-1: the 20p piece provides a rough scale).

Reactors (i)-(iv) were fitted to the flow apparatus using the appropriate size Swagelok nuts and ferrules. The reactors were then filled with a known amount of heterogeneous catalyst. In experiments that did not require the reactor to be completely filled with catalyst, sand was put into the bottom of the reactor, before filling the rest of the reactor with a known amount of catalyst on top. To hold the catalyst in place and avoid any movement of the catalyst into the expansion system or BPR, a metal frit was positioned at the bottom of the reactor and glass-wool was also inserted in the top of the reactor.

Reactor (v) has been used previously within the Clean Technology Group as a reactor for continuous enantioselective hydrogenation where only very small amounts of expensive supported homogeneous catalyst were available.[7] The outside of the reactor was made from 316 stainless steel while the gasket, which was filled with heterogeneous catalyst, was made from aluminium (Figure 2-5). The gasket was porous enough to allow passage of liquids and gases, but not porous enough to allow the catalyst to escape. The reactor (v) was heated during a

reaction by surrounding it in a heating block and band heater which was attached to a Eurotherm heating controller.

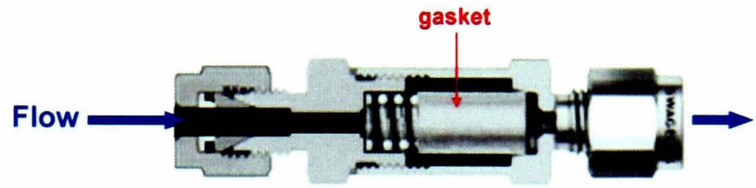


Figure 2-5: Cross-section of reactor (v). Catalyst was held inside the aluminium gasket.

In Chapter 3, reactor (v) was filled with a heterogeneous Pd catalyst and used in initial debenzylation experiments when studying the chlorinated *N*-benzyl-anilines. At the end of the debenzylation experiments, the reactor was opened up and the catalyst emptied. Upon closer inspection of the aluminium gasket it appeared that corrosion had occurred. A microscope was used to take a closer look (Figure 2-6).

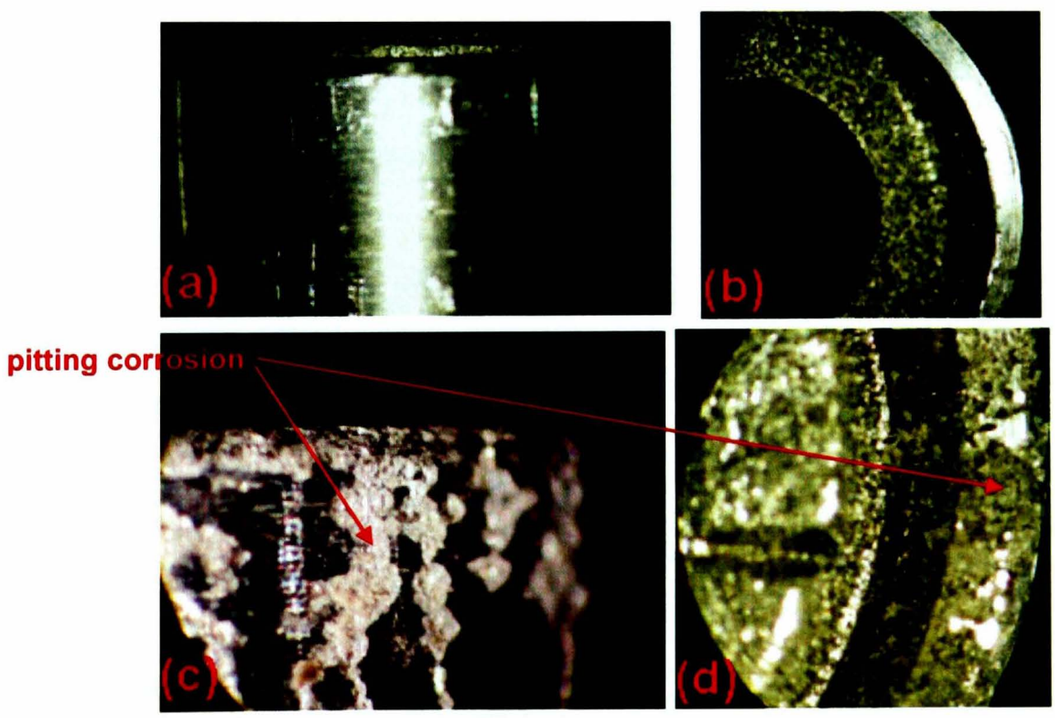


Figure 2-6: Compare the pictures of an un-used aluminium gasket (a) side-on and (b) from above with those of a gasket (c) side-on view and (d) view from above which has suffered significant pitting corrosion due to HCl. This highlights the importance of choosing reactors that are made of appropriate materials.

While the outside of the reactor remained unaffected, pictures (c) and (d) clearly show that the gasket had suffered significant levels of corrosion. It is believed that corrosion occurred due HCl, a product of dechlorination, attacking the aluminium surface of the gasket.

The corroded reactor pictures highlight the fact that careful consideration must always be given to the types of material that are used in construction of a high pressure apparatus. The materials should be chosen based on their compatibility with the solvents, starting materials and products that are to be used. It should be noted that the other reactors (i)-(iv), made completely from 316 stainless steel, were regularly inspected after each experiment for signs of corrosion, however none was detected.

2.5 Mk I Type Autoclave

The Mk1 type autoclave (Medimix) (Figure 2-7) has been used in the Clean Technology Group at Nottingham as a vessel for conducting polymerisations, for a number of years.[10-12] In this Thesis, it has been used as a vessel for hydrogenation and debenzylation reactions to compare reactions that were conducted in batch, with those performed in a flow system. Batch reactions have also been performed in the presence, and absence, of CO_2 to find out whether the presence of CO_2 had any direct effect on reaction selectivity. One set of experiments has also performed in the presence of high pressure C_3H_8 (instead of CO_2) to compare the effects of changing the type of reaction medium.

2.5.1 Description of Autoclave

The autoclave consists of a head and body section that can be screwed together with a sealing force of 220 Nm (Figure 2-7). The body section had a volume of 60 mL. An 1/8" inlet/ outlet tube was attached to the head of the autoclave using an Autoclave Engineers fitting. The inlet/ outlet tube was then connected to an SSI tap so that the vessel could be isolated from the system if needed. Another 1/8"

Autoclave Engineers fitting held in place a thermocouple which was used to monitor the temperature inside the vessel. For reactions that required heating, the vessel was surrounded by a band heater, which was linked to a heating controller, and then surrounded by an insulating jacket. To prevent any overpressures inside the vessel, it was attached to a BPR which was set to a certain overpressure (~20 bar).

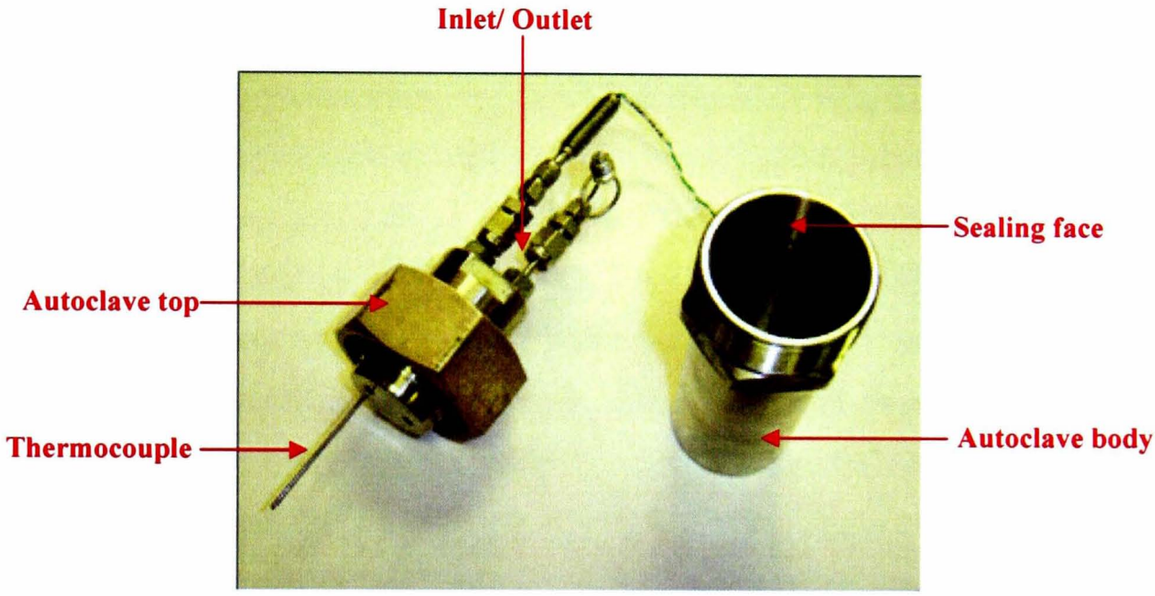


Figure 2-7: The 60 mL Mk1 type autoclave used in batch hydrogenation and debenzylation reactions.

2.5.2 SOP for Batch Reactions Conducted Inside the Mk1 Type Autoclave

Below is a SOP for debenzylation and hydrogenation reactions conducted in batch using the 60 mL Mk1 type autoclave:

1. The catalyst to be used was weighed and added to the autoclave.
2. The amount of substrate was measured and added to the autoclave.
3. A magnetic stirrer flea bar was added to the autoclave.
4. The autoclave was sealed at a force of 220 Nm using a torque wrench.
5. The autoclave was then connected to a H_2 cylinder and flushed with H_2 several times to remove any residual air trapped in the autoclave.
6. A pre-calculated pressure of H_2 (1-2 bar) was added to the autoclave using a low-pressure flammable cylinder head.

7. Liquid CO_2 was added to the autoclave by connecting it to the Jasco PU-986 pump.
8. The autoclave was then weighed and once the correct amount of CO_2 had been added the band heater and insulating jacket (equipped with thermocouples) were fastened and the reaction vessel clamped into place on a magnetic stirrer.
9. The BPR was set to the correct overpressure for the experiment and attached to the autoclave *via* an SSI tap and 1/16" tubing.
10. The SSI tap was opened thereby opening the system to the BPR.
11. The heating controller trip was set and the heater switched on.
12. After the reaction had proceeded for the required amount of time, the heating controller was turned off and the autoclave allowed to cool.
13. Once cool, the autoclave was depressurised. This must be done *slowly* (usually at a rate of 1 bar every 30 seconds) to avoid any loss of material through the BPR.
14. Once the pressure had been released from the autoclave, the top could be removed using the torque wrench and the product mixture removed from the vessel.
15. The catalyst was separated from the product mixture by filtration leaving the products ready for analysis.

For experiments that were conducted in the absence of high pressure CO_2, steps 7 & 8 were not required. For experiments performed in the presence of high pressure C_3H_8 the same protocol was used, except for step 7 where a refrigerated reciprocating pump was used to supply the C_3H_8 to the vessel. When performing mechanistic studies inside the batch vessel, deuterium was used instead of hydrogen. The experiment was performed in the same manner to that described above, except a cylinder of D_2 was used instead of H_2.

2.6 H-Cube Hydrogenation Apparatus

The H-Cube apparatus was designed by Thales Nanotechnology as a lab-scale continuous flow hydrogenation unit that can be used for screening a wide variety of hydrogenation reactions over a short period of time.[1,13]

Reactions have been conducted using the H-Cube apparatus to compare flow hydrogenation reactions conducted in the presence and absence of high pressure CO_2. All experiments conducted on the H-Cube apparatus were conducted at AstraZeneca (Charnwood).

2.6.1 Description of the H-Cube Apparatus (Figure 2-8)

All of the continuous flow apparatus discussed thus far have been designed and built in-house using commercially available components. The H-Cube apparatus, which was used in Chapter 4.9, is a commercial piece of apparatus and was used as supplied.

The H-Cube is displayed in Figure 2-8 and is the size of a large shoe box. The apparatus can be split into four major components: (1) touch-screen operating system: (2) substrate delivery system; (3) hydrogen generation unit; (4) reactor and CatCart system.

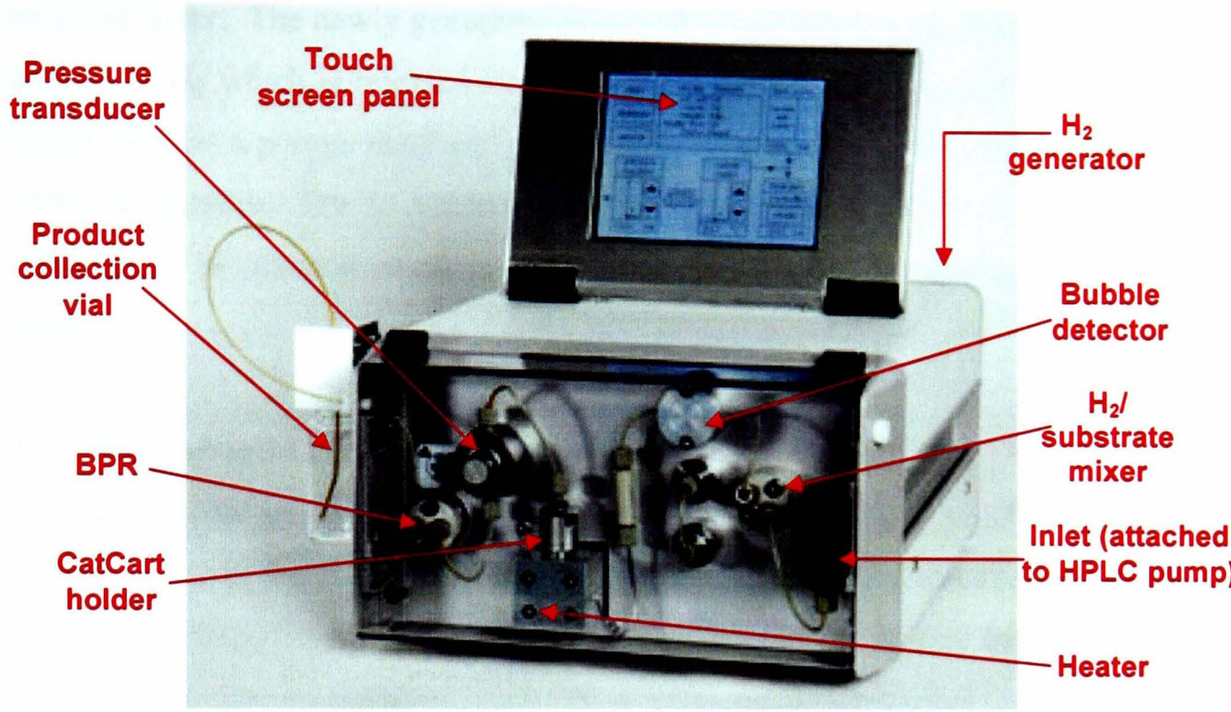


Figure 2-8: Picture of the H-Cube apparatus designed for continuous flow hydrogenation by Thales Nanotechnology.[1,13]

1. Touch Screen Operating System

This user interface displays operational parameters such as flow rate, pressure and temperature. Flow rate can be set from 0.1 to 3.0 mL/ min. while temperature and pressure can be set to a maximum of 100 °C and 100 bar, respectively.

2. Substrate Delivery System

The starting material was dissolved in solvent and delivered to the H-Cube *via* a HPLC pump (WellChrom K-120).

3. Hydrogen Generation Unit

One of the major advantages of the H-Cube apparatus is that the H_2 is produced through the electrolysis of water and therefore the use of bulky H_2 cylinders is not required. The anode side of an electrolytic cell is charged with water, and the protons migrate to the cathode under the effect of an applied current where they are reduced, producing H_2 gas (99.99 % purity). The oxygen, formed by the discharge of hydroxide ions at the anode, is removed from the cell with the

recycled water. The newly generated H_2 enters a motorised valve that controls the amount of H_2 which is released into the system *via* the H_2/ substrate mixer. The mixer contains a porous titanium frit where H_2 is forced through to reduce the size of the H_2 bubbles. The H_2 bubbles are then fed into the substrate stream creating diffusion of H_2 into the substrate solution ensuring efficient mixing of the two phases.

4. Reactor and CatCart System

The gas/ solvent mixture is forced through the bubble detector, which determines if there is H_2 in the reaction line, and then into a heating unit. Heating of the CatCart is controlled *via* a Peltier system which heats the reactor block, and the reaction line. The temperature of the block is accurately controlled and monitored using a thermocouple. The catalyst cartridges (CatCart) which are embedded in the heater block are available in three different sizes (Figure 2-9).

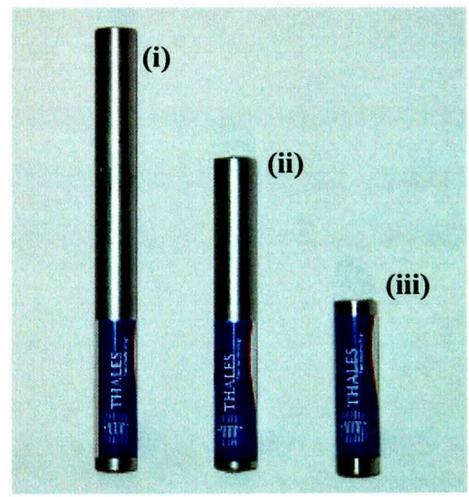


Figure 2-9: Different sizes of CatCart compatible with the H-Cube: (i) 70 mm; (ii) 55 mm; (iii) 30 mm length.

In all experiments discussed in this Thesis only the smallest type of CatCart was used (30 mm length, 4 mm internal diameter). Many different kinds of supported metal catalyst are available as pre-packed CatCarts, however, only the 5 % Pd/C catalyst was used for experiments mentioned in this Thesis. The catalyst particle

size is kept between 30 and 40 μm to allow uniform flow and pressure through the catalyst column.

There are filters placed at each end of the cartridge to prevent particles of the catalyst flowing into the reaction line. The substrate/ H_2 mixture flows through microchannels formed by the packed catalyst (Figure 2-10),[14] the ratio of catalyst surface area to substrate is therefore very high, leading to increased reaction rates.

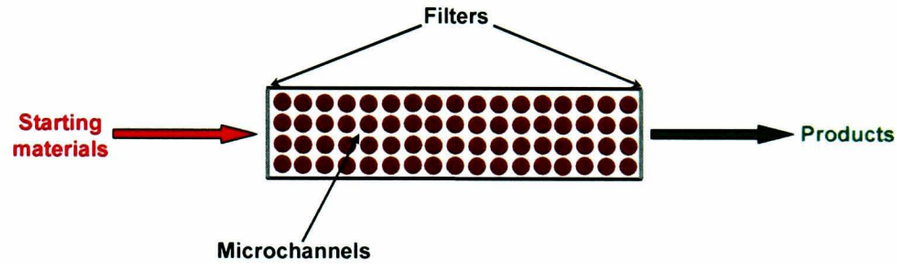


Figure 2-10: Schematic of CatCart. The interaction between the three phases,H_2 gas/ liquid substrate/ solid catalyst, is very high due to the efficient mixing between substrate and H_2 and due to the high mass transfer rates inside the microchannels of the catalyst.[14]

After passing through the catalyst bed, the reaction mixture flows through a BPR at which point depressurisation occurs and the products can be collected in a collection vial. All reaction tubing is made from stainless steel (0.5 mm internal diameter)

2.6.2 SOP for the H-Cube Apparatus

Described below is a standard operating procedure for all continuous flow experiments conducted using the H-Cube apparatus:

1. Turn H-Cube apparatus on using the switch at the back of the unit.
2. Fill water reservoir which is situated at the back of the unit.
3. Insert new CatCart into holder using finger tight fittings.
4. Insert HPLC line into reservoir of solvent (THF or EtOH).
5. Set flow rate on touch screen to that desired for experiment (1.0 mL/ min) and switch on HPLC pump to wash system with solvent for 10 minutes.

6. Stop flow of solvent by turning HPLC pump off and put HPLC line into substrate solution.
7. Using touch screen, input desired reaction conditions such as temperature and H_2 pressure.
8. Wait for system to build pressure until touch screen reads 'STABLE' (~2 minutes).
9. Switch HPLC pump on.
10. Discard the reaction mixture that is produced in the initial 5 minutes run-time.
11. Now that system has equilibrated, begin collecting samples for analysis every 5 minutes.
12. Once enough samples have been collected stop flow of substrate by switching HPLC pump off.
13. If other reactions conditions are required then hit 'STOP & KEEP H_2' on touch screen and lower reactor temperature to 30 °C then return to step 4.
14. If experiments are finished switch off HPLC pump and hit 'STOP' on touch screen to vent H_2 pressure (NOTE: system will make a hissing noise as H_2 is released).
15. Turn H-Cube apparatus off using switch at the back of the unit.

Although it has been shown that the CatCarts are reusable, a new cartridge was used for each set of reaction conditions tested to eliminate the chances of catalyst deactivation. At the end of the experiment the CatCarts were deactivated in vials containing sodium hydrogen sulfite solution.

Samples taken for analysis from the H-Cube were treated with NaOH solution and then extracted into diethyl ether before run on the GLC instrument.

2.7 Catalysts

All catalysts that were mentioned in this Thesis are heterogeneous catalysts (Table 2-2). Most of the catalysts that have been used in flow and batch experiments were supplied by Johnson Matthey (JM). 5% Pd on Activated Carbon was purchased from Sigma-Aldrich. The CatCart catalysts were used as supplied with the H-Cube apparatus.

To ensure that the catalysts were fully reduced and highly active, H_2 was flushed over the surface for at least 20 minutes at 80 °C prior to pumping the substrate.

Table 2-2: Types of catalyst used for debenzylation and hydrogenation in this Thesis.

Active Metal	Carrier	Name	Form	Batch N°.
2 % Pd	Silica/ Alumina	JM Type 31	Granular	2R51/ 52
2% Pd	Silica	2% Pd/Si	Granular	98218
2% Pd	Alumina	2% Pd/Al	Granular	98262
2 % Pd	Acidic Carbon	2 % Pd on Acidic C	Extrudates*	M02161
5% Pd	$CaCO_3$	JM Type 21	Powder	DLR0320
5% Pd	Alumina	JM Type 5R335	Powder	M05227
5% Pt	Charcoal	JM Type 18	Paste	5R18/ 361
2% Rh	Alumina	2% Rh/Al	Granular	M01055
5% Pd	Act. Carbon	5% Pd on Activated C	Powder	U03398
5 % Pd	Carbon	5% Pd/C CatCart	CatCart	N.A.

** catalyst was crushed for use in flow reactors (particle size 53 - 212μm*

2.8 Analytical Techniques

For all debenzylation experiments the main analytical tools were Gas-Liquid Chromatography (GLC) and Gas-Liquid Chromatography - Mass Spectroscopy (GC-MS). For all hydrogenation studies the same analytical tools were used but where necessary High Performance Liquid Chromatography (HPLC) was also used to determine the diastereoselectivity of product mixtures. Nuclear Magnetic Resonance (NMR) Spectroscopy was used in combination with GC-MS to help identify many of the products that have been mentioned in this Thesis. NMR was also used during all synthetic studies to confirm the identity of the product. All

compounds synthesised were fully characterized by NMR, I.R., mass-spec, melting point (m.p.), and polarimetry where appropriate.

2.8.1 Gas-Liquid Chromatography

The main analytical tool for all work described in this Thesis was GLC. A Shimadzu GC-2010 equipped with AOC-20i Autosampler and a Flame Ionisation Detector (FID) was used. Different methods were developed to afford efficient separation of all components present in the reaction mixture. In all cases an achiral 30 m RTX-5 column (0.52 mm ID, 0.25 μm film thickness) was used, the carrier gas was helium. Samples were taken from the flow or batch reactors and diluted for analysis (1: 1 mixture diluted in the reaction co-solvent) and placed in 2 mL septa capped vials. Analysis of the chromatograms was performed using LabSolutions V2.0 software.

As compounds ionise differently in the FID, a standard calibration was performed to accurately determine the concentration of each different component in a sample. From this data it was possible to extract useful information such as conversion and selectivity:

Conversion

$$\% \text{ Conversion} = \left[\frac{moles(sm_0) - moles(sm)}{moles(sm_0)} \right] \times 100$$

where: *moles(sm)* = moles of starting material in reaction mixture

moles(sm_0) = moles of starting material at the beginning

Diastereoselectivity

This calculation was used for to calculate diastereoselectivity during all diastereoselective hydrogenation experiments.

$$\%\ cis\text{- diastereoisomers} = \left[\frac{moles(cis)}{moles(cis) + moles(trans)}\right] \times 100$$

where:

moles(cis) = moles of *cis*-diastereoisomers

moles(trans) = moles of *trans*-diastereoisomers

The diastereoselectivity toward the *trans*- diastereoisomers was calculated in a similar manner.

Chemoselectivity

An example of how chemoselectivity was calculated in the hydrogenation reaction of *rac*-sertraline imine is provided below:

$$\text{Chemosel}^{y}\text{ toward sertraline} = \left[\frac{moles(cis) + moles(trans)}{\sum moles(cis) + moles(trans) + moles(\text{other})}\right] \times 100$$

where:

*moles(*other*)* = moles of all other products in reaction mixture

Chemoselectivity toward the other by-products in the hydrogenation reaction were calculated in a similar manner.

Chemoselectivity was calculated in a slightly different manner for debenzylation reactions. Upon debenzylation, toluene and the deprotected amine are formed in equal quantities. Under reaction conditions, the concentration of toluene is found to be constant since toluene does not undergo any further reaction. However, the deprotected amine can participate in other reactions. All chemoselectivity data presented in Chapter 3 therefore relates to any reaction of the deprotected amine (hydrogenation or hydrogenolysis), or starting material. The concentration of toluene is not required in the calculation. Chemoselectivity in Chapter 3 was calculated in the following manner:

$$\text{Chemosel}^{y} \text{ toward deprotected amine} = \left[\frac{moles(\text{amine})}{moles(\text{amine}) + moles(\text{other} - \text{toluene})}\right] \times 100$$

where:

*moles(*amine*)* = moles of deprotected amine

moles(other – toluene*)* = moles of all other products, except toluene

Chemoselectivity toward other by-products (except toluene) were calculated in a similar manner.

2.8.2 Gas-Liquid Chromatography - Mass Spectroscopy

Gas-Liquid Chromatography - Mass Spectroscopy (GC-MS) was performed to identify by-products formed during hydrogenation and debenzylation experiments. The instrument used was a Thermo Finnegan Polaris Q ion trap GC-MS, equipped with an RTX-5 MS column attached *via* a heated transfer line to the ion trap mass spectrometer. The GC-MS uses an AS-2000 autosampler to inject 0.1 μL of sample into the injector (250 °C). As with GLC, helium was used as the carrier gas. The ion trap was capable of electron impact (EI) and chemical ionisation (CI).

2.8.3 High Performance Liquid Chromatography

The instrument used was a Water 600 E HPLC equipped with a UV-VIS detector set to 154 nm. A chiral HPLC column (Diacel Chirasil OD-H column, 30 cm) was used with a mobile phase of 2% IPA in *n*-hexane with 0.2 % diethylamine. The flow rate was set to 1.0 mL/ min and the temperature isothermal at 25 °C.

High Performance Liquid Chromatography (HPLC) was used as the primary analytical tool to calculate diastereoselectivity during diastereoselective hydrogenation studies in Chapter 4. GLC could also be used calculate diastereoselectivity, however, a by-product, was found to overlap with the peak corresponding to the *trans*-diastereoisomers. Although, the by-product was not

detected in significant quantities by GLC, it was felt that HPLC would complement the results obtained by GLC. The agreement between GLC and HPLC was generally very high at ≥ 98 %.

The ratio of diastereoisomers produced during the diastereoselective hydrogenation studies was calculated from the peak areas of each stereoisomer obtained from HPLC:

$$\%\ cis\text{- diastereoisomers} = \left\{\frac{[(1S,4S)+(1R,4R)]}{[(1S,4S)+(1R,4R)+1S,4R+1R,4S)]}\right\}\times 100$$

$$\%\ trans\text{- diastereoisomers} = 100\% - (\%\ cis\text{- diastereoisomers})$$

where:

(1S,4S) = peak area of (1*S*,4*S*) enantiomer

(1*R*,4*R)* = peak area of (1*R*,4*R*) enantiomer

(1*S*,4*R)* = peak area of (1*S*,4*R*) enantiomer

(1*R*,4*S)* = peak area of (1*R*,4*S*) enantiomer

2.8.4 Nuclear Magnetic Resonance Spectroscopy

Nuclear Magnetic Resonance (NMR) spectroscopy was used as the main analytical tool for all synthetic studies. It was also used to identify some products in hydrogenation and debenzylation reactions. All ^{1}H NMR spectra were recorded on a Jeol 270 MHz spectrometer at ambient temperature. Data are reported as follows: chemical shifts in ppm relative to residual $CHCl_3$ or TMS on the δ scale; multiplicity (b = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or combinations there of); integration; coupling constants and assignment. ^{13}C NMR spectra were recorded on a Jeol 270 MHz spectrometer at ambient temperature. Data are reported as follows: chemical shifts in ppm relative to residual $CHCl_3$ or TMS on the δ scale and assignment.

2.8.5 Other Techniques

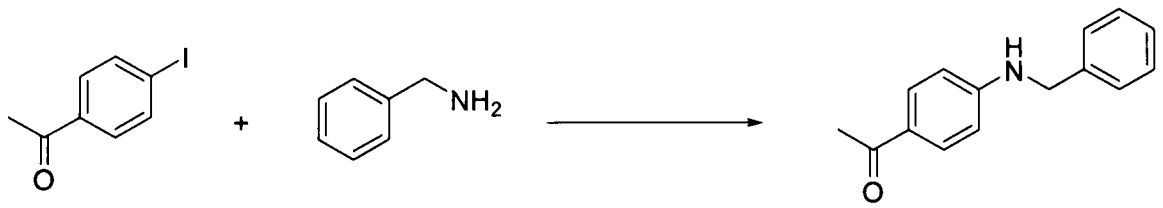
Infrared spectra were recorded in the range 4000-600 cm^{-1} on a Perkin-Elmer 1600 FT-IR instrument at ambient temperature. Melting points are uncorrected and were determined using a Mel-temp II melting point apparatus. High resolution mass-spec (HRMS) were obtained using electrospray ionization (ESI) techniques using a VG Autospec instrument. Optical rotations were obtained using a Jasco DIP 370 digital polarimeter. $[\alpha]_D$ values were measured at the concentration and temperature shown.

2.9 Synthetic Studies

All substrates were synthesised according to literature procedures and are referenced. All substrates have been synthesised previously with the exception of one molecule which is marked with an asterisk (*) to represent that it has not been reported in any previous literature. Any imines synthesised were either used immediately in hydrogenation studies or stored in the freezer under anhydrous conditions to avoid decomposition. All reagents were used as supplied.

2.9.1 Substrates used in Debenzylation Studies

Synthesis of 1-(4-(benzylamino)phenyl)ethanone (26)

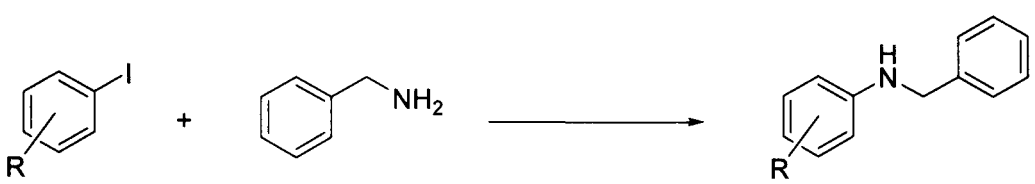


27 **32** **26**

CuI **(28)** (5.25 g, 27.5 mmol, 10 mol %) and K_2PO_4 (117 g, 0.55 mmol) were dissolved in a mixture of IPA (300 mL) and ethylene glycol (30.8 mL, 0.55 mmol). To this was added, sequentially, the 1-(4-iodophenyl)ethanone (**27**) (67.8 g, 0.276 mmol) and benzylamine **(32)** (35.5 g, 0.331 mmol). The reaction mixture was stirred at reflux for 20h before being cooled to room temperature and quenched by addition of water (150 mL). The organic layer was separated and the

aqueous layer was extracted with diethyl ether (4 × 150 mL). The combined organic layers were washed with brine (200 mL) and dried over Na_2SO_4. Then the solvents were removed *in vacuo* to afford the crude product. Column chromatography (3: 1 ether/ petrol ether) was then used to purify the product as a white solid (37.8 g, 61 %). R_f = 0.26 (3: 1 ether/ petrol ether). ^1H NMR (270 MHz, $CDCl_3$); δ 7.84 (2H, d, J = 8.4 Hz, Ar-**H**), 7.32 - 7.36 (5H, m, Ar-**H**), 6.80 (2H, d, J = 8.4 Hz, Ar-**H**), 4.41 (2H, s, C**H**$_2$), 2.52 (3H, s, C**H**$_3$). ^{13}C NMR (67.5 MHz, $CDCl_3$); δ 196.5 (**C**=O), 151.7, 138.0, 130.9, 128.9, 127.7, 111.7 (Ar-**C**), 47.7 (**C**H_2), 26.1 (**C**H_3). υ_{max} ($CHCl_3$) 3428, 2861, 1661 cm^{-1}. HRMS (ESI) required for $C_{15}H_{16}NO([M+H]^+)$ 226.1232, found 226.1225. m. p. = 87-88 °C.

General Procedure for Synthesis of *N*-Benzyl-chloroanilines[15]



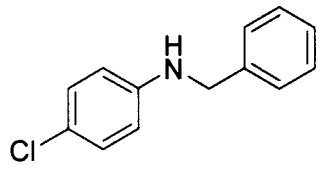
R = *p*-Cl **29**
R = *m*-Cl **30**
R = *o*-Cl **31**

32

R = *p*-Cl **33**
R = *m*-Cl **34**
R = *o*-Cl **35**

CuI **(28)** (5.25 g, 27.5 mmol, 10 mol %) and K_2PO_4 (117 g, 0.55 mmol) were dissolved in a mixture of IPA (300 mL) and ethylene glycol (30.8 mL, 0.55 mmol). To this was added, sequentially, the iodobenzene (65.7 g, 0.276 mmol) and benzylamine (35.5 g, 0.331 mmol). The reaction mixture was stirred at reflux for 20h before being cooled to room temperature and quenched by addition of water (150 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (4 × 150 mL). The combined organic layers were washed with brine (200 mL) and dried over Na_2SO_4. Then the solvents were removed *in vacuo* to afford the crude product. Column chromatography (97: 3 ether/ petrol ether) was then used to purify the product.

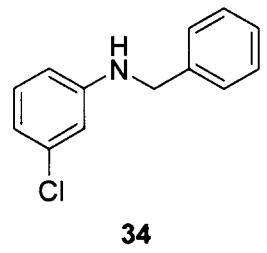
_N_-Benzyl-_p_-chloroaniline (33)



33

Yield = 75 %. R_f = 0.30 (97: 3 ether/ petrol ether). ^{1}H NMR (270 MHz, $CDCl_3$); δ 7.28 - 7.37 (5H, m, Ar-**H**), 7.12 (2H, dd, J = 8.6, 1.5 Hz, Ar-**H**), 6.56 (2H, dd, J = 8.6, 1.5 Hz, Ar-**H**), 4.32 (2H, s, C**H**$_2$), 4.07 (1H, bs, N**H**). ^{13}C NMR (67.5 MHz, $CDCl_3$); δ 146.5, 138.4, 129.2, 128.8, 127.5, 122.0, 114.0 (Ar-**C**), 48.4 (**C**H_2). υ_{max} ($CHCl_3$) 3631, 3441, 2852 cm^{-1}. HRMS (ESI) required for $C_{13}H_{13}ClN([M+H]^+)$ 218.0737, found 218.0799. m. p. 48-49 °C.

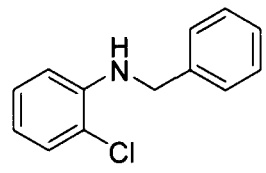
_N_-Benzyl-_m_-chloroanline (34)



34

Yield = 48 %. R_f = 0.34 (97: 3 ether/ petrol ether).^{1}H NMR (270 MHz, $CDCl_3$); δ 7.30 - 7.41 (5H, m, Ar-**H**), 7.10 (1H, t, J = 8.0 Hz, Ar-**H**), 6.72 (1H, ddd, J = 8.0, 2.0, 0.8 Hz, Ar-**H**), 6.65 (1H, dd, J = 2.0 Hz, Ar-**H**), 6.52 (1H, ddd, J = 8.0, 2.0, 0.8 Hz, Ar-**H**), 4.33 (1H, s, C**H**$_2$), 4.14 (1H, bs, N**H**). ^{13}C NMR (67.5 MHz, $CDCl_3$); δ 149.3, 138.9 (Ar-**C**), 135.1 (**C**-Cl), 130.4, 128.9, 127.6, 127.5, 117.5, 112.6, 111.2 (Ar-**C**H), 48.2 (**C**H_2). υ_{max} ($CHCl_3$) 3630, 3450, 3424, 2856, 1588 cm^{-1}. HRMS (ESI) required for $C_{13}H_{13}ClN([M+H]^+)$ 218.0737, found 218.0728.

N-Benzyl-*o*-chloroaniline (35)



35

Yield = 25 %. R_f = 0.34 (97: 3 ether/ petrol ether).^{1}H NMR (270 MHz, $CDCl_3$); δ 7.31 - 7.44 (6H, m, Ar-**H**), 7.15 (1H, dt, J = 7.6, 1.3 Hz, Ar-**H**), 6.67 - 6.73 (2H, m, Ar-**H**), 4.80 (1H, bs, N**H**), 4.44 (2H, s, C**H**$_2$). ^{13}C NMR (67.5 MHz, $CDCl_3$); δ 144.0, 138.7, 129.6, 128.9, 128.0, 127.9, 127.5, 117.5, 111.6 (Ar-**C**), 48.0 (**C**H_2). υ_{max} ($CHCl_3$) 3672, 3441, 2855 cm^{-1}. HRMS (ESI) required for $C_{13}H_{13}ClN([M+H]^+)$ 218.0737, found 218.0977.

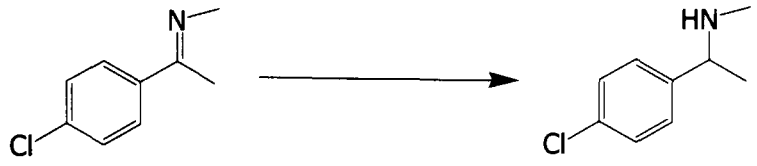
2.9.2 Substrates used in Hydrogenation Studies

(E)-N-[1-(4-Chlorophenyl)ethylidene]methanamine (36) [16]

37 **36**

1-(4-chlorophenyl)ethanone (**37**) (20.00 g, 0.129 mol) was dissolved in IPA (25 mL) and cooled to 0 °C, then monomethylamine solution (33% in abs. EtOH, 55.0 mL, 0.440 mol) was added. Activated molecular sieves (5Å, 30.00 g) were added and the mixture was heated at 40 °C with stirring for 24 hours. The mixture was filtered to separate the molecular sieves from the product solution, then the filtrate was cooled to –15 °C. The product (*E*)-N-[1-(4-chlorophenyl)ethylidene]-methanamine (**36**) was separated by filtration as a white crystalline solid (20.4 g, 95 %). ^{1}H NMR (270 MHz, $CDCl_3$); δ 7.71 (2H, d, J = 8.5 Hz, Ar-**H**), 7.35 (2H, d, J = 8.5 Hz, Ar-**H**), 3.35 (3H, s, C**H**$_3$), 2.23 (3H, s, C**H**$_3$). ^{13}C NMR (67.5 MHz, $CDCl_3$); δ 165.8, (**C**=N), 139.5, (Ar-**C**),135.8, (**C**-Cl), 128.5, 127.9 (Ar-**C**H), 39.6, (N**C**H_3), 15.0 (CC**H**$_3$). υ_{max} ($CHCl_3$) 3257, 2949, 1637 cm^{-1}. LRMS (ESI) required for $C_9H_{11}NCl$ ($[M+H]^+$) 168.0580, found 168.09. m.p. 60-61 °C.

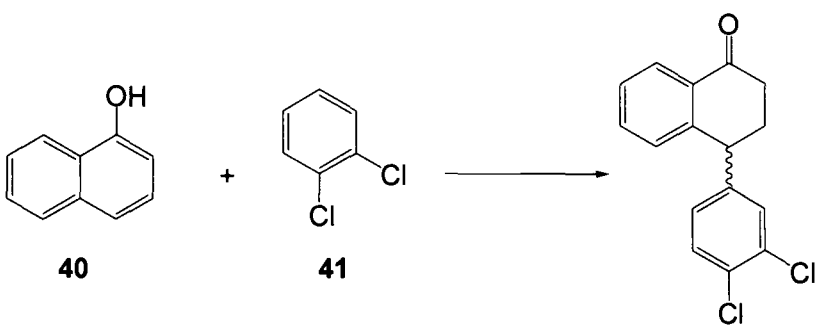
1-(4-Chlorophenyl)-N-methylethanamine (38)



36 **38**

Crude product isolated as a pale yellow oil upon removal of solvent *in vacuo* from product mixture obtained during continuous flow hydrogenation of **(36)** in CO_2 over Pt/C catalyst (purity = 98 % by GLC). ^{1}H NMR (270 MHz, $CDCl_3$); δ 7.23 (4H, d, J = 5.6 Hz, Ar-**H**), 3.59 (1H, q, J = 6.6 Hz, C**H**), 2.25 (3H, s, CH_3), 1.44 (1H, s, N**H**), 1.28 (3H, d, J = 6.6 Hz, C**H$_3$**). ^{13}C NMR (67.5 MHz, $CDCl_3$); δ 143.9 (Ar-**C**), 132.5 (**C**-Cl), 128.6, 128.1 (Ar-**C**H), 59.7 (**C**H), 34.5, 24.0 (**C**H_3). υ_{max} ($CHCl_3$) 3696, 3666, 3329, 2939, 2853, 2796, 1684 cm^{-1}. LRMS (ESI) required for $C_9H_{13}NCl$ ($[M+H]^+$) 170.0737, found 170.15.

rac-Tetralone (39) [16]

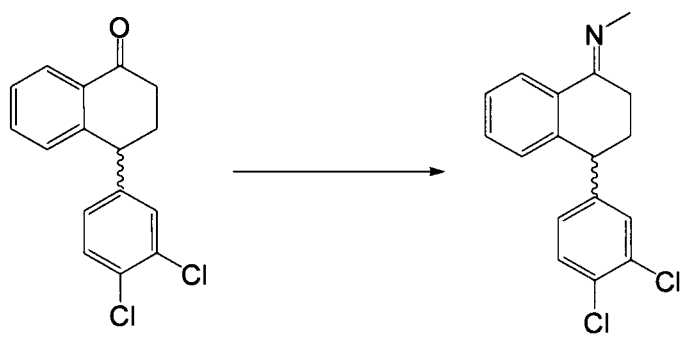


40 **41** **39**

To a solution of 1-napthol **(40)** (20.0 g, 0.139 mol) in 1,2-dichlorobenzene **(41)** (170 mL, 1.15 mol) anhydrous $AlCl_3$ (46.2 g, 0.347 mol) was heated to 100 °C and stirred for 1 hour. The mixture was then cooled to room temperature and poured into ice (225 g) and conc. HCl (75 mL), followed by addition of CH_2Cl_2 (200 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 60 mL). The combined organic layers were washed with water (100 mL), stirred with Celite (25 g) and activated carbon (15 g) then filtered; the solvents were then evaporated in vacuum. To the oily residue, methanol (50 mL) was added which afforded crystallisation. The product was then filtered and washed

twice with MeOH to leave *rac*-tetralone (**39**) as a white solid (22.3 g, 55 %). ^{1}H NMR (270 MHz, $CDCl_3$); δ 8.12 (1H, dd, J = 7.7, 1.6 Hz, Ar-**H**), 7.48 (1H, m, Ar-**H**), 7.42 (2H, d, J = 8.3 Hz, Ar-**H**), 7.24 (1H, d, J = 2.2 Hz, Ar-**H**), 6.98 (2H, dd, J = 8.3, 2.2 Hz, Ar-**H**) 4.28 (1H, dd, J = 8.0, 4.6 Hz, C**H**CH_2CH_2), 2.73 - 2.65, (2H, m, $CHCH_2C\mathbf{H_2}$), 2.54 - 2.42 (1H, m, 1 × $CHC\mathbf{H_2}CH_2$), 2.33 - 1.80 (1H, m, 1 × $CHC\mathbf{H_2}CH_2$). ^{13}C NMR (67.5 MHz, $CDCl_3$); δ 197.3 (**C**=O), 144.9, 144.0, 133.9, 132.8, 132.7, 131.0, 130.6, 130.5, 129.3, 128.0, 127.6, 127.4 (Ar-**C**), 44.6 (**C**-H), 36.5, 31.7 ($\mathbf{C}H_2$). υ_{max} ($CHCl_3$) 2949, 2870, 1682 cm^{-1}. HRMS (ESI) required for $C_{16}H_{13}Cl_2O$ ($[M+H]^+$) 291.0343, found 291.0324. m. p. 101-102 °C.

