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Heterogeneous Heck-reactions catalyzed by Pd-substituted mixed Ce-Sn-Oxides

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Abstract

The aim of this thesis is to determine the main parameters for the conceptual development of a continuous synthesis step for the production of rosuvastatin. Statins such as rosuvastatin are drugs that can lower cholesterol levels. Which can lead to an increase of the risk of heart diseases. In particular, this thesis focuses on the addition of an important side group via a Mizoroki-Heck coupling reaction. For the reaction a palladium substituted mixed Ce -, Sn - oxide catalyst is used. For optimization an example reaction, the cross coupling of iodobenzene and 3-buten-2-ol is performed. First experiments are carried out in batch and with the obtained results a continuous process is designed and tested. Seven catalysts with different ratio of tin and cerium are tested. Also different bases are used in the batch experiments. Finally, in order to get a better understanding of the reaction different substances are investigated to test their influence on the outcome.

It could be shown that a catalyst with high tin content and low cerium gave the best conversion. A solvent mixture with 70 vol.% ethanol and 30 vol.% water in combination with K_2CO_3 as base gave the best results. With the used Pd-substituted Ce-Sn-oxide catalysts, a conversion of iodobenzene more than 90% was achieved after 120 min.

The Heck reaction in continuous flow was carried out in the so-called "Plug and Play reactor". The production of 4-phenyl-but-3-en-2-ol was possible in the continuous flow reaction. A side reaction that occurred in the continuous experiments was the formation of biphenyl by homo-coupling of the iodobenzene.

Overall, the approach to use the Pd substituted Ce, Sn -oxide catalyzed Heck reaction seems to be an attractive alternative to conventional synthetic routes.

Kurzfassung

Das Ziel dieser Arbeit ist es, die Haupteinflussparameter für die konzeptionelle Entwicklung eines kontinuierlichen Syntheseschrittes zur Herstellung von Rosuvastatin zu bestimmen. Statine wie Rosuvastatin sind Wirkstoffe, die den Cholesterinspiegel senken können. Ein hoher Cholesterinspiegel kann das Risiko von Herzkreislauferkrankungen erhöhen. Dieser Syntheseschritt ist die Addition einer wichtigen Seitengruppe durch eine Mizoroki-Heck Kupplungsreaktion. Für die Reaktion wird ein Palladium-substituierter Ce- Sn- Oxid Katalysator verwendet. Als Beispielreaktion dient die Kreuzkupplung von Iodbenzol und 3-Buten-2-ol. Erste Versuche werden im Batch durchgeführt und mit den erhaltenen Ergebnissen wird ein kontinuierlicher Prozess entworfen und getestet. Sieben Katalysatoren mit verschiedenen Anteilen von Zinn und Cer werden getestet. In den Batch-Experimenten werden auch verschiedene Basen verwendet. Zum besseren Verständnis der Reaktion werden verschiedene Substanzen und deren Einfluss auf den Umsatz getestet.

Es konnte gezeigt werden, dass ein Katalysator mit hohem Zinn- und niedrigem Cergehalt den besten Umsatz ergab. Ein Lösungsmittelgemisch aus 70 vol.% Ethanol und 30 vol.% Wasser mit K_2CO_3 als Base lieferte das beste Ergebnis. Mit den verwendeten Pd-substituierten Ce-Sn-Oxid-Katalysatoren konnte ein Umsatz von Iodbenzol von mehr als 90% nach 120 min erreicht werden. Die kontinuierliche Synthese wurde im sogenannten "Plug and Play Reaktor " durchgeführt. Die Herstellung von 4-Phenyl-but-3-en-2-ol war in einer kontinuierlichen Reaktion möglich. Eine Nebenreaktion, die dabei auftrat, war die Bildung von Biphenyl durch Homokupplung des Iodbenzols.

Die Verwendung der Pd-substituierten Ce -, Sn - Oxid-katalysatoren für Heck-Reaktionen scheint eine attraktive Alternative zu herkömmlichen Synthesewegen zu sein.

Acknowledgment

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List of Abbreviations

API	active pharmaceutical ingredient
cat	catalyst
°C	degrees Celsius
C	carbon
conv	conversion
conc	concentration
DMF	dimethylformamide
EtOH	ethanol
Enol	alkene with a alkohol side chain
GC	gas chromatography
HPLC	high pressure liquid chromatography
KET	ketone-enol tautomeric
L	ligand
L	liter
LDL	low density lipoproteine
MTBE	methyl *tert*-butyl ether
min	minute
NMR	nuclear magnetic resonance
PSD	particle size distribution
PTFE	polytetrafluoroethylene
SC	solution combustion
T	temperature

t	time
t_R	retention time
TBAB	tetra-*n*-butylammonium bromide
TEA	triethylamine
TEOA	triethanolamine
TLC	thin layer chromatography
UV	ultra violet
v/v	volume fraction

1 Introduction

1.1 Statins

The class of drugs called statins are one of the most therapeutically effective drugs available for reducing low density lipoprotein (LDL) concentration in the bloodstream of humans. Statins are used in the treatment of hypercholesterolemia, hyperlipoproteinemia and atherosclerosis.[1]

One goal of this thesis is to develop an approach to link the building blocks for Rosuvastatin, the active pharmaceutical ingredient (API) of the cholesterol lowering drug Crestor® (AstraZeneca)(Figure 1.1).

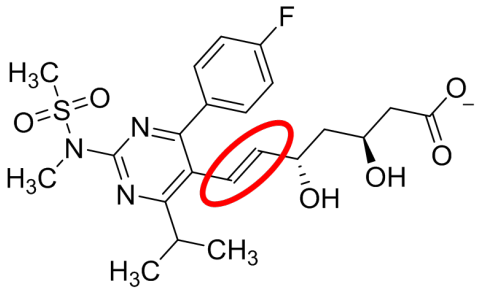


Figure 1.1: Structure of Rosuvastatin, the active pharmaceutical ingredient (API) of the cholesterol lowering drug Crestor® (AstraZeneca)

Many statins have a C=C double bond in their molecular structure[2] so a main step in statin synthesis can be done by a Heck reaction. The Heck reaction is a palladium catalyzed coupling reaction where two hydrocarbon fragments are connected with a C=C double bond.

1.2 Pd-catalyzed coupling reactions

Reactions where a bond between two hydrocarbon fragments (organic halide, olefine or organometallic compound) is formed, are considered as coupling reactions. What these reactions have in common is that they proceed in present of a transition-metal catalyst such as palladium. The two main types of couplings are homogeneous coupling, where two reactants of the same species are coupled; and the cross coupling reaction, where two different substances are combined.[3]

The importance of the cross coupling reaction in organic synthesis was acknowledged with the Nobel Prize in chemistry in 2010 for R.F. Heck, E. Negishi and A. Suzuki for their palladium catalyzed cross coupling reactions in organic synthesis.[4]

1.3 Heck reaction

In the Mizoroki-Heck coupling reaction, often abbreviated as Heck reaction, a halide is substituted at an unsaturated hydrocarbon bond with the aid of a base and a palladium catalyst. A general reaction equation can be written as showed in Figure 1.2[3]

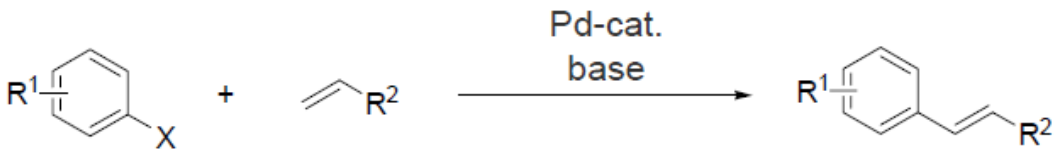


Figure 1.2: Heck reaction scheme

For the reaction mechanism of the Mizoroki-Heck coupling some suggestions have been proposed since the publication of the reaction in 1972.[5] However, many of those schemes serve only as a working hypothesis, a commonly used Heck reaction catalytic cycle with a homogeneous catalyst is shown in Figure 1.3.[6]

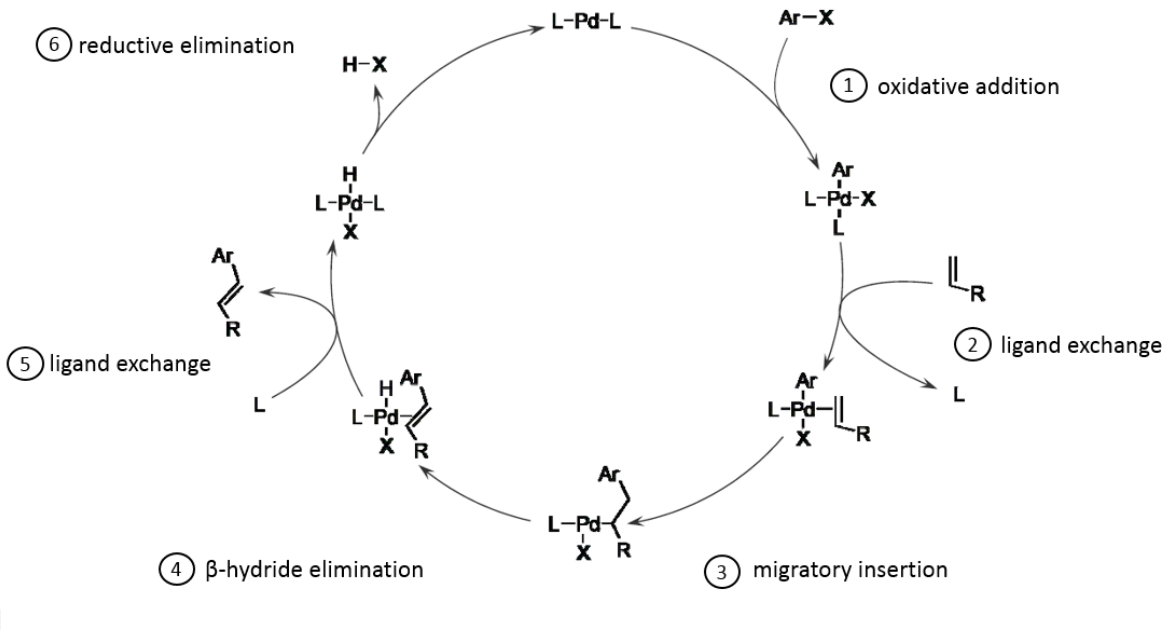


Figure 1.3: Catalytic cycle with a homogeneous ligand Pd catalyst [6]

The Heck reaction cycle starts with the oxidative addition of the halide (step 1), where the Pd inserts between the halide and the carbon bond. Afterwards one of the ligands is exchanged with the alkene molecule (step 2). In the next step, the alkene bond inserts into the C-C bond, generating a relatively unstable σ-bond, and the ligand migrates towards the palladium catalyst (step 3). Due to this unstable σ-bond, an internal rotation of the generated alkyl-palladium species is possible, leading to a *cis*-configuration (step 4). This step is necessary to provide the subsequently β-H- elimination generating the desired *trans*-form of the alkene coupling product (step 5). In the cycle closing step the catalyst is regenerated by reductive elimination by a base (step 6). [6]

Most aromatic and heteroaromatic hydrocarbons with halides or pseudo-halides can be used in the Heck reaction. [7] Heck reactions are an important step for the industrial production of fine chemicals. For example Naproxen® the API of an anti-inflammatory drug, an anti-asthma agent Singulair® or the herbicide Prosulfuron® are produced by synthesis routes using a Heck reaction. [8] The Heck reaction can also be used for intermolecular reaction such as cyclization. [9]

1.4 Heterogeneous catalysts

In the past homogeneous catalysts were often used for cross-coupling reactions.[10] Homogeneous catalysts require ligands (L), frequently phosphates are used, which may be difficult to handle (air sensitive) and removal of the catalyst from the product can be difficult.[11] In contrast, a heterogeneous catalyst is in a different phase than the reactants. The catalyst is usually solid and the reactants are liquid or gaseous[12] which results in some major advantages compared to homogeneous catalysts:

- easy removal and reuse of the catalysts
- possibility to use the catalysts in packed-bed flow application
- minimize contamination of product

Heterogeneous catalyst can be divided into two groups:[12]

- Supported catalysts are mostly defined as those where a non-catalytic carrier material is used, on which a thin layer of the active catalysts is deposed.
- Bulk catalytic materials are generated as a new solid phase, with a homogeneous distribution of the catalytic active centers.[13]

1.4.1 Solution combustion method

Solution combustion (SC) is an effective method for synthesis of small particles and it is used for the production of fine oxide powders for different advanced applications including bulk catalysts.[14] For the formation of a metal oxide powder by SC a combination of metal salts in an aqueous solution with a fuel is prepared. Glycine or urea are frequently used as fuels. The solution is heated till the reaction is initiated, an exothermic reaction occurs that is self-sustaining within resulting in a porous solid as final product. In some cases it needs subsequent heat treatment to form the product.[15] The so produced porous catalysts can, for example, be used in a packed bed reactor.

