MASTER

Continuous-flow synthesis of CF3-vinylic compounds via Heck-type coupling

Spijkers, L.

Award date:
2014

Technische Universiteit
Eindhoven
University of Technology

/ **Department of Chemical Engineering and Chemistry**

Micro Flow Chemistry and Process Technology

Student:
Luuk Spijkers,
(0619855)

Supervisor:
Dr. Timothy Noël

Daily coaches:
Ir. Stefan Stouten
Natan Straathof MSc.

Professor:
Prof. Dr. Volker Hessel

Date:
November 2014

Eindhoven,
The Netherlands

Continuous-flow synthesis of CF$_3$-vinylic compounds via Heck-type coupling

Where innovation starts

(This page is intentionally left blank)

ABSTRACT

In this thesis the continuous-flow synthesis of CF_3-vinylic compounds via Mizoroki-Heck-type coupling in micro flow is investigated. Since the early 1970's cross-coupling in flow has become very important in both industry and research, a lot of progress was made in the next decades [1].

New applications of micro reactors were developed, for example; organic gas-liquid synthesis can be performed under continuous operation while previously these reactions were often carried out in batch systems, resulting in poor mass transfer and misdistribution[2].

The research in this thesis is focused on overcoming problems encountered in organic gas-liquid synthesis by creating a continuous operation using micro flow technology. By taking relevant and present-day chemistry, which coupling of CF_3 groups is definitely part of, as starting point, numerous results involving the coupling of CF_3-vinilyc compounds in micro flow have been achieved.

Results show that the conditions provided by using micro reactor technology are excellent for the performed alkenylations. High yields were obtained in relatively short times, compared to batch reactions.

TABLE OF CONTENTS

1. INTRODUCTION

A BRIEF INTRODUCTION

Ongoing drug development continuously leads to more effective compounds that can influence specific organic mechanisms. At the same time the complexity of these structures increases. Therefore the industry is constantly looking for methods to increase efficiency, lower costs and implementing novel technology to create these complex compounds.

Micro flow process technology is one of the novel technologies that can be deployed in the field of fine chemistry to improve chemical processes. Micro flow systems provide improved heat- and mass transfer, potentially increasing production by order of magnitude. In addition, the improved process control allows for unconventional operating conditions or even entirely new chemistry[3].

The increasing use of fluorine in novel medicine development has led to new challenges and opportunities. Fluorine atoms are used to increase the half-life of a compound and have lipophilic properties, making passing the blood barrier easier[4]. Especially when a long half-life is desired, for example anti-depressants or pesticides, fluorine is used to prevent oxidation of the molecule.

Transition metals are used for creating specific and coordinated bonds between molecules. Different synthesis routes involving these catalysts have been explored and developed since the beginning of organic chemistry. In the late 19th and in the 20th century it was discovered that using transition metals leads to improving reaction conditions, making high energy demand reactions possible under milder conditions[5][6][7][8].

Palladium is one of these transition metals used as catalyst for organic synthesis. Examples of palladium based catalysis are the Suzuki-Miyaura coupling[9], Kumada coupling[10], Negishi coupling[11], Stille coupling[12], Suzuki[13] coupling, Hiyama coupling[14], Sonogashira coupling[15], the Wacker process[16], the Buchwald-Hartwig amination[17] and the Mizoroki-Heck coupling[18]. In the pharmaceutical industry these coupling reactions are very popular; "cross-coupling[19]" is used in a variety of syntheses of complex medicines[1].

This study will describe and discuss the research performed which combined the previous stated subjects; micro flow technology, fluorine chemistry and catalysis.

The goal of the research is to investigate possibilities to enhance and improve reaction conditions by the use of micro flow technology, creating a stable continuous system capable of performing organic synthesis under mild conditions with the use of catalyst. In particular the field of fluorine chemistry is explored for its significant applications in the medical industry. Since there are numerous catalyst systems qualified to be applied in organic synthesis, the focus will be at the possibility of implementing the system into a simple micro flow system. One of the reactions that is easy applied in micro flow is the Mizoroki-Heck reaction, a cross-coupling that is used to synthesize a lot of pharmaceutical products[1].

Figure 1: Scope of the research

The Mizoroki-Heck reaction is a very selective vinylation and will be discussed in the next chapter.
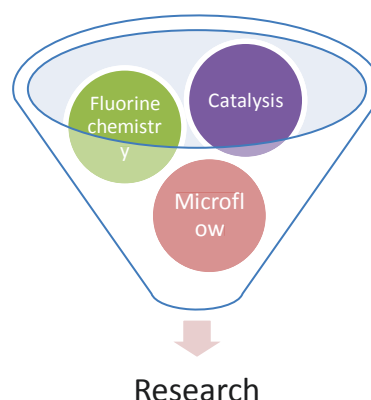
2. THEORY

THE MIZOROKI-HECK REACTION

The Mizoroki-Heck reaction can be considered as one of the most important reactions in modern organic chemistry. It is a coupling between an unsaturated halide or triflate with an alkene in the presence of a base and a palladium catalyst to form a substituted alkene[20][21]. At the moment it is considered the most efficient route for the vinylation of aryl/vinyl halides or triflates[22]. The Mizoroki-Heck reaction is better known as the "Heck reaction" even though there are more variations. However, the Mizoroki variant is by far the most used reaction in the industry/research[23].

As the name suggests, the "Heck" reaction is named after Richard F. Heck, who received the Nobel Prize in Chemistry (2010) for his work on the development of this particular reaction. Heck wondered what would happen if an organo Pd-species lacking a β-hydrogen atom would react with an olefin[23], and therefore designed the following experiment which became an enormous success;

Scheme 1: One of the first olefination experiments performed by Heck in 1968 [5] [6] [7] [8] [9] [10] [11]
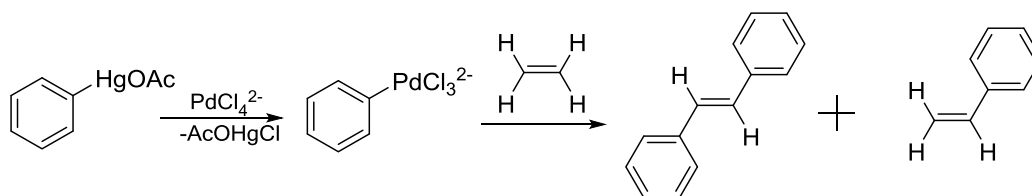
The contribution of Tsutomo Mizoroki on the Heck-reaction scheme was to substitute the toxic and hazardous aryl mercury salts by aryl iodides, creating the final form of the Mizoroki-Heck reaction, represented in Scheme 2. In the following decades the reaction further refined by the introduce of Mizoroki-Heck specific ligands for the catalyst[24] and aryl iodides could be substituted for numerous other chemicals;

Scheme 3: Mizoroki-Heck reaction performed by Mizoroki in 1971[2]
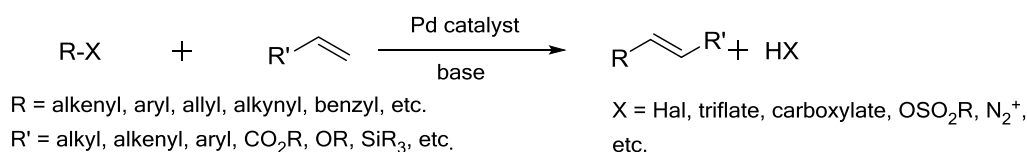
As stated before, there are more reactions that are related to the Heck reaction, Tsutomu Matsuda substituted the aryl halides for aryldiazonium salts, creating the reaction known as the Matsuda-Heck reaction. The difference with the Mizoroki-Heck reaction is that the use of phosphine is not required, reaction occurs at room temperature and a base is mostly not needed.

Beyond the Mizoroki-Heck and the Matsuda-Heck reaction there is also a reaction scheme called oxidative Heck coupling which uses aryl organo-metallics. The oxidative-Heck reaction does not necessary requires a base, works at room temperature but needs an external oxidant.

Table 1: Comparison of different aspects of variants of the Heck reactions

	Mizoroki-Heck	Oxidative Heck	Matsuda-Heck
Aryl-source	aryl halides	aryl-organometallics	aryldiazonium salts
Mechanism	neutral, cationic or anionic	mostly cationic	cationic
Necessity for added base	always	substrate dependent, mostly not needed	substrate dependent, mostly not needed
Typical react. temp.	$60 - 140^0C$	room temperature	room temperature
Solvents	polar, high boiling (DMF, MeCN)	polar, moderate BP (Alcohols, ethers)	polar, moderate BP (Alcohols, ethers)
External oxidant	no	Required	No
Phosphines	compatible	incompatible, with few exceptions	incompatible

It was decided to use the Mitzoroki-Heck reaction in this study, based on high temperature capability when using a high boiling solvent, making it suitable for the transition to micro flow.

MICRO REACTORS

Micro reactor technology is, even after about 20 years research, a relatively new technology in the field of process engineering. Micro reactors were initially used for several gas-phase applications, pointing in the bulk-chemistry direction. The first micro reactors able to perform liquid-phase reactions were developed in the late 1990s[25]. Flow Chemistry has given hereto an enourmous boost within the last 10 years.

The Hauptabteilung Versuchstechnik (HVT) was one of the first institutions that developed micro reactors. Interestingly, [26], their first step into microfluidics was the creation of separation nozzles for uranium enrichment. Other major founding fathers were the Pacific National Laboratory (PNNL) and the Institut fuer Mikrotechnik Mainz GmbH (IMM), rooting likewise HVT in micromachining (and catalysis for PNNL). The technology developed drastically with publications rising from 150 in 2002 to 1000 in 2011[27]. The number of commercial applications of micro reactors are increasing, in 2006 there were an average of 40 companies worldwide using micro reactors for production[28]. This number should be today being enlarged by a factor of 3-6; yet it is difficult to get an appropriate source for this (as there is no recent market study).

The advantages of micro reactors are, among more, making endothermic reactions fast or handling fast exothermic reactions which are difficult to control, because of the superior heat transfer due to the high surface to volume ratio. The synthesis of materials can be done very efficiently and with just the right activation input needed, for example the combustion of propane which can be performed at temperatures as low as 300 degrees Celsius[29].

Micro reactors can even handle reactions with instable intermediates, dangerous substances and reactions with low selectivity or yield. The residence time in a micro reactor is usually low

compared to batch as is the volume of the reactor, making it a very safe alternative for chemistry with toxic intermediates processes at explosive operating conditions[30].
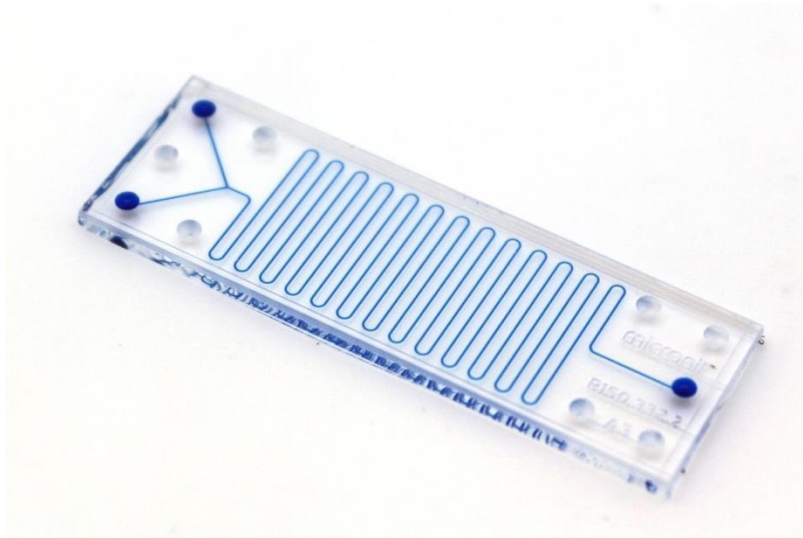

Figure 2: Micro reactor with 2 inlets and 1 outlet

The flow regime in microfluidic chips and in flow chemistry capillaries (as under is typically laminar. This can be determined using the Reynolds-number, which gives an indication for the flow regime;

$$Re = \frac{\rho \cdot v \cdot d}{\mu} \quad [1]$$

with;

$$Laminar\ flow, \quad Re < 2300$$
$$Turbulent\ flow, \quad Re > 3500$$

Taking typical values for ρ, v, μ and d for flow chemistry capillaries, a Reynolds number in the order of $10^1 - 10^{-1}$ is usually obtained:

ρ	10^3	$[\frac{kg}{m^3}]$
v	10^{-3}	$[\frac{m}{s}]$
d	$10^{-3} - 10^{-4}$	$[m]$
μ	10^{-4}	$[Pa \cdot s]$

Yet, it should be noted that true microstructured reactors, developed typically for demanding mixing issues (mixing-masked reactions) and highly exothermic reactions, are operated at (much) higher velocities. Such (ultra)fast reactions are not seldom performed within a few seconds or even below. Assuming $v = 10^{-1} - 10^{-2}[\frac{m}{s}]$, Reynolds numbers can be in the order of 100-1000. This gives large playground for using convective mixing in a regime which is commonly characterized as transition regime (between laminar and turbulent). Accordingly, a large number of micromixers have been

Figure 3: Micromixer

7

developed for convection (or chaotic advection/recirculation, as it is called sometimes); when viewing literature certainly >100 different types.

Apart from that, mixing in micro flow capillaries (as used for flow chemistry) therefore occurs via diffusion but there are several solutions to improve mixing behaviour. In a liquid-phase system a micro mixer can be used to mix two or more streams of chemicals, in a gas-liquid system the mixing behavior can be improved by creating a Taylor-flow regime in the micro reactor, increasing the diffusion between the two phases.

There are numerous micro mixers on the market which are useful for the true microreaction applications as mentioned above. For flow chemistry investigations with reaction time scales in the order of some minutes to some ten minutes (as given in this study), however, there is mostly no need for complex mixing devices. Here, the diffusion time is low compared to the overall residence time in the micro flow system. The diffusion time can be calculated by the following equation;

$$t = \frac{d^2}{2D} \quad [2]$$

A typical diffusion time value for a micro flow system would be between 10 and 100 seconds and this is relatively low as compared to reaction times of 10 – 40 min as used, i.e. 600 to 2400 seconds (needing some attention at its lower boundary though).

| d | $10^{-3} - 10^{-4}$ | $[m]$ |
| D | 10^{-9} | $[\frac{m}{s^2}]$ |

T-type micromixers present a pragmatic way to induce such bilamination-diffusion mixing and actually are expected to have an even better performance, as depicted here, due to initial frontal collision of the streams and geometric focusing thereafter for a certain flow path within the mixer device (typically to a diameter of 200 μm).

A cross-mixer is used in this study to improve gas-liquid mixing behavior. The cross mixer is configured as stated in Figure 4. This configuration induces bubble formation of the gas phase, either by jet mode and subsequent decay (shown in the right-hand image) or by dripping mode, and thereafter creating a stable Taylor flow.

Figure 4: Schematic view of a cross mixer and the Taylor flow created in the cross mixer

FLUORINE CHEMISTRY
Fluorine might be best known by most people for its application in toothpaste. Also, the application in refrigerators as a cooling gas, when combined with chlorine/hydrogen/carbon. But fluorine has more applications, some of them in the field of nuclear warfare. It is used for the production of uranium but also applied in rocket fuels.

