Methoxycarbonylation of alkenes with biomass-derived CO

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Publication date: 2016

Document Version
Publisher's PDF, also known as Version of record

Link back to DTU Orbit

Citation (APA):
Methoxycarbonylation of alkenes with biomass-derived CO

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Ph.D. Thesis
October 2015
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Department of Chemistry
DTU - Technical University of Denmark
In loving memory of David Bowie
Preface

The present thesis and the work contained within was performed at the Centre for Sustainable Chemistry and Catalysis, a part of the Department of Chemistry at the Technical University of Denmark, conducted in the period from the 15th of March 2012 to the 14th of October 2015. The project was funded by FTP.

The author performed entirely the experimental work.

I would like to express my gratitude to my supervisor, Assoc. Prof. Anders Riisager, for three years of interesting chemistry within the area of valorization of biomass. Within this project, I would like to thank Dr. E. J. García-Suárez, since he provided much needed support within homogeneous catalysis and practical chemistry.

I would also like to thank Mayra and Raju for their support, which luckily turned into a beautiful friendship. A special thank goes to Martin, without whom I would have had bigger issues in the completion of this thesis.

Friends have aided and assisted me during these years: names are pointless, they all know they have a special place in my heart.

My biggest thank goes to my family, which made possible for me to arrive here. I am sure they know what “emotional rollercoaster” means. All my love is for you.

Copenhagen, 13th October 2015

Dario Paolicchi
Abstract

The production of chemicals, fuels and energy from renewable feedstock, such as biomass, has seen increasing interest in the last decade. One of the key issues regarding biorenewables is the reduction of the oxygenation grade in molecules, the removal of oxygen. This thesis focuses on the removal of oxygen, in the form of carbon monoxide, and use in a tandem reaction for the methoxycarbonylation of alkenes. Furthermore, the production of γ-valerolactone (GVL), a promising green fuel has been exploited.

Chapter 1: Introduction provides a walk-through of subjects like biomass and its utility, dehydration of sugars, the importance of the furanoic platform and carbonylation reactions. All these arguments are described in detail, taking into account the current and past research, accurately chosen in order to offer an insight for next chapters.

Chapter 2: Experimental, deals with the analytical techniques and the catalytic setups of the reactions.

Chapter 3: Results and Discussion, is divided into two main parts. The first one reports and discuss the data obtained after the methoxycarbonylation reaction of 5 HMF (5-hydroxymethyl furfural), to yield methyl heptanoate (MH), methyl levulinate (ML), and GVL, the three products we investigated. The catalytic system is optimized, following the indication given by the results of the reactions. All the steps of the process are deeply discussed in this section. Consideration on the reaction time, on the choice and the quantity of the acidic catalyst, the nature and the amount of the palladium precursor and the phosphine ligand, a screening of the reaction temperatures, and an investigation regarding
different substrates (with a furanic backbone), alkenes and alcohols have been done. Our catalytic system proved to be valid to give good yields in a one-pot reaction from HMF to valuable products. All the data are gathered after GC-FID, GS-MS and HPLC analysis, run using naphthalene as internal standard.

The second part examines the methoxycarbonylation reaction applied to different carbohydrates. Insights on the kinetics of the reaction and the reactivity of various carbohydrates can be inferred from the analysis of the reported data. Through this screening, our catalytic system proved to be active on a broad range sugars, from monosaccharides to polysaccharides, such as inulin and starch.

Chapter 4: Conclusions, it summarizes the results, future perspectives and possible developments.
Resumé

Produktionen af kemikalier, brændstoffer og energi fra vedvarende råmaterialer, såsom biomasse, har oplevet en stigende interesse i det sidste årti. En af de centrale udfordringer vedrørende biomasse er reduktionen af iltnings graden i molekylerne heri. Denne afhandling fokuserer på fjemelse af oxygen, i form af carbonmonoxid og anvendelsen i en tandem reaktion for methoxycarbonylering af alkener. Endvidere til produktion af γ-valerolacton (GVL), et lovende grønt brændstof.

Kapitel 1: Introduktion, giver en gennemgang af emner som biomasse og dens anvendelighed, dehydrering af sukker, betydningen af "furanoic"-platform og carbonyleringsreaktioner. Alle argumenter beskrives i detaljer, med hensyn til nuværende og tidligere forskning, nøjagtigt udvalgt til at give et indblik i baggrunden for de næste kapitler.

Kapitel 2: Eksperimentbeskrivelser, beskriver de analytiske teknikker og opsætningen af de katalytiske reaktioner.

