Studies on process intensification for process chemistry by the use of continuous flow technology

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Contents

List of Abbreviation

Reagents	
DMF	*N*,*N*-dimethylformamide
NBD	norbornadiene
THF	tetrahydrofuran
Chemical structure	
Ac	acetyl
Bu	butyl
Bn	benzyl
Et	ethyl
Me	methyl
Ph	phenyl
Instrumental analysis	
FT	Fourier transform
IR	infrared spectroscopy
ICP	inductively coupled plasma
MS	mass spectrometry
NIR	near-infrared spectrometry
NMR	nuclear magnetic resonance
PAT	process analytical technology
UV	ultraviolet
Unit	
d	day
h	hour
min	minute
ppb	parts per billon
rpm	revolutions per minute

Experiment

conc	concentration
N.D.	not detected
temp	temperature
OD	outside diameter
PFA	perfluoroalkoxy alkanes
RC	reactor column

Organization

ACS	American Chemical Society
CMO	contract manufacturing organization
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
GCI	Green Chemistry Institute

Others

API	active pharmaceutical ingredient
BET	Brunauer–Emmett–Teller
Capex	capital expenditure
CoGs	cost of goods
Opex	operating expenditure
PMI	process mass intensity
R&D	research and development
TBR	trickle bed reactor
TRI	toxic release inventory
WHSV	weight hourly space velocity

Chapter 1

General introduction

1-1. Process intensification

There still has not been a clear definition of process intensification, however, by an often used definition, it is "the strategy for achieving dramatic reductions in the size of the plant at a given production volume".[1] The key words to define process intensification are *innovative* and *substantial* and they describe the means of achieving a dramatic leap in process and plant efficiency, in which the degree of reduction should be at least one order of ten level, through the means of novel ideas in addition to conventional equipment and processing method improvements. Process intensification generally can be divided into two categories, hardware technologies, such as novel equipment, and software technologies, such as new processing methods, as shown in Table 1-1.[2,3] In addition, this approach can involve shrinking the total occupied footprint of equipment and the operating plant by cutting the number of unit operations and/or devices involved. Furthermore, intensification can be achieved through the use of all relevant apparatus to the limits of their production capability, *e.g.* through the use of high pressure, high temperature and high substrate concentration. One of the enabling technologies for process intensification is continuous flow technology.

Table 1-1. Process intensification and its components, proposed by Stankiewicz and Moulijin[2]

Process intensification					
Equipment		Methods			
Equipment for carrying out chemical reactions	Equipment for operations not involving chemical reactions	Multifunctional reactors	Hybrid separations	Alternative energy sources	Other methods
Examples					
Microreactors	Static mixers	Reactive extraction	Membrane absorption	Ultrasound	Supercritical fluids
Spinning disk reactor	Compact heat exchanger	Membrane reactors	Membrane distillation	Microwaves	
Monolithic reactors	Microchannel heat exchangers	Chromatographic reactors	Adsorptive distillation	Electric Fields	

Over the past 15 years, the attention with process intensification has been growing. In fact, it was selected by the American Chemical Society (ACS) Green Chemistry Institute (GCI) Pharmaceutical Roundtable as one of the top 5 "Key Green Engineering Research Areas for Sustainable Manufacturing", along with continuous processing, in 2007.[3]

Through process intensification, materials, waste, energy, equipment and plant footprint, inventory, production time, cost (capex and opex) as well as environmental impact of the process, may all be reduced. On the other hand, productivity, safety and mobility of

equipment may be increased. As a result, profit (economic benefit) can be elevated, along with the social and environmental benefit (Figure 1-1).

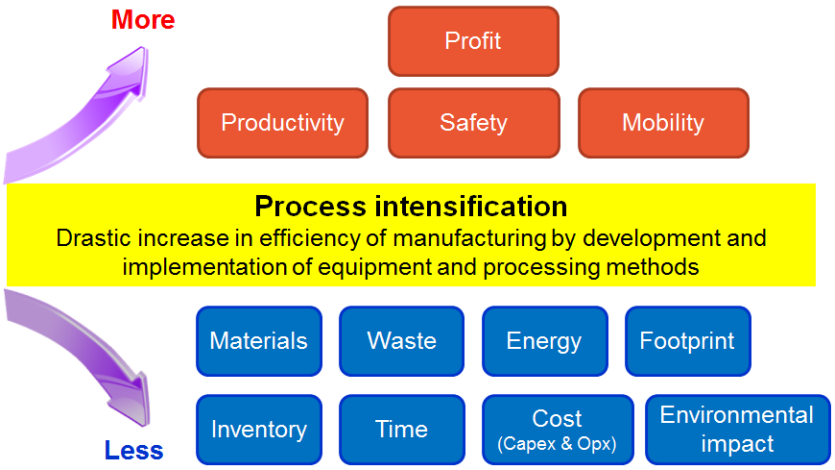

Figure 1-1. Benefits from process intensification

1-2. Continuous flow technology

There are two general ways for chemical manufacturing, namely batch and continuous processing. Continuous flow technology can give some potential benefits over traditional batch processing (Figure 1-2). First, there can be an opportunity to increase yield, selectivity and consistency in quality in some cases, by exploiting the efficient mixing and heat exchange, accurate control of the reaction conditions and the reaction time. Actually, in batch, several features - time consuming reagent feeding, hot spot generation, non-homogeneous mixing, poor heat transfer and temperature gradients - can cause problems. Second, safety can be increased in continuous processes due to the smaller reaction volume, and thirdly, easy scale-up can be achieved just by prolonging the running time of the system (scaling-out) or

using multi-reactors in parallel (numbering up) without expanding reactor volume. Also, in flow reaction, product is removed from the reaction conditions just after completion of reaction, and quenched immediately, which can prevent subsequent degradation. Lastly, special reaction conditions can be more easily used, such as photochemical reaction, high pressure and temperature reaction.

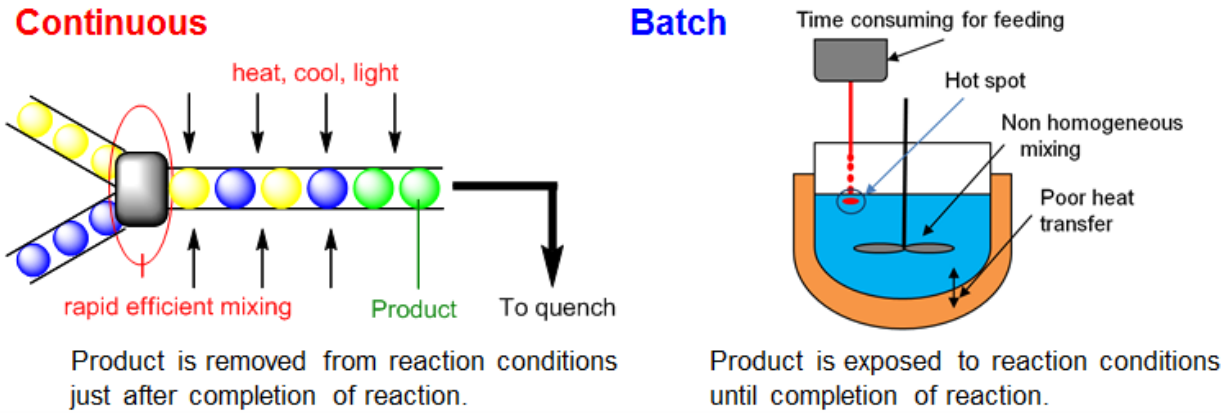

Figure 1-2. Schematic diagram of continuous and batch processes

Kobayashi and co-workers divided the continuous flow systems into four types (Figure 1-3).[4] In type I, substrates and/or reagents (A and B) are flowed and reacted inside the reactor. In type II, one of the reactants (B) is supported onto a solid in a column and the substrate is flowed through the fixed bed reactor.[5h] One of the issues for this type of reactor is that the supported reactant must be changed or regenerated when it has been consumed. In type III, a homogeneous catalyst is flowed through the reactor with substrates and/or reagents and reaction occurs in the reactor. The main issue for type III is that a step to separate the product

from the catalyst is necessary. In type IV, a heterogeneous catalyst is packed in a reactor and substrates and/or reagents are reacted by passing through the fixed bed reactor. This type of reactor enables a process to be developed without a specific step to separate the catalyst and, furthermore, the fixed catalyst can be continuously used for as long as the catalyst activity is maintained. Therefore, type IV is regarded as an ideal method for a continuous process, from the viewpoint of green sustainable chemistry, to reduce waste.

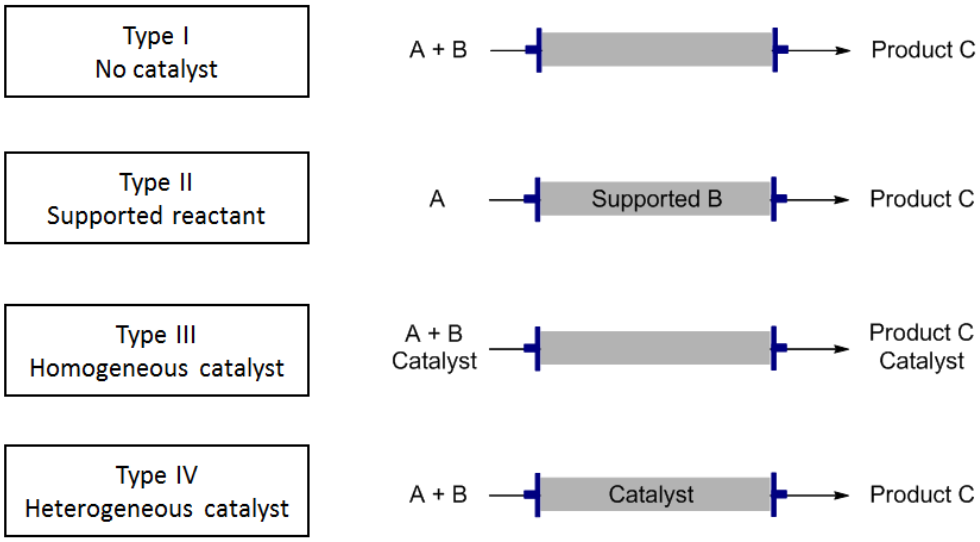

Figure 1-3. Types of continuous flow systems[4]

Continuous flow technology has been brought to both academic and industrial attention as an enabling technology and a considerable number of studies have been conducted in this field over the past two decades.[5] The technology plays an important role for green sustainable chemistry and engineering in a variety of aspects, such as waste minimization, safety improvement, energy and cost efficiency.[6]

The petrochemical industry tends to operate continuous processes, whereas pharmaceutical and fine chemical industries are still dominated by batch manufacturing methods, however, they have been slowly incorporating continuous processing into their processes for decades.[7] As a recent remarkable work, Novartis-MIT Center for Continuous Manufacturing team demonstrated the end-to-end continuous manufacturing of an API (Active Pharmaceutical Ingredient), aliskiren hemifumarate.[5k,8] The manufacturing process consists of two synthetic steps, salt formation, crystallization and formulation processes, to give the drug product as tablets. The volume of the continuous reactor is 0.7 L and with a high productivity, 0.8 tons of the API can be obtained per year. The required unit operations and processing time at a given production volume was dramatically reduced from 21 operations and 300 h for the batch process to 13 operations and 48 h for the continuous manufacturing.

All in all, most of the big pharmaceutical companies are continuing to invest significantly in this field.

1-3. Process Chemistry[9]

In general, there are two types of chemistry in the R&D divisions of the pharmaceutical industry, that is medicinal chemistry and process chemistry. To put it briefly, medicinal chemistry focuses on "what to make", whereas process chemistry looks at "how to make". The main role of process R&D is to supply high quality APIs according to the development

schedule of the drug candidates, with the following 4 missions:

1. Accelerating drug development speed by rapid process development and API supply

Urgency is very important for process R&D in the pharmaceutical industry. Considering the huge R&D costs and the impact of the development period on the earnings (Table 1-2), the importance to shorten the development period through rapid process development and API supply, is increasing more and more. Furthermore, in the case of a drug with annual 400 million dollar sales, even one day delay in filing of the drug can cause a loss of 1 million dollars of sales every day.

Table 1-2. Some statistics relevant to the pharmaceutical industry[9]

Factor	Value
Cost to bring a drug to market	$1,300,000,000
Annual cost of a US chemist or engineer for an employer	$200,000-$300,000
Portion of drug candidates that fail in pre-clinical or clinical studies	About 95%
Portion of approved drugs that recoup development costs	About 30%
Average time of development	8 years
Period for exclusive sales of a patented drug (US)	20 years
Years to recoup investment costs	20 – Development time

2. Stable supply of API with high quality

The quality of supplied API is very important. Before clinical studies, the quality of API is set in specifications and its effectiveness and safety must be confirmed through non-clinical studies. Once specifications for the quality of the API are set, the quality of the API and the impurities profile must be controlled. For this purpose, optimization of the process, including workup, crystallization and purification, should be conducted.

3. Cost reduction of API

Process chemists have to establish cost-effective manufacturing processes to minimize CoGs and maximize business income. For this purpose, route selection, reagent selection and optimization of the process must be conducted.

4. Establishing robust manufacturing processes with safer and less environmental impact

A failure to supply the API or intermediates for a project can cause a delay in completing important toxicological tests and clinical studies, which will have a very big impact economically, as described above. Therefore, process R&D is required to establish robust and reliable processes for stable supply of the API, depending on the development stage and scale-up requirements (Table 1-3).

Table 1-3. Perspective on the drug development and required batch size for API[9]

	Discovery	Early development	Late development	Routine manufacturing
Purpose		Tox batches Phase 1	Phase 2 Phase 3	Commercial
Batch size	mg - g	kg	1– 100 kg	>100 kg
Emphasis	expedient	convenient	practical	efficient

Process safety is the top priority. In case of serious accident, such as fire and explosion, the company can suffer not only human and physical damages and shortage of APIs, but also tarnished corporate reputation, and with increased scale-up the greater will be the impact. Process chemists must always develop and scale up their processes with safety aspects in mind, even though rapid development speed and tight deadlines for API supply are required.

Over and above all else, process chemists are required to consider the environmental impact of the processes they develop, in what is called "Green Chemistry" considerations. The pharmaceutical industry has much higher E-factors, one measure of process sustainability that is defined as the weight ratio of waste/product, than does the petrochemical industry (Table 1-4). One of the reasons lies on the higher level of chemical complexity and quality standards in the pharmaceutical industry, however, efforts to improve yield, reduce waste and increase productivity should be made for developing greener manufacturing processes.

Table 1-4. Comparison of wastes generated by different segments of the chemical industry[9]

Industry segment	Product Tonnage	E-factor
Petroleum	10^6-10^8	<1
Fine chemicals	10^4-10^6	1-5
Bulk chemicals	100-10^6	5-50
Pharmaceuticals	10-1000	25-100

1-4. Purpose of this study

"Process intensification" and "continuous flow technology" would be a very useful strategy and technology to achieve the process chemistry missions. Many enabling technologies, such as continuous flow technology, have become available in recent years. However, a particular challenge that has not been fully met, is how to move easily and safely to scale up reactions, in research laboratories, from milligrams to kilograms. It is very important in terms of rapid process development in the pharmaceutical industry.

The purpose of this study is to achieve process intensification using continuous flow technology and develop a rapid reaction condition screening method using PAT (Process Analytical Technologies) in a research laboratory, and to demonstrate high throughput syntheses using bench-top reactors in a fume cupboard. Some examples are shown, with a focus on heterogeneous hydrogenation reactions, from the viewpoint of process chemistry.

1-5. References

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Chapter 2

Process intensification for the continuous flow hydrogenation of ethyl nicotinate

2-1. Introduction

2-1-1. Heterogeneous hydrogenation

As all chemists know, reactions using heterogeneous catalysis, especially catalytic hydrogenation reactions, are well used reactions in organic synthesis. In fact, it is said that heterogeneous catalysis plays a part in the production of more than 80% of all chemical products[1] and somewhere between 10–20% of the reactions used to produce chemicals today are catalytic hydrogenations.[2] But traditional batch hydrogenation used in fine chemical production, such as for pharmaceuticals, agrochemicals, fine chemicals, flavors, fragrances and dietary supplements, has some significant safety issues. First, hydrogenation is generally exothermic, and accumulation of reagents may cause runaway reactions. Second, catalyst addition and filtration is hazardous, hence closed filtration systems are necessary, and thirdly, hydrogen gas in the headspace can be extremely hazardous and its amount increases as the reaction vessel gets bigger. On the other hand, continuous hydrogenation has some significant advantages over batch, in some cases. For example, it can simplify catalyst handling by avoiding the filtering and cleaning from the tank. Also, it can increase reactivity and selectivity, by accessing very high pressures and high local catalyst loadings. In addition, it is

a well-known fact that smaller is safer in hydrogenation reactions due to the highly flammable nature of the gas.

Process chemists in pharmaceutical industries are sometimes requested to conduct heterogeneous hydrogenation reactions, at between several hundreds of grams and kilograms scale, and they often use time-consuming approaches, such as repeating batches using something like a 1L volume autoclave many times or outsourcing to a CMO (contract manufacturing organization) having facilities and capabilities to do that. In these circumstances, a particular challenge that has not been fully met is how to move rapidly and safely to scale-up hydrogenation reactions from milligrams or grams to hundreds of grams or kilograms in a research laboratory setting. It is precisely under these circumstances that new tools using continuous flow technology can greatly assist the process development.

2-1-2. Trickle bed reactor

Trickle bed reactors (TBRs) are chemical reactors, specifically, fixed bed catalytic reactors in which gas and liquid generally flow in a cocurrent downward mode (Figure 2-1). The main application of TBRs lies in the petroleum refining industry, more specifically in hydroprocessing.[3] There are several flow regimes in a TBR and the behavior of the flow is dependent on the liquid and gas flow rates (Figure 2-2), the physical properties of the fluids and the geometrical characteristics of the packed bed.[3d] When the values of the liquid and gas

mass flow rates are low, it is said that the liquid trickles over the surface of the packed catalyst in the form of rivulets and films and the gas flows in the remaining void volume of the packed catalyst (Figure 2-3). This flow regime is called the trickle flow.[3a,b,d] However, the hydrodynamics in the reactor is very complex and the precise understanding is still limited.

This type of reactor features low catalyst attrition. In an example of hydrogenation of a polymer with Pt/Al_2O_3 catalyst, it has been reported that the catalyst longevity was 1 week when the reaction was conducted with upward flow, on the other hand, it increased dramatically to more than 1 year, even using the same catalyst and reaction conditions, when the flow was downward.[4] Use of this reactor has potential to increase reactivity and selectivity over batch processing, due to higher mass transfer between gas and liquid and higher contact areas between gas and catalyst.

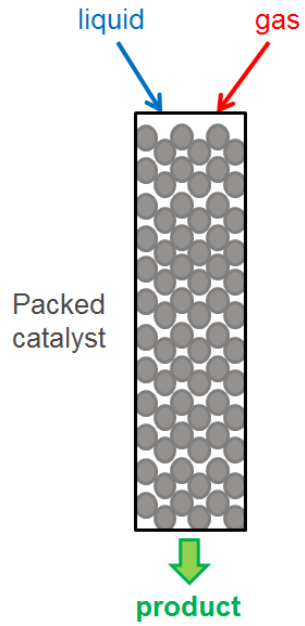


Figure 2-1. Trickle bed reactor (TBR)

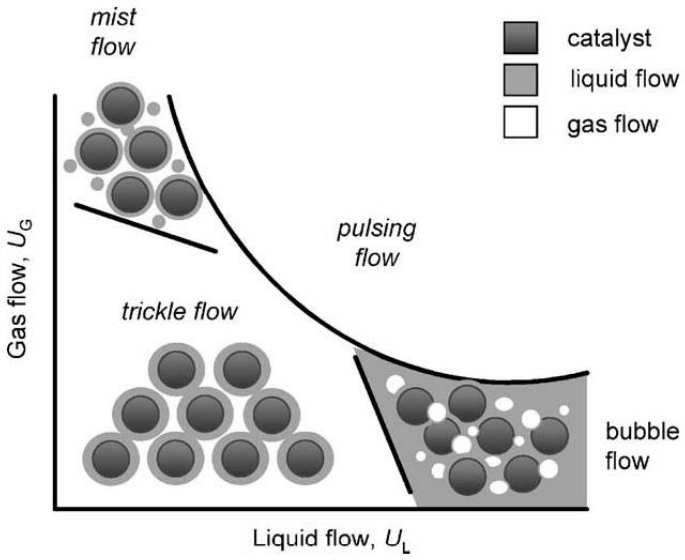


Figure 2-2. Schematic illustration of the location of the trickle, mist, bubble and pulsing flow regimes depending on gas and liquid flow rates[3b]

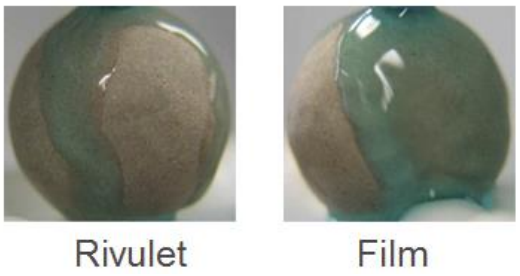


Figure 2-3. Form of rivulet and film[3a]

2-2. Flow reactors used in this study

In this study, two types of commercially available flow reactors, H-Cube® and FlowCAT™ were used for continuous hydrogenation reaction.

2-2-1. H-Cube®

H-Cube® is a bench-top standalone hydrogenation reactor employing continuous flow technology (Figure 2-4). The features of H-Cube® are summarized below.[5]

- A continuous-flow of substrate is combined with hydrogen, generated *in-situ* from the electrolysis of water.
- The hydrogen/substrate mixture can be heated and pressurized up to 100°C and 100 bar, respectively.
- The mixture is then passed through a disposable packed catalyst cartridge (CatCart®), where the reaction takes place, and the product continuously elutes out of the CatCart® and into a collection vial.
- Various CatCart® cartridges, over 100 heterogeneous and immobilized homogeneous catalysts, are available from the maker, ThalesNano.
- The movement of the mixture of gas and liquid over the catalyst cartridge is upward.