1.5 Flow chemistry

Reactors used for chemical synthesis are categorized into batch reactors and continuous reactors. In a batch reactor, the concentration of chemical species including starting materials and products changes with reaction time. In a plug flow reactor at steady state, the concentration of the chemicals remains constant over time, but it differs at a different location in the reactor.[16]

In the past, continuous flow processing has considered more of an industrial value for large-scale synthesis in chemical industry, now this technology is adopt for small-scale laboratory synthesis. There are clear benefits, especially when working with hazardous intermediates or when rapid heat dissipation and efficient mixing are needed.[17]

1.6 Preliminary work

A main part of this work is based on the dissertation of Lichtenegger Georg, who worked with the same catalysts for Suzuki-Miyaura coupling reactions.[18] Also the used reactor for the continuous synthesis was developed during his dissertation in cooperation with OneA Engineering.[19,20]

2 Results

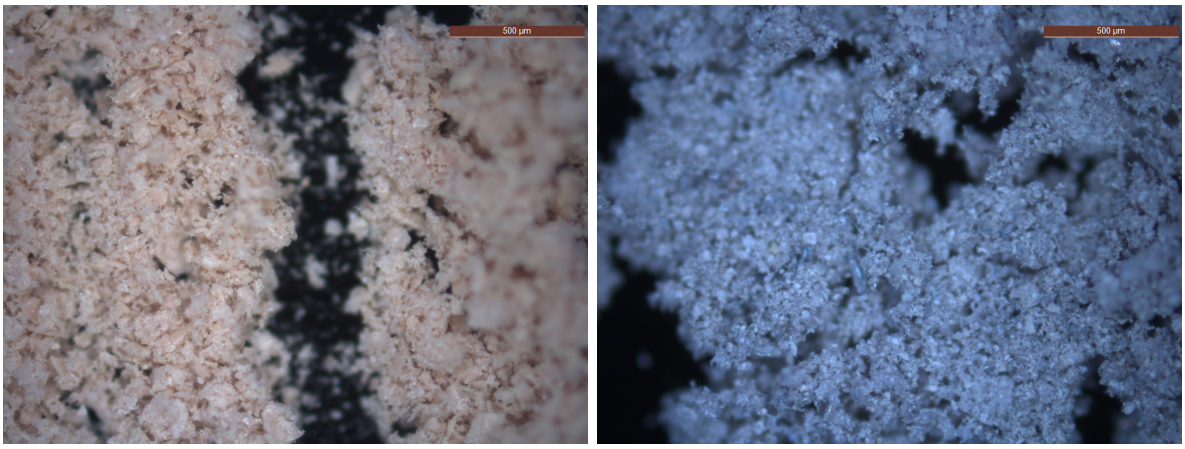
2.1 Catalyst preparation

The solution combustion method is a rapid and inexpensive preparation method to form a palladium substituted mixed Ce -, Sn - oxide catalyst.[21] The catalyst can be produced within hours and with a muffle furnace and basic lab equipment. To prepare the catalyst, appropriate amounts of tin(II) oxalate (SnC_2O_4), ammonium cerium (IV) nitrate ($(NH_4)_2Ce(NO_3)_6$, palladium(II) chloride($PdCl_2$,) and glycine ($C_2H_5NO_2$) were mixed. This mixture was placed in a crystallization dish, dispersed in 2 mL of water and put in an ultrasonic bath for 30 minutes. Afterwards the formed homogeneous viscous liquid was treated in a muffle furnace preheated at 350°C. The mixture ignited, initiating a self-propagating combustion reaction, which yielded a voluminous, porous solid. This solid was ground with mortar and pestle and heated again up for another 8 h. The produced catalyst itself appears as porous with a light brown to yellow color. The obtained powders were directly usable as catalyst for the cross-coupling reactions.[18] Seven catalysts with varying amounts of Ce and Sn were prepared in order to check the influence of these metals on the reaction performance (Table 2.1).

Table 2.1: Used catalyst compositions

No.	molecular formula
1	$Ce_{0.99}Pd_{0.01}O_{2-\delta}$
2	$Ce_{0.79}\ Sn_{0.20}\ Pd_{0.01}\ O_{2-\delta}$
3	$Ce_{0.59}\ Sn_{0.40}\ Pd_{0.01}\ O_{2-\delta}$
4	$Ce_{0.495}\ Sn_{0.495}\ Pd_{0.01}\ O_{2-\delta}$
5	$Ce_{0.40}\ Sn_{0.59}\ Pd_{0.01}\ O_{2-\delta}$
6	$Ce_{0.20}\ Sn_{0.79}\ Pd_{0.01}\ O_{2-\delta}$
7	$Sn_{0.99}\ Pd_{0.01}\ O_{2-\delta}$

The second heating, after the grounding with mortar and pestle, was done at different temperatures from 350°C, to 500°C-650°C till up to 1000°C for catalyst 7. Results of the Heck reaction indicated that heating of the catalyst in the range of 500-650°C increases its activity. Heating it up to 1000°C deactivates the catalyst. This effect could not be explained by sintering of the particle, because the particle size distribution of the catalyst 7 (with no cerium) shows even smaller particles for the higher heated fraction (Figure 2.2). Also a change in color was recognized,(Figure 2.1) so this indicates a chemical change at the catalyst. According to literature the palladium oxide has a melting point of 750°C and it is also known that at temperature higher than 800°C the palladium oxide decomposes to palladium metal and oxygen gas.[22] This might explain the loss of activity after heating the catalyst up to 1000°C.



(a) cat 7 350°C (b) cat 7 1000°C

Figure 2.1: Microscope pictures of cat 7 heated at 350°C / 1000°C.

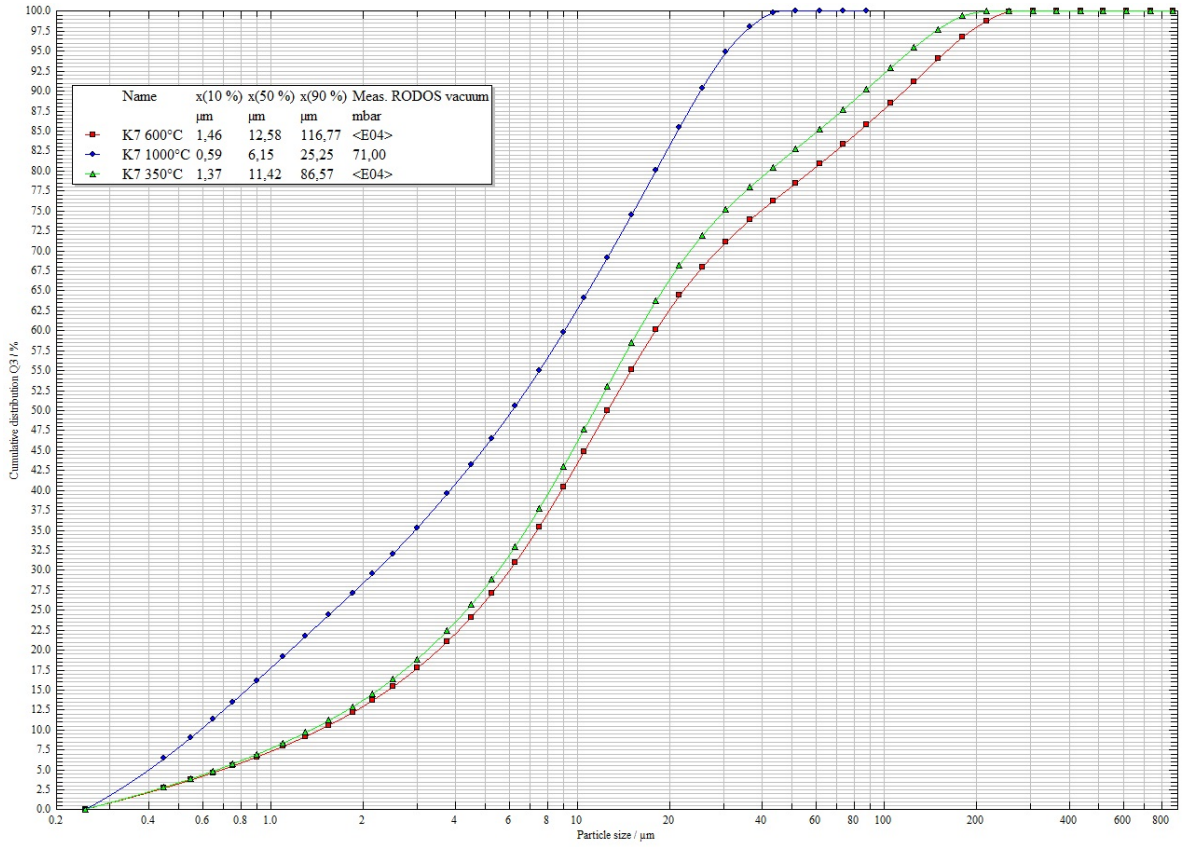


Figure 2.2: Particle size distribution of the catalyst 7 ($Sn_{0.99}$ $Pd_{0.01}$ $O_{2-\delta}$) prepared at T=350°C , T=600°C, T=1000°C

2.2 Optimization of reaction conditions

For optimization of the Heck reaction the cross-coupling of iodobenzene and 3-buten-2-ol to form 4-phenyl-but-3-en-2-ol was chosen. (Figure 2.3) It was selected because the product has some similarity with satins such as rosuvastatin (Figure 1.1) and this reaction shows a fast reaction rate. With these compounds the optimization of the reaction parameters was done.

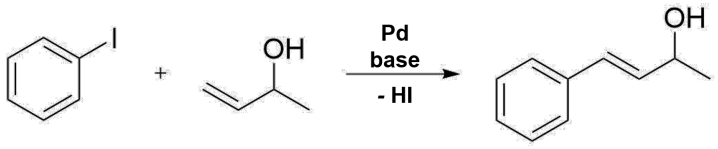


Figure 2.3: Scheme of the reaction of iodobenzene with 3-buten-2-ol to form 4-phenyl-but-3-en-2-ol

In a typical experiment a round flask was filled with 0.70 mmol of iodobenzene, 1.5 molar equivalents of the 3-buten-2-ol, 1.5 molar equivalents of base, 100 μL of anisole (internal standard) and 20 mL of a solvent. The filled flask was placed in an oil bath and the mixture was stirred and heated at 80°C. The first sample was taken before 5 mg of the catalyst were added. The samples from the reaction solution were taken after 15, 30, 60, 90 and 120 minutes.

2.2.1 Influence of catalyst composition

The first task in optimization was the investigation of the influence of the catalyst composition. For this the ratio of cerium and tin in the catalyst was varied. The amount of palladium stays the same for all runs. Notably, an increase of the activity was observed with increasing amount of tin.

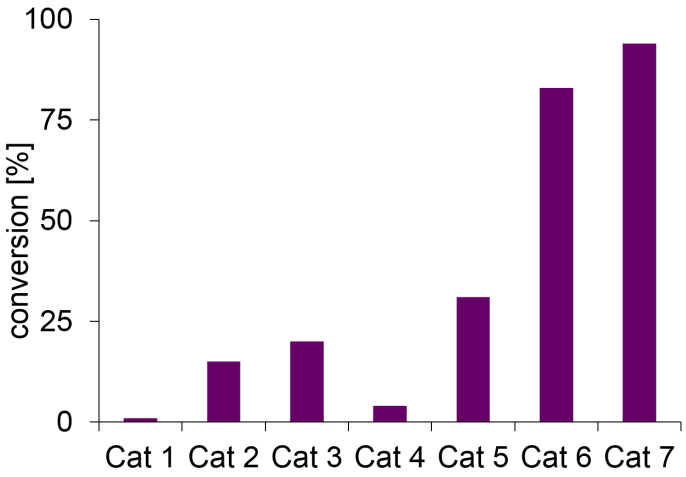


Figure 2.4: Different catalysts and the achieved conversion of iodobenzene by the example Heck reaction; 5 mg of each cat, after 120 min at 80°C, solvent mixture 70 vol.% ethanol and 30 vol.% water and 1.05 mmol K_2CO_3

As can be seen in Figure 2.4 the catalyst 7 with no cerium gave the best results, based on the conversion of iodobenzene and is therefore used for the further experiments.

2.2.2 Base

The last step in the Heck reaction cycle is the regeneration of the catalyst by reductive elimination in the presence of a base. (Figure 1.3) This means one important factor for a Heck coupling reaction is the used base. In order to find a properly working base different inorganic and organic bases were tested. For each experiment the same amount of base 1.05 mmol (1.5 mol equivalent to iodobenezene) was used to be able to compare the influence of the different used bases. (Table 2.2)

Table 2.2: Tested bases and achieved conversion of iodobenzene; after 120 min; 80°C; 5 mg cat 7; solvent mixture 70 vol.% ethanol and 30 vol.% water

Base	Conversion[%]
K_2CO_3	95
Cs_2CO_3	71
NaOH	20
KOH	18
NaAcetat	3
Triethylamine	<1
Triethanolamine	<1

It can be seen in Table 2.2 that K_2CO_3 gives the best conversion for the tested reaction and that organic bases such as triethanolamine (TEOA) or triethylamine (TEA) are not useful for these settings. It was found that the strength of the base is not the main parameter, the pK_a value did not correlate with the determined conversion.

Since K_2CO_3 revealed the highest conversion it is used for the further experiments.

2.2.3 Solvent

The solvent composition can have an influence on the reaction rates. In the investigated reactions the solubility of the used chemicals is one main point. The amount of dissolved inorganic base such as K_2CO_3 in organic solvents is very low, but high in polar solvents such as water, for the hydrocarbons usually the opposite is the case.[23] Some findings concerning the influence of different solvents and mixtures are shown in Table 2.3.