Kapitel 3: Resultater og Diskussion, er opdelt i to hoveddele. Den første del rapporterer og diskuterer data om tre undersøgte produkter fra methoxycarbonyleringen af HMF; henholdsvis methylheptanoat (MH), methyl levulinat (ML), og GVL. Det katalytiske system blev optimeret gennem analyse og diskussion af resultaterne, fra samtlige trin i processen. Betragtninger om følgende resultater er yderligere diskuteret; reaktionstider, mængden af syre, samt typen og størrelsen af palladium forstadiet og phosphin-ligander, reaktionstemperatur, og undersøgelser vedrørende forskellige substrater (med en furanic-
backbone), alkener og alkoholer. Det optimerede katalytiske system gav pålidelige resultater, samt værdifulde reaktionsprodukter med gode udbytter i en one-pot reaktion fra HMF. Alle data er opgivet fra GC-FID, GS-MS og HPLC-analyse, med naphthalen som intern standard.

Den anden del beskriver og diskutere methoxycarbonylering anvendt på forskellige kulhydrater, for at give indsigt i reaktionskinetikken og reaktiviteten af for disse udledt gennem analyse af data. Gennem denne screening viste vores katalytiske system en generel alsidighed ved at være aktiv på en lang række sukkerarter, fra monosaccharider til polysaccharider; såsom inulin og stivelse.

Kapitel 4: Perspektivering og konklusion, opsummering af resultater, fremtidsperspektiver og mulige udviklingsforløb.
Chapter 3. Results and discussion

3.1 From HMF to MH and GVL

3.1.1 Activation of the catalyst
3.1.2 Influence of the acid concentration
3.1.3 Time study
3.1.4 Catalyst loading
3.1.5 Palladium precursor and phosphine ligand screening
3.1.6 Temperature screening
3.1.7 Substrate screening
3.1.8 Alkene and alcohol screening