H-Cube® is a well-known reactor in the flow chemistry field and over 530 application examples have been published.[6]

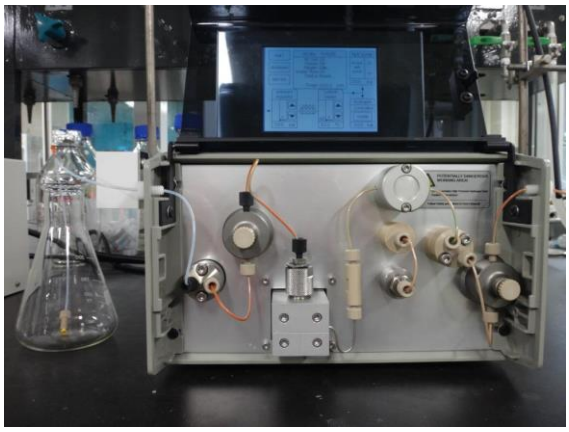


Figure 2-4. Photograph of H-Cube® and a CatCart® cartridge.

2-2-2. FlowCAT™

FlowCAT™ is a bench-top reactor for continuous flow chemistry catalytic reactions (Figure 2-5, Figure 2-6).

The features of FlowCAT™ for heterogeneous continuous reaction are summarized below.[7]

- A continuous-flow of substrate is combined with gas (*e.g.* hydrogen, oxygen and carbon dioxide) supplied from a cylinder.
- The gas/substrate mixture can be heated and pressurized up to 350°C and 100 bar, respectively.
- The mixture is then passed through a packed catalyst, where the reaction takes place, and the product continuously elutes out of the catalyst bed and into a collection vessel.
- The catalyst should be packed by the user.
- The movement of the mixture of gas and liquid over the catalyst bed is downward (trickle bed reactor).
- The processing conditions are controlled via software (see experimental section).

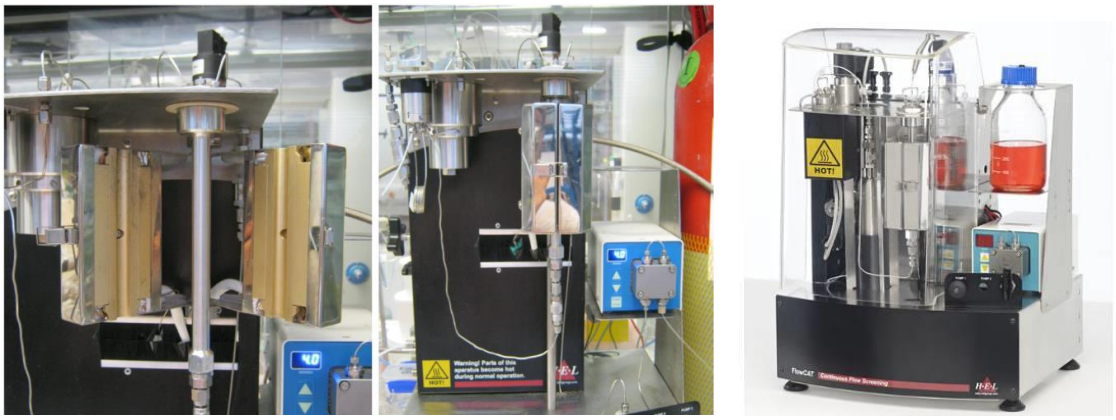


Figure 2-5. Photographs of FlowCAT™ (left: column reactor; middle and right: whole system)

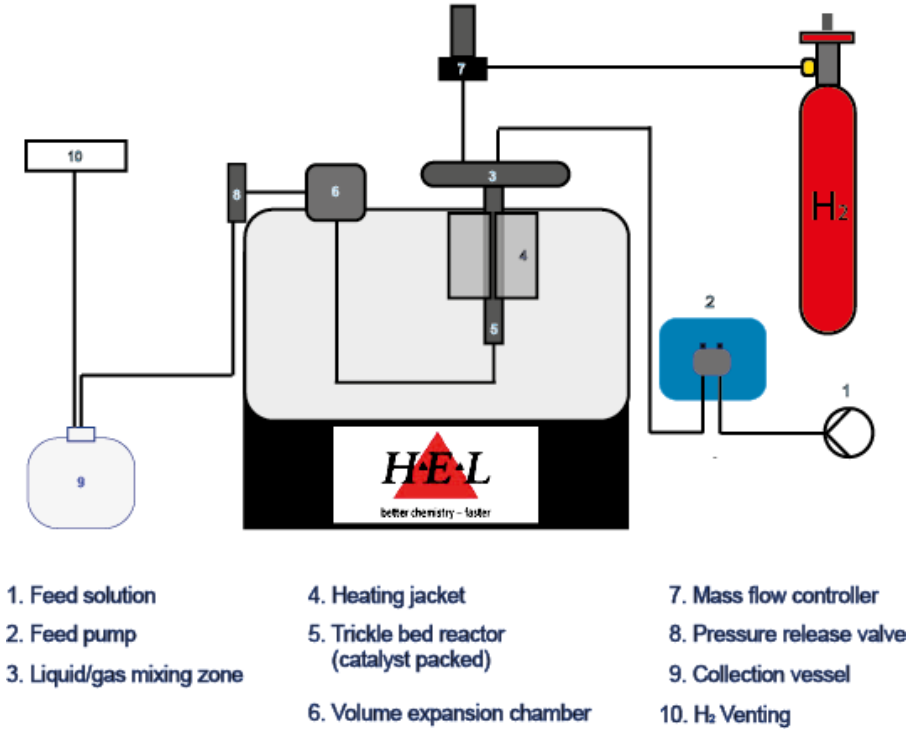


Figure 2-6. Schematic view of FlowCAT™

2-3. Partial hydrogenation of ethyl nicotinate

2-3-1. Background

Substituted pyridines are interesting intermediates for the preparation of many biologically

active molecules containing a piperidine core (Figure 2-7).[8] Also, enantiomerically pure piperidine derivatives are important building blocks for pharmaceuticals, but they are much more expensive than pyridine derivatives, as shown in the following examples (Figure 2-8).[9]

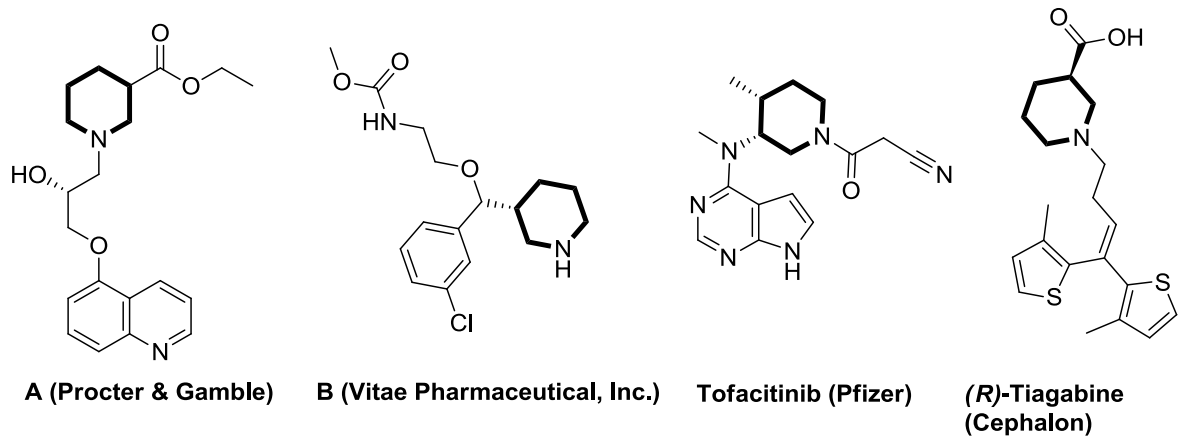


Figure 2-7. Examples of biologically active molecules containing a piperidine core

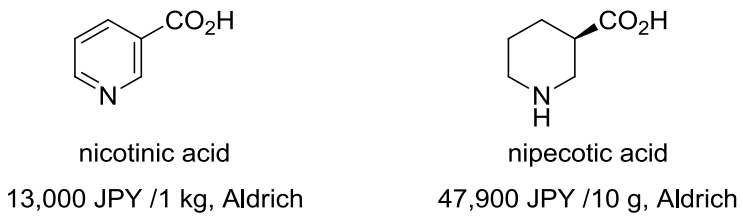
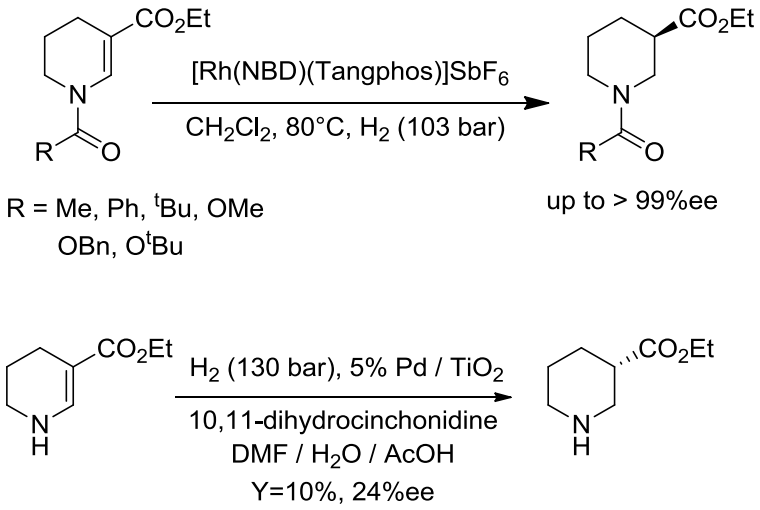


Figure 2-8. Examples of price for pyridine and enantiomerically pure piperidine compounds

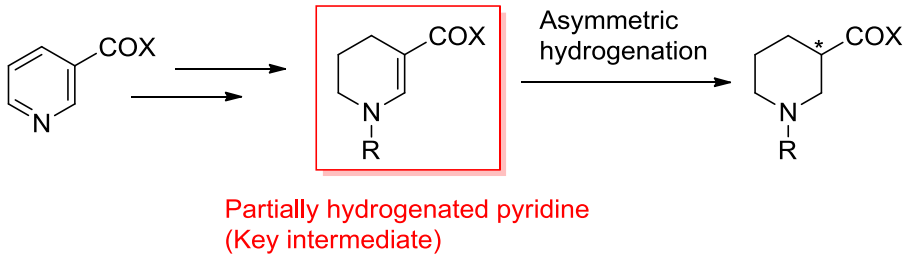
It is known that hydrogenation of some nicotinic acid derivatives having carbonyl groups at the 3-position selectively gives the partially hydrogenated pyridine products, in the appropriate reaction conditions.[10] The subsequent asymmetric hydrogenation of this compound gives the enantiomerically pure piperidine, as shown in the following examples

(Scheme 2-1).[10,11] This strategy is used as an approach to aquire enantiomerically pure piperidines, and the partially hydrogenated pyridines are key intermediates (Scheme 2-2).

Scheme 2-1. Examples for asymmetric hydrogenation of partially hydrogenated pyridines



Scheme 2-2. Approach to enantiomerically pure piperidines

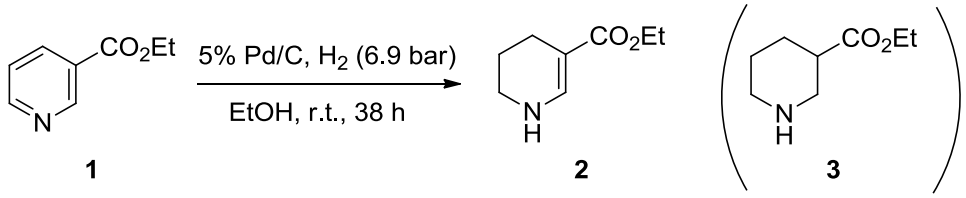


A several hundreds of grams to kilogram scale synthesis of the partially hydrogenated ethyl nicotinate (**2**) from ethyl nicotinate (**1**) was required in an asymmetric hydrogenation program for enantiomerically pure piperidine derivatives. For this purpose, the batch reaction was

investigated first using an autoclave system (see experimental section).[12]

I soon recognized that the chemical transformation was difficult under the conditions reported previously,[10] and using 5% Pd/C as a catalyst under moderately high pressure hydrogen (100 psi ≈ 6.9 bar) gave 85% conversion for products **2** and **3** (7:1 average ratio) over 38 h, at room temperature (Table 2-1).

Table 2-1. Hydrogenation of **1** under batch mode conditions



1 **2** **3**

Ratio of reaction mixture (%, determined by ^{1}H-NMR)		
1	**2**	**3**
14.8	73.8	11.4

Then, I examined the H-Cube® to evaluate its capability and quickly found I was able to reproduce the results described previously by Kappe and co-workers.[13] However, upon extended reaction time some variability was noticed. Additionally, I was never able to isolate more than 72% of the partially hydrogenated product and the throughput of **1** was only 10.9 g d^{-1} (Table 2-2). The result clearly showed that H-Cube® could not practically achieve the target quantities, owing to engineering constraints such as the limitations in the hydrogen flow rate (30 mL/min at a maximum) and the size of the catalyst cartridges (amount of

packed catalyst is up to 0.3 g).

Table 2-2. Hydrogenation of **1** under flow mode conditions using H-Cube®

Ratio of reaction mixture (%, determined by ^{1}H-NMR)			Isolated yield of **2** (%)
1	**2**	**3**	
6.4	76.7	16.8	71.6

I decided to begin an investigation with the aim of safely delivering a throughput in excess of a kilogram per day (kg d^{-1}) in a research laboratory environment. This would need considerable process intensification with the currently available equipment. In order to deliver material in our target quantities, I identified the FlowCAT™ reactor as a potentially suitable device for the scale up and process intensification studies.

2-3-2. Results and discussion

One practical aspect of major importance, when dealing with this kind of process, is the packing of the reactor column. According to a suggestion on reactor packing given by the FlowCAT™ maker, the use of the usual wet Pd/C (particle size 0.010-0.015 mm), with inert glass beads (particle size 0.425-0.590 mm) to prevent catalyst clogging, was investigated (Figure 2-9), but it failed due to blockage of the catalyst bed and it was judged that if the proportion of glass beads was increased to prevent blockage, it would be an inefficient

catalyst loading for high throughput. Therefore, I decided to try some granule catalysts.

Figure 2-9. Reactor packing suggestion by the maker (right-hand photograph shows an image of the column packing, with catalyst shown in deep blue and glass beads in light blue)

During my screening, I noticed that the performance of the run was highly dependent on catalyst particle size, with too small particles leading to frequent blockages and too large particles being associated with channeling and reduced mixing.

Due to the capacity of the trickle bed reactor (reactor column 1, RC1, 6 mm i.d., 3 mL internal volume; reactor column 2, RC2, 12 mm i.d., 12 mL internal volume, Figure 2-10), it was possible to pack the column with a charge of 2.6 g of catalyst for RC1.

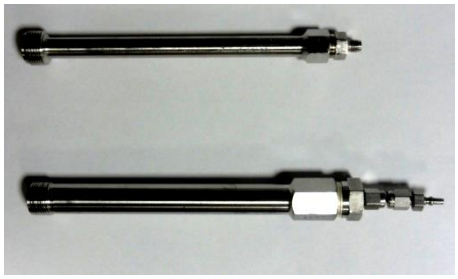


Figure 2-10. Photograph of RC1, top, and RC2, bottom, reactor columns.

For the initial study, I used granule Pd/C catalysts (Table 2-3). I started to screen my system at room temperature with 10% Pd/C.[14] Using a H_2 feed of 0.1 L min^{-1} and system pressure of 20 bar, I was able to selectively obtain 78% conversion to **2** (liquid flow rate 2.0 mL min^{-1}) (run 1). Increasing the temperature to 60°C and the flow rate to 5.0 mL min^{-1} (system pressure of 20 bar and gas feed of 0.2 L min^{-1}) gave a throughput of 54.78 g d^{-1}, but with the disadvantage of reducing the **2**/**3** selectivity (run 5). The best result was achieved using 5% Pd/C[15] (run 6), although this arrangement gave a lower product output (21.6 g d^{-1} throughput). I recognized that the concentration of the starting material was a limiting parameter under these conditions, but any attempt to increase the molarity of the solution above 0.05 M failed, resulting in incomplete consumption of the starting material. The purpose of this study was to achieve high throughput with no less than the selectivity obtained in batch (Table 2-1).

Table 2-3. Partial hydrogenation of ethyl nicotinate with Pd/C using FlowCAT™ reactor RC1

run	catalyst	conc. of **1** (M)	flow rate (mL min^{-1})	temp. (°C)	pressure (bar)	H_2 flow (L min^{-1})	ratio (%)[a]			throughput of **1** (g min^{-1})[d]
							1	**2**	**3**	
1	10% Pd/C[b]	0.05	2.0	25	20	0.1	22.0	78.0	N.D.	0.015
2	10% Pd/C[b]	0.05	2.0	40	20	0.1	1.1	84.2	14.7	0.015
3	10% Pd/C[b]	0.05	2.0	25	40	0.1	15.2	71.3	13.5	0.015
4	10% Pd/C[b]	0.05	4.0	60	20	0.2	1.1	78.8	20.1	0.030
5	10% Pd/C[b]	0.05	5.0	60	20	0.2	4.8	75.1	20.1	0.038 (54.78 g d^{-1})
6	5% Pd/C[c]	0.05	2.0	40	20	0.1	1.0	90.7	8.3	0.015 (21.60 g d^{-1})
7	5% Pd/C[c]	0.05	4.0	60	20	0.2	1.8	78.4	19.8	0.030

[a]Ratios are based on crude ^{1}H-NMR data. [b]Particle size 0.40−0.80 mm.[14] [c]Particle size 0.30−0.85 mm.[15] [d]Throughput is calculated by the following formula: Molar concentration of feed solution (M) / 1000 x molecular weight of **1** x flow rate (mL/min)

I decided, therefore, to screen different supported forms of Pd catalyst and found that Pd/Al_2O_3[16,17] exerted a beneficial catalytic activity in terms of both productivity and selectivity. In this particular case, the catalyst particle size was of extreme importance, with particles ranging between 0.1 and 0.25 mm being the most efficient. As shown in Table 2-4, running the reaction at 60°C and a liquid flow rate of 3.0 mL min^{-1} delivered an improved

productivity of over 260 g d^{-1} (run 7). Also of importance was that under those conditions considerably higher concentrations of the material feedstock were tolerated (up to 0.4 M).

Table 2-4. Partial hydrogenation of ethyl nicotinate with Pd/Al_2O_3 using FlowCAT™ reactor RC1

run	catalyst	conc. of **1** (M)	flow rate (mL min^{-1})	temp. (°C)	pressure (bar)	H_2 flow (L min^{-1})	ratio (%)[a]			throughput of **1** (g min^{-1})[d]
							1	**2**	**3**	
1	5% Pd/Al_2O_3[b]	0.1	2.5	40	24	0.2	N.D.	88.5	11.5	0.038
2	5% Pd/Al_2O_3[b]	0.2	2.5	50	23	0.2	6.4	83.3	10.3	0.076
3	5% Pd/Al_2O_3[b]	0.2	3.0	60	24	0.2	2.4	86.5	11.1	0.091
4	5% Pd/Al_2O_3[c]	0.2	4.0	50	20	0.2	1.8	83.2	15.0	0.121
5	5% Pd/Al_2O_3[c]	0.2	4.0	50	20	0.1	11.0	76.7	12.2	0.121
6	5% Pd/Al_2O_3[c]	0.4	2.0	50	20	0.2	3.2	80.1	16.7	0.121
7	5% Pd/Al_2O_3[c]	0.4	3.0	60	20	0.2	0.9	84.0	15.1	0.181 (260.64 g d^{-1})

[a]Ratios are based on crude ^{1}H-NMR data. [b]Particle size 0.25−0.50 mm.[16] [c]Particle size 0.10−0.25 mm.[17] [d]Throughput is calculated by the following formula: Molar concentration of feed solution (M) / 1000 x molecular weight of **1** x flow rate (mL/min)

The robustness of the system was evaluated by conducting an experiment for 22.5 h, following the conditions reported in run 7 (Table 2-4), and I found no decrease in either

selectivity or catalytic performance of the system while producing a throughput of over 240 g of material overall (Scheme 2-3, Table 2-5, Figure 2-11).

Scheme 2-3. Long run experiment for the partial hydrogenation of ethyl nicotinate

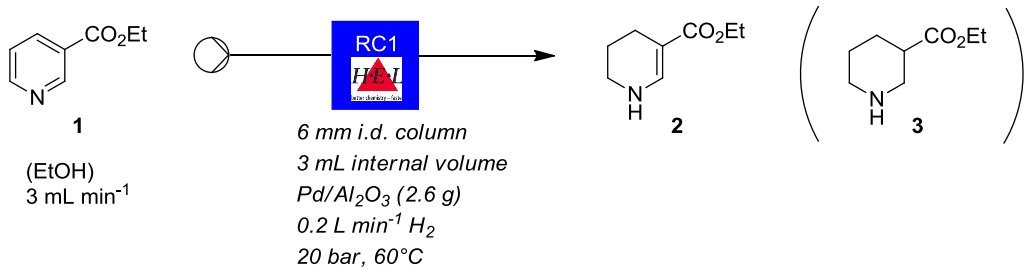


Table 2-5. Long run experiment over 22.5 h, with related data points regarding conversion of **1** to **2** and **3**

analysis point	run time (h)	total time (h)	ratio (%)[a]		
			1	**2**	**3**
1	2.0	2.0	1.0	83.8	15.2
2	3.5	5.5	0.9	82.7	16.4
3	4.5	10.0	1.0	84.0	15.0
4	5.0	15.0	0.9	83.3	15.8
5	2.0	17.0	1.0	83.0	16.0
6	5.5	22.5	1.0	84.1	14.9

[a]Ratios are based on crude ^{1}H-NMR data.