Table 2.3: Tested solvents and solvent mixtures

Solvent	Note
EtOH 98%	base not dissolved
H_2O 100%	iodobenzene not dissolved
EtOH / H_2O 7/3	conversion of 95%
EtOH / H_2O 1/1	iodobenzene dissolved at higher T; conv. 97%
EtOH / H_2O 3/7	iodobenzene partially dissolved
Propane-1,2-diol	purification of the product difficult
DMF	base not dissolved

It could be shown a high water content in the reaction solution leads to a split in aqueous-, organic- and a solid- (catalyst) phase. (Figure 2.5). In such a 3-phase reaction a slower substance transfer takes place and there is the risk of phase separation of the mixture. This is a problem especially later for the pumping in the experiments with the packed bed reactor. Currently only one pump and one feeding vessel are used, but in a future setting that can be solved with two pumps and a mixing zone.

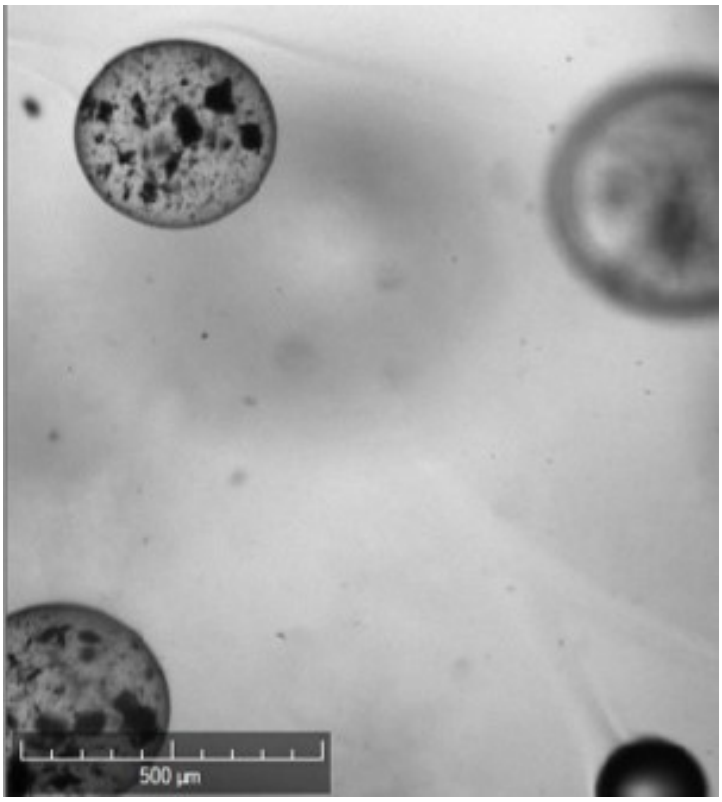


Figure 2.5: 3-phase reaction: cat 7 (particle); iodobenzene (disperse phase); EtOH/H_2O (continuous phase) picture taken with Crystalline ®Technobis crystallization systems)

In a non-polar solvent only organic bases have a sufficient solubility, but they lead to low conversions as shown in the preliminary experiments. An other important point is the limitation of the reaction temperature due to the boiling point of the solvent. This restriction could be overcome by a pressurized reactor. For the most reactions mentioned the solvent consists of 70% ethanol and 30% water. The boiling point of this mixture is about 85°C, thus the temperature of the heated oil bath was set to 80°C.

To summarize the findings of the experiments so far, the best conditions for the Heck reaction of iodobenzene and 3-buten-2-ol were the catalyst 7 ($Ce_{0.99}Pd_{0.01}O_{2-\delta}$), K_2CO_3 as base dissolved in a mixture of 70 vol.% ethanol and 30 vol.% water and a temperature of 80°C.

2.3 Substrate screening

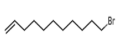
In addition to the example reaction other halides and unsaturated hydrocarbons were tested. The conversion of the reactions is very diverse depending on the combined chemicals (Table 2.4). The calculated conversion is in all cases corresponding to the starting halide. All the reactions were done with the same amount of cat 7 at 80°C and with K_2CO_3 as base. 0.7 mmol of the halide and 1.05 mmol alkene in a mixture of 70 vol.% ethanol and 30 vol.% water for two hours.

Table 2.4: Tested substances and achieved conversion after 2 h at 80°C with 5 mg cat 7

Nr.	Halide	Alkene	Halide	Alkene	Conversion[%]
1	Iodobenzene	3-Buten-2-ol			95
2	Iodobenzene	5-Hexen-2-one			65
3	Iodobenzene	Acenaphthylene			42
4	Iodobenzene	4-Phenyl-1-butene			26
5	Iodobenzene	Ethylvinylether			8
6	4-Iodotoluene	3-Buten-2-ol			53
7	4-Iodotoluene	5-Hexen-2-one			63
8	4-Iodotoluene	4-Phenyl-1-butene			14
9	1-Iodo-3,4-dimetylbenzene	3-Buten-2-ol			68
10	1-Iodo-3,4-dimetylbenzene	5-Hexen-2-one			31
11	4-Iodophenol	3-Buten-2-ol			90
12	4-Iodophenol	Ethylvinylether			8
13	1-Bromo-4-iodobenzene	3-Buten-2-ol			76
14	2-Iodotoluene	3-Buten-2-ol			65

In some of the experiments no product could be detected after 2 hours at 80°C. (Table 2.5)

Table 2.5: Tested substances with no product detectable after 2 h at 80°C with 5 mg cat

Nr	Halide	Alkene	Halide	Alkene
1	Iodobenzene	1-Hexene		
2	Iodobenzene	11-Bromo-1-undecene		
3	Iodobenzene	Acrolein		
4	Iodobenzene	Styrene		
5	Iodobenzene	Vinylimidazole		
6	Iodobenzene	Vinylacetat		
7	Iodobenzene	Dicyclopentadiene		
8	4-Bromotoluene	3-Buten-2-ol		
9	5-Bromopyrimidine	3-Buten-2-ol		
10	4-Bromoaniline	3-Buten-2-ol		
11	2-Aminopyrimidine	3-Buten-2-ol		
12	4-Bromotoluene	5-Hexen-2-one		
13	4-Chlorotoluene	5-Hexen-2-one		
14	4-Bromobenzonitril	5-Hexen-2-one		
15	4-Bromoanisol	5-Hexen-2-one		
16	4-Bromoaniline	5-Hexen-2-one		
17	4-Bromoacetophenone	5-Hexen-2-one		
18	Phenylboronicacid	5-Hexen-2-one		
19	4-Bromotoluene	Styrene		
20	4-Iodotoluene	1-Hexene		

The effect of the leaving group ability is an important factor for this Heck coupling reactions. Iodide is a much better leaving group than bromide,[6] thus the iodide components react with the alkene but the bromides do not. Another outcome of these experiments is that close to the C=C double bond, an electron-rich functional group such as alcohol or ester is useful.[24] A long alkene with no functional group reacts slow compared to that with side chains. But these are just preliminary conclusions and more detailed investigation is needed to prove this theory. One reaction that occurs in the batch experiments was that very reactive substrates (styrene, vinylimidazole and acroleine) were found to undergo polymerization during the reaction.[25]

2.4 Recyclability test

As for optimization the model reaction of iodobenzene and 3-buten-2-ol using potassium carbonate as base was chosen for the examination of the recyclability catalyst 7. After a reaction time of 120 minutes, the catalyst was filtered off using a frit and was washed with ethanol. After drying at 105°C the remaining catalyst was weighed and reused in a new batch. This second run was not successful meaning no product was formed.

In a modified test, after 120 minutes of reaction, additional iodobenzene and 3-buten-2-ol were inserted, but did not lead to higher product formation. (Figure 2.6) That might be a hint of poisoning by a product or other deactivating of the palladium catalyst during the reaction, as other studies show this catalyst can be recycled several times when used for a Suzuki-Miyaura cross-coupling reaction.[18] That deviation can be caused by the different chemicals.

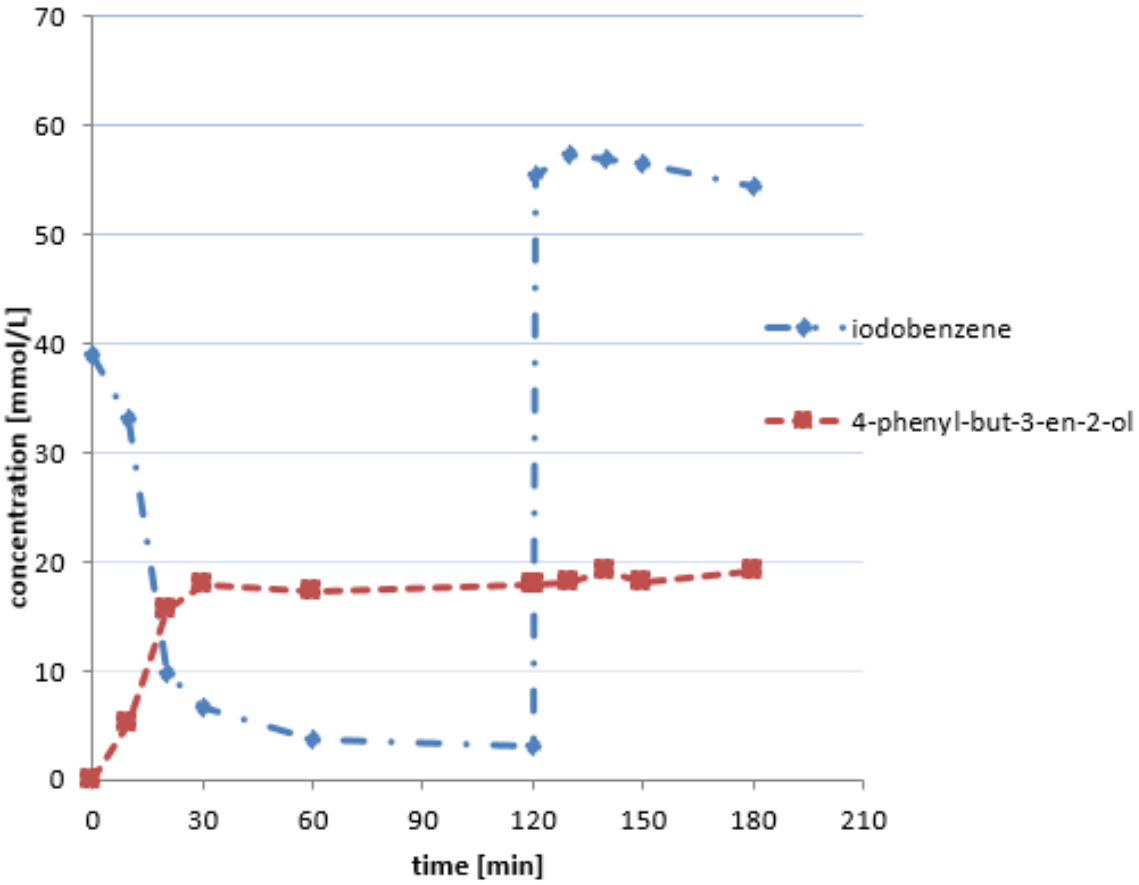


Figure 2.6: Concentration of iodobenzene and 4-phenyl-but-3-en-2-ol with additional start material after 2 h.

2.5 Keto-Enol Tautomerism

The reactions in which 3-buten-2-ol was used show a side reaction similar to the known Keto-Enol tautomerism (KET). Tautomers are constitutional isomers that differ by the location of a proton. For the KET the relocation of the proton is combined with the shift of the double bond from C=C to the C=O. Usually the ketone has a lower free energy and so equilibrium heavily favors the formation of the keto form. Acids and bases can catalyze this reaction and can change the chemical equilibrium as well.[26] In the structure of 3-buten-2-ol the C=C double bound is not next to the alcohol group but one bond away, so the substance is stable at room temperature. But under the reaction

condition a relocation of the double bound and the proton is possible, so a mixture of the ketone and enol is produced.(Figure 2.7) Instead of the desired 4-phenyl-but-3-en-2-ol some 4-phenyl-2-butanone is formed. As other studies show, the used base and solvent can influence whether the keto or enol form is produced.[27]

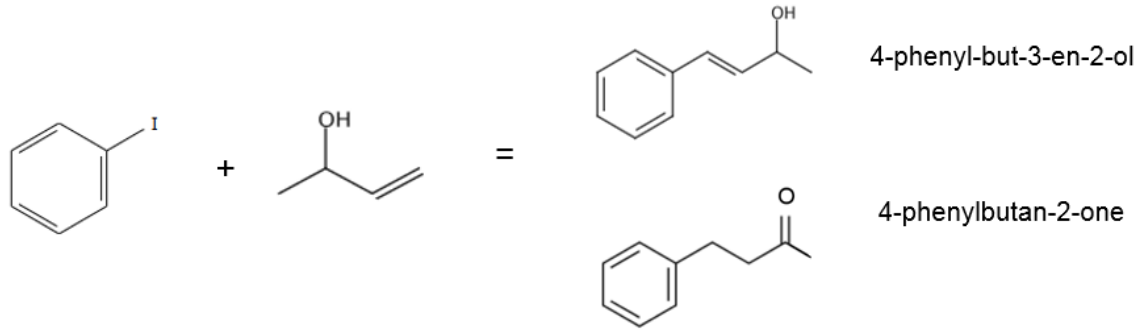


Figure 2.7: Scheme of the reaction of iodobenzene with 3-buten-2-ol to form a mixture of 4-phenyl-but-3-en-2-ol and 4-phenyl-2-butanone

The different products can be distinguished by their NMR spectra and the GC, but are not detected separately in the HPLC-UV chromatogram. This might be because the separation in the used column is too small or the result of a rearrangement of the molecular structure, caused by low pH value of the HPLC solvent or the properties of the solid phase.