Off all elements, fluorine is the most electronegative; it has 5 electrons in the 2p shell. Therefore it reacts with most other elements, including metals[31].

Fluorine, and especially carbon-fluor bonds, have numerous applications in the pharmaceutical industry. At the moment at least 20% of the pharmaceutical medicine contain at least one fluorine atom and over 150 different fluorine containing pesticides are available on the market.

The research described in this thesis will make use of CF_3 groups, CF_3 groups have specific properties making them suitable for applications in the medical industry.

TRIFLUOROMETHYL GROUPS

CF_3 groups are for numerous reasons used in pharmaceutical products. High biological activity is achieved by the prohibition or delay of oxidation of the molecule making it last longer inside an active body. Trifluoromethyl groups will increase the lipophilic value of the molecule, making the molecule more suitable to pass the blood-barrier.

Table 2: Hansch constant for several compounds

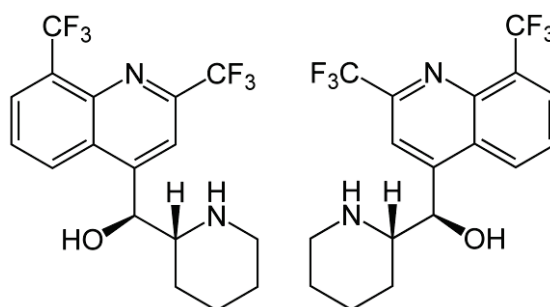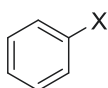| Substituent [X]	Π
H	0.0
F	0.14
CH_3	0.56
Cl	0.71
CF_3	0.88
Br	0.86
OCF_3	1.04
I	1.12
SCF_3	1.44
$CH(CH_3)_2$	1.53

Figure 5: (R,S)-rel-2,8-bis(trifluormethyl)chinolin-4-yl]-(2-piperidyl)methanol, better known as Lariam®

The above table shows the Hansch constant (π), the number which presents the lipophilic properties of a molecule[4]. As shown, the lipophilic constant is increased when hydrogen molecules are substituted for fluorine, making it easier for a molecule to pass the cell barrier.

Examples of trifluoromethyl group containing medicines are Prozac, a very well-known anti-depressant (half-life 1-3 days)[32] and Lariam[33], even containing 2 CF_3 groups, used for the preventions and treatment of malaria (half-life 2 to 4 weeks).

The research described in this thesis will focus on the coupling of the trifluoropropene group, which is used in various chemicals for medical/environmental purposes;
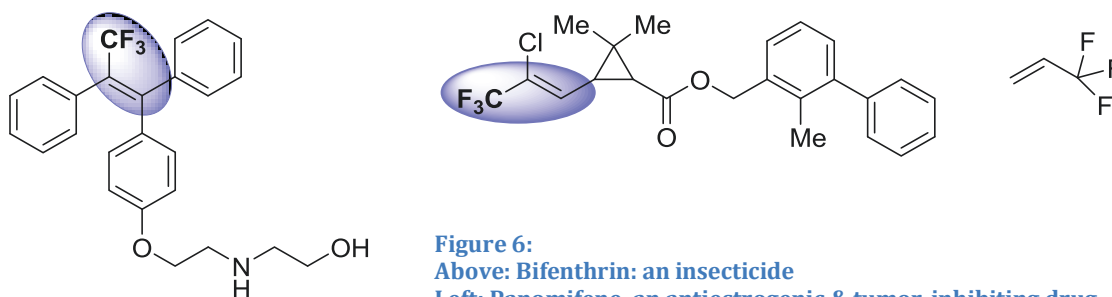
Figure 6:
Above: Bifenthrin: an insecticide
Left: Panomifene, an antiestrogenic & tumor-inhibiting drug
Right: Trifluoropropene group

ADVANTAGES OF FLUORINE-CHEMISTRY[34]:

- $CF_{(1,2,3)}$ groups are used to increase the lipophilic value when combined with arenes, the resulting molecules have less resistance passing the blood barrier.
- Little interference on the biological function of a molecule when it substitutes a hydrogen or hydroxyl group, due to its small size.
- Preventing fast oxidation of the molecule and therefore increasing its biological half-life drastically.
- Little change in the pKa values when functional group substituted by fluorine.

The Heck-mechanism

The mechanisms involving the Mizoroki-Heck-coupling are well investigated and differ when compounds are left out or substituted, for example the electron negativity of the catalyst or reactions without base.

A representation of the simplified Mizoroki-Heck reaction scheme is as follows:
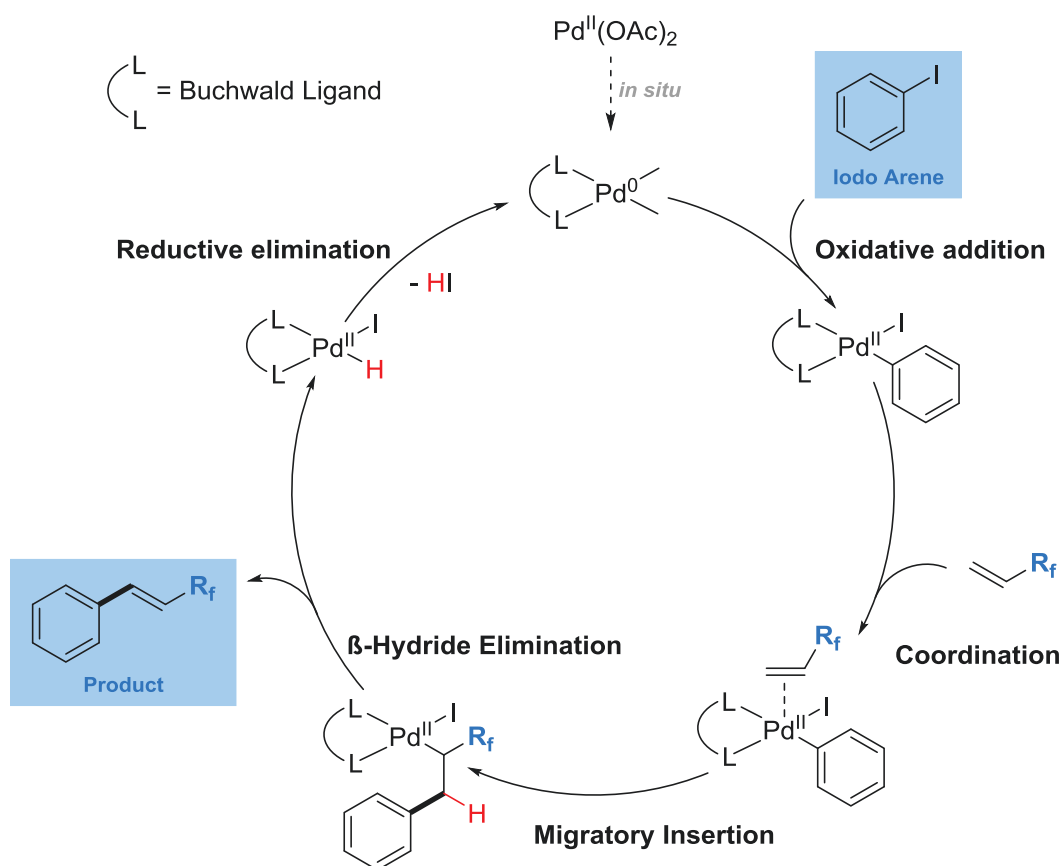
Figure 7: Heck mechanism

The active catalyst is generated from dissolving palladium acetate and a ligand in a solvent so it can form the catalyst complex. The palladium forms in this case a complex with a bidentate, a ligand which can coordinate to the metal on two points. Mizoroki-Heck coupling prefers a selective, bulky ligand[23]. An example of such a ligand is tBuXPhos, Figure 8.

Figure 8: tBuXPhos coupled to palladium

A palladium complex in situ is able to undergo an oxidative addition by an halo arene, represented as an iodo arene in the mechanism.

Oxidative addition changes the oxidative state of the complex from 0 to II, making the complex more suitable/able to perform the coordination step. With the oxidative addition the palladium will position itself between the halogen and the benzene. The oxidative addition of iodo arene is never the rate limiting step in the Mizoroki-Heck coupling[35].
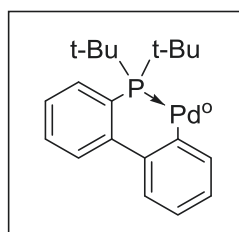
Coordination of an alkene takes place forming a π-complex with the palladium. This is the rate limiting step in the cycle. Migratory insertion allows the alkene to coordinate with the benzene and the palladium complex.

β-hydride elimination leads to the formation of a palladium-alkene complex, where the alkene will be eliminated. Reductive elimination can follow after β-hydride elimination, which is essentially the reverse of an oxidative addition. A base is needed to perform reductive elimination in the Mizoroki-Heck coupling.

The palladium complex returns to the original state after the HI is eliminated. Also the oxidative state returns from II to 0.

The mechanism of Mizoroki-Heck coupling is stereospecific, a trans-substituted double bond will keep its configuration. The reaction tolerates a lot of functional groups, making the use of protective groups unnecessary.

PREVIOUS RESEARCH

No exact previous research is done in trifluormethylation of arenes through heck-coupling in micro flow but literature about other experiments involving trifluoromethylation of arenes has been studied.

In 1981 Fuchikami, Yatabe and Ojima performed a batch synthesis of the arylation of 3,3,3-trifluoropropene trough Mizoroki-Heck-coupling[36]. Different catalysts, bases and solvents were studied, including the use of ligands in certain experiments.

The research also included the Mizoroki-Heck-coupling of iodo arene with trifluoropropene under temperatures ranging from 70°C till 120°C involving a palladium catalyst with ligands.

Scheme 4: Olifination performed by Fuchikami in 1981
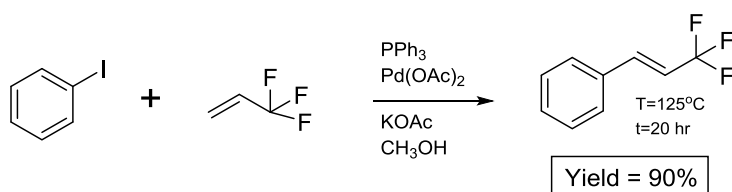
Literature about the Heck-coupling gave insight in the optimal reaction conditions when performing Mizoroki-Heck coupling. The experiment of Fuchikami was performed in 1981, literature showed a lot of progress since the original experiment, especially concerning ligand development. The use of so called "bulky-ligands" is found to be increasing yield. Choice of base incluences selectivity[23].

Buchwald ligands are such bulky electron-rich dialkylbiaryl phospines and are known to improve reactivity in palladium catalysis[37]. These highly active reagents have also been extensively applied in the synthesis of pharmaceuticals, natural products, polymers, and new materials. The structure of the dialkylbiaryl ligand is directly correlated to the efficiency of catalysts containing these ligands[38].

Research in literature showed that a challenge is to be found in the formation of biphenyl, a common side product when performing Mizoroki-Heck coupling with iodo arene, especially in reactions under high temperature, using DMF as solvent[39].

3. EXPERIMENTAL

Experiments were performed with strict procedures to ensure that data and results could be compared with;

- All experiments were performed under Argon.
- To be sure that no reaction takes place before entering the reactor in the flow setups, the ligand and substrates are added through two different syringes.
- A back pressure regulator (BPR) was added to the flow setups to prevent instabilities in the system due to the possibility of gas formation when operating above boiling temperature of the solvent The BPR also increases gas solubility when used in the gas-liquid system.
- A cross or T-mixer is added in the flow setups to improve the mixing behavior. In the batch setup a magnet was added for continuous stirring.

BATCH SETUP
Reactor:

The reactor consisted of a 10ml glass pressure tube (2) with a closed Teflon cap (1). The pressure tube was placed in an oil bath (3) which is placed on a stirrer/heater (6). The reaction mixture (4) is continuously stirred with a magnetic stirrer (5).
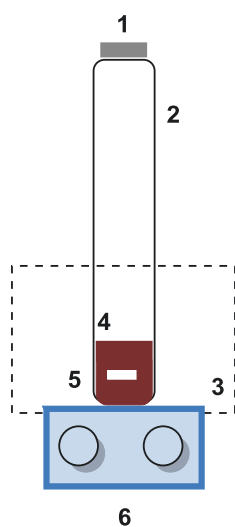

Figure 9: Batch setup

CONTINUOUS FLOW LIQUID SETUP

All capillary tubing and micro fluidic fittings were purchased from IDEX Health and Science. The combination of syringe pump (1) (Fusion 200 Classic) and disposable syringes (BD Discardit II or NORM-JECT, 2 – 10 mL) were available from VWR International. The syringes were connected to the capillary (2) using ¼-28 flat-bottom flangeless fittings. The capillary tubing (3) was of high purity PFA (1/16″ • 500 μm ID). The liquid mixing was carried out in a Cross Tefzel Micro mixer (X) (500 μm ID, P-729 PEEK Cross or similar *T-mixer*).

Reactor. The reactor (5 – 7) was made out of a high purity PFA capillary tube (1/16″ 500 μm ID 2.5 m), with 90% of the capillary length wrapped around a metal construction and fixated with an elastic rubber. The metal construction was put in the oil bath which was placed on a heater/stirrer. The reactor had a volume of 200 μL. On the reactor outlet was fitted a back-pressure-regulator (40 psi), (or P785 PEEK BPR Assembly) and followed through a rubber septum (8); accordingly the reaction mixture can be collected in a sealed environment under inert atmosphere (Argon).
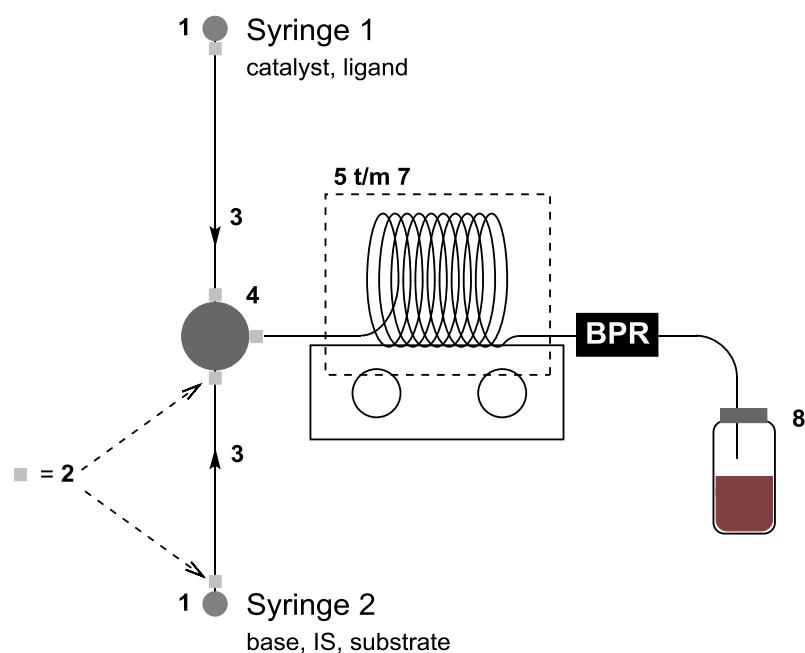

Figure 10: Liquid flow setup

CONTINUOUS FLOW GAS-LIQUID SETUP

All capillary tubing and micro fluidic fittings were purchased from IDEX Health and Science. The combination of syringe pump (1) (Fusion 200 Classic) and disposable syringes (BD Discardit II or NORM-JECT, 2 – 10 mL) were available from VWR International. The syringes were connected to the capillary (2) using ¼-28 flat-bottom flangeless fittings. The capillary tubing (3) was of high purity PFA (1/16″ • 500 μm ID). The liquid mixing was carried out in a Cross Tefzel Micro mixer (X) (500 μm ID, P-729 PEEK Cross or similar *T-mixer*).