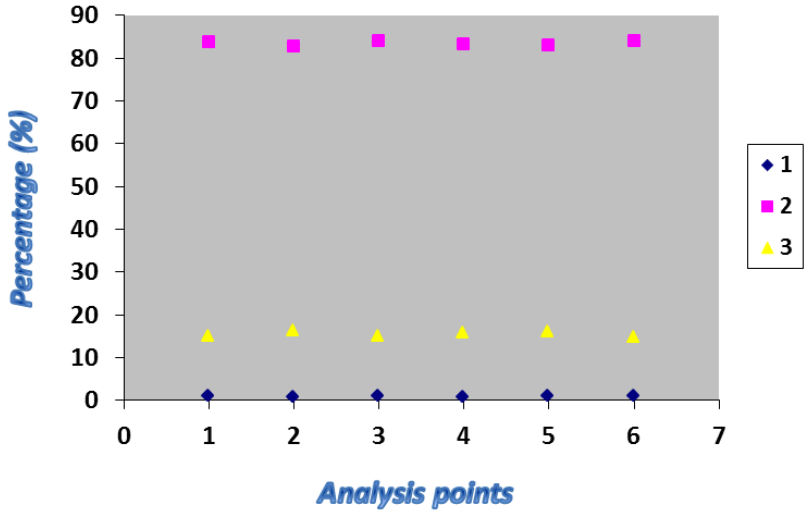


Figure 2-11. Analysis points of the long run experiment for the partial hydrogenation of ethyl nicotinate over 22.5 h.

Although this productivity was more than 25-fold the throughput obtained with the H-Cube®, I believed further process intensification was possible. Thus, the reactor column was increased to 12 mL internal volume (RC2, Figure 2-10) to accommodate a larger quantity of catalyst (13 g), and a corresponding increase in productivity was anticipated. After screening different parameters (Table 2-6) using RC2, the concentration could be increased to 0.8 M and the flow rate adjusted to 7.0 mL min^{-1} to obtain a throughput of 1219 g d^{-1}, with complete consumption of the starting material and only slightly reduced selectivity compared to the result using RC1 (run 7). The achieved WHSV (Weight Hourly Space Velocity), which denotes the quotient of the mass flow rate of the reactant divided by the mass of the catalyst in the reactor and is one of performance indices to evaluate the productivity of continuous heterogeneous catalytic reaction, was 3.91 h^{-1} (1218.95 g d^{-1}/24

h/13 g). In run 5, higher throughput was achieved, but the selectivity was lower than that in the batch reaction.

Table 2-6. Partial hydrogenation of ethyl nicotinate with Pd/Al_2O_3 using FlowCAT^{TM} reactor RC2

run	catalyst[b]	conc. of **1** (M)	flow rate (mL min^{-1})	temp.[c] (°C)	pressure (bar)	H_2 flow (L min^{-1})	ratio (%)[a]			throughput of **1** (g min^{-1})[e]
							1	**2**	**3**	
1	5% Pd/Al_2O_3	0.5	10.0	65	20	0.6	0.6	74.4	25.0	0.756 (1088.35 g d^{-1})
2	5% Pd/Al_2O_3	0.8	6.0	45	20	0.6	1.2	78.7	20.1	0.726 (1044.82 g d^{-1})
3	5% Pd/Al_2O_3	0.8	6.0	65	12	0.6	N.D.	62.9	37.1	0.726 (1044.82 g d^{-1})
4	5% Pd/Al_2O_3	0.8	6.0	65	20	0.6	N.D.	61.3	38.7	0.726 (1044.82 g d^{-1})
5	5% Pd/Al_2O_3	0.8	8.0	65	20	0.6	N.D.	69.9	30.1	0.967 (1393.09 g d^{-1})
6	5% Pd/Al_2O_3	0.8	8.0	55	20	0.4	19.2	67.5	13.3	0.967 (1393.09 g d^{-1})
7[d]	5% Pd/Al_2O_3	0.8	7.0	55	20	0.6	N.D.	75.8	24.2	0.846 (1218.95 g d^{-1})

[a]Ratios are based on crude ^{1}H-NMR data. [b]Particle size 0.10−0.25 mm.[17] [c]Temperature of the external heating jacket. [d]10 h run. [e]Throughput is calculated by the following formula: Molar concentration of feed solution (M) / 1000 x molecular weight of **1** x flow rate (mL/min)

Compound **2** was isolated in 73% yield (purity >99%) just via concentration under *vacuo*,

followed by dissolution of the material collected in CH_2Cl_2 and then washing away the byproduct **3** with a citric acid 10% solution.[13] The reaction was run for 10 h under the optimized conditions, processing 507 g of starting material (run 7). Additionally, negligible leaching of the Pd catalyst (below 9.5 ppb) was detected by inductively coupled plasma-mass spectrometry (ICP-MS) analyses.

During the course of the optimization study to determine the reaction condition, I felt that what seems to be lacking is a systematic and efficient optimization method. The topic will be examined in chapter 4.

2-4. Full hydrogenation of ethyl nicotinate

2-4-1. Background

A metal catalyzed saturation of pyridine rings is a well-known approach for piperidine core formation in pharmaceutical compounds.[18] However, it generally requires unfavorable reaction conditions for process chemistry, such as high temperature, elevated hydrogen pressure, long reaction time and the use of unfavorable solvents. In fact, full hydrogenation of ethyl nicotinate with a heterogeneous catalyst has been conducted using acetic acid (AcOH) as solvent in batch processes.[19] Even in flow reaction, Kappe and co-workers reported that "full hydrogenation of ethyl nicotinate to **3** was unsuccessful using the EtOH and Pd/C conditions" and the transformation was conducted using Pt/C and AcOH as solvent at 100°C

to provide 92% of the final ethylpiperidine 3-carboxylate (**3**).[13] Nevertheless, the use of Pt/C would be more expensive on scale than a Pd catalyst, and also AcOH is not a preferred solvent for larger scale reactions.[20] In this case, **3** was isolated by concentration of AcOH to dryness due to the solubility of **3** in water, and it is an unrealistic procedure at large scale.

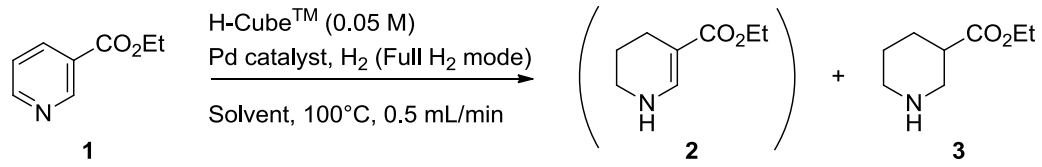
This section describes a process intensification study for full hydrogenation of ethyl nicotinate using practical conditions and favorable solvents for process chemistry.

2-4-2. Results and discussion

I started screening different solvents and catalysts in the H-Cube® apparatus using the available catalyst cartridges (Table 2-7). The use of H-Cube® is useful for the rapid screening of catalysts due to the easy exchangeability of the pre-packed catalyst cartridge.

The results of solvent screening with 10% Pd/C show that ethyl acetate (AcOEt) gave the best conversion (run 4). Interestingly, I found that 10% Pd/Al_2O_3 gave almost full conversion to the desired product **3**, with very good selectivity and no byproduct observed (run 5).

Table 2-7. Solvent and catalyst optimization study for the full hydrogenation of ethyl nicotinate **1** with Pd catalyst cartridges using the H-Cube® apparatus

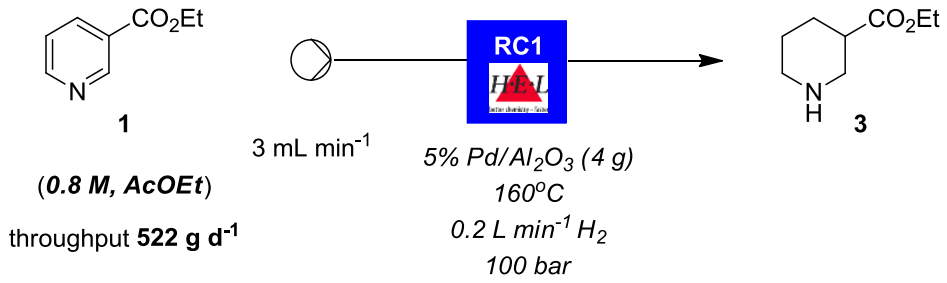


run[a]	catalyst (CatCart®)	solvent	ratio (%)[b]		
			1	**2**	**3**
1	10% Pd/C	EtOH	N.D.	39.4	60.4
2	10% Pd/C	THF	N.D.	32.4	67.6
3	10% Pd/C	toluene	N.D.	41.7	58.3
4	10% Pd/C	AcOEt	N.D.	30.6	69.4
5	10% Pd/Al_2O_3	AcOEt	N.D.	9.3	90.7

[a]Conditions: 0.05 M feed solution, full hydrogenation mode, 100°C, 0.5 mL min^{-1}.
[b]Ratios are based on crude ^{1}H-NMR data.

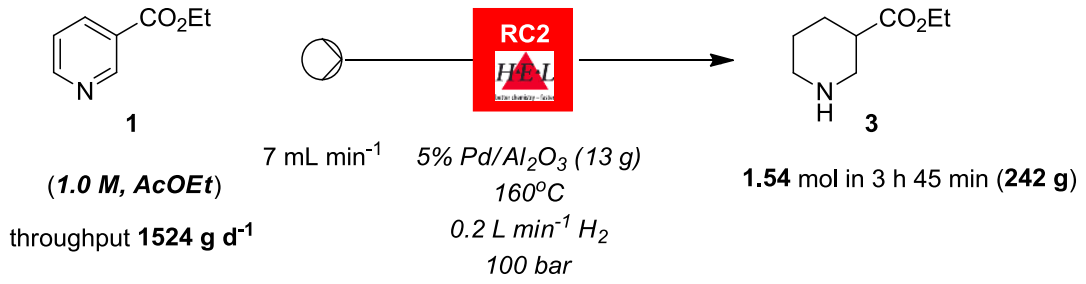
The hydrogenation process was then transferred to the FlowCAT™ platform using the RC1 trickle bed reactor. Given the results obtained with Pd/Al_2O_3[17] as catalyst in the section 2-3-2, I decided to use this material to perform the full hydrogenation. After just a few experiments, it was easily found that by running the reaction at 100 bar hydrogen pressure, 160°C and 3 mL min^{-1}, with a hydrogen feed equating to 0.2 L min^{-1} and a 0.8 M AcOEt solution of **1**, I could obtain pure product **3** free from partially hydrogenated by-product **2**. This system successfully delivered a throughput of 522 g d^{-1} of compound **3** (Scheme 2-4).

Scheme 2-4. Full hydrogenation of ethyl nicotinate with Pd/Al_2O_3 using FlowCAT™ reactor (RC1)



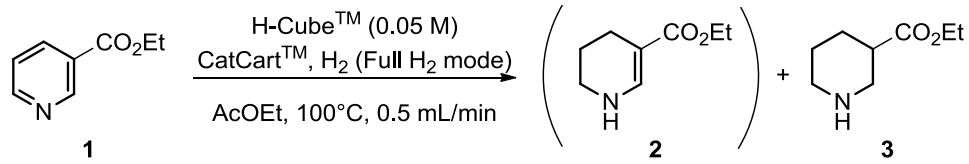
During further process intensification studies, it was anticipated that the use of the larger reactor RC2 should be able to increase the throughput to >1000 g d^{-1}. Accordingly, with the 12 mL reactor (RC2), a productivity of 1524 g d^{-1} (WHSV 4.88 h^{-1}) was achieved, using a 1.0 M solution of the starting material. In one long run experiment a quantity of 242 g (isolated yield 99%, purity >99%) of material was collected over just 3 h and 45 min, simply *via* removal of AcOEt by concentration (Scheme 2-5). As in many other fixed bed reactor processes, here the use of continuous flow offers huge advantages from the viewpoint of process chemistry, as it enables the removal of troublesome operations (*i.e.* filtration of catalyst, washing procedure).

Scheme 2-5. Full hydrogenation of ethyl nicotinate with Pd/Al_2O_3 using FlowCAT™ reactor (RC2)



Nonetheless, I wanted to check the suitability of the system for higher productivity. After a more careful screening of different catalysts, I realized that the use of a 0.05 M solution of **1** in AcOEt gave almost fully hydrogenated product with Rh/Al_2O_3 catalyst, using the H-Cube® platform (Table 2-8, run 3).

Table 2-8. Catalyst screening study for the full hydrogenation of ethyl nicotinate **1** using the H-Cube® apparatus



run[a]	catalyst (CatCart®)	solvent	ratio (%)[b]		
			1	**2**	**3**
1	5% Pd/Al_2O_3	AcOEt	N.D.	46.5	53.5
2	5% Pt/Al_2O_3	AcOEt	5.4	32.8	61.8
3	5% Rh/Al_2O_3	AcOEt	N.D.	1.5	98.5
4	5% Ru/Al_2O_3	AcOEt	100	N.D.	N.D.

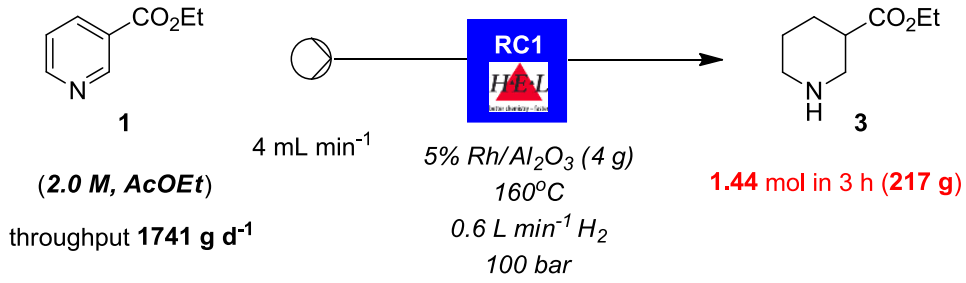
[a]Conditions: 0.05 M AcOEt solution, full hydrogenation mode, 100°C, 0.5 mL min^{-1}.
[b]Ratios are based on crude ^{1}H-NMR data.

The use of the FlowCAT™ system with RC1 and Rh/Al_2O_3[21] catalyst gave an outstanding 1741 g d^{-1} throughput (WHSV 18.14 h^{-1}), which was seen as a genuine improvement over previously reported procedures (Scheme 2-6a). Beyond that, it was found that the system was

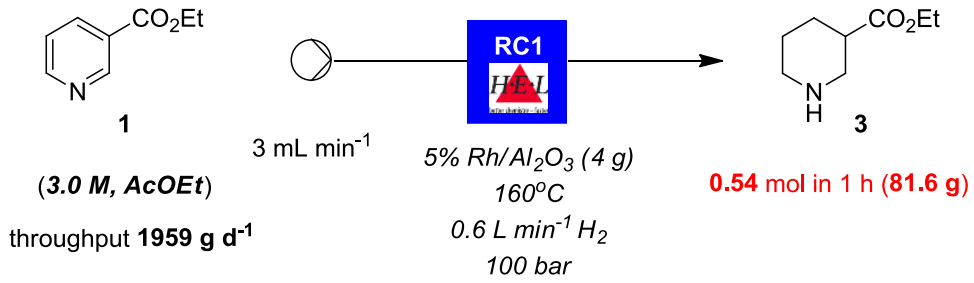
able to tolerate even higher concentrations of starting material, as a 3 M solution of ethyl nicotinate was successfully processed (Scheme 2-6b).

Scheme 2-6. (a and b) Full hydrogenation of ethyl nicotinate with Rh/Al_2O_3 using FlowCAT™ reactor (RC1)

a)



b)



Under the optimized conditions, I was able to continuously produce 81.6 g of material in just 1 h (99% purity), and the total amount of material processed over five different experiments was 530 g using the same catalyst bed (overall 6.5 h) without any degradation of the catalyst, which equates to 1959 g d^{-1} throughput (WHSV 20.41 h^{-1}) of material. An examination to the gas stoichiometry for Scheme 2-6b shows that the ratio of hydrogen to substrate is represented as follows:

[(0.6 L min^{-1})/22.4 L mol^{-1})]/[(3.0 mol L^{-1}) (0.003 L min^{-1})]

= 2.98 mol H /mol ethyl nicotinate

This calculation suggests that I am working at the current limit of the gas feed to the RC1.[22]

Pleasingly, ICP-MS analyses showed that leaching of Rh catalysts is very low with all values detected below 10 ppb.

2-5. Consideration on catalyst reactivity

It may be helpful to consider catalyst surface area for understanding of catalyst activity in the reactions (Table 2-9, Table 2-10, Figure 2-12, Figure 2-13). Regarding the Pd catalyst, 5% Pd/Al_2O_3 with the finest particle size showed the highest reactivity for hydrogenation of ethyl nicotinate (Table 2-9), however, it doesn't directly relate to the surface area (Table 2-10).

Table 2-9. Comparison of granule catalysts for higher throughput partial hydrogenation reaction of ethyl nicotinate[a]

run	Pd catalyst	conc. of **1** (M)	flow rate (mL min^{-1})	temp. (˚C)	ratio (%)[b]			throughput of **1** (g day^{-1})[c]
					1	**2**	**3**	
1	a	0.05	4.0	60	1.1	78.8	20.1	43.2
2	b	0.05	4.0	60	1.8	78.4	19.8	43.2
3	c	0.2	3.0	60	2.4	86.5	11.1	131.0
4	d	0.4	3.0	60	0.9	84.0	15.1	260.6

[a]Representative data from Table 2-3 and 2-4. [b]Ratios are based on crude ^{1}H-NMR data. [c]Throughput is calculated by the following formula: Molar concentration of feed solution (M) / 1000 x molecular weight of **1** x flow rate (mL/min) x 60 (min) x 24 (h)

Table 2-10. Surface area (BET method) information for the catalysts provided by Johnson & Matthey

Catalyst	Particle size (mm)	Surface area (m^2 g^{-1})
10% Pd/C (a)	0.4–0.8	1250
5% Pd/C (b)	0.3–0.85	1050
5% Pd/Al_2O_3 (c)	0.25–0.5	110
5% Pd/Al_2O_3 (d)	0.1–0.25	200
5% Rh/Al_2O_3 (a)	0.02–0.1	950
5% Rh/Al_2O_3 (b)	0.3–0.8	110

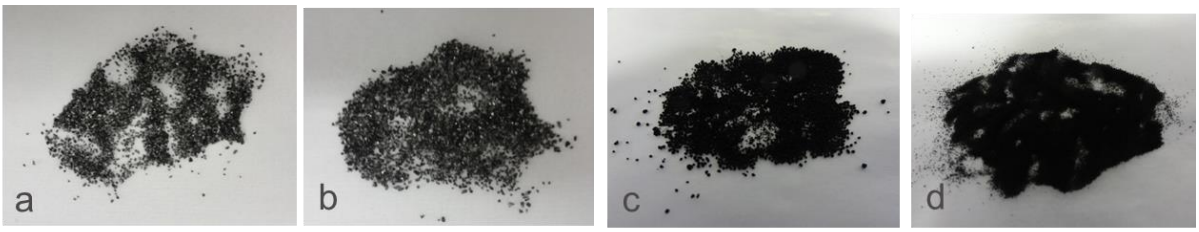


Figure 2-12. Photographs of granule Pd catalysts
a) 10% Pd/C, particle size: 0.4–0.8 mm; b) 5% Pd/C, particle size: 0.3–0.85 mm;
c) 5% Pd/Al_2O_3, particle size: 0.25–0.5 mm; d) 5% Pd/Al_2O_3, particle size: 0.1–0.25 mm.

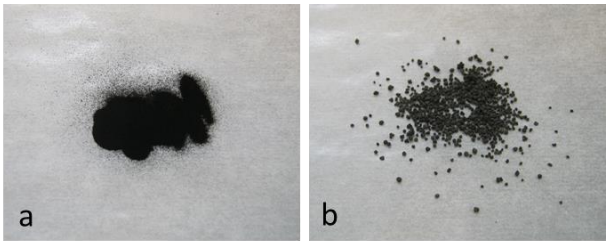


Figure 2-13. Photographs of granule Rh catalysts
a) 5% Rh/Al_2O_3, particle size: 0.02–0.1 mm; b) 5% Rh/Al_2O_3, particle size 0.30-0.80 mm.

In fact, Pd/C catalysts, which showed lower reactivity in the reaction, have much larger surface area than do the Pd/Al_2O_3 catalysts. Although I could not compare the effect of catalyst support using catalysts with the same metal loading and particle size due to their unavailability for the study, it is speculated that the specific properties of Al_2O_3 support are responsible for the increased reactivity over carbon support according to the results shown in Table 2-7 (run 4 and 5).

To get more understanding on the reactivity of the catalyst in a trickle bed reactor, further chemical (*e.g.* dispersion of metal, interaction between catalyst support and compounds) and chemical engineering (*e.g.* hydrodynamics of gas and liquid on the catalyst) approaches are inevitably required. However, it is too complicated to be examined in detail here and it will be a future task in this field.

2-6. Conclusion (Chapter 2)

In conclusion, I reported a study on a specific process intensification program for hydrogenation reactions (partial and full hydrogenation of ethyl nicotinate) that can be carried out in a research laboratory environment. The use of flow technologies allowed for easy and safe operating at high pressure and temperature, which enabled the use of high substrate concentrations and high flow rates. H-Cube® was useful for rapid solvent and catalyst screening of the reaction, due to the pre-packed catalyst cartridge system, but it was not suitable for laboratory process intensification due to engineering constraints, such as the

limitations in the hydrogen flow rate and the size of the catalyst cartridges. On the other hand, FlowCAT^{TM} is equipped with a larger column reactor (3 or 12 mL) and is more flexible (*e.g.* hydrogen flow rate, packing method of catalyst). Appropriate selection of catalyst particle size and use of trickle flow with FlowCAT^{TM}, leads to high reactivity due to increased contact surface area among the gas, liquid and catalyst, which enables higher productivity. Under the agreements of the laboratory safety protocols (University of Cambridge), the process achieved a throughput of 1219 g d^{-1} (WHSV: 3.91 h^{-1}) for the partial hydrogenation, whereas the productivity for the full hydrogenation process reached 1959 g d^{-1} (WHSV: 20.41 h^{-1}) of throughput from a benchtop reactor, FlowCAT^{TM}.

These results represent significant process intensification examples of hydrogenation reactions in a research laboratory and will be benchmarks in this field.

2-7. References

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(15) The catalyst was kindly provided by Johnson & Matthey (particle size 0.30−0.85 mm, product code 110002CPS10-20/lot. M14058), website: http://www.matthey.com/ (accessed August 13, 2016).

(16) The catalyst was kindly provided by Johnson & Matthey (particle size 0.25−0.50 mm, product code 110002APR5-10/lot. M14040), website: http://www.matthey.com/ (accessed August 13, 2016).

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(21) The catalyst used in the trickle bed reactor was a mixture (Rh_A and Rh_B, 1:1, w/w) of two different sizes of Rh/Al_2O_3 materials kindly provided by Johnson & Matthey (Rh_A particle size 0.02−0.10 mm, product code 110002 CPR 10−20 / lot. DJZ0052 and Rh_B particle size 0.30−0.80 mm, 110003APO5-10 / lot. M14102), website: http://www.matthey.com/ (accessed August 13, 2016).