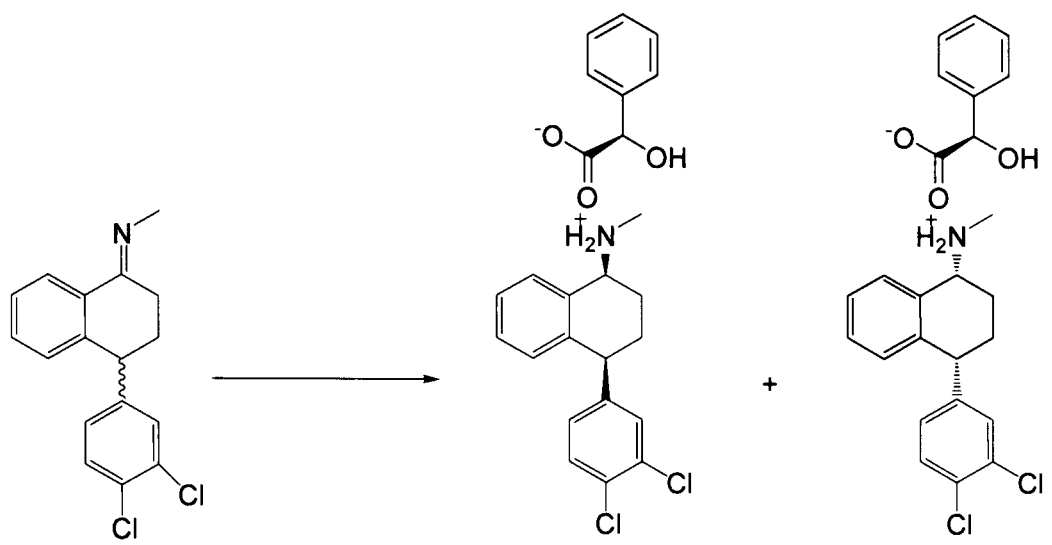
rac-Sertraline imine (42) [17]



39 **42**

rac-Tetralone (**39**) (22.3 g, 0.077 mol) was dissolved in IPA (100 mL) and cooled to 0 °C, at which point monomethylamine solution (33% in abs. EtOH, 31.3 mL, 0.263 mol) was added. The mixture was then heated at 40 °C with stirring until reaction was complete (24 hours). The mixture was then cooled to –15 °C and the product *rac*-sertraline imine **(42)** separated by filtration as a yellow crystalline solid (22.0 g, 95 %). ^{1}H NMR (270 MHz, $CDCl_3$); δ 8.19 - 8.24 (1H, m, Ar-**H**), 7.27 - 7.38 (3H, m, Ar-**H**), 7.20 (1H, d, J = 2.1 Hz, Ar-**H**), 6.88 - 6.92 (2H, m, Ar-**H**), 4.16 (1H, dd, J = 6.9, 4.4 Hz, C**H**), 3.32 (3H, s, $C\mathbf{H_3}$), 2.49 - 2.57 (2H, m, 2 × $C\mathbf{H_2}$), 2.24 - 2.36 (1H, m, $C\mathbf{H_2}$), 2.07 - 2.19 (1H, m, $C\mathbf{H_2}$). ^{13}C NMR (67.5 MHz, $CDCl_3$); δ 165.6 (**C**=N), 144.5, 140.5, 134.1, 130.7, 130.6, 130.5, 130.4, 130.2, 128.0, 127.5, 125.7 (Ar-**C**), 44.3 (**C**H), 33.8 ($\mathbf{C}H_3$), 30.6, 24.5 ($\mathbf{C}H_2$). υ_{max} ($CHCl_3$) 2942, 2359, 1631 cm^{-1}. HRMS (ESI) required for $C_{17}H_{16}Cl_2N$ ($[M+H]^+$) 304.0660, found 304. 0651. m.p. 146-148 °C.

Synthesis of cis-(1S, 4S) (43a) and cis-(1R, 4R)-Sertraline Mandelate Salts (43b)[18]



42 **43a** **43b**

A suspension of *rac*-sertraline imine (**42**) (1.00 g, 3.29 mmol) in MeOH was treated with $NaBH_4$ (370 mg, 9.87 mmol) which was added in two separate portions. The reaction was exothermic and an ice bath was used to keep the temperature < 30 °C. The reaction was stirred for 2 hours before the solvent was removed *in vacuo* to leave a yellow oil which was dissolved in ether (15 mL) and washed with water (3 × 15 mL). The organic layer was separated and dried over $MgSO_4$. The mixture was then filtered and the solvent removed *in vacuo*. The *cis*-sertraline [(**44a**) & (**44b**)] diastereoisomers were then separated from the *trans*-sertraline diastereoisomers [(**44c**) & (**44d**)] by column chromatography (20:1 Ethyl acetate / *n*-Hexane). R_f = 0.54 & 0.32 respectively (20: 1 Ethyl acetate/ *n*-Hexane).

The *cis*-sertraline enantiomers [(**44a**) & (**44b**)] (410 mg, 1.34 mmol) were dissolved in abs. EtOH (5 mL) and treated with *D*-(–)-mandelic acid (213 mg, 1.40 mmol). The resulting mixture was warmed on a steam bath to effect solution and held overnight at room temperature to afford *cis*-(1*S*, 4*S*)-sertraline mandelate (**43a**) as a white crystalline solid while *cis*-(1*R*, 4*R*)-sertraline mandelate (**43b**) remained in solution. The precipitate was then separated from the liquor by filtration, washed with ether (5 mL) and then recrystallised from hot abs. EtOH to provide *cis*-(1*S*, 4*S*)-sertraline mandelate (**43a**) as a white crystalline solid. *cis*-

(1*R*, 4*R*)-sertraline mandelate (**43b**) was separated from the product mixture liquor by evaporation of the solvent *in vacuo* to afford a white solid.

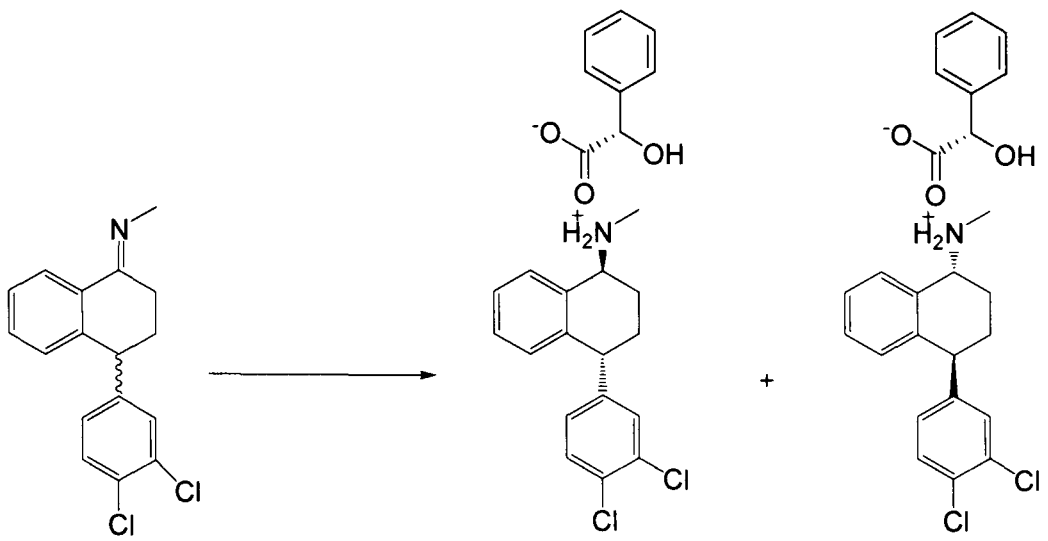
cis-(1S, 4S)-Sertraline Mandelate (43a)

^{1}H NMR (270 MHz, $CDCl_3$); δ 7.11 - 7.39 (10H, m, Ar-**H**), 7.01 (1H, dd, J = 8.1, 2.1 Hz, Ar-**H**), 6.81 (1H, d, J = 7.6 Hz, Ar-**H**), 4.87 (1H, s, C**H**OH), 3.93 (1H, dd, J = 8.4, 4.9 Hz, NHC**H**), 3.81 (1H, t, J = 4.5 Hz, NHCHCH$_2$CH$_2$C**H**), 2.12 (3H, s, C**H$_3$**), 1.77 - 2.10 (4H, m, 2 × C**H$_2$**). ^{13}C NMR (67.5 MHz, $CDCl_3$); δ 178.0 (**C**OOH), 145.7, 142.2, 139.6, 132.7 (Ar-**C**), 131.0, 130.7 (**C**-Cl), 130.6, 130.5, 129.7, 129.3, 128.4, 128.2, 127.5, 127.3, 126.9, (Ar-**C**H), 74.3 (**C**HOH), 55.6, 44.8 (**C**H), 29.0 (**C**H$_3$), 27.3, 22.5 (**C**H$_2$). υ_{max} ($CHCl_3$) 3436, 2927, 2870, 2725, 2353, 1714, 1632 cm^{-1}. m. p. 243-244 °C.

cis-(1R, 4R)-Sertraline mandelate (43b)

^{1}H NMR (270 MHz, $CDCl_3$); δ 7.08 - 7.38 (10H, m, Ar-**H**), 7.00 (1H, dd, J = 8.3, 2.1 Hz, Ar-**H**), 6.85 (1H, d, J = 7.4 Hz, Ar-**H**), 4.89 (1H, s, C**H**OH), 3.89 - 3.97 (2H, m, 2 × C**H**), 2.20 (3H, s, C**H$_3$**), 1.77 - 2.10 (4H, m, 2 × C**H$_2$**), 1.22 (1H, bs, N**H**), 1.19 (1H, s, O**H**). ^{13}C NMR (67.5 MHz, $CDCl_3$); δ 178.0 (**C**OOH), 145.1, 141.5, 139.7, 139.7 (Ar-**C**), 132.5, 130.9 (**C**-Cl), 130.8, 130.6, 130.2, 129.9, 129.5, 128.4, 128.2, 127.5, 127.3, 126.7 (Ar-**C**H), 74.3 (**C**HOH), 55.9, 44.9 (**C**H), 29.5 (**C**H$_3$), 27.5, 23.4 (**C**H$_2$). υ_{max} ($CHCl_3$) 3663, 3433, 2927, 2869, 2728, 1715 cm^{-1}. m. p. 242-243 °C.

Synthesis of trans-(1S, 4R) (43c) and trans-(1R, 4S)-Sertraline Mandelate Salts (43d)[18]



42 **43c** **43d**

A suspension of *rac*-sertraline imine (**42**) (1.0 g, 3.29 mmol) in MeOH was treated with $NaBH_4$ (370 g, 9.87 mmol) which was added in portions. The reaction was exothermic and an ice bath was used to keep the temperature < 30 °C. The reaction was stirred for 2 hours before the solvent was removed *in vacuo* to leave a yellow oil which was dissolved in ether (15 mL) and washed with water (3 × 15 mL). The organic layer was separated and dried over $MgSO_4$. The mixture was then filtered and the solvent removed *in vacuo*. The *cis*-sertraline [(**44a**) & (**44b**)] diastereoisomers were then separated from the *trans*-sertraline diastereoisomers [(**44c**) & (**44d**)] by column chromatography (20:1 Ethyl acetate/ *n*-Hexane). R_f = 0.54 & 0.32 respectively (20: 1 Ethyl acetate/ *n*-Hexane).

The *trans*-sertraline enantiomers [(**44c**) & (**44d**)] (410 mg, 1.34 mmol) were dissolved in abs. EtOH (5 mL) and treated with *L*-(+)-mandelic acid (213 mg, 1.40 mmol). The resulting mixture was warmed on a steam bath to effect solution and held overnight at room temperature to afford *trans*-(1*S*, 4*R*)-sertraline mandelate (**43c**) as a white crystalline solid while *trans*-(1*R*, 4*S*)-sertraline mandelate (**43d**) remained in solution. The precipitate was then separated from the liquor by filtration, washed with ether (5 mL) and then recrystallised from hot abs. EtOH to provide *trans*-(1*S*, 4*R*)-sertraline mandelate (**43c**) as a white crystalline solid.

trans-(1*R*, 4*S*)-sertraline mandelate (**43d**) was separated from the product mixture liquor by evaporation of the solvent *in vacuo* to afford a white solid.

trans-(1S, 4R)-Sertraline Mandelate (43c)

^{1}H NMR (270 MHz, $CDCl_3$); δ 7.12 - 7.46 (9H, m, Ar-**H**), 6.98 (1H, d, J = 2.1 Hz, Ar-**H**), 6.82 (1H, d, J = 7.3 Hz, Ar-**H**), 6.75 (1H, dd, J = 8.3, 2.1 Hz, Ar-**H**), 4.81 (1H, s, C**H**OH), 4.05 (1H, t, J = 4.9 Hz, NHC**H**), 3.96 (1H, t, J = 5.9 Hz, NHCHCH$_2$CH$_2$C**H**), 2.17 (3H, s, C**H$_3$**), 1.53 - 2.29 (4H, m, 2 × C**H$_2$**). ^{13}C NMR (67.5 MHz, $CDCl_3$); δ 178.0 (**C**OOH), 146.3, 142.2, 139.6, 132.6 (Ar-**C**), 130.9, 130.7 (**C**-Cl), 130.6, 130.5, 130.5, 129.3, 129.2, 128.2, 127.9, 127.4, 127.3, 126.8 (Ar-**C**H), 74.4 (-**C**HOH), 55.7, 43.4 (**C**H), 29.2 (**C**H$_3$), 28.0, 22.2 (**C**H$_2$). υ_{max} ($CHCl_3$) 3696, 3604, 3433, 2927, 2855, 1715 cm^{-1}. m. p. 251-252 °C.

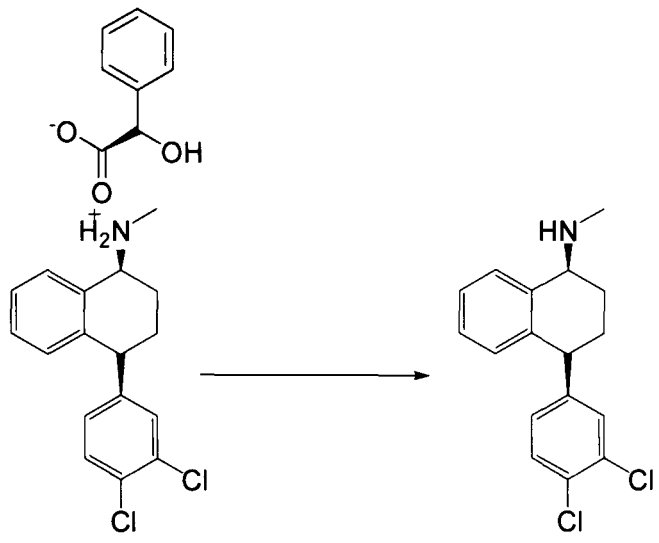
trans-(1R, 4S)-Sertraline Mandelate (43d)

^{1}H NMR (270 MHz, $CDCl_3$); δ 7.13 - 7.42 (9H, m, Ar-**H**), 7.00 (1H, d, J = 1.9 Hz, Ar-**H**), 6.82 (1H, d, J = 8.3 Hz, Ar-**H**), 6.76 (1H, dd, J = 8.3, 1.9 Hz, Ar-**H**), 4.96 (1H, s, C**H**OH), 4.02 - 4.17 (2H, m, 2 × C**H**), 2.26 (3H, s, C**H$_3$**), 1.62 - 2.05 (4H, m, 2 × C**H$_2$**). ^{13}C NMR (67.5 MHz, $CDCl_3$); δ 178.0 (**C**OOH), 145.9, 140.8, 139.6, 132.6 (Ar-**C**), 130.9, 130.7 (**C**-Cl), 130.5, 130.5, 130.3, 129.3, 128.9, 128.4, 127.9, 127.8, 127.5, 126.7 (Ar-**C**H), 74.0 (**C**HOH), 55.8, 43.5 (**C**H), 28.9 (**C**H$_3$), 28.1, 22.0 (**C**H$_2$). υ_{max} ($CHCl_3$) 3698, 3604, 3433, 2927, 2855, 1715 cm^{-1}. m. p. 254-255 °C.

General Procedure for Synthesis of Pure Sertraline Stereoisomers [18]

The sertraline mandelate salt was suspended in ethyl acetate (20 mL/ mmol) and then treated with 10% aqueous NaOH solution (20 mL/ mmol), thereby converting the amine to the free base. The aqueous layer was washed twice with ethyl acetate and then the combined organic layers were then concentrated *in vacuo* to afford the pure stereoisomer of sertraline.

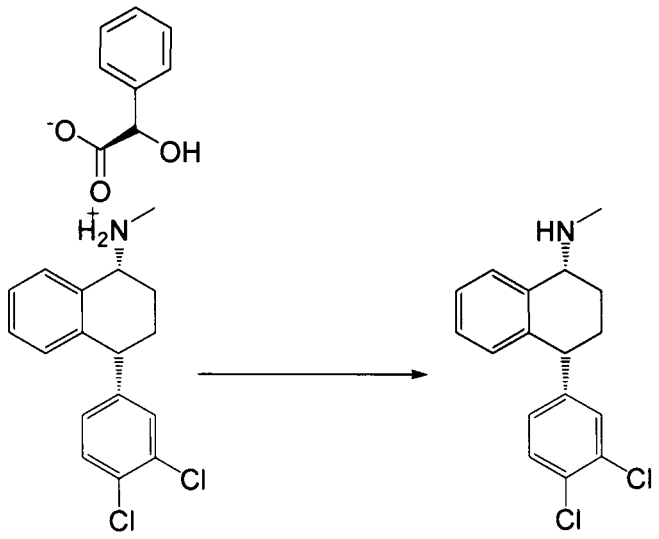
cis-(1S, 4S)-Sertraline (44a)



43a **44a**

Yield from imine (**42**) = 22 %. ^{1}H NMR (270 MHz, $CDCl_3$); δ 7.34 - 7.39 (2H, m, Ar-**H**), 7.20 - 7.28 (2H, m, Ar-**H**), 7.12 (1H, dt, J = 7.7, 1.5 Hz, Ar-**H**), 7.00 (1H, dd, J = 8.3, 2.0, Ar-**H**), 6.81 (1H, d, J = 7.7 Hz, Ar-**H**), 4.00 (1H, dd, J = 9.0, 5.5 Hz, NHCHCH$_2$CH$_2$C**H**), 3.74 (1H, t, J = 4.1 Hz, NHC**H**), 2.56 (3H, s, C**H$_3$**), 1.98 - 2.12 (3H, m, 1 × C**H$_2$** and 2 × CH$_2$C**H$_2$**), 1.80 - 1.89 (1H, m, 1 × C**H$_2$**), 1.39 (1H, bs, N**H**); ^{13}C NMR (67.5 MHz, $CDCl_3$); δ 147.6, 139.6, 138.8 (Ar-**C**), 132.4, 130.8 (**C**-Cl), 130.4, 130.1, 129.9, 129.3, 128.4, 127.3, 126.7 (Ar-**C**H), 57.4 (NH**C**H), 45.5 (NHCHCH$_2$CH$_2$**C**H), 34.6 (**C**H$_3$), 28.6, 25.8 (**C**H$_2$). υ_{max} ($CHCl_3$) 2940, 2860, 2794 cm^{-1}. HRMS (ESI) required for $C_{17}H_{18}Cl_2N$ ([M+H]$^+$) 306.0816, found 306.0794. $[\alpha]_D^{19}$ +54.7 ($CHCl_3$, *c* 1.00). This data is in good agreement with that obtained from analysis of an authentic sample kindly donated by Kemprotec Ltd.

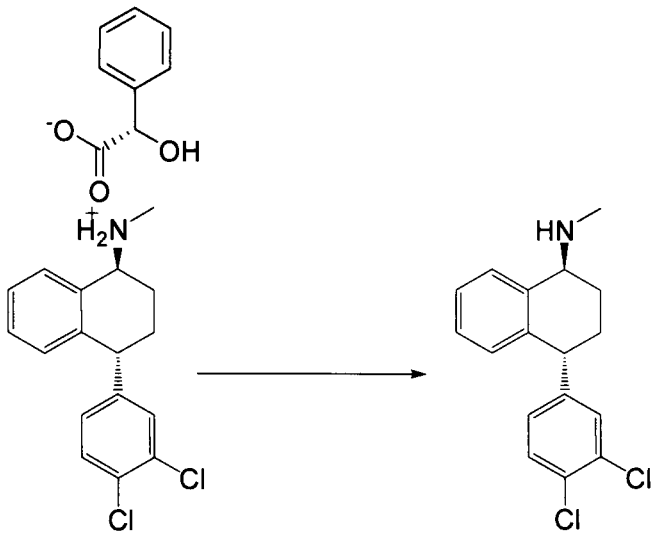
cis-(1R, 4R)-Sertraline (44b)



43b **44b**

Yield from imine (**42**) = 20 %. ^{1}H NMR (270 MHz, $CDCl_3$); δ 7.34 - 7.39 (2H, m, Ar-**H**), 7.19 - 7.28 (2H, m, Ar-**H**), 7.12 (1H, dt, J = 7.5, 1.5 Hz, Ar-**H**), 7.00 (1H, dd, J = 8.3, 2.1, Ar-**H**), 6.81 (1H, d, J = 7.5 Hz, Ar-**H**), 4.00 (1H, dd, J = 9.0, 5.5 Hz, NHC**H**CH_2CH_2CH), 3.74 (1H, t, J = 4.1 Hz, NHC**H**), 2.56 (3H, s, C**H**$_3$), 1.98 - 2.12 (3H, m, 1 × C**H**$_2$ and 2 × CH_2C**H**$_2$), 1.80 - 1.89 (1H, m, 1 × C**H**$_2$), 1.35 (1H, bs, N**H**). ^{13}C NMR (67.5 MHz, $CDCl_3$); δ 147.6, 139.6, 138.8 (Ar-**C**), 132.4, 130.8 (**C**-Cl), 130.4, 130.1, 129.9, 129.3, 128.4, 127.3, 126.7 (Ar-**C**H), 57.4 (NH**C**H), 45.5 (NHCHCH_2CH_2**C**H), 34.6 (**C**H_3), 28.6, 25.8 (**C**H_2); υ_{max} ($CHCl_3$) 2934, 2860, 2795, 1590, 1466, 1131 cm^{-1}. HRMS (ESI) required for $C_{17}H_{18}Cl_2N$ ($[M+H]^+$) 306.0816, found 306.0798. $[\alpha]_D^{20}$ –32.0 ($CHCl_3$, *c* 1.00).

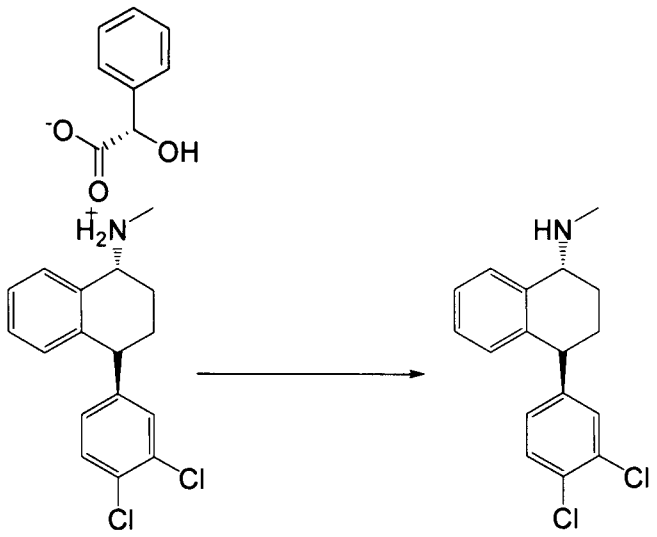
trans-(1S, 4R)-Sertraline (44c)



43c **44c**

Yield from imine **(42)** = 24 %. ^{1}H NMR (270 MHz, $CDCl_3$); δ 7.46 (1H, d, J = 7.6 Hz, Ar-**H**), 7.33 (1H, d, J = 8.3 Hz, Ar-**H**), 7.11 - 7.27 (3H, m, Ar-**H**), 6.83 - 6.88, (2H, m, Ar-**H**), 4.15 (1H, t, J = 5.5 Hz, $NHCHCH_2CH_2C\mathbf{H}$), 3.80 (1H, t, J = 5.5 Hz, NHC**H**), 2.53 (3H, s, $C\mathbf{H_3}$), 2.37 (1H, ddd, J = 16.0, 10.4, 5.5 Hz, $NHCHC\mathbf{H}_2CH_2CH$), 1.96 (1H, ddd, J = 15.1, 10.4, 5.5 Hz, $NHCHCH_2C\mathbf{H}_2CH$), 1.70 - 1.81 (2H, m, 1 × $NHCHC\mathbf{H}_2CH_2CH$ and 1 × $NHCHCH_2C\mathbf{H}_2CH$), 1.37 (1H, bs, N**H**). ^{13}C NMR (67.5 MHz, $CDCl_3$); δ 147.7, 139.8, 138.1 (Ar-**C**), 132.3, 130.7 (**C**-Cl), 130.2, 130.2, 130.0, 128.7, 128.3, 127.2, 126.9 (Ar-**C**H), 57.2 (NH**C**H), 44.4 ($NHCHCH_2CH_2\mathbf{C}H$), 34.1 ($\mathbf{C}H_3$), 28.8, 24.7 ($\mathbf{C}H_2$). υ_{max} ($CHCl_3$) 2939, 2860, 2795 cm^{-1}. HRMS (ESI) required for $C_{17}H_{18}Cl_2N$ ($[M+H]^+$) 306.0816, found 306.0802. $[\alpha]_D^{20}$ –15.5 ($CHCl_3$, *c* 1.03).

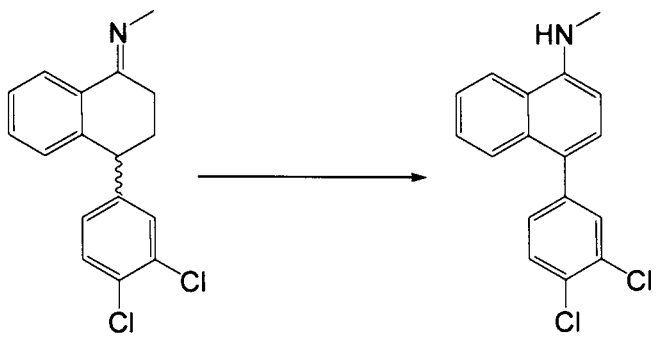
trans-(1R, 4S)-Sertraline (44d)



43d **44d**

Yield from imine **(42)** = 23 %. ^{1}H NMR (270 MHz, $CDCl_3$); δ 7.47 (1H, d, J = 7.4 Hz, Ar-**H**), 7.33 (1H, d, J = 8.3 Hz, Ar-**H**), 7.11 - 7.27 (3H, m, Ar-**H**), 6.82 - 6.88, (2H, m, Ar-**H**), 4.15 (1H, t, J = 5.8 Hz, NHC**H**CH_2CH_2CH), 3.80 (1H, t, J = 5.1 Hz, NHC**H**), 2.53 (3H, s, C**H**$_3$), 2.37 (1H, ddd, J = 16.0, 10.2, 5.8 Hz, NHCHC**H**$_2CH_2CH$), 1.96 (1H, ddd, J = 15.3, 10.2, 5.1 Hz, NHCHCH_2C**H**$_2$CH), 1.69 - 1.82 (2H, m, 1 × NHCHC**H**$_2CH_2CH$ and 1 × NHCHCH_2C**H**$_2$CH), 1.50 (1H, bs, N**H**). ^{13}C NMR (67.5 MHz, $CDCl_3$); δ 147.6, 140.0, 138.1 (Ar-**C**), 132.3, 130.7 (**C**-Cl), 130.2, 130.2, 130.0, 128.7, 128.3, 127.3, 126.9 (Ar-**C**H), 57.1 (NH**C**H), 44.4 (NHCHCH_2CH_2**C**H), 34.0 (**C**H_3), 28.8, 24.6 (**C**H_2). υ_{max} ($CHCl_3$) 2934, 2860, 2795 cm^{-1}. HRMS (ESI) required for $C_{17}H_{18}Cl_2N$ ($[M+H]^+$) 306.0816, found 306. 0795. $[\alpha]_D^{20}$ +15.7 ($CHCl_3$, *c* 1.00).

Conjugated-sertraline (45)*



42 **45**

rac-Sertraline imine (**42**) (100 mg, 0.329 mmol) was dissolved in CH_2Cl_2 (5 mL) then DDQ (108 mg, 0.476 mmol) was added to produce an orange coloured solution after 5 minutes. The reaction mixture was diluted with CH_2Cl_2 (5 mL) and washed with $NaHCO_3$ solution (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Column Chromatography (9: 1 ether/ n-hexane) afforded conjugated sertraline (**45**) (72 mg, 73 %) as a pale yellow oil. R_f = 0.4 (9: 1 ether/ n-hexane) ^{1}H NMR (270 MHz, $CDCl_3$); δ 7.88 (1H, dd, J = 6.3, 2.1 Hz, Ar-**H**), 7.84 (1H, dd, J = 6.3, 2.1 Hz, Ar-**H**), 7.57 (1H, d, J = 2.1 Hz, Ar-**H**), 7.54 - 7.43 (3H, m, Ar-**H**), 7.32 (1H, d, J = 7.8 Hz, Ar-**H**) 7.31 (1H, d, J = 7.8 Hz, Ar-**H**), 6.69 (1H, d, J = 7.8 Hz, Ar-**H**), 5.00 (1H, bs, N-**H**), 3.08 (3H, s, C**H**$_3$). ^{13}C NMR (67.5 MHz, $CDCl_3$); δ 141.5 (**C**-N), 132.3, 132.1, 131.8, 130.6, 130.2, 129.8, 129.7, 128.1, 126.4, 126.2, 125.1, 123.5, 120.3 (Ar-**C**), 31.3 (**C**H_3). υ_{max} ($CHCl_3$) 3696, 3605 cm^{-1}. LRMS (ESI) required for $C_{17}H_{14}Cl_2N$ ($[M+H]^+$) 302.0503, found 302.12.

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Chapter 3

Continuous flow Debenzylation in $scCO_2$

3 Continuous Flow Debenzylation in $scCO_2$

3.1 Introduction

The pharmaceutical industry is the largest producer of waste per Kg of product when compared to other sectors of the chemical industry.[1] Although the excessive use of organic solvents is likely to be the major contributor to this figure, the use of protecting groups in the synthesis of drug molecules is likely to further reduce atom efficiency.

Catalytic removal of the benzyl protecting group accounts for approximately 40 % of all heterogeneous catalytic reactions performed in the pharmaceutical industry. Therefore, continuous flow debenzylation in the presence of $scCO_2$ has been investigated as a potentially more efficient alternative to the traditional batch process.

Studies were initially conducted on the catalytic debenzylation of a model system to find out the optimum conditions required for performing continuous flow debenzylation in the presence of $scCO_2$. Chemoselective *N*-debenzylation in the presence of other reducible functional groups, such as chloro or carbonyl substituents have also been investigated.

Our studies have highlighted the advantages and in some cases, limitations of conducting debenzylation as a continuous flow process in the presence of $scCO_2$.

3.2 Protecting Groups

The manipulation of functional groups is essential in multi-step organic synthesis. To avoid side reactions during chemical transformation of a complex organic molecule, some functional groups may need to be protected while carrying out reactions directed at other functional groups in the same substrate.

Some criteria for such a protecting group include: (i) it must be selectively attached to the functional group for which it is intended; (ii) it should remain inert under the reaction conditions intended for functional group manipulation; (iii) it must be easily removed at the end of the transformation sequence under conditions that will not compromise the other functional groups in the molecule.[2]

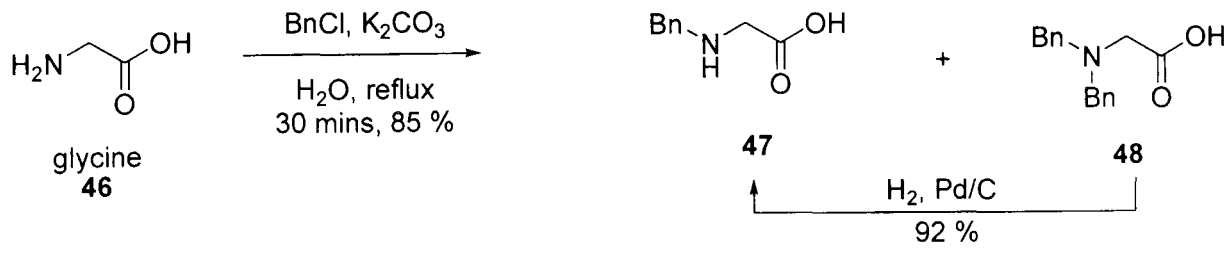
3.3 The Benzyl Protecting Group

As organic synthesis has advanced, a huge variety of different protecting groups have been developed that can be used to protect temporarily every different type of functional group. The benzyl group is one of the most commonly employed protecting groups in organic synthesis due to its ease of introduction and inherent stability. Benzyl protecting groups are most commonly used to protect *O*- or *N*-functionality but can also be used to protect *S*- functional groups.

In this Chapter, research has been focused on benzyl groups that are used to protect amines.

3.3.1 Protection of the Amine Functional Group

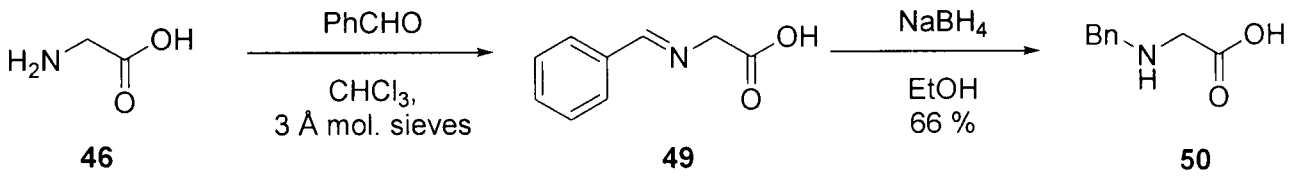
One of the most common ways to protect an amine with a benzyl group is to react the amine with a benzyl halide in the presence of a base, such as K_2CO_3 (Scheme 3-1).[3]



Scheme 3-1: Protection of the amine functional group can provide *mono*- and *bis*-benzylated products. The second benzyl group can be removed *via* hydrogenolysis if the *mono*-protected species is required. [3]

Under the conditions described above, primary amines, such as glycine **(46)** are likely to undergo *mono-* and *bis-* protection. If *bis*-protection is not required, the second benzyl protecting group can be removed by hydrogenolysis.

An alternative method of protection is reductive amination. In the example below, benzylaldehyde is reacted with the primary amine **(46)** to produce a Schiff base **(49)**. Either hydride reduction ($NaBH_4$) or catalytic reduction (Pd/C, H_2) can then be performed to provide the *mono-* benzylated, secondary amine **(50)** in high yield (Scheme 3-2). [4]



46 **49** **50**

Scheme 3-2: Reductive amination route to a benzyl protected amine. [4]

Once attached, the *N*-benzyl protecting group will be stable under basic and mildly acidic conditions.[3]

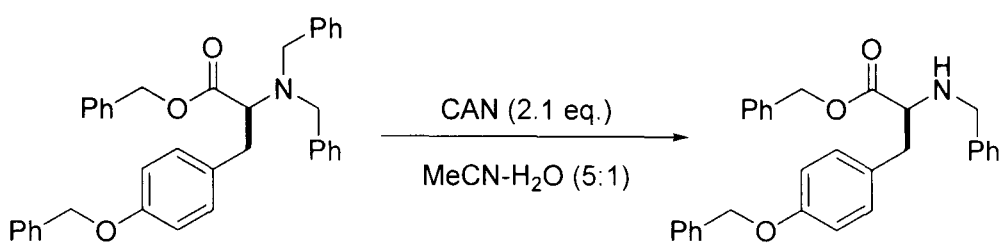
3.3.2 Deprotection of the Amine Functional Group

A variety of methodologies have been developed for benzylic deprotection, with removal *via* catalytic hydrogenolysis being the most widely used method. However, there are many other non-catalytic methods that can be employed to efficiently remove benzyl protecting groups and these will also be discussed here.

Non-Catalytic Debenzylation

Although catalytic debenzylation is preferred, there remains a great deal of interest in any method, catalytic or otherwise, that will facilitate selective debenzylation and consequently a variety of non-catalytic methods currently exist.[5-12]

The best example of non-catalytic debenzylation is Ceric Ammonium Nitrate (CAN) mediated *N*-debenzylation, which has been shown to be a useful method for selective cleavage of unbranched *N*-benzylic substituents in the presence of α-branched *N*-benzyl substituents (Scheme 3-3). It is also useful for debenzylation in the presence of *N*-benzyl amide, *O*-benzyl ether, *O*-benzylphenolate and *S*-benzyl ether functional groups .[13-16]



51 **52**

Scheme 3-3: An example of non-catalytic chemoselective debenzylation using Ceric Ammonium Nitrate (CAN). [17]

In this example, an *N*-benzyl group was selectively removed in the presence of other *N*-benzyl and *O*-benzyl groups in excellent yield, [17] which would be difficult to achieve under standard catalytic reduction methods.

A major drawback of non-catalytic hydrogenolysis, such as CAN mediated debenzylation, is that large amounts of waste are generated. In the example provided above, 2.1 equivalents of reagent are required to facilitate deprotection; this is much less atom efficient than a catalytic process. Although many non-catalytic methods are highly selective, an added drawback of using them is their versatility since they are generally not applicable over a broad substrate range. This is why it is important to develop an efficient catalytic process that can be used over a broad substrate range, with high levels of selectivity.

Catalytic Debenzylation

Catalytic hydrogenolysis is the method commonly used in industry for the removal of benzyl protecting groups.[18] This is because it is extremely atom efficient and the product can easily be separated from the (heterogeneous) catalyst by filtration.

Debenzylation is usually performed over a heterogeneous Pd catalyst, although there are also examples of Ni, Pt and Rh, or other bimetallic catalysts being used.[19-22] Experimentally it has been shown that Pd is the catalyst of choice for debenzylation since it offers the highest level of activity compared to the other noble metal catalysts. It is also advantageous because it is possible to tune the properties of the Pd catalyst to enhance selectivity. This can be achieved either by alloying the Pd with another metal, or by changing the metal loading and type of catalyst support.[21,23]

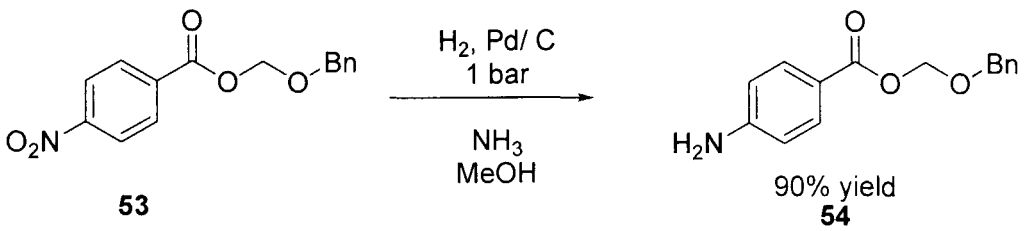
3.4 Selective Debenzylation

3.4.1 Chemoselective Hydrogenation in the Presence of a Benzyl Protecting Group

Before discussing examples of selective debenzylation reactions, it is important to cover some of the methods that have been developed to selectively reduce certain functional groups in the presence of a benzyl protecting group.

It is no surprise that, under reducing conditions, selective hydrogenation in the presence of *O*- or *N*-benzyl groups can be problematic. This is particularly true in the presence of an *O*-benzyl group since benzyl ethers are cleaved under very mild reaction conditions.

Sajiki and co-workers found that *O*-debenzylation could be suppressed by modifying a Pd/C catalyst with a nitrogen containing base. In the example below, this method afforded selective reduction of a nitro group, in the presence of a benzyl ether (Scheme 3-4).[24,25]



Scheme 3-4: Modifying the Pd/C catalyst with a base (NH_3) afforded selective nitro group reduction in the presence of a benzyl ether. [25]

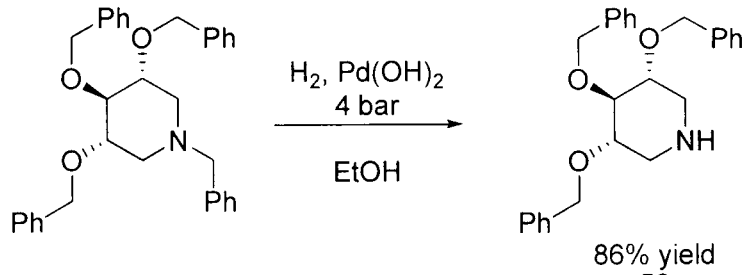
In another example transfer hydrogenation was used to reduce selectively a C=C bond in the presence of a benzyl ether. Transfer hydrogenation can often be a more selective alterative to reduction in the presence of molecular hydrogen due to the mild reaction conditions employed.[26] In the example below, Bajwa and co-workers were able to show that the C=C bond of **(55)** could be selectively reduced using 1,4-cyclohexadiene as the hydrogen transfer agent (Scheme 3-5).[27,28]

Scheme 3-5: Selective reduction of a C=C bond without removal of a benzyl ether under transfer hydrogenation conditions. [27]

3.4.2 Selective Debenzylation in the Presence of Multiple Benzyl Groups

When a molecule possesses more than one benzyl group it is usually necessary to remove only one of these groups during a particular step in synthesis. In the presence of multiple *N*-benzyl groups, it has been shown that the order of reactivity toward hydrogenolysis is quaternary > tertiary > secondary > primary when the reaction is performed under ambient conditions.[29-31] However, experimentally it has been shown that the order of reactivity can be reversed by performing the reaction at high temperature and pressure (*ca.* 150 °C and 60 bar).[32]

Hydrogenolysis of *O*-benzyl groups is generally accepted to take place more readily than that of *N*-benzyl groups.[29] This means that removal of an *N*-benzyl group in the presence of an *O*-benzyl group can be problematic. However, it has been shown that *O*-debenzylation is promoted by acid, and retarded by alkali base which can help to reverse the selectivity toward *N*-debenzylation.[33] For instance, 20 % $Pd(OH)_2$ (Pearlman's catalyst) was used for selective cleavage of the *N*-benzyl group from pyridine **(57)**, providing the unprotected amine **(58)** with its benzyl ether groups intact (Scheme 3-6).[34] It was reasoned that the amine removed any trace of free acid in the reaction, whilst $Pd(OH)_2$ was a good choice of catalyst since it is relatively non-acidic compared to Pd/C catalysts.