Summary

3.2 From sugars to MH and GVL

3.2.1 Palladium precursor influence
3.2.2 Time study
3.2.3 Sugar screening

Summary

Chapter 4. Conclusions

4.1 From HMF to MH and GVL
4.2 From sugars to MH and GVL

Appendix A Publications

A1. Oral presentation
# List of Abbreviations and Symbols

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Name</th>
</tr>
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<tbody>
<tr>
<td>acac</td>
<td>Acetylacetonate</td>
</tr>
<tr>
<td>2,3-Ad.</td>
<td>2,3-Addition</td>
</tr>
<tr>
<td>AL</td>
<td>Angelica lactones</td>
</tr>
<tr>
<td>Bn</td>
<td>Benzyl</td>
</tr>
<tr>
<td>BINAP</td>
<td>2,2′–bis(difenilfosfino)–1,1′–binaftile</td>
</tr>
<tr>
<td>bpy</td>
<td>2-2′-bipyridine</td>
</tr>
<tr>
<td>BRIC</td>
<td>Brazil Russia India China</td>
</tr>
<tr>
<td>Cys</td>
<td>Cysteine</td>
</tr>
<tr>
<td>dba</td>
<td>Dibenzylideneacetone</td>
</tr>
<tr>
<td>DHH</td>
<td>2,5-dioxo-6-hydroxyhexanal</td>
</tr>
<tr>
<td>DMC</td>
<td>Dimethylcarbonate</td>
</tr>
<tr>
<td>DMS</td>
<td>Dimethylsuccinate</td>
</tr>
<tr>
<td>DNPH</td>
<td>2,4-dinitrophenylhydrazine</td>
</tr>
<tr>
<td>DP</td>
<td>Degree of Polymerization</td>
</tr>
<tr>
<td>dppp</td>
<td>1,3-Bid(diphenylphosphino)propane</td>
</tr>
<tr>
<td>DTBPMB</td>
<td>1,2-Bis(di-tert-butylphosphinomethyl)benzene</td>
</tr>
<tr>
<td>[EMIM]Cl</td>
<td>1-Ethyl-3-methylimidazolium chloride</td>
</tr>
<tr>
<td>Et</td>
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</tr>
<tr>
<td>exc.</td>
<td>Excess</td>
</tr>
<tr>
<td>FA</td>
<td>Formic acid</td>
</tr>
<tr>
<td>Symbol</td>
<td>Abbreviation</td>
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<tr>
<td>---------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>GC-FID</td>
<td>Gas chromatography flame ionization detector</td>
</tr>
<tr>
<td>GC-MS</td>
<td>Gas chromatography</td>
</tr>
<tr>
<td>GPX</td>
<td>Glutathione peroxidases</td>
</tr>
<tr>
<td>GVL</td>
<td>γ-valerolactone</td>
</tr>
<tr>
<td>His</td>
<td>Histidine</td>
</tr>
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<td>HMF</td>
<td>5-hydroxymethylfurfural</td>
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<td>4-HNE</td>
<td>4-hydroxynonenal</td>
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<td>4-HPA</td>
<td>4-hydroxypentanoic acid</td>
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<td>HPLC</td>
<td>High-performance liquid chromatography</td>
</tr>
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<td>hv</td>
<td>Ultraviolet</td>
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<td>ILs</td>
<td>Ionic liquids</td>
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<td>LA</td>
<td>Levulinic acid</td>
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<td>Low Process Oxo</td>
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<td>Lysine</td>
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<td>MeMBL</td>
<td>5-methyl-3-methylenedihydrofuran-2-one</td>
</tr>
<tr>
<td>MF</td>
<td>Methyl formate</td>
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<td>MH</td>
<td>Methyl heptanoate</td>
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<tr>
<td>ML</td>
<td>Methyl levulinate</td>
</tr>
<tr>
<td>MP</td>
<td>Methyl propanoate</td>
</tr>
<tr>
<td>MPV</td>
<td>Meerwein–Ponndorf–Verley reduction</td>
</tr>
<tr>
<td>Ms</td>
<td>Mesyl</td>
</tr>
<tr>
<td>MSA</td>
<td>Methansulfonic acid</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
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<td>--------------</td>
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<tr>
<td>MMS</td>
<td>Monomethylsuccinate</td>
</tr>
<tr>
<td>MTHF</td>
<td>Methyl tetrahydrofuran</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance</td>
</tr>
<tr>
<td>OAc</td>
<td>Acetate</td>
</tr>
<tr>
<td>Ph</td>
<td>Phenyl</td>
</tr>
<tr>
<td>pKₐ</td>
<td>Acid dissociation constant</td>
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<tr>
<td>PMe₃</td>
<td>Trimethylphosphine</td>
</tr>
<tr>
<td>PPh₃</td>
<td>Triphenylphosphine</td>
</tr>
<tr>
<td>ppm</td>
<td>Parts per million</td>
</tr>
<tr>
<td>PRX</td>
<td>Peroxiredoxine</td>
</tr>
<tr>
<td>PTSA</td>
<td>p-toluensulfonic acid</td>
</tr>
<tr>
<td>PUFA</td>
<td>Poliunsaturated fatty acids</td>
</tr>
<tr>
<td>PVP</td>
<td>Polyvinylpyrrolidone</td>
</tr>
<tr>
<td>ROS</td>
<td>Reactive Oxigen Species</td>
</tr>
<tr>
<td>SA</td>
<td>Succinic Acid</td>
</tr>
<tr>
<td>Shvo catalyst</td>
<td>{[Ph₄(η⁵-C₄CO)]₂H]}Ru₂(CO)₄(µ-H)</td>
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<tr>
<td>t-Bu</td>
<td>tert-butyl</td>
</tr>
<tr>
<td>THFA</td>
<td>Tetrahydrofuryl alcohol</td>
</tr>
<tr>
<td>TOF</td>
<td>Turnover frequency</td>
</tr>
<tr>
<td>TON</td>
<td>Turnover number</td>
</tr>
<tr>
<td>TPP</td>
<td>Triphenylphospine</td>
</tr>
<tr>
<td>TPPTS</td>
<td>3,3’,3”-Phosphanetriyltris(benzenesulfonic acid)</td>
</tr>
<tr>
<td>Ts</td>
<td>Tosyl</td>
</tr>
<tr>
<td>Wilkinson catalyst</td>
<td>Rh(PPh)₃Cl</td>
</tr>
<tr>
<td>wt</td>
<td>Weight</td>
</tr>
<tr>
<td>----------</td>
<td>--------</td>
</tr>
<tr>
<td>W</td>
<td>Water</td>
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</table>
Chapter 1.

Introduction

1.1 Introduction

In the last century, world has a high dependence on oil as it is the main source for chemicals and energy. Nowadays, due to the exponential economic growth of emerging countries BRIC (Brazil, Russia, India and China) the demand for oil is expected to increase significantly in the coming years. Taking into account the present energy consumption, the reserves are able to give energy for approximately 50 years more [1]. As a result, of the finite of fossil fuels in combination with the growth in oil demand, the development of new and sustainable sources for fuels and bulk chemicals is required. Furthermore, the use of fossil fuels determines a rapid growth of the CO₂ levels in the atmosphere, and its harmful impact on the environment of the planet earth. The concentration of CO₂ went beyond 400 ppm for the first time in 2014, while the upper safety limit is 350 ppm (Figure 1). This trend is not going to stop soon, and it is going to increase the depletion of the ozone layer.
In this sense, biomass is the one of the most attractive alternative feedstock for chemicals and energy production, as it is the only widely available carbon source apart from oil and coal [3].

Several solution have been displayed, like increasing the use of a safer nuclear energy (the accident of Fukushima proved that the current technology is not safe enough), or favoring the burgeoning of natural gas and biomass industry.