A method to separate the two products by HPLC measurement is the formation of a derivative of one of the products. In this case the acylation of the alcohol with acid anhydride was done, as described in Sigma-Aldrich Derivatization Reagents[28] The derivation product, an ester, appears as an additional peak in the GC. (Figure 2.8)

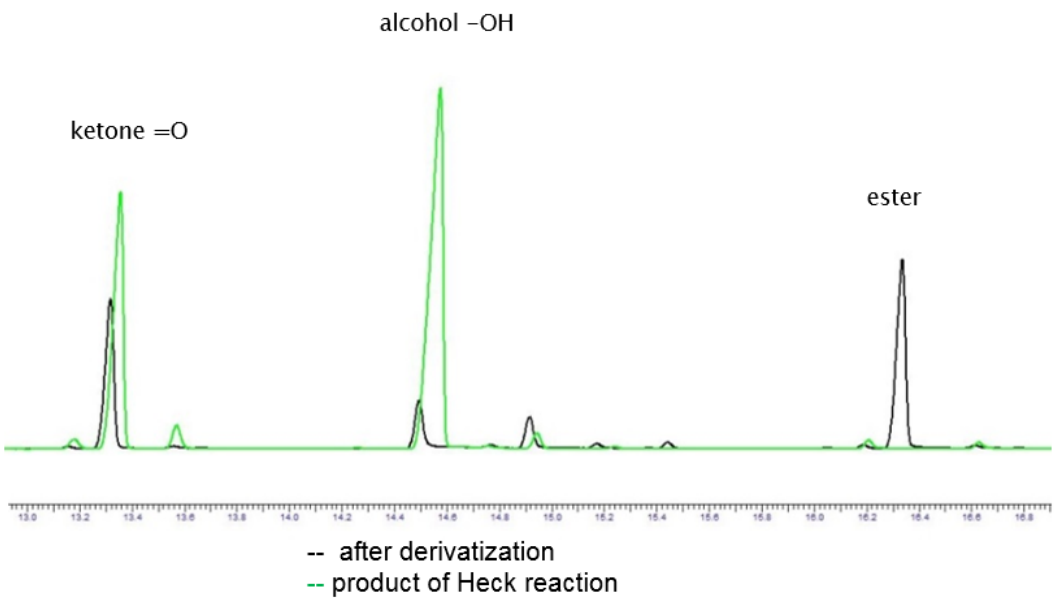


Figure 2.8: GC-chromatogram before and after derivatization, peaks of ketone, alcohol and the ester produced by the derivatization

Interestingly, preparative chromatography using silica gel converts the ketone to the desired enol. The test of the used solvent in mobile phase was negative, so it is possible the silica gel causes this conversion. It is known that the pH value has an influence on tautomers. Silica gel has a low pH-value.[29]

To confirm this theory a HPLC column filled with silica gel has been attached in the plug and play reactor (described in detail in chapter 3.8). A solution containing the mixture of 4-phenyl-but-3-en-2-ol and the corresponding ketone diluted in ethanol/water 7/3 was pumped through the heated (80°C) column. A rearrangement to the enol form could be observed, detected by GC. (Figure 2.9).

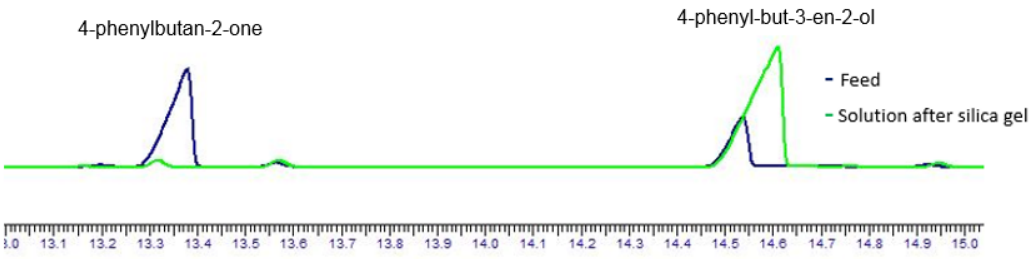


Figure 2.9: GC-chromatogram of feed and product solution of a typical Heck reaction after silica gel filled column

Thus, seems that silica gel is responsible for the rearrangement to the required enol form.

2.6 Conversion / Yield

For all reactions the progress was followed by means of HPLC. However, the concentration of iodobenzene and the concentration of the product measured by HPLC is not corresponding. (Figure 2.10) At the beginning the product formation and the reduction of starting material are according to the expectation from stoichiometry, but then they set apart, what led to a mismatch in conversion compared to yield (Figure 2.11). Usually this can be observed when side products are formed or the product is degenerating, but in this case it was not possible to detect any side product with HPLC-UV-detector or GC with a flame ionization detector.

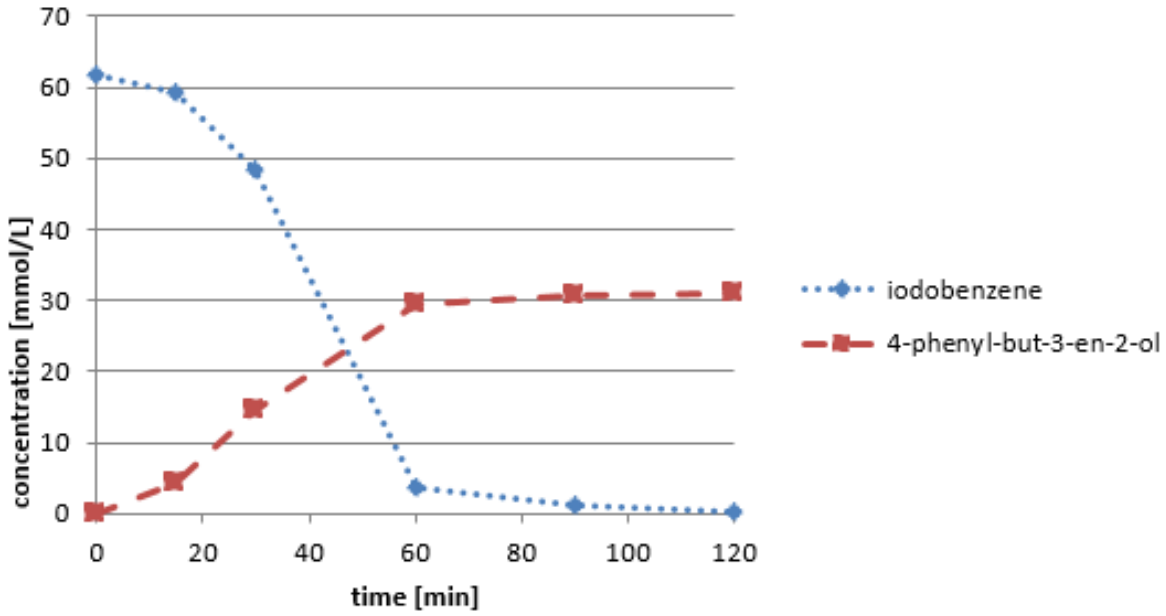


Figure 2.10: Concentration of iodobenzene,4-phenyl-but-3-en-2-ol, during a typical Heck reaction 6 samples,120 min.

So far there is no explanation for the mismatch in concentration of educt and product. The calibration was done twice, and also another person did the same experiment with the same gap in product concentration. The solubility of the product should not be the problem as the calibration was done with a much higher concentration (50 mmol/L) than in the reaction solvent (Appendix A). Also an adsorption of the product on the catalyst was considered. To check if there was adsorption, the filtrated catalyst was washed with hexane and also with water to desorb the product, but it was not possible to detect any product in the solvents. At the moment it is not clear what the reason for this mismatch could be.

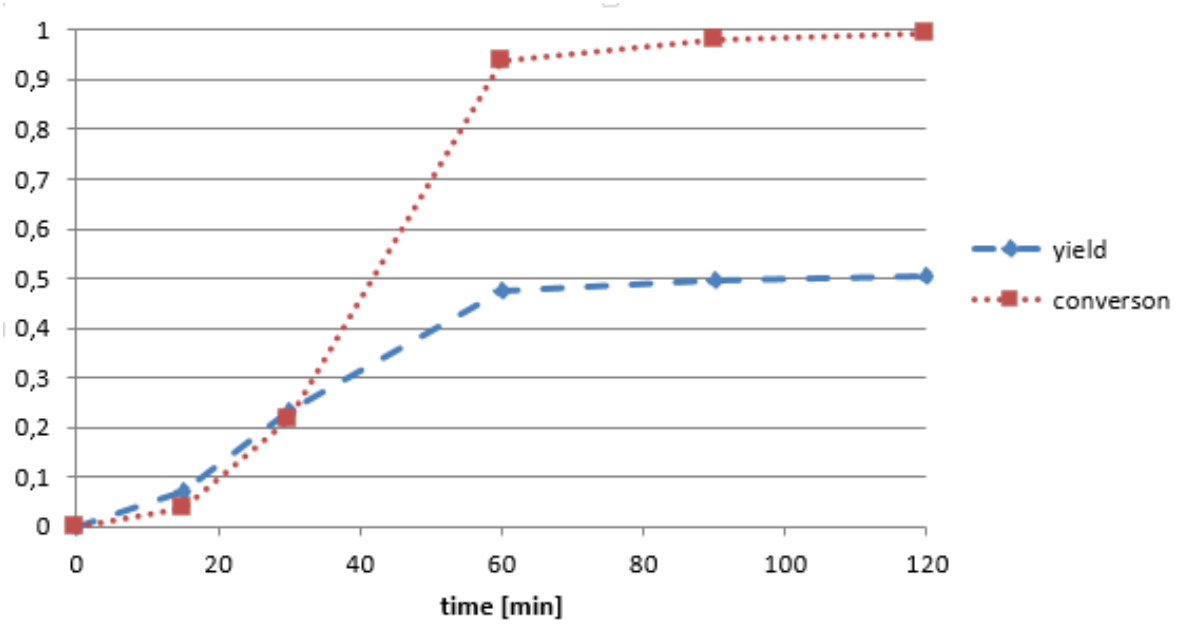


Figure 2.11: conversion and yield for standard reaction, calculated from the concentration of iodobenzene and 4-phenyl-but-3-en-2-ol, over 2 h with cat 7.

2.7 Additives for Heck reaction

For further optimization some additives were tested which are known to enhance a Heck reaction. One way to improve the selectivity and conversion of a Heck-coupling reaction could be the addition of silver-ions to the reaction mixture.[30][31] In contrast to literature, the reaction with the silver salt ($AgClO_4$) added showed a dramatic decrease of conversion compared to the standard reaction. Also adding other salts, for example $CaCl_2$ or CuCl, had a negative effect on the conversion of the reaction. So foreign ions in the reaction solvent can cause problems, that might be an issue for an industrial application, where the reaction solvent might contain ions from previous production steps or impurities.

It has also been published that adding tetrabutylammoniumbromid (TBAB) as a phase-transfer catalyst could lead to better results.[32][33] 1.05 mmol TBAB were added to a standard reaction solution, after 120 min no significant improvement in conversion of

the iodobenzene could be detected.

So it is not recommended to use this modification in reactions with this catalyst and conditions.

2.8 Pyrimidine

To get better and comparable results, closer to the structure of Rosuvastatin, experiments with 5-bromo-pyrimidin as halide were carried out. Pyrimidine is a six-membered heterocyclic aromatic compound with two nitrogen atoms in the ring, similar to the one in the center of rosuvastatin. (Figure 2.12 and Figure 1.1)

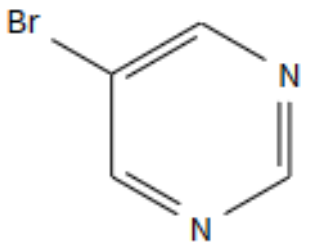


Figure 2.12: Structure of 5-bromo-pyrimidine

Under standard reaction conditions (80°C) no product was formed. Even with ten times more catalyst no product could be detected. The reason for this might be that bromide is not such a good leaving group, as is already could be observed in the substrate screening or poisoning of the catalyst by the pyrimidine. The chemically similar poly(4-vinylpyridine) was already used for palladium catalyst poisoning test.[34] So an experiment with higher reaction temperature (140°C) was done. As solvent propane-1,2-diol (best solvent for rosuvastatin)[35] was used. With 5 mg of catalyst after 5 hours a conversion of 34% to the corresponding 5-bromo-pyrimidin was achieved. It was not possible to purify the product, detected as HPLC peak, to confirm the formation of the expected but-3-en-2-ol-(5-pyrimidin) by NMR analysis. To avoid the problems with the purification another experiment with the original 7/3 ethanol /water solvent was done. In order to

to reach this high reaction temperature with this liquid a pressurized vessel is needed. Therefore, a HPLC column with closed end caps was used (Figure 2.13). With the higher temperature (140°C) there was a reaction and it was possible to purify the product, but only the ketone could be detected. As seen by other reactions, the iodo- instead of the bromo- compound might react at lower temperature, and it could be possible that the rearrangement of the enol to the ketone would not occur.