57 **58**

Scheme 3-6: Selective removal of the *N*-benzyl group from (57) using Pearlman's catalyst. Cleavage of the benzyl ether groups was not detected. [34]

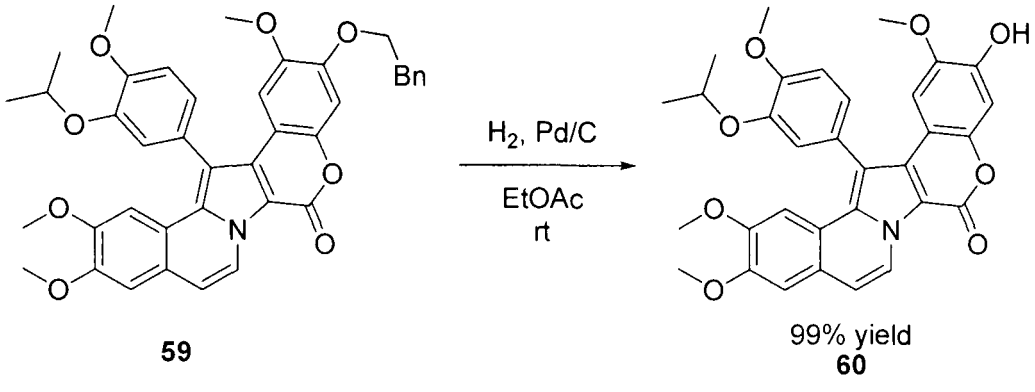
3.4.3 Chemoselective Debenzylation in the Presence of Reducible Functional Groups

For synthetically useful protection, it is essential that the benzyl protecting group can be removed selectively in the presence of other reducible functional groups. In this Chapter chemoselective debenzylation in the presence of a carbonyl and in the presence of a chloro group have been investigated.

Debenzylation in the Presence of Carbonyls

In batch reactions over a Pd catalyst and at low temperature, it has been shown that *O*- and *N*-debenzylation is generally possible without reduction of carbonyls or aromatic substituents.[29] For instance, in the synthesis of Lamellarin, an anti-HIV

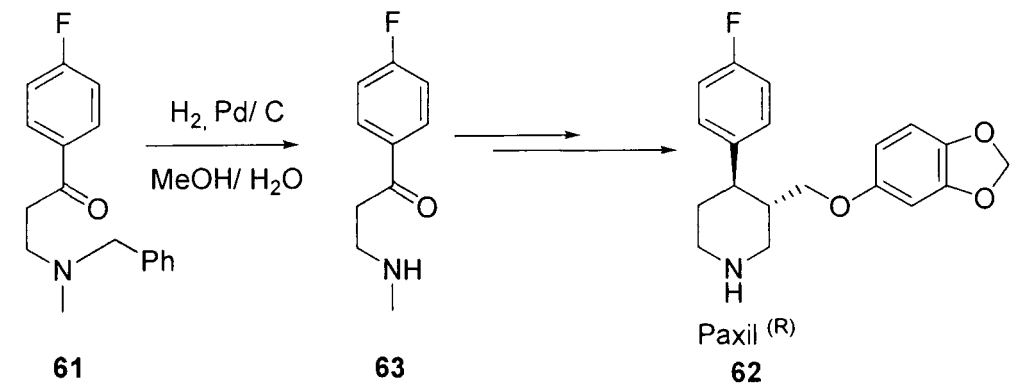
drug, *O*-debenzylation of **(59)** proceeded without reduction of the carbonyl, or aromatic substituents, to the final stage intermediate **(60)** in high yield.[35] In this case, high levels of selectivity were obtainable by conducting the reaction at room temperature over 2 hours.



59 **60**

Scheme 3-7: Selective removal of an *O*-benzyl group is possible without hydrogenation of carbonyl or aromatic functionality. [35]

Another example, is the debenzylation of **(61)**, which is an intermediate in the synthesis of Paxil® **(62)**, a drug that is effective in the treatment of depression and is mentioned later in Chapter 4.3.[36] The *N*-debenzylation was performed at room temperature for one hour and proceeded with 96 % yield without any hydrogenation of the carbonyl group (Scheme 3-8).



61 **63** **62**

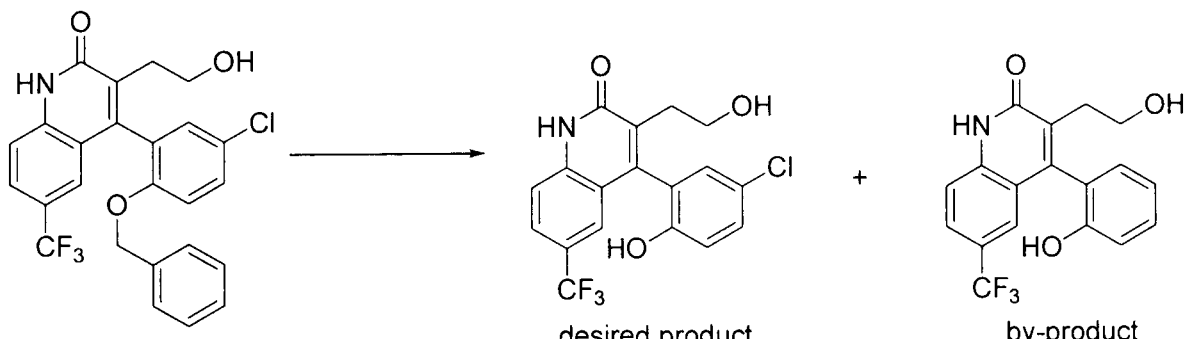
Scheme 3-8: The debenzylation of (61) is one of the steps in the synthesis of Paxil® (62) and takes place without carbonyl reduction.[36]

Debenzylation in the Presence of Halogens

Pd catalysts are often the most active metal catalyst for debenzylation; however, Pd is also active toward dechlorination and inevitably this can lead to major selectivity problems.[37,38]

4-Aryl-quinolin-2(1H)-ones are a range of molecules that have been developed by Bristol Myers Squibb Co. for the treatment of strokes, epilepsy, asthma and other diseases which arise from dysfunction of cellular membrane polarisation and conductance.[39]

During development of 4-(5-chloro-2-hydroxyphenyl)-6-(trifluoromethyl)-3-(2-hydroxyethyl)quinolin-2(1H)-one **(64)**, debenzylation of the intermediate aryl chloride proved troublesome.[40] Competitive dechlorination afforded the dechloro analogue **(65)** which was difficult to remove from the product by selective recrystallisation (Scheme 3-9).



Scheme 3-9: An example of chemoselective debenzylation in which removal of the chloro substituent must be avoided. [40]

PtO_2 (Adams' catalyst) and Pt/C were initially tested as catalysts for this reaction and although they provided the desired selectivity, complete removal of the benzyl group was not possible, even after long reaction times. Focus then turned to using a Pd catalyst when it was found that the ratio of **(64)**:**(65)** was directly correlated with the dielectric constant of the solvent employed. Thus, the dechloro compound **(65)** was formed in up to 35 % yield in solvents such as MeOH with a

high dielectric constant (32.7 at 25 °C), while solvents with a low dielectric constant such as ethyl acetate (6.02 at 25 °C) provided only 1-2 % yield of dechloro compound **(65)**.

Unfortunately the product **(64)** is highly insoluble in ethyl acetate and tended to precipitate out on the catalyst, dramatically inhibiting the rate of reaction. Attention then focused on performing the reaction in acidic media. When the reaction was performed over Pd/C, in the presence of 5 mol % HCl, the ratio of **(64)**:**(65)** increased to 40:1. Unfortunately, this was at the cost of a dramatically slower reaction rate.

They eventually solved the dechlorination problem by performing the reaction in the presence of a chloride salt, tetrabutylammonium chloride (TBACl). The chloride salt is proposed to poison the Pd catalyst selectivity toward dechlorination whilst maintaining high rates of debenzylation. Varying the ratio of TBACl:**(66)** had a dramatic effect on selectivity (Table 3-1). Under optimal conditions this reaction afforded a ratio of **(64)**:**(65)** of 101:1.

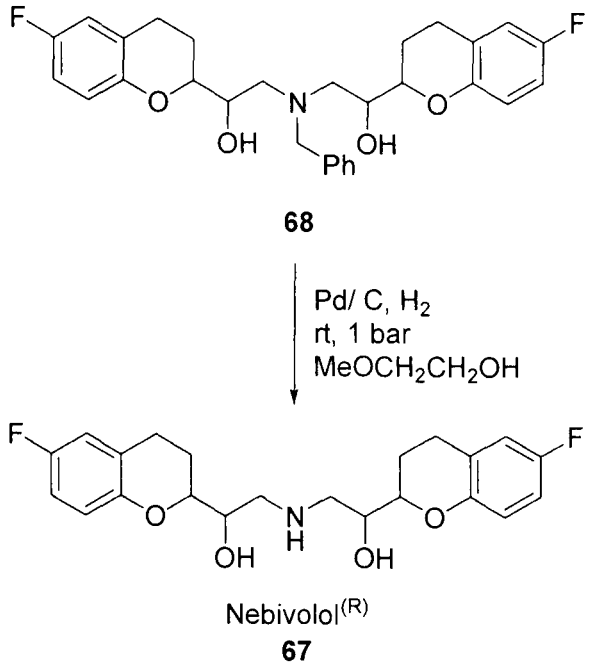
Table 3-1: Dechlorination of (64) can be suppressed by adding a chloride salt (TBACl) as a dechlorination inhibitor to afford selective debenzylation.[40]

TBACl	Composition (%)			ratio
(equiv.)	(66)	(64)	(65)	(64):(65)
0	0.2	75.7	22.8	3.3:1
0.5	-	96.2	2.4	40:1
1.1	0.1	96.6	1.7	57:1
5.0	1.0	91.3	0.9	101:1

(Conditions: MeOH as solvent; 2.8 bar H_2 pressure; 5 % Pd/ C cat.; reaction time 18 hrs)

The rate of dehalogenation decreases with increasing electronegativity of the halogen, and so the ease of hydrogenolysis follows the following pattern: RI > RBr > RCl > RF.[41-43] The cleavage of an R-F bond is difficult, therefore the presence of a fluoro group is unlikely to cause a problem during debenzylation. For example, in the final stage of synthesis toward the target Nebivolol® **(67)**, the

N-benzyl protecting group was successfully removed from intermediate **(68)** by performing the reaction over a Pd/C catalyst at room temperature. This was accomplished without any defluorination or aromatic ring hydrogenation. Nebivolol® **(67)** is a highly effective beta-blocker and has been found to be useful in the management of hypertension.[44]



Scheme 3-10: Debenzylation of (68) is the final step in the synthesis of Nebivolol® (67). Chemoselective debenzylation is not often a problem in the presence of fluorine. [44]

3.5 Aims and Objectives

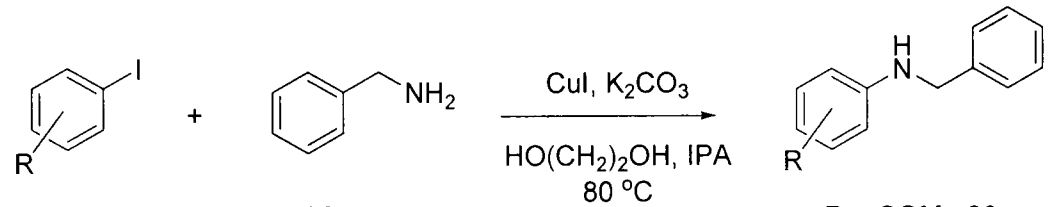
Debenzylation is one of the most common heterogeneous reactions performed in the pharmaceutical industry. It was the aim of the research discussed in this Chapter to develop a more efficient continuous flow process by conducting debenzylation in a fixed bed flow reactor, in the presence of $scCO_2$ and thus help to tackle an important problem that is faced within the pharmaceutical industry.

Studies were initially performed on a model substrate to assess the optimum operating conditions. Studies were directed at ascertaining how selectively debenzylation could be performed in continuous flow when in the presence of other reducible functional groups (-Cl and -COMe).

3.6 Synthesis of *N*-Benzyl Protected Substrates

Of all the *N*-benzyl-protected substrates that have been studied, it is only *N*-benzylaniline that is commercially available. All other benzyl-protected anilines had to be synthesised. All details of synthetic procedures were provided in Chapter 2.9

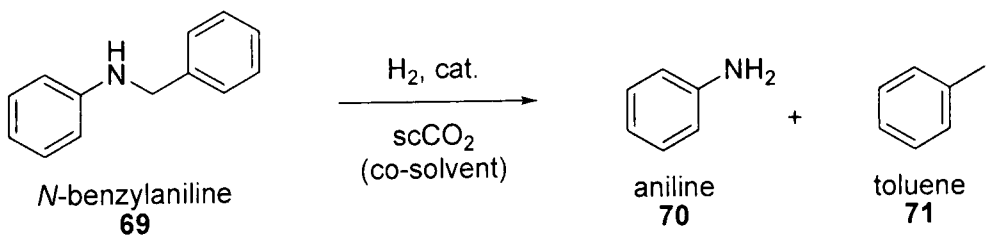
A coupling reaction between benzylamine **(32)** and the appropriate iodobenzene was used to synthesise a range of benzyl-protected anilines.[45] The coupling reaction was chosen because it could be efficiently scaled-up and avoided the use of toxic and air-sensitive reagents.



Scheme 3-11: General synthetic route to all substrates that were studied in debenzylation reactions. [45]

3.7 Debenzylation of *N*-benzylaniline in $scCO_2$

N-benzylaniline **(69)** was chosen as the model substrate to begin our studies on continuous flow debenzylation since it is cheap and commercially available.



Scheme 3-12: Debenzylation of the model substrate (69) should proceed to yield only the desired product aniline (70) and toluene (71) as a by-product.

It is well known that amines can react with CO_2 to form carbamates.[46-48] However, another reason for choosing **(69)** as the model substrate is that the amine formed upon hydrogenolysis, aniline **(70)** is an aromatic amine. This means that the lone pair of electrons on the nitrogen are delocalised and therefore will not be sufficiently nucleophilic to react with CO_2.

If aniline **(70)** were hydrogenated, then cyclohexylamine would be formed. Cyclohexylamine is significantly more basic than aniline and could react with CO_2 to produce a carbamate, which would precipitate and most likely block the flow reactor. Hydrogenation of aniline must therefore be avoided.

Although catalytic *N*-debenzylation has been studied for many years as a batch process, very little research has been conducted into continuous flow *N*-debenzylation. Therefore, one of the aims of the model studies on *N*-benzylaniline **(69)** was to assess what kind of reaction conditions would afford both high levels of conversion and selectivity in a continuous flow debenzylation reaction.

3.7.1 Variation in Temperature

It should be noted that all benzyl-protected anilines that have been studied in this Chapter are solid under ambient conditions. Therefore, in all continuous flow studies, a co-solvent was used to dissolve the substrate so that it can be efficiently pumped into the reactor. MeOH, a solvent often used in debenzylation reactions, was used as co-solvent in the initial debenzylation studies.[3,32]

Debenzylation of *N*-benzylaniline **(69)** and similar substrates are typically conducted in batch over a Pd catalyst, in the presence of H_2 (1-2 bar H_2 pressure), at low temperature (25-40 °C) for anywhere between one and twenty four hours.[29,49] For continuous flow debenzylation, the residence time will be significantly less than in a batch reactor, therefore it is imperative that the temperature of the catalyst bed is high enough to facilitate high levels of catalytic

activity and conversion, but without substantial loss in selectivity. Therefore, the effect on conversion and selectivity of changing temperature of the catalyst bed was investigated (Figure 3-1). All experiments on the model substrate **(69)** were conducted using the large-scale continuous flow apparatus (refer to Chapter 2.2 for details of apparatus).

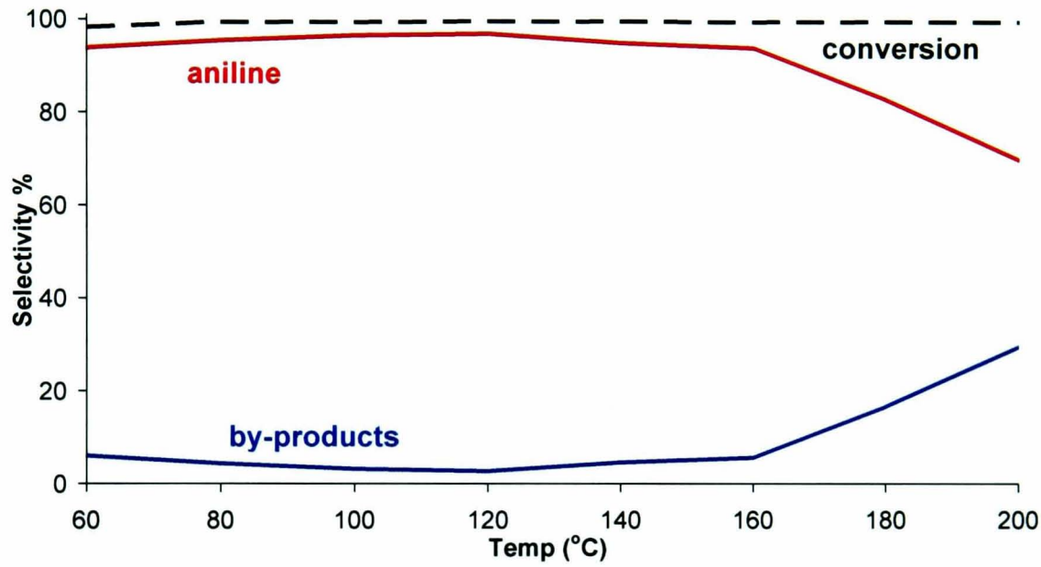


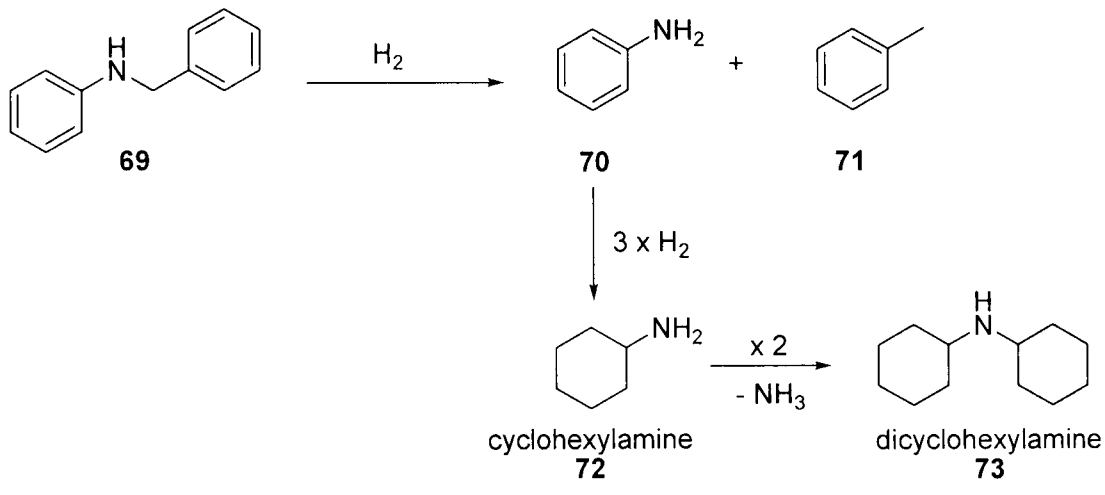
Figure 3-1: Variation in temperature has a significant effect on selectivity for the debenzylation of (69). Loss in selectivity is largely due to hydrogenation of aniline (70).

(Conditions: reactor type = (i), system pressure = 125 bar, flow rate expanded CO_2 = 647 mL/ min, organic flow rate = 0.7 mL/ min, mass of 2 % Pd on Si/Al catalyst = 2.2 g, H_2 to substrate ratio = 3:1, solution concentration in MeOH = 0.6 M)

It should be noted that selectivity, as displayed in results Tables and Figures in this Chapter, does not include toluene. Instead, selectivity relates to the relative change in product composition between aniline and any by-products formed from hydrogenation of aniline or the starting material. Toluene is inert under all reaction conditions.

The continuous flow debenzylation of **(69)** was attempted at temperatures between 60 and 200 °C, over a Pd on Si/Al catalyst (JM Type 31). At all temperatures, the activity of the Pd catalyst was high; as evident by the near quantitative conversion, even at 60 °C (Figure 3-1).

Selectivity toward aniline was highest at temperatures between 80 and 120 °C. Under these conditions, the small drop in selectivity was due to hydrogenation of aniline **(70)** to form cyclohexylamine **(72)**. At temperatures > 120 °C, selectivity toward aniline **(70)** decreased due to formation of cyclohexylamine **(72)** which also underwent dimerisation to form dicyclohexylamine **(73)**. By-products **(72)** and **(73)** were identified by GC-MS and their identity clarified by comparisons with authentic samples (Scheme 3-13).



Scheme 3-13: By-products formed during the debenzylation of *N*-benzylaniline (69) over a Pd catalyst.

3.7.2 Variation in Catalyst Metal

Although Pd catalysts are the most common type of catalyst used for debenzylation reactions, there are also examples of Pt and Rh catalysts offering high levels of selectivity.[20,22] Therefore, it was important to screen other catalysts to make sure that Pd offered the highest level of both activity and selectivity for the model reaction when conducted in continuous flow.

A Pt and a Rh catalyst were tested and their performance compared with the best Pd catalyst (Table 3-2). Since each type of metal catalyst is likely to be active under different reaction conditions, each metal catalyst was tested at various temperatures to find the optimum conversion and selectivity for the debenzylation of **(69)**.

Table 3-2: Comparison between the performance of a Pd, Pt and Rh catalyst for the continuous flow debenzylation of (69)

Entry	Type of Catalyst	Temp. (°C)	Conversion (%)	Selectivity (%)	
				Aniline (70)	Other [(72) & (73)]
1	2 % Pd on Si/Al	80	100	94	6
2	5 % Pt on Charcoal	120	2	100	0
3	2 % Rh on Alumina	80	26	77	23

(Conditions: reactor type = (i), system pressure = 125 bar, flow rate CO_2 expanded= 647 mL/ min, organic flow rate = 0.7 mL/ min, mass of catalyst = 2.2 g, H_2 to substrate ratio = 3:1, solution concentration in MeOH = 0.2 M)

The first point to note about both the Pt and Rh catalysts are that their activity was very poor in comparison to Pd. The Pt catalyst was tested at elevated temperature in an attempt to increase conversion however even at 120 °C conversion was minimal (2 %).

The Rh catalyst was more active than Pt; however, it became completely deactivated after only 30 minutes on-stream. This is very poor compared to the Pd catalyst which remained active, without any signs of deactivation, for over 5 hours on-stream.

The studies on variation of catalyst metal are a good example of the problems that are faced when finding a suitable catalyst for continuous flow reactions. Although Rh and Pt are not as active as Pd they may still be useful in a batch debenzylation process if they offer superior selectivity since the reaction could be left for a long period of time, perhaps 24 hours. In contrast to batch, for continuous flow the catalyst must be sufficiently active to facilitate high conversion over a period of minutes.

From our studies it can be concluded that Rh and Pt are unsuitable for continuous flow debenzylation.

3.7.3 Variation in Pressure

Temperature and pressure can be varied independently in continuous flow reactions. For reactions conducted in the presence of CO_2, a change in pressure will lead to a change in density of the SCF, and changes in particular around the critical point, can have a dramatic effect on reaction selectivity.[50]

The debenzylation of *N*-benzylaniline **(69)** was investigated at pressures between 75 and 200 bar to find out how changes in pressure affect conversion and selectivity during continuous flow debenzylation (Figure 3-2).

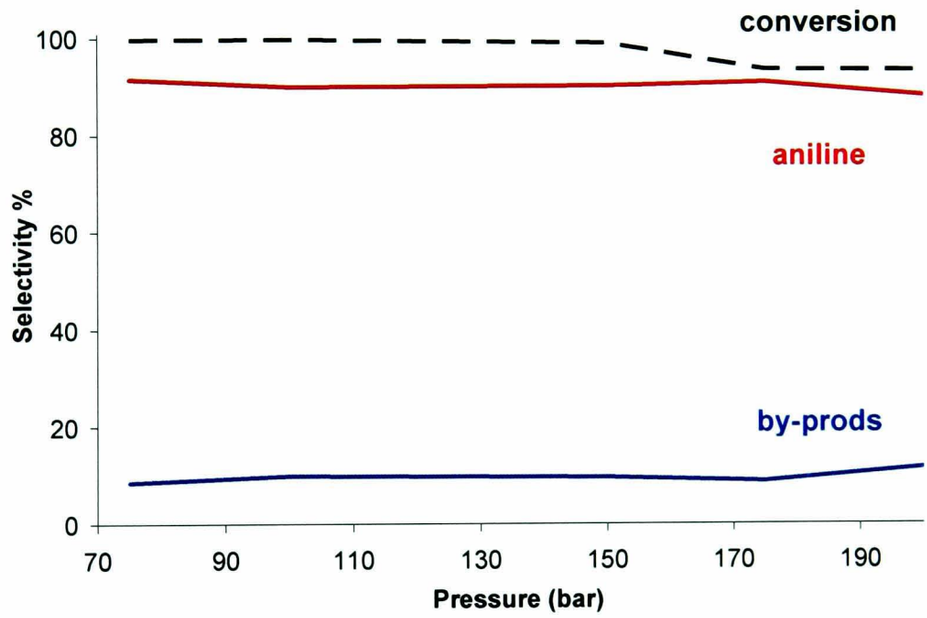


Figure 3-2: Change in pressure between 75 and 200 bar had little effect on selectivity during debenzylation of (69).

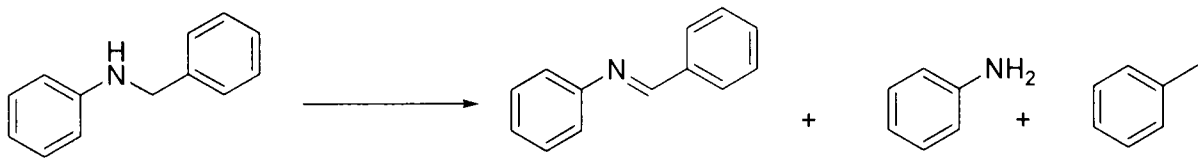
(Conditions: reactor type = (i), flow rate expanded CO_2 = 647 mL/ min, organic flow rate = 0.7 mL/ min, mass of 2 % Pd on Si/Al catalyst = 1.1 g, temp. of reactor & mixer = 150 °C, H_2 to substrate ratio = 3:1, solution concentration in MeOH = 0.2 M)

Conversion and selectivity toward aniline **(70)** decreased by only 5 % across the pressure range investigated. The drop in selectivity at pressure > 170 bar may have occurred because the reaction was conducted at high temperature (140 °C) and therefore an increase in residence time at high pressure could have led to an increase in the rate of aniline hydrogenation. However, the change in selectivity is not very significant.

3.7.4 Variation in H_2 to Substrate Ratio

When studying a debenzylation (or hydrogenation) reaction it is important to investigate the effects of H_2 concentration on reaction selectivity, particularly when competing reactions, such as hydrogenation and hydrogenolysis can occur. Therefore the debenzylation of **(69)** was investigated at H_2 to substrate ratios between zero and 10:1 (Figure 3-3).

In the absence of H_2 it was anticipated that no reaction would occur. However, conversion of the starting material was 30 % in the absence of H_2 at 120 °C, with selectivity toward aniline only 50 %. The drop in selectivity in this case was not due to hydrogenation of aniline **(70)** but instead disproportionation to form *N*-benzylideneaniline **(74)** (Scheme 3-14).



69 **74** **70** **71**

Scheme 3-14: Disproportionation of *N*-benzylaniline (69) can occur in the presence of a Pd catalyst and in the absence of H_2 at 120 °C to form *N*-benzylideneaniline (74), aniline (70) and toluene (71)

It is suggested that *N*-benzylideneaniline **(74)** was formed *via* disproportionation, rather than just dehydrogenation since aniline and toluene were also detected.

In the presence of only one equivalent of H_2, disproportionation is no longer favoured and debenzylation predominates with selectivity toward aniline **(70)** excellent at 98 %. As H_2 to substrate ratio was increased from 1:1 to 10:1, selectivity dropped by 5 % due to hydrogenation of aniline.

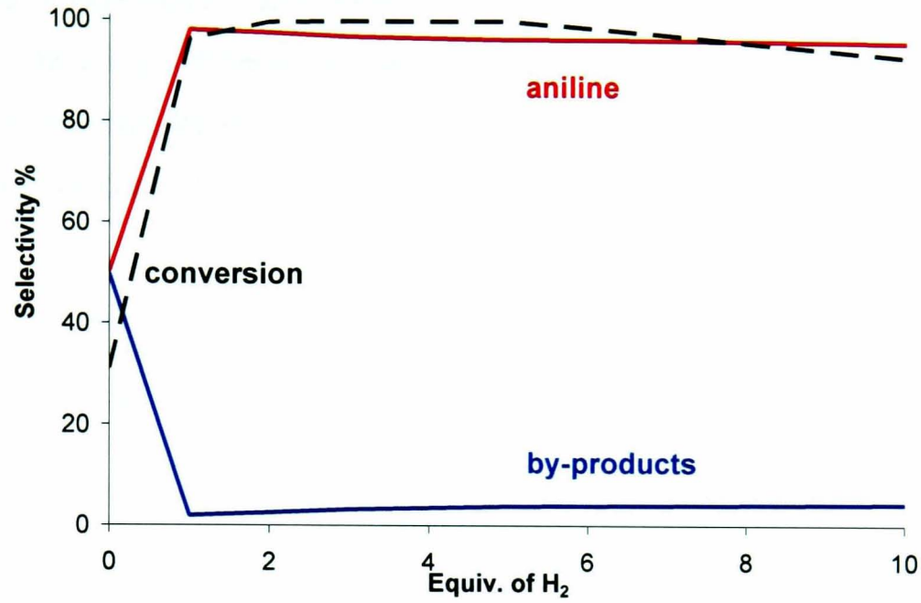


Figure 3-3: Variation in H_2 to substrate ratio during the continuous flow debenzylation of (69).

(Conditions: reactor type = (i), system pressure = 100 bar, flow rate CO_2 expanded= 647 mL/ min, organic flow rate = 0.7 mL/ min, mass of 2% Pd on Si/Al catalyst = 2.2 g, temp. of reactor & mixer = 120 °C, solution concentration in MeOH = 0.6 M)

At H_2 to substrate ratios > 6:1 conversion dropped from 100 % to 91 % at 10:1. A similar drop in conversion at a H_2 to substrate ratio of 7:1 was also found for the hydrogenation of citral in $scCO_2$.[51] The high concentrations of H_2 present may lead to a phase transition from single to two phase which may explain the small drop in conversion at high concentration of H_2 in our system.

3.7.5 Variation in Concentration of Organic in CO_2

The concentration of the organic mixture in CO_2 is an important variable in supercritical reactions since changes in reaction mixture composition can bring about significant changes in phase behaviour which can significantly affect the rate of reaction. The debenzylation of **(69)** was performed in continuous flow at different flow rates of substrate solution. With all other reaction conditions constant, changing the flow rate of organic will change the composition of the reaction mixture with respect to the main solvent, CO_2.

A series of experiments were performed by varying flow rate of organic, with each experiment using a different quantity of catalyst (Figure 3-4). This would allow us to probe whether the ratio of catalyst to substrate also has any effect on reaction selectivity or conversion.

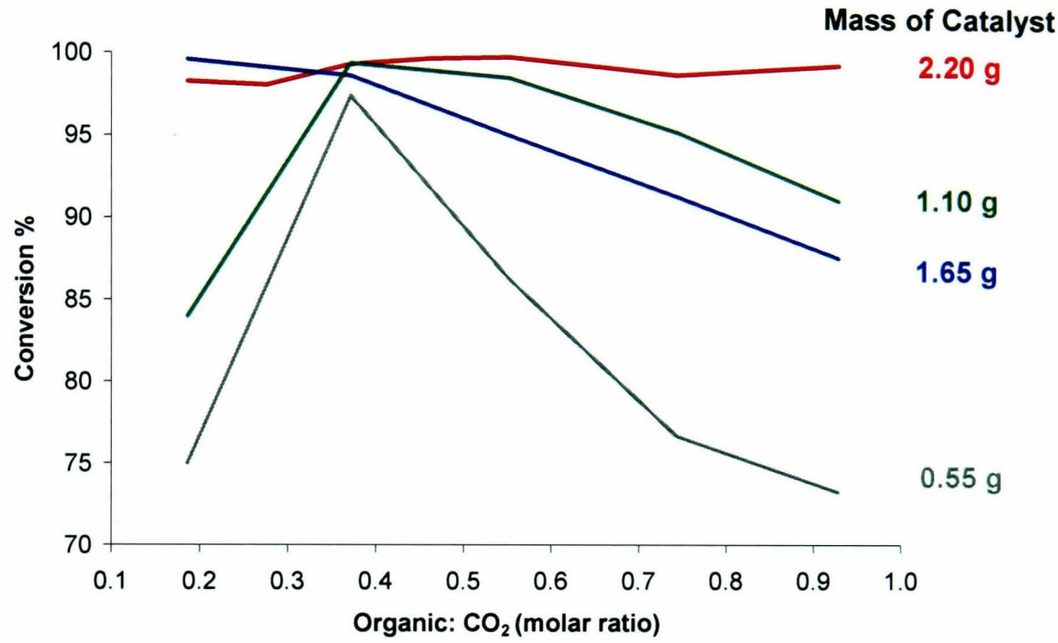


Figure 3-4: Variation in ratio of organic: CO_2 during the continuous flow debenzylation of the model substrate (69) and its effect on conversion.

(Conditions: reactor type = (i), system pressure = 125 bar, flow rate expanded CO_2 = 647 mL/ min, organic flow rate = 0.7 mL/ min, mass of 2% Pd on Si/Al catalyst = 2.2 g, temp. of reactor & mixer = 80 °C, H_2 to substrate ratio = 3:1, solution concentration in MeOH = 0.6 M)

It was found that under all reaction conditions, selectivity remained constant, even when comparing reactions conducted at high and low catalyst loadings. The most significant effect of changing the ratio of organic to CO_2 was conversion (Figure 3-4).

At a high catalyst loading of 2.2 g changing the flow rate of organic, and hence ratio of organic: CO_2 had little effect on conversion. However, as the catalyst loading was reduced from 2.2 g down to 0.55 g drastic changes in conversion were recorded.

At 0.55 g catalyst loading, when the molar ratio of organic in CO_2 was very small (at low flow rate of organic) conversion was only 75 %. However, upon increasing the ratio of organic in CO_2 up to 0.38, a maximum of 97 % conversion was recorded. As the molar ratio of organic: CO_2 was further increased from 0.38 conversion started to fall until it was 73 % at an organic: CO_2 molar ratio of 0.93. Note that the ratio of organic: CO_2 is based on the number of moles of the co-solvent (MeOH) compared to the number of moles of CO_2 per minute.

As the ratio of organic: CO_2 is increased from 0.38 it is likely that the reaction mixture exhibits progressively more biphasic character. Under completely biphasic conditions the concentration of organic in the liquid phase would be high but the concentration of H_2 low, and *vice versa* in the gaseous phase. The poor solubility of H_2 in the liquid phase is therefore limiting the rate of reaction and therefore conversion drops as the system becomes more biphasic.

3.7.6 Variation in Co-solvent

Toluene **(71)** is a by-product of catalytic debenzylation. It would therefore be economical if toluene could be used as a co-solvent since this would avoid an extra solvent separation step in a commercial process. Toluene was therefore tested as co-solvent for the debenzylation of **(69)** in the presence of $scCO_2$ over a Pd catalyst (Table 3-3).

At 80 °C, using toluene as co-solvent, conversion of substrate was negligible and therefore has not been reported. At 100 °C, conversion was only 7 % and selectivity significantly lower than when MeOH was used as co-solvent (Entries 1 and 2, Table 3-3). In an attempt to increase conversion to a level that was synthetically useful, temperature was further increased.

Table 3-3: Comparison between the continuous flow debenzylation of (69) conducted using MeOH and toluene as co-solvent

Entry	Co-solvent	Temp. (°C)	Conversion (%)	Selectivity (%)	
				Aniline (70)	Other
1	MeOH	80	100	94	6
2	Toluene	100	7	86	14
3		200	95	78	22

(Conditions: reactor type = (i), system pressure = 100 bar, flow rate expanded CO_2 = 647 mL/ min, organic flow rate = 0.7 mL/ min, mass of 2% Pd on Si/Al catalyst = 2.2 g, H_2 to substrate ratio = 3:1, solution concentration in MeOH = 0.6 M)

At 200 °C, conversion was 95 %, which is still lower than for the same reaction conducted under optimum conditions using MeOH as co-solvent (Entry 3, Table 3-3). Selectivity at 200 °C was poor due to hydrogenation of aniline and also formation of the dehydrogenated by-product **(74)**. At high temperature of 200 °C, dehydrogenation becomes favourable, thus leading to formation of **(74)**.

Debenzylation reactions are often performed in protic solvents, such as alcohols, although acetic acid is also sometimes used. From our results it has been shown that toluene is an unsuitable solvent for continuous flow debenzylation since it is impossible to obtain synthetically useful levels of conversion without it having a detrimental effect on selectivity.

3.7.7 Summary

Our studies have shown that Pd is the best type of metal catalyst for continuous flow debenzylation due to its superior activity toward debenzylation and low activity toward aromatic hydrogenation. Rh and Pt are not sufficiently active to be useful in continuous flow debenzylation.

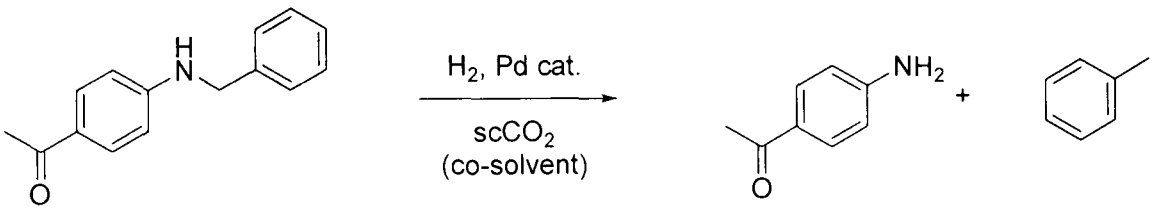
The optimum temperature for continuous flow operation is 80 °C; at higher temperature hydrogenation of aniline will occur. Pressure and H_2 to substrate ratio

have very little effect on debenzylation of this model substrate, although the concentration of H_2 should be high enough to avoid dehydrogenation and disproportionation of the starting material. Toluene is unsuitable as a co-solvent for continuous flow debenzylation compared with MeOH since it was not possible to achieve high levels of conversion without decreasing selectivity.

Under optimum conditions it is possible to quantitatively remove the benzyl group from **(69)** by performing the reaction in the presence of a Pd catalyst at 80 °C with 95 % selectivity toward aniline.

3.8 Chemoselective Debenzylation in the Presence of a Carbonyl

To begin investigating chemoselective debenzylation as a continuous flow process, the debenzylation of 1-(4-(benzylamino)phenyl)ethanone **(26)** was studied. In this set of experiments the goal was to avoid hydrogenating the carbonyl group and afford ketone **(75)** selectively.



1-(4-(benzylamino)phenyl)ethanone **26** | 1-(4-aminophenyl)ethanone **75** | **71**

Scheme 3-15: Continuous flow debenzylation of 1-(4-(benzylamino)phenyl)ethanone (26) in $scCO_2$

Since all debenzylation substrates from this point onward had to be synthesised, the small-scale continuous flow apparatus was used to avoid wasting large quantities of substrate.

3.8.1 Variation in Temperature

Initially studies were conducted under the optimum conditions found for the model substrate. However, it was soon realised that substrate **(26)** is much less

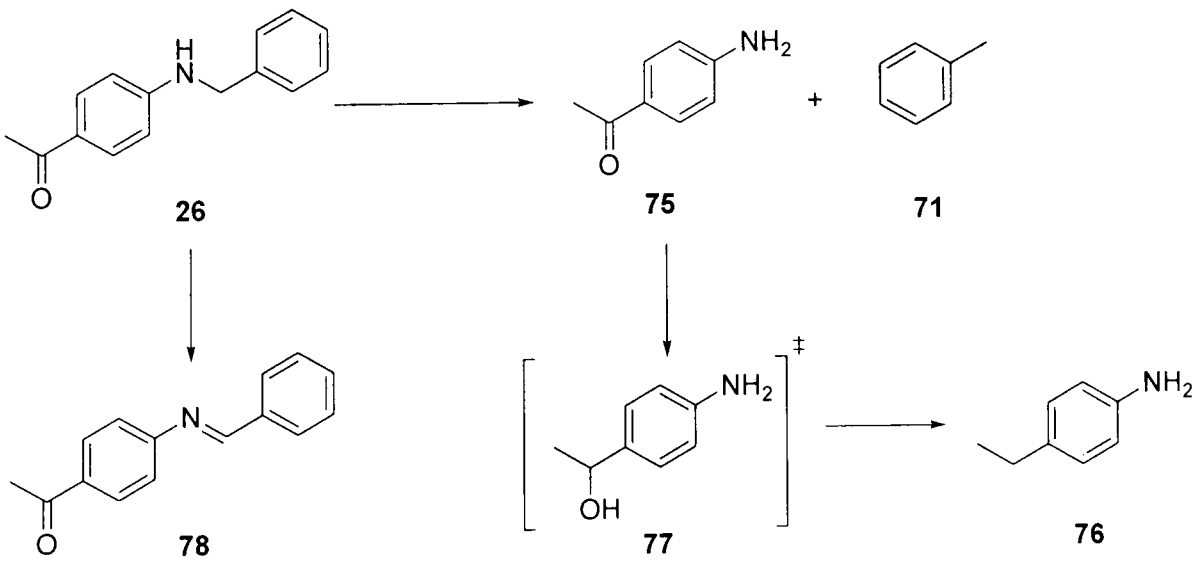
susceptible toward debenzylation than the model substrate **(69)**. In an attempt to increase conversion, a series of experiments were performed at increasingly higher temperature up to 200 °C (Table 3-4).

Table 3-4: Debenzylation of (26) performed between 120 and 200 °C.

Entry	Temp. (°C)	Conversion (%)	Selectivity (%)		
			(75)	(76)	other
1	120	25	95	5	0
2	160	25	79	16	5
3	200	42	36	39	25

(Conditions: reactor type = (iii), system pressure = 125 bar, flow rate CO_2 = 0.5 mL/ min, organic flow rate = 0.4 mL/ min, mass of 2 % Pd/C catalyst = 0.6 g, H_2 to substrate ratio = 3:1, solution concentration in MeOH = 0.2 M)

Upon analysing the product mixture by GLC and GC-MS it was found that the major by-product, at all temperatures was not the alcohol **(77)** as expected, but *p*-ethylaniline **(76)**. It is proposed that the carbonyl is hydrogenated to form the alcohol **(77)** but before it has time to desorb from the catalyst surface, hydrogenolysis of the C-O bond proceeds to produce **(76)**.



Scheme 3-16: Debenzylation of (26) proceeds over Pd/C to form ketone (75) and toluene (71). Ketone (75) is then hydrogenated and immediately undergoes hydrogenolysis to form (76). Dehydrogenation of the starting material will also occur at high temperature to form (78).