Reactor. The reactor (5 – 7) was made out of a high purity PFA capillary tube (1/16″ 500 μm ID 2.5 m), with 90% of the capillary length wrapped around a 100 mL disposable syringe and fixated with an elastic rubber. The syringe was put completely in the oil bath which was placed on a heater/stirrer. The reactor had a volume of 2000 μL. On the reactor outlet was fitted a back-pressure-regulator (5 or 40 psi (0.3 or 2.8 bar), P-790 or P785 PEEK BPR Assembly, respectively) and followed through a rubber septum (8); accordingly the reaction mixture can be collected in a sealed environment under desired atmosphere (for example; Argon).

Gas-inlet. A single-gauge gas-regulator (9) (stainless steel, 0 – 30 psi, ¼″ NPFT inlet, Sigma-Aldrich) was connected to the CF_3-propene gas container. A closing valve (10a) (stainless steel, 1/8″ connections, Swagelok) was situated between the gas-regulator and the gas/mass flow controller (MFC) (11), and connected with stainless steel tubing and fittings (Swagelok). The gas flow-rate was controlled by an uncalibrated MFC for gas (11a) (stainless steel, F-201CV Digital MFC, EL-FLOW Select, 0.1 – 5.0 mLn min^{-1}, 1/8″ connections, Bronkhorst BV Netherlands) combined with a digital display (11b) (B2 Bright R/C module, IP-40, 1.8″ color TFT with four buttons, Bronkhorst BV Netherlands). An emergency closing valve (12) (500 μm ID) was connected to the MFC with a stainless steel connector (1/8″ connections) prior to the gas carrier capillary (3a).
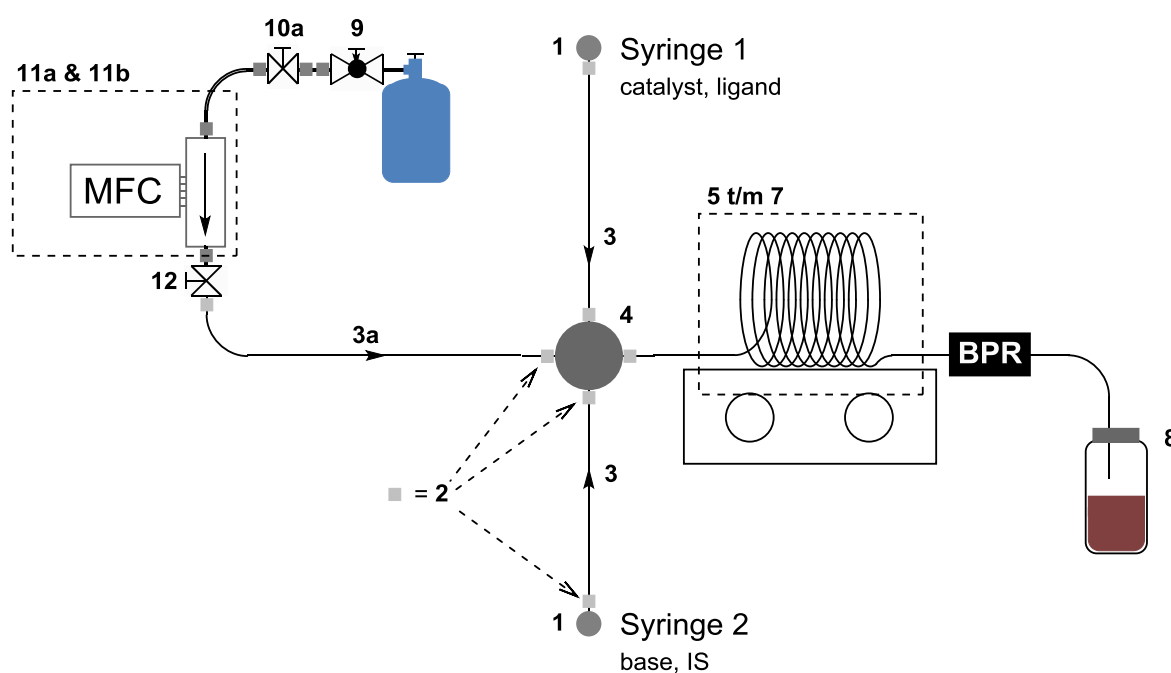

Figure 11: Gas-liquid flow setup

GENERAL PROCEDURES

BATCH REACTIONS

An oven dried 10ml vacuum tube was obtained and filled with 1 eq. palladium(II)acetate [Pd(OAc)$_2$] accompanied by 3 eq. ligand, in the order of 0,5 – 4 mol% of catalyst and 1,5 – 12 mol% ligand. A stir magnet was present in the tube. The vacuum tube was closed and flushed for approx. 10 minutes with argon.

After flushing approx. 5ml solvent was added, under argon overpressure, and the mixture was stirred at room temperature for approx. 15 minutes (catalyst-complex formation). After the catalyst was formed, 1 to 3.5 equivalents, depending on the experiment, iodo arene was added, accompanied by 1 to 3.5 equivalents of perfluorohexene.

Then the internal standard was added (50 – 100 μL a,a,a,-trifluorotoluene) and finally the base, 3 equivalents. The pressure tube was filled with solvent until the volume of 10ml was reached. After adding the rest of the solvent the mixture was putted immediately in the pre-heated oil-bath and stirred.

Typical observations included immediate color shift from light yellow/red to dark red/black when reaching the heated zone of the reactor, the observation of boiling mixture and palladium tarnish on the reactor wall. Collection was done after the desired reaction time. The mixture was quantified by GC/MS, GC-FID and/or ^{19}F-NMR analysis.

CONTINUOUS FLOW LIQUID REACTIONS

Two oven dried calibrated 5ml volumetric flasks were obtained. The first flask was filled with 1 eq. palladium(II)acetate [Pd(OAc)$_2$] accompanied by 3 eq. ligand, in the order of 1 mol% of catalyst and 3 mol% ligand. A stir magnet was present in the flask. The flask was closed and flushed for approx. 10 minutes with argon.

After flushing the volumetric flask was filled up to the 5ml marker with solvent, under argon overpressure, and the mixture was stirred at room temperature for approx. 15 minutes (catalyst-complex formation).

The second flask was closed and flushed for approx. 10 minutes with argon. Then it was filled with 1 to 3.5 equivalents iodo arene, accompanied by 1 to 3.5 equivalents of perfluorohexene, depending on the experiment. Then the internal standard was added (50 – 100 μL a,a,a,-trifluorotoluene) and finally the base, 3 equivalents. The volumetric flask was filled up to the 5ml marker with solvent, under argon overpressure, and the mixture was stirred briefly at room temperature.

After the flasks were prepared, the mixtures were transferred into a 5ml BD-Plastic syringe and mounted on the syringe pump.

The syringe pump was set on the desired speed and the mixture was pumped in the reactor. Typical observations included immediate color shift from light yellow to dark red/black when reaching the heated zone of the reactor. Collection was done after reaching steady state inside the reactor (1.5 reactor lengths). The mixture was quantified by GC/MS, GC-FID and/or ^{19}F-NMR analysis.

CONTINUOUS FLOW GAS-LIQUID REACTIONS

Two oven dried calibrated 5ml volumetric flasks were obtained. The first flask was filled with 1 eq. palladium(II)acetate [Pd(OAc)$_2$] accompanied by 3 eq. ligand, in the order of 1 mol% of catalyst and 3 mol% ligand. A stir magnet was present in the flask. The flask was closed and flushed for approx. 10 minutes with argon.

After flushing the volumetric flask was filled up to the 5ml marker with solvent, under argon overpressure, and the mixture was stirred at room temperature for approx. 15 minutes (catalyst-complex formation).

The second flask was closed and flushed for approx. 10 minutes with argon. Then it was filled with substrate (approx. 1.5 mmol). The internal standard was added (50 – 100 μL a,a,a,-trifluorotoluene) and finally the base, 3 equivalents. The volumetric flask was filled up to the 5ml marker with solvent, under argon overpressure, and the mixture was stirred briefly at room temperature.

After the flasks are prepared, the mixtures were transferred into a 5ml BD-Plastic syringe and mounted on the syringe pump.

The trifluoropropene gas flow was established and maintained at a constant flow rate, creating a Taylor flow and an excess of gas in the reactor.

The syringe pump was set on the desired speed and the mixture was pumped in the reactor. Typical observations included immediate color shift from light yellow to dark red/black of the slugs when reaching the heated zone of the reactor. Collection was done after reaching steady state inside the reactor (1.5 reactor lengths). The mixture was quantified by GC/MS, GC-FID and/or ^{19}F-NMR analysis.

4. RESULTS

OPTIMIZATION (BATCH):

Kinetics, reactant interaction, external factors (heat) and internal factors (reaction length) were studied by a series of batch experiments. Optimization was performed with 1H,1H,2H-Perfluoro-1-hexene in a liquid batch system.

Scheme 5: Mizoroki-Heck coupling performed in batch
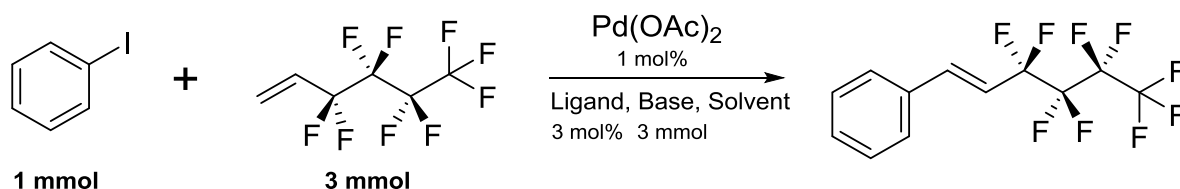
The Mizoroki-Heck reaction mechanism is valid (independently of continuously performed reactions or batch reactions), all components are premixed. Effect of base, ligand, catalyst concentration and solvent were studied. Catalyst concentration will be altered in flow experiments; the main goal of varying the catalyst concentration in batch experiments was to determine reaction kinetics.

Reaction time and the influence of operating time were also investigated.

EFFECT OF LIGAND

Results from literature suggest that bulky ligands are the most suitable for Pd-catalyzed heck-reactions[23]. Buchwald-ligands were chosen to investigate in this study for their bulky and selective properties in Mizoroki-Heck coupling as explained in the Theory section.
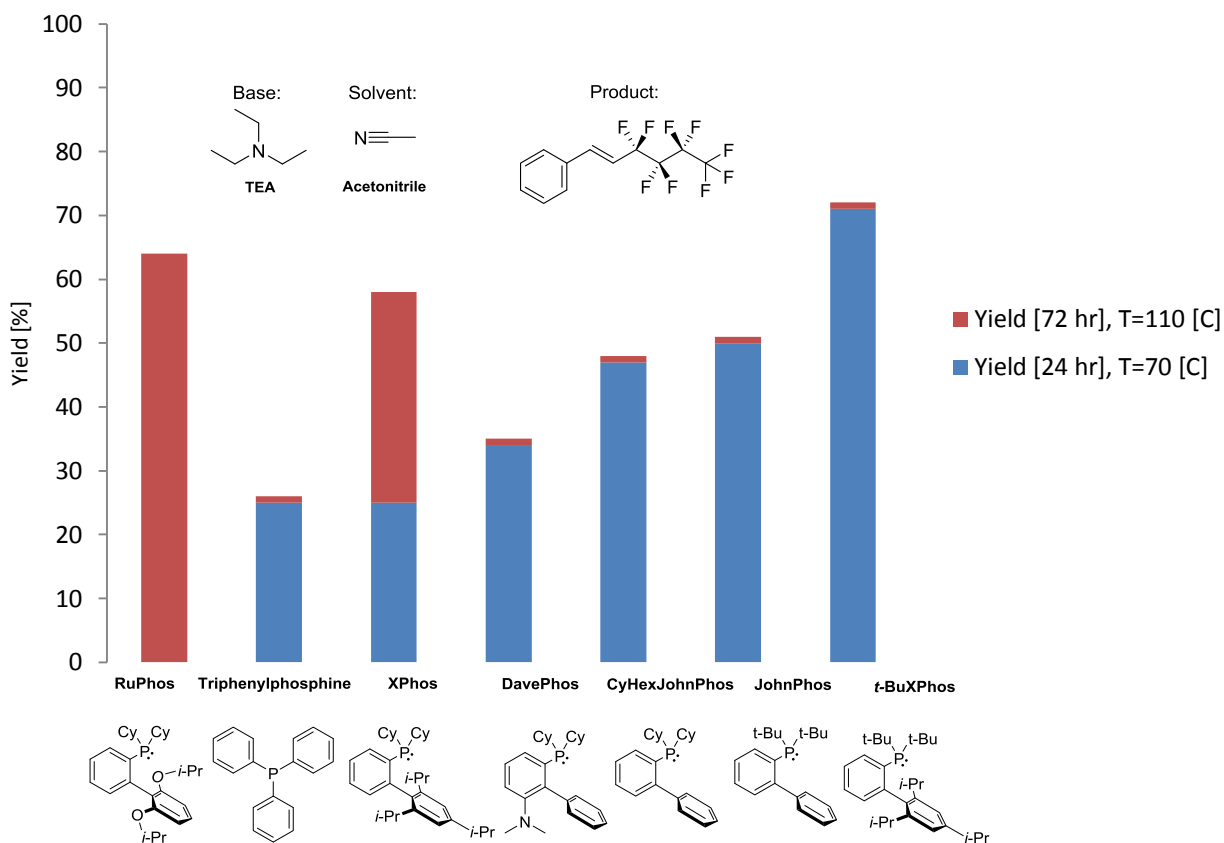

Figure 12: Results ligand selection

[a] during analysis with GC-FID it was observed that the reaction with JohnPhos as ligand obtained a higher *conversion* than t-BuXPhos. However, selectivity was significantly lower and with ^{19}F-NMR it turned out that the reaction with t-BuXPhos had higher yield. Except for RuPhos, all ligands dissolved after heating.

Results in Figure 12 represent the yield of product after 24 hours and 72 hours. It is noticed that the catalyst system with RuPhos is not thermodynamically activated at a temperature of 70⁰C, which is partly the case for XPhos. RuPhos shows no activity at all, the catalyst complex containing XPhos showed moderate activities compared to other ligands.

Color shift was noticed after heating of reaction mixture; starting with yellow/red (depending on the ligand) to dark brown and eventually black. A silver tarnish on the side of the reactor was observed in all cases, differing from a light shade of silver to full coverage of the reactor, indicating that the reaction could be complete or the catalyst deactivated by oxygen [40]. The silver tarnish is likely metallic palladium, which is inactive for the Mizoroki-Heck reaction. [41].

Above experiments concluded that t-BuXPhos is the most suitable ligand. It is thermodynamically activated at 70⁰C or below and has a high selectivity towards the desired product.