Figure 2.13: HPLC column filled with cat 7

2.9 Flow Experiments

The Heck reactions in continuous flow were carried out in the so-called " Plug and Play reactor ".[19] (Figure 2.14)

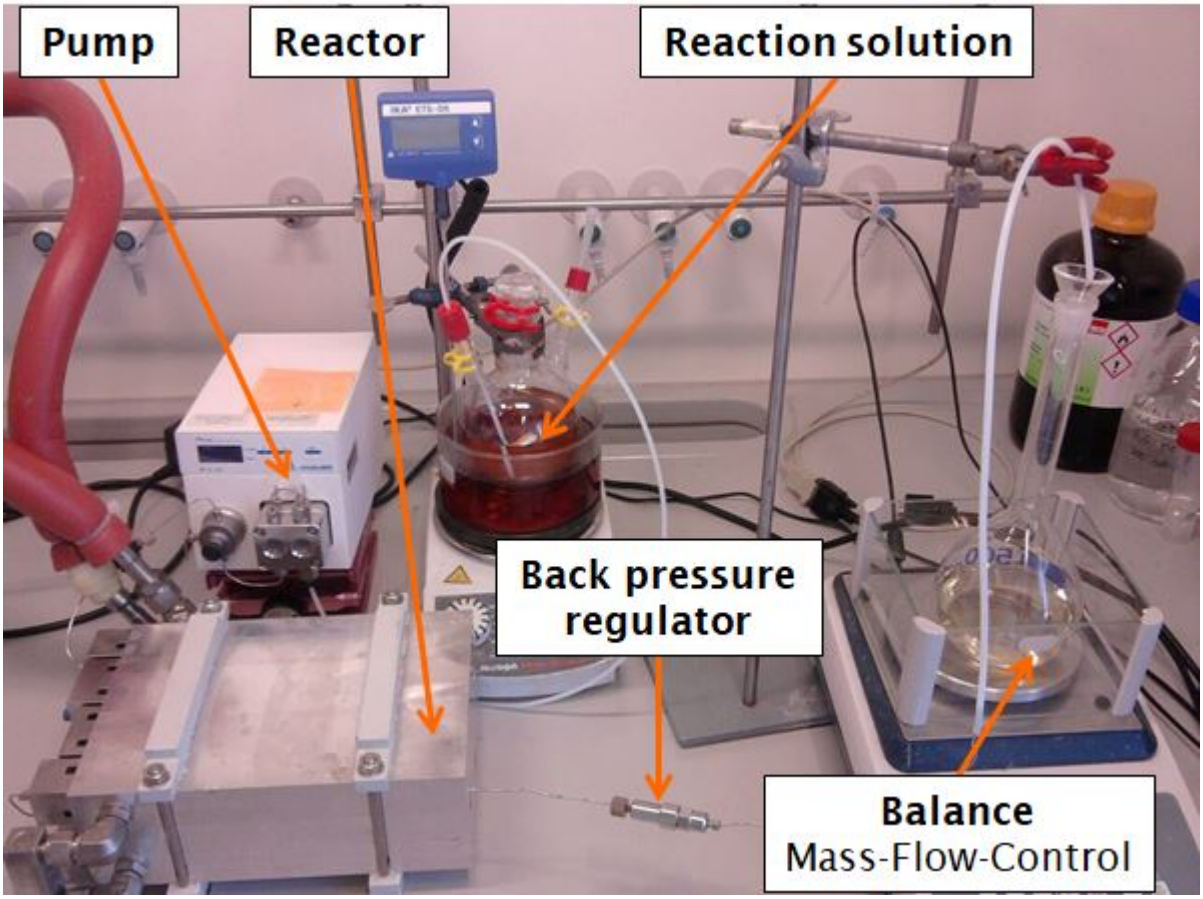


Figure 2.14: Experimental setup for the continuous reaction

The determined settings during the batch experiments were applied to optimize the continuous flow process. Accordingly, two HPLC columns were filled with cat 7 with about 1.9 g each. A solution of iodobenzene, but-3-en-2-ol and K_2CO_3 dissolved in ethanol/water (7/3) was pumped through the reactor modules heated at 80°C with a flow rate of 0.5 mL/min.

The production of 4-phenyl-but-3-en-2-ol is possible, but as was determined in the preliminary experiments, the product flow contains also the ketone. During the experi-

ment the concentration of the product decreased and that of the iodobenzene was getting higher, what can be seen as a hint that the performance of the catalyst is lowering over time. The reasons for that can be the poisoning of the catalyst, the blocking of active sites on the surface or the leaching of the palladium into the reacting solvent and thus removed from the reactor. In Figure 2.15 one can see that it was not possible to reach a steady state during the 6 h of reaction.

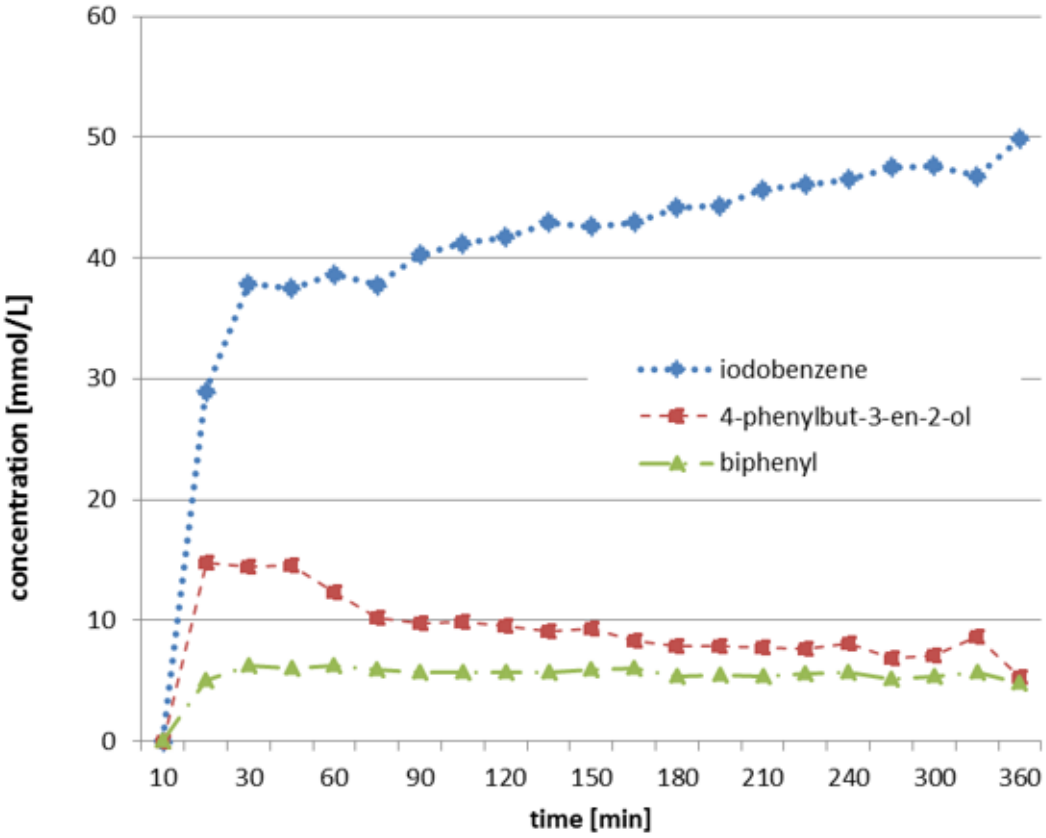


Figure 2.15: Concentration of iodobenzene,4-phenyl-but-3-en-2-ol and biphenyl during flow experiment; flow rate of 0.5 mL/min, two HPLC columns filled with cat 7, 1.9 g each T=80°C

An unexpected result was the formation of biphenyl by homo-coupling of the iodobenzene. This side reaction is known for the cross coupling reactions, but was not observed in the batch experiments. Maybe a reason for this deviation between batch and continuous could be the high amount of catalyst in the fixed bed reactor.

In a modified batch experiment without 3-buten-2-ol also biphenyl was produced, what led to the idea, that a local shortage of the alkene in the reactor leads to that

side product. Separation of the substances in the packed bed or that the 3-buten-2-ol polymerized at the beginning of the reactor could be the reason for this. In an other flow experiment the concentration of 3-buten-2-ol in the feeding solution was increased after 150 min of reaction. For this, 11.5 mmol of 3-buten-2-ol was added to the solution in the reservoir resulting in a doubled concentration. However, the product formation remained constant and also the concentration of biphenyl did not change.(Figure 2.16)

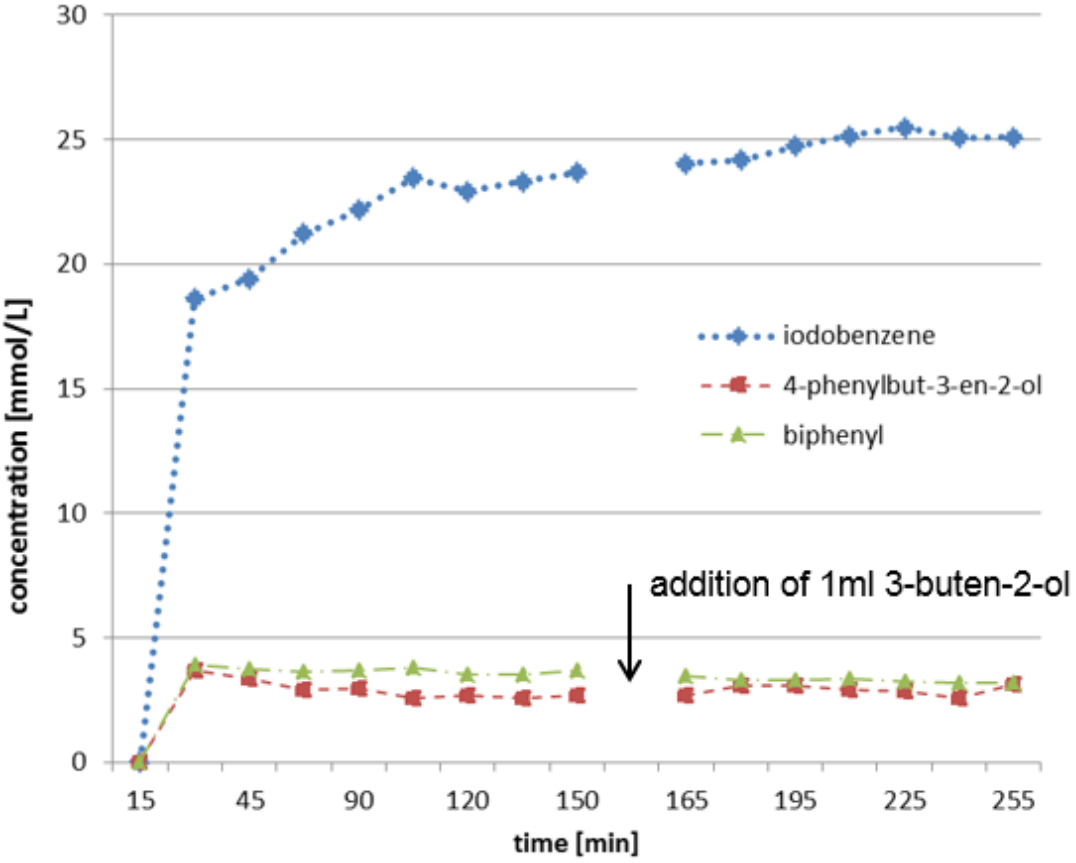


Figure 2.16: Concentration of iodobenzene,4-phenyl-but-3-en-2-ol and biphenyl during the flow experiment with adding 1 mL of 3-buten-2-ol after 150 min, flow rate of 0.5 mL/min, two HPLC columns filled with cat 7, 1.9 g each, T=80°C.

In summary, it could be shown that he palladium substituted tin oxide catalyst can be used in a fixed bed reactor. In continuous flow the formation of biphenyl as a by-product is a challenge to be solved. Also, that after a long time no steady state is reached, is not optimal.