As temperature was increased selectivity decreased mainly due to hydrogenation of the debenzylated product, but also due to dehydrogenation of the starting material to form the benzylidene **(78)**. At the high temperatures required to facilitate debenzylation it is inevitable that dehydrogenation also becomes favourable.

Note that even at high temperature, hydrogenation of the carbonyl of the starting material **(26)** does not occur. This tells us that debenzylation precedes hydrogenation of the carbonyl.

As temperature was increased from 120 to 200 °C conversion only slightly improved to 42 % at 200 °C. It is suggested that the presence of the carbonyl group in the *para*- position of substrate **(26)** is electron withdrawing and therefore deactivating toward debenzylation. Increasing temperature to try and increase the rate of debenzylation has little effect, and unfortunately, selectivity decreases due to hydrogenation and dehydrogenation at elevated temperature.

3.8.2 Variation in Pressure

The effect of changing pressure was investigated for the debenzylation of **(26)** to find out whether this had any effect on conversion, or selectivity (Table 3-5). It was hoped by increasing pressure, and hence residence time over the catalyst bed, that conversion may be increased. Note that a 5 % Pd catalyst was used instead of the 2 % Pd catalyst previously used as it was hoped that increasing the amount of active metal would further increase conversion.

The results in Table 3-5 suggest that increasing the loading of Pd from 2 to 5 % does increase conversion. However, conversion was also significantly influenced by changes in pressure.

Table 3-5: Variation in pressure during the debenzylation of (26) has a significant effect on conversion.

Entry	Pressure (bar)	Conversion (%)	Selectivity (%)		
			(75)	(76)	other
1	75	19	88	9	3
2	100	52	73	25	1
3	150	67	63	36	1
4	200	93	64	36	0

(Conditions: reactor type = (iii), flow rate CO_2 = 0.5 mL/ min, organic flow rate = 0.4 mL/ min, mass of 5 % Pd/Al catalyst = 0.6 g, temp. of reactor = 160 °C, H_2 to substrate ratio = 3:1, solution concentration in MeOH = 0.2 M)

At low pressure, conversion was poor at only 19 %, although selectivity toward the desired product, ketone **(75)** was high. As pressure was increased up to 200 bar conversion started to increase significantly until at 200 bar when conversion was 93 %.

Increasing the metal loading and system pressure have shown that high levels of conversion can be achieved. However, selectivity toward the desired product is still poor due to hydrogenation and hydrogenolysis of ketone **(75)**.

3.8.3 Variation in H_2 to Substrate Ratio

During the debenzylation studies on **(26)** conducted thus far it has not been possible to prevent reduction of the carbonyl of the ketone **(75)**. It was hoped that varying the concentration of H_2 may lead to some changes in reaction selectivity.

Before testing the debenzylation substrate **(26)**, a series of experiments were performed at different H_2 to substrate ratios using only the product of debenzylation, 1-(4-aminophenyl)ethanone **(75)** (Figure 3-5).

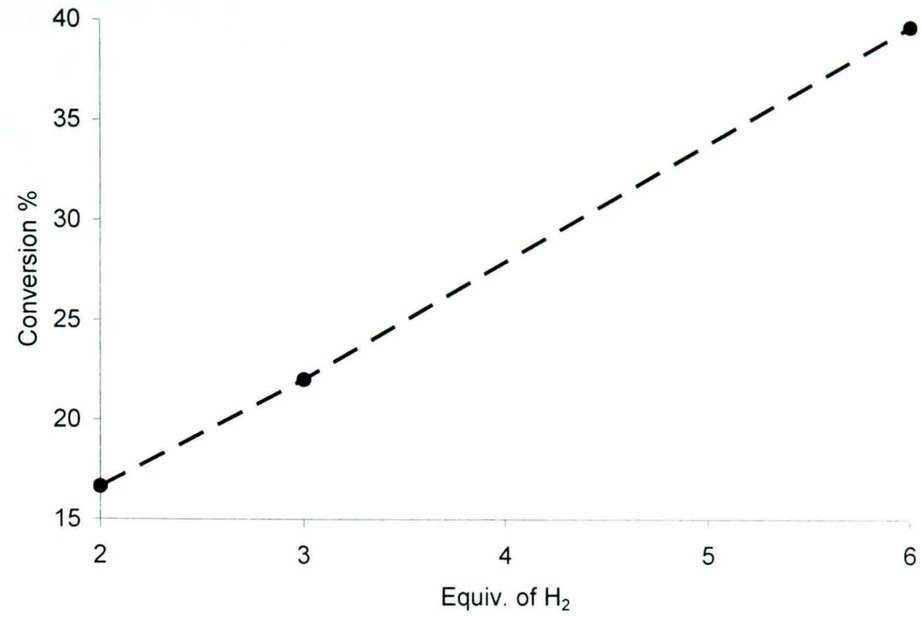


Figure 3-5: Hydrogenation of 1-(4-aminophenyl)ethanone (75) in $scCO_2$ as the ratio of H_2 to substrate was varied.

(Conditions: reactor type = (iii), system pressure = 200 bar, flow rate CO_2 = 0.5 mL/ min, organic flow rate = 0.4 mL/ min, mass of 5 % Pd/Al catalyst = 0.6 g, temp. of reactor = 180 °C, solution concentration in MeOH = 0.2 M)

Under all reaction conditions, the only product detected was *p*-ethylaniline **(76)**, as had been expected from the debenzylation studies.

The results from the hydrogenation of 1-(4-aminophenyl)ethanone **(75)** suggest the availability of H_2 is rate limiting. Conversion appears to exhibit a linear relationship with respect to the concentration of H_2.

To find out if the rate of hydrogenation of ketone **(75)** can be controlled by varying the concentration of H_2, the debenzylation of **(26)** was performed at a H_2 to substrate ratio of 2:1 (Entry 1, Table 3-6).

Unfortunately, even at a H_2 to substrate ratio of only 2:1, where conversion of ketone **(75)** was anticipated to be 15 %, selectivity is poor at only 64 %. Increasing the ratio of H_2 to substrate leads to a slight increase in conversion, but as expected, the amount of **(76)** also increases (Entries 2 & 3, Table 3-6).

Table 3-6: Variation in H_2 to substrate to ratio can effect reaction selectivity during the debenzylation of (26)

Entry	H_2 to substrate ratio	Conversion (%)	Selectivity (%)		
			(75)	(76)	other
1	2:1	81	64	34	2
2	3:1	93	59	41	0
3	5:1	96	47	53	0

(Conditions: reactor type = (iii), system pressure = 200 bar, flow rate CO_2 = 0.5 mL/ min, organic flow rate = 0.4 mL/ min, mass of 5 % Pd/Al catalyst = 0.6 g, temp. of reactor = 160 °C, solution concentration in MeOH = 0.2 M)

3.8.4 Summary

The selective debenzylation of 1-(4-(benzylamino)phenyl)-ethanone **(26)** is difficult to achieve compared to the model substrate **(69)**. A catalyst loading of at least 5% Pd is required to facilitate synthetically useful levels of conversion.

The substrate is deactivated toward debenzylation compared to the model substrate, presumably due to the presence of the electron withdrawing COMe group. By operating at higher temperature and pressure and with only 2:1 ratio of H_2 to substrate it was possible to achieve high levels of conversion, but unfortunately selectivity was poor.

Hydrogenation of the carbonyl of ketone **(75)** is rapid over Pd under the conditions tested and subsequently leads to hydrogenolysis to provide *p*-ethylaniline **(76)**. Lower operating temperatures would likely decrease the degree of hydrogenation. However, high temperature is required to facilitate debenzylation of the deactivated substrate.

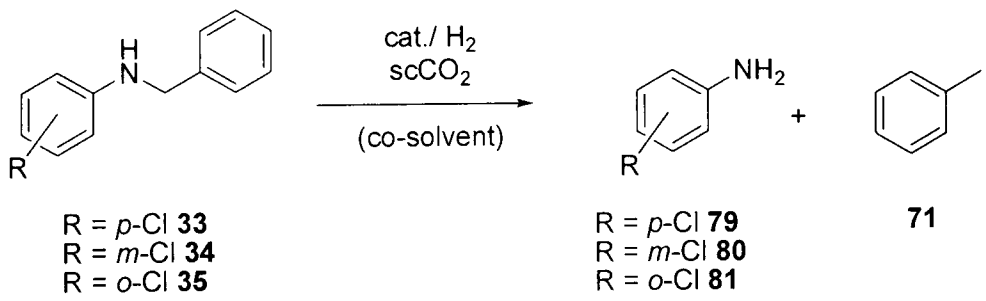
It was decided to stop debenzylation studies on **(26)** and begin investigating chemoselective debenzylation in the presence of a chloro group.

3.9 Chemoselective Debenzylation in the Presence of an Aryl Chloride

Hydrogenolysis of chloro groups is a major problem during debenzylation, particularly when using Pd which is active toward dechlorination. To find out whether dechlorination is a big a problem in continuous flow, the debenzylation of various chlorinated benzyl-protected anilines has been studied in $scCO_2$. The products of debenzylation, chloroanilines, are interesting target molecules since they are intermediates in the synthesis of pharmaceuticals such as, diazepam[52] and also herbicides, such as anilophos.[52]

3.9.1 The Position of the Chloride and its Effect on Conversion and Selectivity

Three different chlorinated *N*-benzylanilines were initially studied. Each substrate has a chloro group in either the *para*- **(33)** *meta*- **(34)** or *ortho*- **(35)** position with respect the amine group. The aim of these experiments was to find out whether the position of the chloro substituent has any effect on reaction selectivity or conversion. The desired product in this set of experiments was a chloroaniline, any dechlorination or hydrogenation of the aromatic ring should be minimised.



Scheme 3-17: Debenzylation of a range of chlorinated *N*-benzylanilines has been studied as a continuous flow process in $scCO_2$

In the first set of experiments, the debenzylation of **(33)**, **(34)** and **(35)** was performed under the optimum conditions found for the model system (Table 3-7). When poor levels of conversion were obtained, the temperature of the catalyst bed was increased to try and increase conversion.

The *para*- substituted substrate **(33)** was tested first and quantitative conversion was achieved at 120 °C (Entry 1, Table 3-7). Note that 120 °C was the lowest temperature that afforded quantitative conversion.

Table 3-7: Variation in conversion and selectivity during the debenzylation of *para*- (33), *meta*- (34) and *ortho*- (35) *N*-benzyl-chloroanilines.

Entry	Substrate	Temp. (°C)	Conversion (%)	Selectivity (%)		
				Chloro aniline	aniline	other
1	**(33)**	120	100	42	52	6
2	**(34)**	120	68	69	20	11
3	**(35)**	200	44	63	21	16

(Conditions: reactor type = (iii), system pressure = 125 bar, flow rate CO_2 = 0.5 mL/ min, organic flow rate = 0.4 mL/ min, mass of 2 % Pd/C catalyst = 0.2 g, H_2 to substrate ratio = 3:1, solution concentration in MeOH = 0.2 M)

Dechlorination occurred to a much more significant extent for the *para*-substituted aniline than for any of the other substrates, with selectivity toward *p*-chloroaniline **(79)** at only 42 %. Note that the results displayed in Table 3-7 represent fractions that were collected from the flow reactor after 20 minutes on-stream. The importance of time-on-stream will be discussed in the following section of this Chapter.

Debenzylation of the *N*-benzyl-*m*-chloroaniline **(34)** (Entry 2, Table 3-7) proceeded with a lower level of conversion than that of *N*-benzyl-*p*-chloroaniline **(33)**. Selectivity was again poor due to dechlorination of *m*-chloroaniline **(80)** and also dechlorination of the starting material.

Debenzylation of *N*-benzyl-*o*-chloroaniline **(35)** did not occur at 120 °C, therefore the temperature of the catalyst bed was increased to 200 °C. Even at such an elevated temperature, conversion of starting material was poor at only 44%. As with the previous chlorinated substrates, selectivity was poor due to dechlorination

of *o*-chloroaniline **(81)** and starting material. The level of dechlorination was approximately the same as for *N*-benzyl-*m*-chloroaniline **(34)** debenzylation.

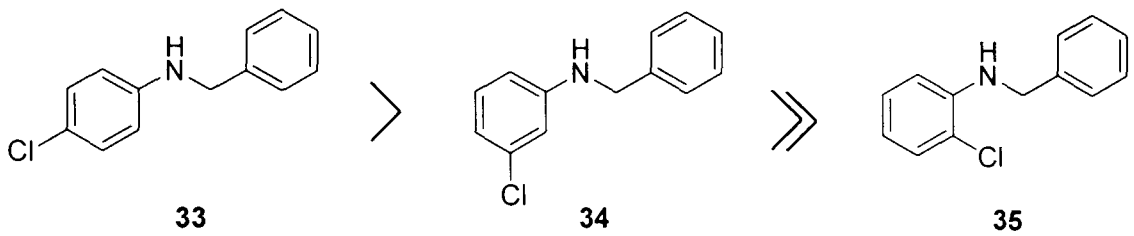
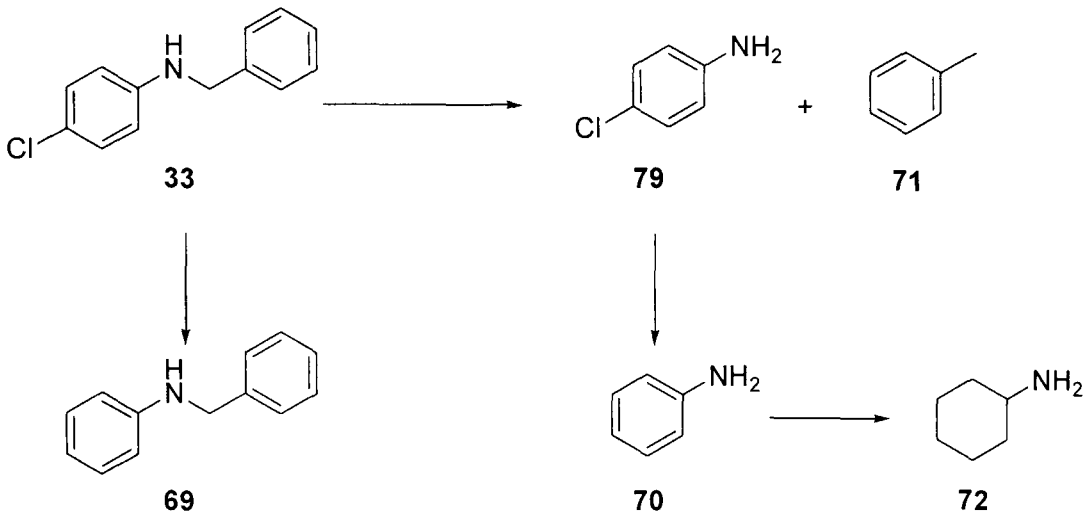


Figure 3-6: Order of reactivity toward debenzylation upon moving the chloro group from the *para*- to *meta*- and *ortho*- position

The order of reactivity of the different substrates toward debenzylation is displayed in Figure 3-6. The order of reactivity may be due to steric effects. *N*-benzyl-*p*-chloroaniline **(33)** has its chloro group situated far away from the N-C bond, where as *N*-benzyl-*o*-chloroaniline **(35)** has a chloro group situated next to the N-C bond. The position of chloro group in the *ortho*- position makes it difficult for the molecule to adsorb flat onto the catalyst surface and therefore difficult for hydrogen to attack the C-N and facilitate hydrogenolysis.

Apart from aniline **(70)**, and dechlorinated starting material **(69)**, the only other by-product formed during debenzylation of the chloro- substituted *N*-benzyl-anilines was cyclohexylamine **(72)**. Cyclohexylamine **(72)** was only present in > 3 % for reactions that were conducted at 200 °C (Scheme 3-18).

Due to the lower activity toward debenzylation of the *ortho*- and *meta*- substituted benzylanilines, all future studies on reducing dechlorination were conducted on *N*-benzyl-*p*-chloroaniline **(33)**.



Scheme 3-18: An example of the various reaction pathways that can occur over a Pd catalyst during debenzylation of chlorinated *N*-benzylanilines. Debenzylation of *N*-benzyl-*p*-chloroaniline (33) produces *p*-chloroaniline (79) which can undergo dechlorination to form aniline (70), the major by-product present in the reaction mixture.

Note that the very first continuous flow debenzylation experiment on *N*-benzyl-*p*-chloroaniline **(79)** was performed inside a pot reactor, reactor type (vi). The pot reactor consists of an aluminium gasket, which is used to hold the catalyst. This unit is then sealed inside a stainless steel frame. At the end of the experiment the catalyst was emptied from the reactor, however it was clear that the aluminium gasket had suffered severe corrosion, presumable due to attack by HCl (see Chapter 2.4 for details). Experiments were no longer performed using the pot reactor and instead only reactors made completely from stainless steel were used. The experiment using the pot reactor highlights an added practical problem that is posed by dechlorination.

Before discussing the various methods that have been developed to improve reaction selectivity, it is important to discuss the mechanism of both the debenzylation and dechlorination reaction.

3.9.2 The Mechanism of Debenzylation and Dechlorination

Both debenzylation and dechlorination involve hydrogenolysis of a C-X bond. The first step of a heterogeneously catalysed hydrogenolysis reaction is dissociative chemisorption of H_2 onto the catalyst surface. This is followed by chemisorption of the substrate onto the catalyst surface. Hydrogenolysis then proceeds *via* the stepwise addition of two hydrogen atoms across the C-X bond. Finally desorption of the final product should complete the process.

The rate of hydrogenolysis is very much dependent on the presence of unsaturated functionality near to the bond that is to be cleaved, C-X. For instance, aryl-Cl bond hydrogenolysis will take place at a faster rate than alkyl-Cl bond hydrogenolysis.[29] Similarly, the model substrate in our debenzylation studies, *N*-benzylaniline **(69)** is likely to undergo hydrogenolysis of the C-N bond faster than the corresponding non-aromatic molecule, *N*-(cyclohexylmethyl)-cyclohexanamine. The reason for this is that the unsaturated part of the molecule acts as a 'handle' and brings the C-X bond closer to the catalyst surface, thus promoting overlap between the orbitals of the C-X bond and the *d* and *spd* orbitals of the metal.

Since hydrogenolysis involves chemisorption of the 'handle' and C-X bond, a relatively large ensemble of metal atoms may be required to facilitate bond cleavage. This is why hydrogenolysis is often performed on heterogeneous rather than homogeneous catalysts; homogeneous catalysts allow coordination of only one bond where as a heterogeneous catalyst which is made up from many metal atoms and forms a surface with various different types of active site will be able to accommodate the substrate. Hydrogenolysis is known as a demanding or 'structure-sensitive' reaction because it is believed to occur on only certain catalytic active sites where the coordination number of metal atoms is low, such as corners, edges, and crystal defects.

The presence of substituents on the ring of the model substrate *N*-benzylaniline **(69)** has been proven to affect the rate of the debenzylation reaction.[30,31,53] For instance the presence of an electron withdrawing substituent on the aromatic ring of *N*-benzylaniline **(69)** (such as a COMe group) can decrease the rate of debenzylation by reducing the electron density of the aromatic species; similarly, an electron donating group (such as OH, halogen, or NH_2) will serve to increase electron density in aromatic ring. Sterics can also affect the rate of hydrogenolysis, as has been shown by the presence of a chloro group in the *ortho*-position during debenzylation of *N*-benzyl-*ortho*-chloroaniline **(35)**.

Electronic and steric factors also affect the dechlorination reaction in a similar fashion. For instance, the product of debenzylation of *N*-benzyl-*p*-chloroaniline **(33)** is *p*-chloroaniline **(79)**. *p*-Chloroaniline **(79)** is active toward dechlorination because the C-Cl bond is adjacent to an aromatic group, but also because the molecule contains an electron donating primary amine.[54-57]

From the brief examination of the mechanism of hydrogenolysis it is clear that due to the structure of *N*-benzyl-*p*-chloroaniline **(33)**, both debenzylation and dechlorination of the product *p*-chloroaniline **(79)**, are likely under reaction conditions.

Investigations discussed in the rest of this Chapter have concentrated on understanding not only debenzylation, but also the factors affecting the dechlorination reaction. Several methods have also been developed to increase selectivity by making the dechlorination reaction unfavourable, whilst maintaining activity toward debenzylation.

3.9.3 Variation in Selectivity with Time-on-Stream

When dechlorination occurs, HCl is produced as a by-product. It has been reported in the literature that when dechlorination over a heterogeneous catalyst

occurs, the HCl that is formed can bind to the surface of the Pd, Pt or Ni catalyst causing deactivation.[58-63]

The aim of the following study was therefore to find out whether the presence of HCl is affecting the performance of the Pd catalyst used for the debenzylation of **(33)**. To test the performance of the catalyst, an experiment was performed under a single set of reactions conditions and the product mixture analysed over time (Figure 3-7).

It should be noted that the HCl which is formed can react with the amines present in the reaction mixture which will lead to formation of the hydrochloride salt of the amine. Salts cannot be analysed by GLC and therefore all product mixtures were washed with base to remove the presence of any acid, before extracting the amine products into an organic solvent for analysis.

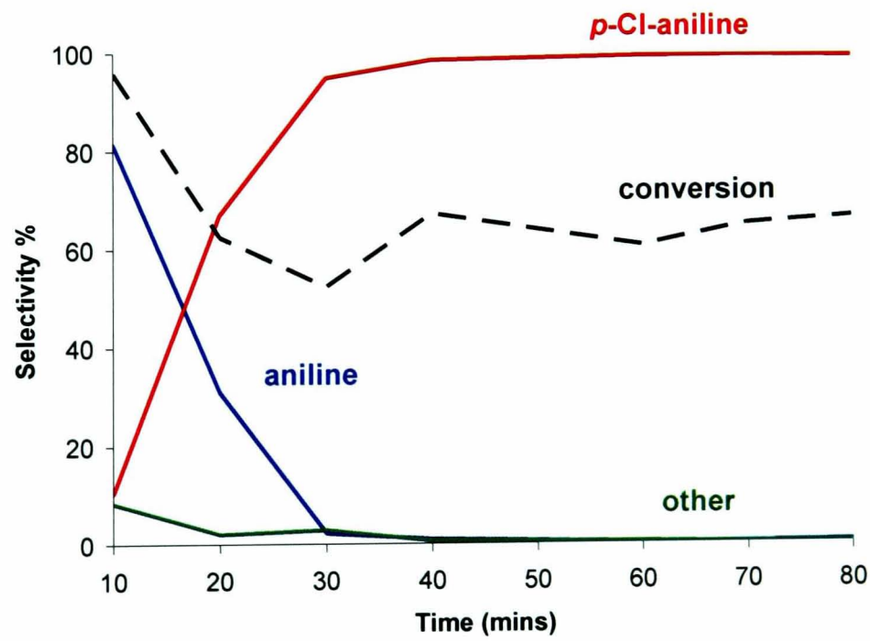


Figure 3-7: Continuous flow debenzylation of *N*-benzyl-*p*-chloroaniline (33). Selectivity changes dramatically with time-on-stream.

(Conditions: reactor type = (iii), system pressure = 125 bar, flow rate CO_2 = 0.5 mL/ min, organic flow rate = 0.4 mL/ min, mass of 2 % Pd on Si/Al catalyst = 0.2 g, H_2 to substrate ratio = 3:1, solution concentration in MeOH = 0.4 M)

In the initial 1 0 minutes on-stream, selectivity toward the desired product, *p*-chloroaniline **(79)** was very poor due to dechlorination. However, as time passes the selectivity toward **(79)** increases until, after 40 minutes on-stream, selectivity toward **(79)** is excellent at 98 %. Selectivity remains constant after 40 minutes for the remainder of the experiment.

In the first 10 minutes on-stream conversion was near quantitative however, after 40 minutes conversion dropped to 60 % where it remained for the rest of the experiment.

The results from Figure 3-7 show that the Pd catalyst becomes selectivity deactivated toward dechlorination over time. It is suggested that HCl binds to the catalytic sites that are responsible for dechlorination, whilst leaving the active sites involved in debenzylation relatively unaffected. The small drop in conversion over time can be attributed to poisoning of only some of the debenzylation active sites with HCl.

3.9.4 Variation in Catalyst Support

According to the literature, studies on catalytic hydrodechlorination have shown that it is spillover hydrogen which is the active species responsible for C-Cl hydrogenolysis, rather than hydrogen present on any of the metal active sites.[64-66] In this case, the process of "spillover" begins with the dissociative adsorption of H_2 onto the metal surface. Transport of the dissociatively adsorbed hydrogen atom from the metal site to an acidic site on the catalyst support completes the spillover process.[67] Some spillover processes occur by transport of the active species through the gas phase, however, it is generally accepted that surface diffusion from metal to support predominates in heterogeneous catalysis.[67] Although spillover hydrogen is inactive in most hydrogenation reactions, a number of publications have reported that it is active in various hydrogenolysis reactions, including C-Cl bond hydrogenolysis.[68-70]

By changing the type of metal support from an acidic support (such as alumina) to a basic support (such as silica) it may be possible to influence the process of hydrogen spillover and therefore the dechlorination reaction. Furthermore, change in catalyst support will affect the dispersion and surface area of the active metal exposed, this too may affect the rate of debenzylation or dechlorination.[67,71]

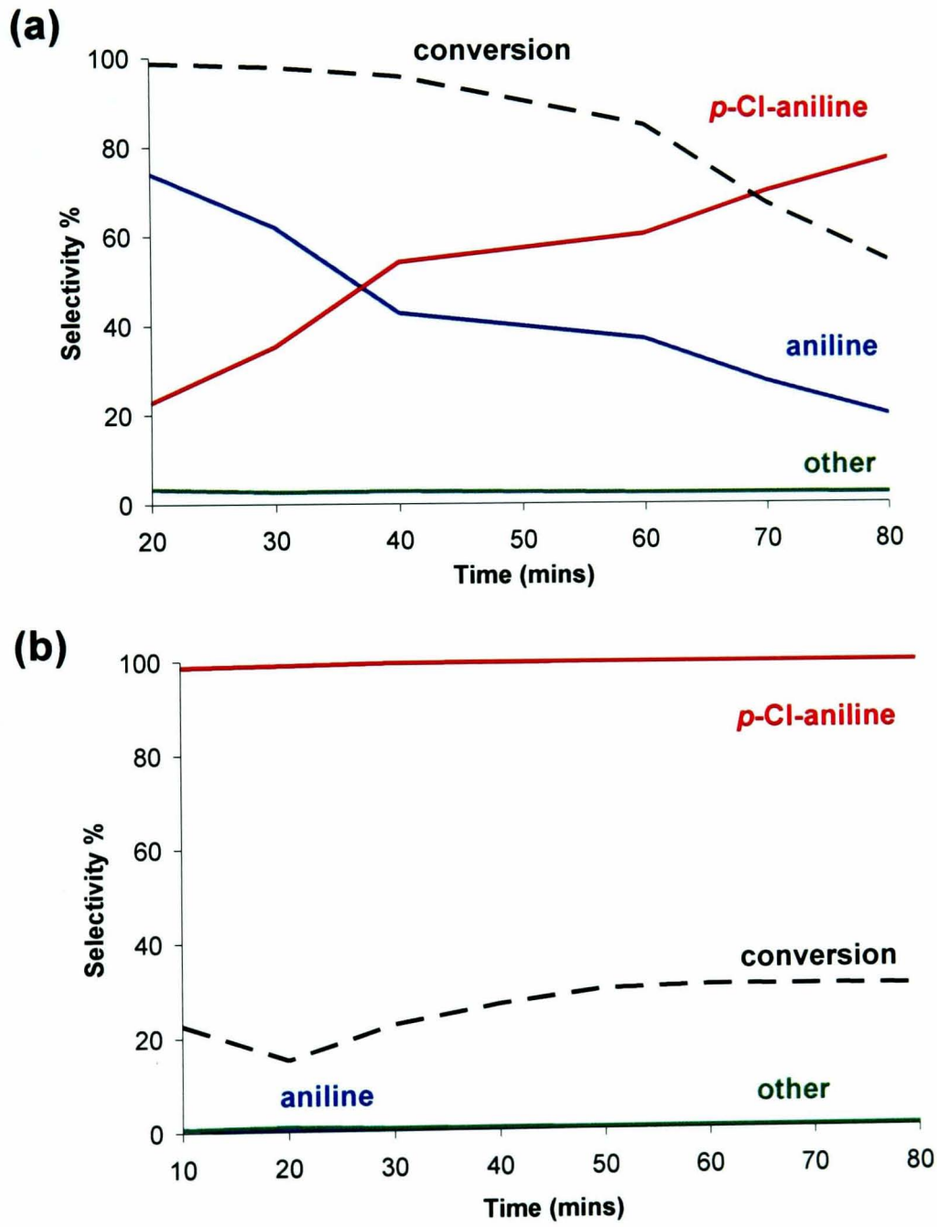


Figure 3-8: Variation in catalyst support during debenzylation of (33) over (a) a Pd on Alumina and (b) a Pd on Silica catalyst.

(Conditions: reactor type = (iii), system pressure = 125 bar, flow rate CO_2 = 0.5 mL/ min, organic flow rate = 0.4 mL/ min, mass of 2 % Pd catalyst = 0.6 g, H_2 to substrate ratio = 3:1, solution concentration in MeOH = 0.4 M)

The debenzylation of **(33)** was conducted over a variety of different Pd supported catalysts to find out whether catalyst support has any significant effects on either the dechlorination or debenzylation reaction.

Figure 3-8 shows differences in selectivity and conversion for the debenzylation of **(33)** when performed over a Pd/Al and Pd/Si catalyst. The catalyst that was originally used for time-on-stream studies back in Figure 3-7 was Pd supported on Si/Al and therefore in theory should exhibit properties in between that of the Pd/Si and Pd/Al catalysts.

The Pd/Al catalyst [(a) Figure 3-8] exhibited a similar time-on-stream profile to the Pd on Si/Al catalyst in that dechlorination was suppressed over time. However, even after 80 minutes on-stream the catalyst had not achieved a steady state. Conversion started to drop after 40 minutes.

An alumina supported Pd catalyst was used by Ayame and co-workers for the continuous flow dechlorination of chlorobenzene.[62] They showed that Pd/Al catalyst was extremely active toward dechlorination due to the efficient spillover of hydrogen from the Pd metal onto the Lewis Acid sites of the alumina. They also observed deactivation of the catalyst over time and were able to prove that this was due to the accumulation of chloride on the catalyst surface, although they did not say exactly where on the catalyst (metal or support) the chloride has been adsorbed.

Our studies appear to complement that of Ayame [62] and show that Pd/Al is an effective catalyst for dechlorination. Over time, the catalyst becomes deactivated toward dechlorination, but as with Pd on Si/Al, debenzylation can still take place, albeit at a reduced level of conversion.

A Pd/Si catalyst was also tested for the debenzylation of *N*-benzyl-*p*-chloroaniline **(33)** [(b) Figure 3-8]. This catalyst exhibited a completely different reaction

profile over time. In this case, selectivity toward all dechlorinated by-products was < 2 %, even in the initial stages of the experiment. The drawback of the Pd/Si catalyst was its activity toward debenzylation, with conversion averaging 30 % over the duration of the experiment.

Halligudi and co-workers studied the dechlorination of chlorobenzene over various different Pd supported catalysts including Pd/Al, Pd/Si and Pd/C.[72] They found that the carbon and alumina supported catalyst both provided the same level of activity, while silica supported palladium was very poor. Our studies are in good agreement with the work of Halligudi. However, our results have also shown that not only does Pd/Si show poor activity toward dechlorination, its activity toward debenzylation is lower than that of the other supported catalysts. It is suspected that the reason for the poor activity of the Pd/Si catalyst is due to the basic nature of the catalyst support.

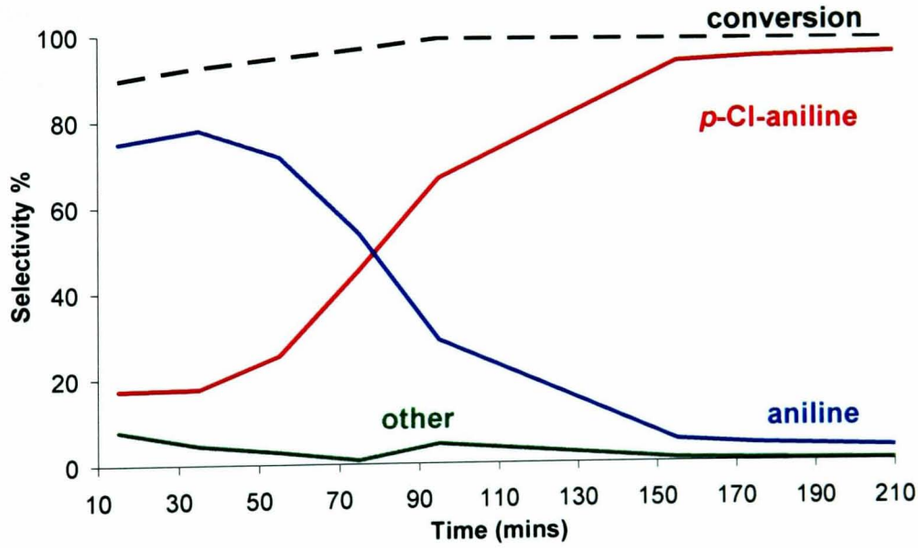


Figure 3-9: Debenzylation of *N*-benzyl-*p*-chloroaniline (33) over Pd/C shows a similar trend in reactivity as the Pd/Al and Pd on Si/Al catalyst.

(Conditions: reactor type = (iii), system pressure = 125 bar, flow rate CO_2 = 0.5 mL/ min, organic flow rate = 0.4 mL/ min, mass of 2 % Pd/C = 0.6 g, H_2 to substrate ratio = 1.5:1, solution concentration in MeOH = 0.2 M)

As a final study into the effect of changing catalyst support, a Pd/C catalyst was tested toward debenzylation of *N*-benzyl-*p*-chloroaniline **(33)** (Figure 3-9).

However, this reaction was performed at a lower concentration of H_2 compared to previous reactions (1.5:1 ratio of H_2 to substrate compared to 3:1) to find out if H_2 to substrate ratio has any effect on selectivity. Also, a more dilute solution of **(33)** in MeOH was used (0.2 M instead of 0.4 M).

The first important point from Figure 3-9 is that changing the H_2 to substrate ratio from 3:1 to 1.5:1 had little effect on the course of the reaction. Also, Pd/C exhibited a similar pattern of reactivity over time as the Pd/Al and the Pd on Si/Al catalysts. The type of carbon used is 'acidic' carbon and therefore it is not too surprising that it exhibits similar reactivity as the other acidic supported catalysts. However, under the reaction conditions tested for the Pd/C experiment, it took 150 minutes for the catalyst to reach a steady state where selectivity toward *p*-chloroaniline **(79)** was high. This is most likely an artefact of pumping a more dilute substrate solution over the catalyst bed, rather than the change in the type of catalyst support. Using a more dilute solution means that there are less substrate molecules passing over the catalyst at any particular time, therefore it takes longer for the active sites involved in dechlorination to become poisoned by HCl.

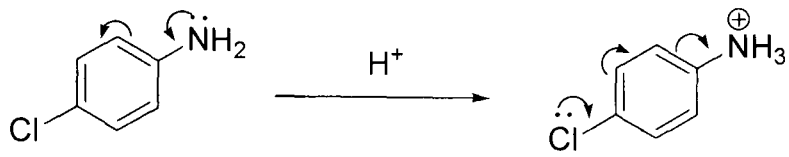
Thus, it has been shown that variation in type of metal support can have a major effect on reaction selectivity. The Pd/Si catalyst was found to be the most selective with only very little dechlorination recorded. Unfortunately the activity of the Pd/Si catalyst toward debenzylation was lower than any of the other catalysts.

3.9.5 Debenzylation in Acidic Media

The debenzylation reaction has thus far been conducted in neutral media, *i.e.* no acid or base has been added. However, the debenzylation and dechlorination reaction can both be significantly affected by acid and base.[38,73,74]

The addition of acid has been investigated for the debenzylation of *N*-benzyl-*p*-chloroaniline **(33)**. It is hoped that presence of acid will enhance selectivity since

protonation of the amine **(79)** will make the nitrogen electron-withdrawing rather than electron-donating (Scheme 3-19). The presence of acid may also help increase the rate of debenzylation by making the amine a better leaving group.[49]



Scheme 3-19: Free amine groups are electron donating, whereas protonated amines are electron withdrawing.[38]

Batch Experiments in the Presence of Acid

A series of debenzylation experiments were performed in a batch reactor in the presence of different types of acid to find out whether the presence of acid affects selectivity for the debenzylation of **(33)** when performed in $scCO_2$. The initial experiments were performed in batch because it is possible to screen a number of different acids in a shorter period of time. In all studies a 2% Pd/C catalyst was tested since this would provide the best contrast with reactions performed in the absence of acid (Table 3-8).

Table 3-8: The batch debenzylation of (33) in the presence of various acids.

Entry	Acid (mol equiv.)	Conversion (%)	Selectivity (%)		
			p-Cl-aniline	aniline	other
1	none	93	28	31	41
2	CH_3COOH *	68	60	17	23
3	CF_3COOH (2.0)	88	29	31	40
4	HCl (1.0)	90	45	25	30
5	H_2SO_4 (1.0)	69	96	1	3
6	H_2SO_4 (2.0)	99	67	14	19

(Conditions: reactor type = autoclave, system pressure = 175 bar, H_2 pressure 1.5 bar, mass of 2 % Pd/C catalyst = 0.0.4 g, 5 mL of 0.2 M solution in MeOH, reaction time 60 minutes)

** A 50:50 (vol/vol) mixture of 100% acetic acid/ MeOH was used*

To begin, a control experiment was performed without any acid (Entry 1, Table 3-8). Under the conditions employed selectivity was poor due to dechlorination of starting material **(33)** and *p*-chloroaniline **(79)**.

The use of a acetic acid/ MeOH mixtures has been reported previously for debenzylation reactions and therefore was the first of the acids tested (Entry 2, Table 3-8).[29] The use of a 50:50 acetic acid/ MeOH mixture definitely improved selectivity, however, conversion dropped to 68 %.

It is well documented that fluorinated molecules exhibit greater levels of solubility in $scCO_2$ than their non-fluorinated analogues. Therefore, it was suggested that trifluoroacetic (TFA) acid might enhance selectivity better than acetic acid (Entry 3, Table 3-8). The level of conversion was higher for the experiment in TFA acid than reported for acetic acid, however selectivity was extremely poor. The experiment performed in TFA exhibits more similarities to the reaction performed in the absence of acid. This suggests that the fluorinated acid was not present in the same phase as the substrate and was most likely present in a separate phase with the CO_2.

HCl was the next acid to be tested (Entry, 4, Table 3-8). It was found that one equivalent of HCl did not have any significant effect on conversion. However, although selectivity was increased, compared with Entry 1, selectivity toward *p*-chloro-aniline **(79)** was still only 45 %.

In the final two batch experiments, H_2SO_4 was added (Entries 5 & 6,Table 3-8). In the presence of only one equivalent of acid, the selectivity was excellent, with selectivity toward all by-products down to only 4 % (Entry 5, Table 3-8). In a final batch experiment, two equivalents of H_2SO_4 were added. Conversion was improved compared to the previous experiment however selectivity was not as high as had been seen previously.

Continuous Flow Experiment in the Presence of Acid

The batch experiments had shown that the addition of acid, in particular H_2SO_4, does suppress dechlorination. However, it was always the aim to develop debenzylation as a continuous flow process. Therefore the debenzylation of *N*-benzyl-*p*-chloroaniline **(33)** was performed in the presence of acid based on the optimum results obtained in the batch experiments.

Two different acids were tested in continuous flow. First, HCl was pumped over the 2% Pd/C catalyst in a reaction mixture which contained only 1.0 equiv. of acid. This experiment was performed at 120 °C, which had been the optimum temperature for previous flow studies. It was found that selectivity was only marginally improved (Entry 1, Table 3-9) at 30 % selectivity toward **(79)**.

Table 3-9: Continuous flow debenzylation of *N*-benzyl-*p*-chloroaniline (33) in $scCO_2$ in the presence of different mineral acids.

Entry	Acid (mol equiv.)	Temp. (°C)	Conver^n (%)	Selectivity (%)		
				4-Chloro aniline	aniline	other
1	HCl (1.0)	120	99	30	41	30
2	HCl (2.0)	120	99	45	30	25
3	HCl (2.0)	80	99	72	13	15
4	HCl (2.0)	60	74	84	10	6
5	H_2SO_4 (1.0)	80	88	89	8	3

(Conditions: reactor type = (iv), system pressure = 175 bar, flow rate CO_2 = 1.0 mL/ min, organic flow rate = 0.4 mL/ min, mass of 2 % Pd/C catalyst = 0.2 g, H_2 to substrate ratio = 6:1, solution concentration in MeOH = 0.2 M)

In a separate experiment, 2.0 equiv. of HCl were added to try and further increase selectivity (Entry 2, Table 3-9). Although selectivity did increase slightly, it was decided to lower the reaction temperature. In previous debenzylation studies lowering the temperature to < 120 °C, led to a major drop in conversion, however due the presence of acid, lowering the temperature still afforded high levels of conversion. Presumably, the presence of the acid helps to lower the activation for

debenzylation by protonating the nitrogen of **(79)**, thereby making the aniline a better leaving group. At 60 °C, conversion dropped to 74 %, however selectivity is the best that has been reported in any of the continuous flow studies over Pd/C at 84 % (Entry 3, Table 3-9).

Although HCl was shown in batch reactions to suppress dechlorination, it was H_2SO_4 that provided the highest level of selectivity (Entry 5, Table 3-9). H_2SO_4 has two acidic protons, compared to HCl, which only has one. It is therefore expected that 1.0 equiv. of H_2SO_4 will have a similar effect on selectivity as 2.0 equiv. HCl. However, in this case the addition of only 1.0 equiv. of H_2SO_4 provided even higher selectivity than when using 2.0 equiv. HCl at 60 °C. Conversion was also significantly improved at 88 % when the reaction was performed in H_2SO_4 at 80 °C.

3.9.6 Variation in Co-solvent to Improve Selectivity

In all debenzylation studies on the chlorinated substrates, MeOH has been used as co-solvent. However, due its protic nature, it is possible that MeOH is not completely inert, and that the protic solvent is increasing the rate of dechlorination. Therefore to find out how change in co-solvent may affect selectivity, THF was tested as co-solvent. THF is aprotic and therefore should provide an interesting comparison between the results obtained for MeOH.

THF as co-solvent led to a totally different reaction profile over the Pd/C catalyst with time-on-stream (Figure 3-10). Previously, with MeOH as co-solvent, dechlorination occurred to such an extent that the catalyst became deactivated toward dechlorination due to HCl poisoning. Using THF as co-solvent dramatically reduces the amount of dechlorination and so the catalyst does not become deactivated in the same way that happened when using MeOH as co-solvent. It is unclear exactly why the change in co-solvent should affect the

dechlorination reaction in such a dramatic fashion, however it has been reported before.[38,73]

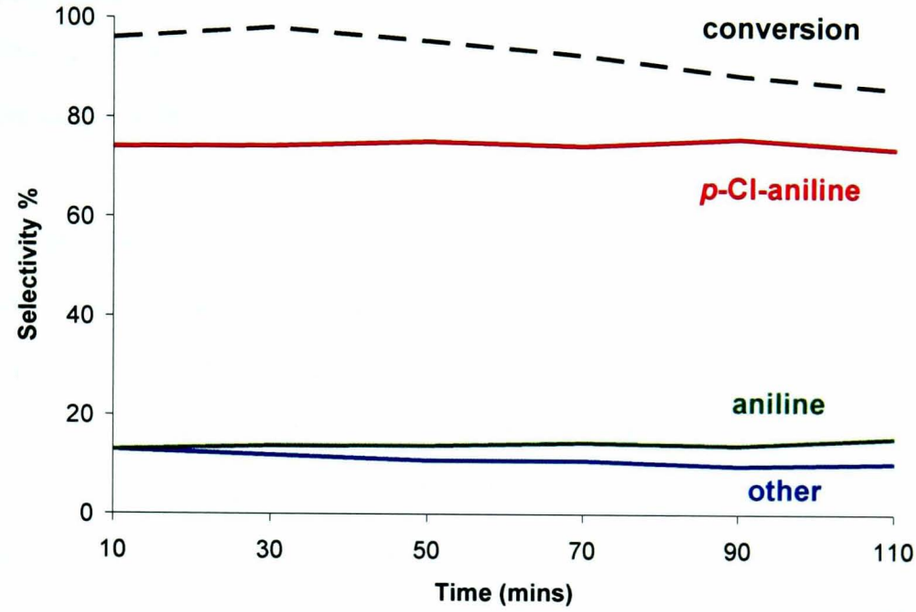


Figure 3-10: Continuous flow debenzylation of *N*-benzyl-*p*-chloroaniline (33) in $scCO_2$ using THF as a co-solvent.