Figure 1. CO₂ levels, provided by the website http://co2now.org/ [2]
Recently, biomass achieved resounding success in the last years, since it can be used for producing both already known chemical, or chemicals with a great potential, like HMF (5-hydroxymethylfurfural), or lactic acid [4, 5]. The most positive aspect of biomass is that it is CO₂ neutral, since the CO₂ released during the use of biomass, is used for the production of biomass itself.

In an ideal and complete biobased economy, chemicals, fuels, and new biomaterials are supposed to be produced in biorefineries.
1.2 Biomass

Biorefinery is a concept that involves the conversion of biomass into chemicals, fuels, heat, and energy, in a combined facility [6]. What is biomass, then? Biomass is a carbon-based mixture of materials, where also hydrogen, oxygen and nitrogen are usually present. Other atoms, such as heavy metals and alkali, are sometimes present in small quantities.

Biomass can be gathered together, into three-generation groups [7]. The first generation biomass production derives from crops, such as wheat, sugar beet and oil seeds. The major issue regarding the first-generation biomass is that they all come from edible resources (agricultural food crops), and then social and economic on the world population may occur, supporting the “food versus fuel” thesis.

Later, lignocellulosic feedstocks have been assessed as the second-generation biomass: these feedstocks come from non-edible sources, so the fuel versus food issue is not involved [8, 9]. It is composed of carbohydrate polymers (cellulose and hemicellulose), and aromatic polymers (lignin).

This kind of biomass can be used from both the cultivation of non-edible plants or, better, via the valorization of waste biomass, deriving from edible crops [10]: huge amounts of waste are generated in the cropping, preparation and usage of agricultural products [11].

Third-generation biomass derives from algae (oilgae). The positive aspects include, among the others, their non-toxicity, the high biodegradability, and an almost
negligible market competition. On the other side, this technology is under development, and still presents high processing costs [12].

1.2.1 Lignocellulosic biomass

Lignocellulosic biomass can be classified into three subgroups: virgin biomass, waste biomass, and energy crops. Virgin biomass comprises trees, and all the naturally occurring plants. Waste biomass is a low route byproduct of different industrial branches, such as agricultural (sugarcane, straw), and forestry (paper mill discards). Energy crops are crops with high percentages of lignocellulosic biomass that will be used to produce second-generation biofuels. An example of an energy crop is switch grass.

Lignocellulosic biomass consists of circa 75% of carbohydrates and 20% of lignin: triglycerides, proteins, terpenes, and alkaloids compose the last 5%. Carbohydrates can be divided into structural polymers, such as cellulose and hemicellulose, and storage carbohydrates, like starch, sucrose, and inulin [13].
Figure 2. Valorization of lignocellulosic biomass

Figure 2 shows the lifecycle of biomass. First, biomass is converted into chemicals and simpler materials through deoxygenation: this step can be achieved via dehydration, decarbonylation and hydrodeoxygenation [14, 15].
Figure 3. Structure of lignocellulosic biomass

Figure 3 shows the enlargement of the a plant, down to the constituting building blocks, cellulose, hemicellulose, and lignin, the three major components of lignocellulosic biomass. Cellulose is a linear polymer, constituted by units of glucose, connected via a $\beta(1 \rightarrow 4)$ glycosidic bond: different chains of cellulose are then grouped into microfibrils, via H-bonds [16]. Hemicellulose is composed by a different kind of hexoses and pentoses, such as glucuronoxylan, xylan, glucomannan, arabinoxylan, and xyloglucan. On the other side, lignin is not a carbohydrate-based polymer, but it is composed by three main aromatic components, p-coumaryl alcohol, sinapyl alcohol, and coniferyl alcohol [17, 18].
Figure 4. Chemical structures of the three major components of lignocellulosic biomass
CHAPTER 1. INTRODUCTION

Figure 4 clearly shows the chemical structures of these polymers: while cellulose is a simple polymer, with the chains tightly bonded via H-bonds, hemicellulose and lignin differs in their constitution [19]. In nature, cellulose is produced in $10^9$ tons per year scale [20].

Since the production of materials, fuels, and energy from biomass has to be sustainable, non-edible starting materials have to be used. Furthermore, the processes for refining biomass are still quite new, and need further improvement and optimization [20, 21].

### 1.2.2 Alternative feedstocks

Lignocellulose is not the only viable alternative to fossil fuels. The most promising alternative feedstocks are the following and their structures shown in Figure 5:

- **Starch**
  Starch is a composite molecule, made up by two different homopolymers: amylase, a linear one, where the glucose monomers are linked with an $\alpha(1\rightarrow4)$ glycosidic bond, and amylopectin, where an $\alpha(1\rightarrow6)$ glycosidic bond is present, every 25-30 glucose subunits. Starch is present in staple food, such as wheat, maize, potatoes, and rice [22, 23].