3 Experimental

3.1 Material

All chemicals were purchased from commercial suppliers and used as received. The water that was used was purified by TKA Ultra pure water system MicroPure Article-No. 8.1205

Table 3.1: Material

Name	Manufacturer	Abbreviations	Purity
Ammonium cerium(IV) nitrate	Sigma-Aldrich	Ce1 H4 N8 O18	98.5%
Tin (II) oxalate	Sigma-Aldrich	Sn C2 O4	98%
Palladium (II) chloride	Aldrich	Pd Cl2	99%
Glycine	Sigma-Aldrich	C2 H5 N1 O2	99%
Potassium carbonate	Sigma-Aldrich	K2 C1 O3	99%
Cesium carbonate	Aldrich	Cs2 C1 O3	99%
Triethylamine	Sigma-Aldrich	C4 H11 N1	99.5%
Sodium hydroxide	Roth	NaOH	99%
Potassium hydroxide	Roth	KOH	50%
Triethanolamine	Merck	C4 H11 N1 O3	99%
Silica gel mesh 0,063–0,2 mm	Macherey-Nagel	O2 Si1	99%
Chloroform	Roth	C1 Cl3 H1	99%
Chloroform-D	Aldrich	C1 Cl3 D1	99%
Ethylacetat	Roth	C4 H8 O2	99%
Ethanol	Roth	C2 H6 O1	99%

Table 3.1: Material

Name	Manufacturer	Abbreviations	Purity
Phosphoric acid	Roth	H3PO4	85%
Acidic anhydride	Aldrich	C4 H6 O3	98%
Iodobenzene	Aldrich	C6 H5 I1	98%
4-Iodophenol	Sigma-Aldrich	C6 H5 I1 01	99%
2-Iodotoluene	Aldrich	C7 H7 I1	99%
1-Bromo 4-Iodobenzene	Sigma-Aldrich	C6 H4 I1 Br1	99%
4-Iodotoluene	Aldrich	C7 H7 I1	99%
1-Iodo 3,5-dimetylbenzene	Aldrich	C8 H9 I1	99%
4-Bromotoluene	Aldrich	C7 H7 Br1	98%
5-Bromopyrimidine	Sigma-Aldrich	C4 H3 Br1 N2	97%
4-Bromoaniline	Aldrich	C6 H6 Br1 N1	97%
2-Aminopyrimidine	Sigma-Aldrich	C4 H5 N3	97%
4-Chlorotoluene	Sigma-Aldrich	C7 H7 Cl1	98%
4-Bromobenzonitril	Aldrich	C7 H4 Br1 N1	99%
4-Bromoanisol	Sigma-Aldrich	C7 H7 Br1 O1	99%
4-Bromoacetophenone	Fluka	C8 H7 Br1 O1	98%
Phenylboronicacid	Aldrich	C6 H7 B1 O2	95%
11-Bromo 1-undecene	Aldrich	C11 H21 Br1	99%
3-Buten-2-ol	Sigma-Aldrich	C4 H8 O1	97%
5-Hexen-2-one	Aldrich	C6 H10 O1	99%
Acenaphthylene	Aldrich	C12 H8	75%
4-Phenyl-1-butene	Aldrich	C10H12	99%
Vinylethylether	Sigma-Aldrich	C4 H8 O1	99%
1-Hexene	Aldrich	C6 H12	99%
Acrolein	Aldrich	C3 H4 01	99%
Styrene	Sigma-Aldrich	C8 H8	99%
Dicyclopentadiene	Fluka	C10 H12	99%

Table 3.1: Material

Name	Manufacturer	Abbreviations	Purity
Vinylacetate	Sigma-Aldrich	C4 H6 O2	99%
1-Vinylimidazole	Sigma-Aldrich	C5 H6 N2	99%
Calcium chloride	Merck	Ca Cl2	99.5%
Silver perchlorate	Aldrich	Ag Cl O4	97%
Copper(I) chloride	Merck	Cu Cl	99.5%

3.2 Catalyst synthesis

To prepare the catalyst, appropriate amounts of tin(II) oxalate (SnC_2O_4), ammonium cerium (IV) nitrate ($(NH_4)_2Ce(NO_3)_6$, palladium(II) chloride($PdCl_2$,) and glycine ($C_2H_5NO_2$) were mixed and ground in a mortar with a pestle. This mixture was placed in a borosilicate dish with 600 mL capacity, dispersed in 2 mL of water and put in an ultrasonic bath for 30 minutes. Afterwards the formed homogeneous viscous liquid was treated in a muffle furnace preheated at 350°C. The mixture ignited within 5 min, initiating a self-propagating combustion reaction, which yielded a voluminous, porous solid. The solid was ground with mortar and pestle and heated again up for another 8 h. This second heating was done at different temperatures from 350°C, to 500°C-650°C till up to 1000°C. The produced catalyst itself appears as porous with a light brown to yellow color. The obtained powders were directly usable as catalyst for the cross-coupling reactions.[18]

3.3 Batch reactions

In a typical experiment a round-bottom flask was used. 0.70 mmol of the halide, 1.5 molar equivalents of the alkene, 1.5 molar equivalents of base and 100 μL of anisole (internal standard) were dissolved in 20 mL of a solvent containing a mixture of ethanol and water 7/3 v/v. The filled flask was placed in an oil bath and the mixture was stirred and

heated at the desired temperature (80°C in most of the experiments). All these reactions were carried out under ambient pressure and without protective atmosphere.

After heating up to 80°C and taking the first sample, 5 mg of the catalyst were added. The samples from the reaction solution were taken after 15, 30, 60, 90 and 120 minutes. 100 μL of the samples were transferred into a 1.5 mL vial and diluted with 1 mL of a mixture 70% methanol with 1:300 phosphoric acid aqueous solution, corresponding with the mobile phase of the HPLC analysis.

Some products were also analyzed by NMR spectroscopy. To get pure samples the reaction solution was filtrated in order to remove the catalyst. Afterwards ethanol was evaporated under reduced pressure. The product was extracted with MTBE (3x 10 mL). The organic phases were combined and evaporated under reduced pressure in order to obtain the product (yellow oily substance). The product was purified by flash chromatography using a mixture of 80% vol. petroleum ether and 20% vol. ethyl acetate as mobile phase and silica gel(mesh 0,063–0,2 mm) as stationary phase. For the Thin-layer chromatography (TLC) the same mobile phase mixture was used, the stationary phase was from Merk TLC silica gel 60 F_{254}. After another evaporation step the produced oily substance was dissolved in deuterated chloroform and analyzed by NMR spectroscopy.

3.4 Analyses

3.4.1 HPLC analyses

HPLC analyses was done using an Agilent 1100 series HPLC system (Agilent, Waldbronn, Germany), with a UV-visible diode array detector. An Agilent Poroshell 120 EC-C18 reversed phase column (50x4.6 mm; 2.7 μm) was used as stationary phase. For analysis a mobile phase consisting of methanol and an aqueous solution of phosphoric acid (water:phosphoric acid = 300:1 v/v) was used. Sample injection volume of 2μL;

Table 3.2: HPLC method solvent composition and flow rate

Time [min]	Methanol %	water:phosphoric acid 300:1 %	Flow [mL/min]
0	40	60	1
3	40	60	1
9	80	20	1
11	80	20	1
13	40	60	1
16	40	60	1

Table 3.3: HPLC wavelengths and retention times for the used substrates

Substance	Retention time t_R [min]	Wavelength [nm]
Anisole (Internal standard)	4.3	270
Iodobenzene	8.7	237
4-phenyl-but-3-en-2-ol	5.1	237
Iodine	0.5	237
1-Iodo 3-5-dimethylbenzene	11	237
4-Iodophenole	5.9	237
4-Iodotoluene	10	237
1-Bromo-4-iodobenzene	10.2	237
2-Iodotoluene	9.9	237
4-Phenyl-1-butene	9.9	252
Chlorotoluene	9.13	270
Bromobenzonitril	4.6	237
Biphenyl	12	237

3.4.2 GC analyses

GC analyses was done with a Perkin Elmer Clarus 500 using an Optima-5 MS capillary column (Machery-Nagel, 30.0 m x 320 μm D 0.25 μm) with a flame ionization detector and N_2 as carrier gas. Sample injection volume of 1 μL; Flow rate: 45 ml/min H_2; 450 ml/min synthetic air; initial temperature 50°C for 5 min; gradient 10°C/min to 250°C, hold for 5 min;

Table 3.4: Retention times in GC

Substance	Retention time t_R [min]
3-Buten-2-ol	2.1
Iodobenzene	9.8
4-Phenyl-but-3-en-2-ol	14.5
4-Phenyl-butan-2-on	13.3
Anisole (Internal standard)	7.1
Biphenyl	15.3

3.4.3 Particle size distribution

The particle size distributions were measured with a HELOS/KR Laser diffraction sensor; Dispersion Method dry 2.0 bar, measuring range: (0.25 - 87.5 μm), evaluation mode: Fraunhofer approximation, software: WINDOX 5.6.0.0

3.4.4 NMR analyses

The products that were analyzed by NMR were diluted with $CDCl_3$. The NMR analysis was done at the Institute of Organic Chemistry of TUGraz. ^1H and ^{13}C NMR spectra were recorded at 300.3600 MHz and at 75.5257 MHz respectively. The results can be seen in Appendix B.

3.5 Additives

The experiments were done as a usual example Heck reaction, but with addition of 1.05 mmol of the salt $AgClO_4$; $CaCl_2$; CuCl; or TBAB, respectively.

3.6 Derivatization

For the derivatization reaction a sample (5 mL) of the reaction solvent (iodobenzene ; 3-buten-2-ol) was taken. First, the solvent ($EtOH/H_2O$) had to be removed by evaporation. The sample was then dissolved in 5 mL of chloroform. 0.5 mL acetic anhydride and 1 mL of acetic acid was added. The mixture was heated to 50°C for 3 hours under stirring. In the next step, chloroform was evaporated and the dilution with the mobile phase for HPLC analyses was prepared.

3.7 Pyrimidine experiments

First experiments with 5-bromo-pyrimidine were performed under standard reaction conditions (80°C, 5 mg cat.), but no product was formed. For the next run, ten times more catalyst was used, with this increase also no reaction product could be detected. For an experiment with higher reaction temperature (140°C) 20 mL propane-1,2-diol was used as solvent. With 5 mg of catalyst after 5 hours a conversion of 34% to the corresponding 5-bromo-pyrimidine was achieved. It was not possible to separate the product from the solvent by evaporation, because of the high boiling point of propanediol (188.2°C). Liquid extraction is not possible because of the high solubility of the product in water and in propandiol.

To be able to reach the high reaction temperature with the 7/3 ethanol/water solvent a pressurized vessel is needed. A HPLC column with closed end caps was filled with 2 mL of solvent(ethanol/water 7/3), 47 mg of cat 7, 1.05 mmol of K_2CO_3 and the usual 0.70 mmol of 5-bromo-pyrimidin and 1.05 mmol of 3-buten-2-ol. After closing the column, it was placed in an oil bath with 140°C. It was not possible to stir the mixture

inside and it is not clear if all organic chemicals are soluble in that small amount of solvent. After 4 hours the column was taken out of oil bath, cooled down and opened. The obtained mixture was filtrated and washed with ethanol and then purified for the NMR spectroscopy as described in 3.3.

3.8 Flow experiments in the plug and play reactor

The experimental setup for the continuous reaction contains, enumerated in flow direction: storage bottle with the reaction solution, Knauer P 4.1 HPLC pump, preheating section of the plug and play reactor, HPLC columns filled with catalyst, back pressure regulator and a collection vessel placed on a balance. The connections between the components were established with steel pipes and screws used in HPLC setups, except the first, before the pump and the last, after the back pressure regulator where tubes made of PTFE was used. For all experiments a back pressure regulator with 20 bar was used. The pump and the balance are controlled via a LabVIEW program, which recorded the pressure and flow rate.[20]

For the Heck coupling reactions in flow two HPLC columns were filled with catalyst 7, about 1.9 g each, and installed in the reactor. The reactor was preheated by the thermostat at a temperature of 80°C and the construction was checked for leakage. To fill the pipes and columns, before the experiments were executed, pure solvent (ethanol/water v/v 7/3) was pumped through. In this way also a washing of the catalyst takes place before the reaction starts. To start the reaction, the feed was switched from pure solvent to the reaction mixture containing the iodobenzene, 3-buten-2-ol and K_2CO_3 dissolved in ethanol/water. The concentration of the substances was the same as determined in the batch experiments. It took 15-30 minutes until the reaction solvent was pumped through the hole setup depending on the flow rate of the pump and the dead space volume in the columns. Samples from the reaction solution were taken every 15 minutes, at the end of the tube directly filled in a 1.5 mL vial. All samples were diluted as described in chapter 3.4.1 and analyzed by means of HPLC-UV.

3.8.1 Conversion of the ketone to the enol on silica gel

For this experiment a HPLC column was filled with 2 g silica gel (mesh 0.063–0.2 mm). The filled column was installed in the plug and play reactor. A solution containing the mixture of 4-phenyl-but-3-en-2-ol and the corresponding 4-phenyl-2-butanone (76 mg) diluted in ethanol/water 7/3 (20 mL) was pumped through the heated (80°C) column. The flow rate was 0.5 mL/min. The outcome was collected and analyzed by GC.

4 Conclusion and Outlook

In this theses different catalysts with the molecular formula $Ce_x\ Sn_{1-x}\ Pd_{0.01}\ O_{2-\delta}$ were successfully used for Heck reaction. The experiments showed that a higher share of tin and less cerium increases the performance of the catalyst. The thermal treatment of the catalyst has an effect on the catalyst activity which should be investigated in detail in further studies. The combination of calcium carbonate as base and ethanol / water mixture as a nontoxic solvent is a good mixture for the Heck coupling reaction with this catalyst. By testing various chemical substances it could be shown that iodide compounds have a higher reactivity than bromide, and that substrates with an electron-rich functional group close to the carbon double bond lead to a higher conversion of the halide.
The recyclability test and the deviation of yield compared to conversion are two challenges that need further investigation.

It is proven that the palladium substituted tin oxide catalyst can be used in a fixed bed reactor in continuous flow. In continuous flow the formation of biphenyl as side product is a problem that needs to be solved. Also the long time till a steady state is reached is not optimal, a previous washing of the catalyst might help. The high pressure drop caused by the small particles in the fixed bed could be reduced by granulation of the catalytic particles. That topic is under investigation in another master theses by Peter Prandner.