(Conditions: reactor type = (iv), system pressure = 175 bar, flow rate CO_2 = 1.0 mL/ min, organic flow rate = 0.4 mL/ min, mass of 2 % Pd/C catalyst = 0.2 g, temp. of reactor = 120 °C, H_2 to substrate ratio = 3:1, solution concentration in MeOH = 0.2 M)

A disadvantage of using an aprotic solvent such as THF is that the addition of mineral acids to further improve selectivity is not possible. This is because aprotic solvents will not solvate mineral acids, and therefore addition of acid would lead to formation of an inhomogeneous solution which cannot be pumped efficiently into the continuous flow system.

3.9.7 Summary

The chemoselective debenzylation of different chlorinated *N*-benzylanilines has been studied as a continuous flow process. It has been shown that the position of the chloro substituent in the *ortho*-, *meta*- and *para*- position has an effect on the rate of debenzylation over a Pd catalyst. While it is possible to achieve high levels of debenzylation activity for both the *meta*- **(34)** and *para*- **(33)** substituted *N*-

benzylanilines, *N*-benzyl-*o*-chloroaniline **(35)** does not undergo debenzylation at an appreciable rate below 200 °C. The proximity of the chloro group to the N-C bond is believed to be the reason for this. The dechlorination of the chloroaniline and starting material is predominant for all chlorinated *N*-benzylanilines, however, the activity of *N*-benzyl-*p*-chloroaniline **(33)** is significantly higher than for the *ortho*- and *meta*- substituted compounds.

All further investigations were performed on the chlorinated substrate which was most active toward debenzylation and dechlorination, *N*-benzyl-*p*-chloroaniline **(33)**. In a study of catalyst performance over time, it was found that in the initial stages of the reaction dechlorination predominates and selectivity toward the desired product, *p*-chloroaniline **(79)** was extremely poor. However, as time progresses, the catalyst appears to become selectively poisoned toward dechlorination, whilst the debenzylation reaction remains relatively unaffected. It should be noted that this trend would be difficult to identify in a batch system, and therefore an advantage of continuous flow operation is that is much easier to see the changes in catalytic activity over time.

It is believed that the catalyst becomes selectively poisoned due to blocking of the dechlorination active sites by the HCl produced from dechlorination. The rate of dechlorination and poisoning of the catalyst can be affected by changing the type of metal catalyst support. Four different types of Pd catalyst were investigated (Pd/C, Pd/Al, Pd/Si and Pd on Si/Al) and it was found that the more acidic supports all exhibited a similar pattern of reactivity over time and became completely deactivated toward dechlorination over time. The performance of the Pd/Si catalyst was very different, only a very small amount of dechlorination was recorded, and selectivity toward the desired product was excellent at 98 %. Unfortunately the drawback of the Pd/Si catalyst was that its activity was significantly lower than for the other Pd catalysts, although it is believed that this may be overcome by using either a higher loading of Pd, or by increasing the ratio of catalyst to substrate.

In an attempt to minimize the dechlorination reaction, experiments were performed in an autoclave in the presence of various acids. From all the acids tested (Acetic acid, TFA acid, HCl, H_2SO_4), it was H_2SO_4 that provided the largest inhibitory effect on dechlorination. Debenzylation of *N*-benzyl-*p*-chloroaniline **(33)** in the presence of H_2SO_4 was then attempted in the continuous flow rig. In the presence of 2 equivalents H_2SO_4, selectivity toward *p*-chloroaniline **(79)** was 89 % and conversion 88 %.

The final strategy that was developed to minimise dechlorination was debenzylation in the presence of an aprotic solvent, THF. It has been shown that selectivity toward *p*-chloroaniline **(79)** was significantly improved in the initial stages of the reaction, however, because **(79)** is highly active toward dechlorination it was not possible to completely avoid this unwanted side reaction.

3.10 Conclusions

The model studies on *N*-benzylaniline **(69)** have shown that a very important reaction in the pharmaceutical industry, catalytic debenzylation can be performed efficiently as a continuous flow process in the presence of $scCO_2$.

Pd, Pt and Rh catalyst were all screened for the model reaction, however, only Pd offers the level of activity that is required in continuous flow. The Pd catalyst was tested over a 5 hour period in which it showed no sign of deactivation.

Chemoselective debenzylation in the presence of a carbonyl and also a chloro group were investigated. Debenzylation of 1-(4-(benzylamino)phenyl)ethanone **(26)** requires a higher loading of Pd and also a higher reactor bed temperature to facilitate synthetically useful levels of conversion. At the high temperatures required for continuous flow debenzylation, further reaction of the desired product, 1-(4-aminophenyl)ethanone **(75)** *via* hydrogenation and then subsequent hydrogenolysis of the C-OH bond cannot be avoided. Based on the work carried

out on the chlorinated substrates, it can be suggested that the addition of H_2SO_4 may have helped to increase selectivity. The addition of acid would protonate the nitrogen of 1-(4-(benzylamino)phenyl)ethanone **(26)**, therefore making the aniline a better leaving group. Unfortunately there was not time to test this theory.

The chemoselective debenzylation of a variety of chlorinated *N*-benzylanilines was studied, with the aim of avoiding any dechlorination of the product or starting material. It has been shown that dechlorination occurs readily in the initial stages of the reaction over a Pd catalyst. However, when the reaction is conducted in continuous flow, it ahs been found that the catalyst becomes poisoned toward dechlorination, most likely due to HCl adsorption; while the majority of the active sties involved in debenzylation remain active. The self poisoning mechanism of the Pd catalyst opens up the possibility of continuous flow debenzylation being an alternative method for chemoselective debenzylation in the presence of chloro substituents. However, the long term stability of the catalyst needs to be fully investigated.

Other strategies that have been developed to minimise dechlorination during the continuous flow debenzylation of *N*-benzyl-*p*-chloroaniline **(33)** include the addition of acid, in particular H_2SO_4 offers the highest level of selectivity. Alternatively, debenzylation in the presence of an aprotic solvent such as THF produced significantly less dechlorination than when the protic solvent, MeOH was used. This strategy may be particularly effective at reducing dechlorination of substrates that are less active toward dechlorination than *p*-chloroaniline **(79)**.

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Chapter 4

Diastereoselective Hydrogenation in $scCO_2$

4 Diastereoselective Hydrogenation in $scCO_2$

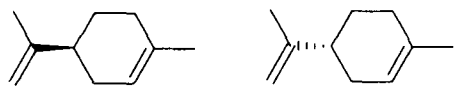
4.1 Introduction

This chapter provides an introduction to diastereoselective hydrogenation and its relevance in the synthesis of the pharmaceutical, Zoloft®. The Chapter then describes progress made on the hydrogenation of the pharmaceutical intermediate, *rac*-sertraline imine **(42)** in $scCO_2$.

4.2 Stereochemistry

4.2.1 Background

A molecule possessing only one chiral centre may exist as either the (*R*)- or (*S*)-enantiomer. Each of these enantiomers will possess the same chemical and physical properties, although they may differ in smell or taste. For example, (*S*)-limonene **(82a)** smells of lemons and (*R*)-limonene **(82b)** smells of oranges (Figure 4-1).

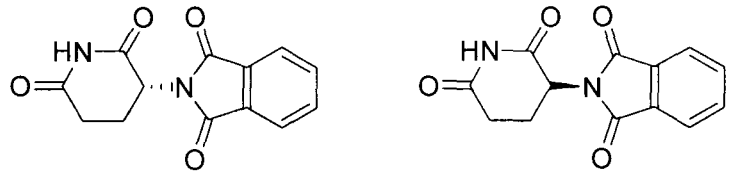


(*S*)-limonene **82a** (*R*)-limonene **82b**

Figure 4-1: (*S*) limonene smells of lemons, (*R*)-limonene smells of oranges

Chirality exists in all life, for example, all amino acids (except glycine) and sugars, which form the backbone of DNA are chiral molecules. Although the existence of chiral molecules has long been known, the pharmaceutical implications of racemic drugs have only been realised in the last twenty years.[1] The problem is that biological messenger molecules and cell surface receptors are chiral; thus drug molecules must perfectly match the symmetry of the messenger molecules and surface receptors. Often, it is the case that one enantiomer is active and the other inactive. However, in some cases the "wrong" enantiomer can have a detrimental

effect, instead of just being inactive. Perhaps the most infamous example of this is the drug thalidomide **(83)** (Figure 4-2).[2]



(*R*)-thalidomide
83a

(*S*)-thalidomide
83b

Figure 4-2: (*R*)-thalidomide is effective in the treatment of morning sickness, (*S*)-thalidomide causes birth defects.

Thalidomide was sold in racemic form in over 50 countries during the 1950s and 1960s to combat morning sickness in pregnant women. Unfortunately, it was found that whilst the (*R*)-enantiomer **(83a)** was effective in the treatment of morning sickness, (*S*)-thalidomide **(83b)** was teratogenic and caused birth defects in babies. Around 15,000 children were affected, and only 8,000 of these survived past their first year.[3] In this case, selling the drug in enantiomerically pure form would not have prevented birth defects from occurring since the enantiomers of thalidomide are actually inter-converted *in vivo* by the liver.

Since the thalidomide tragedy, the testing of biologically active compounds has become much more stringent. A drug can no longer be sold in racemic form until the individual effects of all stereoisomers have been determined. If, for instance, testing of a drug reveals that one stereoisomer is active and the other inactive and easily metabolised within the body, then it may still be possible to sell that drug in racemic form. If, however, the tests reveal that the other stereoisomer could cause adverse effects then synthesis of the optically pure compound must be undertaken.

The strategies that can be applied to the synthesis of optically pure organic molecules can be broadly divided into two: classical stereoselective organic synthesis[4,5] and stereoselective catalysis.[6] Although both of these strategies are

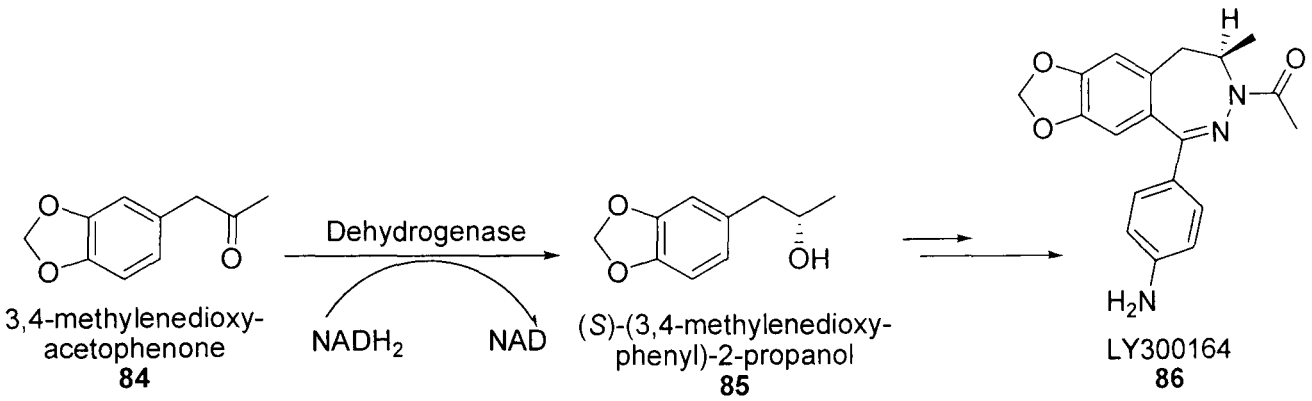
important in the synthesis of optically pure compounds, it is only the latter strategy which will be discussed further.

4.2.2 Stereoselective Catalysis

From the industrial point of view, catalytic processes are preferred since they are often more atom efficient and lead to the generation of less waste. Catalytic methods for producing asymmetric molecules can be divided into three separate classes: homogeneous, heterogeneous and biocatalysis.

Biocatalysis

Biocatalysis offers a highly regio- and stereo-selective route to optically active compounds, and although this field is likely to become more important in the future, it remains the least developed of all three catalytic methods. However, there are some examples where it has been successfully applied.[7-10] For instance, chemists at Eli Lilly found that ketone **(84)** could be reduced using a dehydrogenase to produce the optically pure alcohol **(85)** (> 99% *e.e.* and 96 % yield) which is an intermediate in the synthesis of the pharmaceutically active compound LY300164 **(86)** (Scheme 4-1).[11]

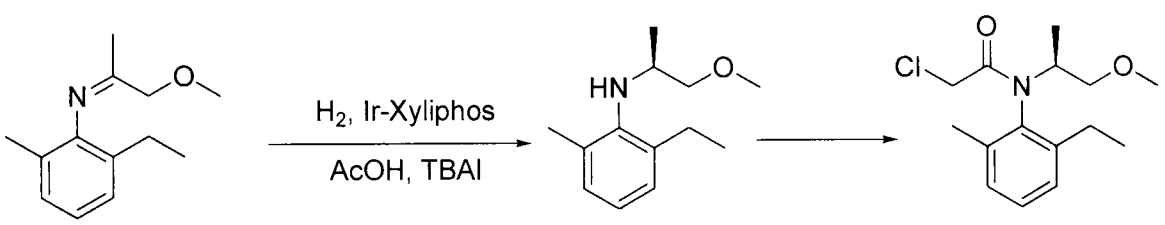


Scheme 4-1: An example of biocatalysis and its application in the synthesis of pharmaceutical LY300164 (86). [11]

Homogeneous Catalysts

Homogeneous catalysts have the advantage that they can be defined on a molecular level. By changing the metal and ligand system, it is often possible to achieve very high levels of selectivity. However, the complexity of these systems also means that catalysts are often substrate specific and expensive to manufacture on an industrial scale.

Despite these drawbacks there are many examples where homogenous catalysis has been applied to the synthesis of optically pure compounds, particularly in the field of enantioselective hydrogenation.[12-16] For example, Blaser *et al.* developed the use of an Ir-diphosphine catalyst **(87)** for the enantioselective hydrogenation of imine **(88)** to synthesise (*S*)-amine **(89)** with 80 % *e.e.* (Scheme 4-2).[17,18]



Scheme 4-2: Synthesis of (*S*)-metolachlor (90) *via* enantioselective hydrogenation of imine (88) using a homogeneous Ir complex (87). [18]

Amine **(89)** is an intermediate in the synthesis of a mass produced herbicide, (*S*)-metolachlor **(90)** Also, as explained in Chapter 1.4, homogeneous enantioselective hydrogenation reactions can be efficiently conducted in $scCO_2$.[19-21]

Heterogeneous Catalysts

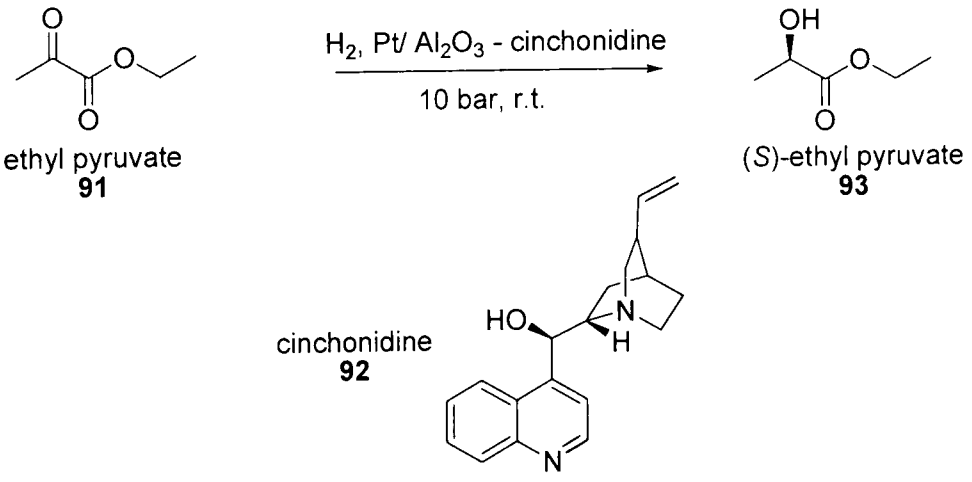
Heterogeneous catalysts have many advantages compared to homogeneous catalysts. The most important of these include: easy separation of catalyst from reaction mixture; possible recovery and recycling of catalyst; simple handling; good stability and availability. These advantages combine to make heterogeneous catalysis an attractive tool for the commercial synthesis of optically pure compounds. The application of heterogeneous catalysis to enantio- and diastereoselective hydrogenation will now be discussed in more detail.

4.2.3 Enantioselective Hydrogenation

The focus of this Chapter is on the diastereoselective hydrogenation of an optically active pharmaceutical intermediate; however much of the literature surrounding stereoselective heterogeneous hydrogenation is focused on the synthesis of enantiomers, rather than diastereoisomers.

Metal Catalysts Modified with a Chiral Auxiliary

It has been shown that high levels of enantioselectivity can be achieved by modifying the surface of a metal catalyst *via* the adsorption of a chiral auxiliary.[22-27] Perhaps the most famous example of this is the enantioselective hydrogenation of α-ketoesters, such as ethyl pyruvate **(91)** (Scheme 4-3).



Scheme 4-3: Enantioselective hydrogenation of α-ketoesters performed over a heterogeneous Pt catalyst modifed with cinchonidine (92). [28]

Here, the Pt surface is modified using cinchonidine **(92)** and hydrogenation then yields enantiomerically pure (*S*)-ethyl pyruvate **(93)** in 97 % *e.e.*[22,28-30] Baiker *et al.* suggest that the cinchonidine is bonded to the Pt surface through d-π interactions, thus rendering the catalyst surface chiral. The ethyl pyruvate is held in a specific orientation by the cinchonidine *via* hydrogen bonding.[31-33]

In this type of system it is crucial that the chiral auxiliary covers as much of the catalyst surface as possible. If only half of the catalyst active sites are covered with modifier then this will inevitably lead to racemic hydrogenation causing a drop in the overall enantioselectivity of the reaction.

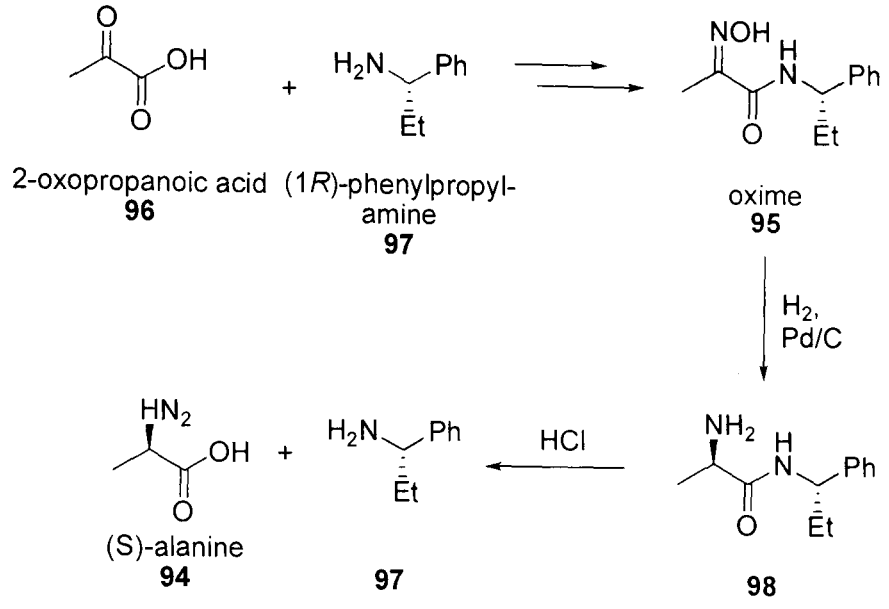
Although it has been shown that high levels of enantioselectivity can be achieved by using this approach it has only been reported for a limited number of reactions and substrates,[22,34] and can only performed efficiently as a batch process.[35]

The Diastereoselective Approach

Although enantiomers are chemically identical, diastereoisomers are not. In this approach to the synthesis of enantiomers from pro-chiral substrates, a covalent bond is formed between the substrate and a chiral auxiliary, thus forming a diastereomeric substrate/ auxiliary complex. The choice of chiral auxiliary is crucial and ideally should satisfy the following criteria[36,37]: (i) be readily available from the chiral pool or inexpensive to synthesise; (ii) easily recoverable; (iii) recyclable without epimerisation of the chiral centre; (iv) possess a chiral centre that is in close proximity to the bond of the substrate that is to be reduced.

Upon hydrogenation it is the substrate/ auxiliary complex which is the source of chirality. The resulting diastereoselectivity depends on the conformational properties of the substrate linked to the chiral auxiliary and also on the mode of adsorption on the catalyst surface. After the hydrogenation step is complete, the auxiliary can be removed to leave the desired product in optically pure form.

This approach can be useful for the synthesis of unnatural amino acids.[37-40] For example, (*S*)-alanine **(94)** can be synthesised by first forming the oxime **(95)** from α-ketoacid **(96)** and (1*R*)-phenylpropylamine **(97)** (Scheme 4-4).[41]

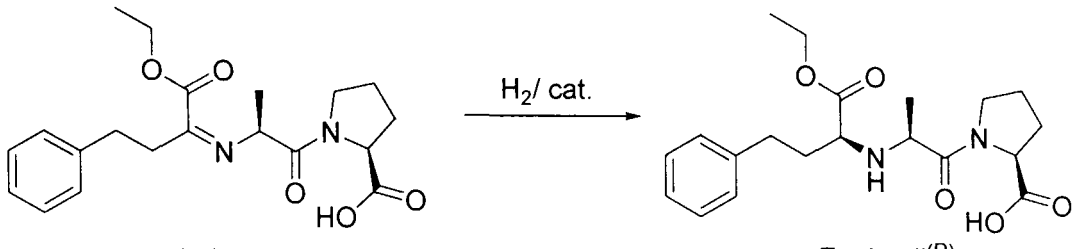


Scheme 4-4: Synthesis of (*S*)-alanine (94) *via* diastereoselective hydrogenation of oxime (95) (58 %Yield, 70 % *e.e.*). [41]

Diastereoselective hydrogenation of oxime **(95)** over Pd/C produces amine **(98)** with 70% *e.e.*. (*S*)-alanine **(94)** can then be obtained by adding strong acid to facilitate hydrogenolysis, leaving the chiral auxiliary **(97)** to be recycled.

4.2.4 Diastereoselective Hydrogenation

The diastereoselective approach to the synthesis of enantiomers, as described above, is a useful introduction to diastereoselective hydrogenation. However, diastereoselective hydrogenation is not restricted to the synthesis of enantiomers. Many pharmaceuticals and agrochemicals contain more than one stereocentre and thus diastereoselective hydrogenation can p rovide an efficient route to a final product or intermediate. For example, the hydrogenation of imine **(99)** was successfully undertaken by Blacklock *et al.* in the synthesis of Enalapril® **(100)**, a drug which is effective in treatment of hypertension (Scheme 4-5).[42]



Scheme 4-5: Synthesis of Enalapril® (100) *via* diastereoselective hydrogenation. [42]

Blacklock *et al.* tested several catalysts for this complex hydrogenation step and found that diastereoselectivity was largely dependent on the type of metal catalyst used. The results of these findings are summarised in Table 4-1. Under optimum conditions using Raney Nickel as catalyst, it was possible to achieve very high levels of diastereoselectivity at a (*S, S, S*):(*R, S, S*) ratio of 95:5.

Table 4-1: Variation in diastereoselectivity for the diastereoselective reduction of imine (99) upon changing the type of catalyst. [42]

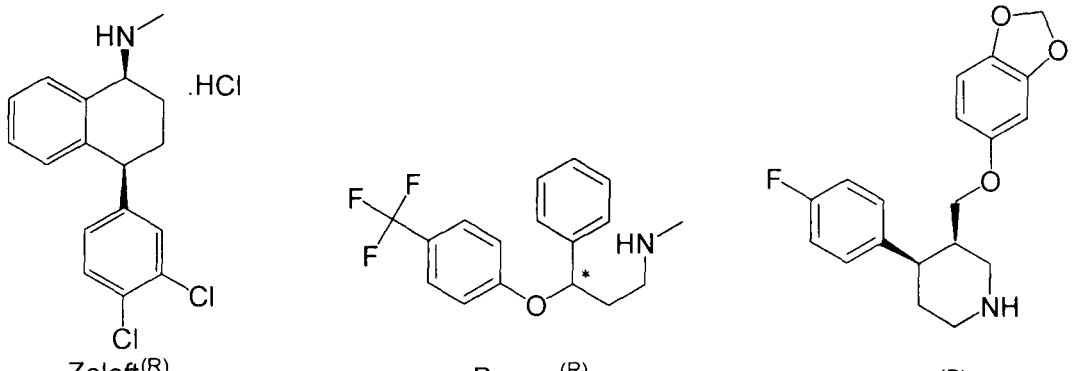
Catalyst	diastereomeric ratio (*SSS*): (*RSS*)
5% Pt/ C	50:50
5% Rh/C	50:50
5% Ru/C	40:60
5% Pd/C	53:47
Raney Nickel	95:5

Heterogeneous hydrogenation can be used for the diastereoselective reduction of various functional groups including C=N[39,43-46], C=O[47-51]and C=C[52-56] groups, as well as of pro-chiral aromatic and heteroaromatics.[57,58] The focus of this Chapter is on diastereoselective reduction of the C=N bond of the pharmaceutical intermediate, sertraline imine.

4.3 *rac*-Sertraline Imine and Zoloft®

4.3.1 Zoloft®

Zoloft® was first developed in the 1980's by Pfizer® when it was found to be effective in the treatment of depression and other anxiety related disorders.[59,60] The active component present in Zoloft® is *cis*-(1*S*, 4*S*)-sertraline hydrochloride **(102)** (Figure 4-3).[61] Zoloft® **(101)**, together with Prozac® **(102)** and Paxil® **(203),** are part of a group of drugs known as selective serotonin reuptake inhibitors (SSRIs). While Zoloft® and Paxil® are sold in enantiomerically pure form, Prozac® is sold in racemic form.



Zoloft(R) 101 Prozac(R) 102 Paxil(R) 203

Figure 4-3: Zoloft® (101), Prozac® (102) and Paxil® (203) are all selective serotonin re-uptake inhibitors (SSRIs).

SSRIs work in the following way: Messages in the brain are passed between nerve cells *via* neurotransmitters, including serotonin. The neurotransmitters are released from the nerve cell into a synapse (the gap between cells) where they are recognised by receptors on the surface of the recipient cell. The symptoms of depression have been attributed to the poor uptake of serotonin at the recipient cell which leads to re-uptake of serotonin at the pre-synaptic nerve cell. SSRIs work by preventing the re-uptake of serotonin at the nerve cell, thus allowing serotonin to stay in the synaptic gap longer than it normally would and therefore giving it a chance to be taken up by the receptors of the recipient cell.[62]

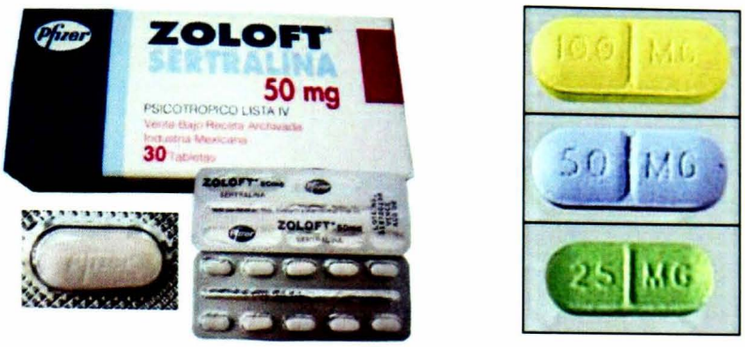


Figure 4-4: Zoloft® - sold as a 25, 50 and 100 mg tablet. [62]

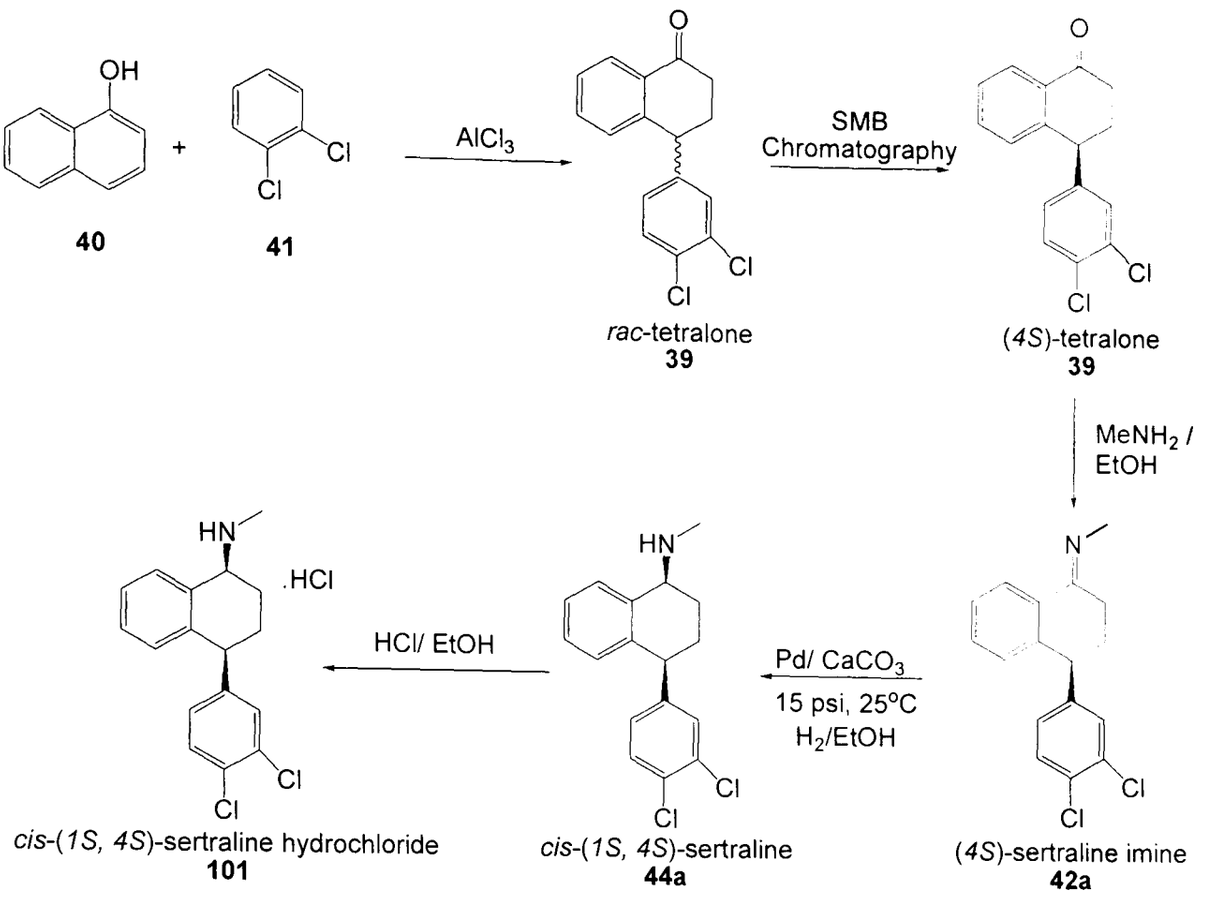
In the United States, Zoloft® is sold in green 25 mg, blue 50 mg or yellow 100 mg tablets (Figure 4–4). In the UK, the brand name drug is called Lustral® and is available as only white 50 mg or 100 mg tablets. Some of the side effects that can occur when taking this drug include insomnia, dizziness, decreased libido and it has also been known to cause weight loss.[63]

In Britain in 2003 the use of Lustral® was controversially banned for people under 18 after studies had shown a link with increasing suicide rates. Similar concerns were raised in the United States, although it was Prozac® that was banned for the treatment of depression in minors.

Despite this controversy, Zoloft® remains a billion dollar selling drug. In 2005, the patent for the brand name drug expired which means Zoloft® will soon be available in generic form around the world.

4.3.2 The Commercial Synthesis of Zoloft®

The commercial synthesis of Zoloft® **(101)** has changed significantly from the original route devised by Pfizer® in the 1980's.[62] Scheme 4-6 shows the current process used by Pfizer to make Zoloft®.[64]



Scheme 4-6: Current Pfizer® route to Zoloft® (101). [64]

Some of the major changes that have been made to the Zoloft® process over the years include the following:

1. Originally a 5-step asymmetric synthesis was used to make the intermediate, (4*S*)-tetralone **(39a)**.[65,66] This method had many drawbacks including the use of expensive and in some cases, dangerous reagents. Furthermore, because of the large number of steps required, the overall yield of (4*S*)-tetralone **(39a)** was very low at 40 %. The intermediate is currently synthesised in racemic form as *rac*-tetralone **(39)** in a single step by combining 1-napthol **(40)** and 1,2-dichlorobenzene **(41)** together with $AlCl_3$.[67] The yield of this step is only 61 % but it is still the most economical route to the tetralone intermediate on a commercial scale.

2. *rac*-Tetralone **(39)** is then resolved using simulated moving bed (SMB) chromatography.[68] The application of this technology represented a substantial risk for Pfizer®, since although it has been successfully applied to the separation of xylenes from C8-aromatics[69], it had never been implemented in a pharmaceutical process. The concept of SMB chromatography is depicted in Figure 4-5 where there are six columns each containing a chiral stationary phase.

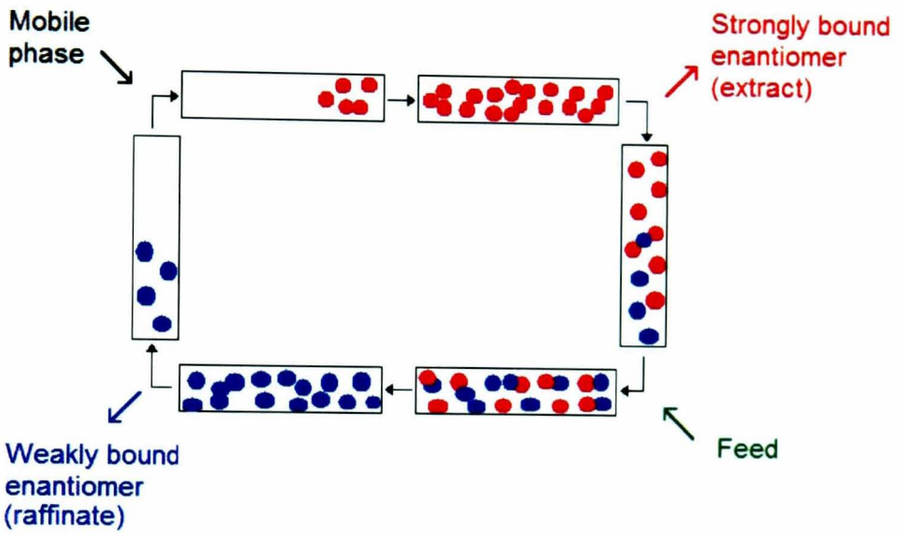
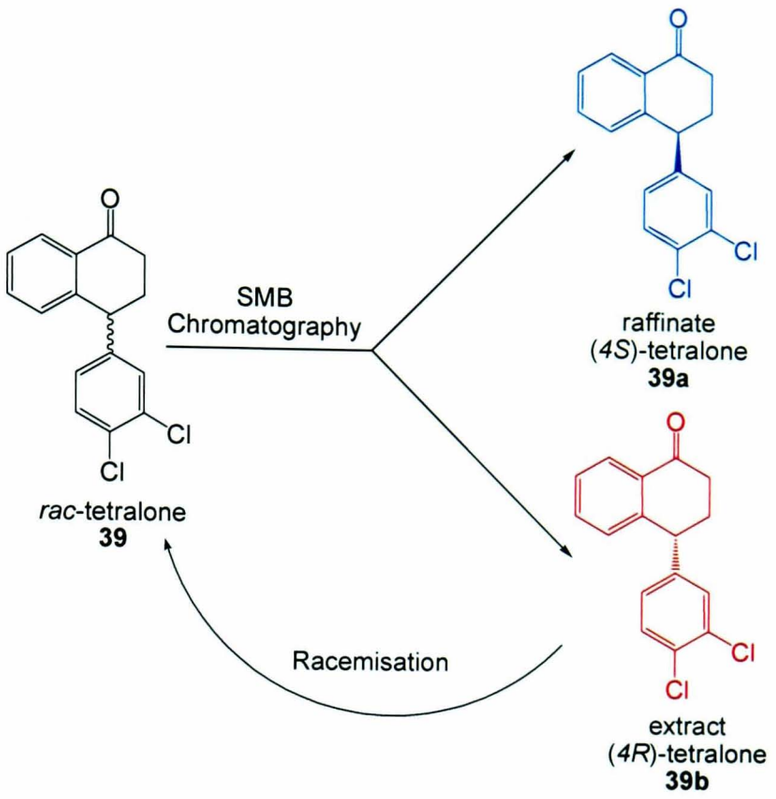


Figure 4-5: A point in time during the Simulated Moving Bed (SMB) Chromatography process which is used to separate *rac*-tetralone (39). [68]

The red and blue circles represent the two enantiomers of *rac*-tetralone, **(39a)** and **(39b)**. (4*R*)-Tetralone **(39b)**, depicted as red circles, is strongly adsorbed to the chiral stationary phase (extract), while (4*S*)-tetralone **(39a)**, depicted as blue circles, is only weakly adsorbed to the stationary phase (raffinate). Figure 4-5 only represents one point in time of feed addition, mobile phase addition, and removal of enantiomers. Moving the points of feed, mobile phase addition and the points of enantiomer removal simulate the moving bed. The unwanted isomer, in this case **(39b)** can be racemised with base and recycled in the separation process to maximize efficiency (Scheme 4-7). SMB chromatography provides the (4*S*)-tetralone **(39a)** in 99.7 % *e.e* and 98.4 % yield.[68]



Scheme 4-7: SMB chromatography was implemented to produce optically pure tetralone (39a).

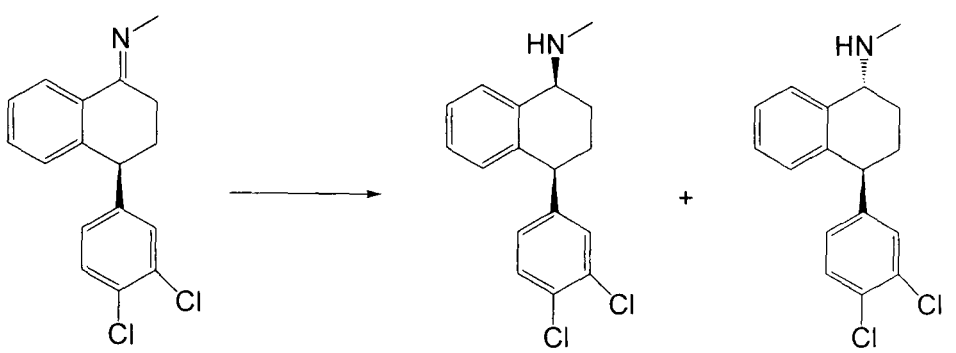
3. $TiCl_4$ was originally needed as a catalyst in the condensation reaction between tetralone **(39a)** and $MeNH_2$. Stringent safety requirements were needed in this step since $TiCl_4$ is extremely reactive. The TiO_2 waste that was generated from this step is also hazardous and therefore had to be disposed of. However, it was found that if the solvent system was changed from THF to EtOH then as the Schiff base **(42a)** was formed, it would precipitate from solution, thus $TiCl_4$ was not required. This avoided the generation of large volumes of TiO_2 waste which was associated with the original process.[70,71]

The improvements made by Pfizer® resulted in the elimination of 440 tons/ year TiO_2 waste and over 40 tons less of the unwanted *trans*-isomer compared with the original commercial route.[72] Solvent requirements were also reduced from 101,400 to 24,000 L/ Kg product. To put that into context, it means that for each Zoloft® tablet (100 mg dose) produced the amount of solvent was reduced from

10.1 to 2.4 L/ tablet. In 2002 Pfizer® were awarded the US Presidential Green Chemistry Award for the changes they had made to the Zoloft® process.[73]

4.3.3 The Reduction of Sertraline Imine

The research discussed in the Chapter focuses on one of the steps in the synthesis toward Zoloft®, the reduction of sertraline imine **(42a)** to make *cis*-(1*S*, 4*S*)-sertraline **(44a)** (Scheme 4-8). Therefore, it is important to review the methods that Pfizer® and other groups have developed over the years to accomplish this step.



(*4S*)-sertraline imine **42a** | *cis*-(*1S, 4S*)-sertraline **44a** | *trans*-(*1R, 4S*)-sertraline **44d**

Scheme 4-8: Diastereoselective reduction of (4*S*)-sertraline imine (42a).

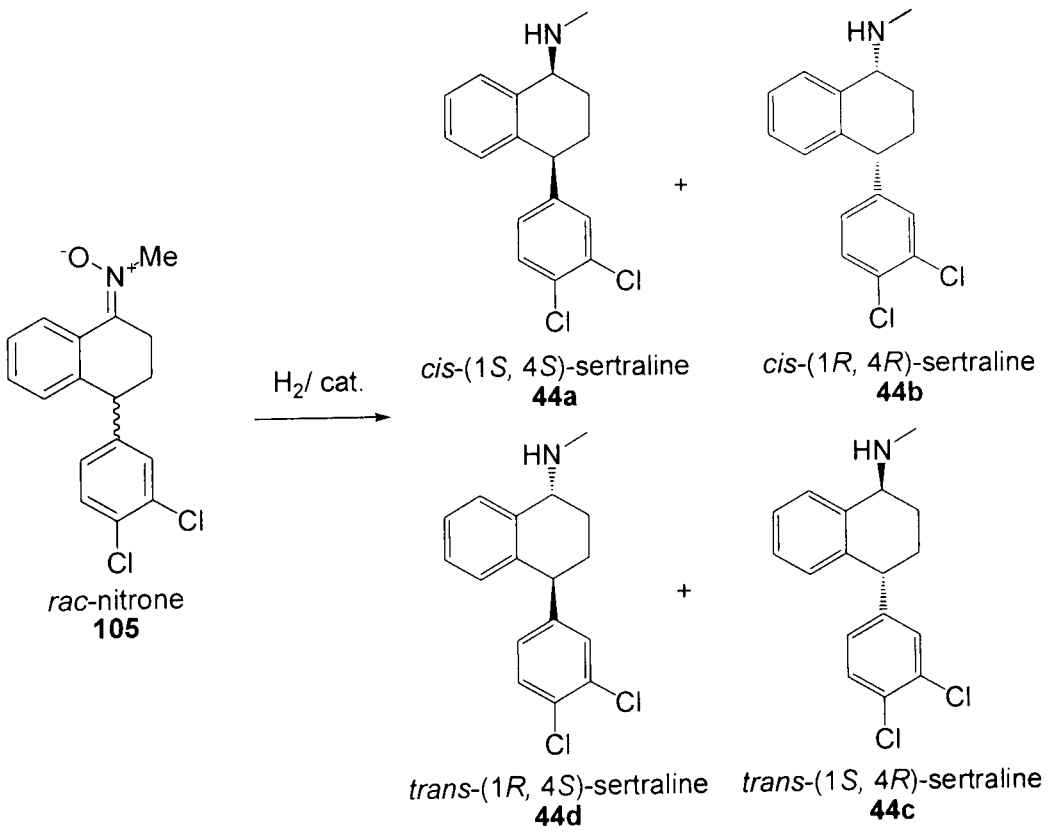
With one stereocentre already in place, diastereoselective reduction of imine **(42a)** was proposed to be the best way to input the second stereocentre. In the earliest stages of process development, $NaBH_4$ was used to reduce imine **(42a)** and produce the diastereomeric amines **(44a)** and **(44d)** as a 50:50 mixture.[62] This method offers no diastereoselectivity and therefore the maximum expected yield from this step can only be 50 %. This method of reduction requires stoichiometric amounts of reagent, making it very atom inefficient.