(22) A gas feed set at 0.6 L min^{-1} produced a gas flow which oscillated in the range of 0.675−0.599 L min^{-1}.

2-8. Experimental

General experimental section

^{1}H-NMR spectra were recorded on a Bruker Avance DPX-400 spectrometer with the

residual solvent peak as the internal reference ($CHCl_3$ = 7.26 ppm). ^{13}C-NMR spectra were recorded on the same spectrometers with the central resonance of the solvent peak as the internal reference ($CDCl_3$ = 77.16 ppm). The multiplicity of ^{1}H signals are indicated as: s = singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublets, t = triplet, q = quadruplet, m = multiplet, br. = broad, or combinations of thereof. Coupling constants (*J*) are quoted in Hz and reported to the nearest 0.1 Hz. Where appropriate, averages of the signals from peaks displaying multiplicity were used to calculate the value of the coupling constant. Infrared spectra were recorded neat on a PerkinElmer Spectrum One FT-IR spectrometer using Universal ATR sampling accessories. Unless stated otherwise, reagents were obtained from commercial sources and used without purification. The removal of solvent under reduced pressure was carried out on a standard rotary evaporator. The solvent and catalyst screening for full hydrogenation reaction of ethyl nicotinate was carried out using an H-Cube®.[5] The optimized flow reactions for scale-up studies were performed using a FlowCAT™.[7] Inductively Coupled Plasma-Mass Spectrometry (ICP-MS) analyses were conducted by Dr. Jason Day (Department of Earth Sciences, University of Cambridge) using a Perkin Elmer Elan DRCII quadrupole based inductively coupled plasma-mass spectrometer. Chameleon technology and Polar Bear Plus were used for the batch mode partial hydrogenation.[12]

*Synthesis of 1,4,5,6-tetrahydropyridine-3-carboxylate (**2**).*[10]

RC1: A solution of ethyl nicotinate in EtOH (0.4 M) was continuously passed through a trickle bed reactor (flow rate 3.0 mL min^{-1}), packed with 2.6 g of 5% Pd/Al_2O_3,[17] heated at 60°C (temperature of column reactor inside). The pressure of the system was set at 20 bar and the H_2 feed was set at 0.2 L min^{-1}. The reaction output was concentrated *in vacuo*. The crude material was dissolved in CH_2Cl_2 (10 mL per g) and washed with a citric acid solution (10%). The organic layer was concentrated *in vacuo* to afford **2** in excellent yield;

RC2: A solution of ethyl nicotinate in EtOH (0.8 M) was continuously passed through a trickle bed reactor (flow rate 7.0 mL min^{-1}), packed with 13 g of 5% Pd/Al_2O_3,[17] heated at 55°C (temperature of the jacket). The pressure of the system was set at 20 bar and the H_2 feed was set at 0.6 L min^{-1}. The reaction output was concentrated *in vacuo*. The crude material was dissolved in CH_2Cl_2 (10 mL per g) and washed with a citric acid solution (10%). The organic layer was concentrated *in vacuo* to afford **2** in excellent yield.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.43 (1H, d, *J* = 6.2 Hz), 4.36 (1H, s broad), 4.08 (2H, q, *J* = 7.0 Hz), 3.19 (2H, m), 2.32 (2H, t, *J* = 6.2 Hz), 1.77 (2H, q, *J* = 6.2 Hz), 1.21 (3H, t, *J* = 7.0 Hz); **^{13}C-NMR (100 MHz, $CDCl_3$)**: δ = 168.86, 142.89, 95.24, 58.84, 40.68, 20.95, 20.60, 14.61; **FT-IR (neat, cm^{-1})**: υ 3340, 2933, 2852, 1656, 1599, 1510, 1446, 1395, 1351, 1298, 1223, 1190, 1169, 1093, 1073, 1050, 943, 880, 763.

*Synthesis of (±)piperidine-3-carboxylate (**3**).*[13,19]

RC1: A solution of ethyl nicotinate in AcOEt (3 M) was continuously passed through a trickle bed reactor (flow rate 3.0 mL min^{-1}), packed with 4 g of 5% Rh/Al_2O_3,[21] heated at 160°C (temperature of the jacket). The pressure of the system was set at 100 bar and the H_2 feed was set at 0.6 L min^{-1}. The reaction output was concentrated *in vacuo* to afford **3** in excellent yield;

RC2: A solution of ethyl nicotinate in AcOEt (1 M) was continuously passed through a trickle bed reactor (flow rate 7.0 mL min^{-1}), packed with 13 g of 5% Pd/Al_2O_3,[17] heated at 160°C (temperature of the jacket). The pressure of the system was set at 100 bar and the H_2 feed was set at 0.6 L min^{-1}. The reaction output was concentrated *in vacuo* to afford **3** in excellent yield.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.09 (2H, q, J = 7.3 Hz), 3.10 (1H, dd, J_1 = 12.4 Hz, J_2 = 3.7 Hz), 2.89 (1H, dt, J_1 = 12.4 Hz, J_2 = 4.0 Hz), 2.75 (1H, dd, J_1 = 12.4 Hz, J_2 = 9.2 Hz), 2.60 (1H, ddd, J_1 = 12.4 Hz, J_2 = 10.5 Hz, J_3 = 2.9 Hz,), 2.39 (1H, m), 1.96 (1H, m), 1.62 (2H, m), 1.42 (1H, m), 1.21 (3H, t, J = 7.3 Hz); **^{13}C-NMR (100 MHz, $CDCl_3$)**: δ = 174.34, 60.18, 48.52, 46.35, 42.46, 27.33, 25.48, 14.17; **FT-IR (neat, cm^{-1})**: υ 3334, 2936, 2854, 2812, 1723, 1445, 1371, 1311, 1177, 1136, 1120, 1027, 937, 855, 749.

Partial hydrogenation with Chameleon technology/Polar Bear Plus (Batch experiment)

The Cambridge Reactor Design (CRD) Chameleon technology is a small volume, multi-vessel unit, which, depending on the configuration, may be used in either batch or continuous mode. The system has been designed to fit the Polar Bear Plus allowing experiments to be performed at temperatures between -40°C and +150°C with precise temperature control for high-pressure liquid, gas-liquid and gas-liquid-solid reactions (Figure 2-14).

Figure 2-14. Chameleon technology and Polar Bear Plus.

In batch, a total of four reactors can be connected individually. The reactor volume for the platform used is 20 mL (Figure 2-15). The system is equipped with a gas manifold and a portable gas reservoir (burette) assembly for gas-liquid reactions. The Polar Bear Plus hot and cold plate is a flexible plate designed to accurately deliver a range of hot and cold

temperatures. It has a compact and portable footprint not much bigger than a standard hotplate stirrer and unlike conventional -40°C circulators; the Polar Bear Plus can be easily relocated in and out of the fume cupboard.

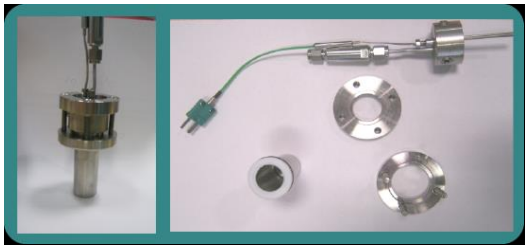
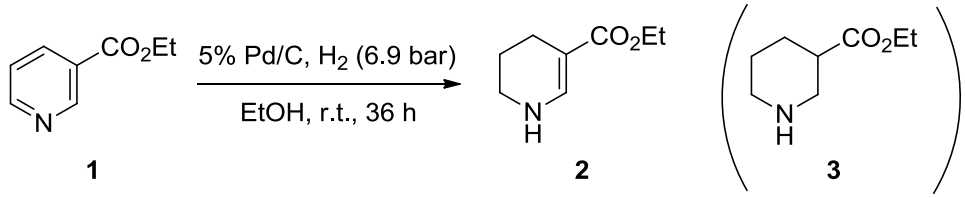


Figure 2-15. Stainless-steel reactor used for the batch mode partial hydrogenation.



Scheme 2-7. Partial hydrogenation of ethyl nicotinate using the Chameleon technology reactor

General procedure

A solution of ethyl nicotinate (1.5 g, 10 mmol) in 5 mL of EtOH was hydrogenated with 50 mg of 5% Pd/C catalyst (Scheme 2-8). The reaction was performed at room temperature, 7 bar hydrogen pressure and stirred at 1000 rpm for 38 hours. The hydrogen pressure was maintained constant throughout the whole experiment. The solution was then filtered through celite and the filtrate was concentrated *in vacuo*. ^{1}H-NMR analysis of the crude mixture showed 85% conversion (**2** vs **3** ratio around 7:1).

FlowCAT™ software safety operation

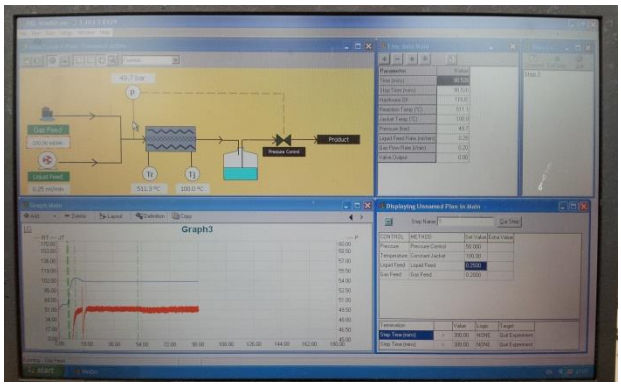


Figure 2-16. Software interface for the WinISO software.

FlowCAT™ uses the WinISO software that allows for full operating protocols to be written and edited on the fly (Figure 2-16). All data is logged from the system at a user defined interval and can be displayed live in a user defined graphical format. In addition to hardware safety protection on the system, WinISO has three additional levels of safety built in. Firstly, hardware safety limits are defined in the software and are not user editable, which means that a user cannot program a value outside of the safety limits and if a fault (*e.g.* blockage, a temperature or pressure rise above the limits of the system) occurs, the system will immediately shut down. Secondly, the user can define a number of safety limits for a given experiment, and each limit will trigger a different user defined safety state (*e.g.* a warning or an instruction to stop feeding or stop heating). Thirdly, a user can define additional safety limits, which apply only to a single step of a given experiment.

Packing procedures for RC1 and RC2 (Partial/Full hydrogenation)

Column packing is a crucial procedure. In order to reduce events such as insufficient mixing or preferential channelling, glass beads (Glass beads acid-washed 0.212–0.300 mm available from Sigma-Aldrich) were used with Pd catalysts (Figure 2-12, a-d) or Rh catalysts (Figure 2-13, a-b) in the packing of either **RC1** or **RC2** reactors (Figure 2-10). A moderate amount of glass beads should be added before and after the catalyst bed in a column reactor (Figure 2-17). In addition, before starting reaction, the column reactor packed with glass beads and catalyst should be tapped several times and pressurized by gas to make a dense packing without unnecessary void spaces.

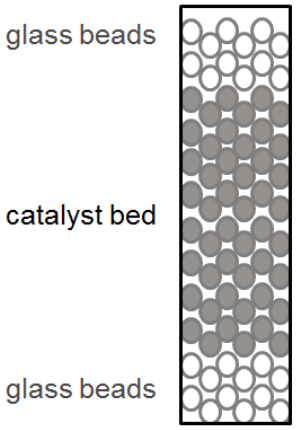
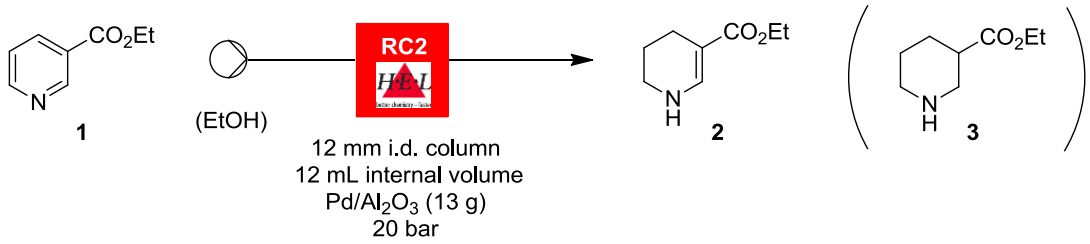
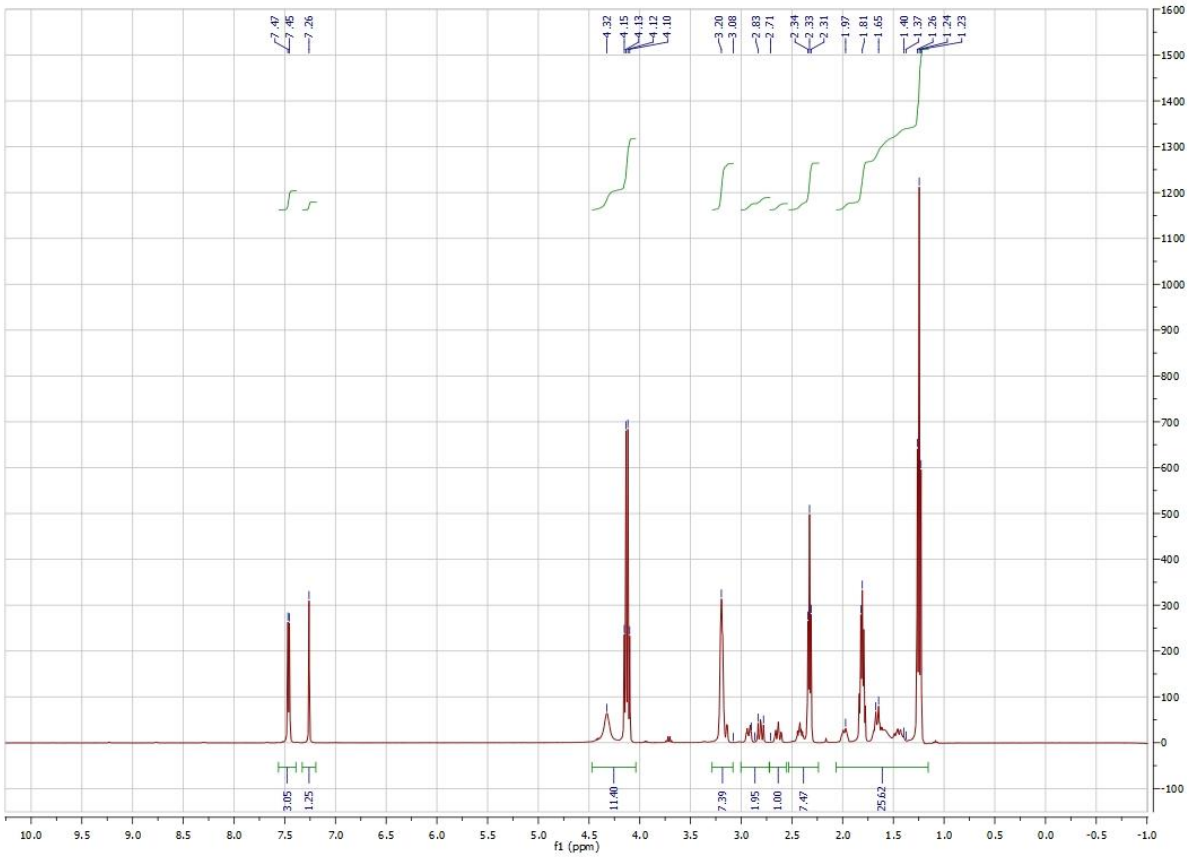
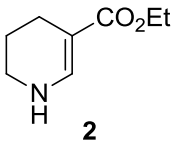


Figure 2-17. Packing method for column reactor

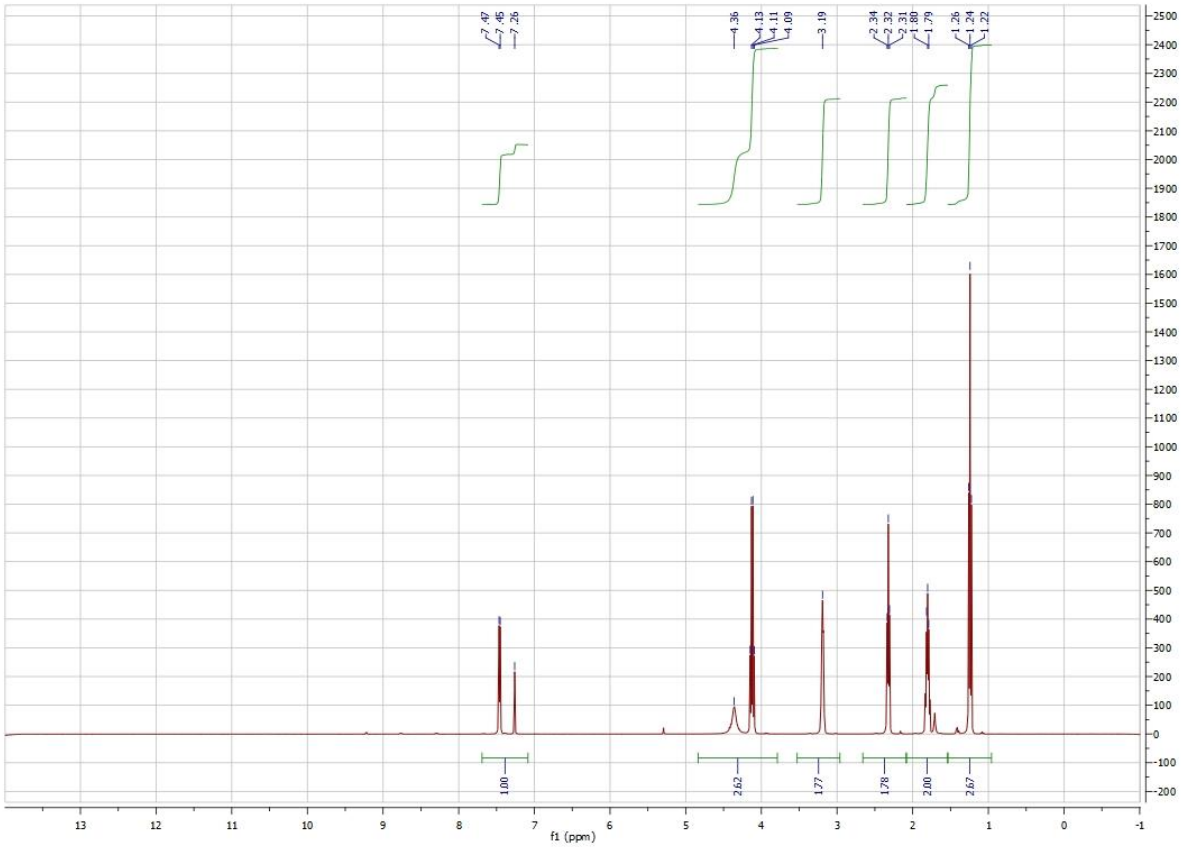
^{1}H- and ^{13}C-NMR data






CO2Et
N
H

2


7.47
7.45
7.26
4.36
4.13
4.11
4.09
3.19
2.34
2.32
2.31
1.80
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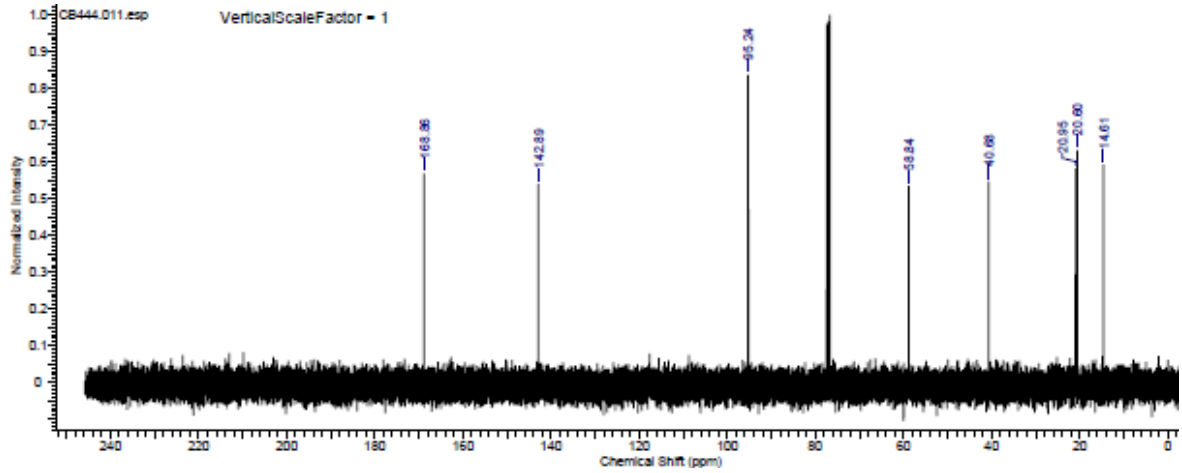
1.77
1.78
2.00
2.67
f1 (ppm)


