Design of Continuous Reactor Systems for API Production

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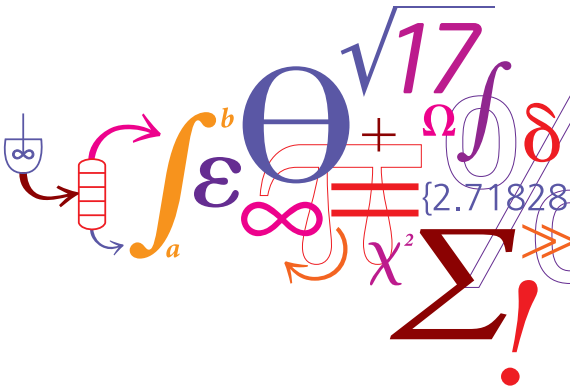

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Ph.D. Thesis
October 2014

DTU Chemical Engineering
Department of Chemical and Biochemical Engineering

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Preface

The industrial PhD project presented within this thesis has been a joint collaboration between H. Lundbeck A/S Department of Chemical Technology & Implementation and the Technical University of Denmark (DTU) at the department of Chemical and Biochemical Engineering in the Combustion and Harmful Emission Control (CHEC) research center. The project took place in the period from August 2011 to July 2014. Most of the laboratory work was conducted at Lundbeck, except for a six (6) month research period at the Massachusetts Institute of Technology (MIT) at the Department of Chemical Engineering in the Klavs Jensen research group.

The thesis is divided into several chapters and a short outline for each chapter is given below. The chapters containing original research with experimental sections have all been written in the appropriate manuscript format for the journals to which they are to be submitted for publication.

Chapter 1: A brief introduction to the pharmaceutical industry, including the motivations for a shift towards flow chemistry and the chemical engineering aspects of continuous production.

Chapter 2: A general discussion on the different aspects of Grignard chemistry, with a focus on flow chemistry.

Chapter 3: This chapter provides a kinetic study of a Grignard addition reaction investigated using flow chemistry. The studied chemistry contains consecutive-competitive reactions.

Chapter 4: The first part of the main case study, in which a flow reactor setup has been used to perform a base liberation of an alkyl halide salt needed for Grignard reagent formation.

Chapter 5: The second part of the main case study, in which a continuous reactor setup has been used for the formation of a Grignard reagent.

Chapter 6: The third part of the main study, in which a Grignard addition to a ketone has been carried out in a continuous reactor setup. Multi-step synthesis of an active pharmaceutical ingredient is demonstrated.

Chapter 7: This chapter demonstrates the scale-up of a laboratory continuous reactor setup used for a Grignard addition reaction that includes handling of solid material.

Chapter 8: This chapter combines the Grignard chemistry demonstrated in the previous experimental chapters. It provides a methodology for reactor design and decision-making processes related to the development of Grignard chemistry in flow.

Acknowledgements

During the last three years of this PhD project I have had the pleasure of meeting many interesting people, through both work-related relationships and those of a more social character.

My four supervisors deserve special thanks for their contributions to this project over the last three years. A huge thank you to my industrial supervisor, Tommy Skovby, for his unconditional belief in my work and his constant support. Many great discussions, both technical and social, have been shared and hopefully many more are still to come. My other industrial supervisor, Michael J. Mealy, likewise deserves thanks, especially for his contributions to the chemical discussions during the project. My main supervisor, Kim Dam-Johansen at DTU, has been a good motivator for the academic parts and has also given me the freedom to do research with a more industrially-oriented perspective. Søren Kiil, my other supervisor at DTU, has also been a driving force for the academic part of the project, always pointing out missing parts that could improve the work and providing me with useful feedback, for which I am thankful.

During the project, I had the opportunity to visit Boston for a six-month research visit to MIT, supervised by Klavs Jensen. I am deeply grateful for the time I spent there and to Klavs for giving me the chance to be a part of his group. Many good friendships have been made with both people from the research group and Bostonians in general. Hopefully I will see you all from time to time, in spite of the distance.

I am grateful that Lundbeck as a company has given me the opportunity to do a PhD on the topic of flow chemistry and there are many colleagues I need to thank. Steen Søgaard, for his interest in continuous production and his belief in me. The people in the workshop, for always being open-minded towards my crazy ideas and for engineering their technical solutions. The factory staff, for sharing their knowledge on production and for providing me with chemicals to use in the laboratory. Thank you to my colleagues at CTI and POL for their interest in my project and for always being ready to help, for which I am deeply grateful. I look forward to more good teamwork.

I would like to thank my friends and family, especially the close friends I have made during my time at DTU, where many of us are now coming to an end and finishing up our studies, but I am sure that we will keep finding reasons to meet. To my friends outside of DTU and to my family, thanks for being there whenever I needed you and for knowing that I am doing “chemistry stuff”. And last but not least, Jen, thanks for putting a smile on my face and for making me happy.

Cheers,

Michael

Abstract

The pharmaceutical industry has experienced many changes over the last few decades. Continuous production has been promoted as one of the more promising methods for making the industry more efficient and sustainable. The primary focus of this thesis is on the performance of Grignard chemistry in continuous reactor setups. Grignard chemistry encompasses a very powerful reaction type frequently applied in the pharmaceutical industry, for the formation of new carbon-carbon bonds. Three Grignard addition reactions have been studied, all having very different behaviors related to aspects of reaction engineering.

A double Grignard addition (two different Grignard reagents) to a lactone was studied with continuous production in mind. The complexity of the reaction was investigated kinetically in order to optimize a potential flow setup. The investigation indicated that reaction temperatures below -40 °C could suppress the formation of an undesired bis-addition product by stabilizing the mono-addition adduct.

A Grignard addition to a poorly soluble tricyclic ketone, previously studied in the laboratory, was transferred to full-scale production. Successful upscaling of the laboratory setup to full-scale production equipment enabled complete replacement of the existing batch production of this intermediate.

The crowning achievement in this work was the realization of continuous laboratory reactor setups capable of manufacturing the entire GMP portion of the synthesis of melitracen HCl at H. Lundbeck A/S. The formation of a carbon-carbon bond between a tricyclic ketone and a Grignard reagent was the primary objective, this being the first step in GMP synthesis. The process was optimized to include one-step hydrolysis and dehydration, followed by phase separation of the product-containing organic phase, which was then precipitated with hydrogen chloride to obtain the final API. The Grignard reagent was also produced in a continuous laboratory setup involving handling of solid magnesium turnings. Likewise, the alkyl halide used in the formation of the Grignard reagent was produced continuously. The three segmented units were able to be coupled to construct a single continuous reactor facility for manufacturing melitracen HCl.

The study of Grignard addition reactions to the three different substrates investigated in this thesis has culminated in a methodology by which reaction engineering decisions can be guided. The methodology provides suggestions on when and how decisions should be made on continuous production methods for Grignard chemistry within pharmaceutical manufacturing. Physicochemical properties, such as solubility, were found to be critical. However, from a business perspective, issues such as the current lifecycle of the API and GMP can make a potential reactor setup non-feasible. If the pharmaceutical industry is to adapt to recent trends towards end-to-end and on-demand pharmaceutical production, access to standard reactor units for commonly-used chemical transformations and methods for timely decision-making are essential. The methodology described herein provides an approach to fulfilling this need for Grignard chemistry in flow reactors.

Dansk Resumé

Den farmaceutiske industri har oplevet mange ændringer i løbet de sidste årtier. Kontinuert produktion har været betragtet som en af de mere lovende metoder at gøre branchen mere effektiv og bæredygtig. Det primære fokus for denne afhandling har været på Grignard kemi med udførsel i kontinuerte reaktor opsætninger. Grignard kemi er meget nyttig former for reaktioner, ofte anvendt i farmaceutiske industri til dannelsen af nye kulstof-kulstofbindinger. Tre Grignard additionsreaktioner er blevet undersøgt, alle med meget forskellige opførelse relateret til ingeniørmæssige reaktionsaspekter.

En dobbelt Grignard addition (to forskellige Grignard reagenser) til en lactone blev studeret med henblik på kontinuert produktion. Kompleksiteten af reaktionen blev undersøgt kinetisk, for at optimere et potentielt kontinuert reaktorsystem. Undersøgelsen viste, at reaktionstemperaturer under -40 °C kunne undertrykke dannelsen af uønskede bisadditionsprodukt, ved stabilisering af den mellemliggende monoaddition addukt.

En Grignard additon til en lavt opløselige tricyklisk keton, tidligere studeret i laboratoriet, blev overført til fuldskala produktion. Succesfuld opskalering af laboratorium opsætningen til en større fuldskala produktionsopsætning muligjorde en fuldstændig erstatning af den ældre batch produktion af dette mellemprodukt.

Hovedstudiet var muliggørelsen af kontinuerte laboratorium reaktoropsætninger, som kan producere alle GMP syntesetrinene af melitracen HCl hos H. Lundbeck A/S. Dannelsen af en kulstof-kulstofbinding imellem en tricyklisk keton og et Grignard reagens var det primære formål, som er det første syntesetrin underlagt GMP. Processen var optimeret til at omfatte en ét-trins hydrolyse og afvanding, efterfulgt af en faseadskillelse af organisk produktfase fra vandigt affald, produktfasen blev efterfølgende fældet med HCl til det endelige API. Dannelse af Grignard reagenset blev også påvist i en kontinuert laboratorieopstilling, der involverer faststofhåndtering af magnesium spåner. Ligeledes var dannelsen af alkylhalidet som blev brugt til Grignard reagenset fremstillet i en kontinuerlig reaktoropsætning. Potentielt, kunne de tre segmenterede opsætninger være koblet sammen til en enkelt kontinuert reaktoropsætning til dannelse af melitracen HCl.

Studiet af Grignard additionsreaktioner til tre forskellige substrater som er dækket i afhandlingen, har kulmineret til en metodologi for beslutningstagen for ingengiørmæssige reaktionsovervejelser. Metoden indeholder forslag om hvornår og hvordan der tages beslutning for kontinuerte produktionsmetoder for Grignard kemi inden for den farmaceutiske produktion. Fysisk-kemiske egenskaber, så som opløselighed, blev fundet kritiske. Desuden, er mere bløde problemer som det nuværende livscyklus status af API og GMP relaterede emner bidrager til afgørelse, hvis en økonomisk attraktiv reaktorløsning skal etableres. Hvis den farmaceutiske industri skal tilpasse sig den seneste tendens med *end-to-end* og *on-demand* farmaceutisk produktion, er det nødvendigt at have standard reaktorenheder for almindeligt anvendte kemiske omdannelser, og metoder til tidlig og hurtig beslutningstagen. Den udviklede metodik beskrevet i denne afhandling giver en god afdækning af Grignard kemi i flow reaktorer.

Contents

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Abbreviations

4-FPhMgBr	4-Fluorophenylmagneisum bromide
10,10-DMA	10,10-Dimethylanthrone
aq.	Aqueous
AcOH	Acetic acid
ACR	Agitated Cell Reactor
ACS	American Chemical Society
AE	Atom Economy
API	Active Pharmaceutical Ingredient
ATEX	Atmosphères Explosibles (Explosive Atmospheres)
Bo	Bodenstein number
BPR	Back Pressure Regulator
cGMP	Current Good Manufacturing Practice
cm	Centimeter
C	Molar Concentration
C-C	Carbon-Carbon bond
CE	Carbon Efficiency
CHN	Elementary Analysis
CNS	Central Nervous System
COBR	Continuous Oscillated Baffled Reactor
CSTR	Continuous Stirred Tank Reactor
D	Dispersion Coefficient
D	Diameter
D_H	Hydraulic Diameter
Da	Damköhler number
De	Dean number
DFT	Density Functional Theory
DME	1,2-Dimethoxyethane
DMPC	3-(*N,N*-dimethylamino)propylchloride
DMPC-HCl	3-(*N,N*-dimethylamino)propylchloride hydrochloride
DMPC-MgCl	3-(*N,N*-dimethylamino)propylmagnesium chloride
DoE	Design of Experiments
Et_2O	Diethyl ether
E-factor	Environmental factor
EMA	European Medicines Agency
EMY	Effective Mass Yield
F	Molar Flow Rate
FDA	Food and Drug Administration
FT-NIR	Fourier Transform Near-Infrared
g	Gram
GCI	Green Chemistry Institute
GC-MS	Gas Chromatography Mass Spectroscopy
GMO	Genetically Modified Organism

GMP	Good Manufacturing Practice
GS	Ground State
GSK	GlaxoSmithKline
h	Hour
HPLC	High Performance Liquid Chromatography
HSE	Health, Safety & Environment
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ID	Inner Diameter
IP	Intellectual Properties
IR	Infrared
j	Species
k	Rate constant
kJ	Kilojoules
KF	Karl Fischer
L	Liter
L	Reactor Length
LCA	Life Cycle Assessment/Life Cycle Analysis
μ	Viscosity
μL	Microliter
μm	Micrometer
m	Meter
m^2	Square meter
min	Minute
mL	Milliliter
MW	Molecular Weight
M	Metal
M	Moles per Liter
Me	Methyl
MeOH	Methanol
MeTHF	2-Methyltetrahydrofuran
MIT	Massachusetts Institute of Technology
MRT	Microreactor Technology
n	Number
nm	Nanometer
NIR	Near-Infrared
NLT	Not Less Than
NME	New Molecular Entity
NMT	Not More Than
Nu	Nusselt number
org	Organic
OD	Outer Diameter
ODE	Ordinary Differential Equation

OFR	Oscillating Flow Reactor
OOS	Out-of-Specification
OOT	Out-of-Trend
Pa	Prandtl number
PAT	Process Analytical Technology
PCM	Polarized-Continuum Model
Pe	Péclet number
PEEK	Polyether Ether Ketone
PES	Potential Surface Energy
PFR	Plug Flow Reactor
Ph	Phenyl
PLS	Partial Least Squares
PMI	Process Mass Intensity
PTFE	Polytetrafluoroethylene
QbD	Quality-by-Design
ρ	Density
r	Rate of reaction
R	Alkyl or Aryl group
R&D	Research & Development
Re	Reynolds number
RMSECV	Root-Mean-Square Error of Cross-Validation
RMSEE	Root-Mean-Square Error of Estimation
RTD	Residence Time Distribution
RX	Alkyl and Aryl Halide
s	Second
sat.	Saturated
STP	Standard Temperature and Pressure
SET	Single Electron Transfer
Sol.	Solubility
SS	Stainless Steel
τ	Residence Time
*t*Bu	*tert*-Butyl
TFA	Trifluoroacetic Acid
TGA	Thermogravimetric Analysis
THF	Tetrahydrofuran
TS	Transition State
ū	Average Flow Velocity
UV-vis	Ultraviolet-visible
v	Volumetric Flow Rate
v	Flow Velocity
vol%	Volume percent
V	Volume
wt%	Weight percent
X	Halide

ZEP	Zero-Point Energy
°C	Degrees Celsius
%w/w	Weight per weight percent

Chapter 1

The Pharmaceutical Industry and Continuous Production

1.1 Introduction

The pharmaceutical industry is highly complex, including many cross-disciplinary fields of science and business. In the last couple of decades the industry has experienced great changes due to the incipient introduction of continuous production methods and reinterpretation of regulations, a process that is still ongoing. The pharmaceutical industry as a whole is classified by the different methods by which the active pharmaceutical ingredient (API) is produced, either organic chemical synthesis (small molecules) or biochemical methods such as fermentation (macromolecules). Besides this overall classification, the pharmaceutical industry is further divided into generic companies and research-based companies. Throughout this thesis, the term pharmaceutical industry refers to the research-based part of the industry, mostly focusing on organic chemical synthesis companies. This first chapter provides an introduction to and overview of the pharmaceutical industry, covering the transformation it has undergone in the last few decades. Understanding the pharmaceutical industry in more detail helps to identify the challenges presently faced by the production part of the industry.[1,2]

1.2 H. Lundbeck A/S

H. Lundbeck A/S (Lundbeck in short form) is a research-based pharmaceutical company using organic synthesis to manufacture APIs. Lundbeck focuses on treatments for the central nervous system (CNS), a strategy that was established back in 1987. Lundbeck was founded in 1915 as a trading company, but has gradually moved towards its present dedication to CNS treatments. The employment of Eduard Goldsmith in 1924 initiated this pharmaceutical production and Lundbeck began to produce pharmaceuticals in the 1930s. It was P.V. Petersen who changed the target to CNS and Lundbeck became a research company with several APIs produced in-house. Today, Lundbeck is one of the leading companies in CNS treatments, with almost 6000 employees worldwide. The headquarters and main research & development (R&D) facilities are located in Valby, Denmark and the production of APIs is carried out in Lumsås, Denmark and Padua, Italy. Tableting facilities are situated in Valby, Denmark and Nice, France.[3,4]

For several years, the main source of revenue came from a refinement of the API citalopram. A method was developed to separate the racemic mixture into the active S-isomer (escitalopram) and the R-isomer, resulting in a new period of patent protection. Escitalopram (Cipralex®) has gone off-patent within the last few years, but it has been replaced with new promising APIs (nalmefene (Selincro®) and vortioxetine (Brintellix®)) to ensure continuous revenue for Lundbeck. As a research-dependent pharmaceutical company, development of new APIs is a key parameter for staying in business. Besides the R&D of new APIs, constant optimization of production is necessary to remain competitive while maintaining production in developed countries with expensive labor costs. Lundbeck was quick to embrace the opportunities for alternative manufacturing procedures (e.g. continuous production) that became possible in 2004, when the Food and Drug Administration (FDA) of the United States (US) reviewed current manufacturing methods based on efficiency within the pharmaceutical industry. At present, Lundbeck has three full-scale continuous reactor setups in operation, with each one being capable of producing three different starting materials used in API syntheses. Approaches have furthermore moved from segmented synthetic steps to potential multistep syntheses, following the same trend as generally seen in flow chemistry. Lundbeck's main manufacturing methods still rely on batch production, as is the case for most pharmaceutical companies.[3,4]

1.3 An Overview of the Pharmaceutical Industry

The pharmaceutical industry is one of the most complex chemical industries and includes multidisciplinary interaction between many sciences. The industry relies heavily on the development of new drugs and protection through different intellectual property (IP) rights. IP is commonly achieved through patents, providing a company with 20 years of protection of the invention.[5–11] Different patent protections are commonly used in the pharmaceutical industry; in particular, patents on structure are highly favored in comparison to process patents, which are often hard to enforce.

The process for developing a new drug candidate for pharmaceutical production is expensive and long. A normal development period of approximately 10 years is not

uncommon, which only leaves 10 years for making profit.[5,12–14] The cost of developing one drug that survives until launch and production release additionally has to cover the large number of target compounds that have been discarded.[8]

In the early discovery period, thousands of potential APIs are synthesized, where many of these are discarded early in the process due to toxicity and/or lack of biological activity. Approaching the clinical trials, the number of potential APIs is narrowed down to less than 10, a number that keeps on decreasing to even less when the phase I studies are begun. The phase I study is also the first human trial (in healthy people), which is why the cost of testing increases significantly. In phase II, often one or two candidates remain and the clinical trials start to include patients with the disease to which the APIs are targeted. In phase III, the final verification of efficacy is demonstrated and the APIs are filed for production if positive results are achieved. The accumulation of costs steadily increases throughout the trial periods, since promising APIs are discarded and in general expenses become larger due to more demanding testing and documentation of their effects. During phase I, approximately 100 healthy people participate, phase II requires 400-500 patients and phase III requires up to 5000. For each phase, the requirements for success become higher. The amount of the APIs used also increases during development, from a few mg to hundreds of kg. An overview of a typical development progress is illustrated in figure 1.1.[8,10,11,15,16]

As the clinical trials progress, the transfer from R&D to routine production slowly begins. During phase I and phase II, the full-scale synthetic route is decided on and optimized. At the beginning of phase III, very few alterations to the production method are accepted. The limited options for alteration during the beginning of phase III are a consequence of the initiation of carcinogenic studies, used to document long-term exposure to the API.

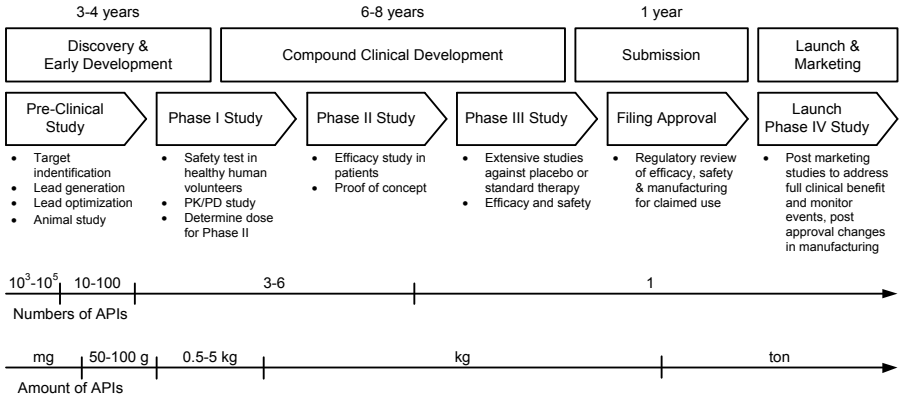


Figure 1.1: General overview of drug development up to launch.[8,10,11,15,16]

The development of new APIs comes with larger expenses in order to regain the losses from the thousands of potential drug candidates that were discarded.[8] In the last few decades, discovery of new APIs has become more challenging and R&D investments

have increased steadily, as has development time. The combination of increased R&D efforts and decreasing numbers of new APIs pushes up the total cost of development.[12] Figure 1.2 shows the trends in the pharmaceutical industry. In the last couple of years, a small increase in the number of New Molecular Entities (NMEs) has been observed and over a 20-year period the annual average number of NMEs was approximately 25.[17]

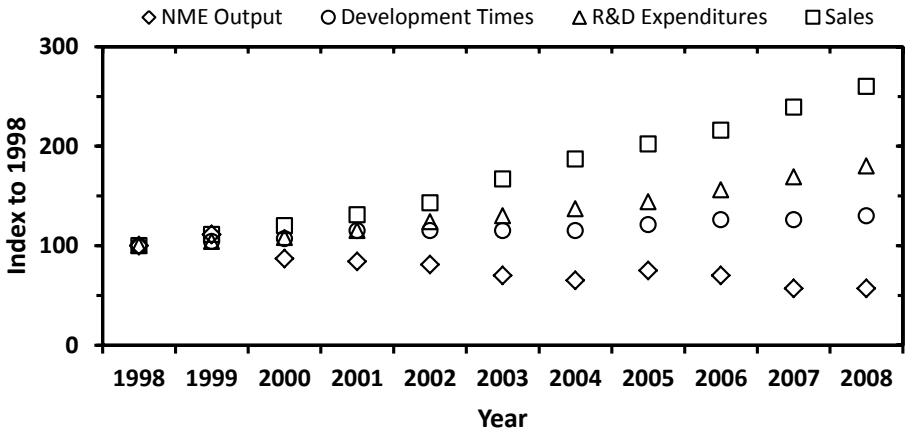


Figure 1.2: Development within the pharmaceutical industry for the period from 1998 to 2008.[18]

The pharmaceutical industry faces a great challenge in increased development costs, since the industry still relies on the development of new APIs and IP protections to stay in business. It is common that once an API goes off-patent, 90% of the market share can be lost within a year.[10,11,19] The first and most simple way to increase revenue is by producing under patent protection for a longer period of time. Expanding the production time under patent protection requires the product to reach the market earlier (i.e. shortening the development time) or the patent to be prolonged. Both concepts are rather unlikely to occur in most situations and alternative ways should be found. Another alternative is efficiency of production (e.g. process intensification and process optimization), hence manufacturing APIs at a lower cost than the original methods through novel solutions.[20] A common cost structure in the pharmaceutical industry is given in figure 1.3, illustrating the importance of R&D to companies but also elucidating the huge expenses related to manufacturing that could potentially be reduced.[21] It is not uncommon for R&D spending on product development to be even higher[12] (30-35%). The raw material is often the most expensive part of the manufacturing costs, accounting for 30-80%. The remaining manufacturing expenses are operational, distributed between labor, plant costs, quality assurance & control, waste treatment, logistics & transport and changing & cleaning.[22]

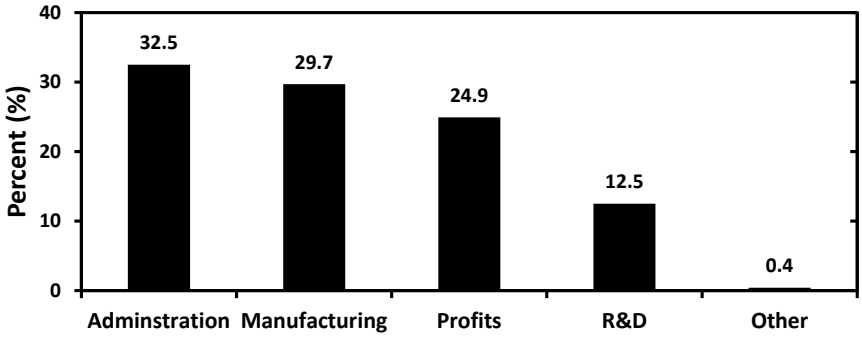


Figure 1.3: The cost distribution in a typical pharmaceutical company.[21]

As the challenges for discovering new APIs have increased, collaborations across boundaries have emerged. Cross-collaborations between academia and industry as well as joint ventures between large pharmaceutical companies have arisen. Joint ventures between big pharmaceutical companies for the development of new APIs are often seen due to the shared risk, meanwhile accepting the downsides of sharing profit. This trend is also supported by the fact that new API development has increased in the academic environment, with a subsequent modification in the pharmaceutical R&D department.[10,23,24] Welch *et al.*[25] provide a good overview of the benefits and downsides of different approaches to collaboration. During the last two decades, significant merging of large pharmaceutical companies has occurred. In 2010, 10 of the biggest pharmaceutical companies could be traced back to 57 companies in 1990.[18]

Due to the consequences that badly-produced medicines can impose on patients, the pharmaceutical industry is perhaps the most strictly regulated chemical industry. The industry subscribes to the concept of GXP, which is a general acronym for Good Practice related to a certain area X. Production has to comply with Good Manufacturing Practice (GMP), where it is the current GMP (cGMP) version that must be met, as the description is frequently revisited and updated. Enforcement of the rules is handled by the regulatory authorities, the three major ones in the world being the US FDA, the European Medicines Agency (EMA) and the Japanese Ministry of Health. All three agencies disseminate the guidelines provided by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). ICH is a professional organization consisting of the regulatory authorities and the pharmaceutical industry in these three regions.[19,26,27]

Regulatory control and documentation rules are very strict and once the manufacturing process for an API has been filed and approved, optimizing the process by alteration becomes very difficult and is often associated with expensive and time-consuming refiling. As a consequence of these strict regulations to protect patients, the industry has impeded its own opportunities for innovation. In 2004, the FDA broke with the general GMP rules of the time and started the debate on how the pharmaceutical industry could still comply with high quality assurance but allow innovative thinking at the same time.[21,28]

As the new regulatory aspects were brought into effect, new control strategies became necessary. Before 2004, the standard procedure for the release of APIs and drugs was through quality analysis by well-defined procedures. Out-of-trend (OOT) or out-of-specification (OOS) APIs were easily detected, since each batch required a release analysis before further processing. Continuous manufacturing does not have the same control of material as batch methods and alternative ways to assure quality have to be established. Process Analytical Technology (PAT) and Quality-by-Design (QbD) are potential methods for achieving the desired quality control. The concepts of QbD and PAT are closely related, as PATs are often used to ensure that a reactor setup's performance is in accordance with the specified QbD description when operated. Development of spectroscopic equipment and measurement methods has progressed strongly and today serves as a very important tool for PATs. Spectroscopic measuring has become very popular due to its non-disruptive methods, from which highly specific data can also be extracted. The measurements are often combined with chemometric data treatment, as the raw data are not always easily interpreted. The more commonly used non-disruptive spectroscopic methods include near-infrared (NIR), infrared (IR), Raman and ultraviolet measurement (UV-vis). In the process of developing a QbD reactor setup, Design of Experiments (DoE) is often used to optimize performance based on static calculation and modelling of the investigated parameters. Simpler measurement methods like temperature, mass flow and pH controllers are commonly applied and prove sufficient and important for QbD in many instances. The above-mentioned methods have been used in the food industry for several years before being merged into the pharmaceutical industry.[1,15,19,29,30]

Discussions on how the pharmaceutical industry can keep up with modern thinking and efficiency have been the target of many debates and publications throughout the last decade.[22,31–34] Stakeholders in the pharmaceutical industry broadly acknowledge that the current state does not comply with modern thinking and actions are already being taken to meet these concepts. Many issues, aspects and concerns have been raised in order to gain a better overview of the challenges the industry is facing. In 2005, interested parties from the American Chemical Society (ACS), the Green Chemistry Institute (GCI) and leading global pharmaceutical companies formed the ACS GCI pharmaceutical roundtable committee.[31] The primary interest of the committee is how the pharmaceutical industry can remain efficient and competitive and in 2007 the committee came up with ten key issues (Table 1.1). The highest ranked key area was continuous processing,[31,35] a topic that since the beginning of the century has attracted great attention within organic synthesis chemistry.[32–34,36–43] However, continuous pharmaceutical production is not an entirely new concept. V.V. Popov[44] suggested back in the 1970s that continuous production could be of great importance for the pharmaceutical industry.

Table 1.1: Ten key issues suggested by the ACS GCI Roundtable to be important for the pharmaceutical industry.[31]

Rank	Main Key Areas	Sub-Areas/Aspects	Votes
1	Continuous Processing	Primary, Secondary, Semi-continuous	12
2	Bioprocesses	Biotechnology, Fermentations, Biocatalysis, GMOs	11
3	Separations and Reaction Technologies	Membranes, Crystallization	11
4	Solvent Selection, Recycling and Optimization	Property modelling, Volume optimization, Recycling technologies, In-process recycling, Regulatory aspects	10
5	Process Intensification	Technology, Process, Hybrid systems	9
6	Integration of Life Cycle Assessment (LCA)	Lifecycle thinking, Total cost assessment, Carbon/eco-footprinting, Social LCA, Streamlined tools	4
7	Integration of Chemistry and Engineering	Business strategy, Links with education	4
8	Scale-up Aspects	Mass and energy transfer, Kinetics and others	3
9	Process Energy Intensity	Baseline for pharmaceuticals, Estimation, Energy optimization	1
10	Mass and Energy Integration	Process integration, Process synthesis, Combined heat and power	0

In an effort to provide sustainability for the pharmaceutical industry, a number of reviews have been published. GlaxoSmithKline (GSK) reviewed their use of solvents and reagents to understand whether better and more clever decisions on reagents and solvents could be made for both production and early candidate development.[45–47] The ACS GCI pharmaceutical roundtable[35] assessed the distribution of consumed material for API production, revealing that reactants only accounted for 7% of the Process Mass Intensity (PMI). The PMI survey showed that solvents and water accounted for 56% and 32% respectively, which is in good agreement with the E-factor comparison of different chemical industries (Table 1.2) made by Sheldon.[48] An overview on how the fine chemical and pharmaceutical industries (7 and 17 companies, respectively) were dealing with green chemistry and sustainability was provided by Watson.[49]

Table 1.2: The E-factor for a selected number of chemical industries.[48]

Industry Segment	Product Tonnage (T)	E-Factor ($kg_{waste}/kg_{product}$)
Oil Refining	10^6-10^8	<0.1
Bulk Chemicals	10^4-10^6	<1-5
Fine Chemicals	10^2-10^4	5-50
Pharmaceuticals	10-10^3	25-100

AstraZeneca, Pfizer and GSK[50] mapped the number of different synthesis routes and chemical transformations that are most frequently used in the synthesis of small molecule APIs (<550 MW). The survey shows that, on average, eight chemical transformations were necessary to achieve the final product of the 128 syntheses investigated. Roughley *et al.*[51] did a similar survey and Pfizer[52] provided an overview of reaction types and methods used in GMP bulk production. Formation of new carbon-carbon bonds accounted for roughly 11-14% of all chemical transformations, with Grignard reactions accounting for approximately 6-9% of this number.[50–52] Lonza[53] provided a survey of 86 synthesis steps in which it was concluded that 63% involved solid material handling. The ACS GCI pharmaceutical roundtable[31] provided an estimate of the frequency of different unit operations used in pharmaceutical chemistry (Figure 1.4). Mapping and categorizing the industry have helped to visualize potential areas where a change of mind-set and common routines could be made.

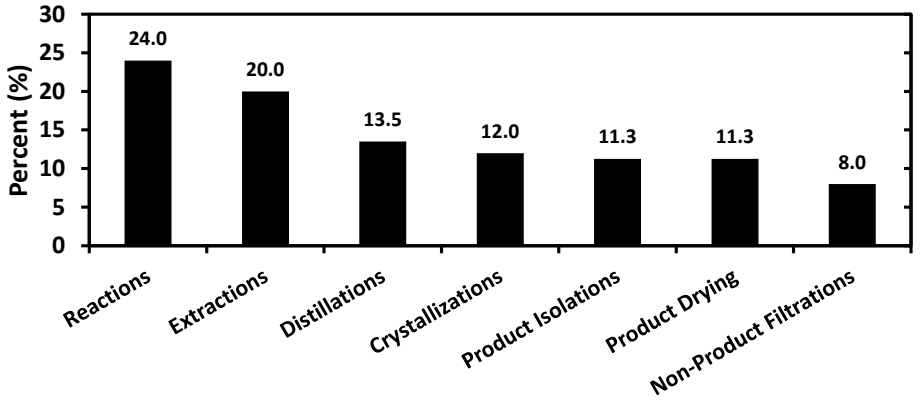


Figure 1.4: Frequency of unit operations applied in the pharmaceutical industry.[31]

1.3.1 Batch or Continuous Production

Batch productions have been the workhorse of the pharmaceutical industry for many decades. In particular, the authorities' definition of how APIs should be manufactured and R&D scientists' preferred synthesis methods in the laboratory have been major driving forces for the prevalence of batch methods. The biggest advantage of a batch reactor may very well be its multipurpose functionality (e.g. reaction, separation, crystallization and distillation), providing great flexibility for manufacturing. Combined with the fact that

development of new APIs mostly proceeds via batch syntheses, the natural choice for scaling of a synthesis is often the batch reactors.[19,22,32]

Continuous production methods are quite the contrary to using batch reactors. The continuous reactors employed are often highly specific for the intended process and often only capable of performing a single operation. The specificity of continuous reactors is among the things that make continuous reactors highly efficient. Continuous reactors are often significantly smaller in dimension compared to batch reactors. The smaller dimensions improve the mass and heat transfer performance of continuous reactors, resulting in more stable operating conditions. A major drawback of continuous reactors is their limited capability for handling solid reactants and special designs or precautions are often necessary. Control strategies also become an important factor when dealing with continuous manufacturing.[19,22,32,54,55]

Comparison of batch technologies with continuous processing elucidates why batch reactors are still in use in the pharmaceutical industry, despite the many great advantages of flow chemistry. As seen in table 1.3, both production technologies have advantages and disadvantages and the choice of one over the other should be based on optimal performance of the given reaction or chemistry.[19,32,56,57]

Table 1.3: Comparison of batch and continuous process technologies; (+) and (-) indicate positive or negative influence.[56,a]

Criterion	Batch Process	Continuous Process
Product Quality	Variable (-)	Constant (+)
Optimal Product Quantities	Small: On-demand	Medium/Large: In store
Process Flexibility	High, Multipurpose (+)	Low, Dedicated (-)
Automation	Low, but complex	High, Straightforward
Labor Cost	High (-)	Low (+)
[b]Process Control Needs	Low (+)	High (-)
Set-Up Times	Long (-)	Minimal (+)
Cleaning	Laborious (-)	In-Design (+)
Start-Up and Shutdown	Not Applicable	Complex (-)
Long Reaction Times	Possible (+)	Difficult (-)
Investment	Low (+)	High (-)
Maintenance and Troubleshooting	Common Equipment (+)	Often Customized (-)

[a]The table is modified for clarification.
[b]The original source[56] has the opposite statement, but this is assumed to be a misprint and has been corrected.