Hydride reduction was later replaced by catalytic hydrogenation using H_2 over a Pd/C catalyst which led to an increase in the *cis*:*trans* ratio to 70:30.[66] However, the major drawback to this method was dechlorination. When the reaction was

performed over Pd/C, the product mixture was found to contain up to 1.5 % dechlorinated by-products which is still a significant amount in a pharmaceutical process.[74] Solvent intensive recrystallisation steps were needed to remove these dechlorinated by-products and to produce an intermediate of high purity.

To help solve the dechlorination problem a patent was filed in 2002 that claimed the addition of phosphoric acid (or derivatives there-of) to a mixture of the imine in the presence of a Pd catalyst would inhibit dechlorination. Using these inhibitors reduced dechlorinated by-products down to < 0.1 %.[75]

In hope of accessing a new and potentially more efficient route to sertraline, Vukics *et al.* investigated the synthesis of Zoloft® *via* the hydrogenation of *rac*-nitrone **(105)** (Scheme 4-9).[76] The main advantage of using nitrone **(105)** instead of sertraline imine **(42a)** is that the former is more stable and easier to handle.



Scheme 4-9: Synthesis of *cis*-sertraline *via* the reduction of nitrone (105). [76]

Several heterogeneous catalysts were investigated for this hydrogenation step and it was found that the *cis:trans* ratio was dependent upon the choice of catalyst

(Table 4-2). The first catalysts tested were Pd/C and $Pd/CaCO_3$. It was found that although diastereoselectivity was high when using these catalysts, the yield was poor due to dechlorination (Entries 1 & 2, Table 4-2,).

Table 4-2: An alternate route to sertraline *via* the reduction of *rac*-nitrone (105): Changes in diastereoselectivity with choice of catalyst. [76]

Entry	Catalyst	*cis:trans* ratio	Yield of *cis*-sertraline (%)
1	Pd/C	85:15	55
2	$Pd/CaCO_3$	86:14	52
3	Raney Ni	92:8	59
4	PtO_2	60:40	69

(Conditions: Pressure = 1 bar H_2, solvent = MeOH, temp. = r.t.)

Vukics *et al.* found that the most diastereoselective catalyst was Raney Nickel (Entry 3, Table 4-2), which provided a *cis:trans* ratio of 92:2. However, as before, the yield of the reaction was poor at 69 % due to dechlorination. Adam's catalyst, PtO_2, (entry 4, Table 4-2) showed almost no diastereoselectivity, yet still provided the best yield of all the catalysts tested since dechlorination did not occur. This method of reduction was not used on a commercial scale by Pfizer®.

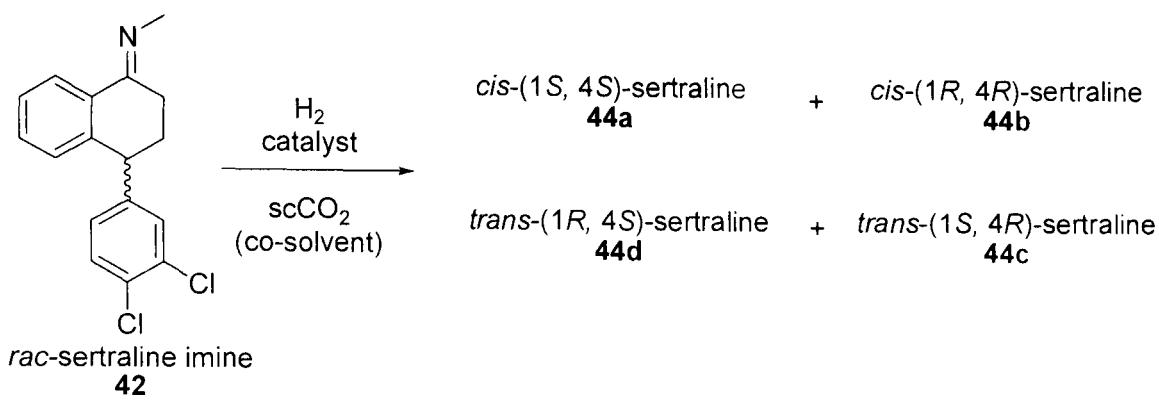
Table 4-3: Methods used by Pfizer® to reduce (4*S*)-sertraline imine (42a). [64,72]

Entry	Reagent\ Catalyst	*cis:trans* ratio	Dechlorinated by-products (%)	Yield (%)
1	$NaBH_4$	50: 50	0.0	50
2	Pd/C	70: 30	1.5	75 - 79
3	$Pd/CaCO_3$	95: 5	1.0	> 94

In the current Pfizer® synthesis of Zoloft®, the reduction of (4*S*)-sertraline imine **(42a)** is performed over a $Pd/CaCO_3$ catalyst, without addition of any dechlorination inhibitors. Under optimum conditions, a *cis:trans* ratio of 95:5 is obtained with < 1.0 % dechlorinated by-products (Entry 3, Table 4-3).[72]

4.3.4 Aims and Objectives

In this Chapter, the hydrogenation of *rac*-sertraline imine **(42)** in high pressure CO_2 is investigated (Scheme 4-10). This substrate was chosen because it offers some very interesting challenges; upon hydrogenation both chemo- and diastereoselectivity must be controlled.



Scheme 4-10: Hydrogenation of *rac*-sertraline imine (42) in $scCO_2$.

Note that the substrate **(42)** is in racemic form. In the pharmaceutical process only the (4*S*)-enantiomer **(42a)** is present but for the purposes of this academic exercise, use of *rac*-sertraline imine **(42)** is sufficient. Upon hydrogenation of the C=N double bond of *rac*-imine **(42)**, a total of 4 stereoisomers of sertraline can possibly be formed. The aim of the studies reported here was to maximise formation of both the *cis*-(1*S*, 4*S*) **(44a)** and *cis*-(1*R*, 4*R*) **(44b)** stereoisomers.

Upon hydrogenation it is not only diastereoselectivity that must be controlled but also chemoselectivity. It has been shown that dechlorination, in particular, can be a significant problem and therefore a great deal of attention has been focused on minimising formation of the dechlorinated by-products.

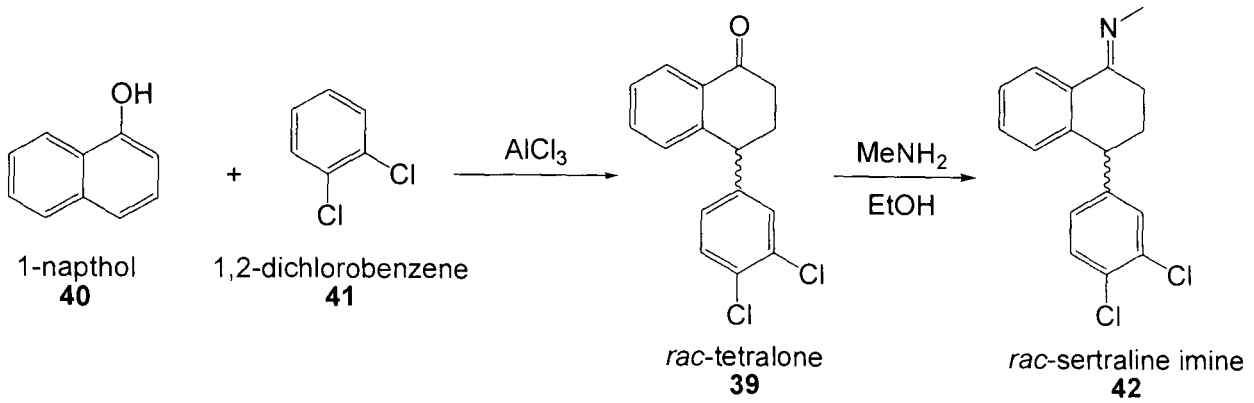
In the commercial Zoloft® process, the hydrogenation of sertraline imine is already very high yielding (> 94 %). However, it is performed as a batch process and a secondary aim of our research has been to investigate whether this reaction can be conducted more efficiently as a continuous flow process in the presence of high pressure CO_2.

4.4 Synthetic Studies

rac-Sertraline imine **(42)** is not commercially available and therefore had to be synthesised before hydrogenation studies could begin. Please refer to Chapter 2.9 for all details of synthetic procedures.

4.4.1 Synthesis of rac-Sertraline Imine

rac-Sertraline imine **(42)** was sythesised in a similar manner to that used in the commercial Zoloft® process (Scheme 4-11). 1-Napthol **(40)** and 1,2-dichlorobenzene **(41)** were combined with $AlCl_3$ in a Friedel-Crafts type reaction to provide *rac*-tetralone **(39)** (Yield=67 %) (Scheme 4-11). $MeNH_2$ was then added to a solution of **(39)** in IPA which afforded the Schiff base, *rac*-sertraline imine **(42)** (Yield=95 %, Purity=99 %).

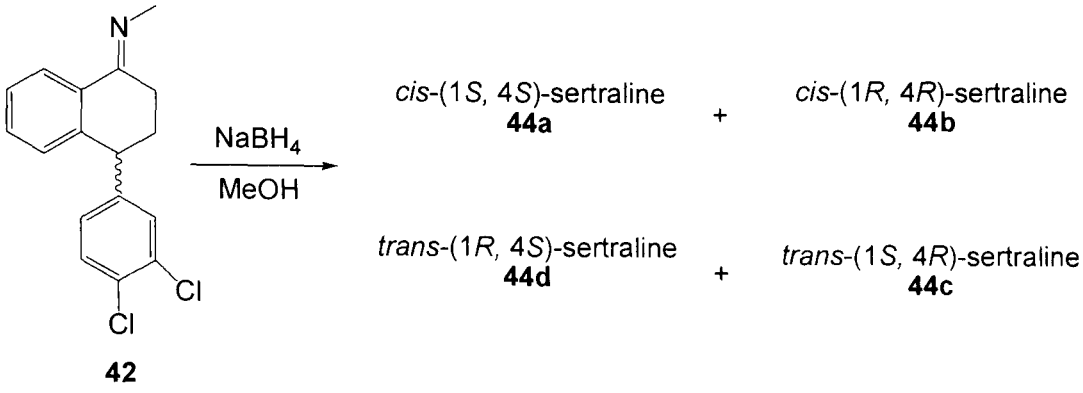


Scheme 4-11: Synthesis of *rac*-sertraline imine (42).

4.4.2 Synthesis of all four sertraline stereoisomers

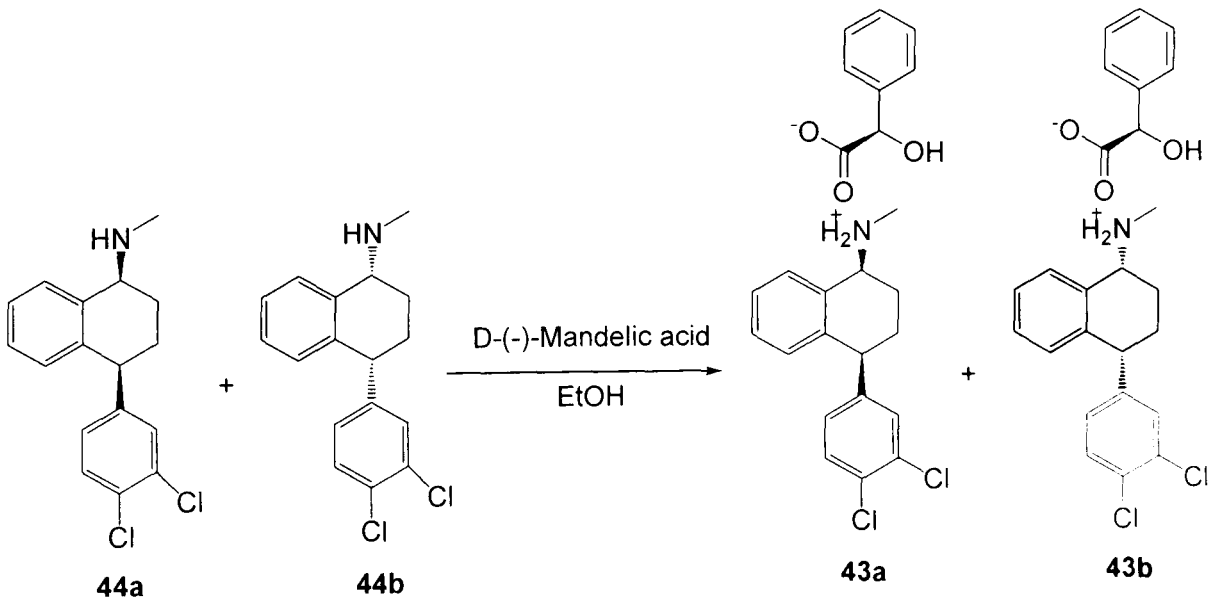
Upon hydrogenation of imine **(42)**, 4 different stereoisomers of sertraline can be formed. During our studies, both GLC and HPLC have been used to measure the diastereoselectivity of this reaction. Therefore, each of the 4 stereoisomers of sertraline had to be synthesised and purified so that they could be used as references for GLC and HPLC analysis.

The first step in obtaining pure sertraline stereoisomers involved reacting imine **(42)** with the reducing agent, $NaBH_4$ (Scheme 4-12). This afforded the 4 sertraline stereoisomers in equal quantities. Column chromatography was then used to separate the *cis*-diastereoisomers **[(44a)** and **(44b)]** from the *trans*-diastereoisomers [**(44c)** and **(44d)**].



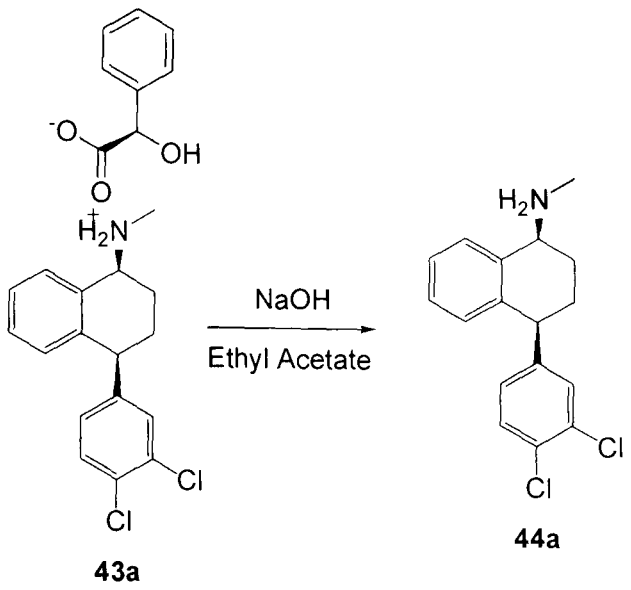
Scheme 4-12: Synthesis and isolation of all four stereoisomers of sertraline, (Part 1 – $NaBH_4$ reduction).

The second synthetic step involved resolution of the two pairs of enantiomers using mandelic acid. For example, *cis*-(1*S*, 4*S*) sertraline **(44a)** was separated from *cis*-(1*R*, 4*R*) sertraline **(44b)** by adding *D*-(–)-mandelic acid to the reaction mixture. The acid reacted with each of the enantiomers to afford the corresponding mandelate salts (Scheme 4-13).



Scheme 4-13: Synthesis and isolation of all four stereoisomers of sertraline, (Part 2 – Selective crystallisation).[60]

One of the mandelate salts remains in solution, whilst the other precipitates and can be separated by filtration. In this example, *cis*-(1*S*. 4*S*)-sertraline mandelate **(43a)** precipitated, leaving *cis*-(1*R*, 4*R*)-sertraline mandelate **(43b)** in solution.[60] The final stage was removal of the mandelic acid residue using NaOH to afford the optically pure sertraline stereoisomer (Scheme 4-14). The *trans*- enantiomers were separated in a similar fashion using *L*-(+)-mandelic acid.



43a **44a**

Scheme 4-14: Synthesis and isolation of all four stereoisomers of sertraline, (Part 3 – Removal of mandelic acid).[60]

The pure sertraline stereoisomers were fully characterised and polarimetry was used to ensure their optical purity (Table 4-4). Note that the higher than expected $[\alpha]_D$ value for **(44a)** may be due to a small impurity present in the polarimetry cell. GLC and HPLC methods were then developed to allow separation of all stereoisomers (see Chapter 2.8 for details).

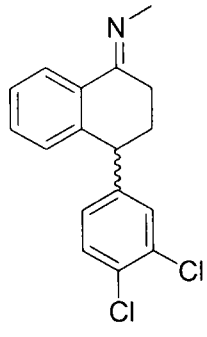
Table 4-4: Polarimetry measurements of pure sertraline stereoisomers.

Sertraline stereoisomer	Observed	Literature *
cis-(1*S*, 4*S*) **(44a)**	$[\alpha]^{19}_D$ +54.7° ($CHCl_3$, *c* 1.00)	$[\alpha]^{23}_D$ +37.9° (MeOH, *c* 2.00)
cis-(1*R*, 4*R*) **(44b)**	$[\alpha]^{20}_D$ –32.0° ($CHCl_3$, *c* 1.00)	$[\alpha]^{23}_D$ –37.2° (MeOH, *c* 2.00)
trans-(1*S*, 4*R*) **(44c)**	$[\alpha]^{20}_D$ –15.5° ($CHCl_3$, *c* 1.00)	$[\alpha]^{22}_D$ –39.2° (MeOH, *c* 2.00)
trans-(1*R*, 4*S*) **(44d)**	$[\alpha]^{20}_D$ +15.7° ($CHCl_3$, *c* 1.00)	$[\alpha]^{22}_D$ +41.0° (MeOH, *c* 2.00)

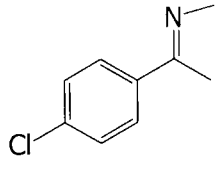
(Note that literature values are for the hydrochloride salt and not the free base [60])*

4.5 Hydrogenation Studies on a Model Substrate

Before commencing hydrogenation studies on an active pharmaceutical it was decided that a model system should first be studied. Therefore (*E*)-*N*-[1-(4-chlorophenyl)ethylidene]methanamine **(36)** was chosen as a model substrate. The key structural similarities between the model compound **(36)** and *rac*-sertraline imine **(42)** are that both contain a secondary imine, as well as the potentially problematic aryl-chloro groups (Figure 4-6).



rac-sertraline imine
42



(*E*)-*N*-(1-(4-chlorophenyl)ethylidene)-methanamine
36

Figure 4-6: Structural similarities between the imine (42) and the model substrate (36) include, an aryl chloro groups and a secondary imine.

The key challenges that were to be addressed during the model studies were dechlorination and carbamate formation:

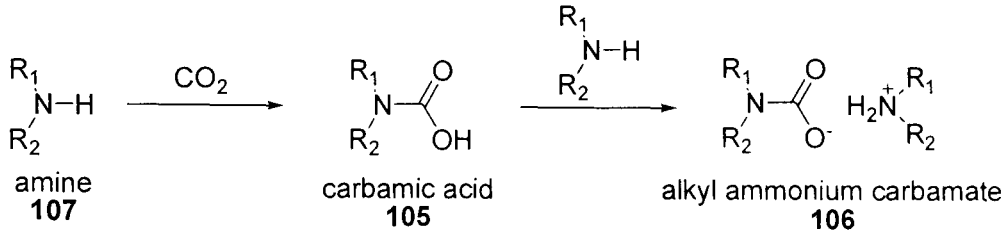
Dechlorination

From the history of the Zoloft® process, it is evident that dechlorination is a major problem when performing the hydrogenation of sertraline imine.[64,72,76] This is because a Pd catalyst is used which is active toward dechlorination. In fact, Pd catalysts are often the catalyst of choice for the treatment of chlorinated organic waste.[77-79] The choice of Pd as catalyst in the Zoloft® process was therefore most likely to be a compromise between activity toward diastereoselective imine hydrogenation, and the unwanted side reaction of dechlorination.

It was hoped that the model studies on imine **(36)** would be useful in assessing the level of dechlorination that might be expected when performing the continuous flow hydrogenation of *rac*-sertraline imine **(42)** in the presence of CO_2.

Carbamate Formation

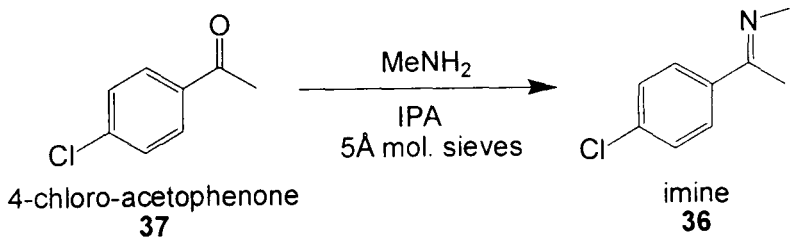
One of the main criteria for CO_2 as a solvent in our system is that it should be inert. However, it is known that CO_2 can react with amines to form carbamic acid **(105)** and carbamates **(106)** (Scheme 4-15).[80-83]



Scheme 4-15: CO_2 can react with amines to produce carbamates. [80-83]

If carbamates were to form, then it is possible that they would precipitate and block the continuous flow reactor. It was hoped that carbamate formation would be avoided in our system by using a substrate which will form an aromatic, rather than aliphatic amine upon hydrogenation. The NH group should therefore be insufficiently basic to react with CO_2 since its electrons will be delocalised into the aromatic ring.

4.5.1 Synthesis of the Model Substrate

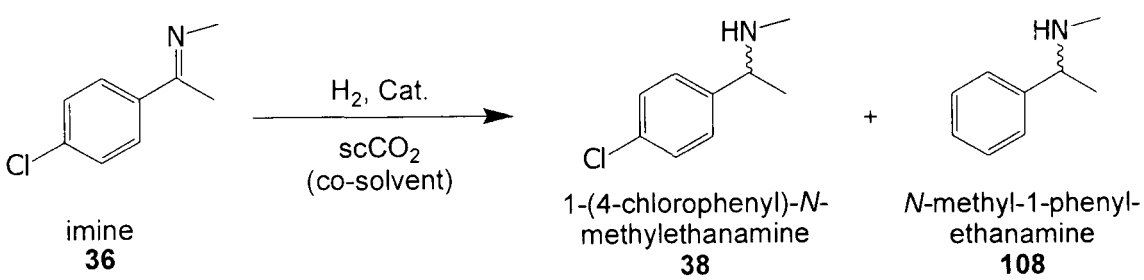


Scheme 4-16: Synthesis of model substrate, imine (36). [71]

(*E*)-*N*-[1-(4-chlorophenyl)ethylidene]methanamine **(36)** is not commercially available and therefore had to be synthesised. This was achieved *via* a condensation reaction between *p*-chloro-acetophenone **(37)** and methylamine (Scheme 4-16) to yield one product, imine **(36)** (Yield=95 %). Molecular sieves were used in this step to remove the water and drive the reaction to completion[71,84]

4.5.2 Hydrogenation of the Model Substrate

With the model substrate synthesised it was possible to begin the hydrogenation studies. It was hoped that the major product upon hydrogenation would be the chlorinated amine **(38)**. If dechlorination did occur then amine **(108)** would most likely be formed (Scheme 4-17). All hydrogenation experiments were conducted on the small-scale continuous flow apparatus.



Scheme 4-17: Hydrogenation of model substrate in $scCO_2$.

4.5.3 Initial Studies over Pd/C

Supported Pd catalysts are used in the commercial Zoloft® process and therefore Pd/C was the first of the catalysts tested for the model system (Table 4-5). In all flow studies a co-solvent had to be used since imine **(36)** is a solid and solids cannot be pumped efficiently. MeOH, a solvent commonly used in imine hydrogenation reactions, was the co-solvent of choice.[85] Hydrogenation of imines is usually conducted at low temperature, therefore the hydrogenation was first conducted at 40 °C (entry 1, Table 4-5).

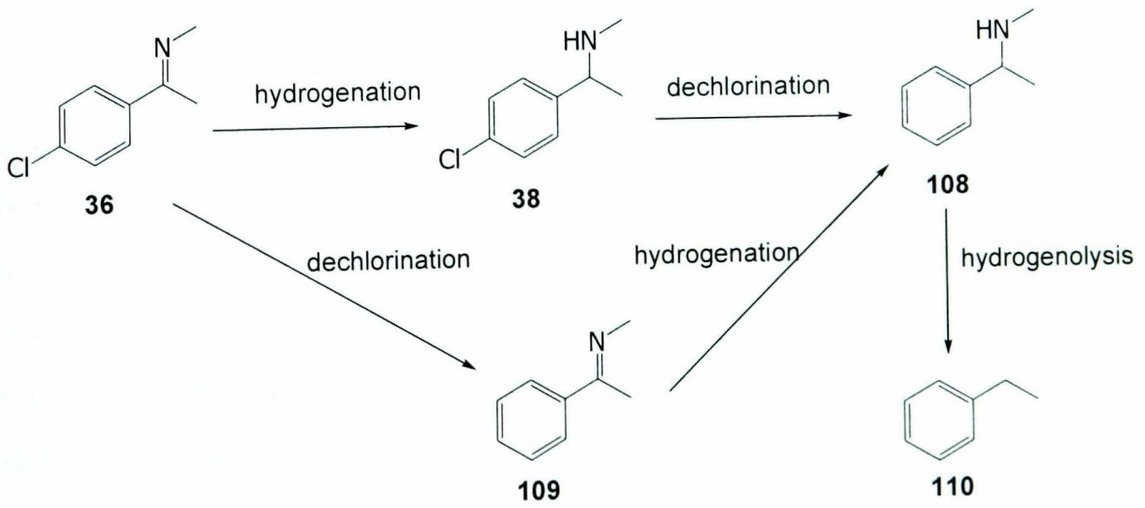
Table 4-5: Continuous flow hydrogenation of imine (36) over Pd/C.

Entry	Cat.	Temp. °C	Co-solvent	Conversion %	Chemoselectivity %			
					(38)	(108)	(109)	(110)
1	Pd/C	40	MeOH	94	12	84	4	0
2	Pd/C	80	MeOH	97	1	70	3	26
3	Pd/C	120	MeOH	98	0	41	2	57

(Conditions: reactor type = (iii), system pressure = 175 bar, CO_2 flow rate = 1.0 mL/ min, organic flow rate = 0.4 mL/ min, mass of 2 % catalyst = 0.8 g, H_2 to substrate ratio = 3:1, solution concentration = 0.2 M)

At 40 °C, near quantitative conversion of imine **(36)** was achieved, however, selectivity towards the desired product, chloro-amine **(38)** was very poor at only 12 %. The major product was the dechlorinated amine **(108)**. Dechlorination of the starting material also resulted in formation of imine **(109)**.

To understand how this reaction proceeded at higher temperature, reactions were conducted at 80 and 120 °C (Entries 2 & 3, Table 4-5). It was found that upon increasing temperature, the amount of dechlorination increased, but also C-N bond hydrogenolysis was also taking place, leading to formation of ethyl-benzene **(110)**. At 120 °C none of the desired product was found in the reaction mixture, it had all further reacted in dechlorination and hydrogenolysis reactions.



Scheme 4-18: Possible reaction pathways during hydrogenation of imine (36) over a Pd/C catalyst.

From these initial experiments, it was possible to map all the reaction pathways that had been found for hydrogenation of imine **(36)** (Scheme 4-18). Note that hydrogenation of the aromatic ring did not occur under any of the reaction conditions. All reaction products that were not commercially available were identified using GC-MS and NMR. Quantitative GC analysis was possible using response factors of structurally similar compounds. Ethyl-benzene **(110)**, which is commercially available, was identified using an authentic sample for reference.

4.5.4 Hydrogenation over Pt/C - Minimising Dechlorination.

Although it was known that Pd catalysts are active toward dechlorination, it was not anticipated that dechlorination would occur to such an extent, particularly given that Pfizer® use a palladium catalyst in the Zoloft® process.

At this point, dechlorination was so prevalent over the Pd/C catalyst, that two options were investigated to improve chemoselectivity: (i) inhibitors, such as phosphoric acid, could be tested to try and suppress the dechlorination reaction, or (ii) the catalyst could be switched from Pd to a different metal catalyst that would be active toward C=N hydrogenation, but was less likely to promote dechlorination.

In our research toward a more efficient Zoloft® process, the use of additives, such as phosphoric acid, is not ideal, since any additives would have to be removed downstream in a commercial process. This would inevitably reduce the atom efficiency of the hydrogenation step. Fortunately, Pt catalysts are known to be less active toward dechlorination but still be active toward imine hydrogenation.[86] Therefore, the next step was to test a Pt/C catalyst for the hydrogenation of model substrate **(36)** (Table 4-6).

At 40 °C (Entry 1, Table 4-6) the activity of the Pt catalyst was not quite as high as the Pd/C; as reflected by a lower conversion of 78 %. However, the most

important point was that no by-products were detected, giving a 100 % chemoselective reaction. Upon increasing the reaction temperature to 80 °C (entry 2, Table 4-6), near quantitative conversion to the desired chloro amine was achieved with no other products detected.

Table 4-6: Continuous flow hydrogenation of imine (36) in $scCO_2$ over a Pt/C catalyst.

Entry	Cat.	Temp. °C	Co-solvent	Conversion %	Chemoselectivity %			
					(38)	(108)	(109)	(110)
1	Pt/C	40	MeOH	74	100	0	0	0
2	Pt/C	80	MeOH	99	100	0	0	0

(Conditions: reactor type = (iii), system pressure = 175 bar, CO_2 flow rate = 1.0 mL/ min, organic flow rate = 0.4 mL/ min, mass of 2 % catalyst = 0.8 g, H_2 to substrate ratio = 3:1, solution concentration = 0.2 M)

4.5.5 Variation in Co-solvent

Having found a catalyst that would avoid dechlorination, it was important to screen other co-solvents. In all of the hydrogenation studies discussed thus far, MeOH had been used as co-solvent. However, it was found that the pharmaceutical intermediate, imine **(42)** was insoluble in MeOH. Therefore, other co-solvents were screened for the model system.

By testing a range of organic solvents, it was found that *rac*-sertraline imine **(42)** was soluble in both toluene and THF. Both of these were tested as co-solvents for the hydrogenation of imine **(36)**.

Under reaction conditions identical to those used previously, it was found that the choice of co-solvent had no effect on reaction selectivity and that no dechlorination was observed over the Pt/C catalyst. Conversion was slightly higher when THF was used as co-solvent, compared with the same reaction in toluene, however, a difference of only 4 % was not considered to be significant.

Table 4-7: Continuous flow hydrogenation of imine (36) over Pt/C using different co-solvents.

Entry	Co-solvent	Conversion %	Chemoselectivity %			
			(38)	(108)	(109)	(110)
1	MeOH	99	100	0	0	0
2	Toluene	94	100	0	0	0
3	THF	98	100	0	0	0

(Conditions: reactor type = (iii), system pressure = 175 bar, CO_2 flow rate = 1.0 mL/ min, organic flow rate = 0.4 mL/ min, mass of 2 % Pt/C catalyst = 0.8 g, temp. of reactor = 80 °C, H_2 to substrate ratio = 3:1, solution concentration = 0.2 M)

4.5.6 Summary of Results from Model System

The most important point is that dechlorination occurs readily when performing the hydrogenation of imine **(36)** in $scCO_2$ over Pd/C, even at low temperature. This level of dechlorination was not anticipated, given that Pfizer® use a Pd catalyst in the Zoloft® process where dechlorinated by-products are formed in only ~1 % of the product mixture.

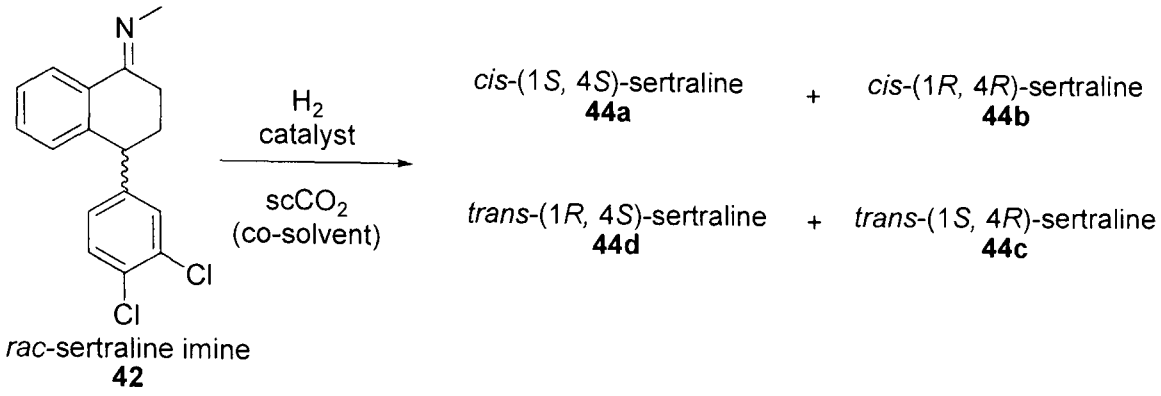
To avoid dechlorination of imine **(36)** a Pt/C catalyst was tested. Pleasingly, it was found to be active toward imine hydrogenation but also completely 100 % chemoselective. At this point in our studies it was unclear whether Pt/C would be a suitable catalyst for future studies on the pharmaceutical intermediate since it would have to exhibit high levels of diastereoselectivity, and chemoselectivity.

Various co-solvents were tested for the hydrogenation of imine **(36)** over Pt/C. It was found that THF was the best candidate for future studies on *rac*-sertraline imine **(42)**.

The final point from the model studies is that carbamate formation was not a problem. It is believed that the aromatic amine that was formed upon hydrogenation of the imine **(36)** is not sufficiently basic to react with CO_2.

4.6 Hydrogenation of *rac*-Sertraline Imine in $scCO_2$

With the model studies and the initial synthesis complete it was possible to begin studies on the continuous flow hydrogenation of *rac*-sertraline imine **(42)** (Scheme 4-19).



Scheme 4-19: Hydrogenation of *rac*-sertraline imine (42).

4.6.1 Varying Catalyst Metal and Support

To begin our studies on the continuous flow hydrogenation of imine **(42)** the same Pt/C catalyst was tested, under the same reaction conditions as those used in the model studies (entry 1, Table 4-8).

Table 4-8: Variation in the catalyst metal/ support combination for the continuous flow hydrogenation of *rac*-sertraline imine (42).

Entry	Cat.	Co-solvent	Conver[n] %	*cis:trans* ratio	Chemoselectivity %		
					sertraline isomers	dechlor[d] by-prod[s]	unknown
1	Pt/C	THF	98	56:44	100	0	0
2	Pd/C	THF	98	87:13	94	3	3
3	$Pd/CaCO_3$	THF	98	95:5	96	2	2

(Conditions: reactor type = (iii), system pressure = 175 bar, CO_2 flow rate = 1.0 mL/ min, organic flow rate = 0.4 mL/ min, mass of 5 % catalyst = 0.5 g, temp. of reactor = 80 °C, H_2 to substrate ratio = 3:1, solution concentration = 0.2 M)

Pleasingly, it was found that the reaction was 100 % chemoselective and no dechlorinated by-products were detected. However, in this reaction, diastereoselectivity is just as important as chemoselectivity and, disappointingly,

Pt/C showed almost no differentiation between forming the *cis*- or *trans*-diastereoisomers; this was reflected in a *cis:trans* ratio of 43:57.

It is interesting that Vukics and co-workers also reported a similarly poor level of diastereoselectivity for the hydrogenation of *rac*-nitrone **(104)**, a very similar molecule to imine **(42)**, when the reaction was performed over a Pt catalyst (refer back to Table 4-2).

The initial studies show that although Pt is inactive toward dechlorination, it is not a suitable catalyst for this reaction since it offers little diastereoselectivity. It was decided to abandon the Pt catalyst, and to revert to Pfizer®s conditions and test a Pd catalyst. It was hoped that the pharmaceutical intermediate **(42)** would be less active toward dechlorination than the model substrate, imine **(36)** and that the Pd catalyst would exhibit higher levels of diastereoselectivity than had been observed for the Pt catalyst (Entry 2, Table 4-8).

Pleasingly, it was found that although dechlorination does occur over Pd/C, it is not as prevalent as in the model system. This was reflected in only 3 % chemoselectivity toward dechlorinated by-products, compared with 70 % for the model system (Entry 2, Table 4-5). One possible explanation for the difference in dechlorination activity is that imine **(36)** was activated toward dechlorination, whereas the pharmaceutical *rac*-sertraline imine **(42)** is not.

Imine **(36)** is activated because it is part of a conjugated aromatic system, and therefore the extended π-system of imine **(36)** is likely to interact more strongly with the catalyst surface than the aromatic system of *rac*-sertraline imine **(42)** which consists of just one phenyl ring. The donating effect of the nitrogen on imine **(36)** would further increase the electron density of the aromatic system. On the other hand, the nitrogen group of *rac*-sertraline imine **(42)** is so far away from the unsaturated aryl-Cl groups that it does not have the same activating effect as

imine **(42)**. Taken together, these effects could lead to an increase in the rate of dechlorination of imine **(36)** compared with the pharmaceutical imine **(42)**.

Diastereoselectivity was also significantly improved over Pd clearly favouring formation of the desired *cis*- diastereoisomers (*cis*:*trans* ratio of 87:13). The differences in diastereoselectivity for the Pd and Pt catalysts can be explained by considering that Pd and Pt each have different electronic properties and therefore will have a different affinity for the substrate, imine **(42)**. The changes in diastereoselectivity can then be rationalised by considering the mechanism of heterogeneous hydrogenation. If it is considered to occur *via* the step-wise addition of H_2, then it is possible that the rate of addition of the second proton is much slower over Pt, than over Pd. If this were true, then rotation of the N-C bond may have time to take place during this transition state, which would allow attack of the second proton from the opposite face of the molecule, producing the *trans*-diastereoisomers.

The results discussed thus far show that the choice of catalyst metal is crucial for the chemo- and diastereoselective hydrogenation of imine **(42)**. However, in the commercial Zoloft® process a change in the catalyst support from Pd/C to $Pd/CaCO_3$ was also reported to improve diastereoselectivity significantly and to a lesser extent, chemoselectivity. To find out how the catalyst support affected the continuous flow hydrogenation of *rac*-sertraline imine in CO_2, a $Pd/CaCO_3$ catalyst was tested (Entry 3, Table 4-8).

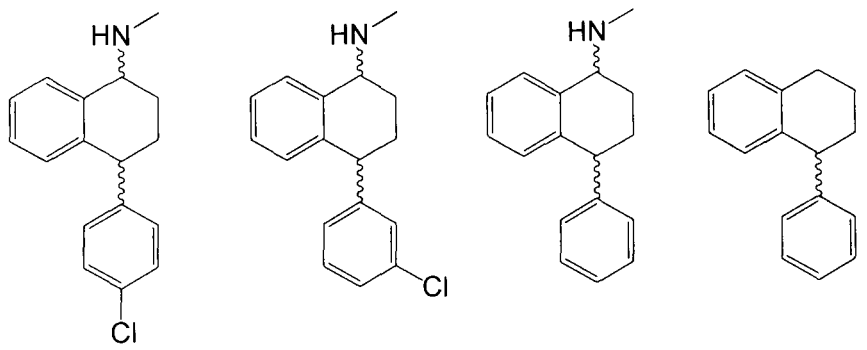
It was found that the same high level of diastereoselectivity as that reported in the batch Pfizer® process could be achieved (*cis*:*trans* ratio of 95:5). Changes in diastereoselectivity with catalyst support are not limited to sertraline imine and have also been reported for the diastereoselective hydrogenation of other substrates.[36,54] The difference in diastereoselectivity can be attributed to the subtle changes in the electronic properties of the catalyst metal which are brought about by changing the metal support.[87,88] These small changes in diastereoselectivity can

then be rationalised in a similar manner to that described above, in that a change in catalyst support can affect the rate of addition of the second proton in the hydrogenation mechanism.

By changing the metal support from carbon to $CaCO_3$, the selectivity toward dechlorinated by-products was also reduced from 3 % to 2 % compared with the same reaction over Pd/C. Again, this difference could be attributed to changes in the electronic interaction between the substrate and catalyst metal upon changing catalyst support.

4.6.2 By-products

So far, chemoselectivity has been compared between the sertraline stereoisomers, dechlorinated by-products, and a by-product labelled "unknown". The dechlorinated by-products that can be formed during the hydrogenation of *rac*-sertraline imine **(42)** over a Pd catalyst are shown in Figure 4-7. GC-MS was used to identify all by-products.



111 **112** **113** **114**

Figure 4-7: By-products formed *via* dechlorination or C-N hydrogenolysis during the hydrogenation of *rac*-sertraline imine over a Pd catalyst.

The *mono*- [**(111)** and **(112)**] and *bis*- **(113)** dechlorinated by-products have been reported in previous literature on Zoloft®.[72] By-product **(114)** has not been reported before, but is formed through hydrogenolysis of the C-N bond of **(113)**. This by-product is only seen in reactions performed at high temperature (> 80 °C).

which is consistent with the pattern of by-product formation seen in the model system.

Dechlorination has been the major contributor to poor levels of chemoselectivity during the hydrogenation of imine **(42)** over Pd catalysts. However, the by-product labeled as "unknown" in the results tables was present in all product mixtures that were collected from continuous flow experiments. In most of the continuous flow studies, the unknown by-product was present at ≤ 3.0 % in product mixture composition. However, in one particular experiment the unknown was present as the major product representing 47 % product mixture composition (Figure 4-8). This was based on a calculation assuming that the response factor of the unknown was the same as that of imine **(42)**.

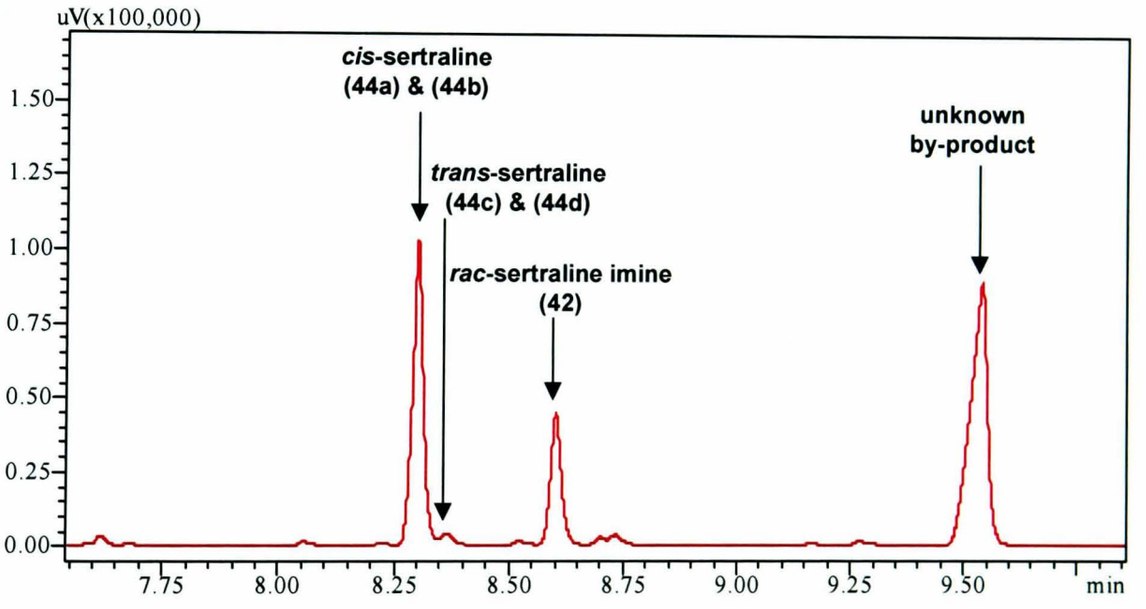


Figure 4-8: GLC chromatogram showing presence of unknown by-product present in 47 % of the reaction mixture.