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Appendix

Appendix A - Calibaration curve

Table 4.1: Concentrations and areas for HPLC calibration for iodobenzene

Conc. [mmol/L]	Area(iodobenzene)
1	36
2.5	68.5
5	163.5
10	327.8
25	694.8
50	1498

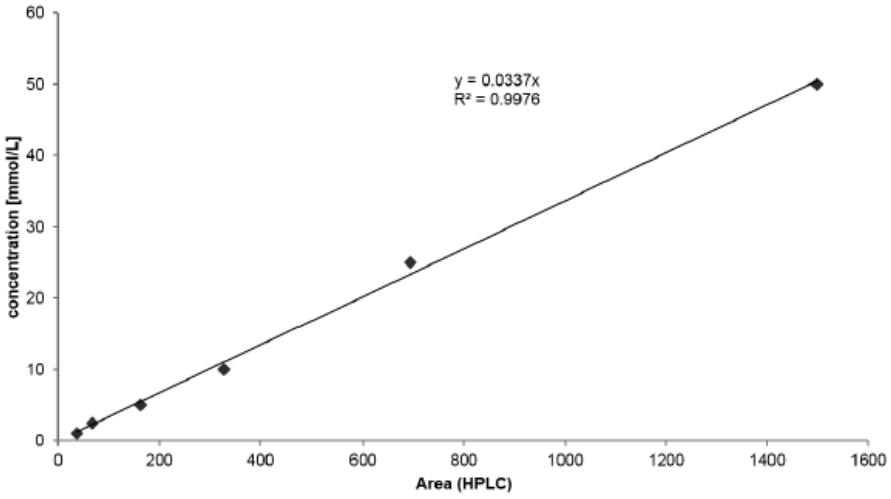


Figure A.1: Calibration curve for iodobenzene

Table 4.2: Concentrations and areas for HPLC calibration for 5-bromopyrimidine

Conc. [mmol/L]	Area(5-bromopyrimidine)
1	10.5
2.5	26.4
5	51.3
10	103.7
25	263.7
50	511.9

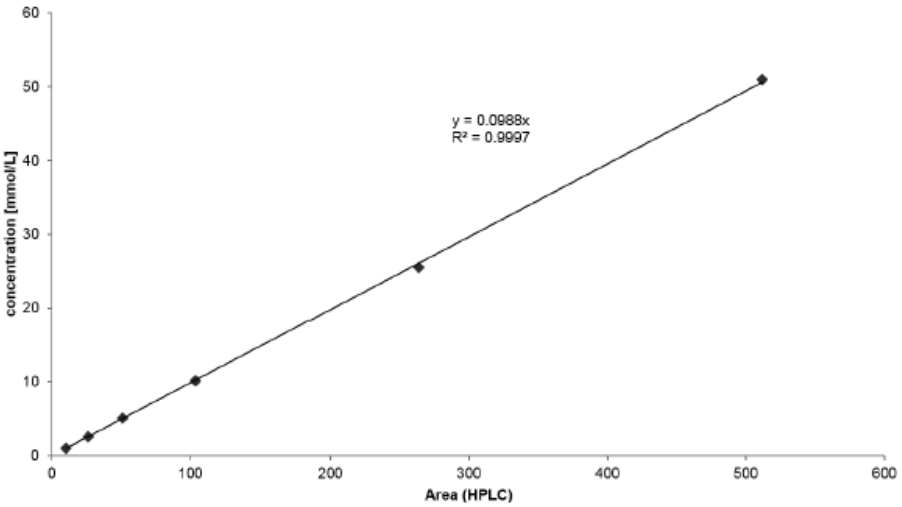


Figure A.2: Calibration curve for 5-bromopyrimidine

Table 4.3: Concentrations and areas for HPLC calibration for biphenyl

Conc. [mmol/L]	Area(biphenyl)
2.5	310.1
5	694.4
5	620
10	1283.7
25	3238.2
50	6151.8

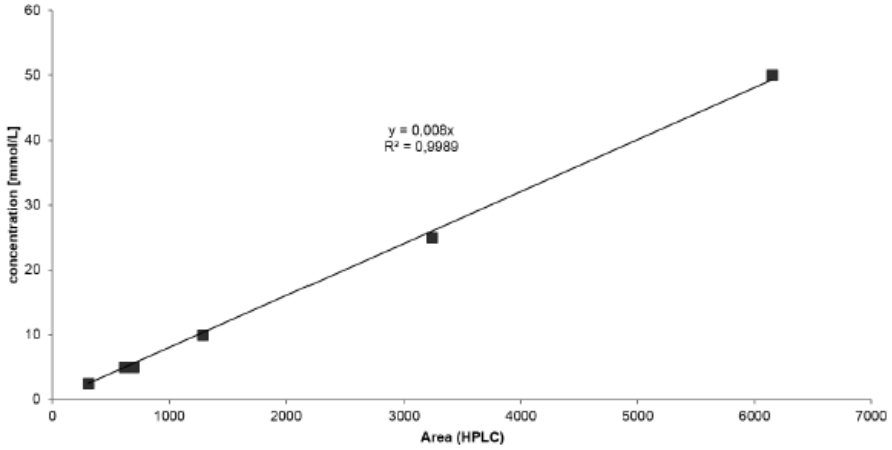


Figure A.3: Calibration curve for biphenyl

Table 4.4: Concentrations and areas for HPLC calibration for 4-phenyl-but-3-en-2-ol

Conc. [mmol/L]	Area(4-phenyl-but-3-en-2-ol)
1	57.3
2.5	140.1
5	285.5
10	569.9
25	1428.1
50	2806.7

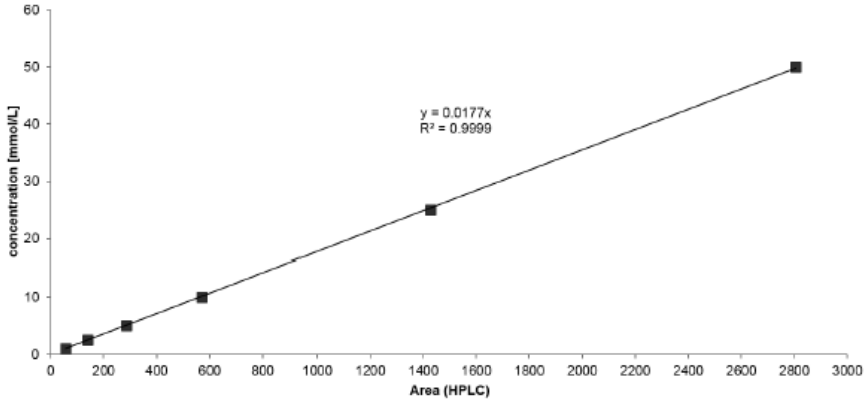
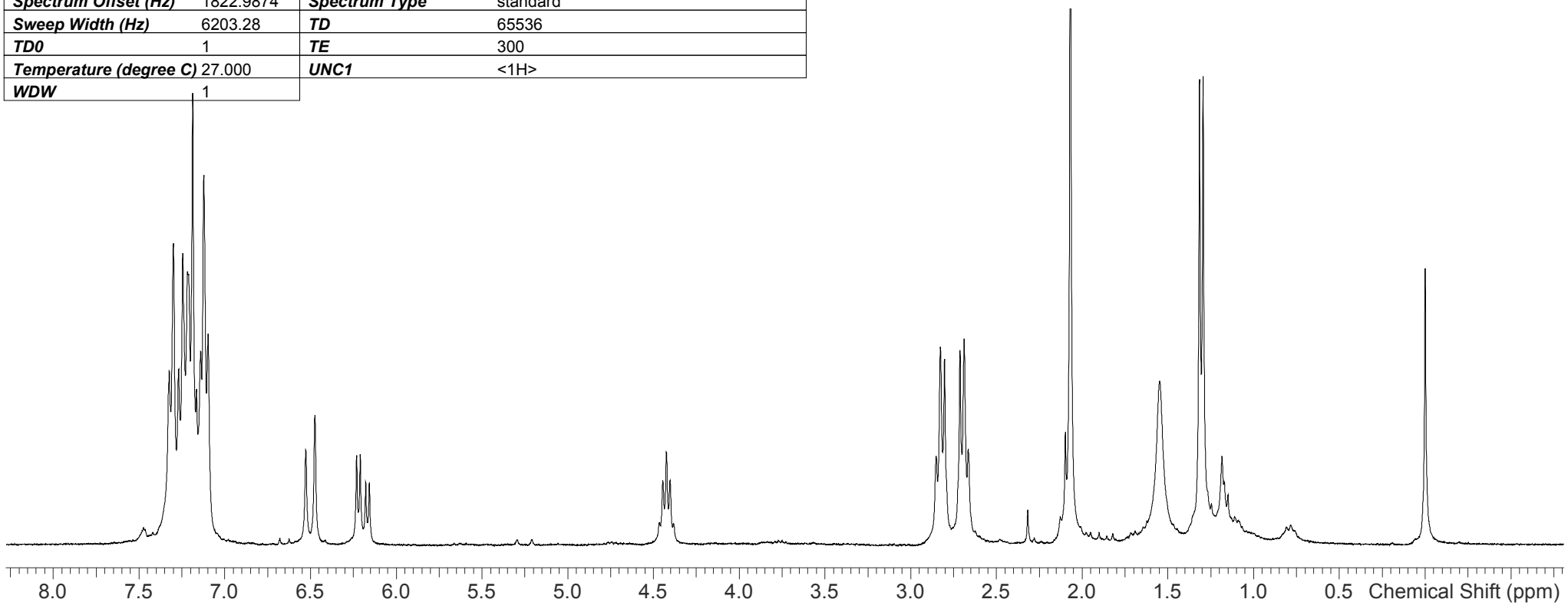


Figure A.4: Calibration curve for 4-phenyl-but-3-en-2-ol

Appendix B - NMR

Acquisition Time (sec)	5.2822	***Comment***	Grabner Phenylbutenol in CDCl3 1.2.2017
D	0.06	***D1***	1
DE	6.5	***DS***	2
Date	01 Feb 2017 14:31:18		
Date Stamp	01 Feb 2017 14:31:18		
File Name	\\tugraz\file\home\nhbgcc\Markus MA\NMR-Daten\10\PDATA\1\1r		
Frequency (MHz)	300.3600	***GB***	0
INSTRUM	<spect>	***LB***	0.3
NS	16	***Nucleus***	1H
Number of Transients	16	***Origin***	spect
Original Points Count	32768	***Owner***	auto300
PC	1		
PROBHD	<5 mm DUL 13C-1H/D Z-GRD Z5517/0078 >		
PULPROG	<zg30>	***Points Count***	32768
Pulse Sequence	zg30	***Receiver Gain***	114.00
SF	300.360031859198		
SFO1	300.361854845953		
SI	32768	***SSB***	0
SW(cyclical) (Hz)	6203.47	***SWH***	6203.47394540943
Solvent	CHLOROFORM-d		
Spectrum Offset (Hz)	1822.9874	***Spectrum Type***	standard
Sweep Width (Hz)	6203.28	***TD***	65536
TD0	1	***TE***	300
Temperature (degree C)	27.000	***UNC1***	<1H>
WDW	1		



Acquisition Time (sec)	1.8175	***Comment***	Grabner Phenylbutenol in CDCl3 1.2.2017
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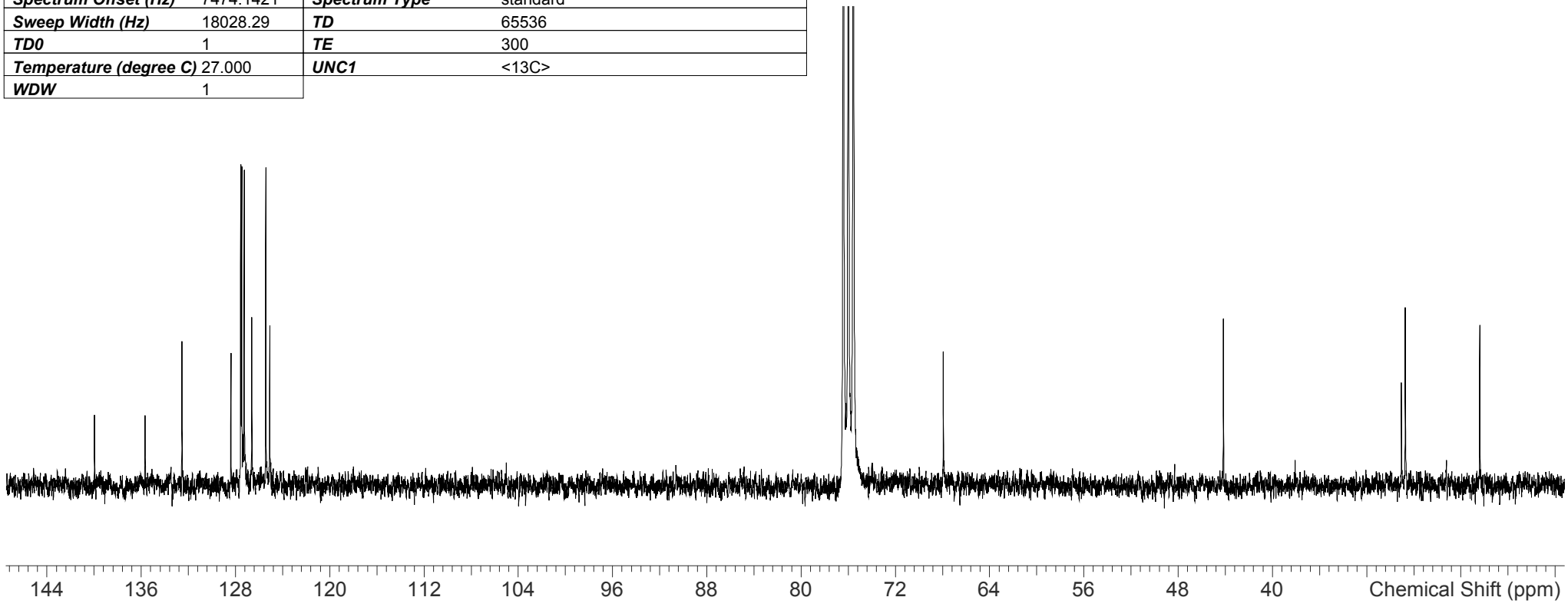
DE	6.5	***DS***	4
Date	01 Feb 2017 15:28:30		
Date Stamp	01 Feb 2017 15:28:30		
File Name	\\tugraz\file\home\nhbgcc\Markus MA\NMR-Daten\11\PDATA\1\1r		
Frequency (MHz)	75.5257	***GB***	0
INSTRUM	<spect>	***LB***	1
NS	1024	***Nucleus***	13C
Number of Transients	1024	***Origin***	spect
Original Points Count	32768	***Owner***	auto300
PC	1.4		
PROBHD	<5 mm DUL 13C-1H/D Z-GRD Z5517/0078 >		
PULPROG	<zgpg30>	***Points Count***	32768
Pulse Sequence	zgpg30	***Receiver Gain***	645.00
SF	75.5256604870272		
SFO1	75.5331346302072		
SI	32768	***SSB***	0
SW(cyclical) (Hz)	18028.85	***SWH***	18028.8461538462
Solvent	CHLOROFORM-d		
Spectrum Offset (Hz)	7474.1421	***Spectrum Type***	standard
Sweep Width (Hz)	18028.29	***TD***	65536
TD0	1	***TE***	300
Temperature (degree C)	27.000	***UNC1***	<13C>
WDW	1		