Calabrese and Pissavini[57] provided an economic assessment of flow chemistry over batch processing for a nitration reaction. The Novartis-MIT collaboration[58] gave rise to an economic comparison between a batch and a continuous process for a selected API synthesis.

1.4 Reaction Engineering Aspects Related to Flow Chemistry

Chemical reaction engineering plays a very important part in the effort to transform the traditional pharmaceutical batch industry into modern time-continuous process methods. In particular, understanding the potentials and limitations of flow reactors is necessary for attempting to make flow reactor setups for production purposes.

The continuous stirred tank reactor (CSTR) and the plug flow reactor (PFR) are perhaps the two most important reactor modules to understand, since many of the other more specialized reactor configurations can be described based on these. One of the main differences distinguishing continuous reactors from batch reactors is that the reaction takes place over space (reactor volume) instead of time. For flow reactors, reaction time then becomes correlated to reactor volume (V) and volumetric flow rate (v), to give the residence time (τ).[59,60]

$$\tau = \frac{V}{v} \tag{1.1}$$

Describing a chemical system is done on the basis of the mass balance, which after rearranging gives the design equations for the different reactors. For ideal reactors under steady state conditions, the design equations for a CSTR and a PFR are given in equations 1.2 and 1.3, respectively.

$$V = \frac{F_{j0} - F_j}{-r_j} \tag{1.2}$$

$$\frac{dF_j}{dV} = -r_j \tag{1.3}$$

The design equations are based on the reactor volume (V), the molar flow rate (F) to a given species (j) and the rate of reaction ($-r$). The molar flow rate is also described as concentration (C_j) multiplied by the volumetric flow rate (v). The design equation for the PFR is comparable to the design equation for a batch reactor.[59] The rate of reaction is determined by the rate constants and the chemistry to be carried out in the reactor. In many situations, the elementary rate law is sufficient for describing the system.[59]

One of the significant differences between a PFR and a CSTR is the mixing behavior. The PFR will in an ideal situation have no axial mixing, resulting in no back mixing. For the CSTR, the picture is completely the opposite and under ideal conditions the mixture within the reactor is the same as in the outlet. For real systems, ideal behavior is rarely observed even in a tubular flow regime, but the effect of this non-ideality can often be neglected. Residence time distribution (RTD) is a common method for expressing the effect of non-ideality.[59,60]

In addition to the RTD, the mixing occurring in the two reactor types is based on different technologies. The CSTR is in general equipped with a mechanical stirring mechanism, such as an impeller or similar device, for mixing in the reactor vessel. The PFR in its simplest version relies on internal forces alone for mixing. The mixing performance of the PFR can be enhanced with static mixers (mechanical forces), resulting

in better mixing performance.[61–65] To describe mixing, the dimensionless Reynolds (Re) number is widely applied, which describes the relation between internal and viscous forces. For pipes, the Re is defined by the density (ρ), the viscosity (μ), the flow velocity (v) and the hydraulic diameter (D_H). For an impeller-stirred vessel, the Re is often defined by the density (ρ), the viscosity (μ), the impeller diameter (D) and the rotational speed of the impeller (N). Large Re values equate to a tubular flow regime ($Re_{PFR} > 3000$, $Re_{CSTR} > 10^4$).[59,66,67]

$$Re_{PFR} = \frac{\rho v D_H}{\mu} \quad 1.4$$

$$Re_{CSTR} = \frac{\rho N D^2}{\mu} \quad 1.5$$

The way of defining the average reaction time in a continuous reactor by τ (equation 1.1) gives rise to some general assumptions on the limitations of the system related to dimensions, mixing and reaction times. If the desire is to have good mixing, the PFR faces challenges for slow reactions.[22] In order to obtain large Re numbers, the flow rate must be high and in the case of slow reactions a very long PFR is required that will additionally result in a large drop in pressure. Since the mixing in a CSTR is not influenced by the flow rate, the CSTR is preferred over the PFR for slow reactions in many situations.[22,43,68]

Since the Re number for a PFR will in many situations result in non-tubular flow regimes, other dimensionless numbers have been defined to assist with the decision on PFR related to mixing performance and its influence on the reaction. One of the most important is the Bodenstein (Bo) number, which describes the convective flow to dispersion. Bo is defined by the average flow velocity ($\bar{u}$), the reactor length (L) and the dispersion coefficient ($\boldsymbol{D}$). The dispersion coefficient accounts for both the diffusion coefficient and the convection. Bo has been applied in small scale systems in particular.[32,66,69]

$$Bo = \frac{\bar{u} L}{\boldsymbol{D}} \quad 1.6$$

Other interesting numbers that should be mentioned are the Damköhler (Da) number and the Dean (De) number, where Da describes the reaction time-scale versus the residence time and the De number describes the vortices in curved pipes.[66,70,71] Similar to the dimensionless numbers discussed for mass transfer, heat transfer is just as important a topic. The Péclet (Pe), Nusselt (Nu) and Prandtl (Pa) numbers are some of the more important numbers; for a deeper discussion of the topic on dimensionless numbers and general mass and heat transport phenomena, see Bird *et al.*[66]

To benefit from the design equations, an understanding of the chemistry and the kinetics taking place is important, especially when dealing with competitive reactions, either consecutive (1.7) or in parallel (1.8).[59] In these two equations, A, B and C are reactants, P is the desired product with rate constant k_P and I is the undesired product with the rate constant k_I.

$$\begin{aligned} A + B &\xrightarrow{k_P} P \\ A + P &\xrightarrow{k_I} I \end{aligned} \qquad 1.7$$

$$\begin{aligned} A + B &\xrightarrow{k_P} P \\ A + C &\xrightarrow{k_I} I \end{aligned} \qquad 1.8$$

A number of studies have been carried out in order to better understand how to manipulate these kinds of reaction challenge.[63,70,72–74]

A couple of the more conceptual reactor configurations for continuous production deserve more detailed description. Multiple injection points PFR is, in its most simple configuration, a number of PFRs connected in series. This kind of reactor configuration is often used in situations where it is desirable to keep one of the reactants at a low concentration (e.g. competitive reactions, exothermic reactions).[75–80] Another commonly applied configuration is multiple CSTRs in series. This type of configuration is often used to narrow down the RTD of the CSTR. A common application for this configuration is for slow reactions that are mixing sensitive.[59,81,82] Similar to multiple CSTRs is the oscillatory flow reactor (OFR). This consists of a tubular reactor divided into a number of cavities by baffles. An oscillating motion makes the small cavities behave like small CSTRs, hence at laminar flow-through a tubular flow regime can be achieved. Besides the mixing sensitive reactions, this conceptual reactor has been used for crystallisation.[83–87] The filter reactor is another conceptual reactor design. This reactor is well stirred, similar to a CSTR, but with a filter at the outlet to retain solid material. This type of reactor has an advantage for any reaction that requires retaining solid material; one example could be a solid reactant with low solubility where the product has high solubility.[88–90]

1.5 Process Scale-up from Laboratory to Full-Scale

In transferring from the laboratory development of APIs to full-scale production, there is a huge change in the way the chemistry is performed to achieve the desired API. In the laboratory search for new APIs, exotic synthesis routes are used, often with narrow operating windows. A direct transfer is therefore often not possible if the process is to be economically feasible. On average, 5-8 synthetic steps are used for commercially available products.[50–52] Besides the challenge of modifying the chemistry, the largest difficulties are the physical phenomena (e.g. mass and heat transfer) observed in a larger reactor. Table 1.4 gives an understanding of how, in particular, the surface to volume ratio changes from the laboratory to a production size batch reactor. Furthermore, parameters such as stirring intensity are effected by the scaling.[1,19,59,91]

Table 1.4: Scale-up from laboratory to production size equipment for batch reactors.

	Laboratory Development	Laboratory Scale-Up	Pilot Plant	Production
Active Volume (L)	0.5	50	500	5000
Diameter (m)	0.086	0.399	0.86	1.85
Height (m)	0.086	0.399	0.86	1.85
Surface Area (m^2)	0.029	0.625	2.904	13.440
Surface/Volume (m^{-1})	58.1	12.5	5.8	2.7

In comparison to the batch reactor scale-up, a similar calculation can be done for tubular flow reactors (Table 1.5).

Table 1.5: Comparison of laboratory to production size equipment for PFR with 10 min residence time.

	Laboratory Development	Laboratory Scale-Up	Production (Small)	Production (Large)
Flow rate (mL/min)	1	50	500	1000
Diameter ID (inch)	1/16	3/8	1	1 ½
Length (m)	5.1	7.0	9.9	8.8
Volume (L)	0.01	0.5	5	10
Surface Area (m^2)	0.025	0.210	0.787	1.050
Surface/Volume (m^{-1})	25.2	4.2	1.6	1.0

As shown in table 1.4 and table 1.5, scale-up of a batch reactor and a tubular flow reactor does not have much effect on the surface to volume ratio, but the center to wall ratio is very different. Continuous stirred tank reactors (CSTRs) are placed somewhere in between batch reactors and PFRs upon scaling.

1.6 Summary

The pharmaceutical industry has in recent decades experienced changes in the way the industry is observed. The number of new pharmaceuticals being developed has generally decreased and many of the previous blockbusters have gone off-patent. At the same time, generic manufacturers keep putting pressure on research and development-based companies by manufacturing off-patent pharmaceuticals more cheaply. Focusing on sustainability and greener processes has also pushed the industry into new directions of more efficient production. Stakeholders in the pharmaceutical industry have generally acknowledged that changes are necessary and the authorities have slightly relaxed the regulatory documentation related to production. It is believed by many that continuous production is one of the key parameters that can make the industry more efficient. The pharmaceutical industry still relies heavily on development by batch processing and the shift towards continuous production is a slow process. Continuous processing is a whole new discipline within the pharmaceutical industry and new technologies and terms such as Quality-by-Design, including spectroscopic on-line measuring for control strategies, have become common. Additionally, cross-disciplinary collaboration between pharmaceutical development and manufacturing departments is essential if a successful transformation to continuous processing is to take place. Furthermore, a general understanding of the reaction engineering aspects of continuous production is important for the transfer from batch to continuous processing to become possible.

Chapter 2

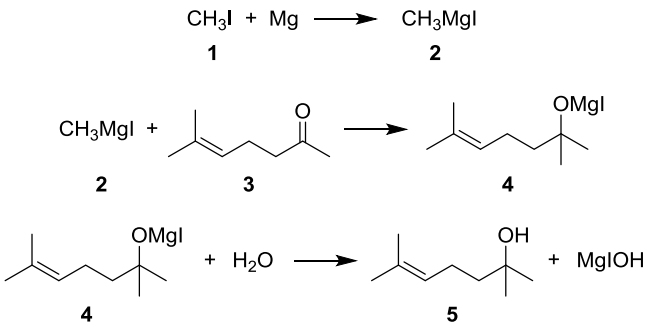
The Grignard Reaction

Even over 100 years after its discovery, the Grignard reaction still serves as an important and common method for the formation of carbon-carbon bonds. The popularity of Grignard reagents is likely due to their wide application and capability of achieving high yields with good selectivity. Of the many different Grignard processes, addition of Grignard reagents to carbonyl groups is perhaps the most well-researched. Over the last decade, flow methods have been used to investigate the Grignard reaction, demonstrating improved outcome of the investigated processes as compared to batch methods. Despite the early proposal of the overall mechanism by Victor Grignard back in the early 20th century, the details of the reaction mechanism are still being studied today.

2.1 Introduction

Grignard reagents are well-known and widely applied organometallic reagents. In 1899, Philippe Barbier reported a tertiary alcohol achieved from the reaction between magnesium, methyl iodide (**1**) and ketone **3** to give tertiary alcohol **5** upon hydrolysis.[92] Barbier's student, Victor Grignard, began to investigate the underlying reaction mechanisms in 1900 and later proposed the mechanism illustrated in scheme 2.1.[93] He was honored with the Nobel Prize in 1912 for his exceptional work within organomagnesium chemistry and for the discovery of Grignard reagents.[94]

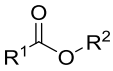
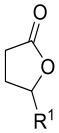
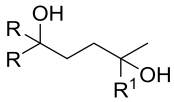
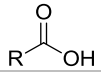
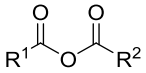
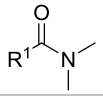
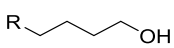
Scheme 2.1: The reaction mechanism proposed by Victor Grignard, based on the tertiary alcohol discovered by Philippe Barbier.[93,94]



Grignard proposed that the first step in the mechanism was the formation of Grignard reagent **2** from alkyl halide **1**, which then adds to the ketone **3** (i.e. the carbonyl functional group). Finally, hydrolysis leads to formation of alcohol **5**.[93] The original reaction, discovered by Grignard, is only one of many ways in which Grignard reagents can react. Table 2.1 shows a selected overview of the scope of the Grignard reaction. Furthermore, Entemann & Johnson have compared the reactivity of different functional groups towards Grignard reagents.[95] Grignard reagents, as well as the magnesium alkoxides formed, are highly sensitive towards water and oxygen. Grignard chemistry is therefore normally performed in an inert atmosphere of nitrogen or argon.[94]

In recent decades, synthetic methods employing other organometallic reagents such as organolithium reactions, palladium-catalyzed cross couplings and other transition metal-catalyzed reactions have become more common.[50,52,96,97] Despite this, the Grignard reaction still serves as a commonly used method, both in the laboratory[51,96] and at production scale.[52,88,98,99] Organometallic reactions account for ca. 13% of the methods used for the formation of new carbon-carbon (C-C) bonds in the development of new APIs.[50,51]

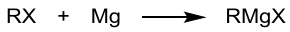
Table 2.1: Reactants and hydrolyzed products from reaction with a Grignard reagent (RMgX), with R being any aryl or alkyl group, X being any halide, M being a metal and *n* being a number.[94,96,100–102]

Reactant	Products	Comments
H_2O	RH	
O_2	ROH	
R^1X	$R-R^1$	
I_2	RI	
MX_n	MR_n	*n* RMgX
		
		
		
		Major product
	R^2OH	By-product
		Minor product
		
CO_2		
		
		
		
		
		High temperature
R^1-CN		Acidic workup

2.2 Formation of Grignard Reagents

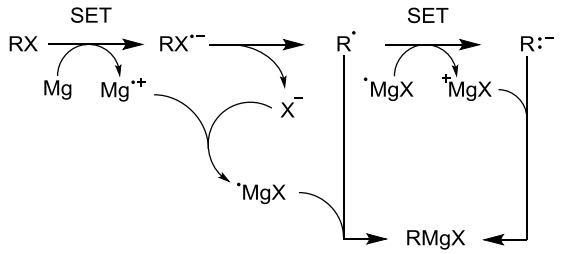
Grignard reagents are formed from a reaction between solid magnesium and alkyl or aryl halide reagents. The reaction is highly exothermic and the energy released is typically in the range of 150 to 350 kJ/mol, which for the most commonly used solvents for the Grignard reaction is enough to keep them at their boiling point.[79,94,103–106] The simplified reaction for the formation of Grignard reagents is shown in scheme 2.2, where the magnesium is inserted between the aryl or alkyl group and the halide.[94]

Scheme 2.2: Simplified expression for Grignard reagent formation between solid magnesium and an alkyl or aryl halide. R is an aryl or alkyl group, X is a halide (Cl, Br, I).[94]



Since the early proposal of the elementary steps in the reaction studied by Grignard,[93] an ongoing debate has progressed on the underlying mechanism of each of the steps. Several reaction mechanisms have been suggested for the formation of Grignard reagents[94,100,107–109] and still to this day no common mechanism has been agreed upon. The most commonly accepted single radical electron transfer (SET) mechanism is illustrated in scheme 2.3.[94,107–109]

Scheme 2.3: The most commonly accepted reaction mechanism for Grignard reagent formation.[108]



It is widely accepted[94,100,107] that the reaction occurs on the surface of the solid magnesium. A fine layer of magnesium oxide is typically present on the surface and protects the magnesium from the atmosphere. Due to the passive nature of magnesium oxide, it is common to activate the magnesium. Activation can be performed in several ways,[110] including dry-stirring, ultrasound or addition of iodine or a highly reactive alkyl halide (e.g. ethyl bromide). Besides the activation of magnesium, refluxing the magnesium together with the solvent helps to overcome the activation energy barrier necessary to initiate the reaction.[94] Starting the formation of a Grignard reagent is a potential risk, since insufficient initiation of the reaction can lead to accumulation of unreacted alkyl or aryl halide in the magnesium-solvent dispersion. If the mixture suddenly initiates, a huge energy release can result in a spontaneous runaway.[94,100,111] Commonly, Grignard reagent formation is carried out at the boiling point of the solvent, where the reflux helps to remove the energy released through constant evaporation and condensation.[94,103] If the formation is carried out at the boiling point of the solvent, the reaction can easily be followed by the temperature,[94,100] but other methods have also been investigated (e.g. NIR, IR).[103,111–114] A number of different magnesium sources exist[94,100,115] and table 2.2 gives an overview of the most common ones and their

advantages and disadvantages. In particular, turnings are commonly used due to their ease of use and limited disadvantages.[94,100]

Table 2.2: Different magnesium sources for the formation of Grignard reagents.[100]

Magnesium Type	Advantages	Disadvantages
Turnings	Ease of Use	Concern about abrasion of glassware and glass-lined reaction vessels.
Powdered	More Reactive	Finely divided powder gives faster oxidation of the surface upon exposure to air. Can be pyrophoric.
Chips (from sublimation)	Higher Purity	Lower surface area results in less reactivity than powdered turnings.
Rieke-magnesium	More Reactive	Requires an extra step in preparation. Residual magnesium halide present in reaction. Residual potassium may be present. Difficult preparation at large scales.

In some cases, alternative methods are used for the generation of Grignard reagents. The reason for using alternative routes can be due to non-accessible RX species, economic considerations, homocoupling issues and other synthetic difficulties.[94] Table 2.3 provides alternative methods for Grignard reagent generation.

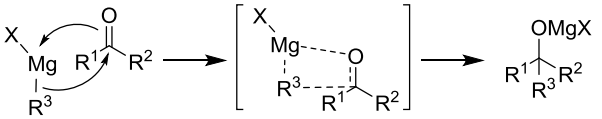
Table 2.3: Alternative Grignard reagent formation methods.[94]

Mechanism	Reaction Type
$R_nM + n\text{MgX2} \rightarrow n\text{RMgX} + MX_n$	Metal-metal exchange
$RH + R^1MgX \rightarrow RMgX + R^1H$	Acid-base reaction of RH with a Grignard reagent
$RMX + Mg \rightarrow RMgX + M$	Oxidative-reductive transmetalation
$RMgX + R^1X^1 \rightarrow RX^1 + R^1MgX$	Metal halide-halide exchange

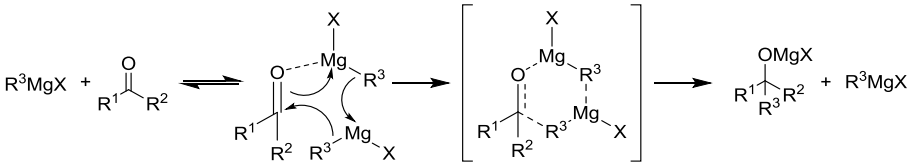
2.3 Grignard Addition Reactions

The reaction between carbonyls and Grignard reagents is one of the most well-studied Grignard processes,[94,96,100,116] where ketones in particular have served as the carbonyl source. A large number of reaction mechanisms have been suggested over time, with the two most prominent being by Meisenheimer & Casper[117] and Swain & Boyles[118], shown in scheme 2.4 and scheme 2.5, respectively. The main difference between these two mechanisms, if simplified, is that the Meisenheimer mechanism results in a second order elementary reaction and the Swain mechanism in a third order elementary reaction due to usage of two Grignard molecules for each coupling.

Scheme 2.4: Reaction mechanism suggested by Meisenheimer & Casper for the reaction of Grignard reagents with ketones and aldehydes (R^1 = H, alkyl or aryl).[116,117]

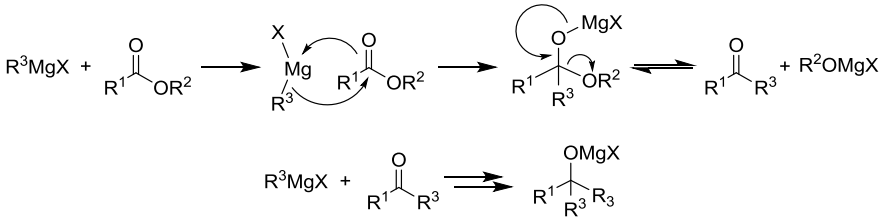


Scheme 2.5: Reaction mechanism suggested by Swain & Boyles for the reaction of Grignard reagents with ketones and aldehydes (R^1 = H, alkyl or aryl).[116,118]



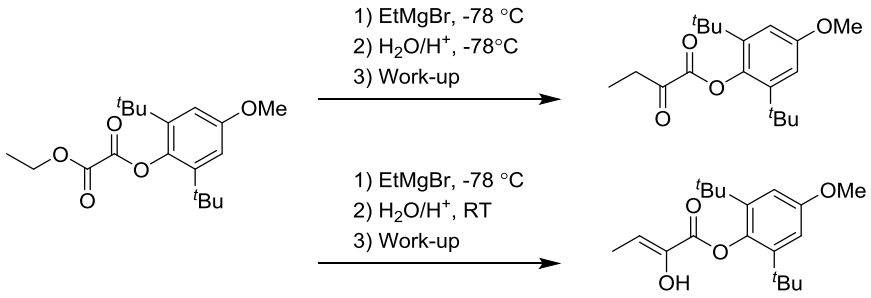
Esters react very similarly to ketones and aldehydes. The primary product from the addition of two equivalents of Grignard reagents to an ester is a tertiary alcohol and a by-product primary alcohol, after the hydrolysis has taken place.[94,96,100,119] The reaction proceeds in two steps, where the second addition is comparable to the one for ketones (scheme 2.4 or scheme 2.5). The mechanism for Grignard addition to an ester is illustrated in scheme 2.6. In the first step, the Grignard reagent adds to the ester, with subsequent collapse of the formed tetrahedral intermediate resulting in the formation of a ketone and a magnesium alkoxide. The formation of the ketone allows the second addition to take place. The collapse of the tetrahedral intermediate is an equilibrium state, which under most conditions is shifted towards the ketone (i.e. the right side).[119]

Scheme 2.6: Reaction mechanism for the reaction between Grignard reagents and esters. The second addition proceeds as for a ketone (R^1 = H, alkyl or aryl).



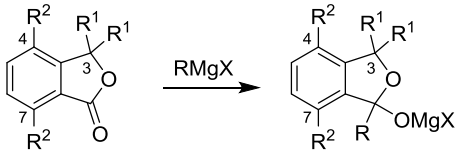
Special cases have been reported where the primary product of the Grignard addition to an ester gives a ketone (mono-addition). Nicaise *et al.*[120,121] documented a stable ketone from a Grignard addition to a diester at -78 °C. The hydrolysis of the magnesium alkoxide was carried out at -78 °C to give the ketone; however, if the mixture was heated to room temperature before hydrolysis the product was an enol (Scheme 2.7).

Scheme 2.7: The Grignard addition to a diester to give a ketone upon hydrolysis at -78 °C.[120,121]



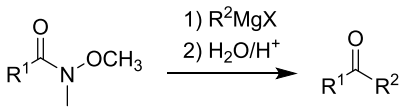
Additions to phthalides have likewise resulted in mono-addition. Smith & Wikman[122] and Hillery & Cohen[123] have suggested that the substitution of hydrogen with methyl or phenyl on the 3, 4 and 7 positions of the phthalide influences its ability to undergo the second addition. A study by Natelson & Pearl[124] showed mono-addition to a phthalide but has not been confirmed by other researchers.[122]

Scheme 2.8: The Grignard addition to a disubstituted phthalide in the 3,3 or 4,7 position, resulting in mono-addition. R^1 and R^2 are a hydrogen, methyl or phenyl, R is an alkyl or aryl, X is a halide.[122,123]



Weinreb ketone synthesis is a possible method if mono-addition to esters is desired (i.e. yielding ketones). The method requires transformation of the ester to *N*,*O*-dimethylhydroxyamide, with a subsequent acidic workup.[125,126]

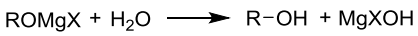
Scheme 2.9: Weinreb ketone synthesis to give a ketone upon acidic workup. R^1 and R^2 are an alkyl or aryl.[125,126]



2.4 Hydrolysis

Grignard reagents are frequently used in organic synthesis due to their capability and ease of use for forming new carbon-carbon bonds.[50,51] The primary product of importance from a Grignard reaction is the alcohol and not the magnesium alkoxide. Hydrolysis of the magnesium alkoxide results in the formation of the desired alcohol upon release of magnesium salts. A proposed reaction mechanism is illustrated in scheme 2.10. Hydrolysis of the magnesium alkoxide is an exothermic reaction, with energy releases of 150 to 250 kJ/mol.[104,127] The magnesium salt is likely to undergo additional reactions with the acid and water used for the hydrolysis.

Scheme 2.10: The hydrolysis of a magnesium alkoxide to yield an alcohol and a magnesium salt.[94,100]



2.4.1 Water and Acid

Hydrolysis is done by the addition of water to the magnesium alkoxide.[94,100] Water is sufficient to carry out the hydrolysis, but the reaction is strongly enhanced by the addition of any acid that can serve as a catalyst.[94,100] The otherwise low solubility of the formed magnesium salts is enhanced under acidic conditions. Common acids to use for hydrolysis are hydrochloric or sulfuric acid, which due to their strong acidity decompose the basic magnesium salts.[94] Hydrochloric and sulfuric acid are also commonly used for dehydration[94,100] and are of limited use if a tertiary alcohol is desired from the addition reaction, because this readily eliminates it. Acetic acid is another commonly used acid. The less acidic nature of acetic acid makes it a common choice if dehydration is to be avoided.[94,100] Acetic acid also tends to form complexes with magnesium salts, which means that the magnesium salts tend to be soluble even under basic conditions. One suggested salt could be magnesium acetate, due to its high solubility in water. Aqueous ammonium chloride solution is an alternative to acetic acid when weak acids are preferred.

2.4.2 Magnesium Salts

The primary product of interest in the Grignard reaction is the alcohol achieved upon hydrolysis of the magnesium alkoxide. The by-products of the hydrolysis are magnesium salts, which due to their low importance in organic synthesis have received far less interest in the literature.[128–132] In a classic batch approach, no special precautions need to be taken with regard to the magnesium salts. Typically, the salts will either be dissolved in the aqueous phase or, in the worst case, precipitate out as solid inorganic salts.[94,100] In either case, the simplicity of batch setup allows easy handling during recovery of the desired product. When considering flow chemistry, magnesium salts are a crucial issue that needs to be accounted for. Magnesium salts can be divided into two main categories: halide salts and hydroxide salts. Halide salts in general have high solubility[133,134] that is only slightly affected by temperature changes. Hydroxide salts tend to have very low solubility in water, but the addition of diluted acid tends to increase their solubility significantly.[i] Under basic conditions, magnesium hydroxide salts are typically gel-like and very sticky.[ii,94,100] Table 2.4 provides values for the solubility of different magnesium salts in water.

Table 2.4: Solubility of magnesium salts in water.[133,134]

Magnesium Salt	Water[a] (g/100 g water)
$Mg(OH)_2$	0.00069
MgO	0.00086[b]
$MgCl_2$	56.0
$MgBr_2$	102.4
MgI_2	146.3
$Mg(CH_3COO)_2$	65.6

[a]at 25 °C, [b]at 30 °C

[i] Observed in laboratory experiments.
[ii] Observed in laboratory experiments.

2.5 Special Cases

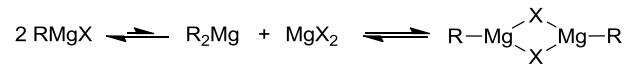
The Grignard reaction and the formation of Grignard reagents are a very complex matter and the reactions are easily influenced by a variety of parameters. Many of these cases have been studied, but despite awareness of their influence on the reaction they still tend not to be included when discussing the overall mechanism,[94,100] unless the study of these is the intention. The Schlenk equilibrium[135] and the Wurtz-Grignard coupling[136–138] are two of the most famous of these special cases and they are briefly described below.

2.5.1 Schlenk Equilibrium

The reaction mechanism proposed by Grignard enabled more detailed study of the chemistry and, due to its versatility, the following decades yielded many new discoveries.[94,100] Among the discoveries in this period is the Schlenk equilibrium found by Wilhelm Schlenk and his son, which describes the stability of Grignard reagents.[135]

The simplified view of Grignard reagents as monomeric reactants was challenged by several studies. The monomeric Grignard reagent exists in equilibrium with its dimeric or higher counterpart, with most being monomeric.[94,100,139,140] The general Schlenk equilibrium is illustrated in scheme 2.11 and is highly influenced by parameters such as the halide and the solvent stabilizing the magnesium.

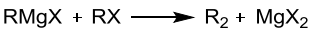
Scheme 2.11: The simplified Schlenk equilibrium, where X represents a halide and R represents an aryl or alkyl group.[135]



2.5.2 The Wurtz-Grignard Coupling Reaction

The Wurtz-Grignard coupling reaction is another observed phenomenon and is closely related to the cross coupling reactions.[94,136–138,140] The Wurtz-Grignard coupling reaction is a metal-halide exchange that mostly takes place during the formation of Grignard reagents. The reaction is a homocoupling, where the formed Grignard reagent reacts with unreacted alkyl or aryl halide. The principle is illustrated in scheme 2.12.

Scheme 2.12: The Wurtz-Grignard coupling reaction. R represents an aryl or alkyl group and X a halide.[136–138]



2.6 Solvents

Grignard reagents are very sensitive towards moisture and oxygen, where protonolysis or oxidation rapidly degrade the product.[94,100] Given the air and moisture sensitivity of Grignard reagents, aprotic polar solvents or non-polar solvents are typically used as storage and reaction media, with only a limited number of these being suitable.[94,100] Despite the sensitivity of Grignard reagents, the Madsen group[141] recently demonstrated Grignard alkylation in the presence of a protic solvent (water). With regard to non-polar solvents, toluene and heptane are the most commonly used, while toluene is still used industrially.[iii] In the case of non-polar solvents such as toluene, trace amounts of

[iii] Two full-scale syntheses are still carried out in toluene solvent at H. Lundbeck A/S.

ether are typically added to stabilize the Grignard reagents. The stabilizing effect comes from the oxygen lone pair in the ethereal solvent that coordinates to magnesium; see Figure 2.1. The magnesium preferably stays in a tetrahedral conformation[94,100,101,140], hence two molecules of ether are needed for each molecule of Grignard reagent.

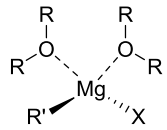
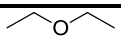
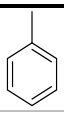
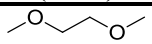


Figure 2.1: Stabilizing effect of solvent molecules on Grignard reagents.[96,101,140]

Ethereal solvents are more commonly used in the synthesis of Grignard reagents.[94,99,100] From an industrial perspective, diethyl ether (Et_2O) has in most cases been replaced by less volatile solvents; however, Et_2O is still used in laboratory synthesis. The low boiling and flash point of Et_2O comprise major hazards in full-scale production and are the main reasons for the use of other ethers. Tetrahydrofuran (THF) has become the industrial standard, as well as the solvent of choice in the laboratory in many cases.[94,100,103,104] Recent changes in regulatory legislation on THF[142] have changed its status to being a suspected carcinogen. Because of these concerns about THF, the sustainable alternative 2-methyltetrahydrofuran (MeTHF) has steadily gained interest.[99,105] Some common data on solvents relevant for Grignard chemistry are provided in table 2.5.

Table 2.5: Properties of commonly-used solvents in Grignard chemistry.

Properties	**Et_2O**	**THF**	**MeTHF**	**Toluene**	**Dimethoxyethane (DME)**	**Dioxane**
Molecular structure						
Boiling point (°C)	34.6	66	80.3	110.6	85	101.1
Flash point (°C)	-45	-14	-11	4	-2	12
Density (g/L)	715	889.2	854	867	868.3	1033
Solubility of solvent in water (%w/w)	6.9	Miscible	14	0.052	Miscible	Miscible
Solubility of water in solvent (%w/w)	1.3	Miscible	4	0.033	Miscible	Miscible
Oxygen lone pair donor	1	1	1	0	2	2
Chelating property	No	No	No	No	Yes	Yes

In addition to the commonly-used ethereal solvents (e.g. Et_2O, THF, and MeTHF), solvents such as 1,4-dioxane and 1,2-dimethoxyethane (DME) find applications within Grignard chemistry. These ethers have two oxygen atoms that provide them with chelating properties. The use of these more special ethers is often seen in crystallographic determination of Grignard reagents.[140,143] The chelating effect of these ethers generally drives the Schlenk equilibrium towards the right (scheme 2.11).

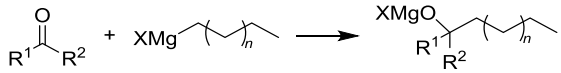
2.7 Grignard Chemistry in Flow Setups

The versatility of Grignard reagents for synthetic purposes, combined with their unique behaviors such as being very exothermic and showing good selectivity, are perhaps part of the explanation as to why several publications and demonstrations of flow setups with Grignard chemistry have been reported. This section presents a selection of Grignard reactions that have been studied in flow reactors.

Some of the first studies on flow chemistry with Grignard reagents were performed by Holm.[144] Throughout the late 1960s and the 1970s, Holm studied the Grignard reaction with the aim of obtaining a better understanding of the mechanism and kinetic behavior of the reactions.[106,139,144–154] The flow system used in many of the studies consisted of two syringe pumps, one containing the Grignard reagent and the other the carbonyl. The two reactant streams were forced through a thin glass capillary tube, merging into one capillary tube by a T-junction. The reaction time was based on residence times calculated from the reactor volume and the flow rate of the streams. Additionally, Holm applied thermochemical analysis and IR spectroscopic measurements to his flow system, allowing data to be collected in real time. Holm's studies led to the accumulation of a valuable body of knowledge about the Grignard reaction.

Krummradt *et al.*[68,155,156] demonstrated that microreactor setup significantly improved the overall yield of the studied addition of Grignard reagents and organometallic reactants to carbonyls; see scheme 2.13. The reaction time was reduced from five hours to less than 10 seconds, mostly due to the better heat transfer achieved within microreactors as compared to batch reactors. The reaction was highly exothermic, releasing up to 300 kJ/mol of energy. This study resulted in the implementation of five parallel minireactors for full-scale production.

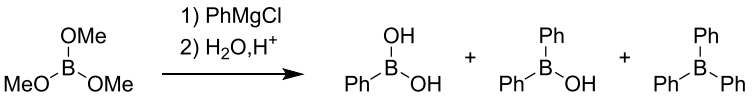
Scheme 2.13: General synthetic scheme illustrating the Grignard reactions demonstrated by Krummradt *et al.* in flow setup. R^1 and R^2 are alkyl or aryl, X is halide.[68,155,156]



Microreactors's ability to improve the yield of Grignard reactions was also demonstrated by Hessel *et al.*,[157–159] who investigated the desired mono-addition of a Grignard reagent to a borate ester to achieve a boronic acid; see scheme 2.14. The reaction was sensitive to the addition of several molecules of Grignard reagents to the borate ester, but this was suppressed by efficient mixing, which led to improved heat and mass transfer conditions. The synthesis was scaled to 10 L/h throughput[159] and it was

possible in the laboratory-scale experiment to operate at ambient temperatures, avoiding the cryogenic temperature conditions necessary for batch synthesis.[158]

Scheme 2.14: Synthesis of phenyl boronic acid via the Grignard reaction utilizing a flow setup.[157–159]



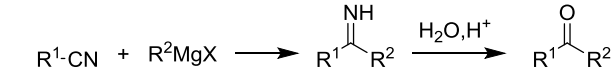
Roberge *et al.*[54,77–79,160,161] have provided a number of small-scale studies and implementations of microreactor technologies in full-scale production for the pharmaceutical contract manufacturer Lonza. Besides the experimental demonstrations, attempts were made to generalize reactions to better estimate the potential benefits achievable through continuous processing.[22,53] One of the main discoveries was that applying multiple injections resulted in a more stable reaction temperature from the exothermic reactions; hence large temperature gradients could be avoided, leading to the suppression of by-product formation, which is otherwise highly sensitive to temperature.[78,79]

A conceptual microreactor system (CYTOS) was investigated by Schwalbe *et al.*[162,163] One of the syntheses explored was a Grignard addition to a diester, known for temperature-sensitive formation of impurities. By using multiple reactors in parallel, the heat of the exothermic and fast reactions was distributed and the reaction could be scaled to a larger throughput, which furthermore provided a better yield.