(Conditions: reactor type = (iii), system pressure = 175 bar, CO_2 flow rate = 1.0 mL/ min, organic flow rate = 0.4 mL/ min, mass of 5 % Pd/$CaCO_3$ catalyst = 0.5 g, temp. of reactor = 80 °C, H_2 to substrate ratio = 3:1, solution concentration in THF = 0.2 M)

The presence of an unknown by-product at > 1.5 % composition would be unacceptable in a commercial process; therefore studies were directed away from optimisation and focused on identifying the unknown by-product.

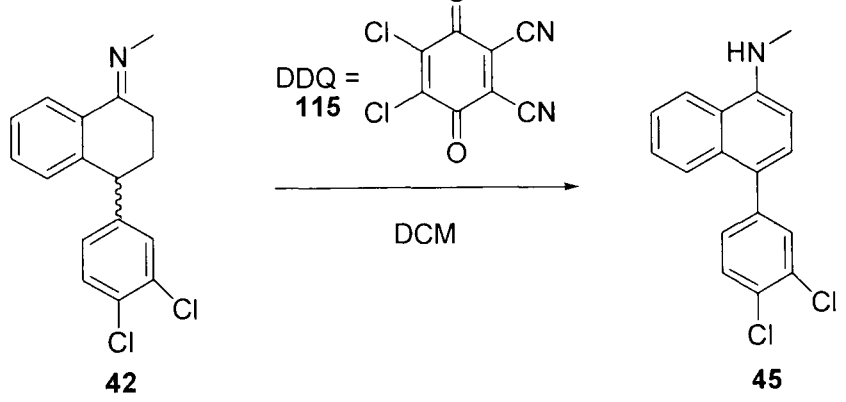
GC-MS was again used as the main analytical tool to help identify this by-product. It showed that the unknown had a very similar molecular ion to that of the starting material, *rac*-sertraline imine (Table 4-9). Also, the existence of multiple molecular ions was consistent with the presence of two chloro groups in the structure.

Table 4-9: Mass-spec data for unknown by-product and imine (42).

Name of compound	$([M+H]^+)$ *
rac-sertraline imine **(42)**	304. 07
Unknown	302.12

** LRMS performed by ESI*

Taking into account the mass-spec data, it was decided that the unknown by-product could have been formed *via* dehydrogenation. This would explain the loss of two protons. To test this idea the dehydrogenation of imine **(42)** was attempted *via* reaction of **(42)** with Dichloro Dicyano Quinone (DDQ) **(115)** (Scheme 4-20).

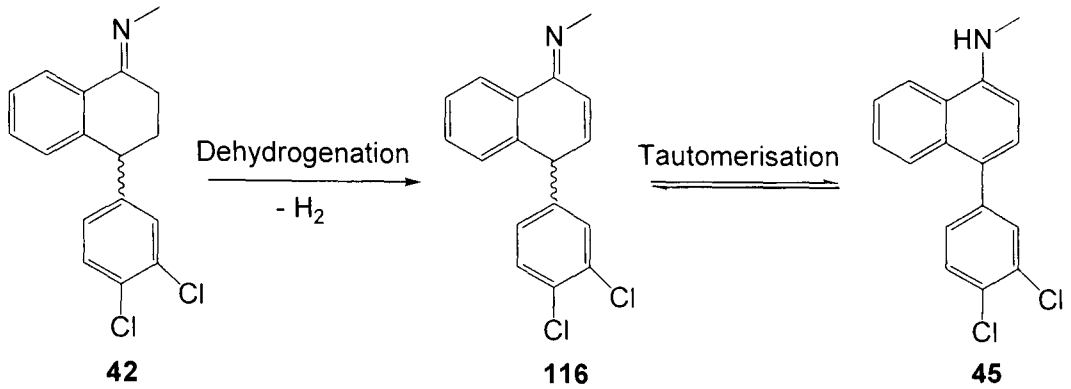


Scheme 4-20: Dehydrogenation of *rac*-sertraline imine (42) using DDQ (115)

DDQ **(115)** is a mild hydride transfer reagent and there are many examples of it being used in the literature for selective dehydrogenation reactions.[89,90] ^{1}H NMR was used to analyse the product mixture from the DDQ dehydrogenation experiment and it was found to contain only product, 4-(3,4-dichlorophenyl)-*N*-methylnaphthalen-1-amine, or, conjugated sertraline **(45)**, as it will be labelled from now on.

4.6.3 Dehydrogenation of rac-Sertraline Imine

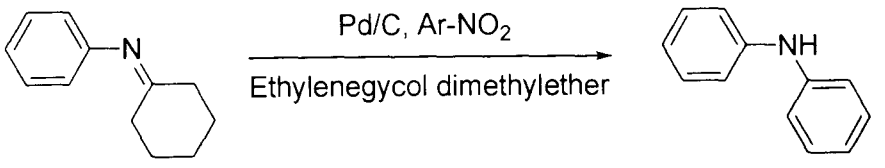
It is believed that conjugated sertraline **(45)** was formed *via* dehydrogenation to produce the intermediate **(116)** (Scheme 4-21), although this intermediate was never isolated from our reaction mixture. It is likely that intermediate **(116)** would then undergo aromatisation to produce amine **(45)**. This is likely to be highly favorable since it would result in a conjugated system.



42 **116** **45**

Scheme 4-21: Proposed reaction mechanism for formation of conjugated sertraline (45) from *rac*-sertraline imine (42).

Formation of conjugated sertraline **(45)** has not been reported in any of the previous Zoloft® literature. However, dehydrogenation is not an altogether unexpected transformation in the presence of a Pd catalyst.[91] For instance, diphenylamine **(117)** can be formed *via* dehydrogenation of imine **(118)** by performing the reaction at temperatures between 140-200 °C, in the presence of a Pd/C catalyst and a H_2 acceptor such as nitrobenzene (Scheme 4-22).[92]

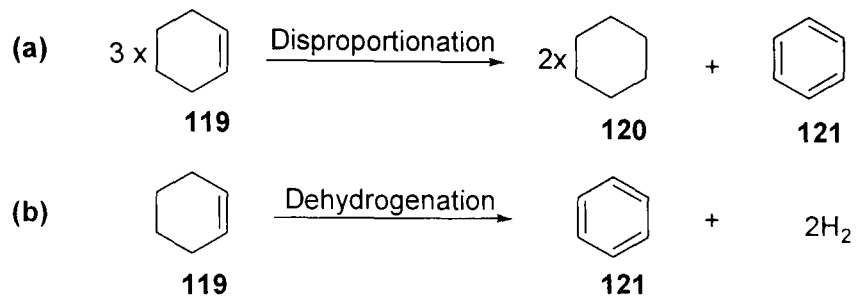


N-cyclohexylidenebenzenamine
118

diphenylamine
117

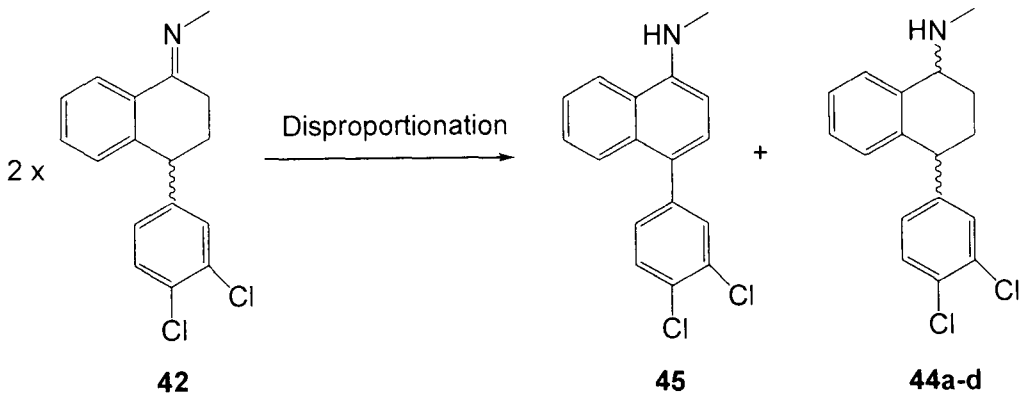
Scheme 4-22: Example of a dehydrogenation reaction carried out in the presence of a Pd catalyst. [92]

Most of the examples of dehydrogenation over metal catalysts in the literature are of relatively simple substrates, such as vinylcyclohexene or limonene.[93-97] There have also been some very interesting studies on cyclohexene **(119)**, where it has been found that two competitive reaction pathways can take place; dehydrogenation and disproportionation. The extent of these transformations can be inferred from the ratio of **(120)**:**(121)** (Scheme 4-23).[98,99]



Scheme 4-23: Reactions of cyclohexene in the absence of H_2 and over a Pd catalyst; at low temperature (< 90 °C) both routes (a) and (b) occur at a similar rate; as temperature is increased, route (b) predominates. [98,99]

In the case of cyclohexene, it was found that when the reaction is performed over Pd/C, disproportionation prevails at low temperature (< 90 °C). Dehydrogenation then competes to an increasing degree as the temperature is increased.



Scheme 4-24: *rac*-Sertraline imine (42) could undergo disproportionation (displayed here), as well as dehydrogenation.

From our results, it is known that *rac*-sertraline imine **(42)** can undergo dehydrogenation to form conjugated sertraline **(45)**. However, it would be interesting to discover whether imine **(42)** shares some of the same reactivity as

cyclohexene **(119)** and participates, not only in dehydrogenation, but in intermolecular hydrogen transfer *via* a disproportion reaction (Scheme 4-24).

To test this theory, a solution of imine **(42)** was pumped over the $Pd/CaCO_3$ catalyst bed, at different temperatures and in the absence of H_2. The products were then analysed by GLC and the ratio of hydrogenated to dehydrogenated products plotted against temperature (Figure 4-9). If it was found that the ratio was equal to 1.0, then it is likely that only disproportionation was taking place over the catalyst surface. If, however, the ratio was closer to zero, then it is likely that only dehydrogenation was occurring.

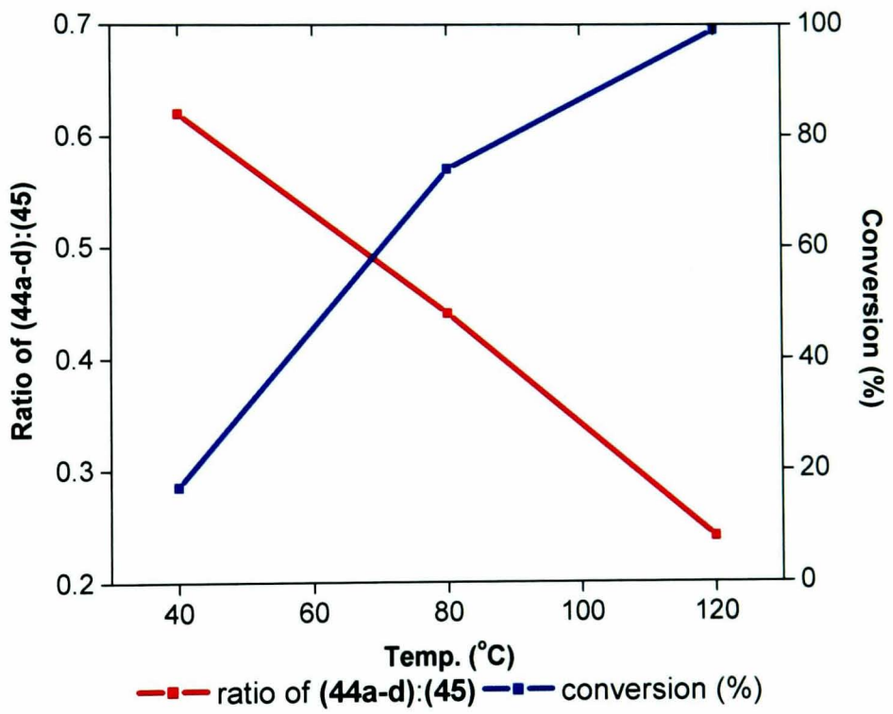


Figure 4-9: Ratio of hydrogenated to dehydrogenated products [(44a-d):(45)] formed in the presence of imine (42) and $Pd/CaCO_3$, in the absence of H_2.

(Conditions: reactor type = (iii), system pressure = 175 bar, CO_2 flow rate = 1.0 mL/ min, organic flow rate = 0.4 mL/ min, mass of 5 % $Pd/CaCO_3$ catalyst = 0.6 g, no H_2, solution concentration in THF = 0.03 M)

At 40 °C, the ratio of **(44a-d):(45)** is high at 0.62, indicating that both dehydrogenation and disproportionation are occurring at the same time. The driving force for disproportionation and dehydrogenation at low temperature is likely to be aromatization and conjugation. As the temperature is increased, the

ratio of hydrogenated to dehydrogenated products decreases, until the temperature is 120 °C, at which point the ratio of **(44a-d)**:**(45)** is 0.24. As temperature increases, so too does conversion of imine **(42)**. At 120 °C, almost none of the starting material, imine **(42)** was detected.

The change in product distribution with temperature that has been found in this set of experiments is very similar to that of cyclohexene; at higher temperature, dehydrogenation predominates over disproportionation.

It is important to point out that the ratio of *cis*:*trans* diastereomers **[(44a)+(44b)]**:**[(44c)+(44d)]** produced *via* disproportionation in this set of experiments, was the same as that produced under standard hydrogenation conditions.

One question that remains to be answered is why is conjugated sertraline **(45)** formed under standard reactions conditions, in the presence of H_2? One explanation for this is that not all of the active sites of Pd are saturated in H_2 under standard reaction conditions. This could be due to poor mass transport of H_2 through the length of the reactor bed, perhaps due to compacting of the powdered $Pd/CaCO_3$ catalyst, making mass transport through the reactor difficult. The active sites that are not saturated in H_2 then participate in dehydrogenation, while those saturated in H_2 participate in hydrogenation.

The experiment which led to 47 % formation of conjugated sertraline **(45)** was one of the first sertraline imine experiments performed, and so the reactor was completely filled with catalyst (0.8 g) to try and ensure high levels of conversion. Therefore, it is likely that the mass transport of H_2 through the reactor bed and into all the catalytic active sites was particularly poor given the large amount of catalyst. Only some of catalyst would be saturated in H_2, leaving the rest to participate in dehydrogenation and disproportionation.

To try and avoid dehydrogenation in future experiments, the reactors were only half filled with catalyst (0.4 to 0.5 g), whilst the bottom half of the reactor contained sand. Sand was added to the reactor to maintain a homogeneous flow throughout the reactor and to avoid the presence of any large dead volumes.

The studies on conjugated sertraline **(45)** have been very important because they suggest that mass transport of H_2 through the reactor bed is far from ideal. This problem may be exacerbated when using powered catalysts, such as $Pd/CaCO_3$, that become heavily compacted inside the high pressure flow reactor. The choice of reactor, mass of catalyst and form of catalyst should be carefully considered if dehydrogenation and disproportionation is to be avoided.

4.6.4 Variation in H_2 to Substrate Ratio

To discover whether the amount of H_2 present in the flow reactor had any effect on reaction selectivity, particularly toward dehydrogenation, a series of experiments were performed at different H_2 to substrate ratios. The ratio of H_2 to substrate was varied by changing the rate at which the H_2 was dosed into the reactor (refer to Chapter 2.1 for more details on H_2 dosage).

Upon varying H_2 to substrate ratio between zero and 10:1 it was found that H_2 to substrate ratio has very little effect on diastereoselectivity and in all cases the ratio of *cis*:*trans* sertraline was between 93:7 and 95:5. Conversion increased from 74 % in the absence of H_2, up to 98% when at a 3:1 ratio of H_2 to substrate; it then remained constant as H_2 to substrate was further increased.

The most interesting results obtained from changing the H_2 to substrate ratio was the variation in chemoselectivity (Figure 4-10).

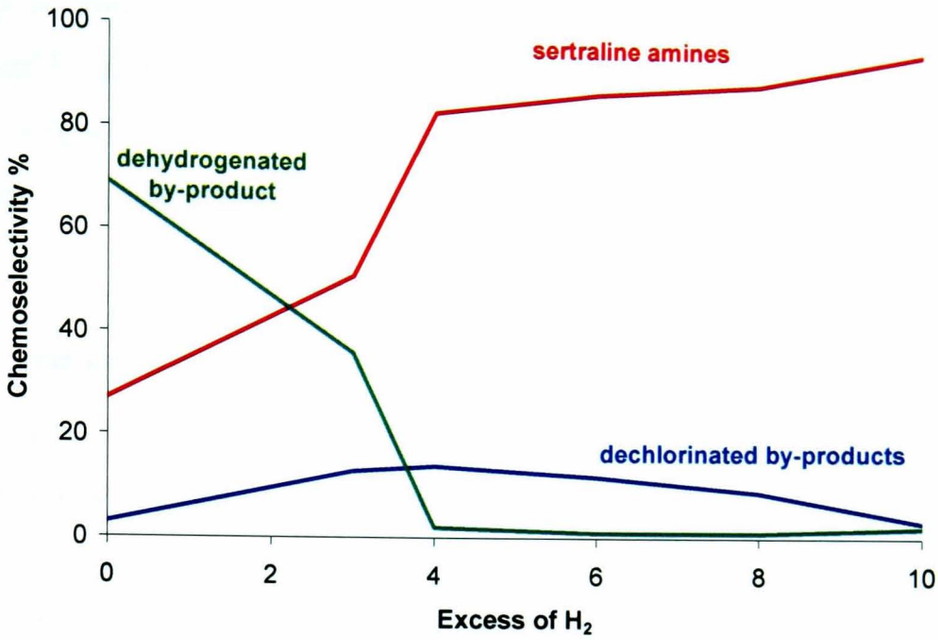


Figure 4-10: Variation in chemoselectivity during hydrogenation of *rac*-sertraline imine (42) at different H_2 to substrate ratios.

(Conditions: reactor type = (iii), system pressure = 175 bar, CO_2 flow rate = 1.0 mL/ min, organic flow rate = 0.4 mL/ min, mass of 5 % $Pd/CaCO_3$ catalyst = 0.6 g, temp. of reactor = 80 °C, solution concentration in THF = 0.2 M)

In the absence of H_2, selectivity toward the dehydrogenated product, conjugated sertraline **(45)** is high at 69 %. Even when the H_2 to substrate ratio was increased to 3:1 a substantial amount of conjugated sertraline **(45)** was still present. As H_2 to substrate ratio was increased further, selectivity toward the desired products also began to increase. At 4:1 the selectivity toward the dehydrogenated product had decreased to 2 %, however the presence of dechlorinated by-products meant that selectivity toward the sertraline amines **(44a-d)** was 83 %. At 10:1 H_2 to substrate ratio, the amount of conjugated sertraline **(45)** and dechlorinated by-products are small, providing excellent levels of chemoselectivity toward the sertraline amines (95 %).

This drop in dechlorinated by-products at large H_2 to substrate ratios suggests that the relative rates of hydrogenation and dechlorination are affected by changes in H_2 concentration. A similar trend was observed by Vannice and co-workers when studying the effect of H_2 pressure on reaction selectivity during the debenzylation and dechlorination of 4-chloro-*N*,*N*-dibenzylaniline.[100]

The drop in dehydrogenated by-products at high concentrations of H_2 can be rationalised by assuming that under these conditions the majority of active sites are likely be saturated in H_2 and therefore hydrogenation, rather dehydrogenation or disproportionation becomes the favoured reaction.

4.6.5 Variation in System Pressure

Hydrogenation reactions that are conducted in the presence of high pressure CO_2 have been known to exhibit significant changes in selectivity and conversion upon changing pressure.[101-104] To find out whether pressure has any significant effect on selectivity or conversion for the hydrogenation of *rac*-sertraline imine **(42)** a series of experiments was conducted at pressures between 125 and 175 bar (Figure 4-11).

This set of experiments was performed using a relatively large amount of catalyst (0.8 g) which would allow us to probe how changes in pressure affect reaction selectivity, and in particular selectivity toward dehydrogenation.

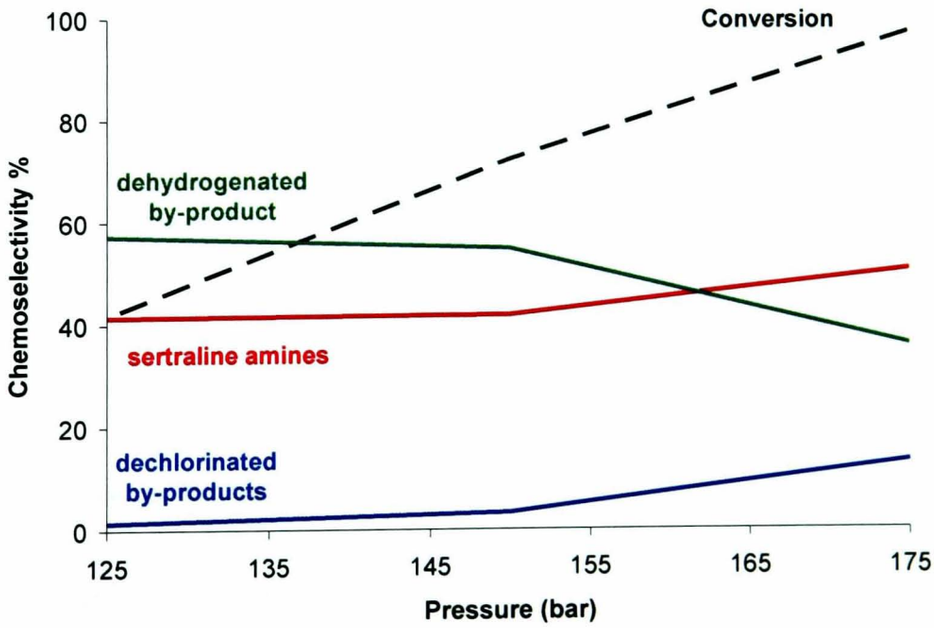


Figure 4-11: Variation in chemoselectivity and conversion during hydrogenation of imine (42) at different system pressures.

(Conditions: reactor type = (iii), CO_2 flow rate = 1.0 mL/ min, organic flow rate = 0.4 mL/ min, mass of 5 % $Pd/CaCO_3$ catalyst = 0.8 g, temp. of reactor = 80 °C, H_2 to substrate ratio = 3:1, solution concentration in THF = 0.1 M)

As pressure was increased from 125 to 175 bar, it was found that conversion increased significantly and that selectivity toward the dehydrogenated by-product **(45)** decreased. This can be explained by considering that the rate of most heterogeneous hydrogenation reactions is limited by the rate at which H_2 diffuses from the reactant solution and onto the catalyst surface.

At low pressure, the reaction mixture would have significantly more biphasic character than at higher pressure; therefore there will exist a CO_2 rich phase which contains a high concentration of H_2, but low concentration of organic substrate. Similarly there will be a liquid phase which contains a high concentration of organic substrate and low concentration of H_2. Under these conditions, there would be a relatively low concentration of H_2 at the catalyst surface, thus conversion to the hydrogenated products would be low, but dehydrogenation would still be able to occur.

At higher pressure the reaction mixture would have significantly more single phase character but since imine **(42)** is relatively insoluble in $scCO_2$, it can be postulated that the reaction mixture would most likely exist as an expanded liquid phase[105], rather than a purely homogeneous supercritical phase. The expanded liquid phase would exhibit a high concentration of both H_2 and organic leading to better mass transport of H_2 onto the catalyst surface and therefore higher rates of conversion of imine **(42)**. Due to the better mass transport of H_2 to the catalyst surface, the amount of dehydrogenated by-product **(45)** decreased.

4.6.6 Variation in Temperature

Continuous Flow Experiments

Often in hydrogenation reactions, temperature is one of the major factors that can affect reaction selectivity, particularly in complex substrates such as *rac*-sertraline imine **(42)**. For this reason, a series of experiments were performed between 40 and 120 °C inside the continuous flow reactor to find out how changes in

temperature affect selectivity and conversion during the hydrogenation of *rac*-sertraline imine **(42).**

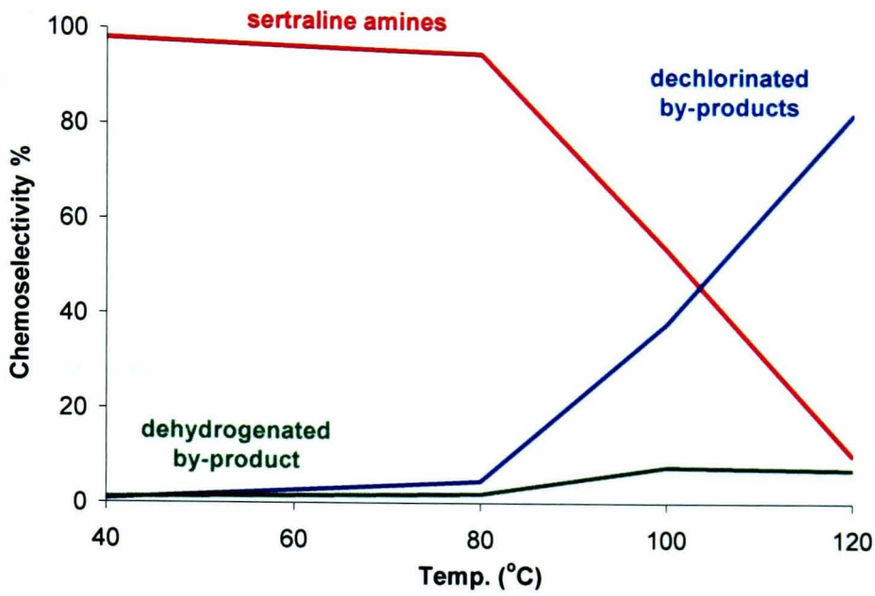


Figure 4-12: Variation in chemoselectivity during the continuous flow hydrogenation of *rac*-sertraline imine (42) at different temperature.

(Conditions: reactor type = (iii), system pressure 175 bar, CO_2 flow rate = 1.0 mL/ min, organic flow rate = 0.4 mL/ min, mass of 5 % $Pd/CaCO_3$ catalyst = 0.4 g, H_2 to substrate ratio = 10:1, solution concentration in THF = 005 M)

It was found that conversion of the starting material was always > 95 % and did not change significantly in the temperature range 40 – 120 °C and has therefore been omitted from Figure 4–12. One experiment was also performed at 30 °C, however, conversion dropped significantly (to < 5 %) and since this would not be a synthetically useful result, these data points are not reported in detail.

Diastereoselectivity was largely unaffected by changes in temperature and remained constant at a *cis*:*trans* ratio of 96:4 (± 1 %) between 40 and 120 °C. This suggests that the energy difference between the *cis*- and *trans*- diastereoisomers is too large to allow interconversion, even at elevated temperature.

Variation in temperature of the catalyst bed brought about a significant change in chemoselectivity (Figure 4-12). At 40 °C selectivity toward sertraline amines **(44a-d)** was excellent at 98 %. However, as the temperature was increased

formation of the dechlorinated by-products [**(111)-(113)**] dramatically increased. At temperatures > 80 °C, hydrogenolysis of the N-C bond occured leading to formation of by-product **(114)** which further decreased selectivity toward the desired products. Formation of by-product **(114)** is included in the "dechlorinated by-products" section of chemoselectivity. At temperatures > 80 °C dehydrogenation had started to occur, leading to formation of conjugated sertraline **(45)**.

Batch experiments

To investigate whether there was any difference in selectivity between reactions conducted in the presence and absence of $scCO_2$, a series of batch hydrogenation experiments were performed. By carrying out reactions in batch it was also possible to directly compare Pfizer®s optimum reaction conditions with the same reaction performed in the presence of CO_2.

According to the most recent literature available on Zoloft® [72], Pfizer perform the hydrogenation of sertraline imine inside a batch vessel at 25 °C over a $Pd/CaCO_3$ catalyst for a period of 40 minutes. A hydrogenation experiment was conducted using *rac*-sertraline imine **(42)**, under the same reaction conditions as those used by Pfizer® inside our own batch reactor, an Mk 1 type autoclave (Entry 1, Table 4-10).

Under Pfizer®s optimum conditions, a *cis*:*trans* ratio of 93:7 was obtained, which is slightly lower than that reported by Pfizer of 95:5. Selectivity toward both dechlorinated and dehydrogenated by-products was low at 2 % and 1 % respectively.

Table 4-10: Comparison between the batch hydrogenation of imine (42) conducted under Pfizer®s optimum conditions in the presence, and absence of high pressure CO_2.

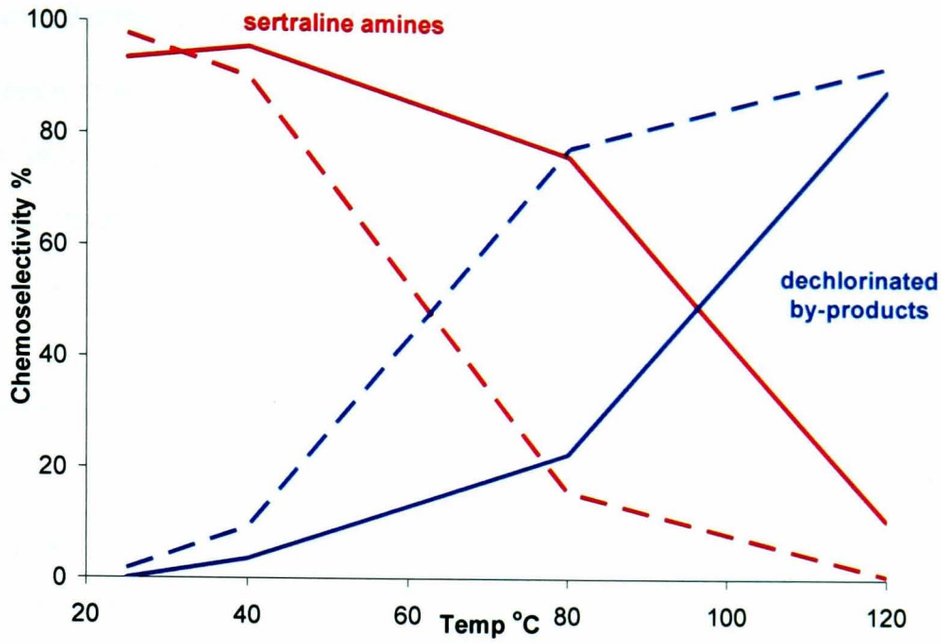
Entry	CO_2	Conversion %	*cis:trans* ratio	Chemoselectivity %		
				sertraline isomers	dechlor[d] by-prod[s]	conj sertraline
1	no	99	93:7	97	2	1
2	yes*	70	93:7	94	0	6

*(Conditions: reactor type = autoclave, H_2 pressure = 1.0 bar, mass of 5 % $Pd/CaCO_3$ catalyst = 0.05 g, temp. reactor = 25 °C, 4.5 mL of 0.05 M solution in THF, reaction time = 40 minutes. * CO_2 pressure 175 bar)*

A second batch experiment was performed inside the autoclave, but this time CO_2 (175 bar) was present (Entry 2, Table 4-10). Under these conditions, the *cis:trans* ratio was exactly the same as the reaction performed in the absence of CO_2 and therefore suggests that CO_2 has no effect on diastereoselectivity. Selectivity toward the dehydrogenated by-product, conjugated sertraline **(45)** was slightly higher at 6 % for the reaction in CO_2 however, no dechlorinated by-products were detected. Conversion was slightly lower for the reaction performed in the presence of CO_2.

From Table 4-10 it is difficult to tell whether CO_2 has any effect on reaction selectivity. Further investigations were therefore undertaken to look at the differences between batch reactions performed in the presence and absence of CO_2 under more forcing conditions, at temperatures up to 120 °C.

The most interesting difference between the batch reactions conducted in the presence and absence of CO_2 is the change in chemoselectivity upon varying the temperature (Figure 4-13).



Key:——— performed in presence of CO_2 — — - performed in the absence of CO_2

Figure 4-13: Chemoselectivity of batch hydrogenation reactions conducted in the presence *, and absence of CO_2.

(Conditions: reactor type = autoclave, H_2 pressure = 1.0 bar, mass of 5 % $Pd/CaCO_3$ catalyst = 0.05 g, 4.5 mL of 0.05 M solution in THF, reaction time = 40 minutes, CO_2 pressure 175 bar)*

Reactions performed in the absence of CO_2 underwent a much more dramatic change in chemoselectivity as temperature was varied. This was highlighted by the fact that the cross-over temperature (the temperature at which selectivity toward sertraline and dechlorinated by-products is equal) was 40 °C higher for reactions that were performed in CO_2, than for reactions that were performed in the absence of CO_2. These suggest that the presence of CO_2 is advantageous in this reaction, since it can allow the hydrogenation of imine **(42)** to be conducted at a higher temperature, whilst still maintaining very high levels of chemoselectivity.

Under all reactions conditions, except at 25 °C, conversion in both sets of experiments was > 99 %. As in the continuous flow studies, variation in temperature did not affect diastereoselectivity and remained constant at 93:7 (± 1.0 %). In all cases, selectivity toward the dehydrogenated by-product, conjugated sertraline **(45)** did not change significantly with temperature and was the same for both sets of reactions at 2-3 %. To simplify Figure 4-13, selectivity toward the dehydrogenated by-product was omitted.

Comparison Between Batch and Flow Results

The residence time inside the continuous flow reactor is significantly smaller than that of the batch experiments. Directly comparing the results from batch and flow experiments might help to deduce whether residence time has a significant effect on reaction selectivity.

The *cis*:*trans* ratio was found to be only marginally better in flow than those conducted in batch. This suggests that diastereoselectivity is not significantly affected by changes in residence time over the catalyst bed and implies that the diastereoselective hydrogenation of *rac*-sertraline imine **(42)** is under thermodynamic, rather than kinetic control.

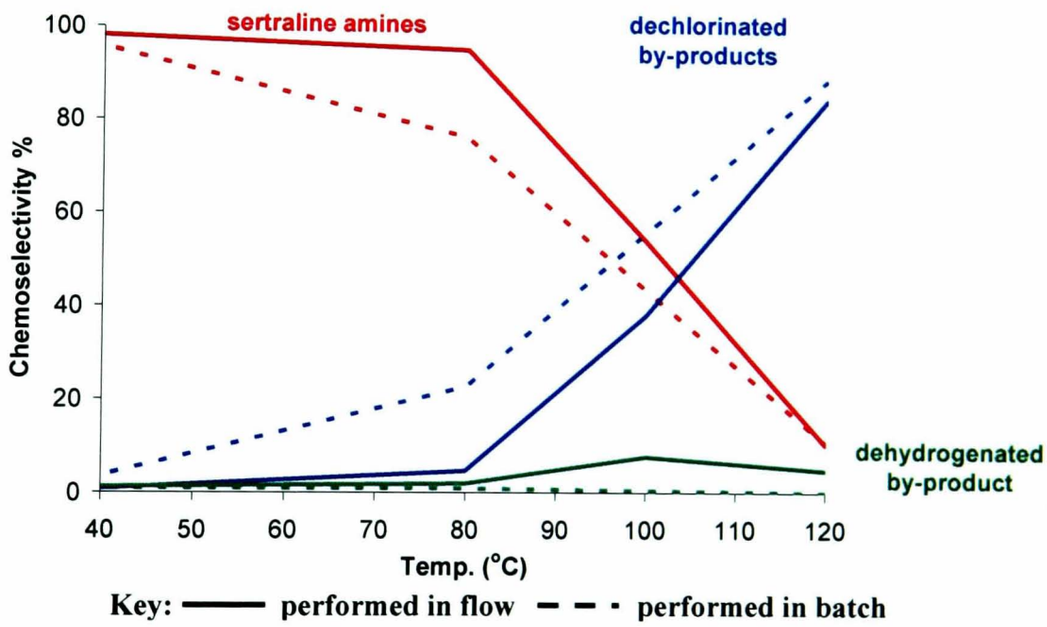


Figure 4-14: Variation in chemoselectivity for the hydrogenation of (42) in $scCO_2$ performed as a batch and flow process.

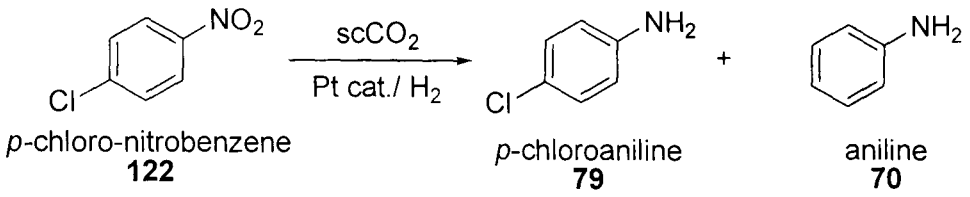
Figure 4-14 shows the difference in chemoselectivity of reactions conducted in the presence of CO_2 as batch and flow processes. Although, the difference in chemoselectivity is not huge, particularly given that the residence time is likely to be ten times greater inside the batch reactor, it is clear that reactions conducted in flow offer superior levels of chemoselectivity. These results imply that, at least to

some extent, the formation of dechlorinated by-products can be affected by changes in residence time.

Note that at high temperature the level of dehydrogenated by-product increases during the reactions that are performed in flow, but not for those performed in batch. This may provide further evidence for the fact that the mass transport of H_2 across the continuous flow reactor is poor.

4.6.7 scPropane vs. scCO₂

In 2005, Ikariya and co-workers published some research on the selective hydrogenation of chlorinated nitro-aromatics in $scCO_2$ (Scheme 4-25).[106] Ikariya found that hydrogenation reactions performed in the presence of $scCO_2$ exhibited less dechlorination and provided higher levels of selectivity toward the desired product, *p*-chloro-aniline **(79)**, than the same reaction performed in the absence of $scCO_2$.



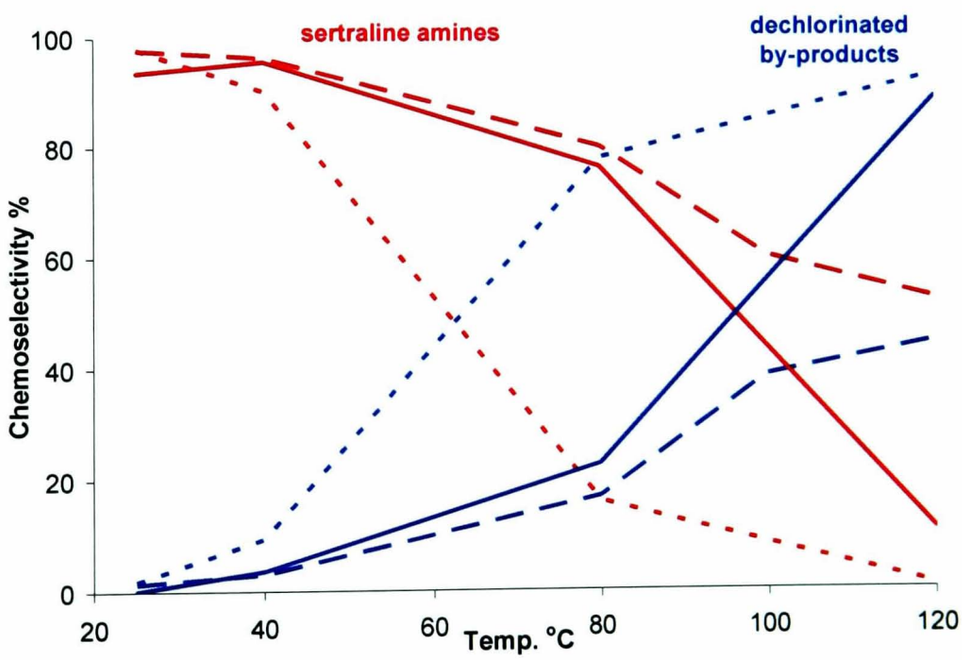
Scheme 4-25: Less dechlorinated by-products are detected during the hydrogenation of *p*-chloro-nitrobenzene (122) in $scCO_2$ compared to the same reaction conducted in the absence of $scCO_2$. Dechlorination is inhibited by CO that selectively binds to those sites involved in dechlorination. [106]

It was proposed that CO selectively poisoned the catalyst toward dechlorination by blocking only those active sites involved in dechlorination, whilst leaving the other active sites responsible for hydrogenation unaffected. The presence of CO on the surface of catalysts that had been used for reactions in $scCO_2$ was proven using FT-IR spectroscopy. The CO is generated in small quantities under reaction conditions from CO_2 *via* the reverse-water-gas shift reaction. CO poisoning of catalysts such as Pd and Pt is not uncommon and can be a major problem in

catalytic reactions, particularly when CO adsorption results in complete catalyst deactivation.[107-109]

To find out if the active sites involved in dechlorination are being blocked by CO in our system, a series of batch experiments were performed in the presence of high pressure propane (C_3H_8). If the selectivity of the hydrogenation reactions conducted in propane were the same as the reactions conducted in the presence of $scCO_2$ then it is unlikely that CO formation is the cause of the enhanced chemoselectivity.

Propane was chosen because it shares similar densities and critical parameters with CO_2, compared with other readily available gases. C_3H_8 was also chosen because it has been used in other hydrogenation reactions, particularly for the hydrogenation of fatty acids and vegetable oils.[110,111]



Key:—— performed in presence of CO_2 ····· performed in the absence of CO_2

— — performed in the presence of C_3H_8

Figure 4-15: Comparison between chemoselectivity of reactions conducted in the presence and absence of CO_2 *and in the presence of C_3H_8.**

(Conditions: reactor type = autoclave, H_2 pressure = 1.0 bar, mass of 5 % $Pd/CaCO_3$ catalyst = 0.05 g, 4.5 mL of 0.05 M solution in THF, reaction time = 40 minutes, CO_2 pressure 175 bar, ** C_3H_8 pressure = 175 bar)*

Figure 4-15 compares the chemoselectivity at various temperatures, of reactions conducted in the presence, and absence of CO_2 with those performed in the presence of C_3H_8. The data suggest that the enhanced level of chemoselectivity at higher temperature is not particular only to CO_2 and that reactions in C_3H_8 also exhibit a high levels of chemoselectivity. Reactions performed in C_3H_8 actually exhibited higher levels of chemoselectivity than the same reactions performed in CO_2! Our results suggest that selective poisoning of the Pd catalyst by CO is unlikely to be the cause of enhanced chemoselectivity during the hydrogenation of *rac*-sertraline imine **(42)** in $scCO_2$.

It should be noted that there are some disadvantages of using C_3H_8 instead of CO_2 for this reaction. Conversion was slightly lower for batch reactions conducted in C_3H_8, particularly at low temperature, compared with the same reactions in CO_2. Thus, continuous flow hydrogenation in C_3H_8 would most likely lead to very poor conversion. CO_2 is also much safer to use as a solvent in hydrogenation reactions since it is non-flammable, where as C_3H_8 is extremely flammable.