- **Inulin**
  Inulin is a polymer consisting in fructosyl groups linked by a $\beta(2\rightarrow1)$ glycosidic bond, terminated, at the reducing end, by a molecule of glucose, linked by an $\alpha(1\rightarrow2)$ glycosidic bond. The DP (degree of polymerization) usually varies between 2 and 60.
fructose units. Inulin is classified as a non-edible source of biomass, since the human body is not able to hydrolyze the β(2→1) glycosidic bond. It is usually present in roots and ryzomes, such as chicory and Jerusalem artichoke [23, 24, 25].

- Sucrose

Sucrose is a disaccharide, formed by a molecule of glucose and a molecule of fructose, linked by a α(1→2) glycosidic bond. It is extracted from sugar cane and sugar beets (to produce sweeteners and as a food additive), and its annual worldwide production reaches the 175 metric tons [26, 27].
Figure 5. Structures of starch, sucrose, and inulin
1.3 The Furanoic Platform

The valorization of biomass leads to several products. One of the most studied reaction is the formation of 5-(hydroxymethyl) furfural (HMF) (Figure 6), an organic compound deriving from dehydration of several hexoses. HMF is one of the 12 bio-based building blocks listed by the US Department of Energy [28]. HMF is a potential “carbon-neutral” source for chemicals [29].

![Figure 6. Molecular structure of HMF](image)

HMF unique structure make it extremely attractive as a starting point for the production of commodity chemicals. HMF is a bifunctional molecule, substituted in the 2 and 5 position, so it can be either oxidized to a dicarboxylic acid, or reduced to a diol: both products may be used for the production of polymers. The furan ring can be hydrogenated in mild conditions to produce fuel molecules. Finally, the heterocyclic structure of this molecule can be found in many pharmaceutically active compounds (Figure 7) [29].
1.3.1 Hexoses dehydration

Dehydration of carbohydrates has been reported for the first time by Newth in 1951 [31], and the first complete review, with deep insight into sugar dehydration, has been reported by Corma in 2007 [32].
From a chemical point of view, HMF is the product of a triple dehydration of hexoses, as shown in Figure 8.

![Figure 8. Dehydration of hexoses to form HMF](image)

Both homogeneous and heterogeneous catalysts, in different medias (aqueous, organic, and ionic liquids), can catalyze the dehydration [33, 34, 35]. The reaction mechanism for dehydration is not clear, yet. It is well assessed that the dehydration coexists with other side reactions, such as the formation of humins. Moreover, the formation of organic acids (levulinic and formic acid) can self-catalyze the reaction [36].

The mechanisms can be divided into two pathways that involve cyclic or acyclic intermediates. Assary et al. have demonstrated the cyclic-pathway to be viable through computational studies [37]: the dehydration route is reported in Figure 9.
Moreau et al. proposed the acyclic route for the first time in 1996: dehydration of fructose was studied using H-mordenites \[38\]. They suggested a primary isomerization of fructose into glucose (or mannose), via a 1,2-enediol. No labeling or spectroscopic experiments confirmed this hypothesis. Later, calculation by Qian et al. demonstrated that the limiting step for the conversion of hexoses into HMF is the protonation of the hydroxyl group \[39\].

Glucose has to be preferred to fructose as a feedstock, since it is more abundant, but its selectivity and reactivity are both much lower. This is because both the pyranose and the furanose tautomers of fructose coexists in aqueous media, leading to
higher reactivity and better selectivity for fructose, when compared with glucose. This kinetics support the idea of a cyclic pathway for the dehydration, where a furanose form is vital for the output of the reaction. An efficient method for glucose dehydration should comprise a catalyst, usually a base or an enzyme, able to isomerize glucose to fructose, and another one able to dehydrate fructose to HMF [40, 41]. This problem has been the first challenge, since the base neutralized the used Brønsted acids, and because the enzymes are too susceptible to changes of the pH of the media. In recent times, some systems have been developed, which comprise CrCl₅/ILs, LA zeolites, and MClₓ in H₂O, and they all achieve yield >60% HMF, directly from glucose. All this methods shows a combination between a Lewis and a Brønsted acid.