In a study by Riva *et al.*,[164] a large number of addition reactions between Grignard reagents and carbonyls were investigated in a flow reactor. Most of the syntheses were carried out at room temperature, with an average yield above 90%. The investigations were carried out in the commercially available Vapourtec flow reactor, where the reactor module was a PTFE tubing.

Mateos *et al.*[165] studied the formation of ketones by nucleophilic Grignard addition to nitrile groups followed by the addition of acid utilizing flow methods; see scheme 2.15. The method was very useful for aryl nitriles reacting with phenyl magnesium halide, but was less suitable for alkyl nitriles and alkyl magnesium halide.

Scheme 2.15: The formation of ketones by nucleophilic addition of Grignard reagents to nitriles. R^1 and R^2 are alkyl or aryl, X is halide.[165]



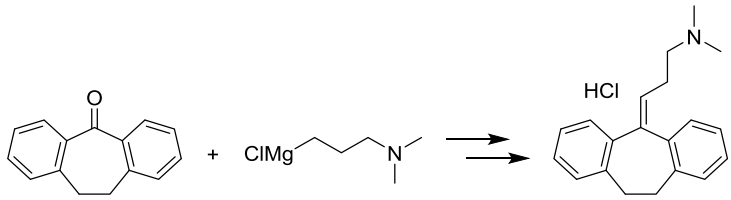
Recently, the Ley group has studied a number of different Grignard reactions.[112,166,167] Their work has resulted in a customized tube-in-tube reactor,[166] where CO_2 diffuses over permeable polymer tubing into another tube to react with a Grignard reagent. The Ley group also utilized spectroscopic measurements in their experiments, where the Mettler Toledo FlowIR was used to determine the concentration of the Grignard reagent.[112]

The Jamison group has also investigated Grignard chemistry in flow setups. Their studies focused on a number of different Grignard reagents and the products formed from reactions with CO_2 or O_2. Their focus was on finding easier and cheaper ways to generate important starting materials for the fine chemical and pharmaceutical industry.[168,169]

A novel heterogeneous continuous reactor setup for a Grignard addition to a tricyclic ketone was developed by Pedersen *et al.*[88–90] for H. Lundbeck A/S, in the effort to modernize an existing batch process method for manufacturing an API intermediate. The main challenge was the low solubility of the ketone in THF, which required large volumes of solvent if a homogeneous flow reactor was to be used. The solution to this quandary was the design of a filter reactor followed by a subsequent multi-injection flow reactor in order to assure complete consumption of the ketone. The setup was later transferred from the laboratory to full-scale by a slight increase in dimensions; see chapter 7.[88]

Kupracz & Kirschning[170] studied the formation of amitriptyline with flow methods (Scheme 2.16). Several organometallic reactions were applied, where the formed tricyclic ketone was reacted with an alkyl Grignard reagent to form the desired alcohol upon hydrolysis. The alcohol was subsequently dehydrated and precipitated as the desired HCl salt.

Scheme 2.16: The synthesis of amitriptyline by Grignard addition to a ketone.[170]



Kopach *et al.*[171,172] recently demonstrated Grignard chemistry in flow by the use of three coupled continuous stirred tank reactors (CSTRs), an alternative flow method to the otherwise commonly-used tubular reactor frequently applied for flow chemistry.

2.8 Summary

Grignard reagents have proven to be highly efficient and important materials for the formation of new carbon-carbon bonds. Grignard chemistry has been applied both at laboratory scale and within the full-scale fine chemical and pharmaceutical industries. Of the many different reactions in which Grignard reagents can participate, addition reactions with esters, ketones or aldehydes to form alcohols may be the most widely applied. The necessity of ethereal solvents in Grignard chemistry has led to a great number of studies on solvent influence on the Grignard reaction. Despite the many findings on solvent effects, full-scale applications have tended to use a limited number of solvent types. Initially, Et_2O was the solvent of choice, but it has now largely been replaced by THF. Over the last decade, THF has slowly been replaced by the greener alternative MeTHF. Academic society has worked industriously on elucidating the underlying chemistry behind the formation of Grignard reagents and their reactions to gain a mechanistic and kinetic understanding. The complex nature of Grignard chemistry, related to the Schlenk equilibrium and the often undesired Wurtz-Grignard coupling reaction, has in reality only produced more questions. As more recent findings within Grignard chemistry, reactions in water and the control of mono-addition to esters have been reported and promise to expand the utility of the reaction. However, many of these special cases are only possible under very specific conditions. During the last decade, Grignard chemistry has been explored using flow methods. Flow methods are very useful for dealing with fast, exothermic reactions like the Grignard reaction. From an industrial point of view, simplicity and efficiency are still the main reasons for the popularity of the Grignard reaction today.

Chapter 3

Sequential Grignard Addition to an Ester via Flow Chemistry: Investigation of Kinetics and Mechanism

The following chapter has been written in the style of a manuscript format. The manuscript is to be submitted to a peer-reviewed scientific journal, expected to be *Organic Process Research & Development*. The authors to be included on the publication are: *Michael J. Pedersen, Stephen Born, Ulrich Neuenschwander, Tommy Skovby, Michael J. Mealy, Søren Kiil, Kim Dam-Johansen and Klavs F. Jensen*.

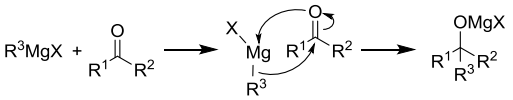
3.1 Abstract

The kinetics of sequential addition of two distinct Grignard species onto a lactone is studied using flow chemistry. The experimental data are shown to be consistent with a kinetic model based on four reaction steps: reduction of ester to magnesium hemiacetal, rearrangement to ketone (forward and backward) and reduction of ketone to tertiary alcohol upon quenching. The experimentally-derived reaction mechanism is supported by ab initio molecular computations and the predicted activation energy is in good agreement with the experimental observations. The Grignard reduction follows a substrate-independent, reductive [2+2] cycloaddition of the Meisenheimer/Casper type. Moreover, the rearrangement equilibrium between magnesium hemiacetal and ketone is characterized and found to be feasible. Mono-addition of the ester carbonyl group is demonstrated for fluorophenylmagnesium bromide at reaction conditions of -40°C with several hours of residence time. For the addition of dimethylaminopropylmagnesium chloride to phthalide, a full diaddition is observed within seconds at temperatures down to -30°C. Working under cryogenic temperature conditions is essential to realizing mono-addition of the ester with Grignard reagents.

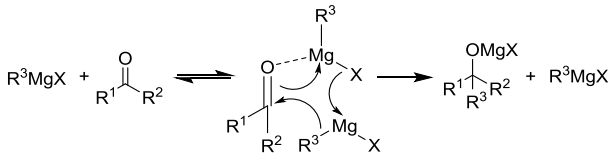
3.2 Introduction

Reactions of Grignard reagents with carbonyls have been intensely studied since the discovery of Grignard reactions in the early 20th century.[93,94] Ketones have been the topic of many, while fewer studies have focused on aldehydes and esters.[116] The Meisenheimer[117] and Swain[118] mechanisms (scheme 3.1 and scheme 3.2, respectively) remain the most widely accepted mechanisms, despite a simplified representation that only considers the reaction between the carbonyl and the Grignard reagent.[116,173] A wide variety of factors, such as the type of solvent and halide and trace metals in the magnesium, have been found to influence the reaction. Underlying equilibria, such as the Schlenk equilibrium,[116,135] are also known to have a strong influence. The Meisenheimer mechanism is a simple bimolecular reaction and is entropically favored compared to the Swain mechanism. The Swain mechanism involves the formation of a bimolecular complex of the Grignard reagent and the carbonyl substrate, with subsequent reaction of an additional Grignard reagent. Moreover, the solvent used (i.e. MeTHF) is highly coordinative, which hinders the formation of higher Grignard aggregates.[105,174] Therefore, our study focused on the Meisenheimer mechanism exclusively.

Scheme 3.1: The Grignard addition mechanism with ketone carbonyl groups as proposed by Meisenheimer and Casper.[116,117]

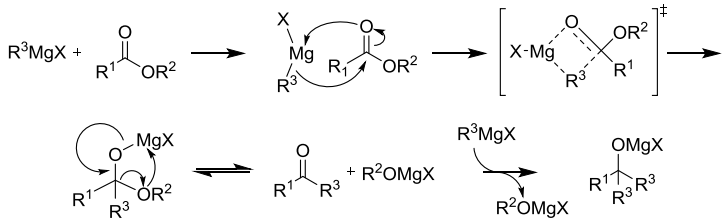


Scheme 3.2: The Grignard addition mechanism with ketone carbonyl groups as proposed by Swain and Boyles.[116,118]



Grignard addition with aldehydes, ketones and esters is generally expected to occur very quickly, with completion in seconds or minutes.[22,94,100,154] Esters are known to react up to 100 times slower than aldehydes or ketones,[100,154] but factors such as the solvent and magnesium used cause deviations from this general trend.[94,99,100] Grignard addition to either ketones or aldehydes results in the formation of mono-addition products. For esters, addition with a Grignard reagent results in a mixture of mono- and diaddition products.[94,119] The carbonyl oxygen in the ester forms a new ketone carbonyl group via an intramolecular rearrangement. The newly formed ketone can undergo a second addition that results in the diaddition product. The reaction can be seen as a consecutive competitive reaction, where two equivalents of Grignard reagents will result in the diaddition tertiary alcohol product upon hydrolysis (scheme 3.3).[119] A few studies have demonstrated mono-addition of esters as the main product under certain conditions.[120,175]

Scheme 3.3: The reaction mechanism of a Grignard addition of an ester.[119] The 4-membered transition state where the Grignard addition takes place is characteristic of a [2+2] cycloaddition mechanism. A description of the reaction of the ketone is given in scheme 3.1 and scheme 3.2.



Knowledge of the reaction rates of a synthesis, including the main impurity formation, is valuable when designing a reactor setup. A detailed understanding of the full reaction mechanism can sometimes be useful, but in most cases a good understanding of the overall reactions at relevant conditions is sufficient for estimating the rate constants, activation energies and pre-exponential factors needed in the design. Kinetic information on the synthesis can be used in the dimensioning of reactor setups, as well for the determination of the optimal configuration for the given chemistry. Furthermore, the knowledge can be used to select the parameters for optimal operation and maximum performance of the chosen reactor setup, i.e. high conversion to the desired products without the formation of difficult-to-remove impurities.[59,60]

Kinetic data may be generated in classic batch experiments with fast mixing of the added reactants.[173,176] At fixed time intervals, samples from the reaction mixture are withdrawn, terminated, and analysed.[176]. The batch method is highly efficient for slow reactions (i.e. reaction times above 30 minutes),[22,177] but becomes difficult for fast ones. The main limitation of the batch method is the time at which samples can be withdrawn and terminated, quenched and analyzed, which provides uncertainty on the actual reaction time.[178] Alternative methods have been used for generating kinetic data for fast reactions (i.e. reaction times less than 5 minutes). Steady state measurements were already being used in flow chemistry to some extent in the 1960s to determine the kinetics of Grignard addition reactions.[144] The advancement of flow chemistry over the last decade and progress in the development of in-line analysis have shown growth in these alternative methods for obtaining kinetic data.[179] The use of microreactor technology combined with in-line analysis, either disruptive measurement methods (e.g. HPLC[180]) or non-disruptive methods (e.g. IR[181,182], Raman[183]), is an alternative to batch methods.

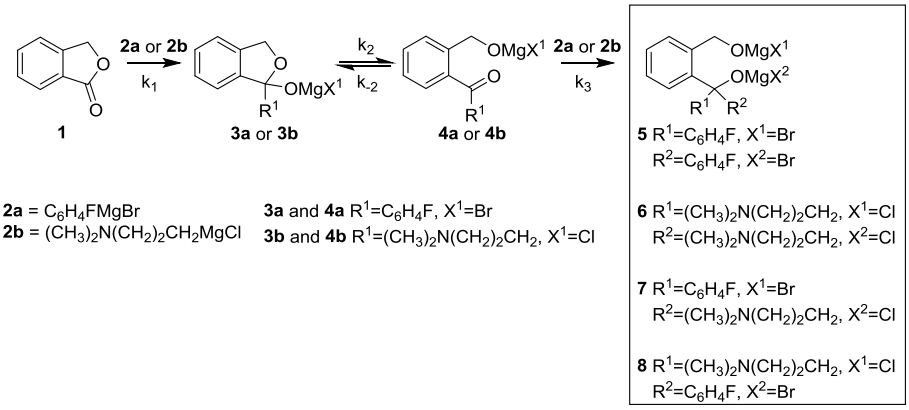
Lately, a number of Grignard reactions and organometallic reactions have been demonstrated in flow reactors.[22,53,54,68,77–79,88–90,112,155–172,184–190] Pedersen *et al.*[88–90] transformed a routine batch process into a continuous reactor setup, in which addition of a Grignard reagent to a ketone slurry suspension resulted in the formation of a key intermediate active pharmaceutical ingredient (API). Kopach *et al.*[171,172] recently demonstrated Grignard chemistry in flow by using three coupled continuous stirred tank reactors (CSTRs). Roberge *et al.*[54,77–79,160,161] utilized microreactor technology for reactions in organometallic chemistry. The Jamison Group[168,169] recently demonstrated a flow setup for reactions between gasses (CO2 and O2) and Grignard reagents. The Ley

Group[112,166,167] covered a large number of different setups for Grignard chemistry in flow. Riva *et al.*[164] used a flow reactor to demonstrate Grignard addition with a large number of carbonyls.

3.3 Chemistry and Investigational Strategy

The synthesis of interest is a Grignard addition between phthalide (**1**), a lactone, and 4-fluorophenylmagnesium bromide (4-FPhMgBr (**2a**)) (scheme 3.4). The phthalide **1** is chosen as a model compound based on its high solubility and its simple structure, limiting the formation of other by-products besides the bis-adduct. The Grignard addition between the ester carbonyl group of phthalide **1** and 4-FPhMgBr **2a** results in the formation of the ketone intermediate (**4a**) upon rearrangement of the magnesium hemiacetal (**3a**). The carbonyl group in the ketone intermediate **4a** can undergo an additional addition with 4-FPhMgBr **2a**, resulting in the formation of an undesired bis-adduct (**5**). The desired product is the mono-addition ketone **4a**, which is supposed to react in a second Grignard addition reaction with 3-(*N,N*-dimethylamino) propylmagnesium chloride (DMPC-MgCl (**2b**)) to form the final product **7**.

Scheme 3.4: The generic synthesis route of the Grignard addition studied within the article. Phthalide 1 is used as a model compound in the generation of the desired product 7 or 8, depending on the addition order of 2a and 2b (e.g. 2a followed by 2b gives 7). The main impurities are bis-adduct 5 and 6.



Studies by Smith and Wikman[122] and Hillery and Cohen[123] suggest that substitution of hydrogen with methyl or phenyl at the carbon 3, 4 and 7 positions influences the probability of the phthalide undergoing the second addition. Natelson and Pearl[124] found formation of mono-addition phthalide, but this has not been confirmed by other researchers.[122]

From a reaction engineering perspective, the synthesis can be considered as a competitive-consecutive reaction between phthalide **1** and ketone **4a** or **4b** towards the first Grignard reagent added, **2a** or **2b**. In order to have reasonable conversion, the optimization of the reaction should focus on a 1:1 ratio of reactants and the kinetic models must therefore describe the reactivity under these conditions.

This contribution explores the kinetics of mono- and diaddition of phthalide **1** with Grignard reagents using a flow setup. The aim is to better understand the choice made in the routine batch synthesis, by studying the underlying reaction rates and mechanisms of the two Grignard reagents required to generate the desired product. The generated data is used to verify the potential for an alternative continuous production method, with a small scale-up of flow reactors in the laboratory.

3.4 Experimental Section

3.4.1 Materials

The following materials used in this study were commercially available: phthalide (**1**) (Sigma Aldrich), naphthalene (Merck, Sigma Aldrich), 4-FPhMgBr (**2b**) 1M in MeTHF (Alfa Aesar) and anhydrous MeTHF (Sigma Aldrich). A 1M solution of 3-(*N,N*-dimethylamino) propylmagnesium chloride (DMPC-MgCl (**2b**)) was prepared by analogy to the method described by Holmes *et al.,*[191] using 1,2-dibromoethane (commercially available)[94] instead of a crystal of iodine for magnesium activation. The concentration of DMPC-MgCl (**2b**) in MeTHF was determined by a NIR spectroscopy calibration curve. The 3-(*N,N*-dimethylamino) propyl was prepared from a 65% aqueous solution (also commercially available as the HCl salt) by liberation of the base in aqueous NaOH (28%) and hexane (both commercially available) and purified by vacuum distillation (40 °C, 50 mbar). All manipulations of Grignard reagents and solutions were performed in oven-dried glassware under a blanket of dry nitrogen using standard cannula and syringe techniques.

3.4.2 Analytical Methods

For the 4-FPhMgBr **2a** only experiment, an Agilent HP GC-MS analyzer (Agilent HP 6890 plus GC and Agilent HP 5973 MS) with an Agilent Technologies (190915-413 HP-5MS) column was used. A 0.1 µL sample was injected, using a split ratio of 100:1. The temperature program was such that the start was at 70 °C, followed by a 30 °C/min ramp up to 300 °C. Good separation was achieved for the main products and no quenched 4-FPhMgBr **2a** or solvent was detectable with the MS, due to the solvent cut-off of 1.5 min elution time to protect the filament. The samples were prepared in CH_2Cl_2 (DCM) and it was not possible to distinguish between **3a** and **4a**.

For the experiment involving 3-(*N,N*-dimethylamino) propylmagnesium chloride (DMPC-MgCl (**2b**)), an in-house HPLC method at Lundbeck was used. The method provided a good separation of phthalide **1**, diaddition product **5**, desired products **7** and **8** (identical upon hydrolysis) and internal standard naphthalene. The mono- and diaddition products of phthalide with DMPC-MgCl (**2b**) were detectable at the beginning of the chromatogram, but the method was not suitable for fully separating them.

3.4.3 Computational Methods

Kinetic modelling was done in MatLab using the ODE45 solver. Density Functional Theory (DFT) geometry optimizations and frequency calculations were made using Gaussian09[192] using the B3LYP functional.[193–195] An all-electron basis set 6-311+G(d,p)

was used on all involved elements. For further refining of the relative energies, single-point calculations were performed on the 6-311++G(df,pd) level. The energies of the stationary points on the potential energy surface (PES), i.e. the molecular ground states (GS) and transition states (TS), were corrected for zero-point energy (ZPE). For taking solvent effects into account, a robust two-layer approach was chosen: calculations were performed with explicit solvent molecules in order to satisfy the valence around the magnesium core. Additionally, a polarized-continuum model (PCM) for tetrahydrofuran (THF) was used to include solvation energies, both at the geometry optimization and the single-point level. For computational feasibility, the explicit solvent molecules were chosen to be H_2O, since THF is too expensive and attempts at using dimethyl ether failed due to the very loose degrees of freedom introduced into the model.

3.4.4 Initial Screening Experiment on Stabilization

Two Harvard PHD 2000 pumps, equipped with 8 mL stainless steel high pressure Harvard syringes, were used for the 4-FPhMgBr **2a** and phthalide **1** solutions. The two reactant streams were pre-cooled before being mixed in a Valco stainless steel T-mixer (ID 0.02") followed by 2" of stainless steel tubing (OD 1/16" ID 0.04") connected to a 20 mL batch vessel at the target temperature. The reaction proceeded for 1 hour under stirring in the batch vessel. The reaction mixture was quenched with 0.5 M HCl at the reaction temperature and left to warm up to ambient temperature for sample preparation and analysis.

3.4.5 Kinetic Experiments

The general flow setup used for the kinetic experiments is illustrated in figure 3.1. For the 4-FPhMgBr **2a** experiments only, three Harvard PHD 2000 pumps were used, equipped with 8 mL stainless steel high pressure Harvard syringes. For the DMPC-MgCl **2b** experiments, two Knauer HPLC Azura P2.1S pumps with stainless steel pistons were used for the DMPC-MgCl **2b** and phthalide **1** and a Syrris Asia pump with 1.0 mL and 0.5 mL syringes was used for the TFA in MeOH stream. In both cases, the Grignard reagent and phthalide **1** were precooled before being mixed in a Valco stainless steel T-mixer ID 0.02". The reaction progressed in a 2.5 m OD 1/16" ID 0.02" stainless steel coil and then terminated in a second T-mixer of PEEK material ID 0.04" at the reaction temperature before samples were collected for off-line analysis.

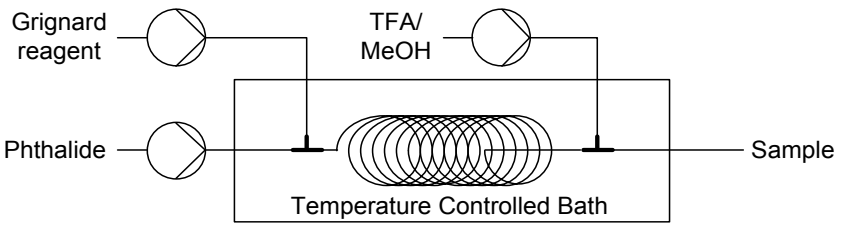


Figure 3.1: The flow setup used in the kinetic experiments. Phthalide 1 and Grignard reagent (2a or 2b) are mixed in a stainless steel T-mixer before entering the SS reactor coil. The reaction is terminated at the second T-mixer with TFA in MeOH at the reaction temperature. Samples are collected for off-line analysis.

3.4.6 Double Grignard Addition Experiments

The double Grignard addition experiments were carried out in the reactor setup illustrated in figure 3.2. Two Knauer HPLC Azura P2.1S pumps with stainless steel pistons were used for DMPC-MgCl **2b** and phthalide **1**. The two reactants were precooled before entering a PEEK T-mixer ID 0.04", with the reaction proceeding in a 10 mL stainless steel coil OD 1/8" and ID 0.08" submerged in the temperature-controlled bath. The product stream passed through a 10 µL diamond window IR flow cell from Mettler Toledo before 4-FPhMgBr **2a** was introduced at room temperature in the second PEEK T-mixer. The second reactor coil was a 20' PTFE OD 1/8" and ID 1/16"; the coil was kept at room temperature and samples were collected at the outlet for off-line HPLC analysis.

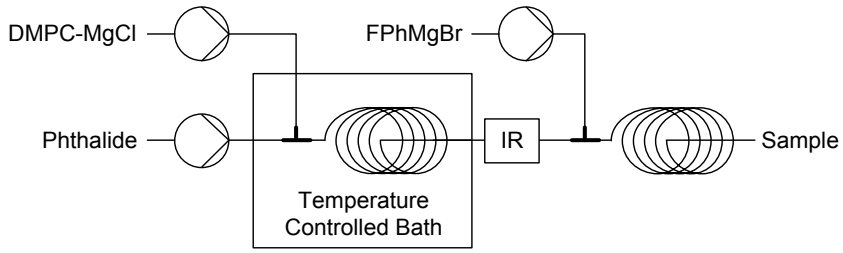


Figure 3.2: The up-scaled reactor setup, combined with an in-line IR flow cell for data collection. The first reactor coil was a 10 mL SS OD 1/8" and ID 0.08" submerged in a temperature-controlled bath. The second reactor coil was made of PTFE tubing 20' OD 1/8" ID 1/16". The T-mixer was of PEEK material ID 0.04". IR spectroscopy was used to follow the reaction between the two reactor coils, combined with off-line HPLC analysis for the outlet samples.

The experiments were carried out with reactant streams of the following concentrations: phthalide **1** 0.25 M, DMPC-MgCl **2b** 0.85 M and 4-FPhMgBr **2a** 1.0 M. Phthalide **1** was used as the limiting reactant, kept at a fixed flow rate of 1.62 mL/min. DMPC-MgCl **2b** was added in 1.05 or 2.10 equivalents to phthalide **1**, corresponding to a flow rate of 0.5 mL/min and 1.0 mL/min. The 4-FPhMgBr **2a** was added as a 1.12 equivalent to phthalide **1**, corresponding to a flow rate of 0.21 mL/min and 0.17 mL/min. A comparison between the reactor setups used in the kinetic experiments and the double Grignard addition experiments is found in table 3.1.

Table 3.1: Comparison of parameters of interest between the reactors used for kinetic experiments and in the double Grignard addition experiments.

	Kinetic Reactor Setup	**Double Grignard Addition Reactor Setup**	
	Reaction coil	**1st Reactor coil**	**2nd Reactor coil**
Reactor Volume (mL)	0.5	10	12.07
Reactor ID (inch)	0.02	0.08	1/16
T-mixer ID (inch)	0.02	0.04	0.04
Flow Rate range (mL/min)	0.008-1.020	2.12-2.62	2.33-2.79
Reaction Temperature (°C)	0 to -40	-10 to -30	Ambient Room

3.5 Results and Discussion

3.5.1 Initial Screening Experiment on Stabilization

Initially, a few semi-batch experiments were carried out to identify whether the magnesium hemiacetal (**3a**) could be stabilized at low temperature conditions. The literature indicates that ester carbonyl groups can be controlled to give the mono-addition product if carried out at -78 °C.[120,121,175] The experiments were conducted with two equivalents of 4-FPhMgBr **2a** to the phthalide **1**.

The undesired diaddition product **5** decreases as the temperature is lowered and is completely absent at -40 °C (figure 3.3). Full conversion of the phthalide **1** was achieved in all experiments, with the exception of -40 °C where minor amounts were still present after 1 hour of reaction. Full conversion was achieved at -30 °C with almost no diaddition product **5** present. The kinetic experiment should therefore be carried out from -30 °C and up, as this seems more suitable for the entire reaction (there is very slow conversion at -40 °C). From a scaling perspective and a cost perspective, a higher temperature is more desirable.

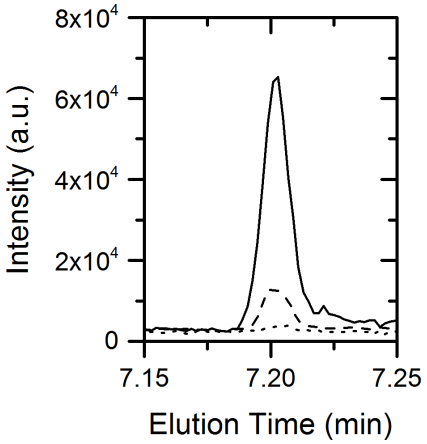


Figure 3.3: The formation of the bis-adduct 5 decreases with temperature (-20 °C (—), -30 °C (- - -), -40 °C (···)).

A deep blue color is observed when the reaction progresses at higher temperatures. The blue color is also known from the actual batch process, where it is seen near the addition point of the 4-FPhMgBr **2a**. The color is therefore assumed to be correlated with the formation of undesired bis-adduct **5**, due to local high concentration and temperature at the addition point. The blue coloring can serve as a good indicator, with its absence indicating that the desired mono-addition is taking place. This theory is further supported by the literature, where a similar color has been observed upon reaction between benzophenone and phenylmagnesium halide.[173,196]

3.5.2 Kinetic experiments on 4-FPhMgBr

The kinetic experiments on 4-FPhMgBr **2a** and phthalide **1** were performed in the range from 0 °C to -30 °C, with one experiment every 5 °C. The initial stability experiment indicated that a low reaction temperature (-40 °C) was necessary to control the undesired bis-adduct **5**. A 1.0 M 4-FPhMgBr **2a** was used in equivalents from 1.1-2.0 to the 0.25 M phthalide **1** solution with naphthalene as internal standard; both reactants were in MeTHF. At temperatures above -15 °C the reaction was completed after 5 minutes, but up to 1 hour residence time was necessary for the -30 °C experiment with 2 equivalents of 4-FPhMgBr **2a**. The TFA quench stream was a 0.5 M TFA in MeOH with a flow rate equal to the combined flow rate of 4-FPhMgBr **2a** and phthalide **1**.

The kinetic data was fitted in MatLab with a least squares curve fit by numerical solution of the mass balance of the plug flow reactor (PFR) design equations with iteration on the rate constants. Several reaction mechanisms were verified for their ability to describe the reaction system under investigation before the final model was chosen. The first reaction between phthalide **1** and 4-FPhMgBr **2a**, illustrated by rate constant k_1 (scheme 3.4), was found to be sufficient to a model of a second order elementary reaction (i.e. the Meisenheimer mechanism). The intramolecular rearrangement between magnesium alkoxide intermediate **3a** and ketone **4a** is a more complex matter. Intramolecular reactions – with comparable activation energies – are generally significantly faster than the reactions that take place between two or more molecules. Moreover, esters will normally have a reaction rate up to 100 times slower than ketones and aldehydes. Combining these general considerations requires that both a forward, k_2, and a backward, k_{-2}, reaction take place between intermediate **3a** and ketone **4a**, establishing an equilibrium. If only the forward reaction, k_2, existed, a pseudo-first order reaction for the formation of bis-adduct **5** would be observed from the data as rate constant k_3. For the reasons detailed above, the Meisenheimer mechanism was the model of choice. The final plug flow reactor (PFR) mass balances are given in equations 3.1-3.5.

$$\frac{d[C_1]}{d\tau} = -k_1[C_1][C_{2a}] \quad 3.1$$

$$\frac{d[C_{2a}]}{d\tau} = -k_1[C_1][C_{2a}] - k_3[C_{4a}][C_{2a}] \quad 3.2$$

$$\frac{d[C_{3a}]}{d\tau} = k_1[C_1][C_{2a}] - k_2[C_{3a}] + k_{-2}[C_{4a}] \quad 3.3$$

$$\frac{d[C_{4a}]}{d\tau} = -k_3[C_{4a}][C_{2a}] + k_2[C_{3a}] - k_{-2}[C_{4a}] \quad 3.4$$

$$\frac{d[C_5]}{d\tau} = k_3[C_{4a}][C_{2a}] \quad 3.5$$

The activation energy of the reaction between 4-FPhMgBr **2a** and phthalide **1** (k_1) was found to be 52±8 kJ/mol with a pre-exponential factor of $2.53 \cdot 10^9$ L/(mol·s) (figure 3.1). A strong correlation was found between the equilibrium rate constants (k_2 and k_{-2}) and the rate constant for diaddition, k_3. Therefore, the formation of ketone (**4a**) was

assumed to be in a pseudo-steady state, which reduced the modelling equations to the following form:

$$\frac{d[C_1]}{d\tau} = -k_1[C_1][C_{2a}] \quad 3.6$$

$$\frac{d[C_{2a}]}{d\tau} = -k_1[C_1][C_{2a}] - k_c[C_{3a}][C_{2a}] \quad 3.7$$

$$\frac{d[C_{3a}]}{d\tau} = k_1[C_1][C_{2a}] - k_c[C_{3a}][C_{2a}] \quad 3.8$$

$$\frac{d[C_5]}{d\tau} = k_c[C_{3a}][C_{2a}] \quad 3.9$$

in which $k_c = k_3k_2/k_{-2}$.

For the combined rate constant expression (k_c), the activation energy was found to be 88±9 kJ/mol with a pre-exponential factor of $2.65 \cdot 10^{15}$ L/(mol·s). This pre-exponential factor is several orders of magnitude higher than expected for a simple bimolecular reaction, since for ordinary diffusion-controlled reactions, approximate pre-factors of $10^{10\pm1}$ L/(mol·s) are expected.[197] However, the pre-factor in the current case represents the entropic contribution from not only a single bimolecular reaction (k_3) but also from the k_2/k_{-2} equilibrium. Since the ring-opened form **4** is entropically highly favored over **3**, the additional factor of ~10^5 is reasonable.

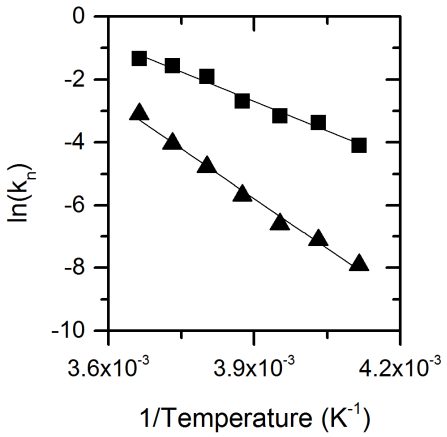


Figure 3.4: The Arrhenius plot of the kinetic data of 4-FPhMgBr 2a reacting with phthalide 1. The k_1 (■) is the rate constant for the mono-addition reaction and the other terms represent the combined rearrangement equilibrium and diaddition reaction k_c (▲).

3.5.3 Kinetic experiments on DMPC-MgCl

In the temperature range 0 to -20 °C, kinetic data for the reaction between DMPC-MgCl **2b** and phthalide **1** were generated for every 5 °C. As in the 4-FPhMgBr **2a** kinetic experiments, phthalide **1** had a concentration of 0.25 M in MeTHF with naphthalene as internal standard. The concentration of DMPC-MgCl in MeTHF was determined to be 0.85 M after the experiments were run, but was assumed to be 1.0 M

throughout the experimental run. This deviation in actual concentration was corrected in the later data treatment. The 0.85 M concentration of DMPC-MgCl **2b** meant that only 0.9 equivalents of DMPC-MgCl **2b** had been added to the phthalide **1**, instead of the intended 1.1 equivalents. Reaction times of between 0 and 4 minutes were investigated (figure 3.5). For all temperatures, approximately 45% conversion of phthalide **1** was achieved. The substrate conversion is equal to half the equivalence of the added DMPC-MgCl **2b**. This suggests that the rearrangement from intermediate **3b** to ketone **4b** is very fast and at the given temperature it was not possible to stabilize intermediate **3b** to suppress the undesired bis-adduct **6**. The very fast reaction of DMPC-MgCl **2b** with phthalide **1**, with a preference for bis-adduct **6**, meant that it was not possible to extract activation energies under these experimental conditions.

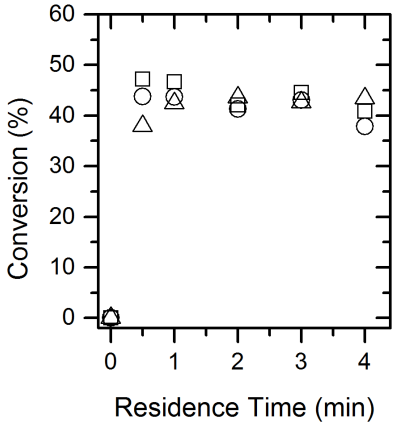


Figure 3.5: Conversion of phthalide 1 as a function of residence time at selected temperatures (0 °C (□), -10 °C (○) and -20 °C (◇)).

3.5.4 Density Functional Theory Characterization

In order to better understand the molecular basis of this process, a density functional theory (DFT) characterization of the potential energy surface was carried out. As solvation is crucial in Grignard-type chemistry, a two-level solvation model was used to account for the ether solvent: first, magnesium was coordinated with three oxygen sigma-donor ligands and second, the whole solvation complex was inserted into a polarizable continuum model of THF. This allowed a realistic description of the energetics during the reaction, e.g. by estimating activation energies or by verifying the feasibility of an equilibrium between intermediate **3** and ketone **4**, for reaction with either 4-FPhMgBr **2a** or DMPC-MgCl **2b**. The DFT results confirmed that the Grignard additions follow the Meisenheimer mechanism. Interestingly, Grignard additions were found to have a 4-membered transition state, indicative of a [2+2] cycloaddition (see scheme 3.3 and figure 3.6). This is in line with the earlier proposition made by Yamazaki,[198] who predicted that four-membered transition states govern Grignard reactions (although his claims included artificial multimetal aggregates arising from incomplete treatment of solvent effects).