CB444.011.esp
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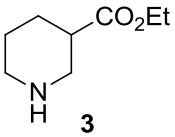
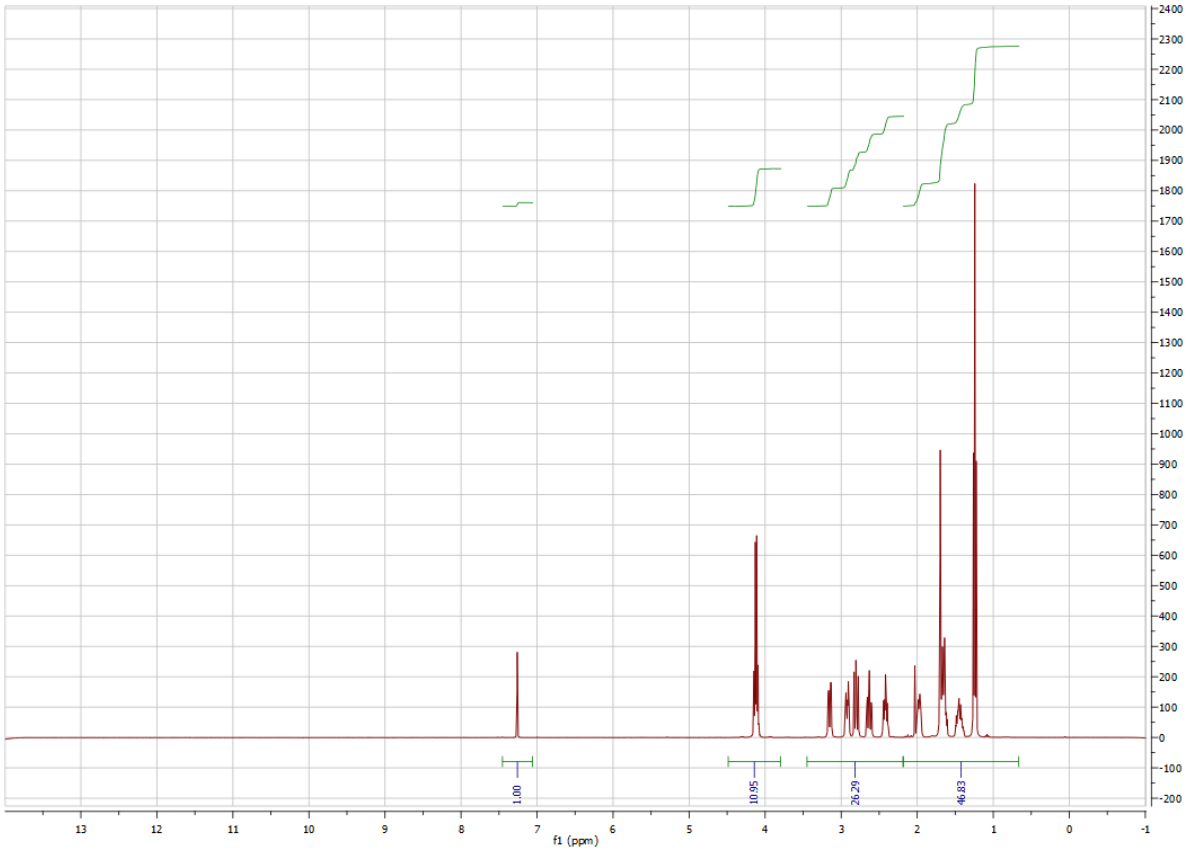
95.24
59.84
40.68
20.95
20.60
14.61
Normalized Intensity
Chemical Shift (ppm)


CO2Et
N
H

3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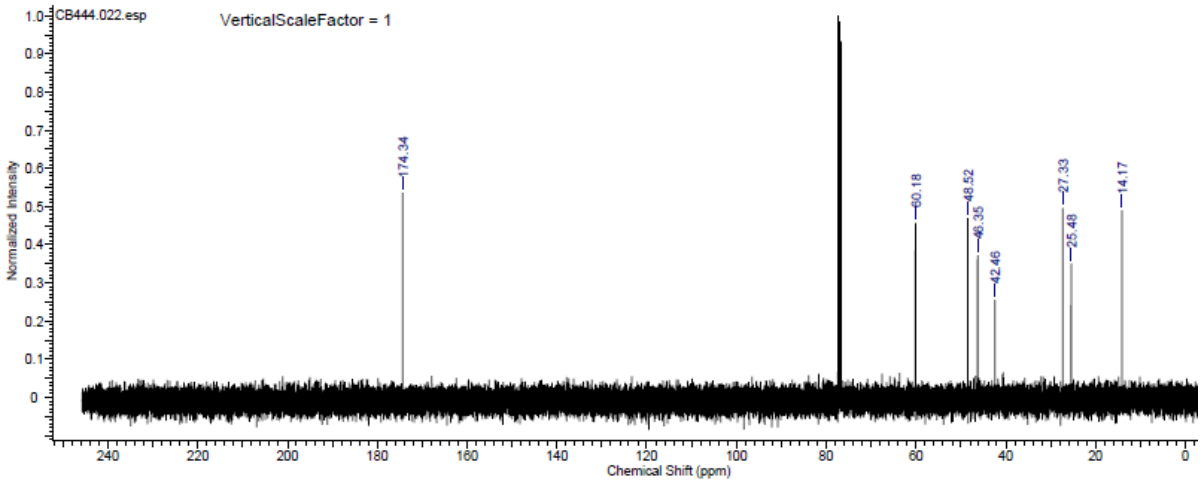
10.95
26.29
46.83
f1 (ppm)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Normalized Intensity
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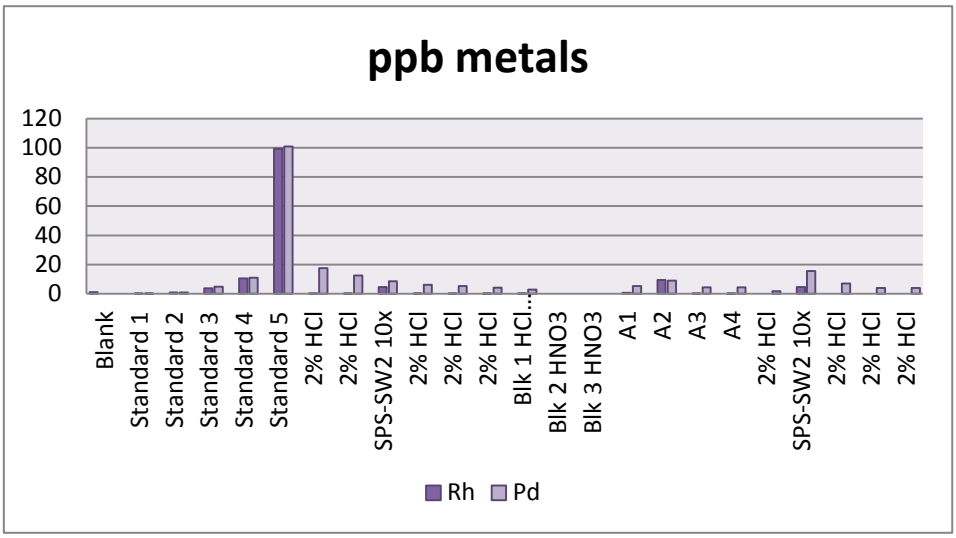
60.18
48.52
46.35
42.46
27.33
25.48
14.17
Chemical Shift (ppm)

ICP analysis

Samples A1-A4 are from this study.



The results show that the residual metals in all analyzed samples (A1-A4) were less than 10 ppb.

Chapter 3

Solvent-free continuous operations using small footprint reactors

3-1. Introduction

Increasingly, there are demands placed on chemical manufacture, particularly arising from enhanced environmental awareness. The green agenda is evolving and correspondingly the industry is changing its approach in terms of planning and execution of chemical processes.

Recently, attempts to incorporate enabling technologies into chemical synthesis have been increasing.[1] In particular, the idea of using small footprint reactor platforms to perform intensive and repetitive tasks represents a very important area of development. This research indeed defines the starting point for intensifying chemical transformations, an essential strategy for future chemical manufacturing processes.

The "process intensification" strategy can be achieved first by using small footprint units for the production of large amounts of material. Second, process intensification can be attained through a reduction in the number of downstream operations, involving liquid separations, purifications, resolution, *etc*. The reduction of downstream operations has very important implications in reducing production timeframes, increasing productivity and reducing the overall process cost. For instance, if a process is set to reduce the quantities of solvents and water required for workup, a clear consequence is that there will be less waste to

process and thus less impact with improved E-factor or PMI (process mass intensity).

As a matter of fact, solvents are the biggest mass contributor to the processes in the manufacture of pharmaceuticals. It is said that solvent use for pharmaceutical batch chemical operation accounts for between 80 and 90% (30% water/60% organic solvents) of the total mass utilization in the process and the amount of waste generated from solvents used in a synthetic processing for an API ranges from 25 to more than 100 kg of solvent per kilogram of API produced.[2,3] Table 3-1 displays the top 20 chemical wastes generated by the pharmaceutical and medicinal/botanical sectors in 2006 from the United States Environmental Protection Agency (EPA) Toxic Release Inventory (TRI) data. It clearly shows that solvents accounted for a large portion of the overall TRI releases.

Waste treatment can be quite costly and there is no doubt that generation of waste is unfavorable, both environmentally and economically. In addition, solvent use can account for 60% of the energy used, which does not include the solvent manufacturing, in the in-process.[2]

Many chemists have focused on designing greener and high yielding reactions. However, it is necessary to keep in mind that the amount of solvent used in the downstream operations is often much greater than that used in the reaction.

As a consequence, the ability to optimize and minimize downstream operations becomes an attractive strategy, especially if all downstream processing could be avoided.

Table 3-1. Top 20 chemical wastes generated by the pharmaceuticals and medicinal/botanical sectors according to the United States EPA TRI in 2006.[2]

Rank	Chemical	Amount generated (10^6 kg $year^{-1}$)
1	Methanol	44.8
2	Dichloromethane	22.3
3	Toluene	12.1
4	Acetonitrile	7.90
5	Hydrochloric acid	7.03
6	Nitrate compounds	5.21
7	Chloroform	3.71
8	*n*-Hexane	2.99
9	*n*-Butyl alcohol	2.86
10	*N, N*-dimethylformamide	2.79
11	Formic acid	2.42
12	*N*-Methyl-2-pyrrolidone	2.02
13	Xylene (mixed isomers)	1.47
14	Arsenic compounds	1.26
15	1,1,2-Trichloroethane	1.23
16	Methyl *tert*-butyl ether	1.20
17	Ammonia	1.01
18	Ethylene glycol	0.82
19	Sulfuric acid	0.71
20	Certain glycol ethers	0.63
Total (top 20 in 2006)		124
Total (for all TRI chemicals)		128

A considerable number of studies have been carried out on solvent-free reactions.[4] They allow high productivity per unit time by accelerating reaction rate and improving volumetric efficiency in such high concentration reaction conditions, in addition to cost advantages for solvent purchase, waste treatment and recycling. Thus, there are some clear benefits in conducting solvent-free reactions, however, those will be minimized in most cases where solvents or complicated operations are necessary for downstream operations after reaction.[5]

One of the disadvantages for solvent-free reactions is that the limited heat capacity without solvent can make temperature control difficult. It makes some reactions under solvent-free conditions too violent or dangerous to use, one of them being the hydrogenation reaction, which is inherently exothermic. Thus, this is an area that continuous flow technologies can be beneficial.

With respect to the downstream operations for heterogeneous hydrogenation in batch processing, filtration of the catalyst and washing the catalyst are inevitably required and these unit operations are difficult to be removed in solvent-free reactions. On the other hand, solvent-free continuous hydrogenation with a packed catalyst bed reactor enables end-to-end production without any downstream operations (Figure 3-1).

Here I report the application of this specific approach, solvent-free process without downstream operations, in order to demonstrate its impact in a laboratory environment.

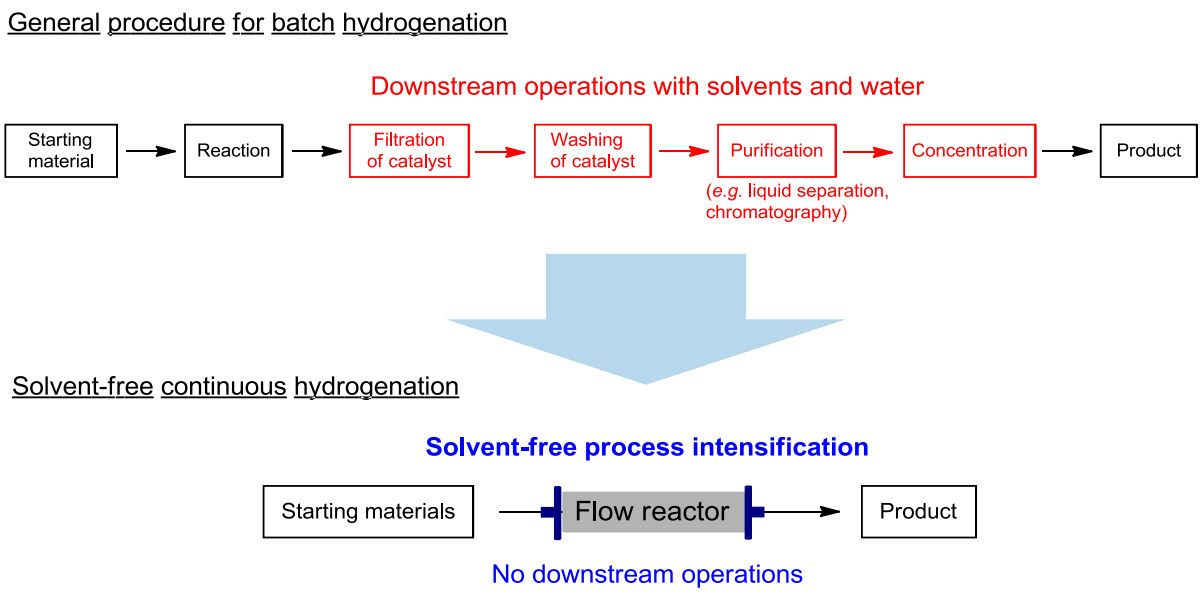


Figure 3-1. Solvent-free process intensification for hydrogenation reactions

3-2. Solvent-free full hydrogenation of ethyl nicotinate

I have reported on the initial intensification of a laboratory process for the partial and full hydrogenation of ethyl nicotinate, using heterogeneous metal catalyzed hydrogenation, in order to achieve a specific high throughput of material (Chapter 2).

To deliver suitable results, I made use of the FlowCAT^{TM}, a small footprint, robust trickle bed reactor that can manage high pressure and high temperature reactions.[6]

To achieve my new goal of removing the need for any downstream processing following a reaction stage, I decided to challenge the system still further.

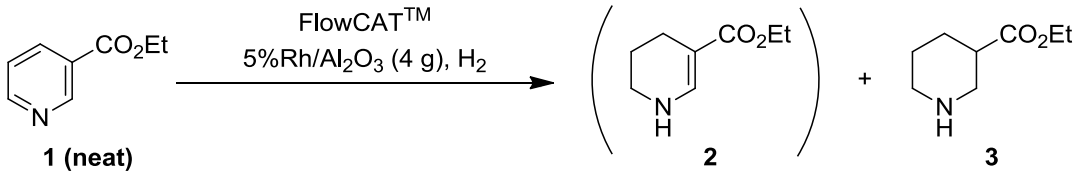
A first set of experiments was therefore conducted to verify the feasibility of a reaction where ethyl nicotinate (**1**) could be delivered without solvent (neat) into the reactor system, where it would be fully hydrogenated to the ethyl piperidin-3-carboxylic acid ester (**3**). I

quickly noticed full hydrogenation was possible and consequently decided to optimize the process. Following initial screening with various conditions, it was found that running the reaction neat with a liquid feed of 0.5 mL min^{-1} and temperature of 140°C resulted in 97% conversion, with a ratio 3:1 of fully/partially hydrogenated material being observed, using 5% Rh/Al_2O_3 as catalyst[7] (run 1, Table 3-2).

I continued these optimization efforts, identifying conditions that led ultimately to almost complete hydrogenation of starting material to the product **3** (around 1% of partially hydrogenated compound was present in the reaction mixture). These conditions (180°C, 0.4 mL min^{-1}, using 4 g of 5% Rh/Al_2O_3) allowed us to develop a robust protocol that could be applied in the laboratory on a multigram scale (run 4).

Indeed, with these conditions in hand, on running the reaction for 1 h, it was possible to isolate 26.7 g of product with a purity of ≥99% (Scheme 3-1), and no downstream processing. I was very pleased to note that under these conditions the throughput of the process would equate to 638 g d^{-1} (WHSV 6.64 h^{-1}), providing the catalyst remained productive.[8]

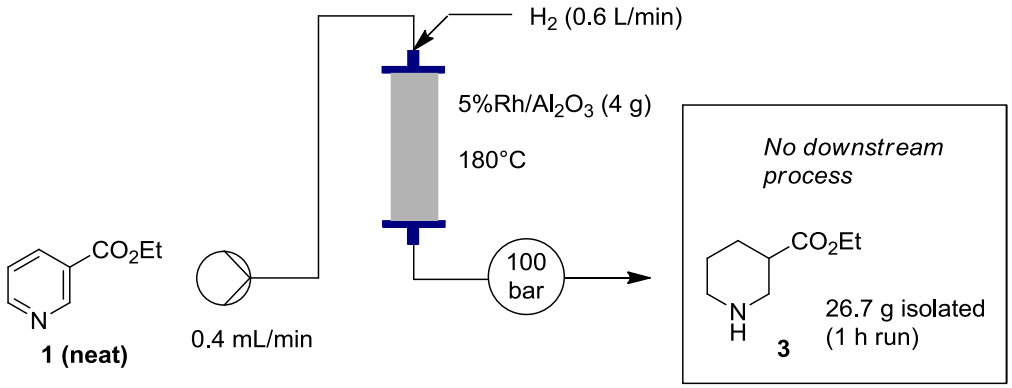
Table 3-2. Full hydrogenation of ethyl nicotinate with Rh/Al_2O_3 using FlowCAT™ under solvent-free conditions



run	flow rate (mL min^{-1})	temp. (°C)	pressure (bar)	H_2 flow (L min^{-1})	ratio (%)[a]		
					1	**2**	**3**
1	0.5	140	100	0.3	3.0	24.3	72.6
2	0.5	160	100	0.4	1.8	10.5	87.7
3	0.5	180	100	0.4	1.2	4.0	94.8
4[b]	0.4	180	100	0.4	N.D.	0.8	99.2

[a]Ratios are based on crude ^{1}H-NMR data. [b]1 h run.

Scheme 3-1. Ultimate process intensification for the full hydrogenation of **1** to **3** under solvent-free conditions



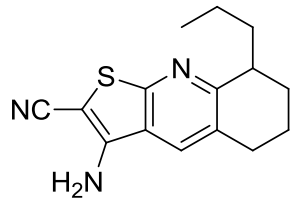
3-3. Two-step continuous ultimate intensified process

3-3-1. Background

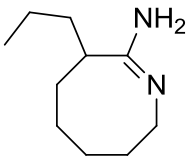
One major benefit of continuous flow processing is the ability to telescope reaction sequences, whereby the output from one reactor is transferred directly into the inlet of the next step (usually passing through one or two downstream processing steps). Under intensification principles, the novel process windows would allow for significant cost savings, increased efficiencies and again reduced environmental impact for the transformations.

Although other groups have reported synthesis under solvent-free (neat) flow conditions,[9,10] it seems that there was a lack of general knowledge and literature regarding the use of small footprint platforms to perform these continuous solvent-free operations, especially on a larger laboratory scale. Accordingly, a sequence of steps under these telescoped flow conditions was selected to highlight opportunities of these methods.

Generation of 2-propyl phenol (**6**) used in the flavor and fragrance industry[11] and 2-propyl cyclohexanone (**7**), which is used as a building block for drug candidate compounds (Figure 3-2),[12-14] on a kilogram-scale were chosen as valuable targets (Scheme 3-2). The transformation process consists of two discrete reactions, namely a Claisen rearrangement[15] followed by a hydrogenation step, starting from a cheap and available feedstock material, allyl phenyl ether (**4**).



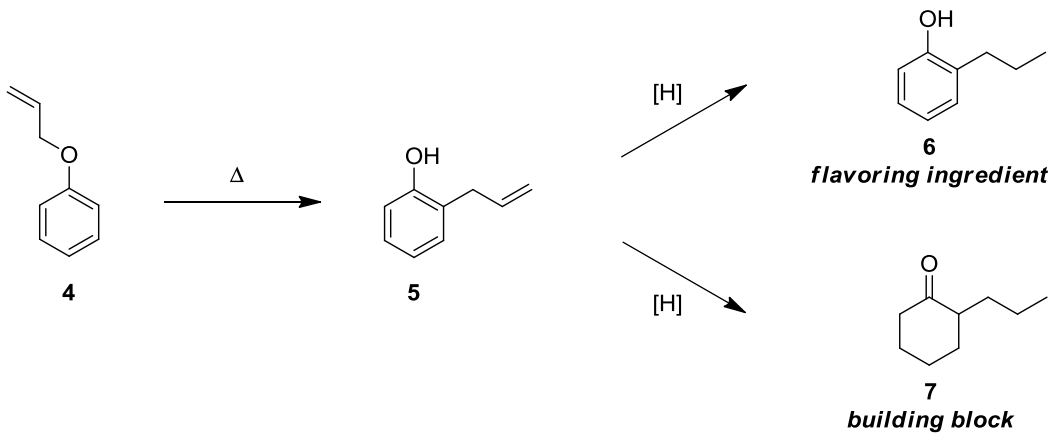
A candidate for inhibiting ksp kinesin activity[12]



A candidate for nitric oxide synthase inhibitors[13]

Figure 3-2. Examples of drug candidate compounds derived from 2-propyl cyclohexanone (**7**)

Scheme 3-2. Envisaged strategy to showcase a two-step fully intensified protocol for the synthesis of target compounds **6** and **7**



3-3-2. Results and discussion

To deliver the first step under intensified conditions, a new powerful, small footprint commercially available reactor was selected in order to process material at very high temperatures and pressures. The Phoenix reactor™ (ThalesNano) allows researchers to conduct reactions within underutilized chemical processing windows (Figure 3-3).[16] Thus the Phoenix reactor™ allows for reactions to be performed between room temperature and 400°C.

Within the central core of the heating elements, different reaction vessels of various size and function can be accommodated. The reaction vessels of 1 and 2 mL can either be used on their own or packed with solid reagents, whereas lengths of 1/16" stainless steel tubing can be coiled around a central column to give a range of known volume reactors that offer a high degree of thermal transfer, allowing for faster flow rates and thus shorter residence times to be used. In this study, a stainless steel tubing reactor was used for an intensified Claisen rearrangement reaction.

Figure 3-3. Phoenix reactor™ (ThalesNano).

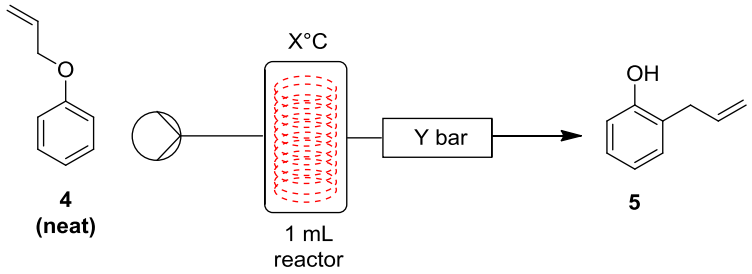
A set of predetermined experiments quickly identified optimum conditions (Table 3-3), affording an impressive 60 g h^{-1} throughput with just 1 min residence time at 320°C and 100 bar of system pressure (run 5).