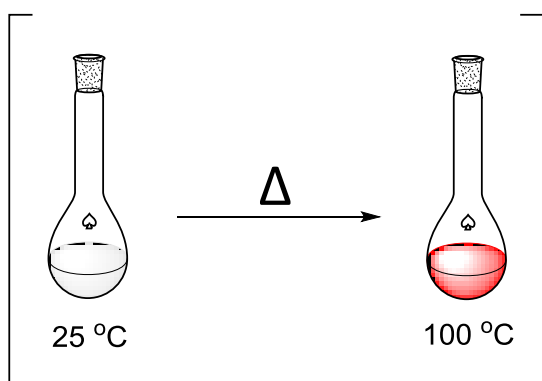Thermodynamic activation was confirmed with the following experiment;

Figure 13: Experimental setup thermodynamic activation

A reaction mixture was stirred at room temperature for 72 hours, no conversion observed with GC-FID. After 72 hours the mixture was heated to 100 °C. Color shift occurred within minutes and GC-FID confirmed that product was formed.

CATALYST CONCENTRATION

Influence of the catalyst concentration is shown in Figure 14.

Figure 14: Results catalyst concentrations
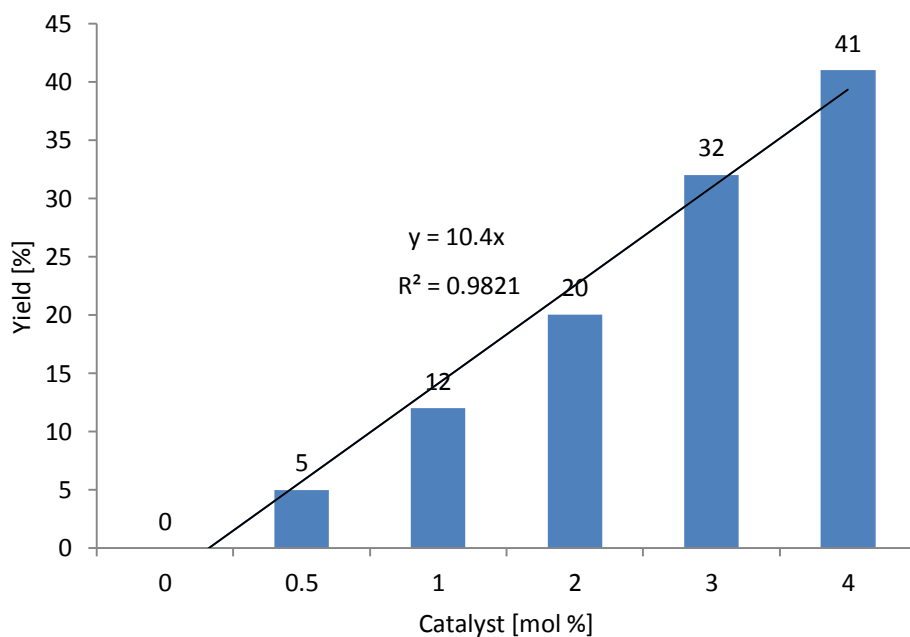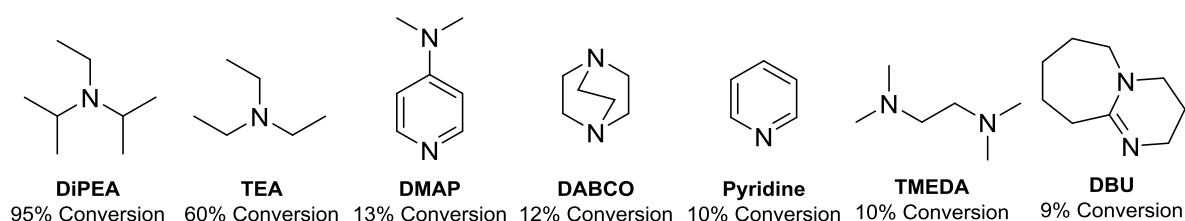Used catalyst is Pd(OAc)$_2$ with tBuXPhos as additional ligand, the catalyst was dissolved in DMF and DiPEA, internal standard and perfluorohexene were added. The reaction mixture was heated to 70°C, reaction time was 30 minutes. To ensure relative short reaction time in optimization, 4 mol % catalyst was used in batch optimization experiments. The x is completed to a round number.

Clear linear increase of yield of the desired product with catalyst concentration is observed, suggesting that the order of the reaction rate is not influenced by the catalyst concentration. Turn-over number is not rate limiting; there is no relative decrease in yield when higher concentrations of catalyst are used.

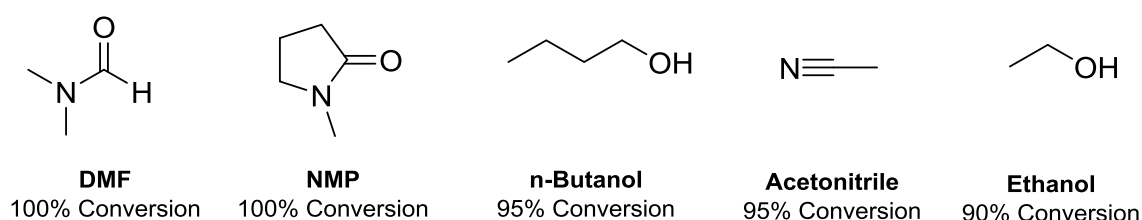## EFFECT OF BASE

Table 3: Effects of different bases

DiPEA	TEA	DMAP	DABCO	Pyridine	TMEDA	DBU
95% Conversion	60% Conversion	13% Conversion	12% Conversion	10% Conversion	10% Conversion	9% Conversion

Results were compared, TEA was the base used in initial experiments. Experiments were performed under 70[o]C, catalyst used was Pd(OAC)$_2$ with tBuXPhos as ligand. All chemicals were dissolved in acetonitrile, reaction time was set to 30 minutes. Analysis was done with GC-FID.

DiPEA performed better than the other bases, this can be attributed to the steric effects of the extra methyl groups, making room for only one hydrogen atom to attack [42]. Because the nitrogen atom is shielded by two isopropylgroups instead of ethyl groups when compared to TEA, it is a stronger non-nucleophilic base.

EFFECT OF SOLVENT

Table 4: Effect of different solvents

DMF	NMP	n-Butanol	Acetonitrile	Ethanol
100% Conversion	100% Conversion	95% Conversion	95% Conversion	90% Conversion

The influence of the base was investigated by using batch setup, Experiments were performed at 70[o]C, catalyst used was Pd(OAC)$_2$ with tBuXPhos as ligand and DiPEA as base. Both DMF and NMP gave 100% conversion. Analysis done by GC-FID. Reaction time was set to 30 minutes.

While both DMF and NMP converted the reaction to 100% it was chosen to continue with DMF as solvent for the price/ml of NMP is higher. Deactivation rate was not investigated, all batch reactions would deactivate over time. DMF and NMP are both polar aprotic solvents, n-butanol and ethanol are polar protic solvents. Since acetonitrile is also a polar aprotic sovent, difference is only seen in the additional oxygen atom in the high end performing solvents.DMF is ultimately chosen for its high boiling point with respect to butanol, acetonitrile and ethanol.

LIQUID FLOW EXPERIMENTS (FLOW OPTIMIZATION)

Experiments were conducted in flow to determine optimal temperature and residence time. Figure 15 is a schematic representation of the setup used.
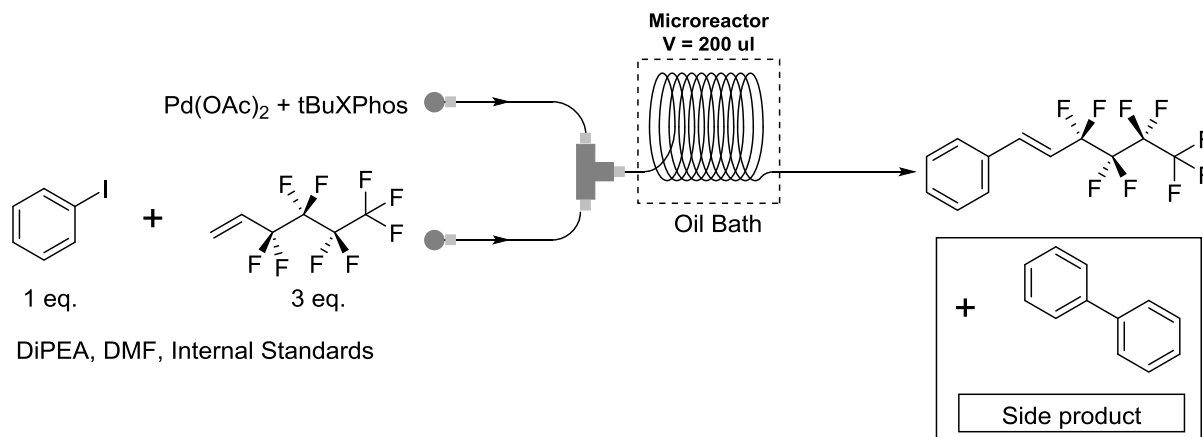

Figure 15: Liquid experimental set-up

To prevent accidental activation of the catalyst, the micro reactor has 2 inlets, so the catalyst is separated from the starting materials. The catalyst precursor and ligand are premixed before being loaded in the syringe leading to the reactor inlet. Both catalyst and starting materials are dissolved in DMF. Biphenyl, represented in the right lower part of the figure, was the common side product obtained.

EFFECT OF TEMPERATURE AND RESIDENCE TIME

The effects of residence time and temperature are shown in Figure 16.
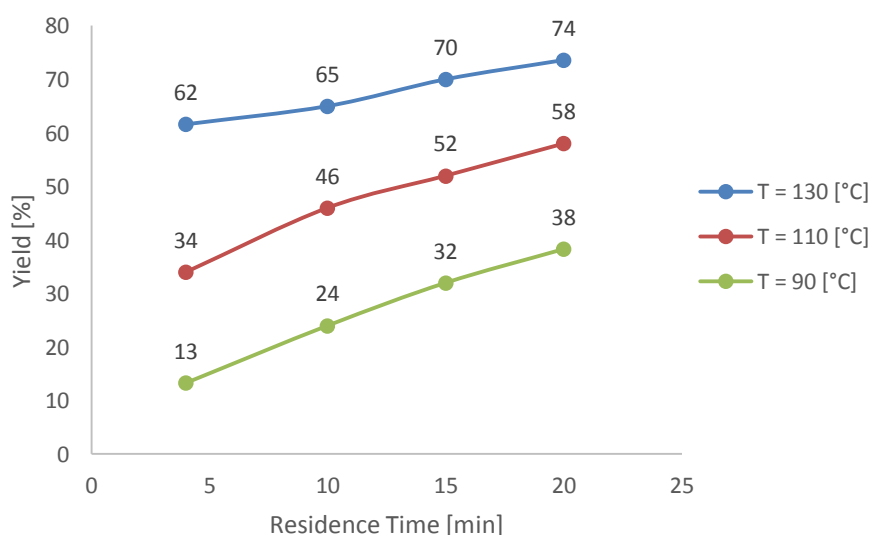

Figure 16: Yield versus residence time in L-L experiments

At a temperature of 130 degrees and a residence time of 20 minutes, full conversion is reached with a maximum yield of 74%. Longer residence time (60 minutes) confirmed maximum yield. Biphenyl was observed as byproduct and isolated[1].

At lower temperatures same selectivity was reached but lower conversion, leading to a lower yield. At higher temperatures, reaction became instable, experiments with temperatures up to 150 °C were performed but gas formation and deactivation of the catalyst was observed, leading to poor results.

Residence times below 4 minutes resulted in an unstable system, leading to decreasing yields over time.

FLOW EXPERIMENTS AT LOW RESIDENCE TIME
High flow rates and small residence times have been investigated to determine reaction kinetics in flow, see Figure 17.
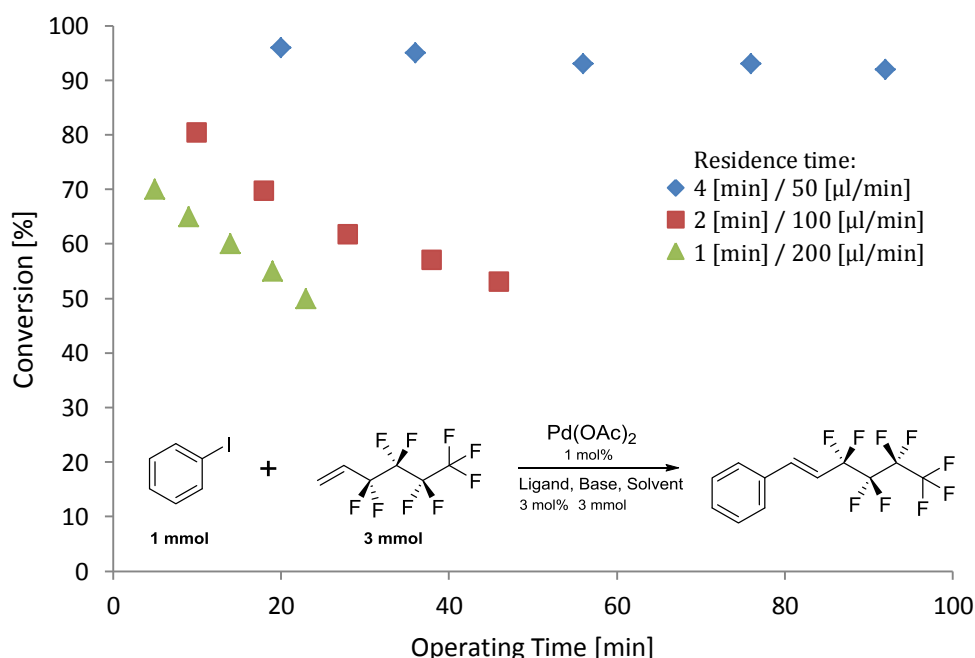

Figure 17: Conversion versus Residence time in L-L micro flow
All experiments were performed in the L-L micro flow set-up displayed in Figure 10**Error! Reference source not found.** with a temperature of 130°C. JohnPhos is used as ligand, DiPEA as base and DMF as solvent.

At shorter residence time and higher flow rates, conversion seemed to decrease with time on stream. At the same time, the formation of particles in the micro flow reactor was observed. After removal of these particles, presuming to be palladium-black particles, the conversion returned to its original value, until particles started to form again.

However, since particle formation was not observed in later setups, further investigation of the effect was abandoned. Several factors could be the cause of this effect, oxygen and reactor material are considered as candidates.

[1] Analasys of the byproduct was done by GC-FID and GC-MS

Using higher residence times, above 4 minutes, the formation of particles did not occur, even in the phase of research where particle formation still was an issue. See Appendix 1: Influence of reactor flushing for further data.

REACTION KINETICS

In order to obtain higher yields of the desired product, it was considered to reverse the ratio of the starting materials of the reaction and calculate the yield based on the conversion of perfluorohexene instead of iodobenzene.