Zhao et al. reported the use of the ionic liquid 1-ethyl-3-methylimidazolium chloride ([EMIM]Cl) as reaction media, sulfuric acid chosen as the catalyst for the dehydration, and CrClₓ salts used for the isomerization [42] (Figure 10). They reported high yields of HMF (68-70%), and proposed the role of the metal salt after NMR investigations. CrClₓ first helps a rapid mutuaroetation between the α and the β anomers of glucose, then mediates the isomerization of glucose to fructose, via a hydride transfer from the C2 to the C1 position, through an enediol intermediate.
Davis et al. found out in 2010 that Sn-zeolite could isomerize glucose to fructose in water, under both neutral and acidic conditions [43]. Later, they reported a combined Lewis-Brønsted acidic method (a Sn-zeolite plus HCl), for the direct conversion of glucose into HMF, with more than 70% of selectivity [44]. The mechanism has been studied using NMR spectroscopy and isotopic labeling. The experiments suggested a hydride transfer mechanism. Similar results have been obtained when homogeneous Lewis acids, such as AlCl₃, and CrCl₃, have been used (~60 mol% of HMF) [45, 46, 47].

1.3.2 HMF production: side reactions

Many side reactions may occur during HMF production, due to the high reactivity of the molecule.
Humins

Humins, for example, can be formed both from direct decomposition of hexoses and from the reaction of the newly formed HMF and hexoses. The first attempt to understand the mechanism behind the formation of humins is reported by Horvath in the ‘80s [48]: he proposed that HMF undergoes an addition next to and alkoxy group, to form humin precursor, DHH (2,5-dioxo-6-hydroxyhexanal), as shown in Figure 11.

![Figure 11. Humin-formation as postulated by Horvath [48]](image)

Following Horvath discovery, many humin-forming reactions have been advanced: aldol addition of DHH to HMF [49]; electrophilic attack of the aldehydic moiety of HMF by the alcoholic group of another HMF [50]; nucleophilic attack on HMF [51]. Several structure have been proposed. Figure 12 shows the ones suggested by Lund (1) [49], and Sumerskii (2) [50], where an aldol addition and an acetal are formed, respectively.
Figure 12. Humin structure, as postulated by Lund (1) and Sumerskii (2)

Currently, the only way humins can be used are fuels or compost.

**Levulinic acid**

Levulinic acid (4-oxopentanoic acid) is a ketoacid, used as a precursor for biofuels, such as methyl-tetrahydrofuran (MTHF), and γ-valerolactone (GVL), and for a wide range of pharmaceuticals and cosmetics. It is accepted that the formation of levulinic and formic acid proceed through rehydration of HMF and it is not coming direct from hexoses (Figure 9) [37]. This is because HMF and levulinic acid are inversely proportional: HMF yields reach an optimum, and a longer reaction time favors the decrease of HMF yields and the increase of levulinic (and formic) acid. Recent NMR studies proved that the aldehydic
carbon in HMF is incorporated in formic acid, while the hydroxymethyl group forms the C5 of levulinic acid [52, 53].

**Other byproducts**

Other byproducts that may be formed during hexoses dehydration are furanic compounds (furfural) [54], organic acids (lactic acid), aromatics (1,2,4-trihydroxybenzene), and retro-aldol products (pyruvaldehyde, glyceraldehyde) [55, 56].

### 1.3.3 GVL – γ-valerolactone

GVL (γ-valerolactone) is one of the most common lactones obtained directly from cellulosic biomass. Its direct production from glucose, the fact that it is retaining the 97% of the energy of glucose, its low vapor pressure, and its intrinsic stability for transportation and storage, has made GVL as a potential green fuel [57, 58].

It is well assessed that GVL comes from the hydrogenation (hydrocyclization) of levulinic acid (LA), or its esters [59]. Figure 13 shows the two possible pathways that can be followed to obtain GVL. In the first one, the ketone group of LA is hydrogenated, leading to 4-hydroxypentanoic acid (HPA). Afterwards, HPA undergoes an acid-catalyzed intramolecular esterification, giving the thermodynamically favored lactone, GVL. The second pathway, on the other way, comprises the formation of angelicalactones (AL, α and
\( \beta \), via LA acid-mediated dehydration, followed by a hydrogenation [60]. The election catalyst for LA hydrogenation is usually a ruthenium one, both in homogeneous [61, 62], or heterogeneous phase [63, 64]. Golden and bimetallic ruthenium catalysts have been reported [65\textsuperscript{a-b}].

![Figure 13. Hydrogenation of LA to GVL [60]](image)

GVL as solvent
Qi proposed GVL as a good solvent for the conversion of biomass into simpler products, such as HMF or LA, in GVL/H2O mixtures, where water works as a help for the dissolution of sugars [66], and GVL as a good solvent for the production of GVL itself [67]. Horváth et al. proposed different GVL-derivatives based ionic liquids, where the anionic part is either a methyl-4-methoxyvalerate or an ethyl-4-ethoxyvalerate, as green bio-ionic liquids [68].

**GVL as fuel**

GVL has the potential of being a good bio-addictive for fuels, due to its lower vapor pressure and its higher stability, compared to ethanol [58]. Moreover, ethanol forms an azeotrope with water, while GVL does not, bypassing the costly and energy-intensive process of distillation.