Reactions performed in C_3H_8 exhibited very low selectivity toward the conjugated sertraline, with a selectivity of only 1-2 %; again the data was omitted from Figure 4-14 for clarity. The ratio of *cis*:*trans* diastereoisomers for reactions performed in C_3H_8 was exactly the same as that produced in reactions CO_2 at 93:7.

From the data collected thus far, it seems that the presence of high pressure CO_2 (or C_3H_8) is beneficial in the hydrogenation of *rac*-sertraline amine. This is most likely an artefact of the physical properties of supercritical fluids (SCFs) rather than any specific chemical properties of CO_2 (i.e. CO poisoning). SCFs are known to exhibit greater diffusivity and lower viscosity than organic solvents. One of the potential benefits of these properties is that SCFs exhibit significantly higher thermal conductivity and consequently heat transfer is enhanced.

It has been shown dechlorination can occur at relatively low temperature in the absence of CO_2. Dechlorination can occur under these conditions due to the formation of hot spots at the catalyst surface which are generated from the exothermic hydrogenation reaction that is taking place on the catalyst surface. In the presence of a SCF, hot spots are much less likely to form on the catalyst surface since heat transfer will be significantly improved. Therefore, at low temperature and in the presence of a SCF, dechlorination can be suppressed.

4.6.8 Variation in Co-solvent

As with the model substrate **(36)**, *rac*-sertraline imine **(42)** is a solid under ambient conditions and therefore a co-solvent was required in all continuous flow studies. In the experiments discussed thus far, THF has been used as co-solvent. To investigate whether the choice of co-solvent has any effect on chemo- or diastereoselectivity it was necessary to undertake a small screen of other co-solvents. Since the 1980s, two different solvents have been reportedly used in the commercial Zoloft® process, THF and EtOH. Therefore EtOH was also tested as a co-solvent in our continuous flow studies (Table 4-11).

Amines have been known to irreversibley bind to heterogeneous metal catalysts and in some cases this can lead to catalyst deactivation.[91,112,113] Therefore both experiments in THF and EtOH were performed under a single set of reaction conditions and samples taken over a period of 70 minutes. This would allow us to find out whether selectivity or conversion is affected with time-on-stream during hydrogenation.

The results from Table 4-11 show that both diastereoselectivity and chemoselectivity were higher when the reaction was carried out in the presence of THF rather than EtOH. The reduced dechlorination in THF may be due to the fact that THF is aprotic whereas EtOH is protic. Protic solvents have been reported to increase the rate of dechlorination, compared with the same reaction conducted in aprotic solvents, in other heterogeneous studies.[79,114]

Table 4-11: Comparison of THF and EtOH as co-solvents for the continuous flow hydrogenation of *rac*-sertraline imine (42).

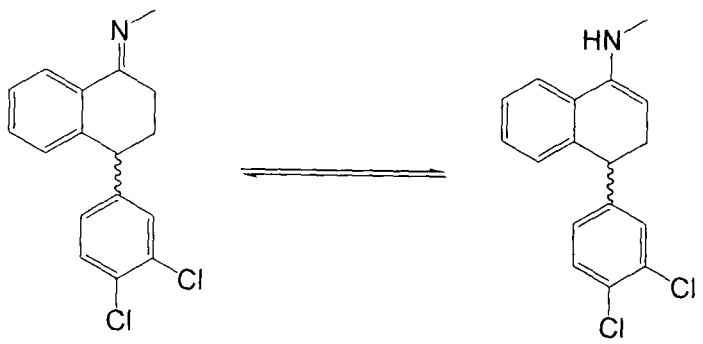
Co-Solvent	Time-on-stream (mins)	Conversion %	*cis*:*trans* ratio	Chemoselectivity %		
				sertraline amines	dechlor[d] by-prod[s]	conjugated sertraline
THF	10	93	94:6	94	3	3
	20	94	95:5	95	3	2
	30	95	95:5	95	3	2
	40	95	95:5	96	2	2
	50	95	95:5	96	2	2
	60	95	96:4	97	1	2
	70	95	96:4	97	1	2
EtOH	10	98	91:9	93	7	0
	20	99	91:9	94	6	0
	30	98	92:8	94	6	0
	40	99	92:8	94	6	0
	50	99	92:8	92	6	0
	60	99	92:8	94	6	0
	70	99	92:8	94	6	0

(Conditions: reactor type = (iii), system pressure 175 bar, CO_2 flow rate = 1.0 mL/ min, organic flow rate = 0.4 mL/ min, mass of 5 % $Pd/CaCO_3$ catalyst = 0.4 g, temp. reactor = 80 °C, H_2 to substrate ratio = 10:1, solution concentration in THF or EtOH = 005 M)

The other differences in conversion, diastereoselectivity and selectivity toward conjugated sertraline **(45)** may be due to the differences in solubility of the CO_2/ H_2/ substrate mixture. Phase behaviour studies would be useful to deduce whether there were any differences in the solubility of the THF and EtOH reaction mixtures. Also, note that samples collected during both sets of experiments did not show any decrease in conversion over the 70 minute period. This suggests that catalyst deactivation, at least on a short time scale, does not occur under reaction conditions in $scCO_2$.

4.7 Mechanistic Studies into the Hydrogenation of *rac*-Sertraline Imine

Imines exist in equilibrium with their enamine tautomer. However, *rac*-sertraline imine **(42)** is a secondary imine, and therefore is likely to be stable as an imine, rather than as an enamine **(123)** (Scheme 4-26).[115] However, under reaction conditions, at high temperature, and in the presence of a metal catalyst, it is possible that tautomerisation may occur.[116,117] It is very important to understand whether any kind of isomerisation process is taking place inside the reactor. Therefore, an investigation was undertaken to confirm that hydrogenation of imine **(42)** proceeds through the imine bond, and not through the enamine tautomer since each would afford the same product.

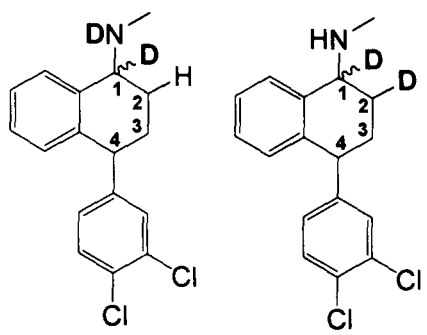


42 **123**

Scheme 4-26: The equilibrium that exists between *rac*-sertraline imine (42) and its tautomer, enamine (123) is likely to be very small under ambient conditions.

To test this theory, the hydrogenation of *rac*-sertraline imine **(42)** was performed in the presence of the $Pd/CaCO_3$ catalyst and deuterium, instead of hydrogen. To avoid using large amounts of deuterium, this experiment was performed inside the Mk1 type autoclave, instead of the continuous flow apparatus. It was hoped that ,by examining the ^1H NMR spectrum of the product mixture, it would be possible to find out exactly where the deuterium had been added. If, as expected, the deuterium had added *via* the imine bond, then a molecule with deuterium attached to the N-C bond would be formed **(124)** (Figure 4-16). If, on the other hand the

deuterium added through the enamine tautomer, then deuterium would be attached to the C–C bond to provide amine **(125)**.



124 **125**

Figure 4-16: If hydrogenation of imine (42) proceeds *via* the imine bond then amine (124) will be formed. If hydrogenation occurs *via* the enamine then amine (125) will occur.

In a ^1H NMR spectrum, NH protons are not always visible. This means that the absence of an NH peak is not evidence for the imine pathway. The analysis is dependent on the presence or absence of a CH_2 peak [C(2)-H]. If it is present then we can say the hydrogenation has proceeded through the imine. If, however, the CH_2 peak is absent, due to formation of CHD then the enamine pathway prevails.

Figure 4-17 shows the ^1H NMR spectra obtained from two different hydrogenations reactions; one was performed in the presence of H_2, and the other in the presence of D_2. The first point to note is that the triplet peak which corresponds to the C(1)-H proton is missing in spectrum **(b)**, thus indicating that a deuterium atom has been added to C(1). This is clearly visible in the expansion provided in Figure 4-17. As anticipated, the NH proton is absent from both spectra and therefore the expansion in alkyl–H region must be studied.

The important point to note is the similarity in the splitting patterns for both sets of spectra, they appear to be almost identical. Although this evidence is not conclusive, it suggests that the reaction proceeds *via* the imine **(42)**, and not through the enamine **(123)**. Further studies are needed to be conclusive.

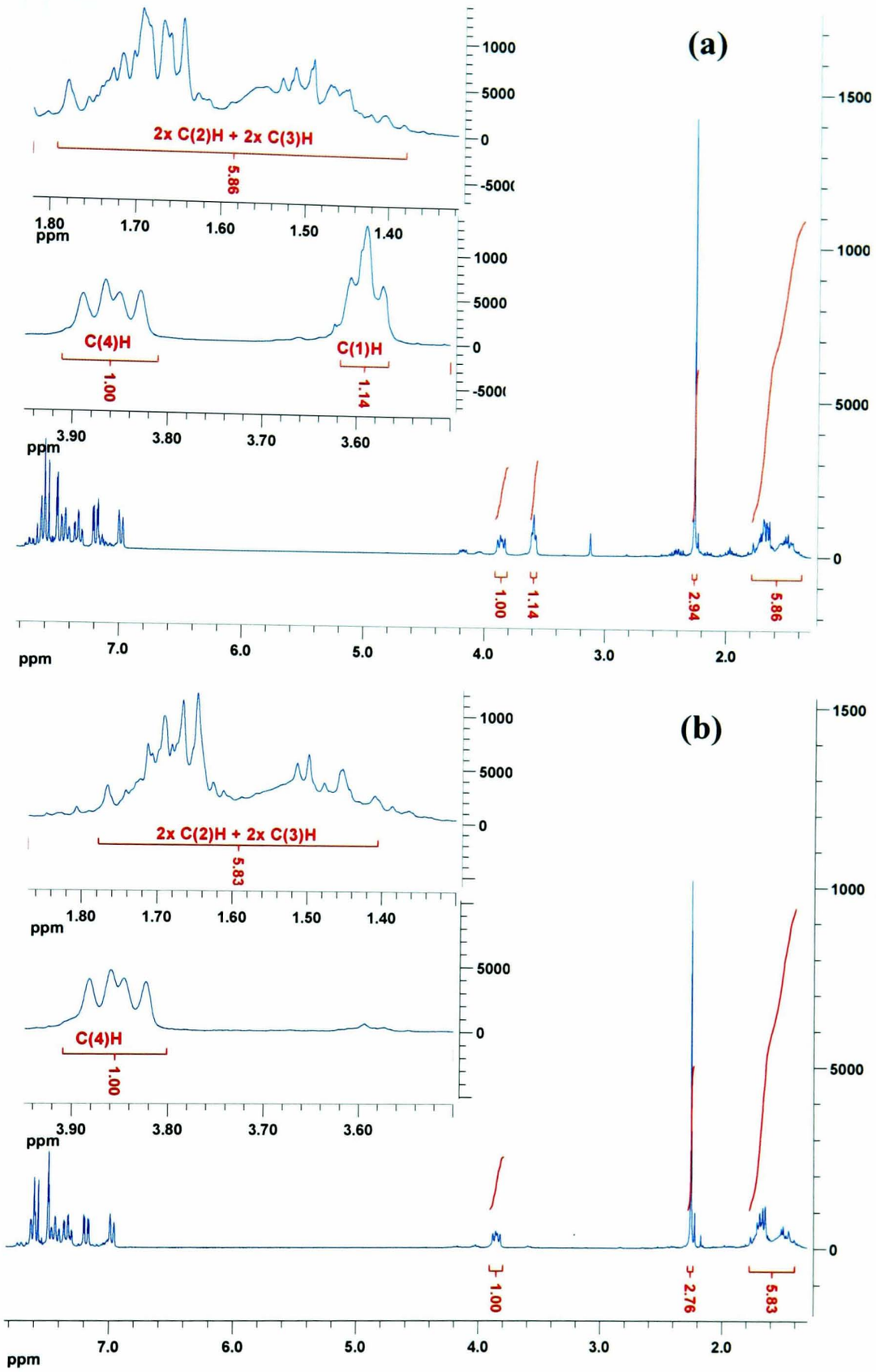
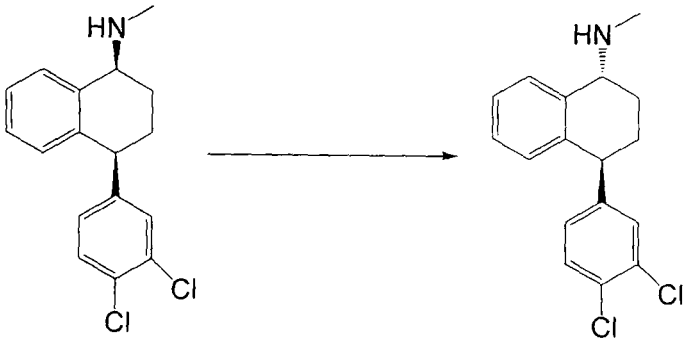


Figure 4-17: ^{1}H NMR spectra & expansions for the hydrogenation of imine (42) in the presence of H_2 (a), and D_2 (b). The absence of C(1)H in (b) indicates inclusion of D_2; similarity in splitting of [2x C(2)H + 2x C(3)H] protons suggests hydrogenation ocurrs *via* C=N bond.

(Conditions: reactor type = autoclave, H_2 or D_2 pressure = 1.0 bar, mass of 5 % $Pd/CaCO_3$ catalyst = 0.05 g, 4.5 mL of 0.05 M solution in THF, reaction time = 40 minutes)

4.8 Epimerisation Studies

In any pharmaceutical process, it is imperative that epimerisation studies are carried out as any interconversions of diastereoisomers may have an effect on the action of the drug molecule. It is known that hydrogenation of *rac*-sertraline imine **(42)** will produce a mixture of both *cis*- and *trans*- diastereoisomers. It was therefore important to perform a control experiment to check the stability of the *cis*- diastereoisomers and confirm that formation of the *trans*- diastereoisomers was not due to the *cis*- diastereoisomers being converted to the *trans*- diastereoisomers *via* epimerisation (Scheme 4-27).



44a **44d**

Scheme 4-27: Epimerisation of the chiral C-N bond of *cis*-(1S,4S)-sertraline to form trans-(1R,4S)-sertraline. A similar schematic can be drawn for the other set of diastereoisomers.

To find out whether epimerisation of *cis*- sertraline was occurring under reaction conditions, a solution of *cis*-(1*S*, 4*S*)-sertraline **(44a)** was pumped over the $Pd/CaCO_3$ catalyst under standard reaction conditions, but in the absence of H_2. The *cis*-(1*S*, 4*S*)-sertraline **(44a)** that was used in this control experiment was provided free-of-charge by Kemprotec Ltd and this sample was also used as a reference in HPLC and other analytical techniques. The author gratefully acknowledges this donation.

Experiments were performed, at 40, 80 and 120 °C in the presence of high pressure CO_2 and a $Pd/CaCO_3$ catalyst. Product mixtures were analysed by GLC analysis. Under all reactions, *cis*-(1*S*, 4*S*)-sertraline **(44a)** was recovered without

any detectable epimerisation. From the data, it is suggested that *cis*- to *trans*-epimerisation dose not occur to any significant extent.

4.9 Continuous Flow Hydrogenation of *rac*-Sertraline Imine in the Absence of CO_2

Batch hydrogenation studies have shown that the presence of high pressure CO_2 allows the hydrogenation of imine **(42)** to be conducted at higher temperature than is often suitable, without any loss in chemoselectivity. To complement the batch experiments, continuous flow reactions were conducted in the absence of CO_2 to see if a similar trend in reactivity exists.

The small-scale apparatus, which has been used for the $scCO_2$ hydrogenation reactions, was not designed for hydrogenation in a purely liquid phase system and therefore mixing of H_2 and organic under those conditions would be relatively poor, resulting in low reaction rates. Instead, the H-Cube apparatus has been used.

The H-Cube is a piece of apparatus that was designed by Thales Nanotechnology as a bench top unit for screening continuous flow hydrogenation reactions.[118] A detailed description of this apparatus was provided in Chapter 2.5. Since the launch of the H-Cube in 2005, there have been a number of publications reporting the selective reduction of a range of functional groups, including imines, using the H-Cube.[119-121]

The apparatus is approximately the size of a large shoe box and one of the major advantages of this apparatus is that the H_2 is generated through electrolysis of water. This avoids the use of bulky H_2 cylinders and means that the unit is very portable. The maximum pressure of H_2 that can be generated inside the reactor is 100 bar, and the maximum operating temperature 100 °C.

The H-Cube system was designed to allow efficient mixing of H_2 and substrate solution. The catalysts that are compatible with this apparatus (known as CatCarts^{TM}) were specially designed with microchannels that promote excellent mass transport of the substrate and H_2 into the catalyst active sites, thus allowing appreciable rates of reaction inside the flow reactor.[122]

Only the catalysts that are supplied in CatCarts can be used with the H-Cube and unfortunately $Pd/CaCO_3$ was not one of the catalysts available. Therefore, a 5% Pd/C catalyst was tested instead. Pd/C catalysts have shown high levels of chemo- and diastereoselectivity, but lower than the corresponding $Pd/CaCO_3$ catalyst.

Initial studies on *rac*-sertraline imine **(42)** were conducted on the H-Cube apparatus to find the optimum conditions for this system. Under these conditions, reproducibility from fraction to fraction was poor due to blockages within the system. The hydrogenation reaction was then performed at temperatures between 40 and 80 °C using a fresh catalyst cartridge for each set of reaction conditions to minimise any chance of catalyst deactivation. In an attempt to prevent blockages from forming a very dilute solution of imine **(42)** was used (Table 4–12).

Table 4-12: Continuous flow hydrogenation of *rac*-sertraline imine (42) performed in the absence of CO_2.

Temp. (°C)	Conver^{n} (%)	*cis*:*trans* ratio	Chemoselectivity (%)		
			sertraline isomers	dechlor^{d} by-prod^{s}	conjugated sertraline
40	100	91:5	42	58	0
	100	95:5	41	59	0
60	100	93:7	30	70	0
	100	93:7	31	67	2
80	96	90:10	20	53	27
	98	90:10	17	34	49

(Conditions: reactor type = CatCart^{TM} 30 × 4 mm, H_2 pressure = 20 bar, organic flow rate = 1.0 mL/ min, 5 % Pd/C catalyst, concentration of solution in THF = 0.025M)

At 40 °C the *cis*:*trans* ratio was excellent at up to 95:5 (Table 4-12). This is comparable with the flow studies conducted in $scCO_2$. However, even at 40 °C, chemoselectivity was extremely poor due to the excessive amount of dechlorination. As the temperature was increased up to 60 °C and then 80 °C chemoselectivity and diastereoselectivity toward the desired products decreased. At 80 °C chemoselectivity was very poor not only due to dechlorination, but also due to dehydrogenation.

Using a more dilute substrate solution had helped to improve reproducibility however, some fluctuations in system pressure still occurred. The reason for the blockages and fluctuations in pressure were due to precipitation of the sertraline amines from the THF solution as their corresponding hydrochloride salts. Precipitation of the amine salts actually took place inside the product vials when they were left standing. Precipitation of the salts inside the apparatus would explain the fluctuations in pressure and blockages. For all GLC and HPLC analysis a homogeneous sample must be used, therefore fractions were washed with NaOH solution to remove the acid, before the products were extracted back into an organic solvent ready for analysis. It should be noted that precipitation did not occur in any of the previous experiments using imine **(42)**.

The results in Table 4-12 show that continuous flow hydrogenation of *rac*-sertraline imine cannot be performed selectively over Pd/C using the H-Cube apparatus, even at low temperature. The level of selectivity was dramatically less than for the same continuous flow reactions, conducted over Pd/C in the presence of $scCO_2$ (refer back to Entry 2, Table 4-8).

It should be pointed out that the two Pd catalysts used for comparison here are made by two different catalyst manufacturers. Pd catalysts are known to exhibit different levels of selectivity, depending on the type of carbon support and also on the method of catalyst preparation. Taking into account these differences, it is still believed that the H-Cube experiments provide further evidence for the fact that the

presence of high pressure CO_2 is beneficial in this reaction as it allows one to perform the hydrogenation of *rac*-sertraline imine **(42)** at a temperature which is high enough to facilitate quantitative conversion and excellent diastereoselectivity, but also without significant dechlorination.

4.10 Continuous Flow Hydrogenation of *rac*-Sertraline Imine under Optimum Conditions in $scCO_2$

The hydrogenation of *rac*-sertraline imine **(42)** has been rigorously investigated and using what has been learnt during these studies, some final experiments were performed under optimum conditions. Two continuous flow experiments were performed in the presence of high pressure CO_2 at 40 °C, over the $Pd/CaCO_3$.

The first experiment was performed using 0.5 g catalyst (Entry 1, Table 4-13) with a H_2 to substrate ratio of 10:1. Under these conditions chemoselectivity was excellent at > 99 % toward the sertraline amines **(44a-d)**. Diastereoselectivity was also excellent at 97:3 as measured by GLC and HPLC. This *cis*:*trans* ratio is actually higher than recorded in the Pfizer® process.

Table 4-13: Continuous flow hydrogenation of imine (42) under optimum conditions.

Entry	Reactor type	Mass of Cat. (g)	xH_2	Conver^n (%)	*cis*:*trans* ratio	Selectivity (%)		
						44a-d	111-114	45
1	(iii)	0.5	10	99	97:3	99.3	0.2	0.5
2	(iv)	0.3	12	87	97:3	99.3	0.7	0.0

(Conditions: CO_2 pressure = 175 bar, flow rate CO_2 = 1.0 mL/ min, organic flow rate = 0.4 mL/ min, catalyst =5% $Pd/CaCO_3$, temp. reactor bed = 40 °C, 0.2 M solution in THF)

Although these results were excellent, it was proposed that formation of conjugated sertraline should be completely avoided at 40 °C if *all* of the catalyst was saturated in H_2. Therefore, a final experiment was performed using a smaller

reactor, containing less catalyst (0.3 g) and a H_2 to substrate ratio of 12:1 (Entry 2, Table 4-13).

Under these conditions it was possible to completely avoid formation of conjugated sertraline. However, conversion dropped slightly to 87 % which indicates that the concentration of substrate was too high given the amount of catalyst present. Nevertheless, this was a very important result and proved that dehydrogenation can be avoided.

4.11 Conclusions

The first diasteroselective hydrogenation of a final stage pharmaceutical intermediate has been performed in $scCO_2$. Generally in a pharmaceutical process any by-product present in the product mixture at > 1.5 % will have to undergo a full toxicological study.[74] Thus 1.5 % serves as the benchmark below which all by-products should be present in our process. Table 4-14 shows the composition of the product mixtures obtained from continuous flow experiments conducted under two sets of optimised reaction conditions. In our studies toward a more efficient hydrogenation process, it has been shown that the hydrogenation of *rac*-sertraline imine can be performed under optimum conditions with a *cis*:*trans* ratio of 97:3 and ≤ 0.7 % by-product formation (*via* dehydrogenation and dechlorination), which, is better than the current batch process.

Table 4-14: Composition of product mixtures from continuous flow hydrogenation of *rac*-sertraline imine (42) under optimum conditions.

Entry	Mass Cat. (g)	xH_2	Composition %				
			rac-sertraline imine	*cis*-sertraline	*trans*-sertraline	dechlor[d] by-prods	conj-sertraline
1	0.5	10	0.4	96.7	2.2	0.2	0.5
2	0.3	12	12.8	84.7	1.9	0.6	0.0

(Conditions: CO_2 pressure = 175 bar, flow rate CO_2 = 1.0 mL/ min, organic flow rate = 0.4 mL/ min, catalyst =5% $Pd/CaCO_3$, temp. reactor bed = 40 °C, 0.2 M solution in THF)

Although it has been shown that this reaction can be performed as a batch process, the highest levels of chemo- and diastereoselectivity have only been achieved when the reaction was performed in continuous flow, and in the presence of high pressure CO_2.

Reactions performed in the presence of $scCO_2$ were more chemoselective than those conducted in the absence of $scCO_2$. The reason for the difference in selectivity is most likely due to the physical properties of $scCO_2$, particularly its ability to efficiently transfer heat throughout the reactor.

The *cis*:*trans* ratio for the hydrogenation of *rac*-sertraline imine **(42)** is largely dictated by the choice of metal catalyst and support used in the hydrogenation reaction. Other reaction conditions, including temperature, pressure and H_2 to substrate ratio have had little effect. The highest levels of diastereoselectivity were achieved when the reaction was conducted in continuous flow and in the presence of $scCO_2$ at 40 °C.

Identifying the by-product, conjugated sertraline **(45)** has been very important in these studies since it has shown that catalyst loading, type of reactor, and form of the catalyst are all important considerations if dehydrogenation is to be avoided. Under optimum conditions, using a small amount of catalyst at a large H_2 to substrate ratio it has been possible to prevent formation of conjugated sertraline.

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Chapter 5

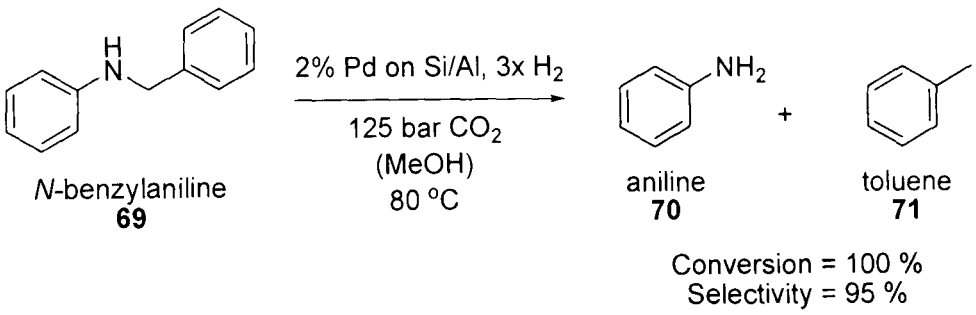
Conclusions and Future Directions

5 Conclusions and Future Directions

This Chapter will bring together the conclusions and future directions from Chapters 3 & 4. Chemoselective *N*-debenzylation in the presence of a -Cl or -COMe functional group was investigated in Chapter 3; while hydrogenation of a pharmaceutical intermediate, *rac*-sertraline imine **(42)** was investigated in Chapter 4. In both Chapters the reactions were performed as continuous flow processes in the presence $scCO_2$.

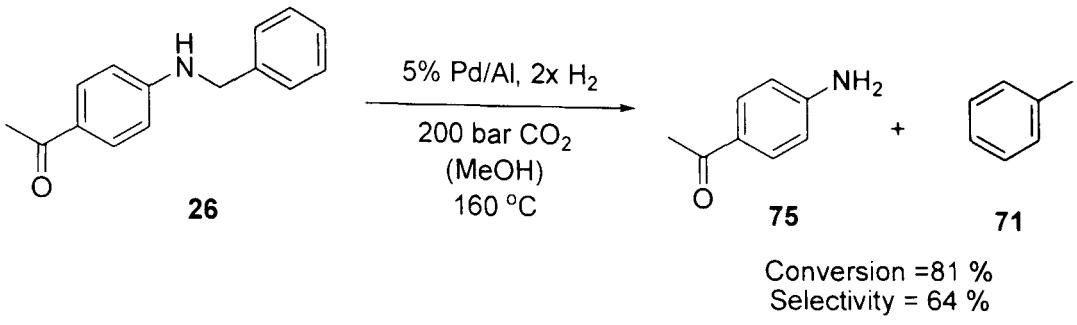
5.1 Summary of Conclusions from Continuous Flow Debenzylation

Studies on a model substrate, *N*-benzylaniline **(69)** have shown that continuous flow debenzylation can be performed with high level of selectivity in $scCO_2$ (Scheme 5-1). A variety of different heterogeneous metal catalysts were tested, however, only Pd offered the high level of activity that is required when working in continuous flow.



Scheme 5-1: Debenzylation of the model substrate (69) under the optimum conditions could be performed with minimal hydrogenation of aniline (70).

With the model studies complete, chemoselective debenzylation in the presence of reducible functional groups was investigated. In the first set of experiments, debenzylation in the presence of a carbonyl was investigated (Scheme 5-2).



Scheme 5-2: It was difficult to avoid hydrogenation of the desired product, ketone (75) due to the high temperatures that are required for the continuous flow debenzylation of (26).

Substrate **(26)** was deactivated toward debenzylation compared with the model substrate **(69)** and therefore high temperature was required to facilitate synthetically useful levels of conversion in continuous flow. Unfortunately, under these operating conditions hydrogenation of the carbonyl of ketone **(75)** was unavoidable. The studies on substrate **(26)** highlighted one of the limitations of performing reactions in continuous flow; high temperatures are required to increase the rate of reaction, which can be detrimental to selectivity.

Another chemoselectivity issue that has been addressed throughout this Thesis is the problem of unwanted removal of chloro substituents during hydrogenation and debenzylation reactions. The chemoselective debenzylation of *ortho*-, *meta*- and *para*- substituted *N*-benzylanilines was initially studied. It was found that the position of the chloro- substituent has a pronounced effect on the rate of debenzylation, and also to a lesser extent on dechlorination (Figure 5-1).

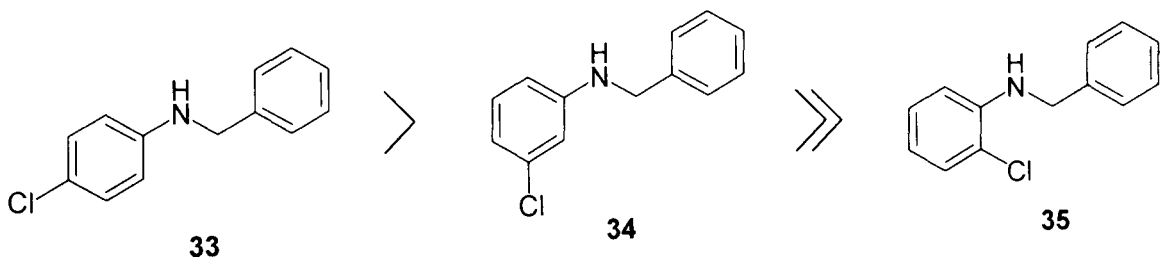
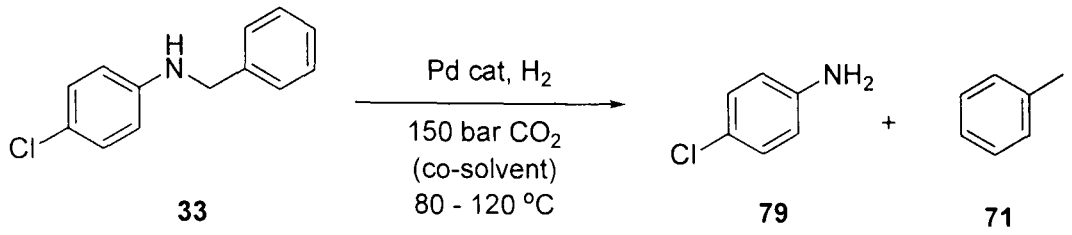


Figure 5-1: Rate of debenzylation of chlorinated *N*-benzylanilines decreases in the following order: *para* (33) > *meta* (34)> *ortho* (35).

Dechlorination was a significant problem during the *N*-debenzylation of the chlorinated substrates **[(33)-(35)]** due to the high temperatures that are required to facilitate continuous flow debenzylation. In subsequent debenzylation studies, aimed at minimising dechlorination, the debenzylation of the *para*- substituted *N*-benzylaniline **(33)** was studied in detail (Scheme 5-3).



33 **79** **71**

Scheme 5-3: Debenzylation of *N*-benzyl-*p*-chloroaniline (33) will lead to dechlorination of desired product (79) when the reaction is performed over a Pd catalyst. Various strategies have been developed to address this problem.

The strategies that have been developed to minimise dechlorination during debenzylation of *N*-benzyl-*p*-chloroaniline **(33)** are displayed below. Each strategy has its own set of advantages and disadvantages, some strategies may also be used in combination to further enhance selectivity:

1. In the initial stages of time-on-stream during the continuous flow debenzylation of **(33)**, dechlorinated by-products dominate the reaction mixture. However, this can be taken advantage of since the catalyst becomes deactivated toward dechlorination over time, but will remain active toward debenzylation (Strategy 1, Table 5-1). This method will only work when the substrate is particularly active toward dechlorination otherwise it will take a long period of time to poison all of the active sites involved in dechlorination.

2. In some cases it may be possible to minimise dechlorination by the correct choice of catalyst metal and support combination. In continuous flow, it has been shown that only Pd offers sufficiently high activity to facilitate debenzylation. Change in metal catalyst support can have a huge effect on selectivity, with Pd/Al, Pd/C and Pd on Si/Al all exhibiting high activity

toward dechlorination. In contrast, Pd/Si and $Pd/CaCO_3$ have both proven to be very selective catalysts for minimising dechlorination during debenzylation and hydrogenation studies (Strategy 2, Table 5-1).

3. Changing the co-solvent from a protic to an aprotic solvent, such as THF, will offer an effective way to minimise dechlorination (Strategy 3, Table 5-1). However, in cases where the substrate is particularly active toward dechlorination and the reaction is performed over a Pd catalyst, as was the case was for *p*-chloroaniline **(79)**, switching to an aprotic solvent will not completely inhibit dechlorination.

4. The relative rate of both debenzylation and dechlorination are influenced by addition of acid. A variety of different acids were tested to suppress dechlorination and it was H_2SO_4 that offered the greatest impact on selectivity. Upon addition of only 1 equiv. of H_2SO_4 in the continuous flow debenzylation of *N*-benzyl-*p*-chloroaniline **(33)**, it was possible to almost completely suppress dechlorination (Strategy 4, Table 5-1). A potential disadvantage of this strategy is that the acid would need to be removed in an industrial process, therefore leading to an extra separation step. In a pharmaceutical process however, many of the intermediates are isolated as salts, therefore the addition of an extra step to remove the acid may not be required.

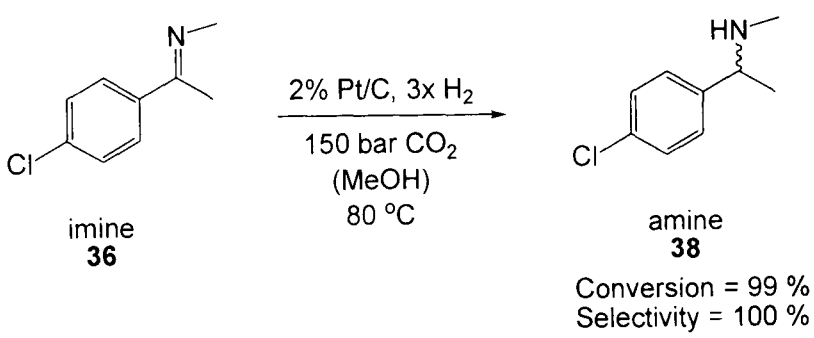
Table 5-1: Conversion and selectivity during the debenzylation of *N*-benzyl-*p*-chloroaniline (33) when using strategies 1-4 to minimize dechlorination

Strategy	Conditions	Conversion (%)	Selectivity toward (79) (%)
1	After pre-poisoning	67	100
2	2% Pd/Si catalyst	30	100
3	THF as co-solvent	88	75
4	1eq. H_2SO_4	88	89

5.2 Summary of Conclusions From Diastereoselective Hydrogenation in $scCO_2$

The diastereoselective hydrogenation of *rac*-sertraline imine **(42)**. an intermediate in the synthesis of the antidepressant Zoloft®,[1] has been investigated as a continuous flow process in $scCO_2$.

In the commercial hydrogenation process, one of the major challenges was avoiding formation of dechlorinated by-products. When formed in significant quantities, these by-products have to be removed through solvent intensive recrystallisation steps. To address the problem of dechlorination, hydrogenation studies were initially conducted on a model substrate, **(36)** to find suitable reaction conditions that would afford selective imine hydrogenation, without dechlorination (Scheme 5-4).



Scheme 5-4: Hydrogenation of the model substrate, imine (36) led to significant dechlorination of amine (38) when the reaction was performed over a Pd catalyst. Selectivity was dramatically improved by performing the reaction over a Pt catalyst.

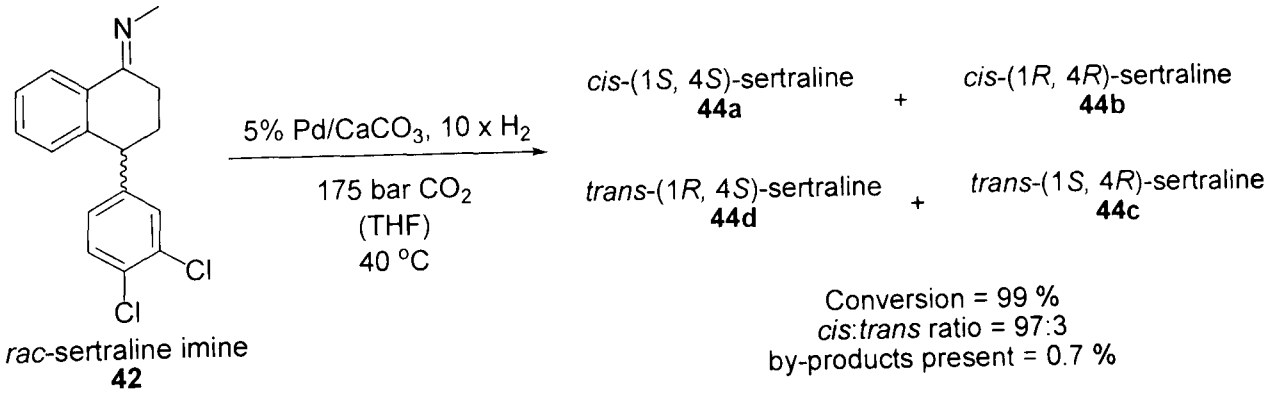
It was found that conducting the reaction over a Pd catalyst led to very poor selectivity due to dechlorination of amine **(38)**. However, by performing the reaction over a Pt catalyst, dechlorination was completely suppressed to provide near quantitative conversion to the desired product, amine **(38)**.

As anticipated from the model studies, performing the hydrogenation of *rac*-sertraline imine **(42)** in the presence of the Pt catalyst afforded chemoselective

imine hydrogenation without any dechlorination. However, chemoselectivity is not the only consideration during the hydrogenation of *rac*-sertraline imine **(42)**: diastereoselectivity is equally important with formation toward the *cis*-diastereoisomers **[(44a) & (44b)]** being required.

The Pt catalyst offered unacceptably low levels of diastereoselectivity and it was not possible to influence this by any change in reaction conditions. Attention then turned back to the use of a Pd catalyst, where research was focused on maximising both chemo- and diastereoselectivity. It was found that Pd catalysts offered superior diastereoselectivity compared to the Pt catalyst, however, two routes to by-product formation needed to be suppressed; dehydrogenation and dechlorination.

By performing the hydrogenation of *rac*-sertraline imine **(42)** at low temperature, in the presence of a Pd catalyst supported on $CaCO_3$ and using THF as co-solvent, it was possible to minimise formation of all by-products whilst obtaining excellent levels of diastereoselectivity (Scheme 5-5).



rac-sertraline imine
42

Scheme 5-5: Diastereoselective hydrogenation of imine (42) can be performed with excellent levels of chemo- and diastereoselectivity by performing the reaction in the presence of $scCO_2$ as a continuous flow process.

Hydrogenation reactions were performed in both the presence and absence of $scCO_2$. It has been shown that reactions conducted in $scCO_2$ exhibit higher levels of selectivity than those performed under the same conditions in the absence of

$scCO_2$. CO_2 has excellent heat transfer properties[2] and one explanation for the increased selectivity in $scCO_2$ is that CO_2 prevents the formation of hot-spots on the catalyst surface through the efficient transfer of heat throughout the reactor.

Table 5-2: Comparison between the current Pfizer process[3] (Entry 1) and the continuous flow process (Entry 2) that has been developed in $scCO_2$ for the hydrogenation of (42).

Entry	Vessel	Pressure (bar)	Reaction time (mins)	Temp (°C)	*cis*:*trans* Ratio	Composition of by-products (%)	
						Dechlor[d]	Dehydrog[d]
1	Batch	1	40-60	25	95:5	< 1.0	N.A.*
2	Flow	175	< 5	40	97:3	0.2	0.5

(Conditions: both processes use a 5% $Pd/CaCO_3$ catalyst; Entry 1 uses THF as solvent; Entry 2 uses $scCO_2$ as solvent and THF as a co-solvent)

** The presence of dehydrogenated by-products is not reported in the literature*

The continuous flow hydrogenation of *rac*-sertraline imine **(42)** in the presence of $scCO_2$ offers many advantages compared with the current industrial process, including increased safety due to the smaller reactor volume and also the presence of CO_2 helps to expand the non-flammable region. It has also been shown that higher levels of chemo- and diastereoselectivity can be achieved than are possible in the batch process.

5.3 Future Directions

Much of the research in this Thesis has been directed at minimising dechlorination. Our results suggest that over a Pd catalyst, dechlorination occurs on different catalytic sties to those involved in debenzylation. This can be advantageous when dechlorination is the unwanted reaction, since the catalyst becomes deactivated toward dechlorination over time. It would be interesting to develop this as a strategy for performing the selective debenzylation of a range of different substrates in continuous flow. For example, if debenzylation was required during the synthesis of an expensive pharmaceutical intermediate, would it be possible to selectively pre-poison the Pd catalyst using a cheap and commercially available chlorinated substrate (such as *p*-chloroaniline) and then use the pre-poisoned catalyst to afford selective debenzylation of the precious pharmaceutical intermediate. To answer this question, the selective debenzylation of a variety of chlorinated substrates needs to be tested. The long term stability of the pre-poisoned Pd catalyst must also be investigated.

To prove the versatility of continuous flow processing in the presence of $scCO_2$ it would be interesting to study the selective hydrogenation of substrates in the presence of *O*-benzyl or *N*-benzyl protecting groups. It would also be interesting to investigate competitive debenzylation of a perbenzylated substrate as further evidence to support that continuous flow processing in the presence of $scCO_2$ offers an attractive alternative for the synthetis of pharmaceuticals.

It has been shown that a complex pharmaceutical intermediate, *rac*-sertraline imine **(42)** can be hydrogenated with high levels of diastereo- and chemoselectivity. Reactions performed in the presence and absence of $scCO_2$ also show that reactions conducted in CO_2 offer superior selectivity. It would be interesting to compare the chemoselective hydrogenation of a range of other pharmaceutical intermediates in the presence and absence of $scCO_2$ to prove that $scCO_2$ offers superior levels of selectivity.

During studies on *rac*-sertraline imine **(42)**, formation of the by-product conjugated sertraline **(45)** was reported; even during reactions that were conducted at low temperature. Formation of conjugated sertraline **(45)** occurs due to a dehydrogenation (or disproportionation) process which takes place, in preference to hydrogenation, on catalytic sites that are not covered in H_2. Although it was possible to minimise formation of **(45)**, it will be important to investigate the effects of using heterogeneous catalysts in different forms (such as powdered, egg-shell, extrudates) to try and minimise this unwanted transformation in future studies.

To summarise Chapters 3 & 4, it has been shown that the hydrogenation of complex pharmaceutical substrates and chemoselective debenzylation can be performed with high levels of selectivity by undertaking these reactions as continuous flow processes in the presence of $scCO_2$.

The opportunity for conducting these reactions in continuous flow may be attractive in the future to the pharmaceutical industry as a potentially more efficient alternative to batch processing. A new first year student working within the group, Geoff Akien, is aiming to build on the research and ideas that have been discussed in this Thesis. This will help to expand our knowledge on the benefits and limitations of using $scCO_2$ as a solvent for the synthesis of pharmaceuticals.

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