The level of intensification was satisfactory for this individual process. However, further intensification studies of the process were explored by increasing the reactor capacity, with the hope that the system would respond linearly.

To achieve this, the 1 mL reactor was substituted for an 8 mL reaction coil. Pleasingly, the

linear increase of the liquid feed (from 1 to 8 mL min^{-1}) afforded the same level of conversion and isolated yield for the product, giving a significant 480 g h^{-1} throughput of material being processed, with 240 g of product being produced after just a 30 min run.

Table 3-3. Intensified Claisen rearrangement for **5** using Phoenix reactor™



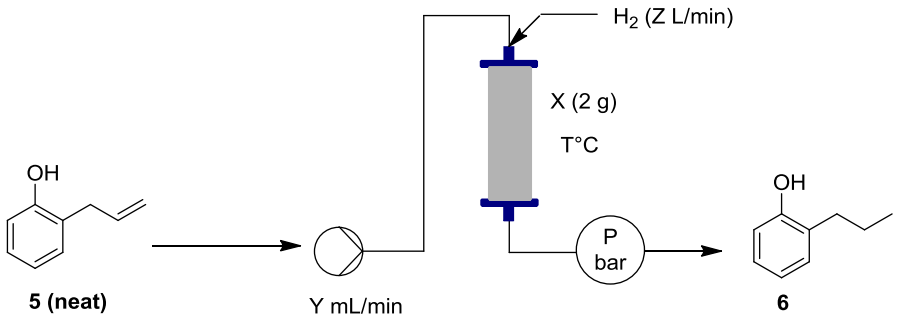
run	residence time (min.)	temperature (X˚C)	pressure (Y bar)	yield[a] (%)
1	2	200	50	1.0
2	2	200	100	1.0
3	2	250	50	5.2
4	1	300	100	69.4
5	1	320	100	94.0

[a]Yields are based on crude ^{1}H-NMR data.

Having quickly intensified the conditions for the Claisen step, the selective hydrogenation of **5** to **6** was focused on. Again, my knowledge in the field of continuous heterogeneous hydrogenation allowed me to generate a table of relevant experiments (Table 3-4), leading to

suitable conditions for selective hydrogenation.

Table 3-4. Neat hydrogenation of **5** to **6** under intensified conditions



run	pressure (bar)	temp. (˚C)	X (catalyst)	Y (mL/min)	Z (L/min)	yield[a] (%)	productivity (g h^{-1})
1	10	80	10% Pd/C	1	0.4	97.4	
2	15	80	10% Pd/C	1	0.4	97.5	
3	**20**	**80**	**10% Pd/C**	**1**	**0.4**	**98.0**	**60 (WHSV: 30.84 h^{-1})[b]**
4	20	100	10% Pd/C	1	0.4	83.8	
5	30	160	10% Pd/C	3	0.6	74.3	
6	20	120	20% Pd/C	1	0.4	72.0	
7	**20**	**120**	**20% Pd/C**	**2**	**0.4**	**94.0**	**120 (WHSV: 61.68 h^{-1})[b]**
8	20	140	20% Pd/C	3	0.4	60.0	

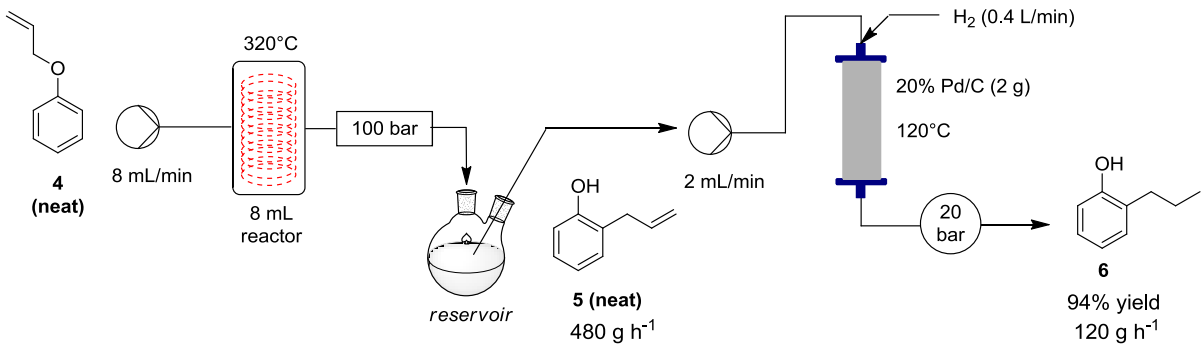
[a]Yields are based on crude ^{1}H-NMR data. [b]Calculated by the following formula: density of **5** (1.028 g/mL) x flow rate (Y mL/min) x 60 min / catalyst amount (2 g)

At a temperature of 80°C, liquid feed of 1 mL min^{-1} (H_2 feed of 0.4 L min^{-1}), and using 10% Pd/C[17] as catalyst (2 g), phenol **5** was hydrogenated to **6** with quantitative conversion and 98% yield (run 3). When the pressure and temperature were increased to achieve higher throughput, the yield decreased due to an over-reduction reaction (run 5).

As another approach to intensify the hydrogenation and increase the productivity of the process, 10% Pd/C was replaced with the higher loading 20% Pd/C.[18] Using this catalyst, a productivity to 120 g h^{-1} (WHSV: 61.68 h^{-1}) was achieved, to give 80 g of **6** in 40 min, while maintaining a very good level of efficiency (≥94% product purity) (run 7).

To prove the concept of telescoping under neat and intensified conditions, the experiments in a sequence were carried out, producing around 100 g of **6** in just 50 min. In this case, the system was adapted in order to start collecting **5** while simultaneously processing it through the next step. This process performance produced **6** in 94% yield (Scheme 3-3).

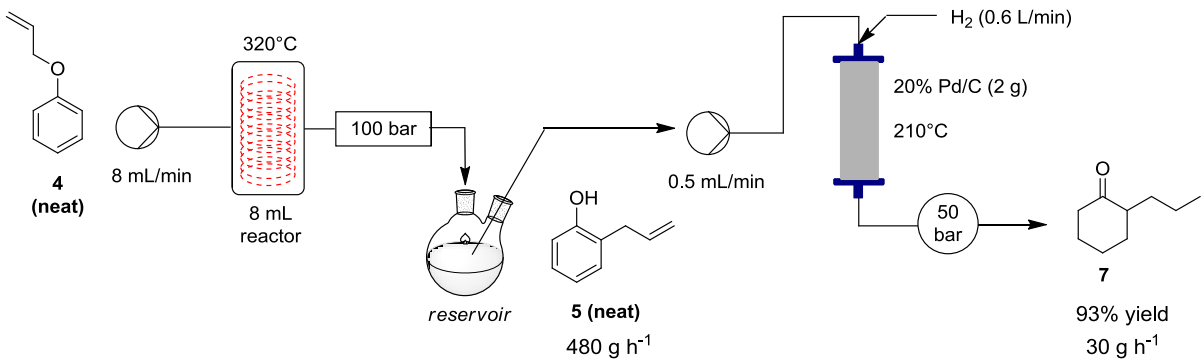
Scheme 3-3. Telescoped intensified Claisen rearrangement and hydrogenation to **6**



Further studies were continued to highlight the flexibility of the platform and the concept. Indeed, the optimum conditions were identified for the selective hydrogenation of **5** to **7** (Scheme 3-4) and then telescoped with the previously mentioned Claisen rearrangement step. The first set of reaction conditions gave me the important information that the solvent-free reaction to produce **7** was mainly dependent on temperature. To maintain a suitable throughput of material, 20% Pd/C[18] is preferred as well as a temperature of 210°C. Under these conditions, compound **7** was obtained with a productivity of 30 g h^{-1} (93% yield).

Similarly to what was reported for the partial hydrogenation of **5**, an attempt for the telescoped synthesis of **7** starting from **4** was investigated. Under these operating circumstances, a production for several grams of **7** (21.9 g for 45 min) was accomplished reliably and with acceptable levels of purity (≥95%, Scheme 3-4).

Scheme 3-4. Telescoped intensified Claisen rearrangement followed by full hydrogenation to **7**



3-4. Conclusion (Chapter 3)

Simple but powerful examples of process intensification under solvent-free conditions for continuous single and telescoped flow operations have been demonstrated. In both cases, it was possible to extend the capabilities of commercially available, small footprint flow reactors. Such an approach in an appropriate environment could lead to significant cost savings and increases in efficiency, which are the goals of process chemistry. These end-to-end productions without any downstream operation are good demonstration studies for an ideal form of manufacturing.

3-5. References

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3-6. Experimental

General experimental section

^{1}H-NMR spectra were recorded on a Bruker Avance DPX-400, DRX-500 Cryo or DRX-600 spectrometer with the residual solvent peak as the internal reference ($CHCl_3$ = 7.26 ppm). ^{13}C-NMR spectra were recorded on the same spectrometers with the central resonance of the solvent peak as the internal reference ($CDCl_3$ = 77.16 ppm). The multiplicity of 1H signals are indicated as: s = singlet, d = doublet, t = triplet, m = multiplet, br. = broad, or combinations of thereof. Coupling constants (*J*) are quoted in Hz and reported to the nearest 0.1 Hz. Where appropriate, averages of the signals from peaks displaying multiplicity were used to calculate the value of the coupling constant.

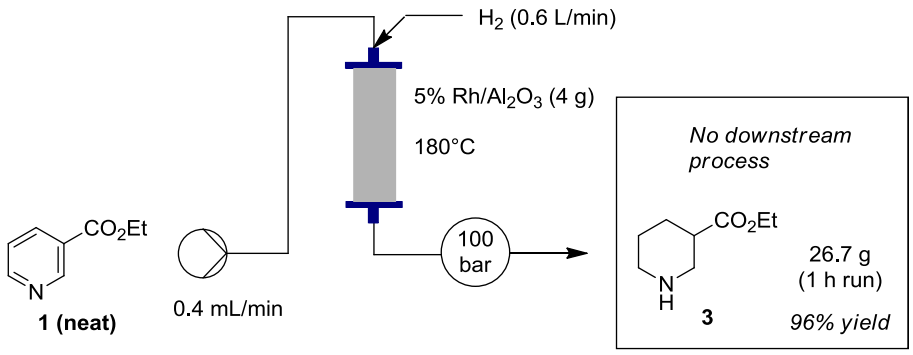
All the flow reactions were performed using the Phoenix platform[16] or HEL FlowCAT^{TM}.[6]

Unless stated otherwise, reagents were obtained from commercial sources and used without purification.

Neat hydrogenation of ethyl nicotinate (1) to ethyl piperidine-3-carboxylate (3)[19]

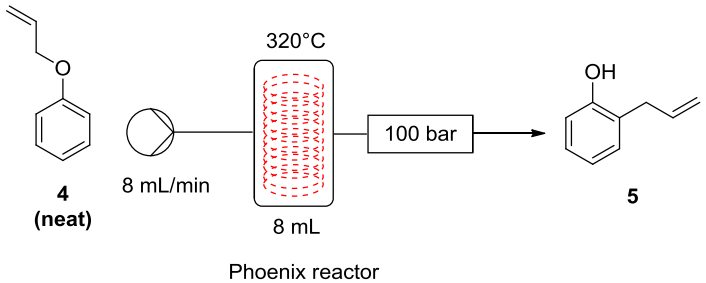
Ethyl nicotinate (neat) was continuously passed through a trickle bed reactor (flow rate 0.4 mL min^{-1}), packed with 4 g of 5% Rh/Al_2O_3,[7] heated to 180°C. The pressure of the system

was set to 100 bar and the H_2 feed was set to 0.6 L min^{-1}. The reactor output was collected in a flask continuously for 1 h to give 26.7 g of product (96% yield). No further downstream processing operation was required.



Neat Claisen rearrangement of phenyl allyl ether (4) to 2-allyl phenol (5)[15]

Allyl phenyl ether (**4**) was continuously pumped (neat) through the Phoenix reactor™ (equipped with 8 mL stainless steel coil reactor) at a flow rate of 8.0 mL min^{-1} and a temperature of 320°C (system pressure was maintained at 100 bar). 2-Allyl phenol (**5**) was obtained in excellent yield (94% purity) without any need for further downstream processing.

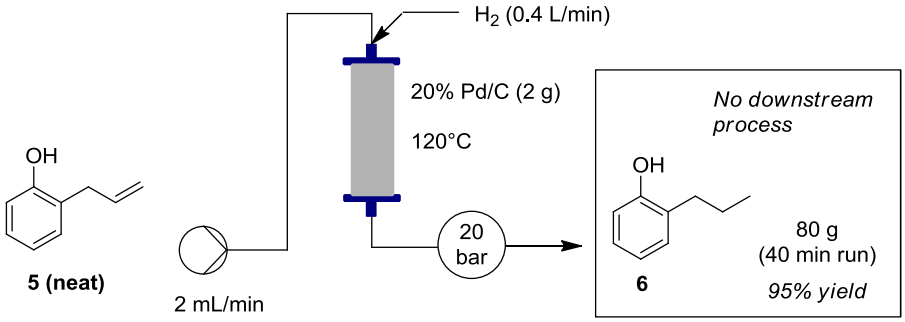


^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.18 (t, *J* = 8.0 Hz, 2H), 6.95 (t, *J* = 7.4 Hz, 1H), 6.86 (d, *J* = 7.9 Hz,1H), 6.11 – 6.04 (m, 1H), 5.21 (t, *J* = 8.0 Hz, 3H), 3.47 (d, *J* = 6.5 Hz, 2H).

^{13}C-NMR (151 MHz, $CDCl_3$) δ 154.04, 136.46, 130.49, 127.92, 125.45, 121.03, 116.48, 115.84, 35.07.

Neat hydrogenation of 2-allyl phenol (5) to 2-propyl phenol (6)[20]

2-Allyl phenol (**5**) was continuously passed through a trickle bed reactor (flow rate 2.0 mL min^{-1}), packed with 2 g of 20% Pd/C,[18] heated at 120°C. The pressure of the system was set at 20 bar and the H_2 feed was set at 0.4 L min^{-1}. The reactor output was collected in a flask continuously for 40 min to give 80 g of **6** (95% yield). No further downstream operation was required.

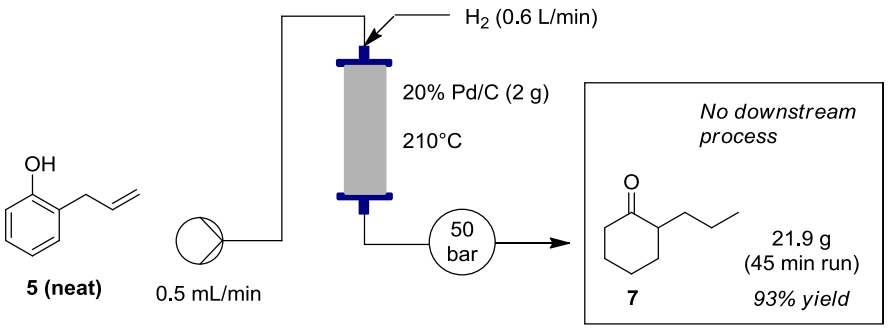


^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.17 – 7.06 (m, 2H), 6.88 (t, *J* = 7.4 Hz, 1H), 6.77 (dd, *J* = 7.9, 0.7 Hz, 1H), 5.50 (s, 1H), 2.70 – 2.53 (m, 2H), 1.78 – 1.74 (m, 2H), 1.08 (t, *J* = 7.4 Hz, 3H).

^{13}C-NMR (151 MHz, $CDCl_3$) δ 153.49, 130.37, 128.72, 127.10, 120.85, 115.39, 32.07, 23.02, 14.08.

Neat hydrogenation of 2-allyl phenol (5) to 2-propyl cyclohexanone (7) [21]

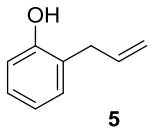
2-Allyl phenol (**5**) was continuously passed through a trickle bed reactor (flow rate 0.5 mL min^{-1}), packed with 4 g of 20% Pd/C,[18] heated at 210°C. The pressure of the system was set at 50 bar and the H_2 feed was set at 0.6 L min^{-1}. The reactor output was collected in a flask continuously for 45 min to give 21.9 g of **7** (93% yield). No further downstream operation was required.



^{1}H-NMR (600 MHz, $CDCl_3$) δ 2.43 – 2.15 (m, 3H), 2.00 (m, 2H), 1.86 –1.52 (m, 4H), 1.41 – 1.03 (m, 4H), 0.84 (t, *J* = 7.4 Hz, 3H).

^{13}C-NMR (151 MHz, $CDCl_3$) δ 213.52, 50.40, 41.86, 33.78, 31.54, 27.98, 24.73, 20.24, 14.11.

^{1}H- and ^{13}C-NMR spectra



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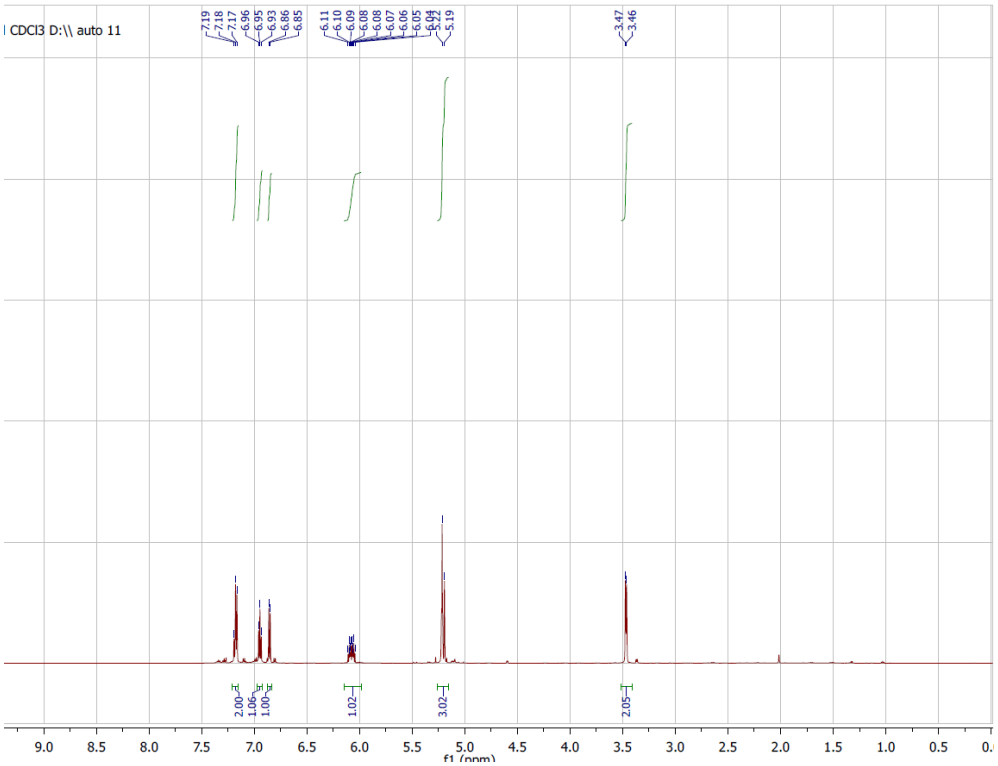