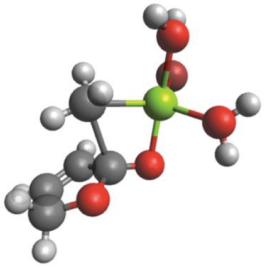


Figure 3.6: The 4-membered transition state of the mono-addition Grignard intermediate.

The DFT potential energy predictions (figure 3.7) reflect the reactivity differences between esters (**1**) and ketones (**4**). Furthermore, even though the transition state for rearrangement could not be localized due to the complex geometries involved, an equilibrium between the cyclic (**3**) and open (**4**) configurations of the mono-addition product was found to be energetically feasible. Thus, the rate constants k_2 and k_{-2} could be merged into an equilibrium constant K_{eq}, supporting the kinetic model expression used above. The DFT characterization showed that the reaction is exothermic by approximately 120 kJ/mol, with little difference between the first and second Grignard additions. Calculations on modified Grignard reagents showed that neither the halide nor the aryl/alkyl of the Grignard reagent causes a large difference in reactivity. Though the experiment shows that there is a structure-activity relationship for the Grignard reagent with **2a** being less reactive than **2b**, the differences are too subtle to be quantitated. In any case, the 91 kJ/mol activation energy found by DFT for the product k_3k_2/k_{-2} (where 70 kJ/mol are from Grignard addition to ketone **4**) is in good agreement with the experimentally-determined value of 88±9 kJ/mol. For k_1, the agreement is only modest, 89 kJ/mol by DFT vs. 52±8 kJ/mol by kinetic modelling. However, the k_1 experimental data appears to be more scattered (figure 3.4) and could be influenced by other factors such as steric configuration. General observation shows that esters as such are less reactive than ketones, which would require an activation energy value of at least 70 kJ/mol for the true k_1, underpinning the prediction by DFT.

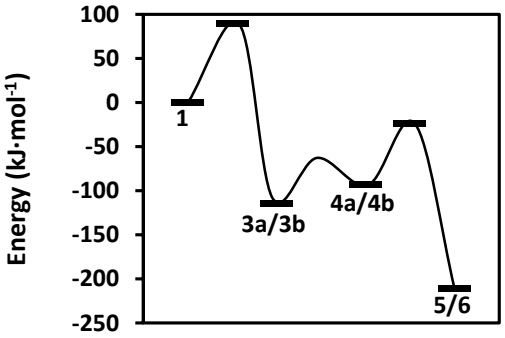


Figure 3.7: DFT characterization of the potential energy surface for reaction of ester (modelled by 2-furanone) with two equivalents of Grignard reagent (modelled by MgMeBrL3). The characterization was carried out with different Grignard reagents. Very little deviation was found when varying halide and aryl/alkyl groups of the Grignard reagent. The numbering of species is according to scheme 3.4.

3.5.5 Double Grignard Addition Experiments

The kinetic experiments formed the basis for the addition of both Grignard reagents to achieve the desired diaddition product. The first decision to make was the addition order of the two Grignard reagents (**2a** and **2b**). It was only possible to generate kinetics for 4-FPhMgBr **2a**, as the DMPC-MgCl **2b** fully reacts within less than 30 seconds at the temperatures studied. To fully suppress the diaddition product **5**, a temperature of -40 °C or lower was necessary, which would result in very slow reaction times in the range of several hours towards the mono-addition reaction of alkoxide **3a**. The slow reaction of 4-FPhMgBr **2a** make it an unsuitable choice for first Grignard reagent and DMPC-MgCl **2b** was chosen as the first Grignard reagent despite the uncertain stability at lower temperatures.

The double Grignard addition experiments (figure 3.8) were investigated at three temperatures (-10 °C, -20 °C and -30 °C). A conversion of 95-99% was achieved for the phthalide **1** at all the settings tried. In the case of 1.05 equivalents of DMPC-MgCl **2b**, the desired product **8** and undesired diaddition product **5** were detected in the HPLC samples. The presence of diaddition product **8** indicates that the DMPC-MgCl **2b** reacted to the desired alkoxide intermediate **3b**. However, it was not possible to suppress the rearrangement to ketone **4b** even at -30 °C, hence bis-adduct **6** was formed simultaneously. Furthermore, the HPLC area of bis-adduct **5** and desired product **8** being of similar size for all three temperatures supports the conclusion of missing stabilization of alkoxide intermediate **3b**. In the case of 2.10 equivalents of DMPC-MgCl **2b**, no desired product **8** or undesired bis-adduct **5** were observed. As the phthalide **1** was almost fully converted, this indicates that bis-adduct **6** was the only product formed.

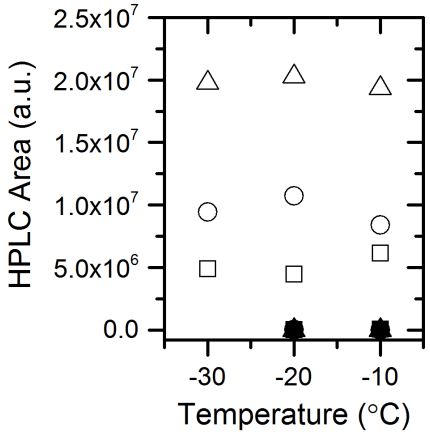


Figure 3.8: The experimental results from the double Grignard addition experiments. For high equivalents of 2.1, no desired diaddition product 8 or bis-adduct 5 are generated, indicating that all of the phthalide 1 has reacted to bis-adduct 6. In all cases, the phthalide 1 was close to fully converted. Phthalide (1.05 eq. □ and 2.10 eq. ■), Product 5 (1.05 eq. ○ and 2.10 eq. ●) and Product 8 (1.05 eq. △ and 2.10 eq. ▲).

3.6 Conclusions

A flow setup has been used in the generation of kinetic data for some selected Grignard additions. The chemistry studied was a competitive-consecutive Grignard reaction involving two different Grignard reagents reacting with a lactone. The addition was studied for temperatures ranging from 0 to -30 °C. For the 4-FPhMgBr Grignard reagent, an Arrhenius plot was generated from the kinetic data based on a two-fold Meisenheimer mechanism with intramolecular rearrangement in between. DFT analysis of the potential energy surface revealed structural and energetic insights into the molecular processes involved in Grignard additions and supported the mechanistic assumptions made in the kinetic model. At -40 °C, the competitive bis-adduct could be suppressed by slowing down the intramolecular rearrangement, simultaneously causing a decrease in the reaction rate for mono-addition. The experimental kinetic data was found to be in good agreement with a DFT characterization of the potential energy surface associated with a two-fold Meisenheimer reaction. For the DMPC-MgCl Grignard reagent, the reaction progressed towards undesired diaddition within 30 seconds even at -20 °C. The very fast reaction time did not allow any kinetic expressions to be derived from the data. Addition of DMPC-MgCl to the phthalide followed by addition of 4-FPhMgBr was tried. Mostly undesired bis-adducts were formed and the slight scale-up of reactor dimensions is believed to have caused larger gradients of temperature and concentration, giving rise to the undesired formation of bis-adduct.

Suppressing the formation of bis-adduct from the lactone reacting with Grignard reagents is possible under cryogenic reaction conditions, but comes at the cost of reduced reactivity towards the desired mono-addition product. In the investigated case, the alkyl Grignard reagent turned out to be significantly more reactive than the aryl Grignard reagent, which is in good accordance with the literature. The exothermic nature of Grignard addition poses a significant challenge if the necessary cryogenic conditions are all to be maintained to ensure the desired suppression of the undesired bis-adduct. Use of multiple injection reactor technology for the Grignard reagent addition could be a rational solution to the heat problem, as this could distribute the energy release, avoiding local hot spot gradients of temperature and concentration.

Chapter 4

A Solvent-Free Base Liberation of a Tertiary Alkylamino Halide by Flow Chemistry

The following chapter has been written in the style of an article manuscript. The manuscript is to be submitted to the peer-reviewed scientific journal *Green Chemistry*. The authors to be included on the publication are: *Michael J. Pedersen, Tommy Skovby, Michael J. Mealy, Kim Dam-Johansen and Søren Kiil*.

4.1 Abstract

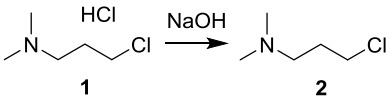
A flow setup for base liberation of a tertiary amine salt and solvent-free separation of the resulting free base has been developed. Production with the flow setup profits from an on-demand approach, which is very useful for labile alkylamino halides. The requirement for obtaining a dry product has been fulfilled by the simple use of a saturated NaOH solution, followed by isolation of the liquid phases with gravimetric separation. The flow setup has an E-factor reduction greater than 2 and a distillation step has additionally been avoided. The method is an excellent demonstration of how flow chemistry can be used to simplify, improve and optimize manufacturing processes.

4.2 Introduction

Isolation and purification of organic compounds by precipitation as salt complexes has been used since the infancy of synthetic organic chemistry.[199] In pharmaceutical tablet production, the final dosage formulation of the active pharmaceutical ingredients (APIs) with excipients requires solid APIs, which are often achieved by salt precipitation. In other parts of the organic synthesis industry, organic salts are often favored as reactants due to their high stability.[22,200–203] Synthetic steps, in which organic salts have been formed with the intent of purifying an intermediate or for storage considerations, are usually followed by a base liberation step to free the organic compound. Commonly, base liberation is carried out by mixing the organic salt with an aqueous base (often alkaline) and an immiscible organic solvent. Extraction of the organic compound from the aqueous phase yields a product-containing organic solvent solution, which is typically dried, solvent swapped or distilled to obtain the organic compound in the needed form.[199]

The commercially available 3-(*N*,*N*-dimethylamino)propyl chloride hydrochloride (DMPC-HCl (**1**)) is a stable starting material frequently used in the synthesis of APIs[51,170,202,204,205] and may be procured as either the pure solid or an aqueous solution. At H. Lundbeck A/S, the syntheses of four different APIs employ the free base (DMPC (**2**)), hence there is a constant demand for this unstable starting material. The reaction is illustrated in scheme 4.1 and takes place in aqueous solution.

Scheme 4.1: The base liberation of DMPC-HCl (1) with NaOH to form DMPC (2).

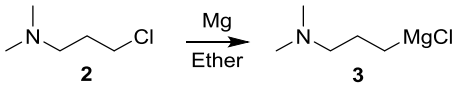


1 **2**

In spite of the common need for the same starting material in several in-house processes, three different batch methods have been employed for the base liberation. The necessary reactants and the overall unit operations applied in the existing methods for base liberation are shown in table 4.1.

The three methods listed in table 4.1 all employ sodium hydroxide as a base for the neutralization step, require an organic solvent for extraction of **2** and include drying the organic phase over an inorganic desiccant. It is of paramount importance that the resulting solution or neat **2** has a very low water content (production specification is less than 0.15% by Karl Fischer titration), since compound **2** is used for preparation of the Grignard reagent 3-(*N*,*N*-dimethylamino)propylmagnesium chloride (**3**) (Scheme 4.2).

Scheme 4.2: The formation of the Grignard reagent 3 from the alkylamino halide 2.



2 **3**

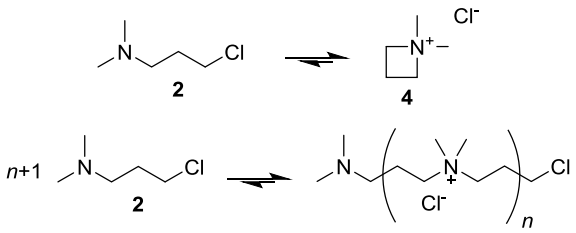
Table 4.1: Overview of the current batch methods used in-house for the base liberation of DMPC-HCl (1).

DMPC Method	Reactants	Unit Operations	Yield (%)
DMPC Distilled	DMPC-HCl 65 wt% NaOH 28 wt% Hexane Water Anhydrous Na_2SO_4 HCl 30%	Mixing Separation Drying Filtration Distillation	80-90
DMPC in Toluene	DMPC-HCl 65 wt% NaOH 28 wt% Toluene Water K_2CO_3	Mixing Separation Drying Filtration	95-100
DMPC in MeTHF	DMPC-HCl 65 wt% NaOH 28 wt% MeTHF Water NaOH Pellets	Mixing Separation Drying Filtration	80-85

Organomagnesium halides cannot be formed without scrupulous exclusion of moisture and exhibit high reactivity towards hydrolysis[140] and different approaches are applied in each of the three methods to exclude water. The alkylamino halide **2**, obtained by the three methods listed in table 4.1, has a limited shelf life due to degradation, e.g. by self-condensation or polymerization as depicted in Scheme 4.1 above. The established shelf lives of distilled **2** and a solution of **2** in toluene are six and 22 days, respectively. The solution of **2** in MeTHF is produced on-demand and not stored.

The degradation of **2** as illustrated in scheme 4.3 is known as the Menshutkin reaction and amines are commonly known to react with alkyl halides to give the highest order amines. The Menshutkin reaction is reversible, but gives rise to several other products depending on which bond is broken. From a chemical reaction engineering perspective, the reaction can be described as a competitive-consecutive reaction. The reaction takes place under mild reaction conditions and is the reason for the short life of the free base **2**. Today, quaternary amines have found great use as phase transfer catalysts and in ionic liquid due to their unique behavior.[206–214]

Scheme 4.3: Initial degradation pathways of DMPC (2).



Since several processes are used internally at Lundbeck to produce **2** and production planning can be complicated by the relatively short shelf life of **2**, the manufacturing approach has been reconsidered. It is obvious that the production set-up would benefit from harmonization of the processes; however, the benefit of producing both solutions from a scaled-up batch distillation were perceived to be minimal even if the different APIs were produced simultaneously. The vacuum distillation method is slow and requires a large energy input to obtain at best a modest yield for such a simple operation. Each of the established methods requires a tedious drying step, with the requisite filtration to remove the drying agent from a malodorous solution containing an alkylating agent – a point that weighed heavily on the desire to implement a more HSE-friendly solution. A major obstacle to converting to a contained, flow-based method was the necessity of refiling some of the API regulatory documentation, since in some instances the conversion of **1** to **2** is described as a step that requires adherence to current Good Manufacturing Practice (cGMP).

The fine chemical and pharmaceutical industries are known for their resource-demanding development and manufacturing. Throughout the last 20 years, the concept of Green Chemistry has been used to describe the lack of efficiency and sustainability within the chemical industry. The E-factor first described by Roger Sheldon is, due to its simplicity, one of the most widely-used metrics in green chemistry; however, other methods such as Process Mass Intensity (PMI), Atom Economy (AE), Carbon Efficiency (CE) and Effective Mass Yield (EMY) are also prevalent.[34,35,49,55,189,215–223] The E-factor describes the amount of waste generated per amount of product produced, thus enabling a general comparison of efficiency among different chemical industries as shown in table 4.2.

Table 4.2: The E-factor related to industry segment.[48]

Industry Segment	Annual Production (tons)	E-factor ($kg_{waste}/kg_{product}$)
Oil Refining	10^6-10^8	~0.1
Bulk Chemicals	10^4-10^6	<1-5
Fine Chemicals	10^2-10^4	5-50
Pharmaceuticals	10-10^3	25-100

The importance of green chemistry in the pharmaceutical industry and how to facilitate the adoption of its principles are an ongoing discussion,[34] with organizations like the recent establishment of the ACS GCI Pharmaceutical Roundtable.[31] There are many approaches to achieving greener production: classic process optimization, alteration of the synthetic route, adoption of sustainable solvent replacements or application of new technologies such as flow chemistry.[34,35,49,55,189,215–220] This chapter describes the harmonization and transformation of the batch manufacturing methods for compound **2** towards a green flow method.

4.3 Chemistry

The base liberation of **1** is a fast and exothermic acid-base reaction between the ammonium salt **1** and NaOH (Scheme 4.1). The free amine **2** decomposes slowly via an intra- or intermolecular Menshutkin reaction in which the tertiary amine reacts with the alkyl halide moiety to form various quaternary ammonium salts. A mixture of impurities is formed from the self-reaction of **2** (Scheme 4.3), leading either to 1,1-dimethylazetidin-1-ium chloride (**4**) or a mixture of polymers of varying lengths. The decomposition processes are evident from the gradual formation of cloudiness in the neat liquid or solutions of **2**. In fact, the neat liquid forms a spectacular display of needles after a relatively short time if stored improperly. The decomposition occurs under even mild conditions, but the rate is accelerated dramatically upon heating. Thus, **2** must be stored cold in order to suppress impurity formation, which further complicates the production logistics and equipment utilization. The decomposition by-products can potentially undergo the reverse Menshutkin reaction; however, this pathway is likely minimized due to crystallization of the ammonium salts.

4.4 Experiments

4.4.1 NIR Calibration of Water Content in DMPC (2)

An at-line NIR calibration model was developed to quantify water content in **2** in the range from 0 to 5 vol%. A standard solution of **2** containing 5 vol% water was prepared from freshly distilled **2**. The remaining calibration samples were prepared by standard dilution with distilled **2**, which after dilution were filtered through a 0.45 µm syringe filter directly into a NIR vial and the raw spectra were collected to generate the calibration curve. The distilled **2** used to prepare the calibration samples was analyzed for residual water content by Karl Fischer titration and a baseline content of 0.059 vol% was found. NIR spectra were collected using a MB160 FTNIR Spectrometer equipped with a standard vial holder and a DTGS detector (ABB Bomem). A PLS calibration model was developed in SIMCA 13.0 (Umetrics AB) using the first derivative of the spectral region of 5600-4460 cm^{-1}. A 1-PLS component model was found sufficient, giving a RMSEE of 0.093 and a RMSECV of 0.098.

4.4.2 Grignard Reagent: A Qualitative Verification Procedure

Ca. 1 g of magnesium turnings was added to a 100-mL Erlenmeyer flask with 10 mL of anhydrous THF and warmed gently by hand while stirring vigorously with a glass spatula to mechanically remove part of the magnesium oxide layer covering the metal surface. Sufficient activity of the metal surface was then ensured by addition of ca. 500 µL of ethyl bromide, whereupon reaction initiation was observed by self-heating to vigorous reflux. As soon as the reaction subsided, 1 mL of **2** was added in two separate portions and the product was deemed sufficiently dry if a new vigorous reflux was observed each time. If water is present, the reaction will not initiate upon addition of **2** and this will be evident in several ways: (1) a new reflux will not be observed, (2) a milky white suspension will be formed instead of a clear metallic solution or (3) a significant delay will be observed prior to obtaining a new reflux.

4.4.3 Initial Prototype

The first flow setup was assembled from PTFE tubing (1/8" OD, 1/16" ID) having a reactor length of 1 m and mixing the reagents in a PEEK T-mixer (0.04" ID). Reagents were dosed at a maximum flow rate of 2.5 mL/min using a two-channel Asia syringe pump from Syrris Ltd. The total flow rate of both reactants at all equivalents was 1.5 mL/min (residence time of 1.32 min). A fraction of 10 mL was collected in a graduated cylinder and the volumes of the aqueous and organic phases were recorded. The pH of the aqueous phase was determined with pH sticks (pH range 0-14). All reagents used in these investigations are bulk commodities.

4.4.4 Drying and Separation Experiment

In order to investigate different drying techniques, a portion of **2** was prepared by mixing a 2:1 ratio of a 65 wt% aqueous solution of **1** with 28 wt% NaOH (aq.) in a separatory funnel. After mixing and allowing the phases to separate, the aqueous phase was discarded and the drying agent was mixed with a portion of **2**. For the centrifugal separation, both a two phase mixture and gravimetrically-separated DMPC (**2**) were tested. For the membrane drying, the experiment was run with similar ratios, but as a flow experiment with a similar setup to that used in the first flow experiments.

In the detailed study of molecular sieves as a drying agent, 10 mL of DMPC (**2**) were transferred to scintillation vials pre-charged with 2 g of pre-dried 0.4 nm molecular sieves and stored at 5 °C.

In the detailed investigation of 50 wt% NaOH solution as a drying agent, volume ratios from 1.25-5 of wet DMPC (**2**) to NaOH 50 wt% were tested.

4.4.5 Stability Experiments

A base liberation was carried out in batch using separation funnels and a 2:1 ratio of DMPC-HCl (**1**) 65 wt% to NaOH 28 wt% solution. Afterwards, drying of the wet DMPC (**2**) was achieved using a 2:1 ratio of the solution of **2** and NaOH 50 wt%. Samples were transferred to scintillation vials equipped with a screw cap and stored at 5 °C or ambient temperature.

4.4.6 Flow Experiment

All tubing was of 1/8" OD and 1/16" ID PTFE material and the T-mixers were of PEEK material with a 0.04" ID. Tubing length after the T-mixers was 1 m. Each of the two decanters was a 100-mL glass hybridization bottle 45GL thread fitted with a homemade Teflon lid made durable for the 1/4-28 HPLC fitting connection. The pump used for the aqueous solution of **1** (65 wt%) and the NaOH solution (28 wt%) was the Asia dual channel syringe pump from Syrris Ltd. fitted with a syringe for a maximum flow rate of 2.5 mL/min. The flow rates of solution **1** and the NaOH 28 wt% were 2.5 mL/min and 1.25 mL/min, respectively. For the wet DMPC (**2**) stream leaving the first decanter, a Knauer HPLC Azura 2.1S pump was used. A similar Knauer pump was used for the NaOH 50 wt%. The flow rate was 1.5 mL/min for the wet DMPC (**2**) and 0.75 mL/min for NaOH 50 wt%. For the last decanter, an Ismatec Reglo RH00 piston pump

was applied for the dry DMPC (**2**) stream. In both decanters, the aqueous waste phases were controlled with gravimetric displacement of the outlet tubing due to lack of pumps. The method worked out very efficiently despite its simplicity. The setup was operated at ambient conditions.

4.5 Results and Discussion

The experimental work was carried out in an iterative sequential implementation process, where small batch experiments were used to determine the parameters for the flow setup to be verified.

4.5.1 Analytical Method Assessment and Development

The routine method for determining the purity of distilled DMPC (**2**) was not suitable for a new solvent-free base liberation method. The distilled method builds on the density of DMPC (**2**), which should be higher than 900 g/L. Neat DMPC (**2**) has a density of 930 g/L, while a 65 wt% aqueous solution has a density of 1100 g/L, with the density of water being roughly 1000 g/L. The hexane used for extraction in the above distilled method has a density of 654 g/L, which is lower than DMCP (**2**). A mixture of hexane and DMCP (**2**) will have a lower overall density and, as such, density of solution is applicable as a useful indicator/measurement of purity in product solutions. When no solvent extractions are performed, traces of water will add to the density of the DMPC (**2**) and no accurate measurement is observed using this method.

A new analytical method was developed for the verification of the base-liberated DMPC (**2**). The method should cover two important factors related to base liberation. It should be capable of verifying the DMPC (**2**) generated with the new solvent-free base liberation method. Besides this obvious need, the method should also be able to determine the water content, since the intended use of the DMPC (**2**) was for the generation of Grignard reagents, in respect to which obtaining dry DMPC (**2**) is of crucial importance. Furthermore, the method should be fit for online analysis purposes. Given these requirements, spectroscopic measurement was the primary choice, with a focus on NIR or IR due to their great affinity for detecting O-H bending and stretching, allowing very low concentrations of water to be determined. Both methods were found to be suited for the purpose and the less costly NIR equipment was chosen. The calibration model for the NIR-predicted values versus the Karl Fischer-determined concentration is shown in figure 4.1.

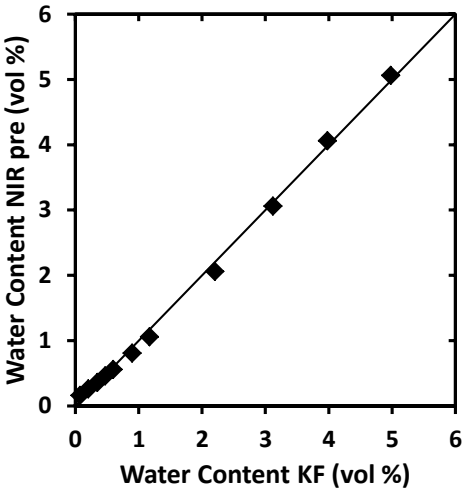


Figure 4.1: The NIR calibration curve for water content in DMPC (2), data points for KF vs. NIR (◆).

4.5.2 Screening Experiments: Proof of Concept

The first indications of the possibility of base liberation of **1**, without the need for an organic solvent extraction, occurred during a study of a Grignard addition employing **3**. The available starting material for the formation of Grignard reagent **3** was the solid salt of **1** and the DMPC in MeTHF method was applied. During one of the many preparations of **2**, the organic solvent and the aqueous NaOH solution were added in reverse order. The result was that the amine separated as an organic layer from the aqueous NaOH without the addition of the MeTHF. This finding led to the intense study of the discovered phenomenon and ultimately to the investigation of a potential flow setup.

A setup where an aqueous solution of **1** mixed with an aqueous solution of NaOH was desirable, as this would be much simpler to handle in a flow setup than solid **1**. One major concern was the ability to achieve phase separation of the free base **2** from the aqueous phase while having more water present from the aqueous solution of **1**, meaning this was to be verified before proceeding with a flow setup. A small batch experiment quickly determined that separation was possible with the commonly-available production solutions and the path towards a flow system with a simple T-mixer and tubing was made possible.

The first flow experiment aimed to shed some light on the importance of stoichiometry between NaOH and DMPC-HCl (**1**), as well as the temperature dependency of the base liberation, known to be sensitive to heat. Figure 4.2 summarizes the results of these experiments. It was found that the equivalency of NaOH to **1** was very important and that the base should be applied at greater than 1 equivalent to achieve the necessary base liberation. The pH of the aqueous phase was higher than 10 for all samples, increasing to 14 for the higher equivalents of NaOH. The water contents of the selected samples were approximately 5 vol%. No temperature dependency was revealed in regard to the base liberation, based on the investigated temperatures. However, a slightly slower

response in separation of the aqueous phase from the organic phase was observed with decreasing temperatures.

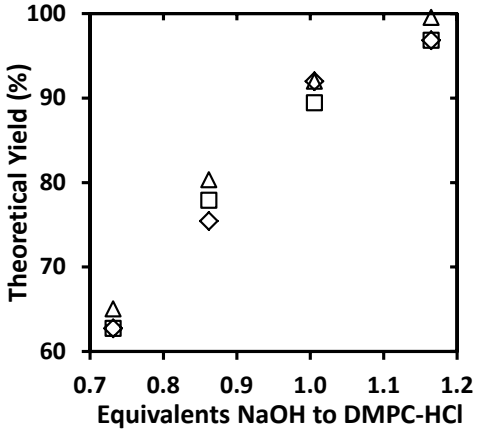


Figure 4.2: Condensed results of the base liberation experiment on DMPC-HCl (1) to determine equivalents and temperature dependency. Investigated temperatures are 0 °C (△), 10 °C (◇) and 20 °C (□).

For the purpose of visualization of the two phase mixture, an experiment was performed with high equivalents where the acid-base indicator phenolphthalein was added to the aqueous solution of **1** (pH 1-2). Upon mixing the aqueous solution of **1** with the NaOH (28 wt%), the colorless solution of **1** segregates into two phases, where the aqueous phase becomes pink (pH>9). Figure 4.3 shows the development of the two phase system.

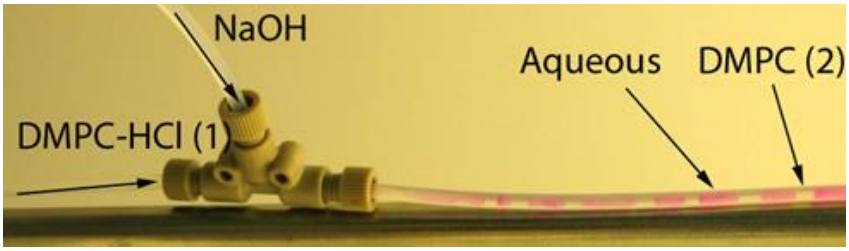


Figure 4.3: The base liberation of DMPC-HCl (1) as flow experiment with phenolphthalein as an acid-base indicator for visualization of the process.

4.5.3 Drying and Separation Consideration

The high water residual of 5 vol% in the free base **2** after the phase separation called for attention, especially due to the later formation of Grignard reagent using the furnished DMPC (**2**). The issue of how to separate the amine organic phase from the aqueous phase also needed to be solved for a full operational continuous setup. Mechanical or chemical manipulation alone or in combination would be necessary to solve the water issue (there should be less than 0.15 vol%). In the previously-mentioned experiment, only gravimetric separation for isolation was applied. The current batch methods all use some kind of solid drying agent; however, from a flow perspective this is not a desirable solution. The alternative is mechanical separation, which in theory looks appealing but might not be

sufficient in practice. Table 4.3 provides an overview of the separation and drying methods considered and tested.

Table 4.3: Potential methods for separation and drying of DMPC (2).

Method	Potential, Requirements and Complications	Verified
Membrane Separation	PTFE membrane is capable of separation of organic and aqueous solutions from each other. The requirement for separation is the hydrophobic PTFE membrane. Despite this known capability, they are often hard to control and have a narrow window of operation if breakthrough aqueous phase or retention of the organic phase should be avoided.[224,225] Furthermore, as soon as the PTFE membrane has been wetted, water is likely to pass through the membrane with very little force.	Discarded after a few trials.
Gravimetric Separation (Decanter)	The gravimetric method is very simple in operation, but was already proven not to be applicable for suppressing residual water in the organic amine phase. However, combination with a suitable drying agent could prove to be a useful setup.	Yes, but not useful alone.
Centrifugal Separation (Hydrocyclone)	A high intensity of gravimetric separation by applying centripetal force, a commonly used method for separation of phases with different density. The method may be very sensitive to fluctuations in composition and it is unknown whether it is sufficient.	Yes, but no better than gravimetric. Was tested as batch setup.
Drying Agents	Used commonly in batch processing for the drying of solvent to assure elimination of water, A solid drying agent can become problematic when applied in a flow setup. For instance, fixation (immobilization) of the solid reagents in a drying column might be necessary and replacement can frequently be required. Often the amount of drying agent needed to obtain low water content is very high.[226,227]	Yes, table 4.4.
Solid	In organic synthesis, a frequently-applied method for drying liquid organic solution is by using brine (i.e. saturated inorganic salt aqueous solution). The most common of these is NaCl solution, due to its rather mild and inert nature.	Yes, table 4.4.

The fact that it was not possible to separate the amine organic phase using any of the applied mechanical methods to reach an acceptable level of dryness altered the investigation in the direction of employing drying agents. A number of agents were evaluated and the conclusions on their capabilities are provided in table 4.4.

Table 4.4: Overview of different drying agents and their applicability for flow setup purposes.

Drying Agent	Response	Efficiency	Capability for Flow
NaOH Pellets (Coarse Size)	Good	Within Specification	Limited
Molecular Sieves (0.4 nm)	Good	Within Specification	Possible
Na_2SO_4 Anhydrous	Slow	Within Specification	Limited
$MgSO_4$ Anhydrous	Slow	Within Specification	Limited
Brine (NaCl sat. aq.)	None	None	High
NaOH 50 wt% aq.	Fast	Within Specification	High

The molecular sieves were studied a bit more intensively than the other solid drying agents, since from a production perspective they prove themselves better suited for a drying column than other commercially available solid drying agents.[227] Figure 4.4 provides the dryness obtained by molecular sieves (0.4 nm) in a batch experiment. To 2 g of molecular sieves in a scintillation vial with a screw cap, 10 mL of wet amine **2** were added and stored at 5 °C during the drying experiment. Despite a rather large number of molecular sieves, the response was rather slow and it was not possible to achieve fully dry DMPC (**2**) regardless of there being only 1.6 vol% water to begin with and after 20 hours the amount was reduced to 0.35 vol%. Further addition of molecular sieves resulted in fully dry DMPC (**2**); however, given the amount needed, the method is found to be insufficient as the sole drying step.

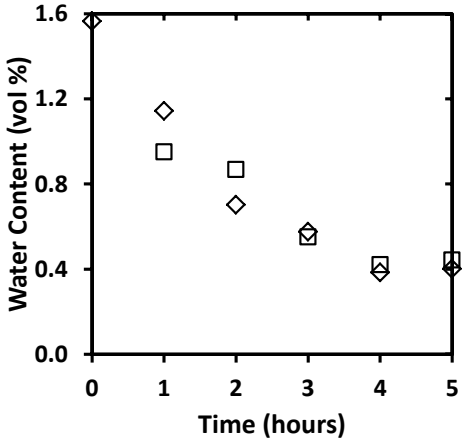


Figure 4.4: Batch drying of wet DMPC (2). A final sample point was taken after 20 hours (0.39 vol%). By adding more molecular sieves it was possible to obtain fully dry DMPC (2). NIR measurement (◇) and Karl Fischer (KF) titration (□) were used for analysis.

Considering flow chemistry, the ability to use a drying agent in a liquid form was appealing. The classic saturated NaCl solution was tried with no success and it was assumed that the addition of water with the brine could not shift the equilibrium of water in the DMPC (**2**). Knowing the capability of NaOH pellets as a potent drying agent in production, the possibility of using a near-saturated NaOH solution (50 wt%) as a liquid drying agent was investigated. At the same time, it was also tested whether shifting to the NaOH 50 wt% solution could be sufficient for direct base liberation in a one-step flow

system. NIR spectra of DMPC (**2**) from different base liberations (NaOH 28 wt% and 50 wt%) subsequently treated with NaOH 50 wt% solution are illustrated in figure 4.5, where the water peak clearly vanishes upon this treatment. Upon base liberation with NaOH 50 wt% a large amount of salt precipitation was observed, hence the idea of using NaOH 50 wt% alone was discarded. Several different volume ratios of wet DMPC (**2**) to NaOH 50 wt% were tested, with no significant difference; however, a ratio of 2:1 was chosen for later purposes in consideration of a more stable process.

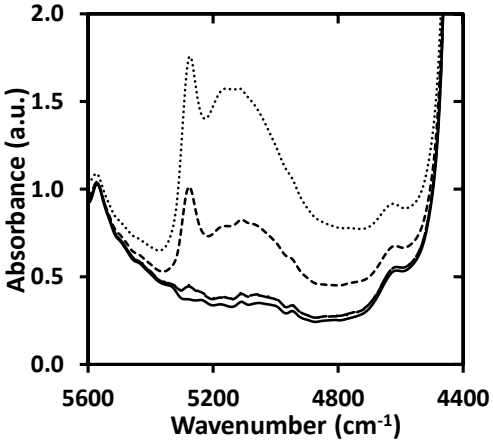


Figure 4.5: The NIR spectra of DMPC (2) treated with NaOH 50 wt% solution for verification of the potential for complete drying. DMPC(—), DMPC 1st Ex. NaOH 28 wt% (····), DMPC 1st Ex. NaOH 50 wt% (- - -), DMPC 1st Ex. NaOH 28 wt% 2nd Ex. NaOH 50 wt% (- · -), DMPC 1st Ex. NaOH 50 wt% 2nd Ex. NaOH 50 wt% (– –).

4.5.4 Stability Investigation

A final issue to be considered before testing a flow setup was the likely degradation of the free amine **2** in such a setup. If DMPC (**2**) is not stable throughout the period necessary for collection of a batch size portion, the setup will not be applicable. A stability study was established based on samples simulating the fractions of phases likely to be found in the setup. One set of samples was kept under ambient conditions, while another identical set was stored at 5 °C. After 2 weeks of storage, almost no difference could be detected between the samples stored at the two different temperatures. After two months, the samples stored under ambient conditions in the laboratory started to show signs of degradation. The samples with separated DMPC (**2**) started to polymerize and, in the samples containing NaOH solutions, a reduction in the organic phase (free amine **2**) was observed. For the samples stored at 5 °C, marginal degradation was observed. The stability experiments suggest that a potential full-scale flow setup should not be left unused for longer periods; however, the sensitivity towards degradation is greatly reduced compared to the free amine from the distilled DMPC method. Nevertheless, a better control strategy may be flushing and emptying the setup when production is on hold for periods of several weeks.