Since the perfluorohexene is the most expensive compound used in the reaction, chosen path is a cost efficient way to obtain higher yields leading to the following results;

Table 5: Ratio of SM vs yield
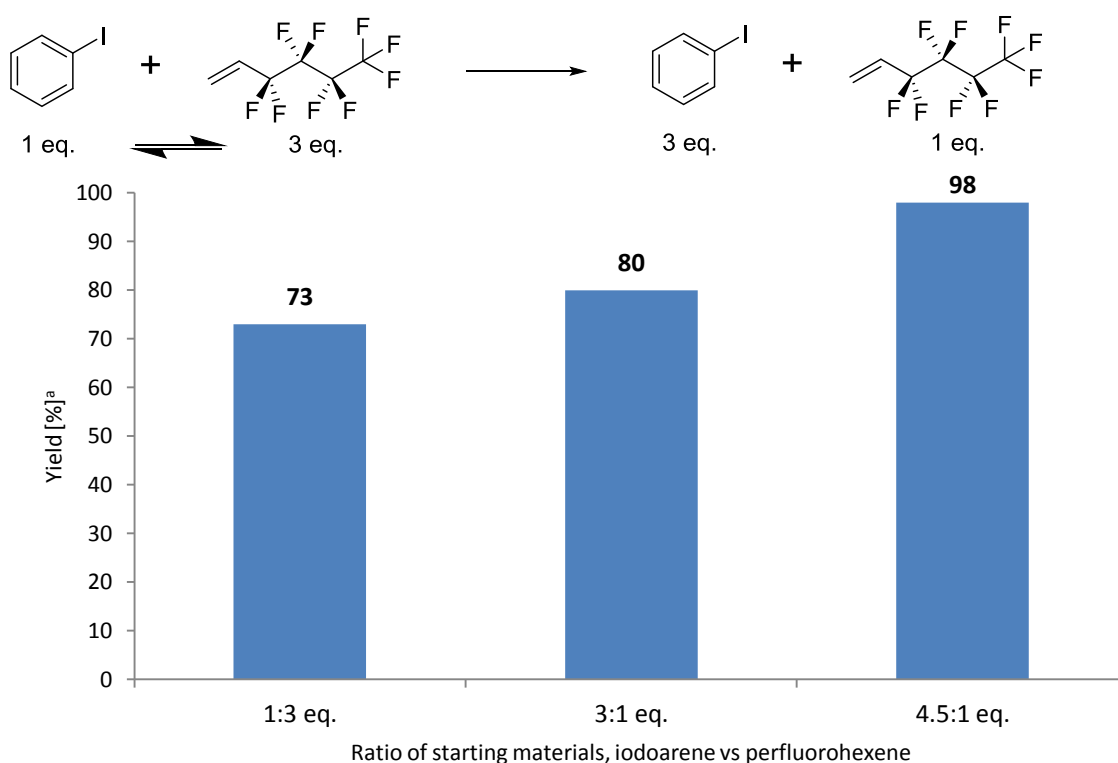
a Reaction was performed with Pd(OAc)$_2$ as catalyst, t-BuXPhos as ligand, DiPEA as base and DMF as solvent. Results were analyzed with ^{19}F NMR, conversion of iodo arene was not measured. Yield is calculated with respect to the transformed perfluorohexene to the desired product. There were no other products found than the desired product with ^{19}F NMR. GC-FID indicated that biphenyl was formed.

A high ratio of iodo arene is needed to obtain high yields, 4.5 equivalents of aryl iodide to perfluorohexene will lead to almost full conversion. ^{19}F NMR confirmed that the selectivity of the perfluorohexene towards the product is 1, there are no other fluorine containing structures formed.

From these results we can conclude that during the insertion step, the perfluorohexene has to compete with the iodoarene, forming both biphenyl and [(1E)-3,3,4,4,5,5,6,6,6-Nonafluoro-1-hexen-1-yl]benzene. The competition becomes more severe when more iodobenzene is added, in other words; the effect of increasing yield is not linear with the increase of iodobenzene.

CIS-TRANS ISOMERISM

The Mizoroki-Heck coupling is known to be stereospecific, therefore isomerism towards cis/trans formation of the product was investigated using ^{19}F NMR and ^{1}H NMR.
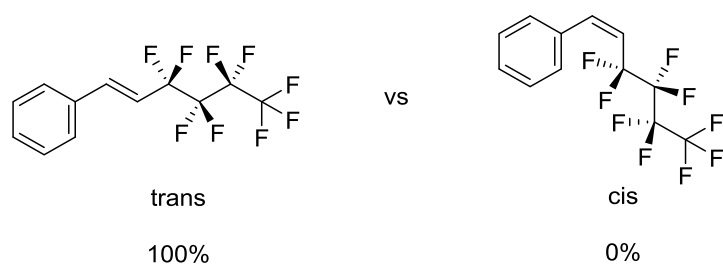

Figure 18: Selectivity towards fluorinated product

All spectrums indicate that there is only one fluorinated product. ^{1}H NMR showes only one structure after isolation, leading to the conclusion that all product formed is the desired trans product.

GAS-LIQUID FLOW EXPERIMENTS

Also investigated was the use of gas 3,3,3-trifluoropropene as a reactant, which required a set-up change to a gas-liquid system. Results are presented in Figure 19.
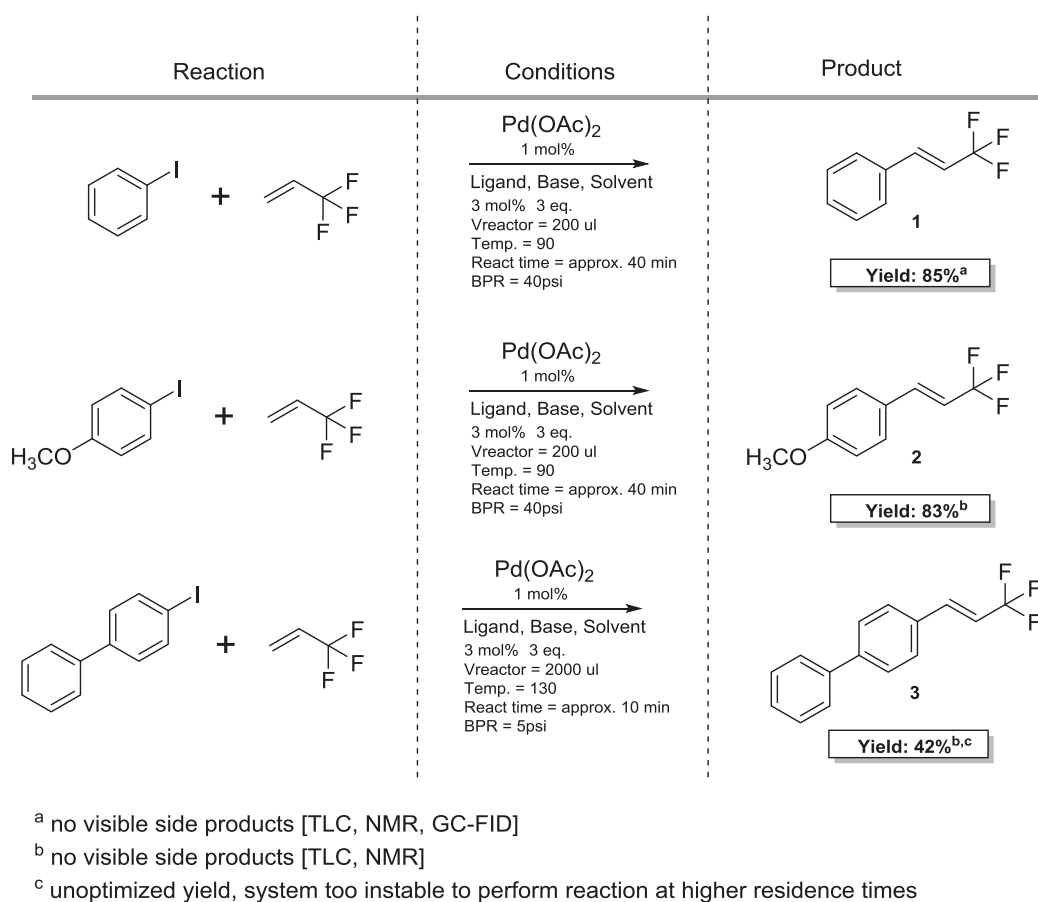

^a no visible side products [TLC, NMR, GC-FID]
^b no visible side products [TLC, NMR]
^c unoptimized yield, system too instable to perform reaction at higher residence times

Figure 19: Gas-liquid Experiments Results

All G-L experiments were performed using the setup displayed in Figure 11 but due to instability problems the setup was changed numerous times. No single optimal setup was found for all investigated substrates. The results obtained with the gas-liquid experiments are displayed with their respective setups.

Problems occurred were instability of the system, reaching the pressure limit of MFC, BPR breakdown and clogging at low flow rates. In experiments with a small reactor volume (200 μl) the system was observed to be extremely instable. The BPR was not capable of handling the gas phase in the reactor. By using a larger reactor (2000 μl) the unstable behavior could be prevented

Problems occurred in experiments due to the pressure limit of the MFC. The limit of the MFC is expected to be 50 psi since the gas supply bottle has a limit of 50 psi.

Switching to a 5 psi BPR would counter the stalling problems but the 5 psi BPR proved to be unsuitable.

Sub-optimal experiments could be performed with the 5 psi BPR, leading to unoptimized yields.
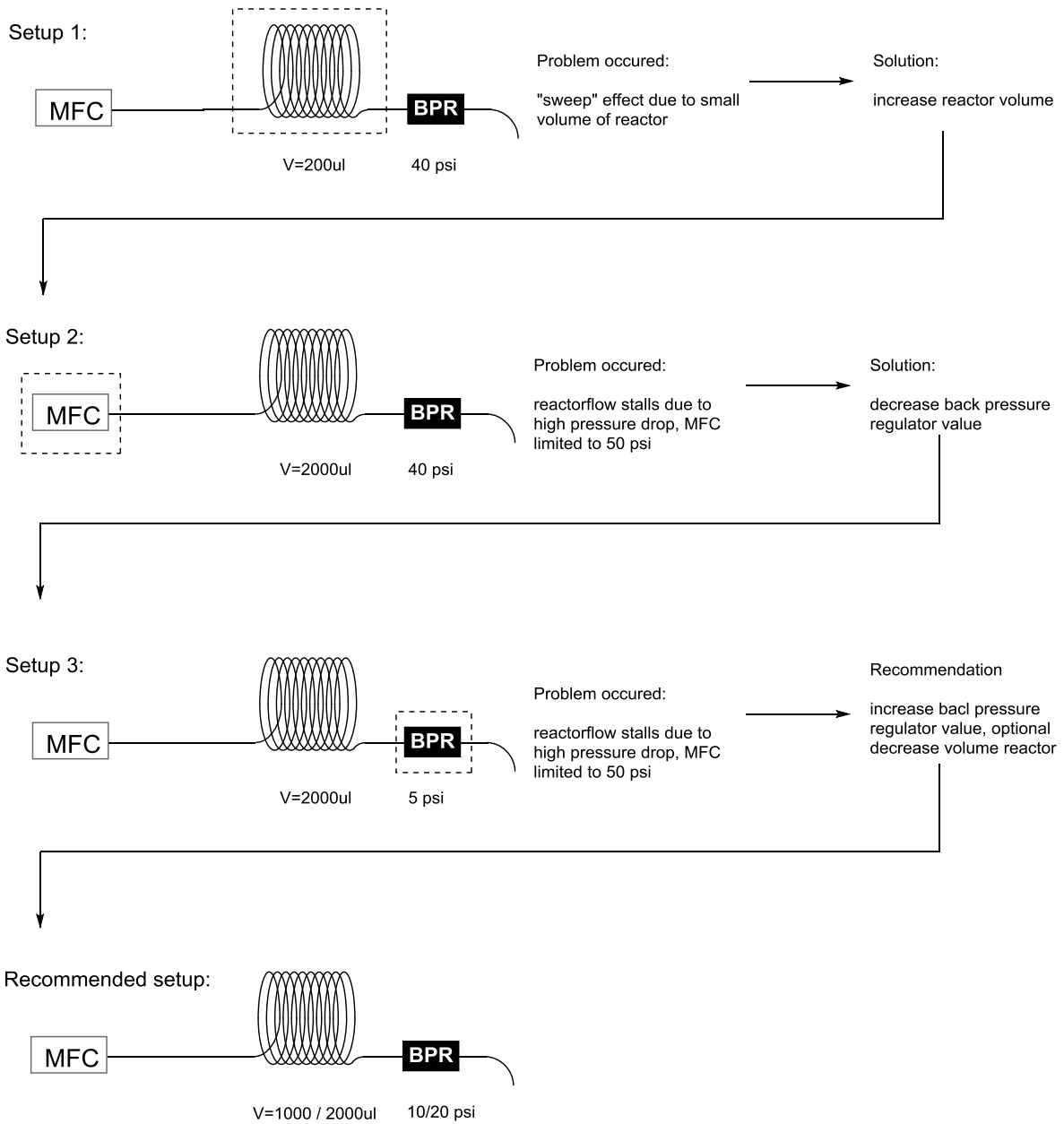
Setup 1:

MFC — [coil] — BPR

V=200ul   40 psi

Problem occured:

"sweep" effect due to small
volume of reactor

Solution:

increase reactor volume

Setup 2:

MFC — [coil] — BPR

V=2000ul   40 psi

Problem occured:

reactorflow stalls due to
high pressure drop, MFC
limited to 50 psi

Solution:

decrease back pressure
regulator value

Setup 3:

MFC — [coil] — BPR

V=2000ul   5 psi

Problem occured:

reactorflow stalls due to
high pressure drop, MFC
limited to 50 psi

Recommendation

increase bacl pressure
regulator value, optional
decrease volume reactor

Recommended setup:

MFC — [coil] — BPR

V=1000 / 2000ul   10/20 psi

Figure 20: Analysis and recommendation of the G-L setup

28

5. CONCLUSION & RECOMMENDATIONS

The goal of the study was to investigate CF_3 vinylation, for its significance in the pharmaceutical industry, with the use of the Mizoroki-Heck cross coupling, using novel methods in catalysis, in a micro flow system.

Preliminary research in batch showed that Mizoroki-Heck-coupling proved to be an efficient route to synthesize the preferred product with high selectivity. The yield could be increased further by the use of bulky Buchwald ligands.

Liquid experiments indicated that Mizoroki-Heck coupling in micro flow was an improvement when compared to its batch counterpart, due to superior heat and mass transfer. Using high temperatures and high flow rates, product could be formed in minutes instead of hours. Yields up to 74% were obtained. By using an excess amount of iodobenzene, 98% of the perfluorohexene was converted to the desired product.

Gas-liquid experiments, involving the coupling of CF_3 on various substrates showed that high yields could be obtained within a hour, using similar reaction conditions compared to batch. Yields up to 85% were obtained without any side products visible, gaining very high selectivity properties.

However, due to instabilities in the gas-liquid system, optimal conditions were not reached. It is recommended that the system is altered to the recommended setup in Figure 21. Limits of the liquid reactor system were extensively researched but proved to be in conflict when applied on a gas-liquid system.
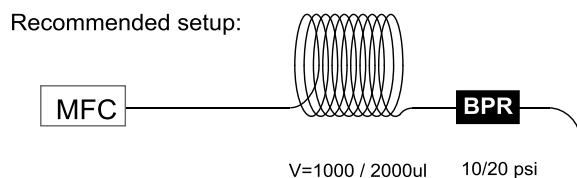

Figure 21: Recommended setup

To counter the problems with instability, altering the system to the configuration stated in Figure 21 is recommended.

Further, it is recommended to investigate the problems experienced with bromo arene as a substitute for iodo arene; it is expected that bromo arene is also a suitable substrate to replace iodo arene in the micro flow gas-liquid experiments. Multiple substrates next to bromo arene were also screened and are expected to be suitable compounds.