2-Methyl tetrahydrofuran (MTHF), produced from GVL catalytic hydrogenation, is considered a potential biofuel and it has been approved by the US Department of Energy as an additive for gasoline. Its suitability comes from the low tendency to polymerize and the inverse solubility in water (its solubility in water decreases with the temperature) [69].

Figure 14 shows how GVL can also be converted into valuable chemicals (caprolactone, 5-nonanone), precursors for polymers (dimethyladipate), and other additives for biodiesel (valerates) [70].
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Figure 14. Production and upgrading of GVL.

**H₂ source for GVL production.**

- Molecular hydrogen

  Historically, molecular hydrogen is the most used hydrogen-source for the reduction of LA to GVL. Homogeneous catalysts, usually Ru-based, are well developed and are reported since the beginning of the Nineties [71, 72]. The yields are usually above
95%. Homogeneous catalytic systems have better TON numbers, because of their deeper and stronger interaction with the substrates. The major drawbacks are the high cost of the ligands (TPPTS, 3,3′,3″-phosphanetriyltris-(benzenesulfonic acid) trisodium salt, costs about 250 €/g) and the poor reusability of the whole catalytic system.

The first attempts to reduce levulinic acid with heterogeneous catalysts are dated back to 1930, when PtO$_2$ was used in anhydrous solvents [73]. Other metals, either noble (Ru, Ir) and not noble (Cu, Pd) over different supports (carbon, SiO$_2$, Al$_2$O$_3$, TiO$_2$,) have been tried with considerably good results (GVL > 90%) [74, 75, 76]. The advantages of using a heterogeneous catalyst are the easy separation, the possibility of limiting the leaching of the metal, the facility in handling, in spite of harsh conditions. Recently, Raspolli et al. have reported LA hydrogenation to GVL under mild conditions [77].

- **Formic acid as hydrogen source.**

Formic acid (FA) is produced in equimolar amounts along with LA during sugars dehydration [78]. Using FA as the reducing source represents the perfect example of the *atom-economy* principle, since a possible byproduct is directly used into a reaction step. In this case, hydrogenation is completed through transfer hydrogenation: this reaction occurs when a molecule, other than hydrogen, is used as a hydrogen donor. Transfer hydrogenation follows the coming path:
The hydrogen donor, (1), can be any organic compound potentially, with an oxidation potential sufficiently low, that the transfer can occur in mild conditions, in order to keep the reaction conditions controllable. Typical donors, used in this kind of reactions, are isopropanol and cyclohexanol. Formic acid represents the best alternative since its produced byproduct is CO₂ (4), volatile and easily separable from the reaction media, while there are acetone and cyclohexanone, for isopropanol and cyclohexanol, respectively.

Recently, Horváth et al. proved transfer hydrogenation valid for levulinic acid reduction into GVL, using the catalytic complex [η₆-C₆Me₆) Ru(bpy)(H₂O)][SO₄], in an acidic aqueous media [80], but this method gave low yields (~20 % GVL), and the over reduced product 1,4-pentandiol. At high temperatures and with the help of metallic catalysts, formic acid can decompose to give H₂ and CO₂. Shvo catalyst proved to be active, but its poor recyclability and its high cost lead chemists to change catalytic system [67].

Qing et al. reported a method of reducing LA to GVL, using the formic acid directly produced from the dehydration of sugars and RuCl₃/PPh₃ with bases, as a catalyst [81]. This process avoid the costly separation of the reaction mixture and the subsequent re-introduction of FA for the reduction reaction. The overall yield was 48% (based on glucose), but poor water resistance and difficult recyclability are the major drawbacks of this catalytic system. The obvious solution has been immobilizing ruthenium on a solid catalyst, such as titania (TiO₂) or silica (SiO₂) [82]. The effect is
an evident increase in the recovery of the catalyst (up to eight times), but a decrease in the hydrogenating activity, when compared with the homogeneous system.

- **Alcohols as hydrogen source**

Another possibility for the reduction of LA to GVL is using alcohols as hydrogen donors. This is possible thanks to the Meerwein-Ponndorf-Verley (MPV) reduction, where aldehydes or ketones can be reduced, using other alcohols as hydrogen donors, according to the scheme depicted in Figure 16.