4.5.5 Flow Setup and Demonstration

The on-demand production of DMPC (**2**) by use of a flow method is illustrated in figure 4.6.

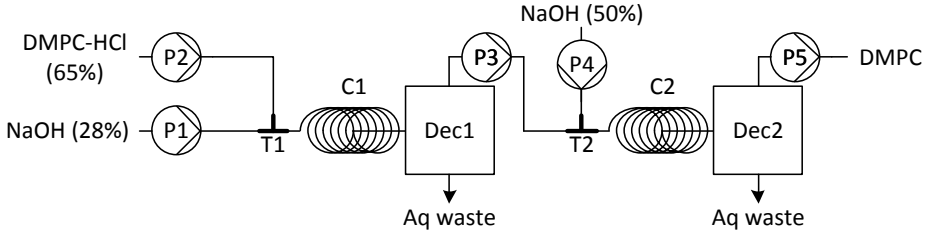


Figure 4.6: Flow sheet for on-demand production of base-liberated DMPC (2) from DMPC-HCl (1) 65 wt%.

The setup was operated for several hours with good stability and operation of the decanters, which were considered to be the weak part of the setup. Samples of DMPC (**2**) were collected from the setup every 30 minutes for water determination by at-line NIR measurement. The first test of the full setup revealed an average residual water content of 0.5 vol% in the DMPC (**2**) coming out of the second decanter. In order to achieve better results, the mixing of the NaOH (50 wt%) with the wet DMPC (**2**) from the first decanter had to be improved. NaOH (50 wt%) is very viscous and a close examination of the flow pattern in the tubing revealed two-phase segregated flow right after the T-mixer. A narrowing of the tube was applied at the outlet of reactor coil 2 with a G22 needle, causing enough disturbance of the flow to achieve sufficient mixing to obtain dry DMPC (**2**) with approximately 0.10 vol% water on average.

4.5.6 Control Strategy and Perspective

For automated operation of the flow setup, simple control strategies could be implemented to ensure high quality and dryness of the final DMPC (**2**). To ensure complete base liberation of the DMPC (**2**) from the DMPC-HCl (**1**), the pH of the aqueous phase from the first decanter after liberation should be higher than 10 and the equivalents of NaOH (28 wt%) to DMPC-HCl (**1**) used should be greater than 1. A pH-meter placed at the outlet of the first decanter could be used to ensure the pH requirement. A mass balance over the decanter, based on the theoretical release of the DMPC (**2**), combined with an in-line NIR prediction of the water content in the DMPC stream should confirm that optimal release is being achieved. Another in-line NIR prediction should be used after the second decanter to confirm the dryness of the DMPC (**2**) and ensure that the residual water content is within specification. The yield should be confirmed by a mass balance over the inlet and outlet streams. A further level of control of the two decanters should be installed to provide information on the separations taking place. In relation to optimization of the process, a significant reduction in NaOH (28 wt%) usage can be achieved if the NaOH (50 wt%) aqueous waste stream is recycled and combined with the waste stream of NaOH (28 wt%), as illustrated by the dashed line on figure 4.7. The potential reduction of NaOH from this recycling is 18-33%.

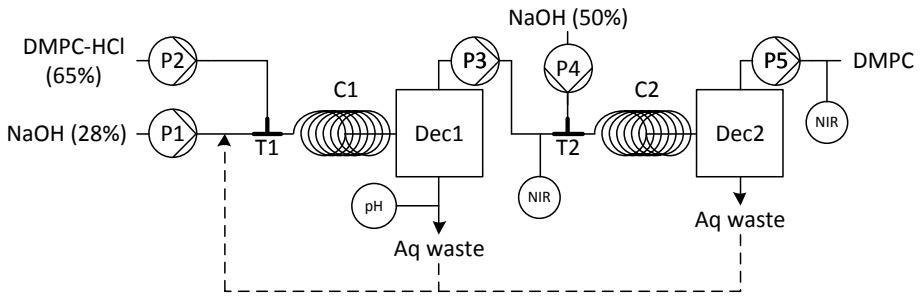


Figure 4.7: Flow sheet for on-demand production of base-liberated DMPC (2) from DMPC-HCl (1) 65 wt% illustrating the necessary control strategies and potential optimization.

4.5.7 Green Factor Assessment

The solvent-free flow method was assessed in comparison to the methods currently applied. In table 4.5, the calculated E-factor and PMI are provided. Other metrics such as the atom efficiency and reaction mass efficiency have not been calculated, as for this one-step synthesis they will be identical for the different synthetic strategies. Only DMPC Distilled and DMPC in Toluene are compared, since these two methods are located at the same production site.

Table 4.5: Comparison of E-factor and PMI for the different methods of DMPC-HCl (1) base liberation.

Method	E-factor ($kg_{waste}/kg_{product}$)	PMI ($kg_{mass\ in}/kg_{product}$)
DMPC in Flow	2.49	3.49
DMPC in Toluene	2.53	3.53
DMPC Distilled	4.73	5.73

In particular, the DMPC Distilled synthesis will become a more sustainable process if the new flow method is implemented. Besides the values used in calculating the E-factor and PMI, the removal of distillation, minimizing the equipment setup, higher yield and reduction in reactant consumption are just a few of the benefits that contribute to the greenness of this transformation. For the DMCP in Toluene, only minor benefits are obtained by using a flow setup based on a simple comparison of the E-factor and PMI achieved. Nevertheless, the better control of DMPC (**2**) concentration in toluene and standardization of base liberation methods justify the consideration of changing this process as well.

4.6 Conclusions

An organic solvent-free flow method for base liberation of DMPC-HCl (**1**) has been developed as an alternative to the routine batch processes currently applied. DMPC (**2**) is a frequently-used reactant in the production of pharmaceuticals. However, its tertiary amine and alkyl chloride functional groups are capable of reacting with each other following the Menshutkin reaction to form quaternary ammonium salts and polymers. Menshutkin reactions are reversible, but the reverse reaction may lead to multiple possible products, since the reversion can occur with any of the four substituents bound to the nitrogen in the quaternary configuration. The degradation is easily detected, as long threads of milky white polymers start to develop in the otherwise clear and transparent DMPC (**2**), and for neat DMPC (**2**) the degradation is relatively fast. The flow method developed is capable of delivering on-demand amounts of DMPC (**2**) with limited waste generation. By changing the batch method to the developed flow method, great simplification can be achieved. Other obvious benefits include the reduction in utilities and energy usage as well as lead time. Due to the removal of the need for extraction solvent and the lowering of energy consumption, such transformation to a flow process is an illustrative example of green thinking in the pharmaceutical industry. Furthermore, it is very likely that this setup can be transferred to other base liberation syntheses, especially when tertiary amines are involved.

Chapter 5

Safe Production of Grignard Reagents in a Continuous Reactor

The following chapter has been written in the style of a manuscript format for potential later publication.

5.1 Abstract

A flow method for production of Grignard reagents has been developed. The method involves a heterogeneous reactor setup capable of handling solid magnesium in a well-mixed reactor with an in-line filter. The setup has been demonstrated for production of 3-(*N*,*N*-dimethylamino)propylmagnesium chloride in 2-methyltetrahydrofuran from 3-(*N*,*N*-dimethylamino)propyl chloride in the laboratory. This laboratory-scale reactor setup is capable of producing liters of high quality Grignard reagent per day. Quality is ensured by an in-line NIR measurement that is also used to determine the concentration. Four additional Grignard reagents have been demonstrated in the laboratory reactor, including one with alkyl halide as a gas (MeCl). A full-scale version of the reactor has been implemented at H. Lundbeck A/S and is used in routine production of three key Grignard reagents.

5.2 Introduction

Flow chemistry has steadily gained ground within the pharmaceutical and fine chemical industry over the last decade.[31,36,38,39,42,88,228] Several arguments have been made for the justification of flow reactors and it is often a combination of these arguments that gives their advantages. The large surface-to-volume ratios and small active reactor volumes in particular are positively emphasized when dealing with hazardous chemistry with either highly exothermic reactions or toxic materials.[32,57,77,161,229] The large surface-to-volume ratio is ideal for better heat transfer and, when combined with a reduction in active volume, it minimizes the risk of accidents in case of a runaway. On a laboratory scale, these two issues may not be important, but upon scaling of the chemistry the advantages of the small flow reactor compared to a larger batch reactor become visible.[54,189]

Grignard reagents are commonly-used reactants in the pharmaceutical and fine chemical industry because of their wide range of applications, especially for the formation of carbon-carbon bonds.[50,51,230] Grignard reagents fit well into the above-mentioned categories of chemistry, where flow processes can improve safety and hazard issues.[79,103,111,127,163] Many alkyl/aryl halides are considered carcinogenic, while from a safety perspective concealed and small active reactor volumes reduce the risk to the operators that are handling them.[231–233] Grignard reagents are commonly formed in ethereal solvents, typically diethyl ether (Et_2O), tetrahydrofuran (THF) or 2-methyltetrahydrofuran (MeTHF), which all have low flash and boiling points.[94] THF has become the industrial standard over Et_2O due to its higher boiling temperature and flash point. THF is likely to be replaced by MeTHF, as THF is a possible carcinogen and, additionally, MeTHF is generated from renewable resources, unlike THF.[94,99,100,105,109,174] The last reactant specie is solid magnesium, which under most conditions is stable but reacts fiercely with water and acid. The formation of Grignard reagents is highly exothermic, with a typical energy release of 150-350 kJ/mol.[79,94,103,104,106] Grignard formation releases large amounts of energy and is enough to keep the commonly-used solvents at reflux. Grignard reagents react vigorously with water, with a large exothermic energy release comparable to the energy release during formation.[94,127]

Grignard reagent formation is commonly carried out in a batch process at solvent reflux.[94,100] All solvents and reactants must be dry and covered by inert atmosphere (e. g. nitrogen and argon) to avoid reaction of the formed Grignard reagent with water and oxygen. The reactor is loaded with magnesium, which is subsequently covered by solvent and heated to the solvent's boiling point. To initiate the reaction and remove the protective oxide layer from the magnesium,[94,234] highly reactive alkyl halide (e.g. dibromoethane) is commonly used in small amounts. To ensure that initiation takes place, the addition to the magnesium-solvent slurry is carried out at a temperature below the boiling point and upon addition a sudden temperature increase should be observed. The same procedure is applied for the alkyl or aryl halide that is to give the desired Grignard reagents, where addition of a small portion to a non-boiling reaction mixture should cause a temperature increase. After assuring good reactivity of the magnesium, a stable addition

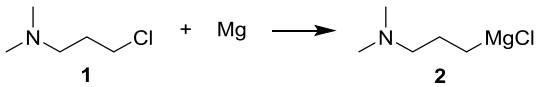
of the alkyl or aryl halide is used throughout the rest of the addition. The reason for these many precautions is to avoid having large amounts of unreacted alkyl or aryl halide that suddenly start to react, with a huge energy release causing runaway of the reaction.[94,100]

The above-mentioned risk factors involved in the production of Grignard reagents could be reduced or completely removed if Grignard reagents were to be produced by continuous processes instead of batch methods. A few examples of continuous formation of Grignard reagents do exist.[112,163,169,185,187,230,235] The common laboratory flow method is a halide exchange, which for full-scale production is less efficient, especially from an economic perspective, due to the generation of waste caused by the halide exchange.[112,163,169,185,187] This chapter demonstrates a new and safe production method for Grignard reagents by a flow method. The aim is to develop a continuous reactor setup with a small active reactor volume and the ability to handle solid magnesium, with the goal of reducing risk while producing Grignard reagents of consistent yield and high quality.

5.3 Chemistry

The Grignard reagent formation focused on in this article is the coupling between magnesium and the alkyl halide 3-(*N*,*N*-dimethylamino)propyl chloride (DMPC (**1**)) to form 3-(*N*,*N*-dimethylamino)propylmagnesium chloride (DMPC-MgCl (**2**)). This routine batch production currently uses one of three different solvent mixtures (toluene/THF, THF and MeTHF), depending on the subsequent usage. The solvent chosen for the continuous reactor is MeTHF, as utilization in the subsequent synthesis steps would most likely benefit from this solvent. The reaction is fast and is highly exothermic after the activation energy is first overcome. Scheme 4.2 illustrates the reaction taking place in order to form the desired DMPC-MgCl (**2**).

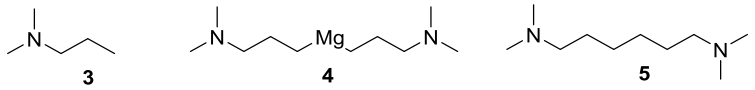
Scheme 5.1: The formation of the Grignard reagent 3-(*N*,*N*-dimethylamino)propylmagnesium chloride (2) from the alkyl halide 3-(*N*,*N*-dimethylamino)propyl chloride (1).



1 **2**

Minor amounts of impurities are commonly formed during the Grignard formation of DMPC-MgCl **2**; the three most common and their formations are described below. One is the quench product (*N*,*N*-dimethylpropan-1-amine (**3**)) of DMPC-MgCl **2** that is present due to trace amounts of water in the solvents and reactants or moisture in the headspace atmosphere of the reactors. (This impurity is only present in trace amounts as strict requirements exist for the dryness of solvents, reactants and nitrogen). The second is the Schlenk equilibrium impurity (**4**) of DMPC-MgCl **2**. The Schlenk equilibrium is empirically known to be well distributed towards the DMPC-MgCl **2** side for the three solvent mixtures used in routine batch production. Impurity **4** is only present in the Grignard reagent and will in later synthetic steps either react or be present as product **3** due to hydrolysis. The third impurity is the homocoupling product (**5**), occurring when DMPC-MgCl (**2**) reacts with itself, and is also empirically known to be insignificant. The structures of the four impurities are illustrated in scheme 5.2.

Scheme 5.2: The three common impurities in the production of DMPC-MgCl 2. From left to right: the quenched product (3), the Schlenk equilibrium product (4) and the homocoupling (5).



5.4 Experiments

5.4.1 Reactor Setup

The current continuous reactor setup (Figure 5.1) consists of a well-mixed laboratory reactor with an in-line filter to retain the solid magnesium. The reactor has no cooling/heating jacket and the reaction is performed at the reflux temperature of the reaction mixture. Cooling is done by condensing the refluxing solvent and by heat loss to the surroundings through the reactor wall. The active volume of the reactor is approximately 450 mL and the volume level is controlled by simple overflow using gravity. Two Ismatec Regloo RH00 stainless steel piston pumps are used for the alkyl halide and the solvent and the two streams are premixed in a T-mixer upon entering. Two pumps provide flexibility to the concentration of DMPC (**1**) in the solvent, by changing the ratio on the two pumps. All tubing is of PTFE material and of 1/8" OD 1/16" ID dimension, with an exception around the NIR flow cell where a slight increase was needed to fit the 1/2" stainless steel NIR flow cell (Cross Flow Cell from Brimrose Corp.). All fittings are Swagelok stainless steel.

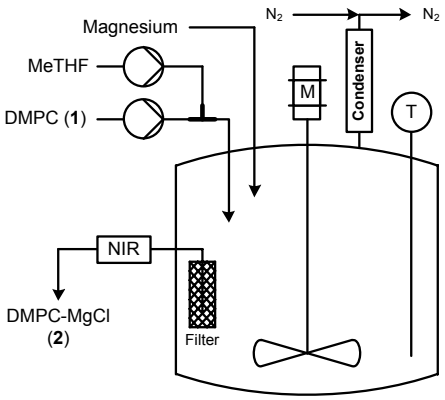


Figure 5.1: The flow sheet of the continuous Grignard reagents reactor setup.

5.4.2 NIR Model Development

To evaluate the quality and concentration in real time, an analytical method was developed. NIR spectroscopy was decided on, since previous in-house experience using NIR spectroscopy for Grignard reagents had been implemented with success. Neither DMPC-MgCl (**2**) nor DMPC (**1**) are commercially available in MeTHF, since both have limited shelf life. In particular, DMPC (**1**) has a very low shelf life, with degradation by polymerization within days. Because of the lack of commercial availability, all calibration samples for the model development were produced.

Initially, NIR spectra were acquired on the three main components in order to identify unique spectral peaks. It was possible to distinguish between the MeTHF solvent and the DMPC-MgCl (**2**), but spectral differences between DMCP (**1**) and DMPC-MgCl (**2**) are less distinct. The raw NIR spectra in the range of 6400-4400 wavenumbers are shown in figure 5.2.

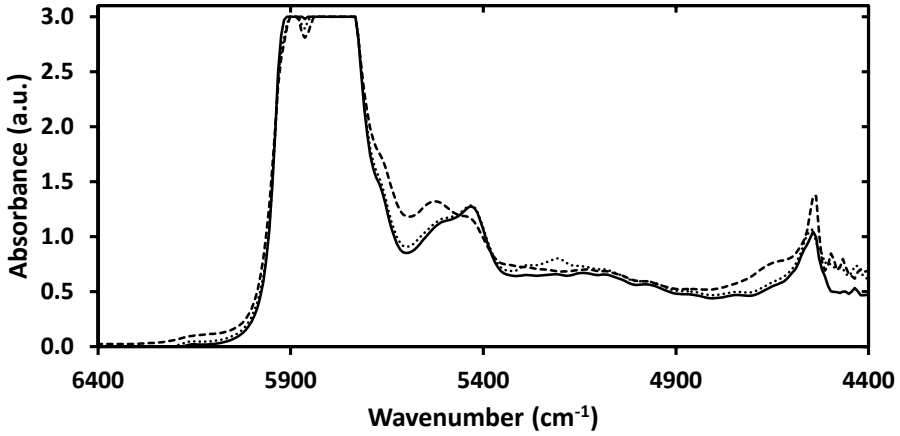


Figure 5.2: The raw NIR spectra of MeTHF (—), DMPC (1) (····) and DMPC-MgCl (2) (---). A distinct difference between MeTHF and the DMPC-MgCl is seen, but less deviation between DMPC-MgCl (2) and DMPC (1) can be found.

A standard batch procedure was used to make six batches of DMPC-MgCl (**2**) in MeTHF for the purpose of developing a NIR prediction model for DMPC-MgCl (**2**) concentration in MeTHF containing unreacted DMPC (**1**). The DMPC-MgCl concentration of each batch was determined with a standard titration of a tricyclic ketone and an in-house HPLC method was used for analysis, not discussed in further detail. A total of 59 calibration samples were made from the four batches by diluting with different amounts of MeTHF and addition of trace amounts of DMPC (**1**). In this way, selectivity and robustness are built into the calibration model as the DMPC (**1**) and DMPC-MgCl (**2**) are varied independently. The 59 reference samples are shown in figure 5.3 as the DMPC-MgCl (**2**) concentration plotted against the DMPC (**1**) concentration. The correlation between samples is very low, giving rise to the development of a robust model.

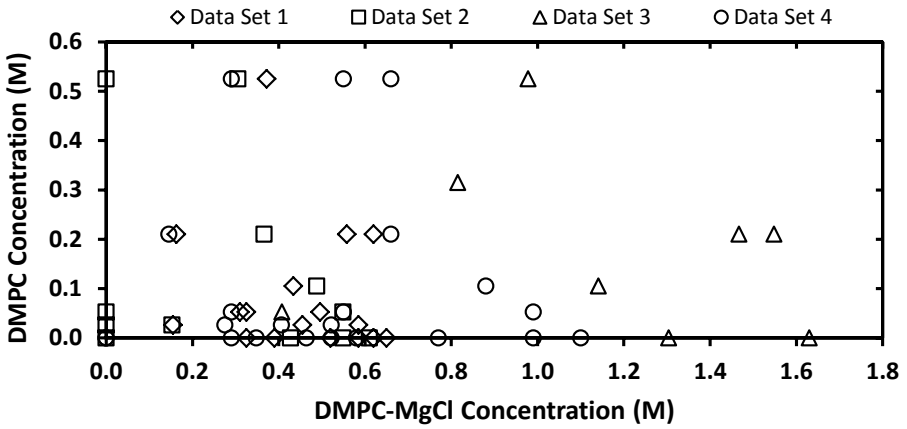


Figure 5.3: Molar DMPC-MgCl versus molar DMPC of the 59 reference samples used for the NIR prediction model to determine concentration of DMPC-MgCl (2).

NIR spectra of all 59 samples were acquired using a Bomem FTPA2000 FT-NIR (ABB Bomem) using a ½" NIR Flow Cell (Cross Flow Cell from Brimrose Corp.) as cuvette. The flow cell was connected to the spectrometer using 500 µm optical fibers. Raw spectra were acquired in the range of 15792-4500 cm^{-1} with a resolution of 16 cm^{-1} and with 64 subscans in each spectrum. Background spectra were acquired on air. The DMPC-MgCl (**2**) concentration model was created from data by reducing the spectral region of interest to 5454-5292 cm^{-1}, centering and taking the first derivative. A partial least squares (PLS) model with five principal components was chosen and the model was cross-validated by the leave-7-out principle. The final PLS model has a cross-validated prediction error of 0.065 M, which is a reasonable error within the 0-1.65M operational window.

An attempt was made to build a PLS model for the potential unreacted DMPC (**1**), but it was not possible to develop a valid model. Despite the inability to develop a PLS model for prediction of the unreacted DMPC (**1**), the reaction progress is stoichiometric, hence from a safety perspective the added DMPC (**1**) should equal the formed DMPC-MgCl (**2**). It is still valuable to keep all samples in the calibration as this will secure selectivity and robustness in the presence of unreacted DMPC. Figure 5.4 shows the NIR PLS model's ability to predict the concentrations of the DMPC-MgCl (**2**) reference samples, using the first derivative spectra of the region 5454-5292 cm^{-1}.

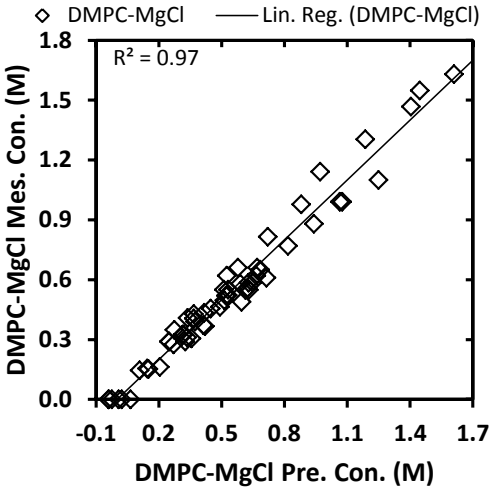


Figure 5.4: A predicted versus measured plot of the final PLS model for DMPC-MgCl (2) determination in MeTHF.

5.4.3 Operational Procedure

5.4.3.1 Start-up

The start-up of a continuous reactor is associated with operation under non-steady state conditions. The reactor is initially flushed with nitrogen to ensure an inert atmosphere before addition of the solid magnesium and subsequently with MeTHF to cover the magnesium turnings. The reactor does not have any active heating since the exothermic reaction is sufficient to maintain reflux under continuous operation. However, during start-up, active heating of the magnesium-MeTHF slurry is necessary and is done with a heat gun pointed towards the reactor wall (stainless steel reactor) under stirring of the mixture until reflux is achieved. The protective oxide layer on the magnesium is removed to ensure good reactivity of the magnesium and is done by the commonly-used method of highly reactive alkyl halide (e.g. dibromoethane).[94,234] Before addition of the dibromoethane, the temperature has to decrease below the reflux point to ensure that the reaction can be visually followed by the temperature increase and re-establishing of the boiling of the MeTHF (e.g. bubbling on the surface of the mixture) upon reaction with magnesium. This procedure is only necessary the first time the reactor is started and afterwards the magnesium turnings left in the reactor are active enough to start upon addition of DMPC (**1**). The choice of no heating unit or having a jacket reactor is merely a matter of keeping the cost of the full-scale reactor down by saving on an otherwise costly heating module. The reaction between DMPC (**1**) and magnesium is observed as foam on top of the liquid surface and other small bubble formations on the magnesium surface, more easily observed when the stirring is stopped. To ensure no accumulation of unreacted DMPC (**1**) during start-up, the feed pumps are turned on and off a couple of times, letting the mixture stop boiling indicating that all DMPC (**1**) has been consumed. Addition of new DMPC (**1**) should make the mixture start boiling again and a switch to continuous operation is made.

5.4.3.2 Continuous Operation and Short Shutdown Periods

Operating the reactor continuously requires constant surveillance of the magnesium turning level in the reactor. The feeding of DMPC (**1**) and MeTHF is carried out by the two pumps and feeding is adjusted to fit a vigorous boiling, but without heavy bumping. The easiest way to fit the flow rates is by an iterative adjusting cycle:

1. Stop pumps
2. Allow boiling in the reactor to settle (approximately 5 minutes for correct flow rate)
3. Adjust flow rate (increase for boiling less than 5 minutes, decrease for boiling longer than 5 minutes)
4. Start pumps with new flow settings and run for 5 minutes before returning to step 1.

Solid magnesium is fed manually through one of the reactor necks. In the laboratory this is easier than building a solid handling device, but this solution is implemented at full scale. The concentration of the product is measured with the NIR flow cell shortly after the overflow from the reactor. The flow cell is mounted in a way that ensures the flow is upwards, thereby avoiding air-bubble issues. The product is collected in nitrogen-flushed and covered bottles. When shutting down the setup for short periods of time, such as overnight, the pump is stopped and everything is left to cool as the reaction stops and the boiling gradually fades. The setup is left standing till the next morning, when feeding of DMPC (**1**) should quickly bring the reactor back to boiling conditions. The NIR measurements are used to ensure that the concentration of DMPC-MgCl increases as expected during addition of DMPC to the reactor. Hereby, accumulation issues can be avoided and we thereby have a safer production setup.

5.4.3.3 Long Shutdown Periods

The reactor can be shut down for long periods of time (e.g. months) without the need for cleaning and dismantling. Shutting down the reactor only requires the active reactor volume to be flushed with pure MeTHF, needing approximately 5 residence times to clean out most DMPC-MgCl (**2**). NIR measurement during this cleaning process could be used to ensure a low concentration of DMPC-MgCl (**2**) in the reactor. It is ensured that the magnesium turnings are well covered with MeTHF and a small overpressure of nitrogen is kept to ensure inert atmospheric conditions. This shutdown procedure is more a matter of safety, as DMPC-MgCl (**2**) is significantly more reactive than magnesium turnings covered with MeTHF in case of any accident.

5.5 Results and Discussions

The choice of operating at reflux temperature was based on a safety assumption, where most energy is consumed while evaporating and condensing the refluxing solvent. The setup was operated for several days, collecting DMPC-MgCl (**2**). This laboratory production included both start-up and short shutdown periods, as well as proof of concept for the long shutdown period. Figure 5.5 shows the operation of the setup for a 140-minute period and the trend curve shown is the NIR prediction of DMPC-MgCl (**2**)

concentration over time. Run-out of DMPC (**1**) caused a decrease in concentration at around 20 minutes. Replacing the bottle of DMPC (**1**) and increasing the ratio of DMPC to MeTHF started a new period of production. The combined flow rate of the DMPC and the MeTHF to the reactor was between 10-30 mL/min, with a ratio of DMPC/MeTHF of 0.15-0.30. At these ratios, the concentration of DMPC-MgCl achieved was 1-2 M and the concentration stability, as seen over a period of time, was within the acceptable performance range of the laboratory equipment. The laboratory reactor is capable of producing more than 10,000 L of Grignard reagent per year if fully utilized (30 mL/min).

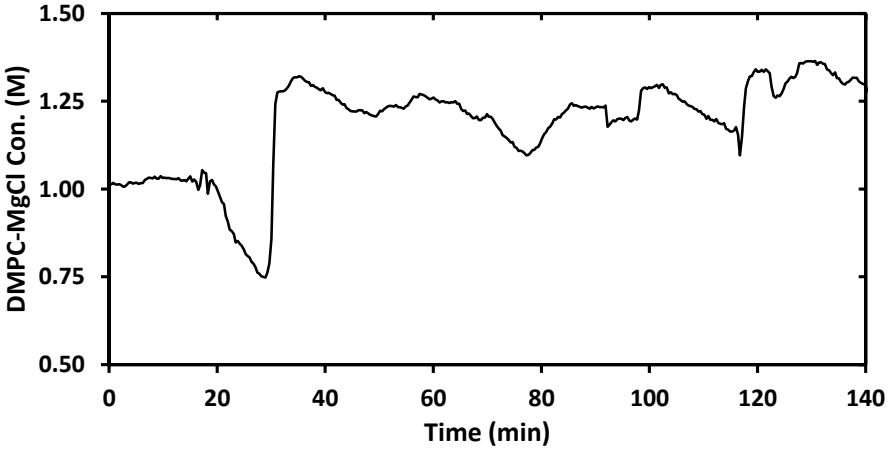


Figure 5.5: The concentration of DMPC-MgCl (2) (—) predicted by the NIR PLS model during operation.

DMPC-MgCl (**2**) formation has not been implemented in a full-scale reactor at this time. Currently four other Grignard reagents have been demonstrated in the laboratory flow reactor along with a subsequent successful full-scale implementation of three of these. One of these Grignard reagents is an alkyl halide that is a gas under ambient conditions and the original reactor was redesigned to meet this challenge by pressurizing the pipe in which the ethereal solvent and alkyl halide were pre-mixed before entering the reactor, resulting in a mixing of two liquids instead of a gas and a liquid.

5.6 Conclusions

A successful transformation of batch production of 3-(*N*,*N*-dimethylamino) propylmagnesium chloride (DMPC-MgCl (**2**)) into a continuous reactor setup has been demonstrated at laboratory scale. The continuous reactor setup differs from most flow setups used to make Grignard reagents, as it is able to handle solid magnesium instead of using the magnesium halide exchange procedure more common for laboratory flow setup. This direct Grignard reagent formation generates less waste compared to the halide exchange method. Furthermore, the later synthetic step will have easier purification and recovery, since no impurities can arise from reactions with the magnesium-carrying reagent that are present if the magnesium halide exchange method is used. The setup has proved itself highly flexible towards different Grignard reagents, with demonstration of five different alkyl and aryl halides as reactants. The setup of three of them has been successfully implemented for full-scale routine production. The laboratory reactor itself is capable of producing more than 10,000 L of Grignard reagent per year if operated at full utilization. The setup also improves the safety of making Grignard reagents, as the active volume is insignificant compared to routine full-scale batch production. Especially during start-up, the addition of alkyl or aryl halide may start the reaction properly and the risk of accumulation of halide reactant that could suddenly initiate has been reduced significantly and is almost non-existent. The implementation of NIR measurement to follow the reaction provides a fast method for quality assurance but also improves safety, as unreacted DMPC (**1**) can be spotted due to correlation with the DMPC-MgCl (**2**) concentration. The full-scale setup is a completely closed system, whereas the laboratory reactor setup is designed with freedom for fast operation but is small enough to be safely operated within a fume hood. The full-scale continuous reactor setup is a safer method in comparison to the old batch method and has reduced the risk of exposure to carcinogenic reactants and products.

Chapter 6

Redesign of a Grignard-Based API Batch Synthesis to Flow Chemistry

The following chapter has been written in the style of an article manuscript. The manuscript is to be submitted to the peer-reviewed scientific journal *Organic Process Research & Development*. The authors to be included on the publication are: *Michael J. Pedersen, Tommy Skovby, Michael J. Mealy, Kim Dam-Johansen and Søren Kiil*.

6.1 Abstract

A current Grignard-based melitracen HCl batch synthesis process has been redesigned to fit a continuous reactor system. The Grignard addition is carried out at room temperature, with subsequent one-step hydrolysis and dehydration of the magnesium alkoxide intermediate. The melitracen is isolated by simple gravimetric phase separation and is crystallized with 2 M HCl in diethyl ether to melitracen HCl. All steps in the laboratory setup are connected and the setup is capable of producing a significant amount of the commercially-needed melitracen HCl. The flow setup has reduced area footprint, energy consumption, synthesis steps and raw material usage compared to the batch process.

6.2 Introduction

The efficiency of the pharmaceutical industry has been a widely discussed topic throughout the past decade. The debate has been broad, ranging from early target drug development to the actual production and distribution of pharmaceuticals.[12,19,31,43,236,237] Expiring patents and empty pipelines have forced pharmaceutical companies to look for alternative methods to remain competitive against generic manufacturers.[21,238,239] Furthermore, the industry has one of the highest solvent-to-carbon ratios, which in combination with the fact that most of these solvents have high environmental impacts has given the industry a somewhat damaged reputation.[48] In addition, the authorities have steadily increased the tightening of legislative requirements for pharmaceutical manufacturing, in both development and production.[31,237]

With respect to the production of active pharmaceutical ingredients (APIs), the focus has especially been on batch methods and their insufficiency, especially their mass and heat transfer properties.[54,77] As early as the 1970s, Popov[44] suggested continuous manufacturing as a method for improving the efficiency of pharmaceutical production. However, it was not until the last decade that progress was seen. The establishment of the pharmaceutical round table and the increased interest from academia and industry have been driving the transformation forwards.[31,39–41,43,88] The authorities have since 2002 acknowledged new production methods and strategies within manufacturing. Process analytical technology (PAT) approaches and Quality-by-Design (QbD) concepts have been important factors in the acceptance of continuous manufacturing by the authorities.[21,240,241]

Earlier publications concerning the new paradigm of pharmaceutical manufacturing often focused on single synthesis steps and unit operations, often with the use of microreactor technology.[33,37] Later trends have changed the focus towards multiple synthesis steps, pharmacy-on-demand and end-to-end manufacturing.[39–41,242] As the trend has moved from single step to end-to-end manufacturing,[39] the previous out-scaling concept[33] of microreactors has also been replaced by mini-scale flow systems.[39,88–90,167] The scale-up of a continuous setup needed to meet full-scale requirements is often minor; hence the benefits such as mass and heat transfer are almost comparable to microreactor technology.[54]

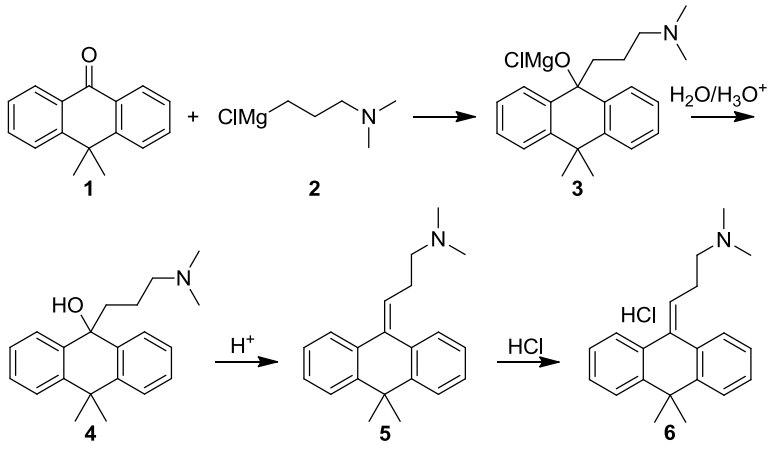
Reactions having multiple phases still pose a significant challenge within flow chemistry.[22,32,243] Flow reactors are known for being poor at handling solid material due to clogging issues, with some exceptions such as packed bed reactors with fixed catalytic material. The pharmaceutical industry is notorious for their usage of solid compounds, either as reactants, intermediates or APIs.[22,243] Low solubility is often a huge obstacle for applying the chemistry to a flow setup, unless alternative methods are applied.[22,236] In cases of high solubility, the simple use of a plug flow reactor (PFR) can be applied, often with great success and larger throughput.[167,244] The challenging part then becomes the purification of the product from impurities and unreacted reactants, as well as the final isolation of the product. Many old batch processes utilize the benefits of precipitation as a

purification step, hence altering an old batch process to fit a flow setup requires new ways to overcome these challenges.[88,236,243]

6.3 Chemistry

As illustrated in scheme 6.1, four synthetic steps are involved in the manufacturing of melitracen HCl (**6**). The four steps are a classic Grignard addition to a ketone, a hydrolysis of a magnesium alkoxide, a dehydration of an alcohol and a salt precipitation to isolate the API. The Grignard addition is between 10,10-dimethylanthrone (10,10-DMA (**1**)) and 3-(*N*,*N*-dimethylamino)propylmagnesium chloride (DMPC-MgCl (**2**)), resulting in formation of the magnesium alkoxide **3**. The magnesium alkoxide **3** is then hydrolyzed to the alcohol **4** and dehydrated to form product **5**. The last step is a crystallization of the API as a salt, where HCl is added to obtain the melitracen HCl (**6**).