Since the catalyst concentration was held on a low value for practical and economic reasons, experiments with higher catalyst concentrations are recommended. To improve catalyst efficiency, transition from a homogene to an immobilized homogene system could be considered.

CITED WORKS

[1] T. Noel and S. L. Buchwald, "Cross-coupling in flow," *Chemical Society Reviews,* vol. 40, pp. 5010-5029, 2011.

[2] T. Noel and V. Hessel, "Membrame Microreactors: Gas-Liquid Reactions Made Easy," *ChemSusChem,* vol. 6, pp. 405-407, 2013.

[3] V. Hessel, K. Jahnisch, H. Lowe and M. Baerns, "Chemie in Mikrostrukturreaktoren," *Angewandte Chemie,* vol. 116, no. 4, p. 410–451, 2004.

[4] IUPAC, Compendium of Chemical Terminology, 1997.

[5] Y. Su, N. J. Straathof, V. Hessel and T. Noel, "Photochemical Transformations Accelerated in Continuous-Flow Reactors: Basic Concepts and Applications," *Chemistry - A European Journal,* vol. 20, no. 34, pp. 10562-10589, 2014.

[6] V. Hessel, "Novel Process Windows – Gate to Maximizing Process Intensification via Flow Chemistry," *Chemical Engineering & Technology,* vol. 32, no. 11, pp. 1655-1681, 2009.

[7] V. Hessel, T. Fukuyama, T. Rahman, I. Ryu, I. R. Baxendale, J. J. Hayward, S. Lanners, S. V. Ley, C. D. Smith, B. Ahmed-Omer, T. Wirth, P. Lob, H. Lowe, K. Koch and J. C. M. van Hest, "Chapter 4. Organic Chemistry in Microreactors," in *Microreactors in Organic Synthesis and Catalysis*, Wiley-VCH GmbH & Co., 2008.

[8] T. Noel and V. Hessel, "Micro Process Technology, 3. Applications," in *Micro Process Technology, 3. Applications*, Wiley-VCH Verlag GmbH & Co., 2014.

[9] R. Martin and S. L. Buchwald, "Palladium-Catalyzed Suzuki-Miyaura Cross-Coupling Reactions Employing Dialkylbiaryl Phosphine Ligands," *Accounts of Chemical Research,* vol. 41, pp. 1461-1473, 2008.

[10] N. Liu and Z. Wang, "Kumada Coupling of Aryl, Heteroaryl, and Vinyl Chlorides Catalyzed by Amido Pincer Nickel Complexes," *Journal of Organic Chemistry,* vol. 76, pp. 10031-10032, 2011.

[11] M. R. Luzung and J. Y. J. S. Patel, "A Mild Negishi Cross-Coupling of 2-Heterocyclic Organozinc Reagents and Aryl Chlorides," *Journal of Organic Chemistry,* vol. 75, pp. 8330-8332, 2010.

[12] S. Mee, V. Lee and J. E. Baldwin, "Stille Coupling Made Easier - The Synergic Effect of Copper(I) Salts and the Fluoride Ion," *Angewante Chemie International Edition,* vol. 43, pp. 1132-1136, 2004.

[13] T. Noel, S. Kuhn, A. J. Musaccio, K. F. Jensen and S. L. Buchwald, "Suzuki–Miyaura Cross-Coupling Reactions in Flow: Multistep Synthesis Enabled by a Microfluidic Extraction," *Angewandte Chemie,* vol. 123, no. 26, pp. 6065-6068, 2011.

[14] J. Lee and G. Fu, "Room-Temperature Hiyama Cross-Couplings of Arylsilanes with Alkyl Bromides and Iodides," *Journal of the American Chemical Society,* vol. 125, pp. 5616-5617, 2003.

[15] K. Sonogashira, Y. Tohda and N. Hagihara, "A convenient synthesis of acetylenes: catalytic substitutions of acetylenic hydrogen with bromoalkenes, iodoarenes and bromopyridines," *Tetrahedron Letters,* vol. 16, no. 50, pp. 4467-4470, 1975.

[16] R. Jira, "A supported aqueous phase catalyst coating in micro flow Mizoroki-Heck reaction," *Angewandte Chemie International Edition,* vol. 48, no. 48, pp. 9034-9037, 2009.

[17] S. L. Buchwald and A. S. Guram, "Palladium-Catalyzed Aromatic Aminations with in situ Generated Aminostannanes," *Journal of the American Chemical Society,* vol. 116, no. 17, pp. 7901-7902, 1994.

[18] S. Stouten, Q. Wang, T. Noel and V. Hessel, "A supported aqueous phase catalyst coating in micro flow Mizoroki-Heck reaction," *Tetrahedron Letters,* vol. 54, no. 17, pp. 2194-2198, 2013.

[19] S. L. Buchwald, "Cross Coupling," *Accounts of Chemical Research,* vol. 41, no. 11, p. 1439, 2008.

[20] R. Heck and J. Nolley, "Palladium-catalyzed vinylic hydrogen substitution reactions with aryl, benzyl and styryl halides," *Journal of Organic Chemistry,* no. 37, pp. 2320-2322.

[21] T. Mizoroki, K. Mori and A. Ozaki, "Arylation of Olefin with Aryl Iodide Catalyzed by Palladium," *Bulletin of Chemical Society Japan,* no. 44, p. 581, 1971.

[22] A. Jutand, "Mechanisms of the Mizoroki-Heck Reaction," in *The Mizoroki-Heck reaction*, John Wiley, 2009, p. 1.

[23] A. Lakshimi Narashima Raju Gottumukkala, "Palladium Catalyzed Carbon-Carbon Bond Formation Under Reductive, Oxidative and Redox Neutral Conditions," Rijksuniversiteit Groningen, Groningen, 2013.

[24] C. Torborg, "Application of Novel Phosphine Ligands in Palladium-Catalyzed Cross-Coupling Reactions," Mathematisch-Naturwissenschaftlichen Fakultat der Universitat Rostock, Rostock, 2009.

[25] P. Watts and C. Wiles, "Recent advances in synthetic micro reaction technology," *Chemical Communications,* pp. 443-467, 2007.

[26] K. Schubert, J. Brandner, M. Fichtner, G. Linder, U. Schygulla and A. Wenka, "Microstructure Devices for applications in thermal and chemical process engineering," *Microscale Thermophysical Engineering,* pp. 17-19, 2001.

[27] V. Hessel, D. Kralisch, N. Kockmann and T. Noël, "Novel Process Windows for Enabling Accelerating and uplifting flow chemistry," *Chemsuschem,* no. 6, pp. 746-789, 2013.

[28] V. Hessel, H. Löwe and P. Löb, "Fit für den Produktionseinstaz," *Chemie Technik,* p. 24, 2006.

[29] V. Hessel, G. Guan, R. Zapf, G. Kolb, Y. Men, H. Loewe, J. Ye and R. Zentel, "Low temperature catalytic combustion of propane over Pt-based catalyst with inverse opal microstructure in a microchannel reactor," *Chemical Communications,* pp. 260-262, 2007.

[30] S. A. Schmidt, "Methyl and ethyl chloride synthesis in microreactors," Laboratory of Industrial Chemistry and Reaction Engineering Process Chemistry Centre Department of Chemical Engineering Åbo Akademi University, Turku/Abo, 2014.

[31] N. Greenwood and A. Earnshaw, Chemistry of the Elements (2nd ed), Oxford: Oxford: Butterworth Heinemann, 1998.

[32] A. Altamura, A. Moro and M. Percudani, "Clinical Pharmacokinetics of Fluoxetine," *Clinical Pharmacokinetics,* vol. 26, no. 3, pp. 201-214, 1994.

[33] La Roche Limited, *Lariam Product Diagram p.3 - 4,* 2011.

[34] H. L. Yale, "The trifluoromethyl group in medical chemistry," *Journal of Medicinal and Pharmaceutical Chemistry,* vol. 1, no. 2, pp. 121-133, 1958.

[35] M. Casey, J. Lawless and C. Shirran, "The Heck reaction: mechanistic insights and novel ligands," *Polyhedron,* vol. 19, no. 5, pp. 517-520, 2000.

[36] T. Fuchikami, Y. Momoko and O. Iwao, "A Facile Synthesis of trans-beta-Trifluoromethylstyrene, trans-2,3,4,5,6-Pentafluorostilbene and their Derivates," *Synthesis Communications,* vol. 1981, pp. 365-366, 1981.

[37] D. S. Surry and S. L. Buchwald, "Dialkylbiaryl phosphines in Pd-catalyzed amination: a user's guide," *Chemical Science,* vol. 2, pp. 27-50, 2011.

[38] Sigma Aldrich, "Buchwald Ligands," Sigma Aldrich, [Online]. Available: http://www.sigmaaldrich.com/chemistry/chemistry-products.html?TablePage=16248151. [Accessed 22 09 2014].

[39] A. L. Gottumukkala, J. Teichert, C. Ferrer, S. Eisink, D. Heijnen, S. van Dijk, A. van den Hoogenband and A. Minnaard, "Pd-BIAN: A highly selective catalyst for the base-free oxidative Heck reaction," no. 76, p. 3498, 2011.

[40] P. Albers, J. Pietsch and S. F. Parker, "Poisoning and deactivation of palladium catalysts," *Journal of Molecular Catalysis A,* vol. 173, pp. 275-286, 2001.

[41] Sigma Aldrich, "Palladium Black," [Online]. Available: http://www.sigmaaldrich.com/catalog/product/aldrich/520810?lang=en&region=NL. [Accessed 22 09 2014].

[42] R. F. Heck, "Acylation, methylation, and carboxyalkylation of olefins by Group VIII metal derivatives," *Journal of the American Chemical Society,* no. 90, pp. 5518-5526, 1968.

[43] R. F. Heck, "The arylation of allylic alcohols with organopalladium compounds. A new synthesis of 3-aryl aldehydes and ketones," *Journal of the American Chemical Society,* no. 90, pp. 5526-5531, 1968.

[44] R. F. Heck, "Allylation of aromatic compounds with organopalladium salts," *Journal of the American Chemical Society,* no. 90, pp. 5531-5534, 1968.

[45] R. F. Heck, "The palladium-catalyzed arylation of enol esters, ethers, and halides. A new synthesis of 2-aryl aldehydes and ketones," *Journal of the American Chemical Society,* no. 90, pp. 5535-5538, 1968.

[46] R. F. Heck, "Aromatic haloethylation with palladium and copper halides," *Journal of the American Chemical Society,* no. 90, pp. 5538-5542, 1968.

[47] R. F. Heck, "The addition of alkyl- and arylpalladium chlorides to conjugated dienes," *Journal of the American Chemical Society,* no. 90, pp. 5542-5546, 1968.

[48] R. F. Heck, "A synthesis of diaryl ketones from arylmercuric salts," *Journal of the American Chemical Society,* no. 90, pp. 5546-5548, 1968.

APPENDIX

APPENDIX 1: INFLUENCE OF REACTOR FLUSHING

During experiments at low residence time it was observed that conversion of the starting material would drop during operating time.

This phenomenon was not expected, especially when residence time was increased, the conversion still dropped.
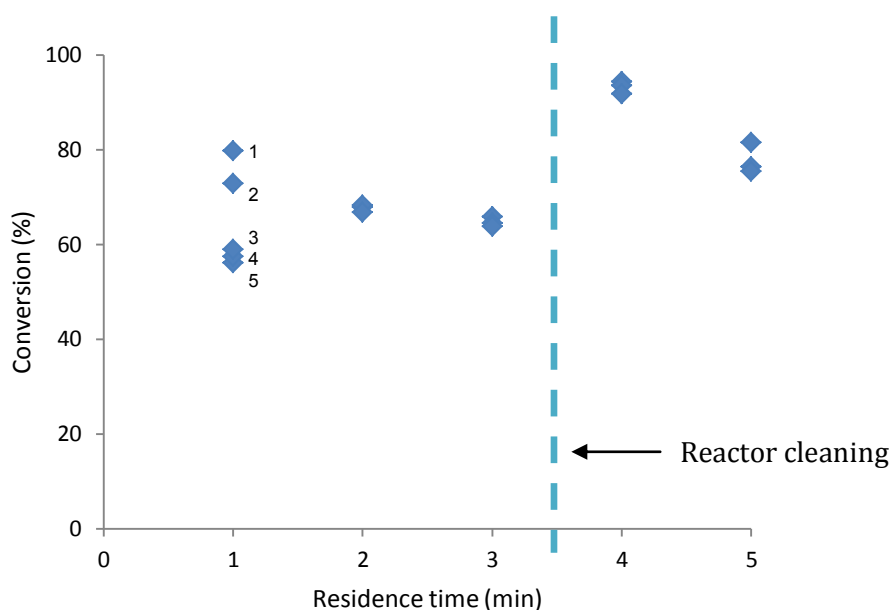

Figure 22: Conversion versus Residence time

Experimental conditions; T = 130°C, base: DiPEA, catalyst: Pd(OAc)$_2$, ligand: JohnPhos, solvent: DMF. Samples 1-5 were taken in consecutive order; sample 1 was taken 1.5 minute after reactor start up, 2-5 each direct consecutive minute after the first sample, 5 samples in 5.5 minutes. Samples with higher residence times [2-3] were also taken sequentially. Same sample taking system was done after the cleaning of the reactor; first sample of RT4 was taken after 4.5 min, etc. Only 3 samples of RT [2-5] were taken for the first 2 samples at RT 1 could not be representative for the system. Reactor cleaning was performed by substituting the feed syringes with syringes filled with acetone. After flushing the reactor with acetone, the acetone was removed by purging the reactor with air.

Figure 22 clearly shows a decrease in conversion at consecutive taken samples. When switched, using the same syringe, to a residence time of 2 minutes, conversion stabilized but continued to decrease.

There was no physical alteration done at the system, only the syringe pump was set to a lower flow rate to obtain a residence time of 2 minutes. The same transition applies to the switch to the residence time of 3 minutes. With increasing residence time, increased conversion was expected. Instead, conversion dropped even further.

The reactor was cleaned after taking samples RT [1-3]. When experiments continued with RT 4, the same effect was observed, mainly when residence time was increased to 5 minutes.

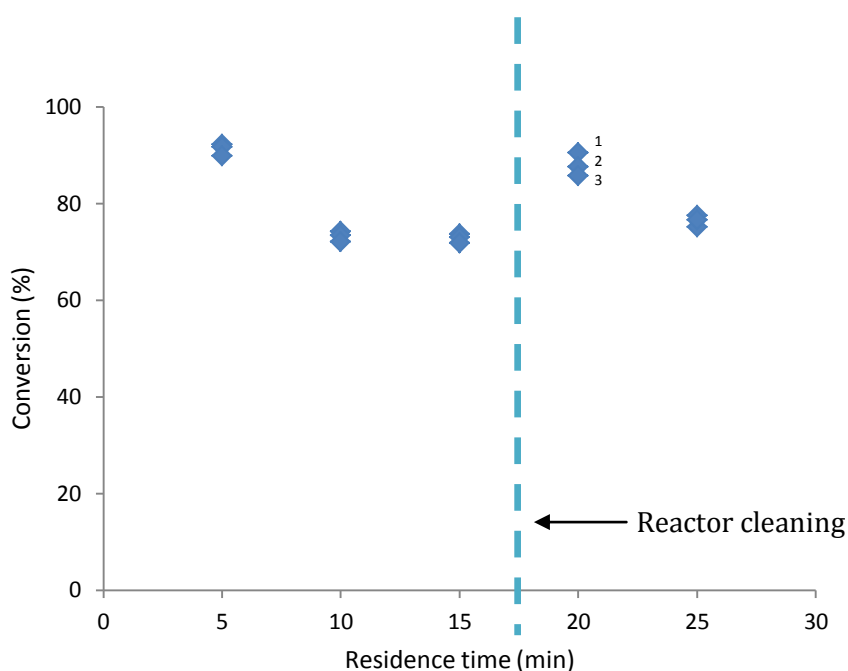Experiments with higher residence times showed a similar effect;

Figure 23: Conversion versus residence time

Experimental conditions; T = 130°C, base: DiPEA, catalyst: Pd(OAc)$_2$, ligand: JohnPhos, solvent: DMF. Samples 1-5 were taken in consecutive order. Reactor cleaning was performed by substituting the feed syringes with syringes filled with acetone. After flushing the reactor with acetone, the acetone was removed by purging the reactor with air.