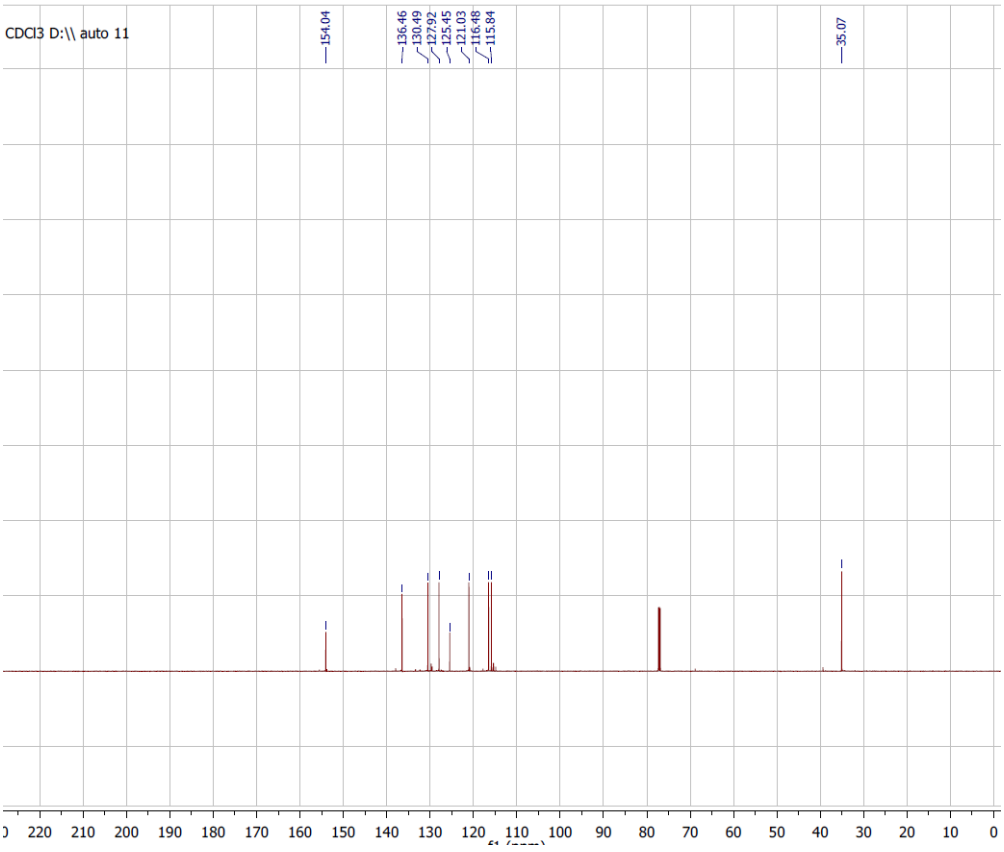

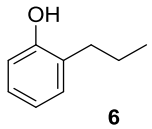
OH

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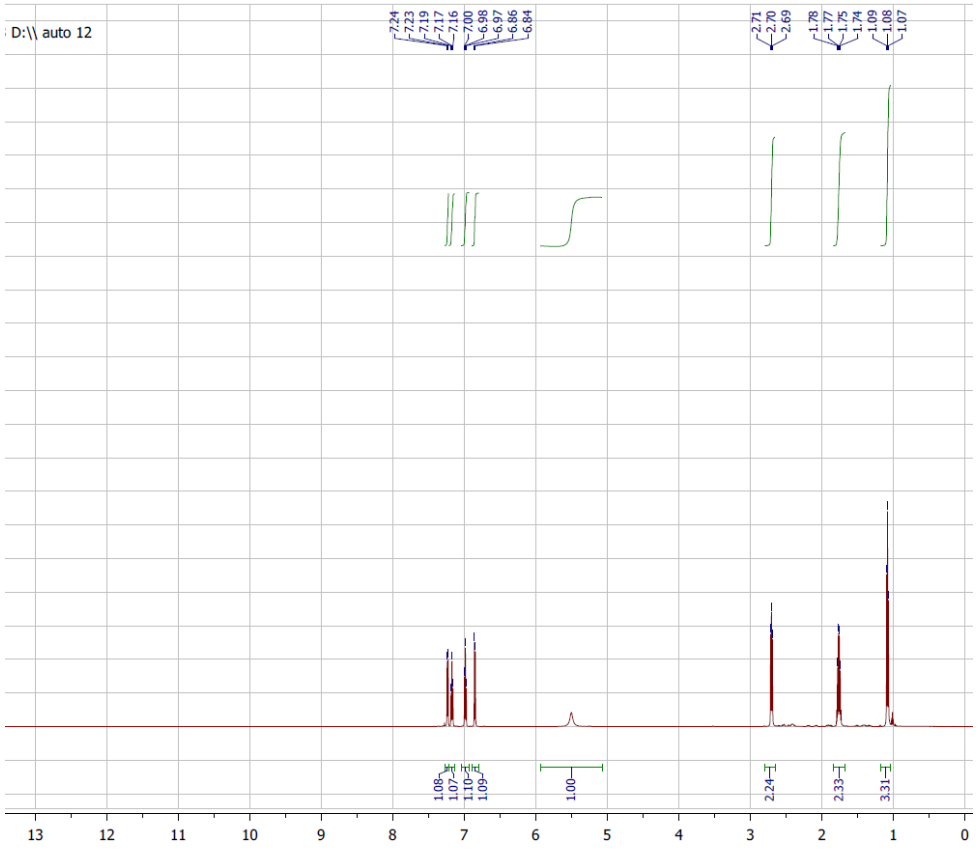
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2.69
1.78
1.77
1.75
1.74
1.09
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1.08
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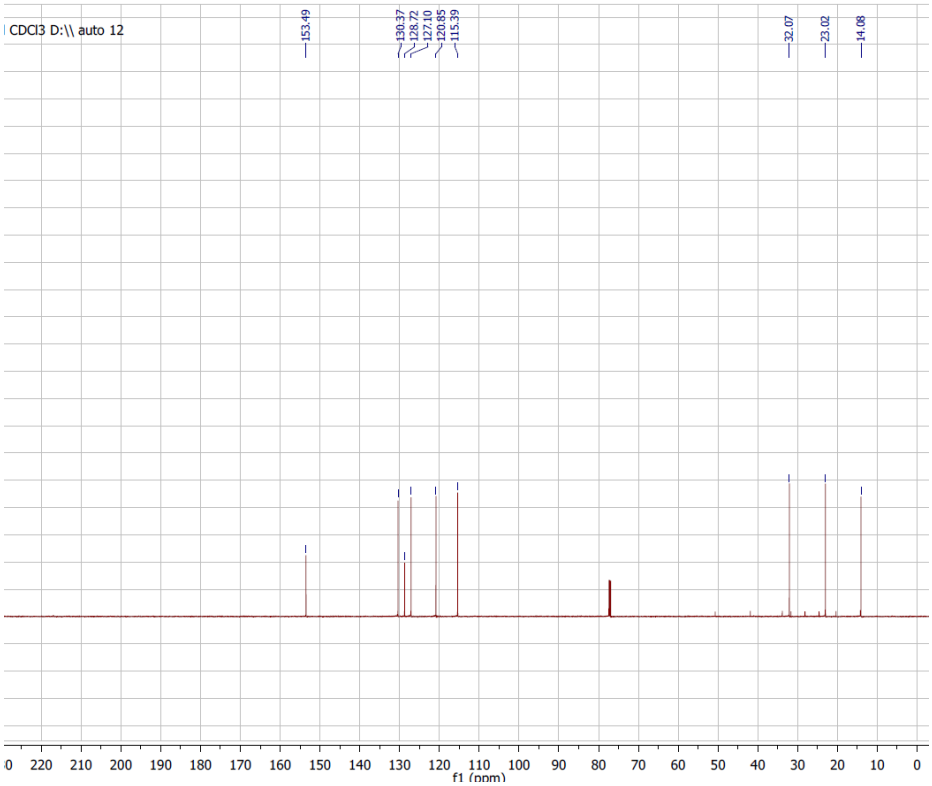
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200
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180
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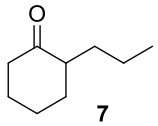
f1 (ppm)



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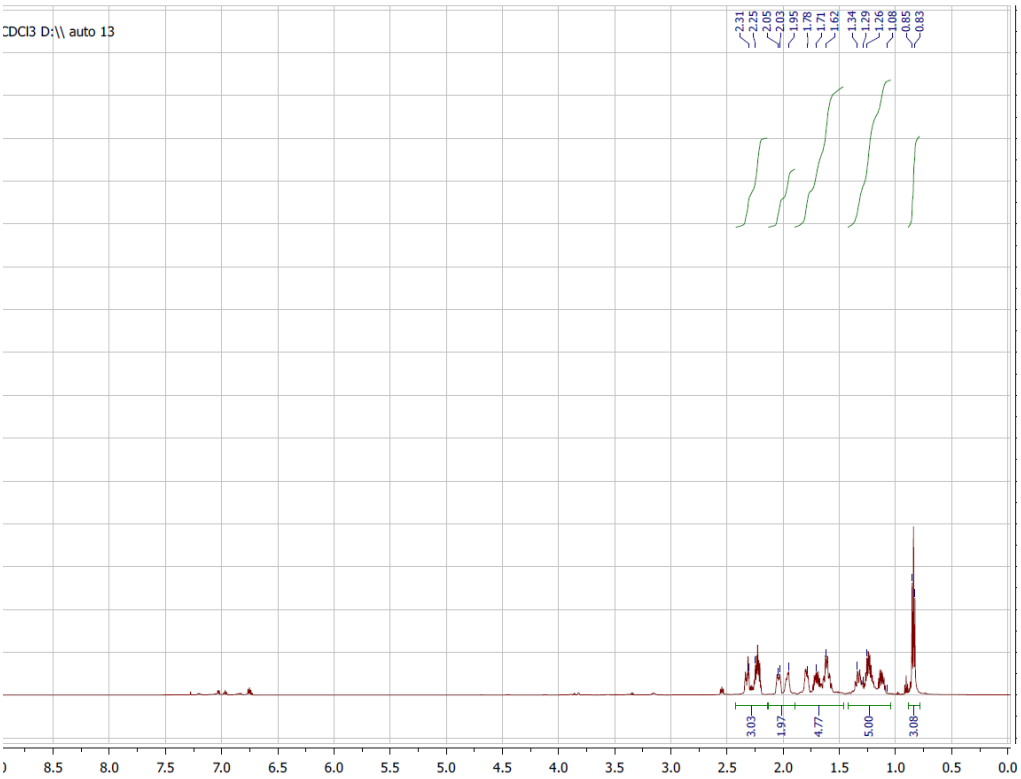
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1.08
0.85
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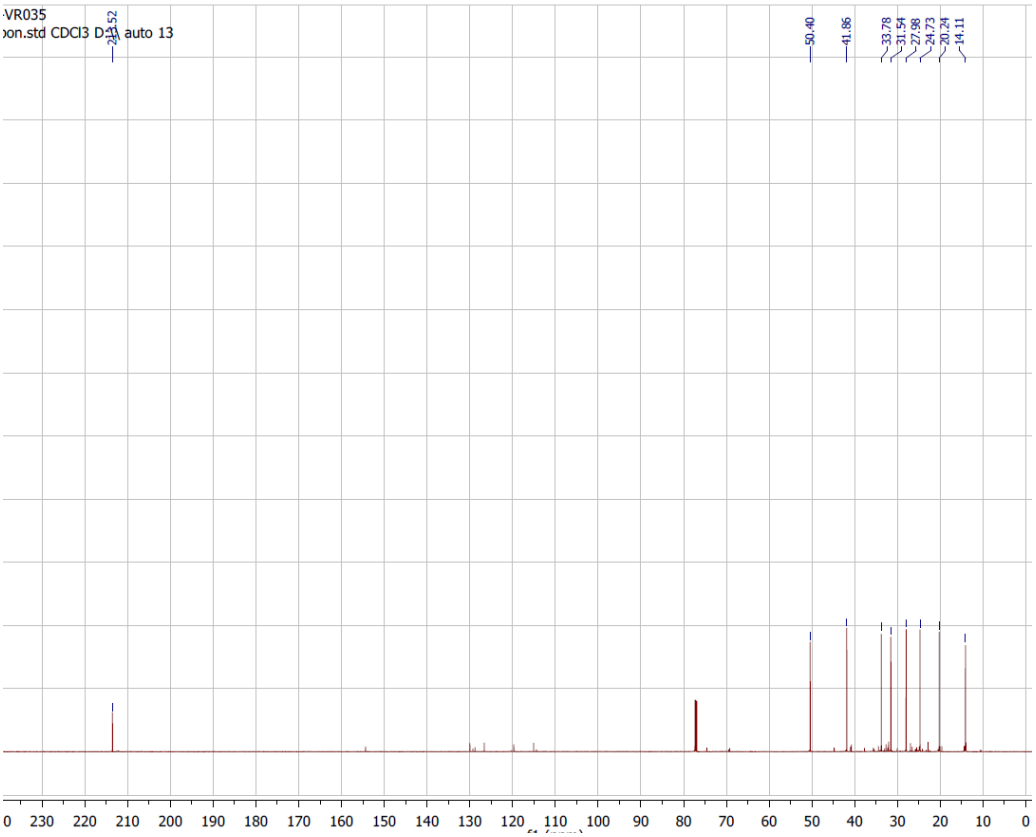
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230
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170
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140
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120
110
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40
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20
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0

Chapter 4

Utilization of PAT for rapid optimization

4-1. Introduction

Process analytical technology (PAT) is a technology for production process control and quality assurance, which is increasingly attracting attention in the pharmaceutical industry. By the United States Food and Drug Administration (FDA)'s definition, process analytical technologies are "systems that enhance process understanding and assist in identifying and controlling critical points in a process. These include appropriate measurement devices, that can be placed at/in- or on-line, statistical and information technology tools, and a scientific systems approach for data analysis to control processes to ensure production of in-process materials and final products of desired quality" [1] and are also described as "a system for designing, analyzing, and controlling manufacturing through timely measurements of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality". [2]

The application of PAT in processes can afford the following benefits:[3]

1. Process understanding and control

More robust processes with higher quality can be created through deep understanding of the chemistry and process by using PAT. The PAT tools enable unstable intermediates and active species, which are difficult to detect and analyze by off-line analysis, to be visualized

and controlled. In scale-up, processes can behave differently at laboratory, pilot and commercial scale. PAT tools can give awareness in real time to adjust the process conditions appropriately and enable smooth bridging between the different scales. In addition, PAT knowledge is helpful to identify the cause of a process failure.

2. Process development efficiency

Off-line testing and data analysis are often time-consuming. On the other hand, real time monitoring with PAT tools can give the required information faster in most cases. An increased understanding of chemical processes and analysis frequency can also accelerate process development, especially optimization studies for the process. Furthermore, technology transfer or control of changes can be conducted efficiently.

3. Manufacturing efficiency

Real time monitoring with PAT tools can shorten the production time by removing tests between the steps and reprocessing or rework of the process, and smoothly moving to the next step just after completing the process. Sampling and data analysis are also time-consuming operations in manufacturing. As an example, a break of the process conditions is necessary for sampling when the process is carried out under harsh conditions (*e.g.* high temperature, high pressure, use of hazardous gases).

4. Safety

PAT tools can minimize the number of samplings and the exposure of workers to hazardous

processes and materials. Additionally, continuous monitoring and automated systems with remote monitoring by PAT can increase process safety and labor safety. It goes without saying that deeper understanding of processes makes for safer processes.

There are a lot of commercially available PAT tools, such as thermocouples, pressure sensors, near-infrared (NIR) spectroscopy,[4] mid-infrared spectroscopy,[5,9] Raman,[6] UV,[7] NMR[8,9] and conductivity[10] and these are utilized for API processes in the pharmaceutical industry.

PAT is also a key technology for continuous processing and a considerable number of studies have been conducted on its application for continuous processes.[11] In addition to process understanding and continuous monitoring of the steady state for continuous processing, utilization of PAT for continuous processes enables rapid optimization at the development stage due to the following three reasons: firstly, reaction conditions (*e.g.* flow rate, reaction temperature and pressure) can be changed easily. Secondly, a lot of reaction conditions can be evaluated continuously. Thirdly, smaller amounts of materials are needed compared to batch in most cases.

As described in Chapter 2, I found it necessary to establish a systematic and efficient optimization method during the course of optimization studies on the reaction condition. Hence I investigated utilization of a PAT tool for continuous hydrogenation reaction of ethyl nicotinate.

4-2. Results and discussion

The ReactIR^{TM} 15 system (Mettler Toledo), which employs Fourier Transform Infrared spectroscopy (FT-IR) for *in situ* reaction monitoring, was selected as a PAT tool to establish a rapid optimization of the continuous hydrogenation processes of ethyl nicotinate (Figure 4-1). ReactIR^{TM} has been utilized increasingly for continuous processes.[3a,12]

Figure 4-1. Photograph of the ReactIR^{TM} 15 system (Mettler Toledo)

First, IR spectra of ethyl nicotinate (**1**), partially hydrogenated (**2**) and full hydrogenated compound (**3**) were measured by injecting standard EtOH solutions of those compounds into the cell of the ReactIR^{TM} system, and several specific wavenumbers were picked up as candidates for the reaction monitoring after mathematically manipulating the raw data. Among the known candidate wavenumbers, a specific one for each compound (**1**: 1435-1410 cm^{-1} speculated as C=C or C=N stretching vibration of aromatic ring, **2**: 1642-1635 cm^{-1} speculated as C=C stretching vibration of alkene, **3**: 917-900 cm^{-1} speculated as C-C stretching vibration of cyclic alkane) was identified throughout the reaction to follow the reaction trend (Figure 4-2).

Figure 4-3 shows an experimental setup for monitoring continuous hydrogenation of ethyl nicotinate with the ReactIR™. The IR is connected directly to the outlet of the trickle bed reactor, FlowCAT™, to monitor the reaction solution coming from the reactor.

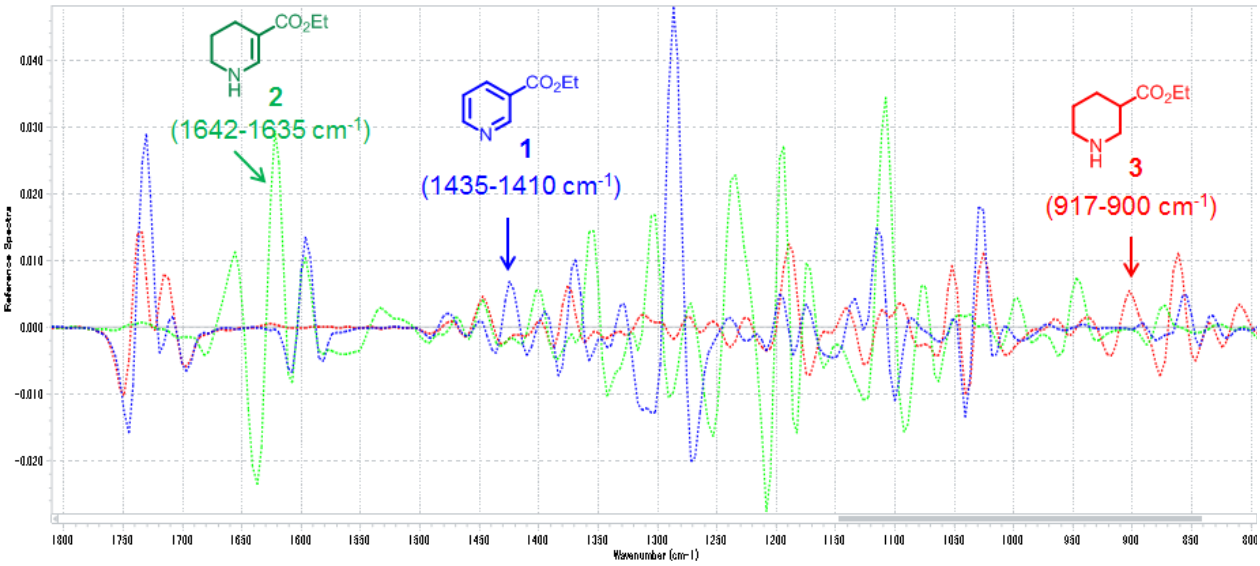

Figure 4-2. Secondary differential IR spectra of compounds **1**, **2** and **3** obtained by subtracting the EtOH spectrum

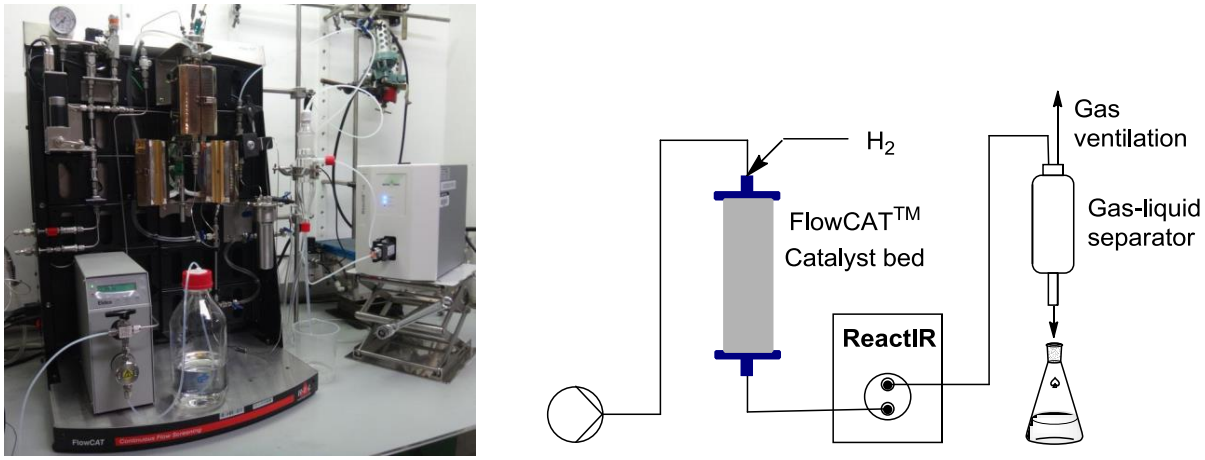

Figure 4-3. Experimental setup for monitoring continuous hydrogenation of ethyl nicotinate with a ReactIR™ system

Using this setup, reaction condition screening was conducted to determine the best conditions with EtOH as solvent, in order to obtain both compounds **2** and **3**, selectively. A total of 13 reaction conditions, employing 5% Pd/SiO_2[13] as a catalyst, were used over time in a single set-up, and a trend graph for the peak area of the identified peaks of each compound was obtained (Figure 4-4, Table 4-1).

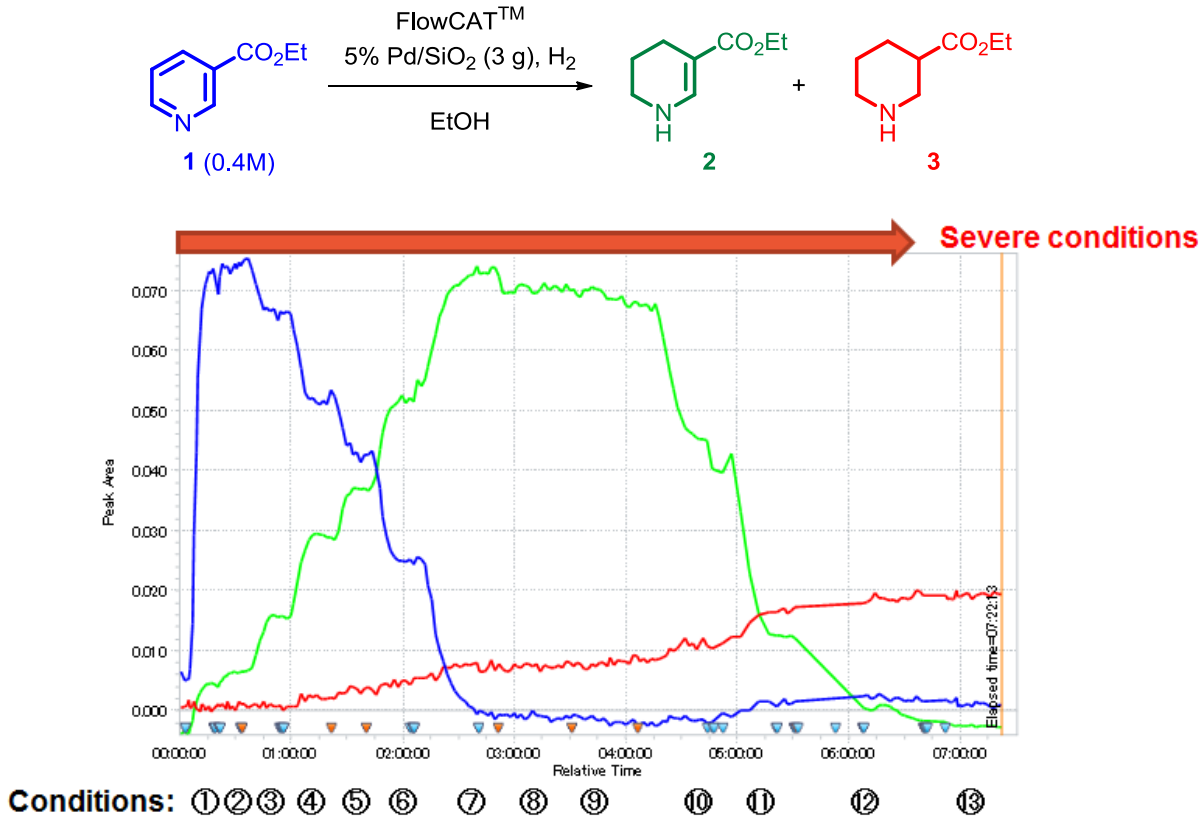

Figure 4-4. Trend graphs of reaction condition screening for continuous hydrogenation of **1** in EtOH (Blue: 1435-1410 cm^{-1} for **1**; Green: 1642-1635 cm^{-1} for **2**; Red: 917-900 cm^{-1} for **3**)

Table 4-1. Reaction conditions for continuous hydrogenation of **1** in EtOH and results by ^{1}H-NMR analysis for some conditions

conditions	flow rate (mL/min)	temp. (˚C)	pressure (bar)	gas feed (L/min)	ratio (%)[a]		
					1	**2**	**3**
1	2.0	40	10	0.2			
2	2.0	40	20	0.2	88.5	9.7	1.8
3	2.0	50	20	0.2			
4	2.0	60	20	0.2			
5	1.5	60	20	0.2	49.5	43.6	6.9
6	1.0	60	20	0.2	29.3	61.3	9.4
7	0.5	60	20	0.2	1.4	85.3	13.3
8	0.5	60	20	0.1			
9	0.5	70	20	0.1			
10	0.5	100	20	0.1			
11	0.5	130	30	0.1			
12	0.5	150	80	0.1	0	2.2	97.8
13	0.5	150	100	0.1	0	1.2	98.8

[a]Ratios are based on crude ^{1}H-NMR data.