Scheme 6.1: Syntheses of magnesium alkoxide 3, alcohol 4 and dehydrated product 5 in the manufacturing process of melitracen HCl 6, from ketone 1 and Grignard reagent 2.



6.4 Current Batch Synthesis

The current batch synthesis involves individual synthetic steps, as illustrated in figure 6.1. DMPC-MgCl **2** is made in-house before it is used, due to its limited storage shelf life, in a toluene-THF solvent mixture. THF is present in trace amounts in order to stabilize the magnesium in the Grignard reagents.[94] A solution of 10,10-DMA **1** is prepared in toluene and is slowly transferred to the DMPC-MgCl **2,** maintaining a temperature of 50°C. DMPC-MgCl **2** is used in an equivalence of 1.6 compared to 10,10-DMA **1**. The formed magnesium alkoxide **3** is hydrolyzed with water and acetic acid (80%). The aqueous phase is discarded and concentrated hydrochloric acid (37%) is used to dehydrate alcohol **4** to form dehydrated product **5**. Toluene is replaced with ethanol by a solvent swap. Crystallization of the dehydrated product **5** from the ethanol phase is done with HCl gas to obtain the final melitracen HCl (**6**), which is subsequently isolated by filtration.

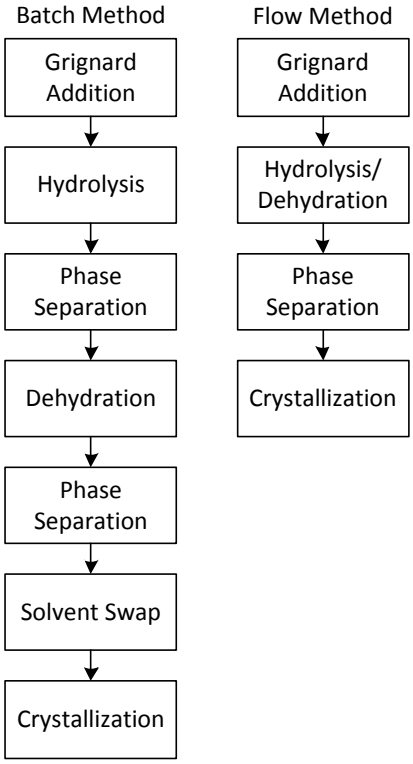


Figure 6.1: The operational steps involved in the current batch method and the simplification achieved by the flow setup.

6.5 Investigational Strategy

The API manufacturing strategy at H. Lundbeck A/S is focused on continuous production. Melitracen HCl synthesis currently occupies significant production facilities and is produced by routine batch synthesis procedures. The process shows potential for being redesigned to fit a continuous reactor setup, with potential for significant simplification of the operation and the synthetic route. This article describes the laboratory work for redesigning the process to fit a continuous reactor setup for the Grignard addition to the final melitracen HCl crystallization.

6.6 Screening Experiments

The routine batch synthesis for production of melitracen HCl **6** was considered suitable for redesign into a flow process, as most of the synthetic steps are categorized as fast reactions.[22] The current batch methods could possibly be transferred directly into a flow setup, providing the common benefits achieved when changing from batch to continuous processing. However, additional savings could potentially be achieved with the flow setup if simplifications of aspects such as the solvent choice and synthetic steps were possible. Classic batch screening experiments were conducted to assist in the decision on and design of a flow setup and, based on these experiments, the flow setup decided on was to be experimentally verified afterwards.

6.6.1 Solubility of Reactants and Products in Solvents

The first consideration in the process for redesigning melitracen HCl **6** synthesis is the solubility of reactants, intermediates and products. Solubility is one of the key parameters when designing a reactor setup and an instructive discussion may be found in Pedersen *et al.*[88] The primary focus was on the Grignard addition step, where reactants 10,10-DMA **1**, DMPC-MgCl **2** and magnesium alkoxide product **3** are of interest. DMPC-MgCl **2** already has a high solubility and was not tested further. 10,10-DMA **1** is a solid starting material and needs to be dissolved before it can react with DMPC-MgCl **2**. The solubility of 10,10-DMA **1** should therefore be tested in potential solvents and at different temperatures. Magnesium alkoxide **3** is not easily isolated, as the magnesium halide part easily reacts with water and moisture. Instead of determining the exact solubility of magnesium alkoxide **3**, a qualitative first estimate of its capability to stay in solution could be sufficient. The requirement is, of course, that the concentration of magnesium alkoxide **3** in the reaction mixture is representative of the concentrations of the 10,10-DMA **1** and DMPC-MgCl **2** intended for the synthesis. The later synthetic steps should be tested accordingly for solubility where necessary, since low solubility in these steps could require a lower concentration of 10,10-DMA **1** and DMP-MgCl **2** to have a fully operational flow setup from start to end of the synthesis.

The solubility experiments on 10,10-DMA **1** focused on three solvents to be verified: toluene, tetrahydrofuran (THF) and 2-methyltetrahydrofuran (MeTHF), all of which are suitable candidates for later full-scale production. The solubility temperature was tested up to 20°C, which is to be considered the high limit due to ambient temperatures if no heat tracing should be applied to pumps and pipes. Figure 6.2 shows the solubility of 10,10-DMA **1** in the three solvents, where THF shows a significantly higher solubility than toluene or MeTHF.

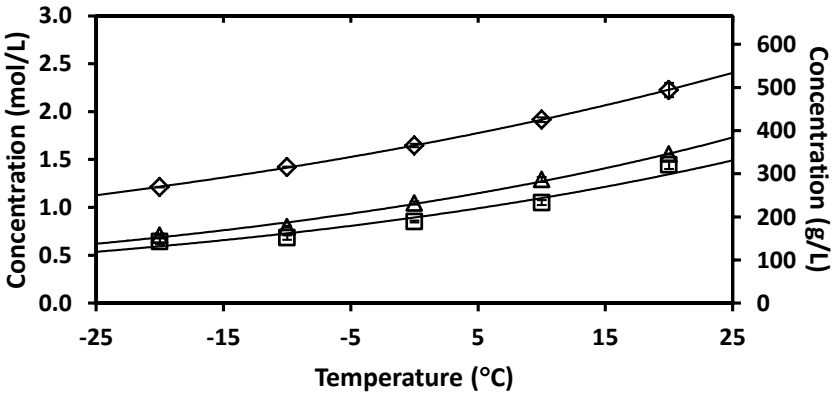


Figure 6.2: The solubility of 10,10-DMA 1 in toluene (□), THF (◇) and MeTHF (△). The 10,10-DMA 1 has high solubility even at low temperatures in the tested solvents. THF has the highest solubility, approximately 100 g/L more 10,10-DMA 1 compared to MeTHF and toluene.

The significantly higher solubility of 10,10-DMA **1** in THF makes it an obvious choice. If toluene were to be continued with, trace amounts of ether would still be needed to stabilize the magnesium in DMPC-MgCl **2**.

The concentration of 10,10-DMA **1** in THF was set to the lower side of 20°C (1.8 mol/L, 400 g/L) to minimize the risk of precipitation while operating a flow setup. The DMPC-MgCl **2** was available at approximately 1.5 M concentration in THF from the production and it was decided to proceed with this concentration. A couple of quick qualitative batch experiments were carried out to verify whether the magnesium alkoxide **3** could remain soluble in the reaction mixture, as it was not possible to isolate the unstable magnesium alkoxide **3** for a solubility study. These experiments came out positive for the desired concentrations of 10,10-DMA **1** and DMPC-MgCl **2** and no further testing of the solubility of magnesium alkoxide **3** was found necessary.

6.6.2 Phase Separation: Organic Phase and Aqueous Waste

A batch experiment, representing the expected concentration for the flow setup, was used to verify the potential for phase separation of THF from the aqueous phase. A requirement for success was that the magnesium alkoxide **3** was mostly distributed in the THF phase. The DMPC-MgCl **2** was slowly added in excess amounts with a dripping funnel to a round-bottom flask of the 10,10-DMA **1** solution. The mixture was afterwards hydrolyzed with water and acetic acid (80%). The addition of the acid caused the pH of the mixture to become slightly acidic (pH ~6) and an one-phase mixture was achieved. The pH was adjusted with aqueous ammonium (25%) and at pH 8 a two-phase mixture appeared. Alcohol **4** was distributed at 63% in the organic phase and 37% in the aqueous, according to HPLC assay. Adjusting the pH in the aqueous phase to 10 with additional aqueous ammonium (25%) resulted in an additional organic phase, with less than 1% alcohol **4** left in the aqueous phase. At pH $\geq$ 10 the tertiary amine is completely deprotonated, which is assumed to force the alcohol **4** out of the aqueous phase and into the organic phase. In acidic conditions the tertiary amine is fully protonated, causing the alcohol **4** to be soluble in both the aqueous and organic phase.

Alcohol **4** in the organic phase was then dehydrated with hydrochloric acid (37%), followed by adjustment of the pH to 10 with aqueous ammonia (25%). Adjusting the pH to 10 allowed a phase separation with more than 99% of the product in the organic phase and with a ~99% purity of the dehydrated product **5**. During the hydrolysis and dehydration, a minor precipitation of solid material was formed that easily dissolved as the reaction progressed and should therefore not be a major concern for a flow setup.

Fortunately, it was found that a well-defined separation of alcohol **4** in THF could be achieved from the aqueous phase by judicious selection of pH. Due to the tertiary amine in alcohol **4**, at acidic pH the amine is protonated, causing it to be soluble in water and form a single phase. At pH higher than 10, the amine is deprotonated, becomes almost insoluble in water and separates cleanly. Had this not been possible, one could consider changing the synthesis solvent to MeTHF, which is not miscible with water, and thus simplify the workup of the product **4** or **5** from the aqueous phase.

6.6.3 One-Step Hydrolysis and Dehydration

The ability to phase separate both the alcohol **4** and the dehydrated product **5** in THF enabled a simplification of the targeted flow method. Ideally, hydrolysis and dehydration should be possible in one step, hence saving a phase separation and combining two synthetic steps into one. Screening for a potential acid for the one-step hydrolysis and dehydration was done, focusing on acetic acid and hydrochloric acid, either separately or in combination. Table 6.1 shows the results of the product formation based on the different acid systems.

Table 6.1: Screening of different acids for direct hydrolysis and dehydration of the magnesium alkoxide 3 to the dehydrated product 5.

Acidic Solution	Product (%)	Phase Separation (%)
HCl 37% (aq.)	Dehydrated **5** (100%)	>99
AcOH 80% (aq.)	Alcohol **4** (100%)	>99
HCl 37% (aq.)/AcOH 80% (aq.) (1:1)	Dehydrated **5** (90%) Alcohol **4** (10%)	>99

As seen in table 6.1, only hydrochloric acid was able to hydrolyze and dehydrate the magnesium alkoxide mixture in one step. The experiment with hydrochloric acid resulted in significant heat development and an immediate precipitation of solids that potentially could be critical, even though it dissolved within a few minutes. An additional set of screening experiments was done to verify the potential of a lower concentration of hydrochloric acid. These experiments were carried out to verify whether the immediate precipitation of solid could be avoided and whether the energy released from the hydrolysis and dehydration could be distributed, as both steps are exothermic. Equal volumes of hydrochloric acid with different concentrations (1, 3, 6, 9 and 12 M) were used. For the concentrations lower than 6 M, it was not possible to achieve full dehydration at ambient temperature. For the concentrations equal to 6 M and higher, full dehydration was obtained, but all concentrations resulted in precipitation of a white solid that dissolved after few minutes of standing. From a production and environmental perspective, the more concentrated hydrochloric acid is the optimal choice; less aqueous waste is generated if the acid used is stoichiometric. Given the fact that precipitation could not be avoided and the production perspective, it was decided to proceed with 12 M hydrochloric acid.

6.6.4 Precipitation of Melitracen HCl from THF

The dehydrated product **5** was crystallized as the final HCl salt in the THF in a batch experiment, in order to remove a solvent swap to ethanol. The crystallization was carried out with 2 M HCl in Et_2O, as this was considered more suited for a later flow process and more easily implemented in the laboratory setup. An equivalence of 1.1 HCl was used and the requirement was an achievement of pH<2. The mixture was kept stirred during the crystallization and carried out at ambient temperature. After 10 minutes, fine white solids started to form, followed by a massive precipitation of melitracen HCl **6**. The melitracen HCl **6** was filtered with a Büchner funnel and washed with THF. The isolated

yield was 80% and within the specifications for the in-house analysis methods used in the routine production (CHN, TGA, UV-vis, HPLC, melting point). Figure 6.3 is a microscope picture of the isolated melitracen HCl **6**. For full-scale production, the HCl gas would still be more desirable for the crystallization and the 2 M HCl in Et_2O merely serves as a proof of concept for the laboratory flow setup.

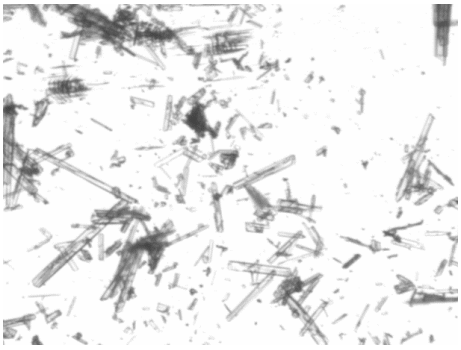


Figure 6.3: Microscope picture of the isolated melitracen HCl 6 from the THF solution.

6.7 Flow Experiments, Results and Discussion

6.7.1 Flow Process

The initial batch screening experiments all indicated that the chemistry should be run in PFRs. This decision is based on several parameters from the screening experiments. In particular, the high solubility of the reactants and products makes the synthesis ideal for PFRs. Additionally, all of the synthesis steps are categorized as fast (full conversion within minutes) and hence small reactor volumes can be used. The final setup is illustrated in figure 6.4 as a flow sheet. All tubing was 1/8" OD and 1/16" ID and made from PTFE; the T-mixer was of PEEK material ID 0.04". All synthetic steps were performed at ambient temperature, with no active cooling or heating. Every step, except for the addition of acetic acid and the decanter phase separation, is exothermic. The decanter was a 100 mL glass bottle, fitted for the purpose with an in-house-made PTFE lid. After the Grignard addition (T1,C1) of DMPC-MgCl **2** to 10,10-DMA **1**, a flow IR 10 µL head from Mettler Toledo was applied for in-line monitoring of the conversion and reaction. After the acetic acid addition (T3,C3), a 100 psi back pressure regulator (BPR) was applied to avoid boiling of the THF due to the hydrolysis and dehydration taking place at the HCl addition (T2,C2). The choice of placing the BPR is due to precipitation of solid material right after the HCl addition that is fully dissolved throughout the acetic acid coil. The HCl precipitation was done by collection of the two streams in a flask. A number of different pumps were used, all of them being positive displacement pumps for dosing purposes. Knauer Azura P 2.1S HPLC pumps with 10 mL stainless steel pump heads (P1 and P2) were used for the 10,10-DMA (**1**) and DMPC-MgCl (**2**); a Syrris Asia pump (dual pump) equipped with 0.5 and 1.0 mL glass syringes was used for both hydrochloric acid (P3) and acetic acid (P4). A Merck-Hitachi HPLC pump with a 10 mL stainless steel pumphead was used for the aqueous ammonium (P5) and Ismatec Reglo RH00 piston pumps were used for the decanter outlet (P6) and the 2 M HCl in Et_2O (P7).

The flow rate was determined in accordance with the maximum capacity of each pump and the limitation was the pump used for the acetic acid.

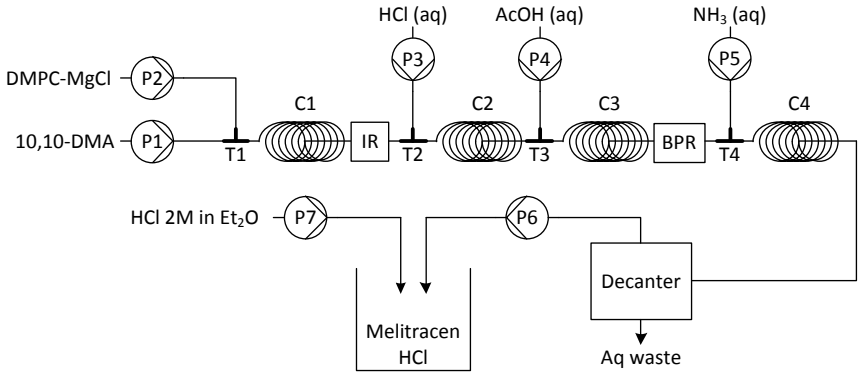


Figure 6.4: Flow sheet of the flow reactor setup for the redesign of the melitracen HCl synthesis.

6.7.2 Stepwise Verification of Flow Reactor Parts

A stepwise implementation and verification of each step was done to minimize the risk of operational problems, while operating the entire setup as illustrated in figure 6.4. The major risks were considered to be clogging issues and separation performance.

The Grignard addition of DMPC-MgCl **2** to 10,10-DMA **1** was the first part to be verified and an equivalence of 1.1 DMPC-MgCl **2** was used to ensure full conversion of 10,10-DMA **1**. Only a few minutes of residence time were needed for the reaction to achieve full conversion of the 10,10-DMA **1**. The reaction was easily followed visually, as the magnesium alkoxide **3** becomes dark red/orange. The product stream was collected in a flask, where it turned to a more orange-like appearance over time.

Implementation of the HCl stream for hydrolysis and dehydration caused boiling of the THF solvent, but full conversion was achieved within minutes. Implementing the acetic acid stream resulted in some alteration of the setup to account for the boiling of the THF, as full conversion was not achieved. A back pressure regulator (BPR) of 100 psi was added to prevent the boiling of the THF (65 °C at STP). The BPR provided a stable flow that ensured a steady residence time in the HCl coil (C2), resulting in the desired full conversion of the magnesium alkoxide **3** to the dehydrated product **5**. Adding the aqueous ammonium stream to the setup caused precipitation of ammonium chloride salt. The precipitate was easily dissolved by addition of water. Due to lack of pumps, it was decided to dilute the acetic acid to 40% from the original 80% and to double the flow rate. From a production perspective, an additional pump with water would be better suited as 80% acetic acid is the standard concentration in production. The BPR was originally implemented right after the HCl coil, but the white solid precipitate later caused clogging of the BPR, so it was moved to be after the acetic acid stream where a full liquid homogeneous phase was present. The choice of not moving it to be after the aqueous ammonium coil was due to a small risk of having precipitation upon the addition thereof, as this was observed in a previous run. At the end of the acetic acid addition during all

adjustments, a full one-phase homogeneous stream was constantly present and it was considered more stable to add the BPR at this point in case of any fluctuation.

Having the entire setup running, the decanter was tested for the setup. A previous flow setup had proved the decanter's capability for separating organic and aqueous phases from each other, so that a single experiment was enough to demonstrate the decanter for this separation. The last stream to be implemented was the 2 M HCl (Et_2O) stream for crystallization. At first, mixing of the two streams was attempted in a T-mixer (2.5 mm ID), but the low pressure pumps used (Ismatec pumps) could not deliver a high enough pressure to avoid clogging. The clogging was caused by evaporation of the solvents due to the low boiling points of both THF and Et_2O and the crystallization of melitracen HCl (**6**) happening in the T-mixer. As an alternative, the two streams (P6 and P7) were pumped individually into the collecting bottle. No optimization was done to control the crystallization, as this was not the scope of the project, and for a full-scale setup HCl gas would be a preferred choice. Figure 6.5 shows the fractions collected from the setup.

Figure 6.5: The collected fractions of product streams from the setup during continuous operation. To the left is the aqueous waste from the decanter, at the center is the organic phase containing dehydrated product 5 and to the right is the crystalline melitracen HCl 6 API and the mother liquid.

6.7.3 Operation of Full Flow Setup

The final flow setup, as illustrated in figure 6.4, was operated for 300 minutes under steady state conditions. The experiment was terminated at the point of complete utilization of the 2 M HCl (Et_2O). For the first 30 minutes the setup was not in steady state due to a bursting of tubing and fittings around the IR flow cell, but a steady state was achieved shortly after replacement of the broken fittings. The flow rate of the system is given in table 6.2 and table 6.3 provides the residence times in the important parts of the reactor.

Table 6.2: The reactor configurations and residence times, along with important observations, for the melitracen HCl 6 synthesis as operated with the flow setup (Figure 6.4).

Reactor Part	Flow Rate (mL/min)	Reactor Volume (mL)	Residence Time (s)	Observation
Coil 1	4.5	4.95	66	Deep red color from reaction. Temperature higher than ambient, lower than the boiling point of THF.
Coil 2	5.5	1.98	21.6	Temperature is above the boiling point of THF, 100 psi suppress boiling. Stream becomes transparent with a white solid that disappears into an one-phase system. pH < 2
Coil 3	8.0	0.99	7.4	One-phase system. pH < 2
Coil 4	9.9	1.98	6.0	Two-phase system. pH > 10
Decanter (Org/Aq)	9.9 (4.5/5.4)	100	606.1	Two-phase system. pH > 10

Table 6.3: The flow rates and concentrations of the different reactants used in the flow setup.

Reactants	Flow Rate (mL/min)	Concentration (M)	Equivalents
10,10-DMA **1**	2.0	1.8	1.0
DMPC-MgCl **2**	2.5	1.5	1.05
HCl (aq.)	1.0	12 (37%)	3.33
AcOH (aq.)	2.50	7 (40%)	4.86
NH_3 (aq.)	1.9	13.4 (25%)	7.07
HCl (Et_2O)	2.25	2	1.25

An IR flow cell was placed after coil 1 and was used to follow and ensure that full conversion of 10,10-DMA **1** was achieved. Figure 6.6 shows the carbonyl peak of the 10,10-DMA **1** as it progressed throughout the experiment. The trend line absorbance intensity of the peak is based on area to zero baseline for the IR region of 1610-1580 cm^{-1} and is given in arbitrary units. The off-line HPLC data in table 6.4 confirms full conversion of 10,10-DMA **1**. The replacement of the tubing caused an exposure of the magnesium alkoxide **3** to the surrounding atmosphere (i.e. moisture in the air), resulting in the deposit of magnesium salts on the IR diamond window. Despite an attempt to clean the window, some deposit was still present, causing the small offset from the zero baseline, which explains why zero is not achieved.

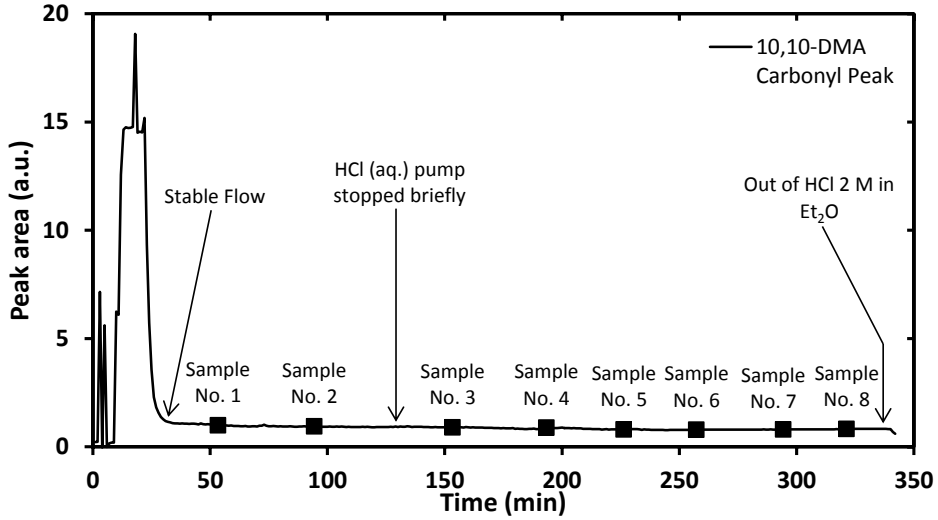


Figure 6.6: The IR data on the flow setup run, following the peak of the carbonyl functional group of 10,10-DMA (1) and the reference samples for off-line HPLC analysis given in table 6.4. Steady state conditions were achieved after 30 minutes; the initial 30 minutes of unstable flow were related to bursting and replacing of tubing and fittings.

A portion of the melitracen HCl (**6**) was collected by filtration in a Büchner funnel, washed with THF and dried in a vacuum oven at 50 °C for 24 hours. The product was subjected to complete release analysis for the API and all product attributes were found to be within specification.

Table 6.4: The HPLC samples, where samples were collected from the aqueous waste stream of the decanter, the crystallized melitracen HCl (6) and the mother liquid, and a few from the organic phase of the decanter.

Sample No.	Compound	Crystallized Product (Area%)	Mother Liquid (Area%)	Decanter Aqueous (Area%)	Decanter Organic (Area%)
1	Melitracen (**5** or **6**)	100	97.65	62.0	No sample
	Alcohol (**4**)	nd	nd	38.0	
	10,10-DMA (**1**)	nd	2.1	nd	
	Other Impurities	nd	0.2	nd	
2	Melitracen (**5** or **6**)	100	97.8	37.8	No sample
	Alcohol (**4**)	nd	nd	62.1	
	10,10-DMA (**1**)	nd	2.0	nd	
	Other Impurities	nd	0.2	nd	
3	Melitracen (**5** or **6**)	100	96.3	20.5	No sample
	Alcohol (**4**)	nd	nd	79.5	
	10,10-DMA (**1**)	nd	3.5	nd	
	Other Impurities	nd	0.2	nd	
4	Melitracen (**5** or **6**)	100	99.0	nd	No sample
	Alcohol (**4**)	nd	nd	100	
	10,10-DMA (**1**)	nd	0.8	nd	
	Other Impurities	nd	0.2	nd	
5	Melitracen (**5** or **6**)	99.9	99.1	nd	No sample
	Alcohol (**4**)	0.1	nd	100	
	10,10-DMA (**1**)	nd	0.7	nd	
	Other Impurities	nd	0.2	nd	
6	Melitracen (**5** or **6**)	100	99.3	nd	100
	Alcohol (**4**)	nd	nd	100	nd
	10,10-DMA (**1**)	nd	0.5	nd	nd
	Other Impurities	nd	0.2	nd	nd
7	Melitracen (**5** or **6**)	100	39.8	39.3	99.8
	Alcohol (**4**)	nd	60.2	60.7	0.2
	10,10-DMA (**1**)	nd	nd	nd	nd
	Other Impurities	nd	nd	nd	nd
8	Melitracen (**5** or **6**)	100	56.4	26.2	100
	Alcohol (**4**)	nd	43.6	73.8	nd
	10,10-DMA (**1**)	nd	nd	nd	nd
	Other Impurities	nd	nd	nd	nd

6.8 Conclusions

A full redesign of a current batch synthesis to a full flow setup has been possible, from the starting material to the final salt crystallization of the active pharmaceutical ingredient, melitracen HCl. The flow process was significantly simplified compared to the batch process, with removal of a phase separation and usage of tetrahydrofuran (THF) only as a solvent compared to the previous toluene-THF solvent mixture. All synthetic steps were carried out at ambient temperature, whereas routine batch production requires active heating (up to 50°C) and cooling in several steps. The crystallization of the melitracen HCl was proved possible in THF with 2 M HCl in diethyl ether (Et_2O) and eliminated a solvent swap to ethanol. The crystallization was not optimized and would most likely be done with HCl gas, with an expected additional gain in yield from the lower volume of solvent. The isolated yield in the given study was approximately 85%. The phase separation achieved with the decanter was higher than 99% product in the organic phase, with a HPLC purity of greater than 99%. The isolated melitracen HCl was analyzed in accordance with the in-house release methods required for current batch production and all measurements were in accordance with requirements. A production of 60 g/h of isolated melitracen HCl can be achieved with the flow setup. Furthermore, the setup demonstrated great robustness towards fluctuations in reactant streams. The one-step hydrolysis and dehydration could potentially be applicable for other Grignard additions, as could the subsequent decanter phase separation.

Chapter 7

Full-Scale Continuous Mini-Reactor Setup for Heterogeneous Grignard Alkylation of a Pharmaceutical Intermediate

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7.1 Abstract

A reactor setup consisting of two reactors in series has been implemented for a full-scale, heterogeneous Grignard alkylation. Solutions pass from a small filter reactor into a static mixer reactor with multiple side entries, thus combining continuous stirred tank reactor (CSTR) and plug flow reactor (PFR) technologies. Through the use of the reactor train in combination with in-line NIR analysis, on scale a 35% reduction in solvent volume was achieved and the formation of a key impurity was suppressed. The mini-reactor solution achieved many of the economic advantages attributed to microreactor technology, while avoiding the difficulties associated with handling of solids in microreactors.

7.2 Introduction

The origin of continuous processing within the pharmaceutical industry can be traced back to Popov,[44] who asserted the relative inefficiency in many cases of batch processes compared to flow methods. Batch and semi-batch reactors provide great flexibility towards different chemistries and are workable for heterogeneous reactions. The flexibility of batch methods requires a number of compromises, such as variation in product quality and large reactor volume, causing poor heat and mass transfer.[19,22] In 2005, the American Chemical Society (ACS) Green Chemistry Institute (GCI) Roundtable was founded as a cooperation between the ACS, GCI and several pharmaceutical companies with the aim of identifying areas that could contribute to sustainable development and process optimization. Among 10 engineering items the group highlighted for improvement of sustainable processing, continuous processing was identified as the most significant contributor.[31]

Due to stringent regulatory requirements, the pharmaceutical industry had not, apart from a few exceptions,[245–247] considered continuous processing as a real option until the early 2000s.[240] The shift in regulatory strategy, first embodied in the FDA's PAT Guidance in 2002, has occurred concurrently with an increased interest in microreactor technology for organic syntheses and an improvement in process analytical technologies.[21,32,36–38,241] The academic world, especially, has embraced microreactor technology for organic syntheses, but little industrial implementation of microreactors for production purposes has been seen.[33,36,54,79,160,248] Most of the advantages observed with microreactor technology, as compared to those of batch methods, are not due to the microstructure of the reactor channel but are merely related to flow chemistry.[54] From a production perspective, only the heat transfer superiority stands out significantly in comparison to meso- or mini-flow reactors.[54] Several articles discuss kilo-scale setups or pilot plant configurations, but only a limited number are found where implemented setups are used in routine manufacturing.[43,249–253] The overall smaller reactor volumes of flow reactors in comparison to batch and semi-batch reactors provide improved safety for processes involving hazardous and explosive reactants, products and/or solvent.[31] Additionally, one of the main barriers to implementation of flow methods is solid material and microreactors are notoriously poor at handling solids.[243] In many pharmaceutical processes, at least one solid component is present and often one of the reactants or the product is in solid form.[22] Roberge et al. have estimated that, from a kinetic perspective, 50% of the reactions employed in the pharmaceutical and fine chemical industries could benefit from microreactor technology; however, only 16% could benefit due to the presence of solid components.[22] Other overall benefits of mini-reactors are easier cleaning, lower capital investment and infrastructure cost, reduced labor requirements, lower energy consumption and footprint reduction. Due to the limitations of microreactors, meso- or mini-flow reactors are poised to become the industrial standard.[19,31]

In reaction engineering, processing of reactants is divided into two categories: homogeneous and heterogeneous.[59] A survey of the flow chemistry literature reveals that the majority of continuous processes are homogeneous, liquid-phase reactions.[32,36] Most heterogeneous flow reactions reported in the literature are typically gas-liquid or solid-catalyzed reactions of liquid or gas.[36] Continuous crystallization has been extensively investigated in, for example, oscillatory flow reactors (OFRs) and this type of reactor also has potential for slurry reactions.[86,87] Despite the fact that solid material (reactants or product) is present in most pharmaceutical and fine chemical syntheses, this is rarely illustrated in the literature, where solubility issues are typically solved by extensive dilution.[36] From a manufacturing and process intensification perspective, dilution is rarely the desired approach.[57] In general, homogeneous reactions can often be the most suitable conditions for flow chemistry and, at the same time, are the easiest to implement. In spite of this, the advantages presented by heterogeneous reaction conditions employing other reactor types cannot be overlooked. Heterogeneous reactors operate on two different principles: retention or residence time. The retention subgroup operates by holding back any solid material; hence the solubility of the product should at least be higher than the reactant of lowest solubility. Such reactor types are very robust towards fluctuations in reactant streams.[90] The residence time subgroup uses a more complex method, where dissolution and reaction rate must be considered more carefully to properly dimension the reactor correctly to ensure full conversion. The beneficial part of such setups (e.g. OFR) is the potential to operate at charges far greater than those that allow complete dissolution of the reactants and product, making the approach interesting for processes where the product solubility is also limited but sensitivity towards fluctuations in process parameters is an evident drawback of the method.

Both homogeneous and heterogeneous reactor configurations have been considered for the full-scale reactor configuration discussed in this article. A homogeneous approach was abandoned, due to the poor solubility of 2-chlorothioxanthen-9-one (**1**) in most solvents; for instance, 35 volumes of tetrahydrofuran (THF) are needed to completely dissolve **1** at the reaction temperature. The excessive solvent consumption could potentially be handled by recycling; however, this would increase both infrastructure cost and energy consumption. The limited solubility of **1** in all practicable solvents, including THF, provided the motivation for a novel heterogeneous reactor design. While there are many potential heterogeneous reactor configurations, the continuous filter reactor setup presented in a previous work[90] was deemed suitable and robust. The reactor setup thus consists of two continuous-flow reactors connected in series: a filter reactor and a side-entry reactor, as illustrated in Figure 7.1. Conceptually, the reactor train can be envisioned as a continuous stirred tank reactor (CSTR) with a filter in the outlet connected to a plug flow reactor (PFR) with multiple feed points.

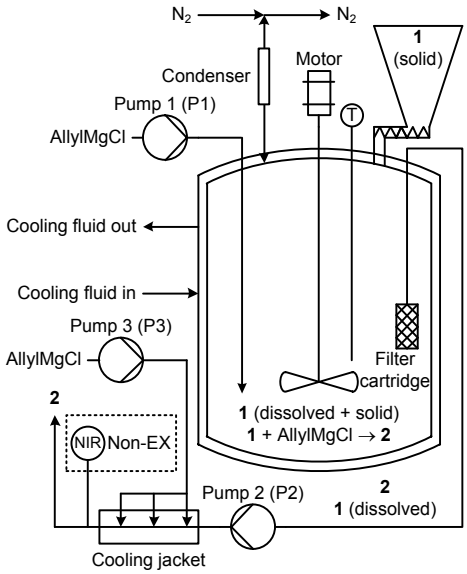
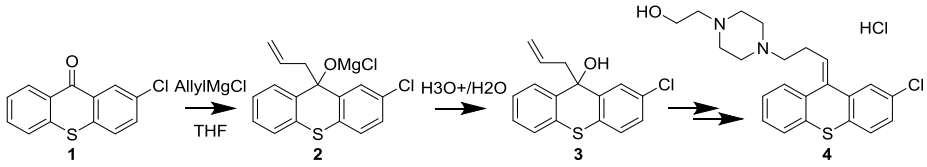


Figure 7.1: Schematic representation of the full-scale reactor setup, representing only the main components of interest. Allylmagnesium chloride (AllylMgCl) is fed to the filter reactor by pump P1 and solid ketone 1 is fed by a screw feeder. A product stream containing alkoxide intermediate 2 and dissolved ketone 1 is withdrawn from the filter reactor by pump P2. P2 feeds the product stream into the side-entry reactor, where the remaining dissolved ketone 1 is processed with allylmagnesium chloride fed by pump P3. An in-line NIR measurement is conducted at the outlet of the reactor setup to ensure that full conversion of ketone 1 is achieved.