While conversion does increase, when compared with the conversion drop at lower flow rates, it is still not increasing with residence time as expected. Reactor cleaning induces the same effect as seen in previous experiments.

One of the possible causes of the decreasing conversion over the operating time is the formation of palladium black during the reaction. It was observed that the forming of particles was immediate from the beginning and continued until reaction stopped. Particles would inhibit on the reactor wall and, when grown to a certain size, let go from the


Figure 24: Particle formation in micro reactor

wall into the flow of the reactor. Eventually they would form large structures and clump together. The flow would remove the particles out of the reactor, there were no incidents of clogging, particles were pushed through the back pressure regulator.
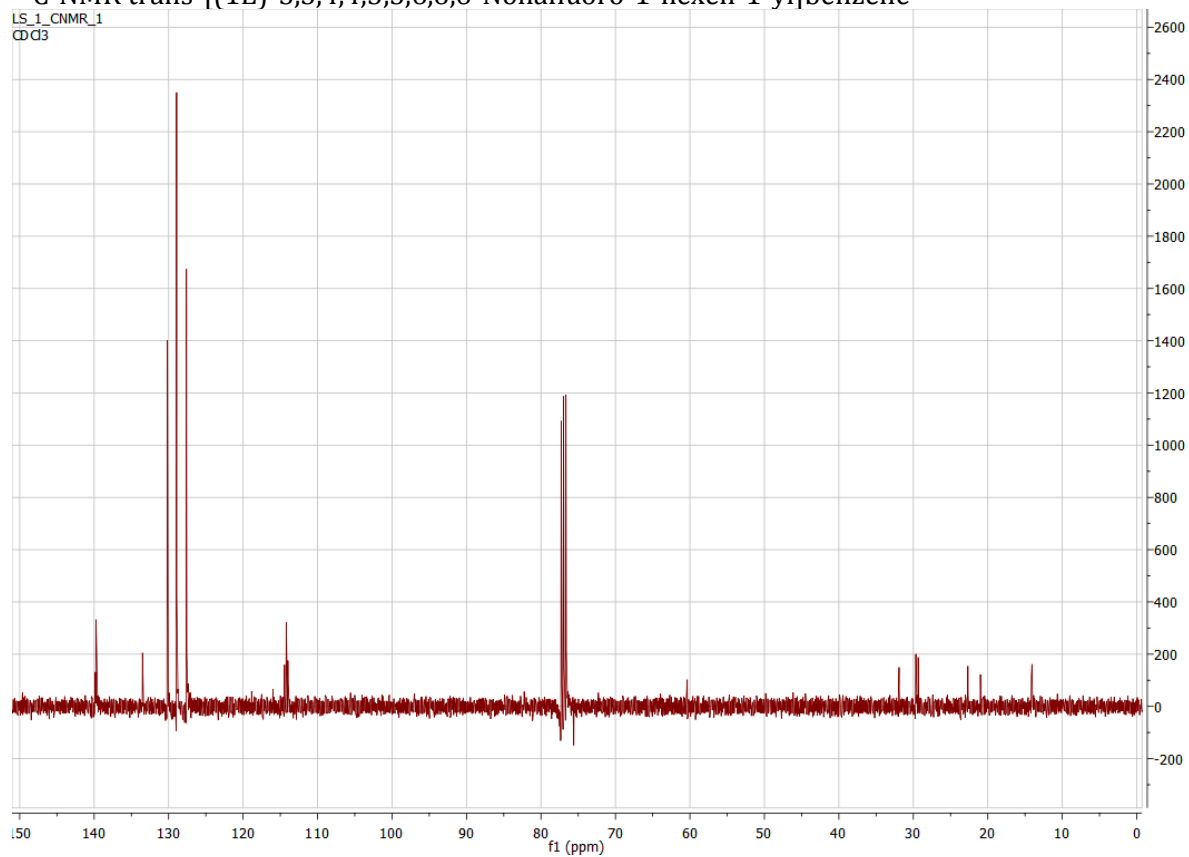
The effect did not occur in later experiments and was not further investigated.
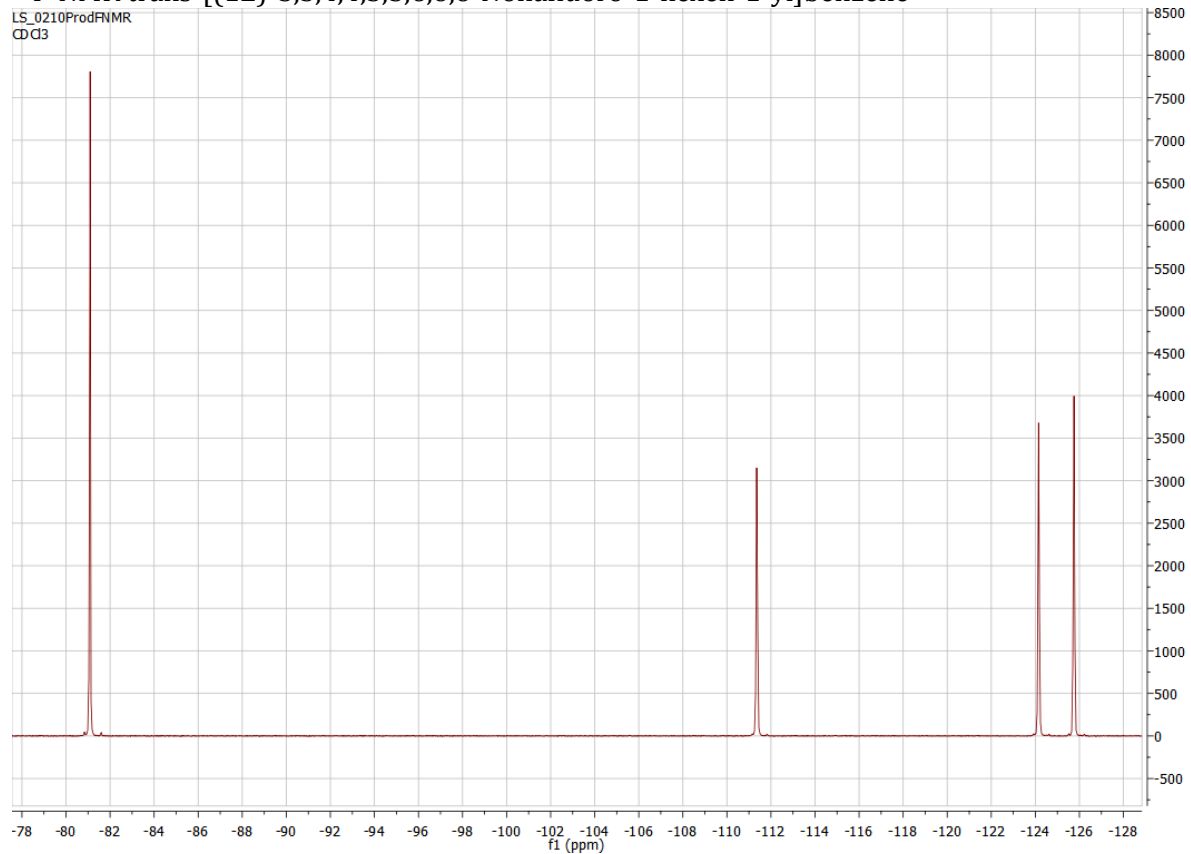
APPENDIX 2: NMR SPECTRA

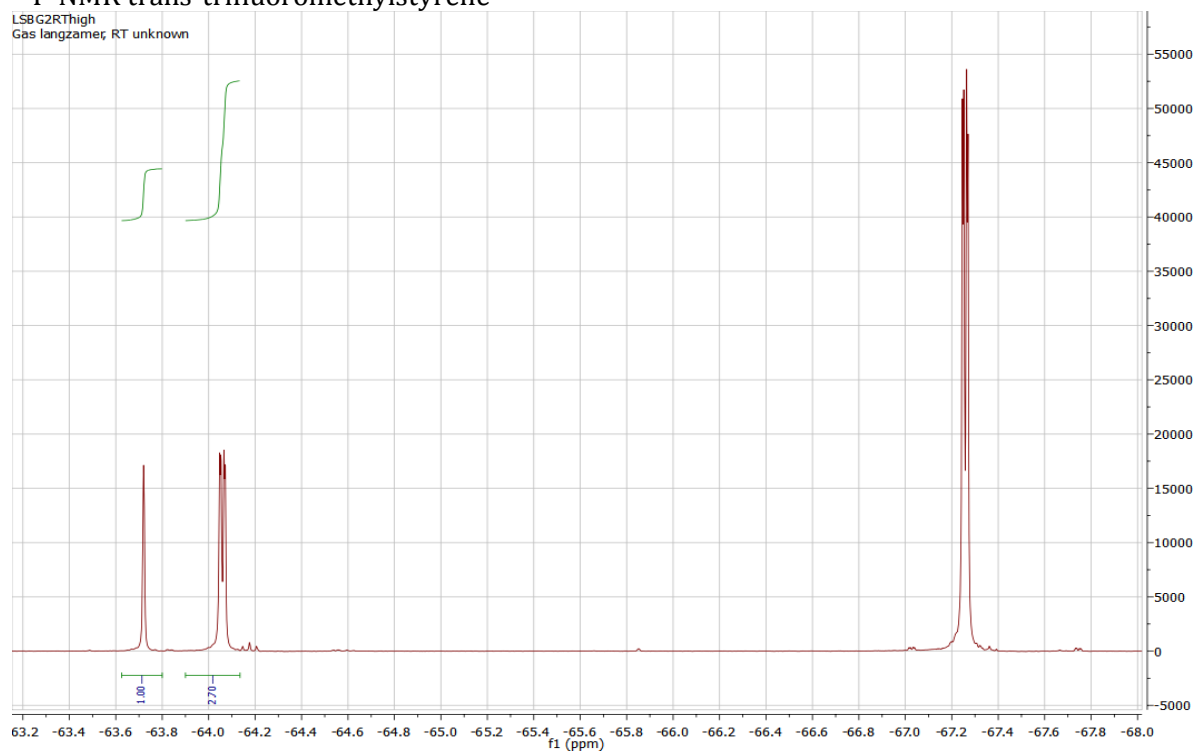## 1H-NMR [(1E)-3,3,4,4,5,5,6,6,6-Nonafluoro-1-hexen-1-yl]benzene
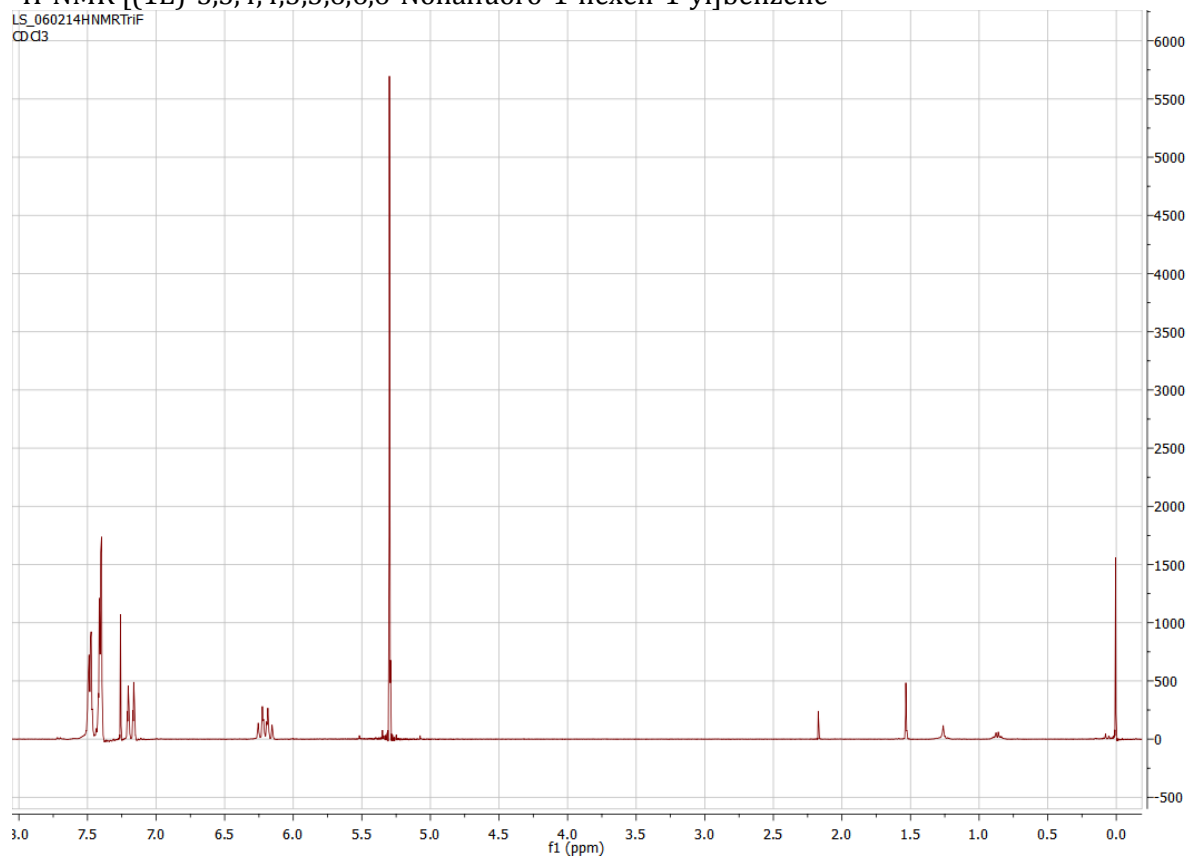
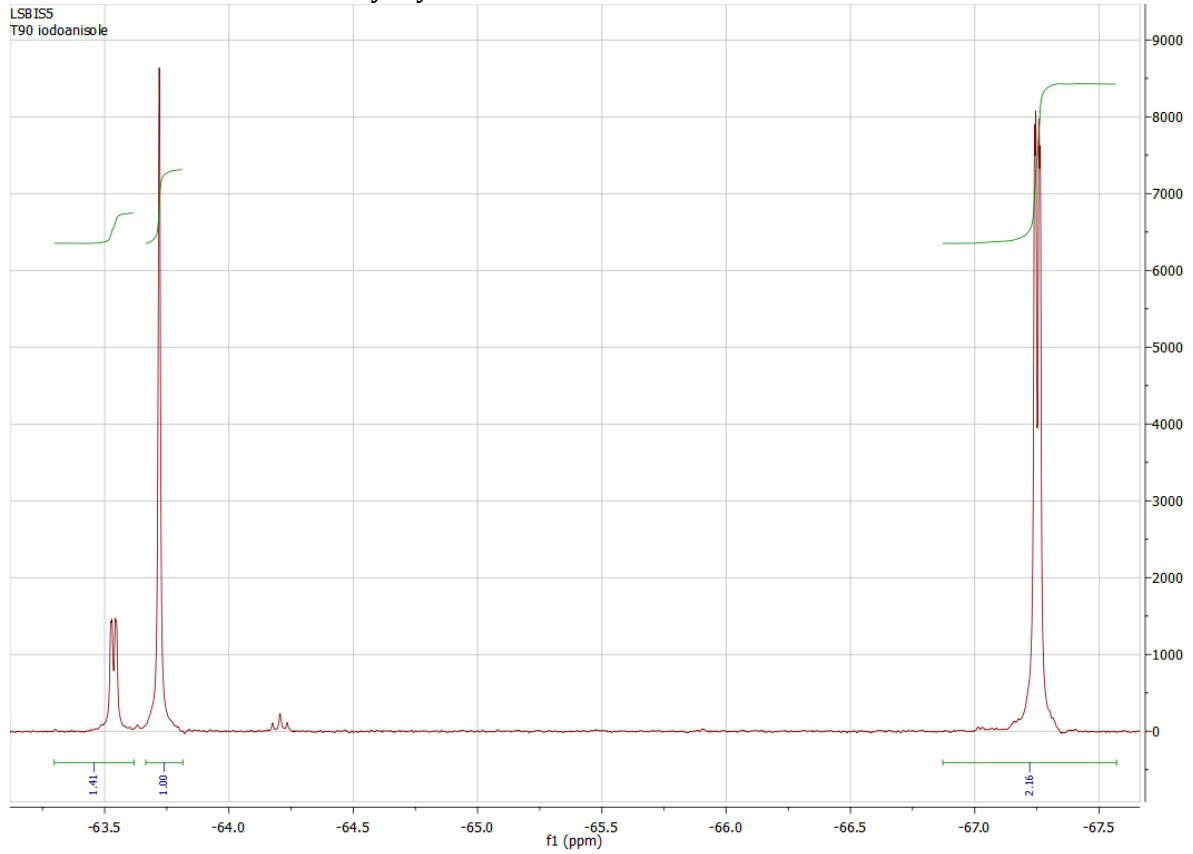## 13C-NMR trans-[(1E)-3,3,4,4,5,5,6,6,6-Nonafluoro-1-hexen-1-yl]benzene