Appendix C - PSD

Sympatec GmbH
System-Partikel-Technik

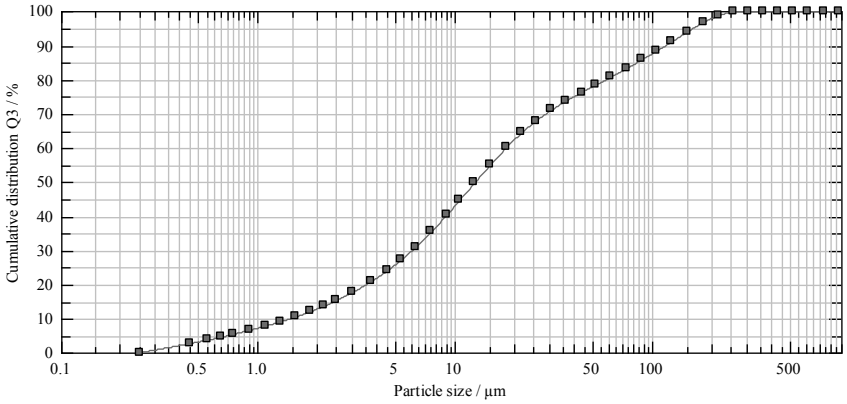
HELOS-Partikelgrößenanalyse
WINDOX 5

HELOS (H2395) & RODOS, R2+R5 2017-10-04
IPPT_Katalysator

x_{10} = 1,46 +/- 0,00 µm	**x_{50} = 12,58 +/- 0,00 µm**	**x_{90} = 116,77 +/- 0,00 µm**
x_{16} = 2,65 +/- 0,00 µm	x_{84} = 77,83 +/- 0,00 µm	x_{99} = 226,55 +/- 0,00 µm
VMD= 35,85 µm	SMD= 3,71	C_{opt} = 2,61 +/- 0,00 % [0,00 %]
RRSB d' = 25,46	**RRSB n = 0,67**	

Massenspezifische Oberfläche: 16171,17 cm²/g Volumenspezifische Obefläche:1,62 m²/cm³

Konditionen:		**Benutzerparameter:**
Produkt:	IPPT_Katalysator	Benutzer: Michael Piller
Auswertung:	FREE (5.6.0.0)	Probe: K7 600°C
Trigger:	Standard_Trocken_tolera..	Nummer: 2,00
Disp.Meth.:	Standard_Trocken_2.0bar..	Nummer:



Verteilungssumme mit Standardabweichung

x₀/µm	Q₃/%	SQ₃/%abs	x₀/µm	Q₃/%	SQ₃/%abs	x₀/µm	Q₃/%	SQ₃/%abs
0,45	2,63	0,00	7,50	35,35	0,00	125,00	91,10	0,00
0,55	3,63	0,00	9,00	40,34	0,00	150,00	93,99	0,00
0,65	4,54	0,00	10,50	44,75	0,00	180,00	96,69	0,00
0,75	5,37	0,00	12,50	49,84	0,00	215,00	98,66	0,00
0,90	6,50	0,00	15,00	55,08	0,00	255,00	99,84	0,00
1,10	7,86	0,00	18,00	60,00	0,00	305,00	100,00	0,00
1,30	9,08	0,00	21,50	64,30	0,00	365,00	100,00	0,00
1,55	10,50	0,00	25,50	67,85	0,00	435,00	100,00	0,00
1,85	12,09	0,00	30,50	71,04	0,00	515,00	100,00	0,00
2,15	13,60	0,00	36,50	73,78	0,00	615,00	100,00	0,00
2,50	15,30	0,00	43,50	76,19	0,00	735,00	100,00	0,00
3,00	17,63	0,00	51,50	78,41	0,00	875,00	100,00	0,00
3,75	20,93	0,00	61,50	80,78	0,00			
4,50	24,03	0,00	73,50	83,23	0,00			
5,25	27,01	0,00	87,50	85,72	0,00			
6,25	30,83	0,00	105,00	88,42	0,00			

gemittelt wurde über die folgenden Messungen:

Datum, Uhrzeit und Gerät	Benutzer	Probe
2017-10-04 16:33:56.9370 3047 H	Michael Piller	K7 600°C

Sympatec GmbH
System-Partikel-Technik

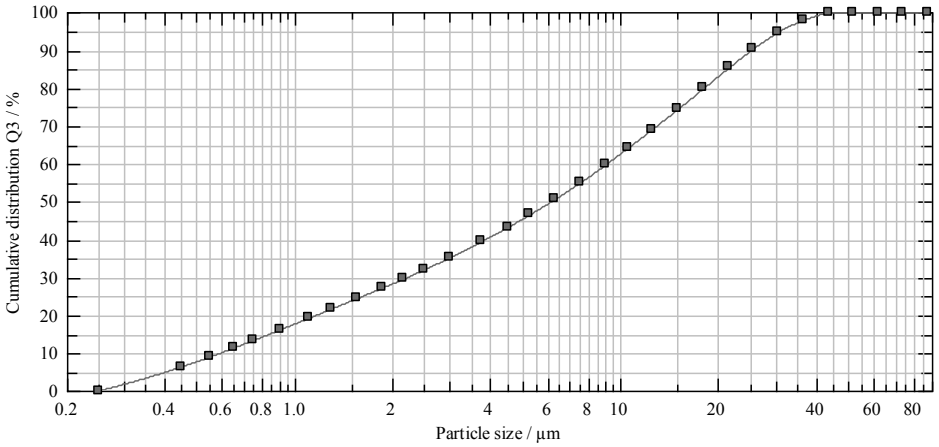
HELOS-Partikelgrößenanalyse
WINDOX 5

HELOS (H2395) & RODOS, R2: 0.25/0.45...87.5µm 2017-10-04
IPPT_Katalysator

x_{10} = 0,59 +/- 0,00 µm	**x_{50} = 6,15 +/- 0,00 µm**	**x_{90} = 25,25 +/- 0,00 µm**
x_{16} = 0,90 +/- 0,00 µm	x_{84} = 20,62 +/- 0,00 µm	x_{99} = 40,70 +/- 0,00 µm
VMD= 9,86 µm	SMD= 1,90	C_{opt} = 3,16 +/- 0,00 % [0,00 %]
RRSB d' = 9,57	**RRSB n = 0,75**	

Massenspezifische Oberfläche: 31629,96 cm²/g Volumenspezifische Obefläche:3,16 m²/cm³

Konditionen:		**Benutzerparameter:**
Produkt:	IPPT_Katalysator	Benutzer: Michael Piller
Auswertung:	FREE (5.6.0.0)	Probe: K7 1000°C
Trigger:	Standard_Trocken_tolera..	Nummer: 1,00
Disp.Meth.:	Standard_Trocken_2.0bar..	Nummer:



Verteilungssumme mit Standardabweichung

x_0/µm	Q_3/%	SQ_3/%abs	x_0/µm	Q_3/%	SQ_3/%abs	x_0/µm	Q_3/%	SQ_3/%abs
0,45	6,32	0,00	3,75	39,46	0,00	30,50	94,77	0,00
0,55	8,96	0,00	4,50	43,14	0,00	36,50	97,92	0,00
0,65	11,29	0,00	5,25	46,43	0,00	43,50	99,72	0,00
0,75	13,36	0,00	6,25	50,41	0,00	51,50	100,00	0,00
0,90	16,07	0,00	7,50	54,89	0,00	61,50	100,00	0,00
1,10	19,11	0,00	9,00	59,73	0,00	73,50	100,00	0,00
1,30	21,66	0,00	10,50	64,03	0,00	87,50	100,00	0,00
1,55	24,34	0,00	12,50	69,04	0,00			
1,85	27,07	0,00	15,00	74,41	0,00			
2,15	29,46	0,00	18,00	79,95	0,00			
2,50	31,97	0,00	21,50	85,37	0,00			
3,00	35,20	0,00	25,50	90,31	0,00			

gemittelt wurde über die folgenden Messungen:

Datum, Uhrzeit und Gerät	**Benutzer**	**Probe**
2017-10-04 16:29:17.6560 3047 H	Michael Piller	K7 1000°C

Sympatec GmbH
System-Partikel-Technik

HELOS-Partikelgrößenanalyse
WINDOX 5

HELOS (H2395) & RODOS, R2+R5 2017-10-04
IPPT_Katalysator

x_{10} = 1,37 +/- 0,00 µm | **x_{50} = 11,42 +/- 0,00 µm** | **x_{90} = 86,57 +/- 0,00 µm**
x_{16} = 2,45 +/- 0,00 µm | x_{84} = 56,89 +/- 0,00 µm | x_{99} = 174,47 +/- 0,00 µm
VMD= 27,92 µm | SMD= 3,52 | C_{opt} = 3,11 +/- 0,00 % [0,00 %]
RRSB d' = 21,13 | **RRSB n = 0,73**
Massenspezifische Oberfläche: 17064,56 cm²/g Volumenspezifische Obefläche:1,71 m²/cm³

Konditionen:		**Benutzerparameter:**
Produkt:	IPPT_Katalysator	Benutzer: Michael Piller
Auswertung:	FREE (5.6.0.0)	Probe: K7 350°C
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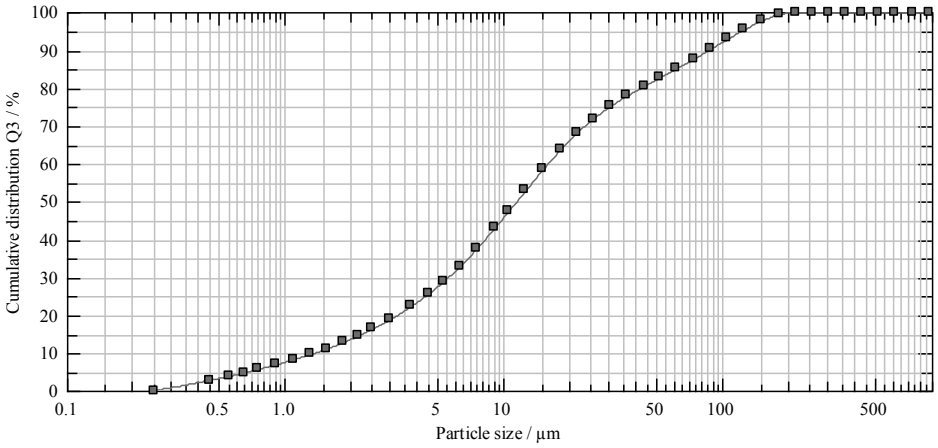
Disp.Meth.:	Standard_Trocken_2.0bar..	Nummer:



Verteilungssumme mit Standardabweichung

x_0/µm	Q_3/%	SQ_3/%abs	x_0/µm	Q_3/%	SQ_3/%abs	x_0/µm	Q_3/%	SQ_3/%abs
0,45	2,74	0,00	7,50	37,64	0,00	125,00	95,35	0,00
0,55	3,79	0,00	9,00	42,91	0,00	150,00	97,66	0,00
0,65	4,75	0,00	10,50	47,54	0,00	180,00	99,30	0,00
0,75	5,62	0,00	12,50	52,89	0,00	215,00	99,89	0,00
0,90	6,83	0,00	15,00	58,41	0,00	255,00	100,00	0,00
1,10	8,27	0,00	18,00	63,61	0,00	305,00	100,00	0,00
1,30	9,58	0,00	21,50	68,13	0,00	365,00	100,00	0,00
1,55	11,10	0,00	25,50	71,82	0,00	435,00	100,00	0,00
1,85	12,82	0,00	30,50	75,09	0,00	515,00	100,00	0,00
2,15	14,45	0,00	36,50	77,91	0,00	615,00	100,00	0,00
2,50	16,28	0,00	43,50	80,39	0,00	735,00	100,00	0,00
3,00	18,78	0,00	51,50	82,70	0,00	875,00	100,00	0,00
3,75	22,31	0,00	61,50	85,11	0,00			
4,50	25,61	0,00	73,50	87,62	0,00			
5,25	28,78	0,00	87,50	90,17	0,00			
6,25	32,84	0,00	105,00	92,88	0,00			

gemittelt wurde über die folgenden Messungen:

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