7.3 Chemistry

One of the synthetic steps in the production of the antipsychotic API **4**, zuclopenthixol hydrochloride (Clopixol), is a classic Grignard alkylation of a ketone. As illustrated in Scheme 7.1, a solution of allylmagnesium chloride in THF is added to ketone **1** to produce the magnesium alkoxide intermediate **2**, which is subsequently hydrolyzed with dilute acid to form compound **3**. The reaction proceeds cleanly; however, an unknown impurity is formed near the equivalence point. The structure of this impurity has not been elucidated. The legacy semi-batch process involved suspension of **1** in THF, addition of allylmagnesium chloride in THF, hydrolysis and isolation of alcohol **3**. The alkylation and hydrolysis are rapid, highly exothermic reactions that require some safety precautions. For several reasons, organometallic reactions can benefit from the advantages of continuous manufacturing and this has been demonstrated by a variety of groups.[22,57,68,159,164]

Scheme 7.1: Synthesis of alcohol 3 and intermediate 2 in the manufacturing process of zuclopenthixol hydrochloride (Clopixol) 4.



7.4 Reactor Constraints

The full-scale continuous reactor setup has been a customized in-house project in cooperation with DTU Chemical Engineering and was designed, built and implemented at H. Lundbeck's API production facility in Lumsås, Denmark. Preliminary laboratory work, including proof of concept, on the synthesis of zuclopenthixol hydrochloride (Clopixol) was conducted at DTU.[89,90,225] As part of our overall continuous manufacturing strategy, the reactors were designed to meet several criteria. Each reactor module should be delivered as complete as possible from the workshop to facilitate a "plug-and-play" approach, minimizing production downtime. Modules should be compact enough to pass freely through existing entrances and corridors in the factories. The equipment should also be highly flexible in daily operations; shutdown should be possible without affecting steady state conditions.

This final constraint was the most troublesome, since it would significantly impact the overall utility of the continuous facility. A long ramp-up to steady state would be time-consuming and generate waste during start-up and shutdown procedures. An additional concern was the stability of the alkoxide **2**, which was initially to be collected in a tank for subsequent batch processing to alcohol **3**. Fortunately, the alkoxide **2** proved to be quite stable and thus the collection period could be prolonged, improving the efficiency of the final batch processing.

7.5 Solid and Liquid Handling

In the interest of intensifying the process as much as possible, it was necessary to ensure that ketone **1** was always in excess in the filter reactor. This reduced the required precision of the solid feeder and, as such, a double volumetric screw-feeder with self-cleaning ability was chosen and operated with small batch feeding sequences. As observed in the laboratory,[90] the solid has a tendency to form bridges; however, in this case scale-up was beneficial as it facilitated the installation of anti-bridge-forming components. The solid feeder can be operated for a complete shift before refilling of the hopper is necessary. In this case, "automation" has a price, as the hopper is one of the largest components of the setup, as can be seen in Figure 7.2.

The choice for liquid handling was the diaphragm pump that is one of the most widely applied pumps for production, in accordance with Good Manufacturing Practice (cGMP) for API manufacturing. Three pumps were needed, all with different specifications regarding precision. The least sensitive pump is the allylmagnesium chloride solution feeding pump, P1 to the filter reactor and the most sensitive pumps are the feeding pumps, P3 to the side-entry reactor and P2 from the filter reactor, which must provide stable flows. The different sensitivities and robustness of the pumps are a result of both the chosen process control strategy and the design of reactor setup compared to conversion degree.

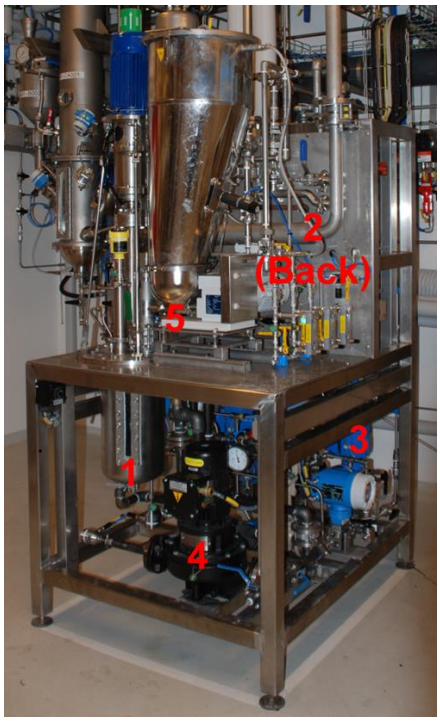


Figure 7.2: Full-scale continuous reactor setup for production of alkoxide ion 2 at H. Lundbeck's production facility in Lumsås. The entire reactor setup is comparable in size to a normal-sized batch vessel in area footprint occupation, but in addition to the filter reactor (1) and the side-entry reactor (2) it includes pumps (3), cooling regulation (4), solid feeding (5) and other ancillary unit operations.

7.6 Filter Reactor

The filter reactor is included in the subcategory of heterogeneous retention reactors described in the Introduction. The reactant of lowest solubility, ketone **1**, must be dissolved in THF in order to react with allylmagnesium chloride. Combining dissolution and reaction of ketone **1** in the same reactor places two operations into a single piece of equipment, thereby reducing the physical size and capital cost of the reactor configuration. The novelty of the filter reactor is the potential for operating heterogeneous syntheses continuously with higher flexibility and robustness.

The concentration of alkoxide **2** leaving the filter reactor is correlated to the concentration of allylmagnesium chloride with adjustment for the volume expansion caused by the dissolved ketone **1**, which is empirically found to be approximately 15-20%.[90] The dissolution rate of ketone **1** was found to be slower than the alkylation reaction rate between the solubilized ketone **1** and allylmagnesium chloride. Therefore, the flow rate of allylmagnesium chloride to the filter reactor must be adjusted to ensure that the reaction mixture is at the saturation point of ketone **1**. The dissolution of **1** is positively influenced by the total surface area of solid particles present in the filter reactor; however, excessively high solid loading may cause viscosity problems.

The total consumption of **1** in the reactor setup is the sum of the ketone **1** reacted in the filter reactor and the **1** leaving with the product stream to be reacted in the side-entry reactor. This amount is used to calculate the conversion of ketone **1** in the filter reactor. The choice of conversion in the filter reactor was based on the formation of "impurity A" and the desired solvent reduction. Impurity A is increasingly formed at near-equivalent addition of allylmagnesium chloride to ketone **1**. A conversion of 85-90% in the filter reactor portion of the reactors was found to be optimal in suppressing the formation of impurity A while still achieving the reduction in solvent consumption.

The filter reactor ended up being a classic vessel design, but an optimized asymmetrical design was considered, as this facilitates a smaller volume-to-surface area with a large top area for installation of probes, sensors, etc.

The potential for filter clogging required that the filter should be easily accessible for replacement, preferably without disturbing the steady state condition within the reactor. In addition, the available filter area should be as large as possible. Having the filter normally positioned at the bottom of the reactor fulfilled only the filter area requirement and to replace the filter, the reactor would have to be emptied (thus disrupting the steady state). Using a filter cartridge submerged from the top of the reactor (see Figure 7.1) fulfilled both requirements, since replacement of the filter could be done with a full reactor and the cylindrical geometry of the cartridge provided a comparatively large filter area.

7.7 Side-Entry Reactor

The necessity of the side-entry reactor is a consequence of how a CSTR functions, where the composition of the product stream is equivalent to the composition within the reactor. A higher conversion of ketone **1** could be achieved in the filter reactor, but an increased formation of impurity A is provoked if operated at near-equivalent addition of allylmagnesium chloride. The side-entry reactor has the purpose of reacting all unconverted ketone **1** that leaves the filter reactor in its outlet stream. The allylmagnesium chloride solution fed into the side-entry reactor is split into three injection points along the reactor length to spread the heat of reaction and suppress impurity formation. Modelling of side-entry reactors has indicated that only marginal improvement is observed if more than three injection points are employed.[75,79]

The flow in the side-entry reactor is not sufficient to satisfy a turbulent flow regime. Considering the mixing sensitivity of Grignard alkylation in general, improving the mixing was needed, in particular as the side-entry reactor has the task of converting the last of the ketone **1** with a minimum of impurity formation. The mixing was improved with static mixers positioned after each T-mixer in the reactor. To further improve the mixing, each feed point was narrowed before the injection into the reactor to increase the linear flow rate of the allylmagnesium chloride upon mixing with the reaction mixture in the T-mixer. All the improvements were based on empirical experience and no optimization was attempted.

7.8 Process Regulation

The mass flow is probably the most important part of the process regulation control and is based on a fixed concentration of allylmagnesium chloride. After careful consideration of the two reactors and their contributions to the transformation of ketone **1** to alkoxide intermediate **2**, it was concluded that the flow rate of the product pump (P2) for flow out of the filter reactor should be fixed. If the flow from P2 were to be a variable parameter, each change would result in an adjustment of both allylmagnesium chloride pumps (P1 and P3) and the entire regulation process would be more complicated. Introducing a fixed flow rate for P2 had two major benefits. Liquid level control in the filter reactor was simplified as considerations of volume expansion, caused by the dissolved ketone **1**, did not need to be accounted for. Additionally, a fixed flow into the side-entry reactor facilitates simpler regulation of the conversion of the remaining ketone **1** entering the side-entry reactor. The fixed flow of P2 and the temperature dependency of ketone **1** in THF[90] led to a simple feed forward process control loop, based on temperature measurement within the filter reactor under the assumption of CSTR-like behavior.

A major concern for continuous operations is the start-up and shutdown phase of a continuous run, which presents a challenge for handling product streams not meeting the product specification. In this application, the equipment is dedicated to intermediate **2** production; therefore, start-up and shutdown cycles occur infrequently. In addition, the lowest operational volume in the filter reactor is ~5 L, which is simply discarded in the event of a complete shutdown. During start-up, a semi-batch-like approach is used to achieve a concentration in the filter reactor approaching the steady state condition. This technique requires fewer residence times for the filter reactor to reach steady state. Even though the concentration during start-up has not achieved the steady state level, the quality of the product stream is equal to that of the steady state, only more dilute. This strategy enables routine production to operate with only an infrequent waste of 5 L on the rare occasion of a complete shutdown of the facility.

7.9 In-line NIR Control

An optical cross-flow cell connected to a near-infrared (NIR) spectrometer was installed after the side-entry reactor for in-line process control at a fixed temperature. A NIR measurement is a non-destructive measuring method in complete agreement with the ICH Q7 PAT description.[26] The NIR installation is used to measure concentrations of ketone **1** and alkoxide intermediate **2**, indicating whether the process is proceeding in accordance with expected temperature regulation. At present, the NIR is not implemented as an automatic feedback regulator, but there is the potential for such. Earlier laboratory experiments have been conducted wherein the NIR measurement was verified for process regulation in a feedback control loop.[89] In the factory, the NIR is used to monitor the process to give operators the opportunity to take action on any malfunction or offset during the synthesis. NIR monitoring during a test of the side-entry reactor's effectiveness can be seen in Figure 7.3. The solid line is the alkoxide intermediate **2** concentration and the dashed line is the ketone **1** concentration. The NIR calibration is

performed on the basis of samplings from the actual processes, which are analyzed by offline HPLC. Quantitative NIR calibrations were developed for ketone **1** and alkoxide intermediate **2**, using standard partial least squares (PLS) regression. As illustrated in Figure 7.3, ketone **1** concentration was initially high due to zero feed of allylmagnesium chloride to the side-entry reactor. The small fluctuation in the concentration of ketone **1** is merely a result of the overall process regulation, monitoring and the pumps. Feeding of allylmagnesium chloride to the side-entry reactor to achieve full conversion of ketone **1** resulted in an immediate decrease in the response from the NIR on ketone **1**, indicating the effectiveness of the side-entry reactor. The initial testing phase clearly illustrated the relevance of retaining NIR monitoring in the full-scale setup.

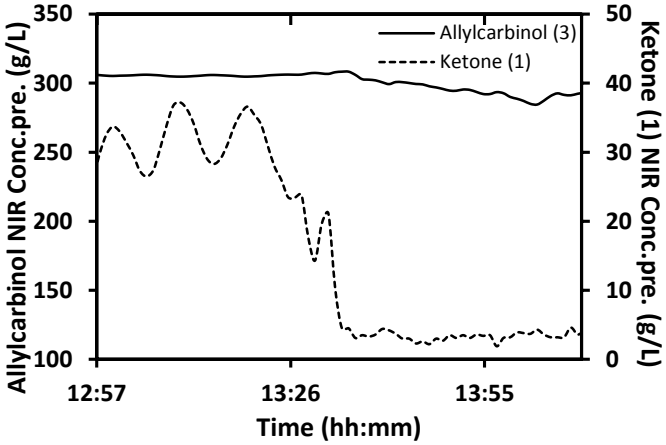


Figure 7.3: In-line NIR monitoring of the process for the full-scale continuous reactor setup. Solid line is the alkoxide intermediate 2 concentration; dashed line is the ketone 1 concentration.

7.10 Implementation

Several minor adjustments were made to the reactor setup during the implementation phase and some of the most important changes are shown in Table 7.1. The first test run showed difficulties for the product pump (P2) in delivering the target flow rate. The issue was related to clogging of the filter cartridge, initially attributed to an excess amount of solid ketone **1**. A switch to a filter cartridge of slightly greater pore size enabled the desired P2 flow rate to be achieved. While the larger pore size reduced the filter reactor's capability to retain solid material, it also caused problems in the NIR measurement due to turbidity too high for valid transmittance spectra measurements. It was expected that ketone **1** was the origin of the problems; in fact, however, alkoxide intermediate **2** had precipitated in the filter reactor, since only minor amounts of ketone **1** were detected. Alkoxide intermediate **2** becomes a sticky and highly viscous mass when it precipitates and helps explain the difficulties with the flow rate and NIR measurements. The temperature was increased to 30 °C, the upper limit from the previous semi-batch method, to circumvent the precipitation and clogging issue. A higher temperature solved the problem and resulted in a less viscous reaction mixture but required a larger fraction of ketone **1** to be processed in the side-entry reactor, a move that increased solvent

consumption. A somewhat lower concentration of the allylmagnesium chloride than anticipated also introduced greater solvent consumption. Nonetheless, these adjustments, albeit minor, have great impact on the operation of the design and illustrate the importance of a flexible design space if a fully functional full-scale reactor configuration is to be achieved.

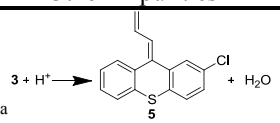
Table 7.1: Design parameters derived from the laboratory experiments and the actual implemented parameters used to achieve a fully functional reactor setup.[a]

Parameter	Design parameter	Actual parameter
Temperature (°C)	15	30
Concentration of allylmagnesium chloride (M)	1.4	1.0-1.1
Pore size filter (µm)	45	500
Flow rate capacity (L/h)	18.8	25
Conversion of ketone 1 in the filter reactor (%)	85	75

[a]Changing the temperature has a strong influence on other parameters (flow rate and solubility).

Table 7.2: Verification data for the test runs of continuous manufactured alkoxide intermediate 2; as shown, all requirements are met.

Product	Analytical Method	Specification (expected)	Test 1	Test 2	Test 3
Product yield **3** + **5**[a,b]	HPLC	NLT 95% by area	99.5	99.5	99.4
Alcohol **3**	HPLC (g/mL)	Confirm NIR +/- 3%	244.4 ±2%	252.6 ±2%	267.7 ±2%
Alkoxide intermediate **2**	NIR (g/mL)	Confirm NIR +/- 3%	218.6	224.1	244.5
Ketone **1**	HPLC	NMT 5% by area	nd	nd	nd
Ketone **1**	HPLC (g/mL)	Confirm NIR +/- 3%	na	na	na
Impurity A	HPLC	NMT 5% by area	0.2	0.3	0.5
Other impurities	HPLC	NMT 1% by area	0.3	0.2	0.1

a 

[b]In refs [90] and [89], the applied HPLC method had a mobile phase with pH 9; however, the validated analytical HPLC method contains mobile phase with pH 4.8, therefore the reaction shown in footnote a is expected.

As part of the implementation, the continuous reactor setup functionality was verified by a number of test runs. Table 7.2 shows that the continuous reactor setup is capable of producing product of high purity based on the isolated alcohol **3**, with an insignificant amount of impurities. It was intended that the NIR measurement should be used to estimate the accumulated alkoxide intermediate **2** for the subsequent processing.

Unfortunately, the deviations between the HPLC and the NIR predictions were too large for this purpose and therefore the subsequent processing of the alkoxide intermediate **2** is based on the mass balance of ketone **1** processed in the reactor setup. In any case, a method for determination of alkoxide intermediate **2** had not previously been available for the semi-batch production.

The total yield of product **3** meets the process specification of not less than (NLT) 95% yield with a purity of NLT 99.5%, where sample preparation has caused a small amount of the product (**3**) to dehydrate to a later-stage product (**5**). The impurity amount is within the not more than (NMT) acceptable range, if the dehydrated product caused by the sample preparation is accounted for.

An overall improvement was obtained in a number of key success areas for the implementation of the continuous reactor setup. In addition to the improved conversion of ketone **1** to alkoxide intermediate **2**, several other factors have influenced the decision to implement a continuous reactor setup. The reduction in solvent consumption from 5.8 to 3.8 L/kg ketone **1** as well as elimination of a solvent swap in a later process stage have been motivating economic factors. The reactor volume was reduced from m^3-scale to liter-scale and a complete continuous setup, including everything such as pumps, cooling loops, etc. at approximately the same size as those of the old batch vessel, alone resulted in a significant reduction in the footprint of the production area. The small reactor volume has led to better temperature control of the reactor with fewer eddies, causing a reduction in energy consumption. The energy and solvent consumption are further reduced due to less frequent cleaning, since the reactor configuration is dedicated equipment, unlike the semi-batch equipment. Benefits such as reduced labor consumption, release of old batch equipment and reduction in the production footprint are more difficult to quantify, but are significant contributors to the overall business case. Table 7.3 summarizes some of the parameters of interest between the legacy semi-batch process, continuous laboratory-scale feasibility studies and the new continuous full-scale process.

Table 7.3: Comparison of the old batch processes against the laboratory continuous reactor setup and the continuous full-scale reactor setup.[a]

Parameter	Full-scale (Semi-batch)	Laboratory (Continuous)	Full-scale (Continuous)
Active Volume	1600 L	250 mL	8 L
Total Size (Area Footprint)	~10 m^2	Fume hood 2 m^2	1.45 m^2 (1.1 m · 1.3 m)
Production time (h)	4	900	<50
Yield (%)	>95%	>96%a	95-99%
Purity	>95%	>99%	96.5-99.8%
Solvent consumption	5.8 L/kg_{CTX}	2.3 L/kg_{CTX}	3.8 L/kg_{CTX}
Cleaning	Each campaign (batch)	Dedicated	Dedicated

[a]The isolated yield is based on the HPLC assay from ref [89].

7.11 Conclusions

A novel full-scale reactor setup for continuous processing of 2-chloro-thioxanthen-9-one (**1**) with allylmagnesium chloride into the magnesium alkoxide intermediate **2** has been designed and implemented successfully in full-scale production. The new continuous reactor setup has replaced the previous semi-batch process that, in many aspects, could be considered as a typical pharmaceutical manufacturing process. The low solubility of ketone **1** in THF motivated the design of a heterogeneous reactor setup capable of handling solid material to avoid the difficulty and expense associated with processing large volumes of solvent. The reactor setup consists of two reactors in series, where the first reactor retains solid reactant, making this reactor robust and flexible towards fluctuations in the processing of solid ketone **1**. The second reactor has the primary function of ensuring full conversion of the unreacted ketone **1** from the first reactor. A significant reduction in reactor volume was achieved relative to the previous semi-batch process in downsizing from cubic meter scale to liter scale. In fact, laboratory studies suggested that an even smaller reactor at milliliter scale could have been sufficient. The regulation of the reactor setup was based on simple measurement of process parameters, combined with the latest methods in process analytical technology to ensure product quality.

Chapter 8

A Reactor Design Methodology for Grignard Reactions in the Pharmaceutical Industry

The following chapter has been written in the style of an article manuscript with the intention of later publication.

8.1 Abstract

In this work, a general method aimed at an easy decision-making process when choosing a reactor design for Grignard addition reactions is proposed. The methodology focuses on the transition from a laboratory setup to full-scale production. This includes a preliminary economic assessment to evaluate the benefits or downsides that can be expected from the chosen reactor design. Three different case studies have been used as the basis for the development of the methodology, all with differences in solubility of reactants and products, as well as impurity formation. A few factors have been found critical in the decision making for the reactor setup for Grignard addition reaction, with the most important ones given below. The solubility of reactants, products and impurities are the most crucial parameters when deciding on a reactor configuration. Basic understanding of the chemistry is essential, including how temperature influences the reaction. Formation of unwanted products can be reduced by taking secondary reactions leading to impurities into account when designing the process. Manipulating the impurity formation by analyzing the temperature dependency of the reactions has been found to be a most useful approach. To evaluate the potential of and make a fast decision on a reactor setup, simple screening experiments and pragmatic approaches in the laboratory can often be sufficient. Hours of development and resources can be saved if these simple and pragmatic approaches are used during the decision process.

8.2 Introduction

Throughout the last decade, the pharmaceutical industry (i.e. research-based companies) has experienced increasing pressure from generic manufacturers and authorities and has struggled to remain competitive with the frequently changing requirements and cheap production of generics, facing challenges such as strict regulations, enhanced environmental requirements, patent expirations, generic competitors and difficulties in new drug discovery, to mention a few. The debate on how pharmaceutical companies can remain competitive and overcome the challenges they are facing have been many and the general opinion of industry, academia and the authorities is pointing towards higher efficiency.[5,6,8–12,18,19,21,31,237,254–257] The view on efficiency in the pharmaceutical industry is no different from other chemical industries. Efficiency is a broad term and, in the early stages of any drug development, it is often associated with fast development of the potential drug candidate.[6–8,12,256,258] Later in the lifecycle of a pharmaceutical product, efficiency concerns the ability to achieve high yields and purities by simple production methods.[15,19,34,38,57,58,256,259–261] Bridging the gap between early development and eventual manufacturing is associated with great costs of both time and resources, such that the ability to make fast decisions is crucial for avoiding later redesign of synthetic routes or post-optimization of existing processes.[5,18,19,21,237,256,262,263]

The pharmaceutical industry is known for protection of intellectual properties by patents or secrecy policies. A patent only provides protection for a limited time of 20 years from the first application[5,10,11,19] and is combined with high expenses for the development of new pharmaceutical products.[7–10,12] If a product can be brought to market and full-scale production faster, a longer period under patent protection to regain the investment can be achieved. Another way to ensure better profits is by optimizing the process, a strategy that applies to both old and new pharmaceutical products.[38,57,58,88,264] However, the pharmaceutical industry lacks the ease of readjusting a process after the full-scale synthesis route has been filed, as strict regulations prevent large changes in process conditions compared to the originally-filed process.[19,20]

Refining production methods and rationalizing the decision-making process for reactor setup configurations have received increasing interest over the last few decades.[264] The urge to formulate standardized descriptions of process implementation, optimization and intensification has resulted in great amounts of written material.[56,265–279] Most of this material covers a broad pallet of general methods to be followed and applied. The procedures are often complex and with multiple steps using advanced investigation methods. Following these methods will require time-consuming studies before a decision can be made. The pharmaceutical and fine chemical industry again separate from the remaining chemical industry, as the complexity of the synthesis routes is often high and non-standard operations are needed if a successful process is to be implemented. Hence, following such standard procedures is not beneficial.[34,38,274,275,280]

A selection of methodologies is now presented, with a short description of the focus of each. Cervera Padrell *et al.*[273,281] applied a process system engineering (PSE) assisted design methodology to a full synthetic route of an active pharmaceutical ingredient (API).

Moseley *et al.* [282,283] have demonstrated a method for synthetic route selections by the use of Kepner-Tregoe decision analysis. Papavasileiou *et al.*[269] demonstrated the efficiency of computer-aided process simulation for the optimization of a pharmaceutical production schedule. The Jensen group[32] made a review focusing on decision making in general for continuous processing. Roberge *et al.*[22,54,78,79] provided detailed documentation on the process implementation made in the effort to transition from batch to continuous production.

Flow chemistry started to become of interest to the fine chemical and pharmaceutical industry in the early 21st century,[31–34,36,37,55,158] with later proposals of general methodologies for deciding on the chemistry that could potentially benefit from flow chemistry.[22,57] Flow chemistry is believed by many to be one of the best ways to stay competitive, as large benefits can potentially be achieved compared to batch processes.[31,33,88] However, few full-scale implementations are currently known.[88,171]

These general methods still lack the ability to allow for fast decision making on potential reactor setup configuration from early development. Additionally, they are unable to easily evaluate whether any benefits could be achieved if an old process were modified. This work provides a methodology specifically aimed at Grignard reaction-based chemistry (particularly addition reaction with carbonyls). The goal is to provide a generic work that describes the procedures and processes that lead to the final decision. As Grignard chemistry is already believed to benefit highly from flow processes,[22,57] the discussions throughout the article often focus on the decision between batch and continuous setups, as these are considered to be counterparts. At best, the method could be generalized to cover other reaction types.

8.3 Categorization of Reactor Concepts

A common categorization and conceptual description of reactor concepts is necessary in order to discuss potential reactor configurations. Three main categories are used throughout this work: batch reactors (batch and semi-batch), homogeneous flow reactors and heterogeneous flow reactors. The definition of homogeneous and heterogeneous flow reactors is based on the (solid) physical state of reactants, intermediates and products observed during operation. Most continuous reactors can, in spite of their complex appearance, be modelled based on different configurations of PFRs and CSTRs in terms of reaction engineering aspects.

8.3.1 Batch Reactor Concept

The batch reactor has for generations been the workhorse of pharmaceutical production due to its characteristics as a multipurpose setup with great flexibility. The biggest disadvantages are the poor mass and heat transfer and the biggest advantage is the multipurpose usage. The batch reactor is not described in more detail here as it is already covered in the literature.[59,60]

8.3.2 Homogeneous Flow Reactor Concept

Homogeneous flow reactors are theoretically much simpler than the heterogeneous flow reactor, as everything stays in solution, from reactants to products. The concentrations of reactants, intermediates and product should be high (if possible neat) for a successful implementation related to throughput and yield. If high concentrations are possible, the focus can be changed towards chemistry and reaction engineering aspects such as impurity formation, heat and mass transfer. Two operational principles can be applied for dissolving the reactant for usage in the homogeneous flow reactor. One is the making of a predefined batch solution, a method commonly applied in the laboratory due to its simplicity. For full-scale implementation, this requires a storage facility. The benefits of this method are an always well-defined concentration and limited equipment needs (often available). The main drawback is the predefined amount of reactant available due to the batch approach. Hence, there is a risk of running out during production. The other method is based on a heterogeneous flow module, where the solution is made on demand in a separation reactor with an excess of solids (for an elaborated discussion, see Pedersen *et al.*[88]). Its benefits are the lack of limitations on the dissolved reactant and smaller equipment. Its main drawbacks are the need for control strategies to determine the concentration (solubility rate and assurance of concentration) and a more equipment-heavy setup (on-line process control). Figure 8.1 illustrates the two homogeneous flow reactor concepts.

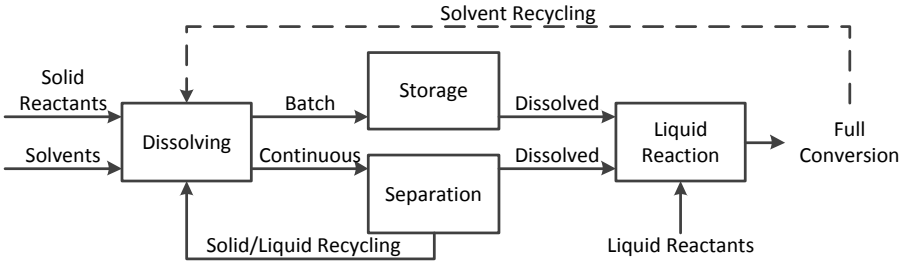


Figure 8.1: A principal visualization of the homogeneous flow concepts.

8.3.3 Heterogeneous Flow Reactor Concept

The heterogeneous flow reactor concept is complex and the solubility of reactants, intermediates and products have to be taken into consideration. The solubility of intermediates and products gives rise to two different concepts.

The first heterogeneous reactor concept is a development of the homogeneous flow reactor with separation, where the reaction is allowed to progress in the dissolving unit. It requires that the intermediates and the products have higher solubility than that of the reactants. The setup is more complex compared to the homogeneous flow reactor, with separation of the solids from the outlet. The most easily-applicable modules for separation are a CSTR (mixing sensitive chemistry can cause problems) or alternatively a vertically-oriented oscillatory flow reactor (OFR)[86] (more difficult to control) with reactants entering the vessel from the bottom, allowing the particles to settle on the bottom by gravitational force. An additional reactor is necessary to react dissolved

reactants as they leave the first reactor. Major benefits can be achieved for low-solubility reactants with high-solubility intermediates or products.

The alternative to the above-mentioned heterogeneous concept has no retention of solid material, hence after a certain residence time in the reactor all the solid reactants will have been dissolved and the remaining part of the reactor can be considered as a liquid-liquid reaction. Since there is no retention of solid material, the intermediates and products formed throughout the reaction can be easily handled if they precipitate. The obvious benefits are the ability to handle reactions with poor solubility of reactants, intermediates and products. The drawback is the risk of fluctuation in conversion throughout the reactor that will require an extensive control strategy to ensure consistency of conversion (solubility rate and reaction rate). Figure 8.2 illustrates the two heterogeneous flow reactor concepts.

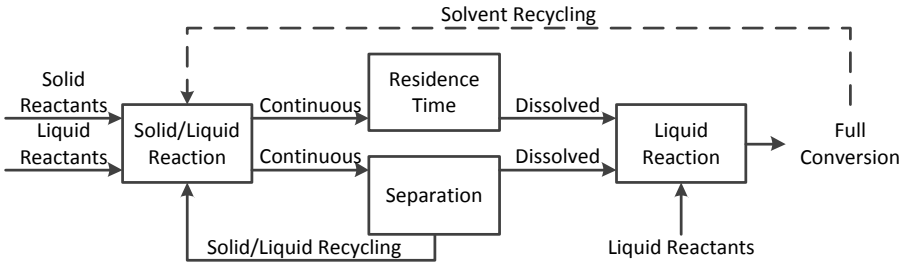


Figure 8.2: A principal visualization of the heterogeneous flow concepts.

8.4 Initial considerations

Operating under the assumption that a process is developed to generate profit, some general considerations on the stages of an API are important. APIs go through several stages before reaching a final product that can be released on the market. This includes everything from early development, scale-up and implementation to the final commercial manufacturing, but also covers the "off-patent" production and final termination of the product from the market. It is early in this lifecycle of the API that decisions on Good Manufacturing Practice (GMP) or non-GMP synthesis steps are made. After the final synthesis has been filed with the authorities, only small deviations from the original route are allowed. This comprises a potential problem in the process of keeping late production of APIs as a profitable business, as it is often the cost of refiling an optimized process that prevents further optimization of the original route. For non-GMP steps it is significantly simpler, as no refiling is required and it can be compared to change to a new supplier of starting material, where quality verification of the final API often will be sufficient.

In close relation to the GMP and non-GMP considerations, the question of whether the synthesis is new or old should also be raised. An old process will typically have undergone multiple optimization processes and thus perform well overall. In addition, large amounts of process knowledge exists, hence committing to an alternative process might limit the benefits over the already existing process. The decision on how to design a reactor setup for a newly-developed synthetic route benefits from not having to take

already existing and authority-regulated processes into account. Comparing an old process with a newly developed one, it should be relatively easier to use a continuous process for a new synthetic route. However, in practice this will require close collaboration between the Research & Development and the Implementation & Manufacturing departments of a company. Traditionally, the development of APIs has been based on batch chemistry, a procedure that is still widely dominant in the pharmaceutical industry.[1] As a natural consequence, the subsequent scale-up taking place throughout the phase I-III trials tends to follow the same principles. The GMP process steps defined during the phase trial periods, as discussed above, are primarily based on batch procedures, hence making later implementation of continuous production difficult. More processes would most likely have been made continuous if no consideration had to be made in relation to GMP steps. Refiling a blockbuster is often a considerable investment, due to the required documentation for the authorities

Developing a continuous process is often more costly than batch chemistry development, since more process knowledge is required to design the reactor setup and more complex process control is often required.[19,22,56] Early development of continuous methods can, however, be profitable, due to the potential long-run benefits from lower production costs. Table 8.1 suggests the likeliness of profit from a continuous setup for different lifecycle stages of a synthetic route for an API.

Table 8.1: Early business case considerations for flow reactor profit.

Profit	Regulatory Consideration	Lifecycle
Likely	Non-GMP	Old or New
Potential	GMP	New
Unlikely	GMP	Old

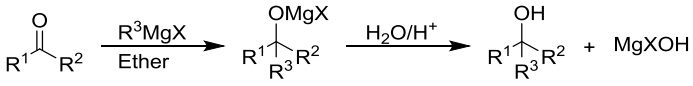
Especially for an old GMP regulated step, the decision to transform a process from batch to continuous often ends up being a case-specific decision. In the end, the final decision will rely on the willingness and the ability of the company to take risks and to believe in future profits from the process and the product. For a new synthesis, similar considerations are at the root of the final decision. Hesitation in making such changes in company structure is obvious, because the outcome of the effort is unknown compared to the well-known methods used today. The company culture as seen today also needs to be broken down and replaced by a much more flexible and stronger collaboration between the development, implementation and manufacturing departments, if success is to be expected.[19,25]

The decision to go for a new synthetic route or a continuous reactor configuration is not always purely related to chemical and physical limitations. Considering the current lifecycle stage of the API and the placement in relation to GMP steps can help in addressing the likeliness of profitable success for a potential flow method without the need to perform a full business case analysis.

8.5 Chemistry

A general understanding of the chemistry will provide useful information that can assist in making the decision upon choosing the most suitable reactor configuration. Many of these findings are not required to be carried out in a specific order or studied in depth, but the information they provide is useful for making the decision to proceed with batch or continuous processing. For Grignard chemistry, reactions typically take place in the liquid phase and if solid or gas phase reactants are present these will therefore not take part in the reaction unless dissolved. In some cases the process can benefit from such properties, e.g. by protecting the product by precipitation. A deeper analysis of solvents and solubility is given in sections 8.9 and 8.10, respectively. By simple evaluation of the chemistry, useful information can be revealed that will be helpful in evaluating and developing the final setup without the need for resource-intensive laboratory experiments. Furthermore, it also indicates whether special care or more thorough investigations of the reaction behavior should be carried out. A generic synthetic route for a Grignard addition reaction followed by hydrolysis is illustrated in scheme 8.1.

Scheme 8.1: A generic representation of a Grignard addition reaction followed by a hydrolysis to yield an alcohol. R1, R2 and R3 are an alkyl or aryl, X is a halide.



8.6 Grignard Addition Reactions

A general classification of the chemistry is often done based on reaction type and order. First, the desired reaction needs to be specified and for a typical Grignard addition reaction a second order elementary reaction is often sufficient for describing the chemistry in relation to reaction engineering aspects. If the carbonyl source is an ester, the common outcome is a diaddition product, hence the reaction becomes a competitive consecutive reaction with both steps being second order elementary reactions.