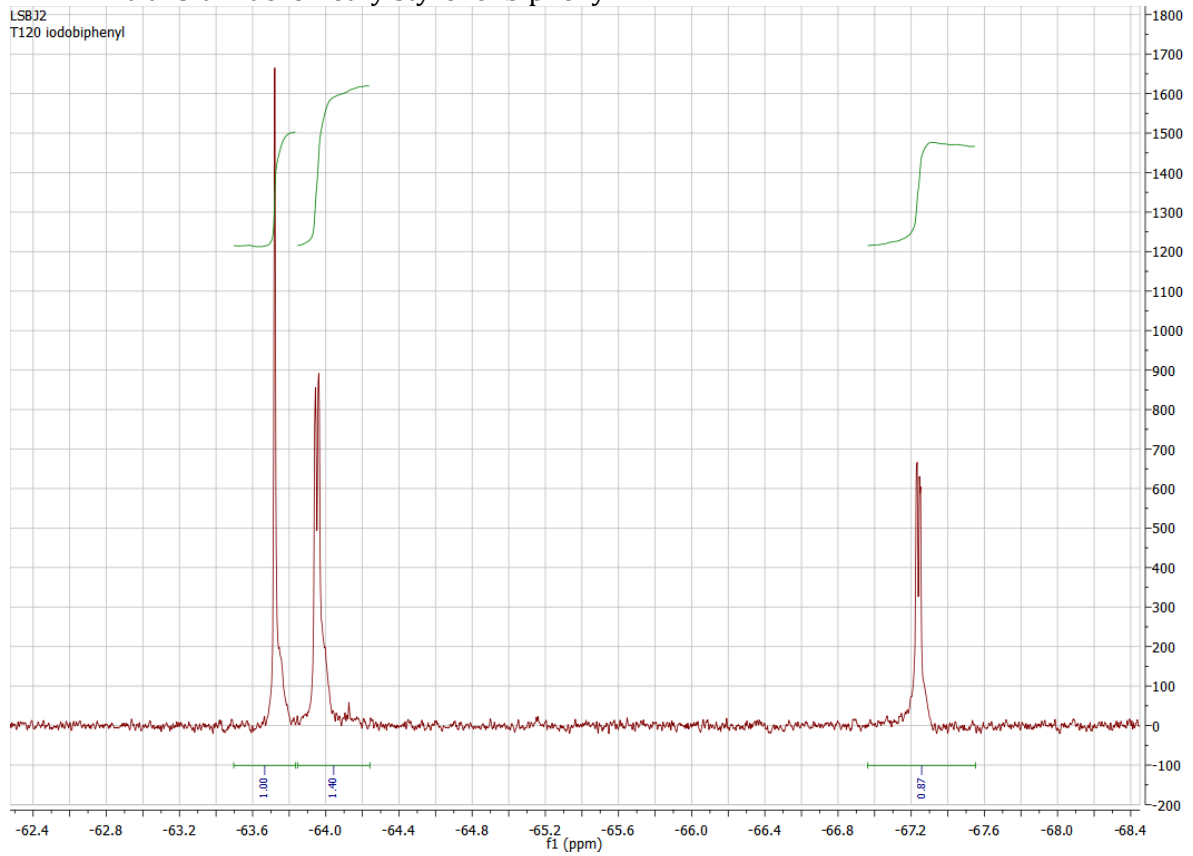¹⁹F-NMR trans-[(1E)-3,3,4,4,5,5,6,6,6-Nonafluoro-1-hexen-1-yl]benzene

LS_0210ProdFNMR
CDCl3

¹⁹F-NMR trans-trifluoromethylstyrene

LSBG2RThigh
Gas langzamer, RT unknown

¹⁹F-NMR trans-trifluoromethylstyrene+anisole


¹⁹F-NMR trans-trifluoromethylstyrene+biphenyl

APPENDIX 3: BROMOBENZENE EXPERIMENTS

Batch and flow liquid experiments were performed with iodobenzene substituted for bromobenzene. While first indication with batch experiments proved to be successful, obtaining a yield of 88%, in comparison with the 73% obtained with iodobenzene under the same reaction conditions, the conversion to flow failed.
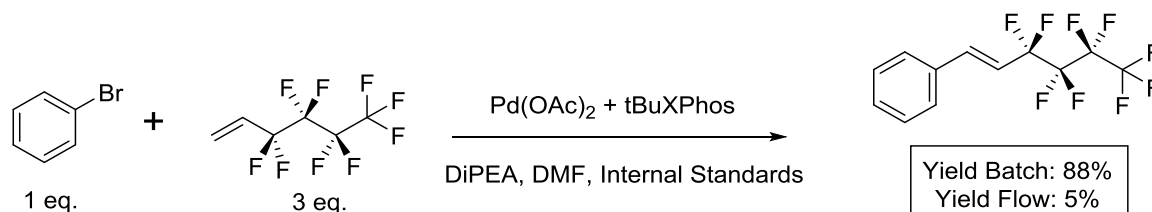

It was observed that the palladium catalyst would immidiatly turn black and precipitate in the reactor. Similar problems occurred in the past with the iodobenzene experiments but this was overcome later.

For the transition to gas-liquid flow experiments was desired in the later stage of the project, the liquid bromobenzene experiments were abandoned. It is however most likely that gas-liquid and liquid experiments with bromobenzene are suitable for the transition to flow.
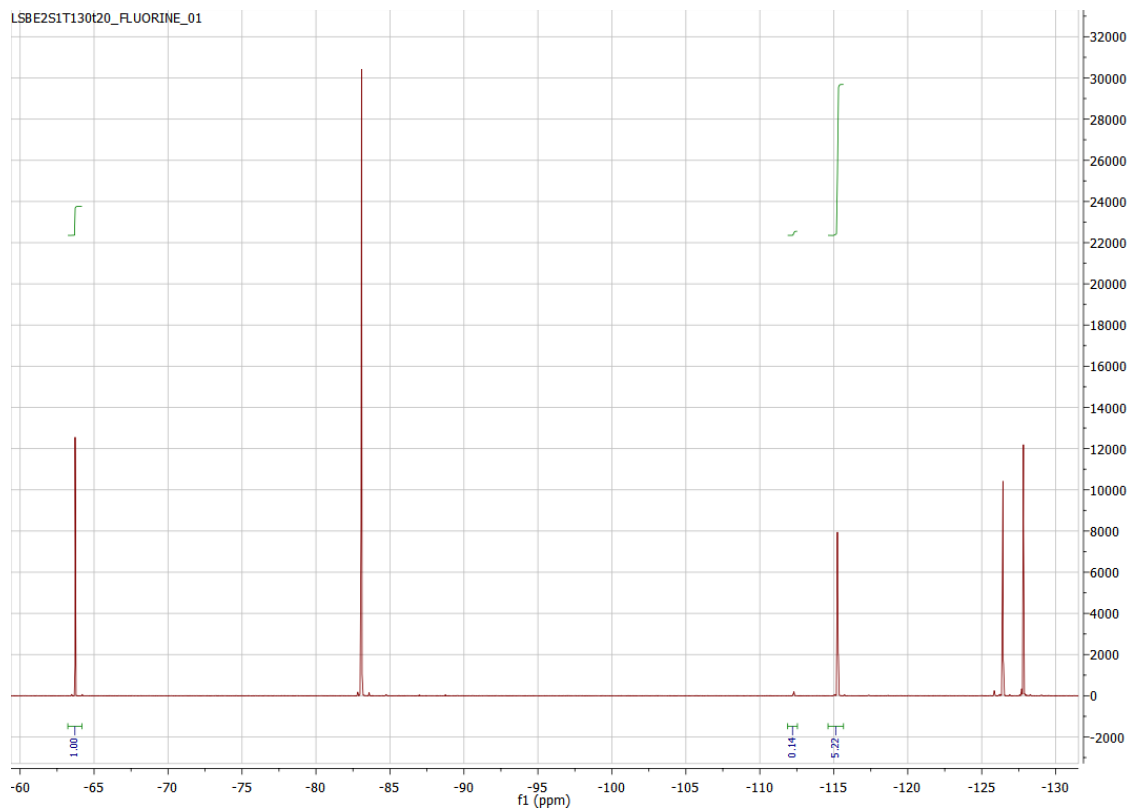
Table 6: Experimental conditions

Parameter	Value
Temperature	70 [^{0}C] (Batch) / 130 [^{0}C] (Flow)
Base	DiPEA
Solvent	DMF
Catalyst concentration	4 mol %
Reaction time	24 hr (Batch) / 20 min (Flow)

19F-NMR trans-[(1E)-3,3,4,4,5,5,6,6,6-Nonafluoro-1-hexen-1-yl]benzene from bromobenzene (Batch)
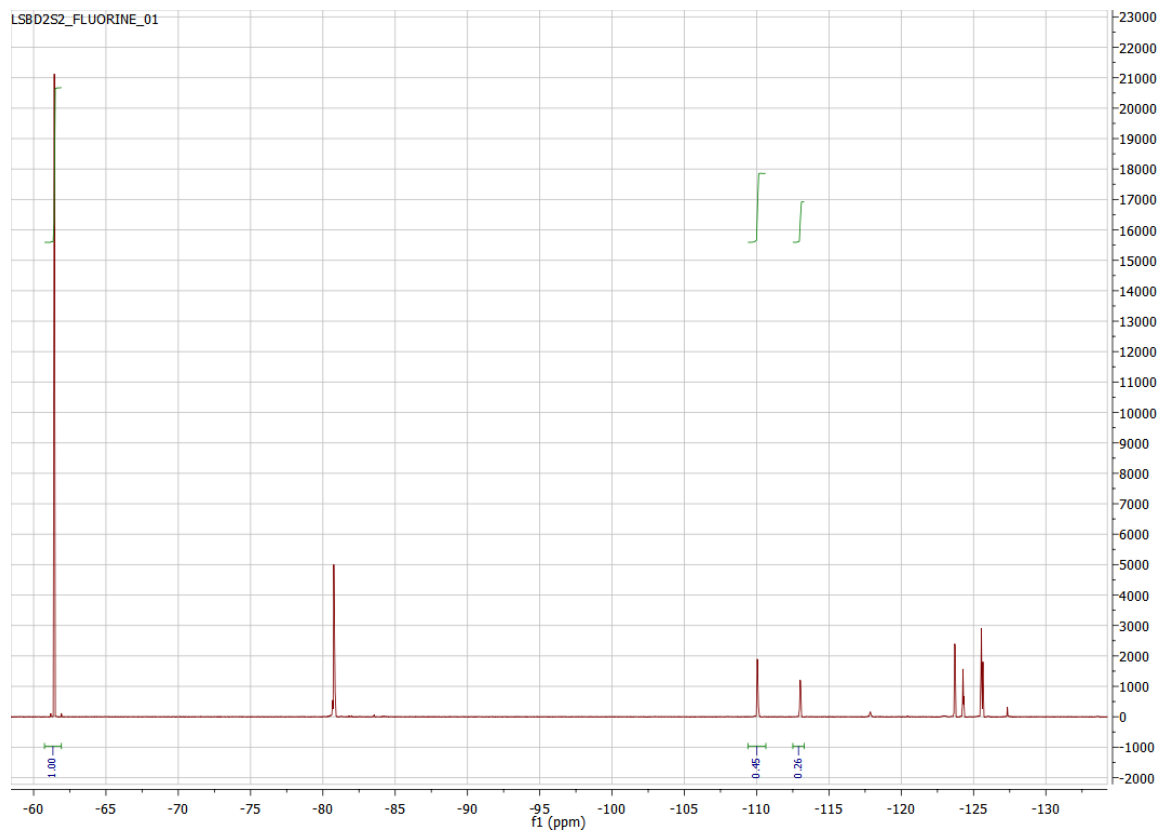
19F-NMR trans-[(1E)-3,3,4,4,5,5,6,6,6-Nonafluoro-1-hexen-1-yl]benzene from bromobenzene (Flow)

APPENDIX 4: CORRECTED YIELD FOR LIQUID FLOW EXPERIMENTS

Calculations performed to determine NMR yields in all represented results are based on the real output signal of the NMR graphs obtained.

When NMR signals of the starting material and end product are added together to calculate the overall mass-balance, it turns out that the signal of the internal standard does not represent the total mass in the reaction mixture.

Therefore a corrected yield is calculated based on the mass balance.

Figure 25: Corrected yields versus residence time

Corrected yields are given in number and are represented by clear colors and have the •as marker. Initial yields are displayed under their reprehensive corrected yield in lighter color and have ◊ as marker.

Corrected yields turned out to be higher than initial yields, especially at higher temperatures. For these products were not all validated by isolation, initial yields are given as representative results.

Mass balance calculations in gas-liquid experiments were not possible due to the unknown gas concentration in the micro flow reactor. The mass flow controller was not calibrated on the used gas.