Some portions coming from the outlet were sampled and measured by ^{1}H-NMR analysis in order to check if the in-line IR trend graph of each compound agrees with the result obtained by ^{1}H-NMR. The trend line of compound **1** (blue line) declined as the reaction conditions

became more severe and it showed that compound **1** was almost consumed in the reaction condition 7. The line of compound **2** (green line) rose over time and peaked for the condition 7, then declined as the temperature and system pressure increased. The line of compound **3** (red line) gradually rose over time. The trend graph showed that the condition 7 gave compound **2** selectively, with compound **1** almost totally consumed, and compound **3** was obtained selectively with almost complete consumption of compounds **1** and **2** in the condition 13. Pleasingly, the ^{1}H-NMR results met the trend well.

Next, reaction condition screening for full hydrogenation to give **3** was conducted with AcOEt as solvent. But, in this case, no specific and appropriate peak of compounds **1** and **3** was identified to draw the trend graph (Figure 4-5).

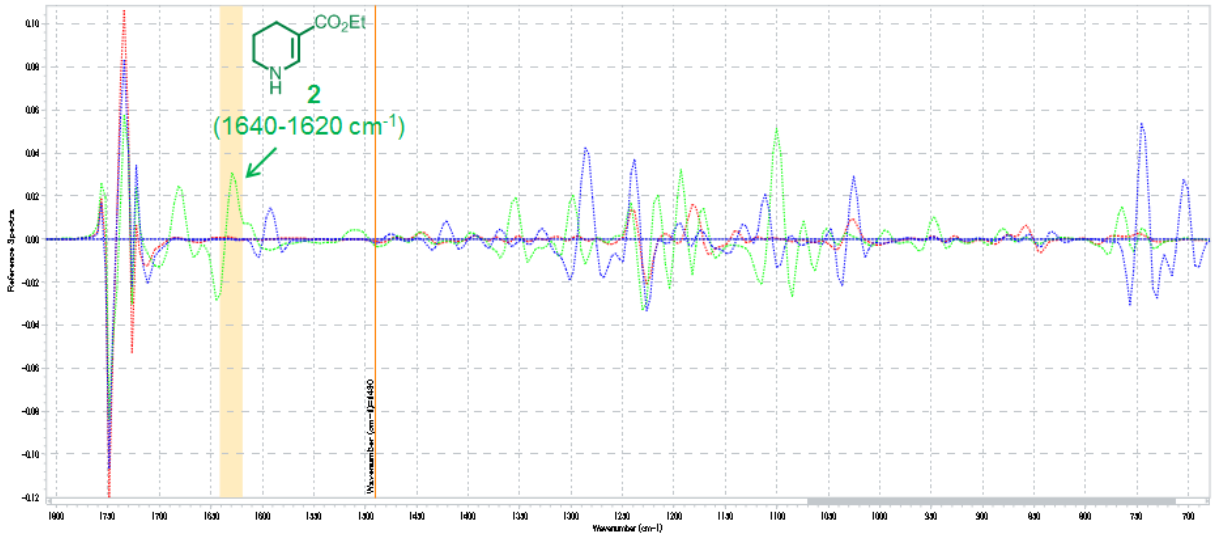

Figure 4-5. Secondary differential IR spectra of compounds **1**, **2** and **3** obtained by subtracting AcOEt spectrum

All of the 9 reaction conditions with 5% Rh/Al_2O_3[14] as a catalyst were changed over time

in one set-up and the trend graph for the peak area of the identified peak of compound **2** was obtained (Figure 4-6, Table 4-2). The trend graph showed that compound **2** was almost consumed in the condition 6 (throughput[15]: 1306 g d^{-1}). When the condition 8 was used for higher throughput (throughput[15]: 1959 g d^{-1}), by changing flow rate from 2.0 to 3.0 mL min^{-1}, the trend line rose, indicating that full conversion to compound **3** was not achieved. Therefore, the flow rate was readjusted to achieve higher throughput with full conversion (condition 9, throughput[15]: 1633 g d^{-1}) and the trend graph showed full conversion was achieved. The ^{1}H-NMR results obtained from portions collected at the outlet corresponded extremely well with the trend.

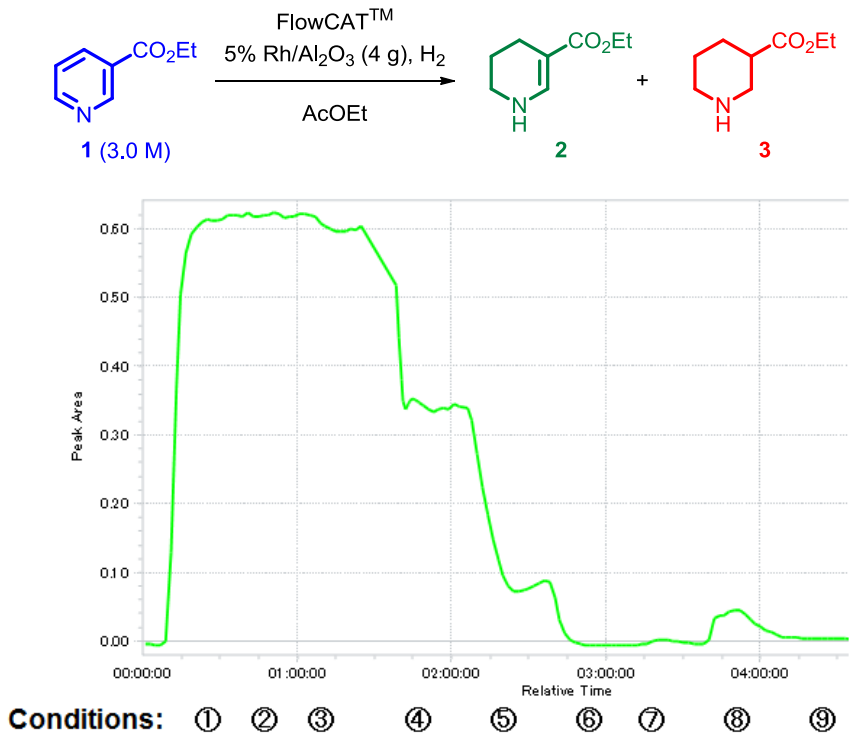

Figure 4-6. Trend graph of reaction condition screening for full hydrogenation of **1** in AcOEt (Green: 1640-1620 cm^{-1} for **2**)

Table 4-2. Reaction conditions for full hydrogenation of **1** in AcOEt and results by ^{1}H-NMR analysis for some conditions

conditions	flow rate (mL/min)	temp. (˚C)	pressure (bar)	gas feed (L/min)	ratio (%)[a]			throughput (g d^{-1})[15]
					1	**2**	**3**	
1	1.0	60	20	0.2	9.6	45.9	44.5	
2	1.0	60	20	0.4				
3	1.0	80	20	0.4				
4	2.0	100	80	0.6				
5	2.0	130	100	0.7				
6	2.0	160	100	0.7	0	0	100	1306
7	2.0	190	100	0.7				
8	3.0	190	100	0.8	13.0	4.6	82.4	1959
9	2.5	190	100	0.8	0	0	100	1633

[a]Ratios are based on crude ^{1}H-NMR data.

The results prove clearly that in-line FT-IR analysis enables rapid qualitative reaction parameter screening for these reactions, though the sensitivity for the trend graph is dependent on the compounds. Once it is confirmed that the trend graph is in agreement with the results obtained by a quantitative analytical method, time consuming off-line analyses can be avoided, which make it possible to dramatically reduce the time for optimization of the procedures.

I tried to apply the in-line FT-IR analysis to the neat hydrogenation reaction of ethyl nicotinate, but unfortunately it failed due to much noise in the spectra making it impossible to obtain clear trend graphs.

4-3. Conclusion (Chapter 4)

In conclusion, I have reported specific examples of PAT utilization for rapid reaction condition screening. For selective partial and full hydrogenation reaction of ethyl nicotinate, in-line FT-IR system made it possible to visualize the reaction conversion and products profile qualitatively, and to identify the best reaction conditions rapidly without sampling and off-line analyses. The results show in-line FT-IR system as PAT would be a very powerful tool for rapid process development through rapid optimization, scale-up and technology transfer in a safer fashion. On the other hand, this method has some limitations, which causes difficulty to draw a reliable trend graph, such as solvents, concentration and sensitivity derived from the compound structure. Hence other PAT tools should be developed to compensate the limitations of FT-IR for real-time monitoring. Likewise, an establishment of real-time quantitative analytical method should be a good future challenge in this field.

4-4. References

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(14) The catalyst was purchased from Johnson & Matthey (particle size 0.10−0.25 mm, product code 110003APO5-10/lot. M15131), website: http://www.matthey.com/johnson-matthey-catalysts (accessed August 18, 2016).

(15) Throughput is calculated by the following formula: Molar concentration of feed solution (M) / 1000 x molecular weight of **1** x flow rate (mL/min) x 60 (min) x 24 (h)

4-5. Experimental

General experimental section

^{1}H-NMR spectra were recorded on a Bruker AVANCE III 500 spectrometer (500 MHz) with the residual solvent peak as the internal reference ($CHCl_3$ = 7.26 ppm).

All the flow reactions were performed using FlowCAT™, monitored by ReactIR™ 15 and analyzed by the iC IR software.

Unless stated otherwise, reagents were obtained from commercial sources and used without purification.

Reaction condition screening for continuous hydrogenation of ethyl nicotinate (1) in EtOH

A solution of ethyl nicotinate in EtOH (0.4 M) was continuously passed through a trickle bed reactor packed with 3.0 g of 5% Pd/SiO_2.[13] The reaction conditions (pump flow rate, temperature, system pressure and gas feed) were changed over time. The reaction output was monitored continuously by a ReactIR™ 15 system and some portions of the output were collected for obtaining ^{1}H-NMR spectra.

Reaction condition screening for continuous full hydrogenation of ethyl nicotinate (1) in AcOEt

A solution of ethyl nicotinate in AcOEt (3 M) was continuously passed through a trickle bed reactor packed with 4.0 g of 5% Rh/Al_2O_3.[14] The reaction conditions (pump flow rate, temperature, system pressure and gas feed) were changed over time. The reaction output was monitored continuously by a ReactIR™ 15 system and some portions of the output were collected for obtaining ^{1}H-NMR spectra.

ReactIR™ 15 system for in-line reaction monitoring

The Mettler-Toledo ReactIR™ 15 is a real-time, *in situ* mid-infrared based system for use in the laboratory. For a continuous flow reaction, it has a DS micro flow cell, which easily connects to the ReactIR™ base unit and consists of an integrated attenuated total reflectance gold sealed diamond sensor (DiComp) with a removable head having a 50μL internal volume. The available optical range is 650-2000 cm^{-1} and 2250-4000 cm^{-1}, excluding the diamond blind spot. The specifications of the ReactIR™ 15 with a DS micro flow cell (DiComp) are summarized in Table 4-3. The DS micro flow cell was connected directly to the outlet of FlowCAT™ by using 1/8" O.D. PFA tubing and 1/4"-28 OmniFit connections for in-line reaction monitoring.

Table 4-3. Specifications of ReactIR^{TM} 15 with a DS micro flow cell (DiComp)

Dimensions (W x H x D)	180 mm x 274 mm x 249 mm
Weight	9 kg
Resolution	4 cm^{-1} maximum
Optical range (Base Unit)	4000 – 650 cm^{-1}
Pressure range	atmospheric – 3.0 MPa
pH range	1 – 14 (DiComp)
Temperature range of flow cell	room temperature – 120°C

Chapter 5

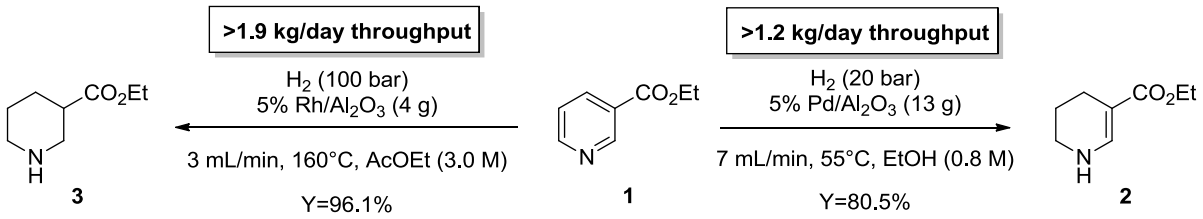
Conclusion

Here I report specific laboratory process intensification studies, including solvent-free reaction examples and PAT development for a rapid reaction condition screening method using an in-line FT-IR system, with focus on heterogeneous hydrogenation reactions, as summarized below.

1. Process intensification for the continuous flow hydrogenation of ethyl nicotinate

A process intensification study for the selective, partial, and full hydrogenation of ethyl nicotinate using a trickle bed reactor was conducted and the process achieved a throughput of 1219 g d^{-1} for the partial hydrogenation, whereas the productivity for the full hydrogenation process reached 1959 g d^{-1} of throughput on a laboratory-scale flow chemistry platform (Scheme 5-1).

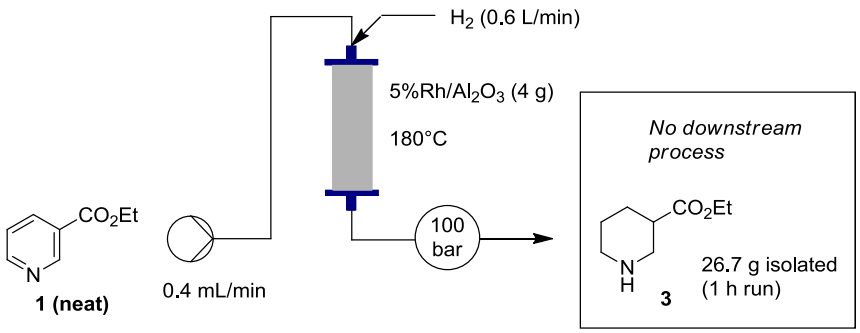
Scheme 5-1. Continuous flow hydrogenation of ethyl nicotinate



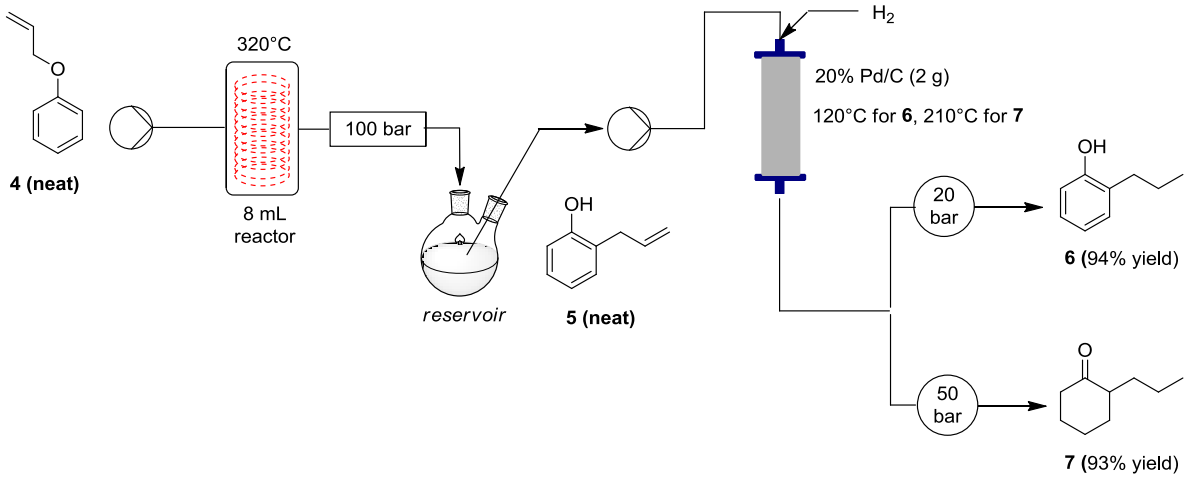
2. Solvent-free continuous operations using small footprint reactors

Continuous full hydrogenation of ethyl nicotinate (**1**), and a telescoped intensified continuous Claisen rearrangement with the subsequent selective hydrogenation to give compound **6** or **7** under solvent-free conditions, were achieved (Scheme 5-2, 5-3). In these cases, it was possible to demonstrate end-to-end production without any downstream operations, which is an ideal form for manufacturing.

Scheme 5-2. Full hydrogenation of **1** to **3** under solvent-free conditions



Scheme 5-3. Telescoped intensified Claisen rearrangement and hydrogenation to **6** or **7**



3. Utilization of PAT for rapid optimization

A rapid reaction condition screening method using an in-line FT-IR system as a PAT tool was developed for selective partial and full hydrogenation reaction of ethyl nicotinate. It enabled the visualization of what is happening in the reaction (*i.e.* reaction conversion and products profile), qualitatively in real time, and helped to rapidly find the best reaction conditions, without time-consuming sampling and off-line analyses.

Process intensification has hitherto been mainly focused on large scale production, however, the above results showed that it is useful and beneficial in a laboratory setting in terms of safety and efficiency for process chemistry. Also, continuous flow technology is a very powerful enabling tool for process intensification, especially heterogeneous hydrogenation reaction, one of the most well used reactions in organic synthesis. It enabled high throughput hydrogenation reactions using a bench-top reactor in a fume cupboard and avoided the traditional time-consuming approaches for production at between several hundred grams and kilograms scale, including the laborious operations in batch. In addition, rapid optimization of continuous processes can be achieved by utilization of PAT. Thus contributing to rapid process development, which is strongly required in the pharmaceutical industry.

The results of these studies represent a good motivation for process development to move in a new direction, to take advantage of continuous flow technology, and constitute possible benchmarks for further development in the field of laboratory process intensification.

List of publication

This PhD thesis is based on the following papers:

1) "Process Intensification for the Continuous Flow Hydrogenation of Ethyl Nicotinate",
   Takashi Ouchi, Claudio Battilocchio, Joel M. Hawkins, and Steven V. Ley,
   Org. Process Res. Dev. **2014**, *18*, 1560−1566.
2) "Solvent-Free Continuous Operations Using Small Footprint Reactors: A Key Approach for Process Intensification",
   Takashi Ouchi, Robbie J. Mutton, Victor Rojas, Daniel E. Fitzpatrick, David G. Cork, Claudio Battilocchio, and Steven V. Ley,
   ACS Sustainable Chem. Eng. **2016**, *4*, 1912−1916.

Presentation at conferences (Poster presentation)

1) "Process Intensification for the Continuous Flow Hydrogenation of Ethyl Nicotinate"
   The 3rd International Symposium on Process Chemistry (Jul. 14, 2015, Kyoto in Japan)
2) "Process Intensification for the Continuous Flow Hydrogenation of Ethyl Nicotinate"
   7th Symposium on Continuous Flow Reactor Technology for Industrial Applications
   (Sep. 29, 2015, Delft in Netherland)

3) “Process Intensification Study for Continuous Flow Hydrogenation”

2nd International Symposium on Continuous Manufacturing of Pharmaceuticals

(Sep. 26, 2016, Boston in the U.S.)

4) "Development of a continuous multi-step synthesis utilizing continuous hydrogenation, for an intermediate of a Takeda API"

Flow Chemistry Congress 2016 (Nov. 2, 2016, Miami in the U.S.)

Invited lecture

1) “Process Intensification: Producing More with Less, Continuous Flow Hydrogenation of Ethyl Nicotinate” at Symposium of the Group for Automated Flow and Microreactor Synthesis (Oct. 31, 2014, Japan)

2) “Continuous Flow Hydrogenation for Process Chemistry” at Continuous process symposium, “Continuous Process for Pharmaceutical Industry” (Sep. 10, 2015, Japan)

3) “Continuous Flow Technology for Development and Manufacturing in Pharmaceuticals” at 1st FlowST symposium (Dec. 5, 2016, Japan)

Other publication and patent

1) “Development of Large-Scale Synthesis using a Palladium-Catalyzed Cross-Coupling Reaction for an Isoquinolone Derivative as a Potent DPP‐4 Inhibitor”,

Misayo Sera, Makoto Yamashita, Yuujirou Ono, Takashi Tabata, Eigo Muto,

Takashi Ouchi, and Hiroyuki Tawada.

Org. Process Res. Dev., **2014**, *18*, 446−453.

2) “Synthesis and Conformational Analysis of 2,11-Disila[3.3]metacyclophanes”,

Tomoo Hayamizu, Hajime Maeda, Takashi Ouchi, Naoki Kakiuchi, and Kazuhiko Mizuno. *Eur. J. Org. Chem.* **2016**, (23), 3934−3938.

3) 「窒素縮合複素環化合物の製造方法」

多和田紘之、山下誠、瀬良美佐代、大内卓、特開 2005−35933.

4) “Production Method for Pyrrole Compound”,

Takashi Ouchi, Giho Goh, Sunmi Kim, Jinsoon Choi, and Hunsoo Park,

PCT/JP2016/069258

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