The next step should be determination of potential impurity formations and their relation to reactants, intermediates and product. For Grignard reactions, many of the impurities are related to multiple functional groups on the reactants and the Grignard reagents themselves. These functional groups may react with the Grignard reagents, causing the unwanted reactions leading to impurities. Contamination by secondary reactions between functional groups on the reactants and the Grignard reagents are, however, often not cause for concern as the carbonyl group will usually be the most reactive of all the functional groups present, reducing the relative influence of undesired reactions. In the ester case, if only the mono-addition product is desired, the diaddition taking place is considered a source of impurity. In general, the amount of impurity formed is often correlated to the temperature, as many of the less reactive functional groups become more active at elevated temperatures.[94,95] The reactivity can be manipulated by temperature regulation, following a standard Arrhenius relationship. However, the reaction conditions should preferably be kept close to ambient if possible, which will reduce the input of energy necessary to maintain the reaction at a fixed temperature. For

Grignard reactions in general, no heating is normally necessary for the reaction to take place (exothermic (150 to 250 kJ/mol)); on the contrary, cooling of the reaction may be necessary.[77,104,127] The general considerations are summarized in table 8.2.

Table 8.2: Considerations for Grignard chemistry.

Functional Group	Chemical Behavior	Reactor Consideration	Additional Remarks
Carbonyl (Aldehyde or Ketone)	Mono-addition product. Wide temperature range applicable. Kinetics of little concern. Exothermic.	No special considerations. Depends on the physical states of the reactant and product; see solubility consideration.	A PFR can be sufficient if the solubility of reactants and products is high.
Carbonyl (Ester)	Mono- and Diaddition products (Mono<Di). Temperature should be low. Kinetics might be important (k_{ester}<<k_{ketone}); see kinetics section. Exothermic.	Mixing and heat transfer are important. Multiple Grignard injections could prove useful. A heterogeneous product reactor is likely to be beneficial ($k_{precipitation}$ competes with $k_{reaction}$). Depends on the physical states of the reactant and product; see solubility consideration.	Special cases where substitutes influence the ester to give mono-addition.[120,121,175]
Carbonyl and Others[94]	Mono-addition product and other cross-reacted impurities (Mono>>Other). Temperature should be low. Kinetics might be important ($k_{carbonyl}$>>k_{other}); see kinetics section. Exothermic.	Mixing and heat transfer are important. Multiple Grignard injections could prove useful. A heterogeneous product reactor is likely to be beneficial. Depends on the physical states of the reactant and product; see solubility consideration.	

Besides the reaction rate order and impurity formation, it is of general interest to understand the requirements for cooling or heating. Due to the exothermic release of energy from a Grignard reaction combined with solvents with low boiling and flash points (see solvent section), most Grignard syntheses are cooled to minimize the risk of a runaway during a batch process from a safety perspective. Formation of temperature gradients within the reactor setup due to poor heat transfer can be critical for a process

and, combined with poor mass transfer, can give rise to impurity formation. As a common approach to distribute heat release and achieve better temperature control, a stepwise dosing concept can be applied. In a batch process, this is known as semi-batch or fed-batch operation. The continuous analogue is a setup with multiple inlets. This concept is also used if one of the reactants should be kept low in concentration to avoid impurity formation, e.g. due to hot spots.[75,76,78,79]

8.7 Hydrolysis, Dehydration and Chemical Reactions

The desired product from a Grignard addition is the alcohol formed upon the hydrolysis of the (unstable) magnesium alkoxide with diluted acid. The alcohol is also commonly dehydrated. The focus is often on the Grignard addition; however, the hydrolysis and potential dehydration are fairly simple reactions and should therefore be considered as part of the potential reactor system. Both steps are exothermic reactions with slightly lower reaction enthalpies than the Grignard addition reaction. If the dehydrated product is the desired product, it might be worthwhile to investigate whether a strong acid (e.g. HCl (aq.) or H_2SO_4 (aq.)) can handle both the hydrolysis and the dehydration in one step.[94] Most likely some acetic acid would still be needed to dissolve the magnesium halide salts formed from the hydrolysis, as acetic acid tends to form highly water-soluble complexes with magnesium.[i] The influence of pH on the solution should be investigated, as this might need to be adjusted for separation of the aqueous phase from the organic phase. Alternatively, a different solvent could be considered at this point.

8.8 Kinetic Investigation

Reaction kinetics can be of great importance in order to choose the most suitable design and dimensions for a setup. Precise studies can be carried out in order to characterize reaction kinetics, helping to identify optimal reaction parameters and conditions and thereby a better dimensioning of the reactor setup. Accurate determination of rate constants often requires that the individual steps of desired and undesired reactions can be well isolated. Often, the focus in kinetic investigation is on the reaction rates, as these determine the operational parameters and dimensioning of the reactor setup.[59,60] However, it is important to keep in mind that these reactions only constitute a small share of the kinetics necessary to determine how a synthesis will progress in a reactor. In a situation with more complex chemical systems (e.g. combined solid dissolution and reaction, combined reaction and precipitation) a more pragmatic approach could be necessary, but with a less precise result. Design of Experiments (DoE) can be a strong tool for extracting combined information on optimal performance when isolation of steps cannot easily be done. Generating kinetic information is often time consuming and, combined with often non-ideal reactor performance, an effort should be made towards it being “need to have” instead of “nice to have”. Rough estimates and more pragmatic methods can sometimes serve much better for fast decision making than precisely determined parameters. As reactors often perform non-ideally, precisely determined rate constants can result in a too-narrow design and a rough estimate would potentially be

[i] Observed in laboratory experiments.

better for understanding the performances and be achieved much more quickly in the laboratory. In general, kinetic investigation is of less importance for Grignard reactions as the chemistry is fast under ambient reaction conditions. As already discussed in the chemistry evaluation, only a few impurities are formed; hence, unless the desire is the mono-addition product of an ester carbonyl or high temperatures with other functional groups, the need for kinetic investigation is limited (Grignard additions are fast reactions[22]). Table 8.3 summarizes below the need for kinetic investigation of Grignard chemistry.

Table 8.3: Reaction order considerations and the need for kinetic investigation.[a]

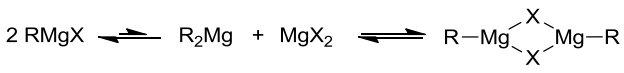
Reaction Type	Functional Groups	Kinetic Investigation Level
A+B → C	Ketone or Aldehyde	Limited to a pragmatic approach.
A+B → C C+B → D	Ester Carbonyl	A detailed understanding might be beneficial.
A+B → C+D	Carbonyl and Others	Less crucial than for ester carbonyl, but rough temperature influence is useful.

[a]All reaction orders are simplified and a more detailed understanding of kinetics and reaction orders is found in the literature[94,100,116,154]

8.9 Solvent Considerations

From a broad perspective, a solvent should be chosen based on its applicability for the chemistry and secondly, aspects such as availability, safety (Atmosphères Explosibles (ATEX)), health and environmental impact (sustainability and pollution) should be considered. When working with Grignard chemistry the range of useful solvents is limited, at least from an industrial perspective. The commonly accepted tetrahedral configuration of the magnesium requires two solvent molecules to stabilize it, molecules that should have lone pair donation properties.[94] The choice of preference is therefore an ethereal solvent such as diethyl ether (Et_2O), tetrahydrofuran (THF) or 2-methyltetrahydrofuran (MeTHF) as the industrial standard. Et_2O has generally been replaced by THF due to safety and MeTHF is currently replacing THF for health and environmental reasons. More exotic ethereal solvents such as 1,4-dioxane or 1,2-dimethoxyethane (DME) could in special cases be tested, but should in general be avoided as they often shift the Schlenk equilibrium (Scheme 8.2)[135,139,140,143] towards the right, resulting in precipitation of the Grignard reagent complex due to the solvents' chelating properties.[140,143] The category of non-donation lone pair solvents includes toluene and hexane, but these should only be used if ethereal solvent is not an option, as trace amounts of ethereal solvent would still be needed.[94]

Scheme 8.2: The simplified Schlenk equilibrium, where X represents the halide and R represents the aryl or alkyl functional parts.[135]



Two solvents stand out for initial screening, THF and MeTHF. Generally, THF exhibits higher solubility of carbonyl reactants compared to MeTHF, the trend being the opposite for Grignard reagents. Another favored property of MeTHF compared to THF is its very low miscibility with water, where THF is fully miscible in most conditions.[174,284] A few comparisons of common solvent properties for THF and MeTHF are provided in table 8.4.

Table 8.4: General solvent properties of preferred solvents for Grignard chemistry.[174,284]

Properties	THF	MeTHF
Molecular formula	C_4H_8O	$C_5H_{10}O$
Molecular weight (g/mol)	72.11	86.13
Molecular structure		
Boiling point (°C)	66	80.3
Flash point (°C)	-14	-11
Density (g/L)	889.2	854
Solubility in water (%w/w)	Miscible	14
Water in solvent (%w/w)	Miscible	4
Oxygen lone pair donor	1	1
Chelating	No	No

8.10 Solubility Considerations

The solubility of reactants, products and impurities (side products or salts) are perhaps the most important part of the decision on a potential flow setup, in contrast to the batch reactor, which can easily handle solids. It should be emphasized that catalysts are not included in this discussion and that solids only refer to materials either formed or consumed during the reaction. A review of 86 reactions at Lonza[22,53] indicated that about 50% of these would not be easily transferred to flow chemistry due to solids. This investigation is backed up by the fact that only a few demonstrations of flow chemistry with solid material have been published.[88,236,243] Some commercially available flow reactors for handling solid material exist, including conceptual reactors such as the Oscillatory Flow Reactor (OFR),[83,86,87] the Coflore Agitated Cell Reactor (ACR)[236] and the filter reactor.[88–90]

The solubility of solids is an important factor for choosing the right reactor configuration. Despite the fact that many reactants are solids and that most intermediates and products are isolated as solids (mostly due to purification, lifetime and storage concerns), most organic synthesis reactions take place in a liquid phase. It is therefore of utmost importance to find a suitable solvent when working with solid reactants.

Solubility is highly influenced by solvent choice and in many situations is also affected by temperature. The solubility should be determined at the expected operation temperature, which will preferably be near to ambient if the chemistry allows it. The preference for ambient conditions should also be seen with respect to sustainability and

eco-friendly viewpoints. If a higher temperature is necessary for the chemistry to progress, a higher concentration could in principle be used as an alternative. This would most likely be a cause for better cooling of the reactor setup, due to the exothermic nature of Grignard reactions. In contrary to reactions that require high temperatures, these are reactions where cryogenic reaction conditions become necessary. To avoid precipitation in a cryogenically-operated reactor, the solubility should be accounted for at the known operation temperature, despite higher concentrations being possible if the solutions are stored in ambient conditions.[285–287]

Co-solvent effects are another factor commonly known to have a strong influence on solubility, but are not discussed further since they are preferably avoided, if possible, due to the obvious complexity they add to a system.[286] Additionally, changes in pressure can cause similar effects on solubility as temperature, but in general the influence is lesser due to the incompressibility of liquids.[287]

To keep the experimental cost to a reasonable level, a limited number of solvents should be picked (see solvent section) and tested for the saturated solubility of the compound within a reasonable temperature span (10 to 30 °C). Knowledge of the saturated solubility is very useful in the later design phase for continuous reactors to set the boundaries for temperature and mass loading. The choice of analytical method depends on the compound, but in most cases dry matter determination is sufficient. In a more long-term approach, spectroscopic measurement with equipment applicable for later control strategies (see PAT and QbD section) could be used. A requirement for this approach would be the development of calibration curves for each compound, a large undertaking that could be profitable if the outcome of the investigation is positive. Regardless of whether a spectroscopic method is chosen, it is recommended that spectra of the samples are taken for potential later development purposes, as the labor cost of this is insignificant. Some intermediates and products (as well as impurities) may be unstable or not easily isolated. If it is not possible to isolate the compound for solubility determination, a different and more pragmatic approach should be applied. The pragmatic solubility method is based on the preferred concentration of reactants in the solvent of choice and a batch synthesis is carried out under the desired reaction conditions. This simple approach provides a useful visual determination of the intermediates' or products' behavior in the solvent (e.g. precipitation, dissolution, solid, solution) but without any exact values. Table 8.5 gives an overview of flow reactors likely to be suitable for different solubility concentrations of reactants and product; separation reactors only work in cases with higher solubility of product than of reactants.

Table 8.5: Flow reactor choice related to solubility of reactants and products.[a]

Solubility	Reactant (Sol. > 1.0 M)	Reactant (1.0M > Sol. > 0.1M)	Reactant (Sol. < 0.1 M)
Product (Sol. > 1.0 M)	Homogeneous Flow Reactor	Heterogeneous Separation Reactor	Heterogeneous Separation Reactor
Product (1.0M > Sol. > 0.1M)	Heterogeneous Residence Time Reactor	Heterogeneous Separation Reactor or Heterogeneous Residence Time Reactor	Heterogeneous Separation Reactor
Product (Sol. < 0.1 M)	Heterogeneous Residence Time Reactor	Heterogeneous Residence Time Reactor	Heterogeneous Separation Reactor or Heterogeneous Residence Time Reactor

[a]Heterogeneous separation reactors only work if the product has higher solubility than the reactants.

8.11 Process Analytical Technology (PAT) and Quality-by-Design (QbD)

In modern process development, different control and regulation strategies are used in order to meet the required specification of the final product and ensure steady and robust production of high quality products. This relates to the concepts of process analytical technology (PAT) and Quality-by-Design (QbD)[1,28–30,241,276,277,279,288] and this section provides an overview of how to gradually implement these throughout the development of a process in the early stages. Later on, full methods should be integrated into the setup. In a flow process, the ability to control the process is a central part, as the outcome of small fluctuations could have significant consequences for the performance. In comparison, a batch reactor may be more flexible towards fluctuations. A good control strategy is the backbone of a continuous reactor setup but is often completely neglected in the development process of the setup in the laboratory, as the goal is to explore the potential of the setup. A great amount of useful data can be collected throughout the early stages of investigation that can later benefit the control strategy's development. In particular, utilization of spectroscopic measurement methods and the raw data generated with these can be good indicators of the likeliness of the developed process being easily controlled or not. At minimum, screening of reactants, solvents and preferably the product should be carried out. Executing a quick spectroscopic screening will provide fast and cheap knowledge on which methods can be useful and whether there are any characteristic spectral fingerprints that distinguish one compound from the others. Besides the spectroscopic techniques, general considerations on potential control strategy with simpler equipment such as pH measurement, conductivity and mass balance can all be useful.

8.12 The Scale-Up versus Scale-Out Discussion

As flow chemistry demonstrations became more common, a discussion of the potential industrial application of these newly applied methods for running organic synthesis began as well.[32–34,37,38,258] Many of the early approaches focused on microreactor technology, which is why full-scale production was considered to be achieved through out-scaling instead of up-scaling, thus maintaining the high mass and heat transfer of the microreactors.[19,33] The out-scaling concept has gradually been replaced by up-scaling approaches. In theory, out-scaling works very well, as it provides flexibility in relation to the demand for the amount to be produced. In addition, the transition from developing the process in the laboratory to full-scale production can be achieved without the normal pilot plant step. Operating multiple microreactor units to meet a certain production need is not as appealing in real life, as each reactor module must be fitted with all necessary measuring equipment, supply units, etc., which will be rather expensive. Alternatively, the streams can be split into each reactor, requiring fewer supply units but resulting in a setup that is significantly harder to regulate and control. Additionally, microreactors' poor ability to handle solid material only sets them further back compared with larger reactor dimensions. The major benefits that are normally claimed to come from microreactors are benefits more or less achieved in relation to the continuous processing rather than to their dimensions.[54] A small increase in the dimensions of a flow reactor provides a small difference in performance in mass and heat flow, hence the classic problem known from batch scale-up is not found to the same extent when working with flow reactors. In addition, the benefits of the slightly bigger dimension that also allows for the handling of solids (to a certain extent) make mini- and meso-scale reactors a better fit for production purposes.

8.13 Case Studies

Three case studies constitute the backbone of this methodology development. All three case studies deal with chemistry already in production and have therefore already been highly challenged in the initial consideration (Table 8.1). Additionally, all involved synthesis steps dealing with Grignard chemistry are GMP related. However, it should be emphasized that, besides the potential transformation to a flow chemistry setup and improved production, these case studies have also served as a learning process leading to this methodology. A can serve as a useful tool for later decision making related to Grignard chemistry. Table 8.6 gives an overview of important parameters for the three case studies and a more detailed discussion on each is given in the following sections.

Table 8.6: A selection of interesting parameters in the evaluation of retrofitting three Grignard addition reactions.

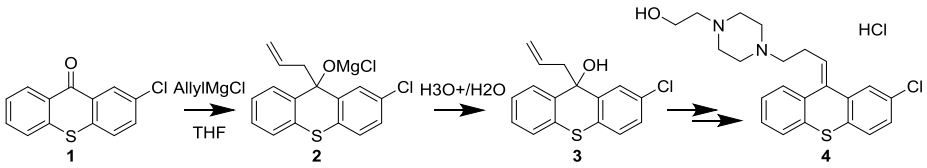
Reaction	Case Study 1 Allylcarbinol	Case Study 2 Escitalopram	Case Study 3 Melitracen HCl
Carbonyl Solubility	≤0.5	≤0.1	≥1
Alkoxide Solubility	≥1	≤0.1[a] High[b]	≥1
Operation Temp.	15-25 °C	Sub-zero	Ambient
Impurity Formation	High near equivalence addition of Grignard reagent	High	Limited
Flow Reactor	Heterogeneous Separation Reactor	Heterogeneous Residence Time Reactor	Homogeneous Flow Reactor (PFR)
Additional Steps	Potential direct hydrolysis and dehydration	Intended hydrolysis	One-step hydrolysis and dehydration, phase separation and salt precipitation
Solvent	THF	MeTHF	THF
Kinetic Investigation	No	Yes	No

[a]Intermediate first addition
[b]Final alkoxide product

8.13.1 Case Study 1: Alyllcarbinol

Case study 1 (Scheme 8.3) involved an old process where the carbonyl is a ketone substrate (**1**) with one additional functional group (Cl). The overall reaction is highly dominated by the carbonyl reacting with the Grignard reagent, but a competitive reaction is known to exist (the impurity has not been determined).

Scheme 8.3: Synthesis of alcohol 3 and intermediate 2 in the manufacturing process for zuclopenthixol hydrochloride (Clopixol) 4.



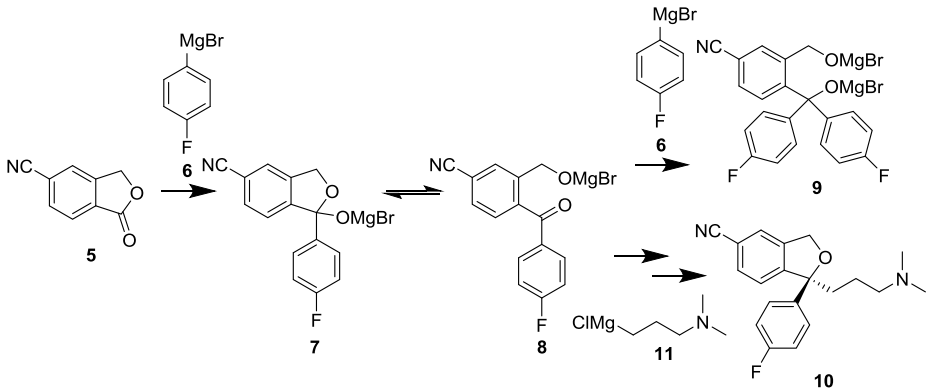
This is also supported by knowledge from production, where impurity formation is especially observed near equivalent addition of Grignard reagent to the ketone substrate and at elevated temperatures. Due to the existing knowledge on how the reaction progresses and the fact that the formation of impurities is found to be low, no kinetic investigation was necessary. The solvent choice was heavily based on the GMP-filed part and only THF was considered. The reaction in the current batch was operated on the lower side of ambient temperature, hence the solubility of the (solid) ketone substrates was investigated for a temperature range of -10 to 60 °C. Solubility of the product (**2**) was found to be significantly higher than that of the reactants and a lower temperature (0 to 20

°C) was chosen to suppress any formation of impurities based on knowledge from the batch reaction. On this basis, a heterogeneous separation reactor followed by a subsequent multi-injection reactor for full conversion in the outlet was chosen as the first reactor setup. Simultaneously with the laboratory work on the reactor, work on the control strategy based on NIR measurement was carried out. The later steps of the process involve hydrolysis with subsequent dehydration. Both steps were demonstrated in the laboratory as segmented experiments from the Grignard addition reactor setup but not implemented at full scale. The setup was demonstrated to be useful in the laboratory and was later scaled up with great success. Some slight modification between the laboratory and the full-scale setup was made to meet functionality requirements. Table 8.6 summarizes the details of the investigation. In Pedersen *et al.*,[88–90] a more detailed discussion on the case study can be found.

8.13.2 Case Study 2: Escitalopram

Case study 2 (Scheme 8.4) involved an existing batch process having a lactone **5** with an additional functional group (CN). The desired outcome of the process was a diaddition to the lactone **5** by two different Grignard reagents (**6** and **11**). The lactone **5** reacts as a competitive consecutive reaction resulting in the formation of impurities, as only mono-addition for each Grignard reagent addition is desired to obtain the final product **10** upon workup.

Scheme 8.4: The Grignard addition to cyanophthalide (5) with two Grignard reagents (4-fluorophenyl magnesium bromide (6) and (3-(dimethylamino)propyl)magnesium chloride (11)), to yield product 10 upon hydrolysis and workup. Bisadduct impurities like product 9 are commonly seen due to competitive reactions.



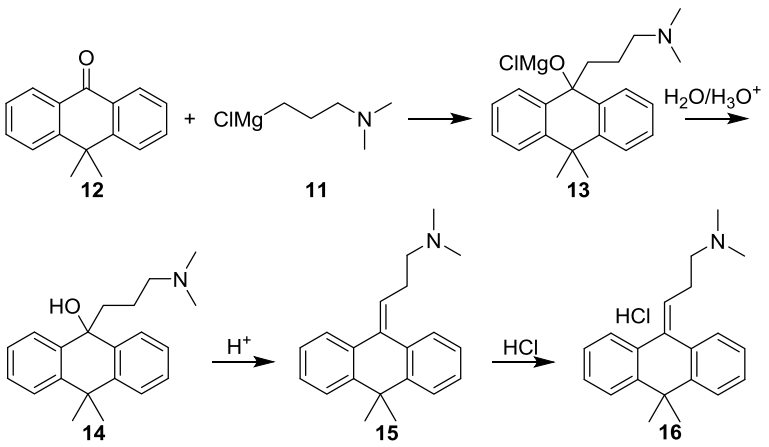
Additionally, the cyano-group adds more complexity to the reaction as this group will compete directly with the lactone for the Grignard reagent. From production, the reaction was known to be sensitive to temperature and thus if the formation of impurities is to be minimized the temperature should be kept low. The two Grignard reagents also behave differently in terms of reactivity, hence the less reactive of these was added first (Grignard reagent **2**). Both THF and MeTHF were considered for the reaction and both are used in the routine batch production. The (solid) lactone has low solubility in both solvents and the same is true for the product of the first Grignard reagent addition. It was decided to progress with MeTHF due to its non-miscibility with water for later phase

separation. A heterogeneous residence time reactor (OFR) was chosen due to the low solubility of both reactants and product. Prediction models for the reactants' and products' subsequent conversion and concentration throughout the reactor were developed early in the process due to the high complexity of the chemistry. Simultaneously, kinetic investigation was carried out on a phthalide model compound, which was chosen in order to study only the addition reaction to the lactone, as this part contributes to the major impurity formation. The kinetic investigation verified the addition order at the given reaction temperature to be the best suited. The investigation also indicated that the diaddition impurity product could be suppressed with cryogenic reaction conditions. The investigation of the reaction in the OFR caused a series of difficulties related to the precipitation product from the first addition reaction. The magnesium alkoxide intermediate turned out to be highly viscous and stuck to the wall of the reactor, significantly reducing mass and heat transfer capability. Without good heat and mass transfer, the chance of suppressing impurity formation is limited. The project was terminated in the end due to the high complexity of the chemistry and unforeseen challenges. The knowledge ultimately obtained from the process is summarized in table 8.6.

8.13.3 Case Study 3: Melitracen HCl

Case study 3 only involved a ketone (**12**) functional group and therefore its chemical analysis should be rather straightforward. The synthetic route is illustrated in scheme 8.5.

Scheme 8.5: Syntheses of alkoxide product 13, alcohol 14 and diene 15 in the manufacturing process for melitracen HCl 16, from ketone 12 and Grignard reagent 11.



The routine batch production was carried out in a solvent mixture of toluene and THF, but pure solvents (toluene, THF and MeTHF) were investigated for solubility of the solid ketone substrate, as later reactions and workup are expected to be easier with pure solvent. All investigated solvents showed high dissolution of the ketone (**12**); THF had a significantly higher concentration and was chosen for that reason. The product (**13**) also had high solubility and a tubular flow reactor was chosen. The temperature was lowered from approximately 55 °C to ambient temperature. No kinetic investigation was needed

and the addition reaction step was relatively easily implemented in the laboratory. The synthesis also includes hydrolysis and dehydration of the formed alcohol (**14**), which was optimized to a one-step synthesis with concentrated HCl. Upon pH adjusting, it was possible to make a phase separation with a simple gravity decanter and an additional precipitation to the final API, the latter of which was not optimized. The API was within production specification and improvement of the process compared to routine production was achieved. Due to the smaller market share of the API, no further action was taken in order to implement the new flow method. The scale-up is considered reasonably simple, due to the simplicity of the laboratory setup and the operational conditions applied. Furthermore, only a minor scale-up is necessary to fulfil the demand of the market.

8.14 Discussion and the Wider Perspective

This methodology has focused on the Grignard addition reactions and provides a step-by-step approach to fit Grignard reactions to suitable reactor configurations at an early stage. If methodologies and decision making for batch versus flow chemistry are really to make a difference, multiple synthesis steps need to be taken into account. For Grignard addition reactions, this involves hydrolysis that could be followed by a dehydration and separation of the organic and aqueous phases. Other methodologies should be developed for different chemistries and a common method of integrating these with each other will be necessary. The general methodological approach developed in this article is illustrated in figure 8.3 and it is believed that it can be fitted to suit other chemistries. The ideal vision for future production should be “plug and play” modules, where fast screening of chemistry results in a fast transfer to full-scale production.

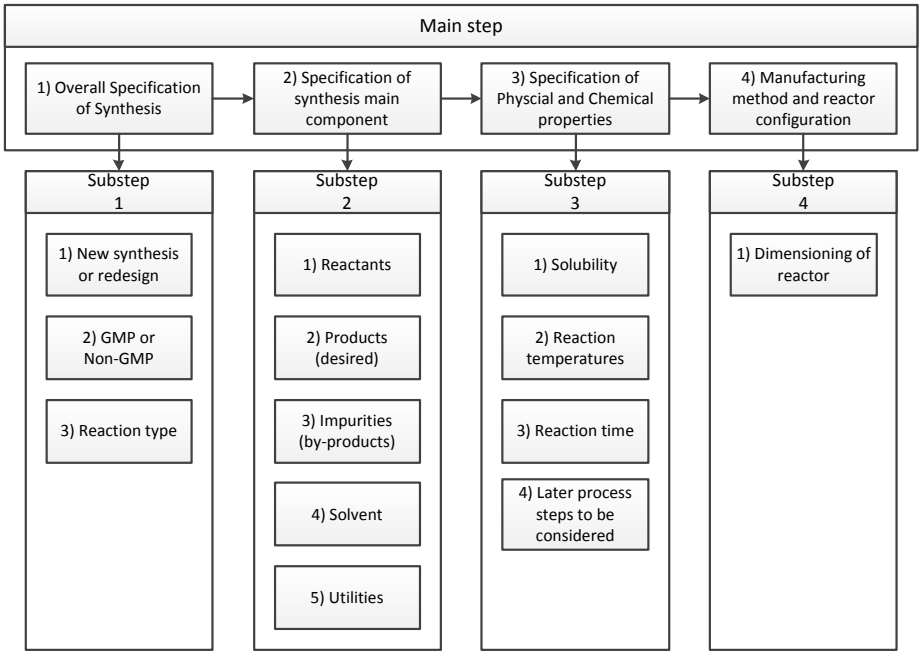


Figure 8.3: The decision tree for reactor design in the case of Grignard chemistry in pharmaceutical production.

8.15 Conclusions

A general methodology has been developed with the purpose of simplifying decision making for reactor design for Grignard reactions. The methodology focuses on the necessary laboratory experiments to perform in order to estimate the potential for a continuous reactor setup. With the increasing interest in continuous pharmaceutical manufacturing, this method aims to assist in making the decision between flow and batch processes. From an industrial perspective, the decision is always based on economic benefit or on health and safety issues. An old process or synthetic route is not always easily changed in the pharmaceutical industry without significant expenses due to regulatory restrictions. The restrictions often change a profitable optimization into a non-profitable one, this being one of the issues making the pharmaceutical industry very different from most of the other chemical industries. Solubility turned out to be the most important factor to have knowledge of when decisions are to be made on reactor configuration, as this will often be the most challenging parameter for reactor setup, especially for flow reactors. Fast screening experiments or a full solubility study can provide the data needed for decision making. A good understanding of the chemistry, especially temperature's influence on the reaction rate and impurity formation, is of significant importance. The biggest flexibility in manipulation can be achieved with flow setups, but as the chemistry becomes more complex the simplicity of the batch reactor may in some situations still prove to be the best choice.

Conclusions

Continuous pharmaceutical production has steadily grown during the last decade, a transformation that many stakeholders believe will make a major contribution to making the pharmaceutical industry more efficient and sustainable. The present trend of end-to-end production and pharmaceuticals on demand is in direct contrast to the earliest flow chemistry demonstrations of single synthetic steps and unit operations. Grignard chemistry has, since its discovery more than one hundred years ago, been a very important reaction type for the formation of new carbon-carbon bonds. The work documented throughout this project has aimed at providing valuable information about Grignard chemistry in flow reactors, with the purpose of developing a methodology for evaluating the potential of Grignard chemistry for various flow setups. The methodology is built on three very different Grignard addition reactions (e.g. solubility, functional groups) used for the synthesis of three APIs (melitracen HCl, zuclopenthixol and escitalopram). The main finding is the importance of reactant and product solubility, which largely dictate which types of reactor technology are likely to be suitable for production. Additionally, the strict regulation of the pharmaceutical industry by authorities can change an otherwise profitable continuous method into a non-profitable one, if refiling of documents becomes necessary. Some of the important findings for the syntheses investigated are summarized below.

Understanding reaction mechanisms is of great value when decisions on reactor design and optimization of yield and purity are to be made. A flow setup and method for generation of reaction data (kinetics) for Grignard addition reactions was developed and the addition of two different Grignard reagents to a lactone was studied. The investigation indicates that the addition reaction follows the Meisenheimer mechanism and involves equilibrium between the two configurations of the mono-addition product. The equilibrium was found to be very sensitive towards temperature and for one of the Grignard reagents it was possible to shift the equilibrium towards monoalkylated product.

A scale-up of a continuous reactor setup for Grignard reagent addition to a ketone with low solubility was investigated. The scale-up demonstrates the relative ease with which a continuous process can be transferred from a laboratory setup to full-scale production, where the small changes in dimensions in particular minimized the physicochemical deviations caused by mass and heat transfer. The continuous reactor setup also proved quite adept at handling solid reactants, which is typically one of the most difficult operations.

Melitracen HCl was used as a case study for the demonstration of continuous production of an active pharmaceutical ingredient. Three segmented setups were developed to facilitate the production of melitracen HCl. While outside the scope of this work, the three setups could readily be coupled to provide full end-to-end production of melitracen HCl, if desired. The three setups each demonstrate some of the advantages that can be achieved with flow processes, such as improved safety, simplification of processing and reduced production cost, to mention a few.

The production of 3-(*N*,*N*-dimethylamino)propylchloride (DMPC) is performed through a base liberation of a HCl salt that originates as either an aqueous solution or a solid. The routine batch process for preparing DMPC requires the use of organic solvent for the extraction and a subsequent vacuum distillation. The flow process simplified the preparation by eliminating the organic solvent-assisted extraction and distillation. In a flow reactor setup, the base liberation of DMPC-HCl was demonstrated by use of 28 wt% NaOH (aq.), followed by a decanter separation of the DMPC from the aqueous phase. The free base from the separation was subsequently mixed with 50 wt% NaOH (aq.) for drying, before a second decanter was used for final separation of the essentially dry DMPC from the aqueous phase. This flow setup is an illustrative demonstration of how a continuous process can improve sustainability and greenness in the pharmaceutical industry by reducing solvent and energy consumption.

Continuous processes have been praised for safer production when dealing with hazardous reactions. Closed reactor systems, smaller active volumes and more efficient heat transfer compared to batch reactors are some of the benefits mentioned when dealing with toxic and exothermic reactions. Grignard reagents are notorious for the risks associated with their production because of the often toxic alkyl/aryl halide, the highly exothermic reactions, low boiling solvents and very reactive organometallics that are formed. A continuous reactor system capable of handling solid magnesium was used for the production of DMPC-MgCl in MeTHF. The flow setup significantly reduces the active volume necessary for production as compared to normal batch methods and minimizes risk in case of runaway reactions. The closed handling of reactants and products and the assurance of concentration and quality by in-line near-infrared spectroscopic measurements have likewise reduced hazard risks when handling toxic compounds. An industrial version of the laboratory reactor setup has been implemented in full-scale production for formation of other Grignard reagents, ensuring consistent quality and safe production.

The batch production of melitracen HCl, an active pharmaceutical ingredient for antidepressant treatment, was redesigned to a continuous process. The solvent was simplified from a mixture of toluene and THF to use only THF. In addition, due to the high solubility of the ketone, the Grignard addition was suited for a plug flow reactor and furthermore the reaction temperature was able to be lowered from 50°C to ambient. The hydrolysis and dehydration were merged into a single synthetic step, causing a reduction in the number of unit operations by removal of a phase separation. Judicious adjustment of the pH generated a two phase system, resulting in near quantitative extraction of the melitracen raw base into the organic phase. A decanter was used for the subsequent separation. A non-optimized precipitation of the melitracen HCl in THF was carried out by use of a 2 M HCl solution in Et_2O, which resulted in an overall isolated yield of 80%. The melitracen HCl was analyzed in accordance with current release procedures for the routine batch production, wherein the product was found to be in full compliance with all specifications, with the exception of the particle size distribution, which was marginally larger than specification. The laboratory setup is capable of producing a significant amount of the current annual production and profits from a significant simplification over the routine production method.

Future Perspective

The major changes that have occurred within the pharmaceutical industry during the last decade have opened doors for new and interesting opportunities. The industry, the authorities and academia have all contributed to the overall discussion on how the pharmaceutical industry can change to become more efficient and sustainable in a highly competitive business regime. In particular, flow processing has received much positive interest and is believed to have a major influence on the changes taking place. The earliest demonstrations focused very much on establishing proof of concept by conducting a single synthetic step and unit operation with the aim of improved performance. As the new technologies have become familiar in academia and to the pharmaceutical industry, the trend has been towards complete synthesis of pharmaceuticals comprised of multiple unit operations. Recent efforts have also resulted in some full-scale implementations reported in the literature, highlighting that pharmaceutical companies believe in the new paradigm of continuous production methods.

The concept of continuous manufacturing has gained a foothold, but major areas are still unexplored. Much work lies ahead before continuous manufacturing in the pharmaceutical industry can rival the more traditional batch production. A better understanding of the possibilities of continuous processing still needs to be established. R&D departments tend to reapply reaction types when developing new syntheses for pharmaceuticals; hence standardized “plug-and-play” reactor modules would ease the transfer between R&D and production. R&D chemists and chemical engineers can utilize each other’s competencies in the effort to develop standardized reactor concepts, ensuring long-term success from the collaboration. Besides the development of modular concepts, it is just as important to understand the limitations of the available technologies in order to make appropriate decisions on which processing approach is preferred. Methodologies are essential for rapid selection of processes suitable for development in flow, but they must be simple if they are to gain acceptance and be implemented in industry. It is paramount that these areas receive proper attention in order to accelerate the momentum of the modernization of the pharmaceutical industry and facilitate the transition to flow manufacturing.

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