![Figure 16. Scheme of the Meerwein-Ponndorf-Verley reduction](image)

Usually, ethanol, 2-propanol (isopropanol), 2-butanol (sec-butanol), and 2-pentanol (sec-amyl-alcohol) are used as sacrificial alcohols, while zirconia (ZrO₂, identified as the most active among metal oxides), and Zr-beta have proved to be the best solid supports [83, 84].
1.4 Carbonylation

A carbonylation reaction is meant to be that reaction when a molecule of carbon monoxide (CO), is introduced into a substrate, both organic and inorganic. It is a widely studied and applied reaction, since carbon monoxide is an abundant and costless reactant. In biology, the term carbonylation may also refers to protein side-chain oxidation: this reaction is promoted by reactive oxygen species and forms reactive aldehydes or ketones, that can react with 2,4-dinitrophenylhydrazine (DNPH), to form hydrazones, as shown in Figure 17 [85].
In chemistry, metal-catalyzed carbonylation is an atom-efficient, straightforward and economic approach, to insert a carbonyl moiety on a molecule, especially when compared with classic acylation (Friedel-Craft), or oxidation reactions. This made
carbonylation reaction as one of the most important industrial processes to manufacture bulk and fine chemicals [86].

Carbonylation are highly attractive reactions, since they have a determined and clear mechanism, a great selectivity and a great tolerance towards a wide variety of different substrates. Carbon monoxide is a cheap, extensively studied and easily available carbon source and represent the unique building block for the introduction of carbonyl moieties on molecules [87]. For these reasons, the utilization of CO is increasing in the bulk and fine chemical industry.

CO is the simplest carbon entity. When employed in palladium-catalyzed carbonylation reactions, it satisfies the needs for the different concepts of green chemistry and atom economy, since it is a ready-available feedstock and it generates no byproducts because it is completely integrated in the products. In addition, the possibility of a direct incorporation of a carbonylic moiety in the final product, made carbonylations highly valuable. Catalytic carbonylation reactions need a combination between an organic substrate in the presence of carbon monoxide, which works as an oxidant. Nowadays, carbonylation reaction can be catalyzed by different transition metals, such as zinc, boron, and indium [88]. This family of reactions represents a useful tool for the production of carbonyl-containing commodity chemicals, like pharmaceuticals, dyes, and agrochemicals (Figure 18).
The first reported carbonylation was the cobalt-catalyzed alkene-hydroformylation, discovered in 1939 by Roelen [89, 90], while he was investigating the presence of oxygenated products during the recycling of olefins after Fischer-Tropsch reactions. In the original experiment, ethylene reacted with carbon monoxide and hydrogen to yield propanal (Scheme 1). When longer-chain alkenes are used, the branched aldehyde is also synthesized (usually in a 4:1 linear-branched ratio). Since oxygen atoms appeared in the product molecule, the reaction was named oxo-reaction, and hydroformylation (formaldehyde is incorporated in the product) only later. The hydrogen used in the reaction might reduce the aldehydes to the correspondent alcohols (oxo-alcohols). Roelen’s hydroformylation is generally considered as the first homogeneous catalytic reaction, and the Oxo-process is the oldest homogeneous catalytic process still in use in the industry.
The use of CO, as carbonyl source for the formation of carbonyl compounds, has rapidly become the broadest used methodology in homogenous catalysis. Several known and new compounds have been synthetized in considerably high yields and the formation of side products greatly reduced, making the overall process “greener” [92].

Carbon monoxide is a flammable, hazardous gas, which make it difficult to handle and to store. In addition, the health of the operator has to be taken into account, since CO cannot be detected from the human body, since it is colourless, odourless and tasteless.

1.4.1 Hydroformylation

Hydroformylation, also known as oxo-synthesis or oxo-process, is the most widespread and used type of homogeneously catalyzed carbonylation reaction, and it is used especially in industrial applications: nowadays the production of aldehydes deriving from hydroformylations accounts for more than 10 million metric tons, annually [93]. This reaction allows the direct introduction of a formyl group (-CHO), and a hydrogen atom on an olefinic double bond (Figure 19). A transition-metallic complex catalyzes the process.
Discovered by Roelen in 1939 [89, 90], hydroformylation, originally called oxo-reaction, is the reaction between an alkene of syngas (a mixture of carbon monoxide and hydrogen) to form aldehydes. It represents the most applied homogeneous catalysis reaction in the chemical industry.

Since both of the sides of the alkenyl double bond are possibly reactive, only ethylene gives a single product, propanal. Two isomers are then produced, when a longer-
chain alkene is used: the linear one and the branched one, that derives from an isomerization towards the thermodynamically more stable, internal alkene (Scheme 3).

Aldehydes are good intermediates for the production of many chemicals, such as alcohols, amines, polyols, and others.

Catalysts and ligands

Metals, usually cobalt or rhodium, usually catalyze hydroformylation. The original catalyst, Co₂(CO)₈, was then reduced \textit{in situ} by the hydrogen coming from syngas, forming the active specie HCo(CO)₄. Later in the Sixties, active rhodium catalysts have been
proven to be active, and since 1970s most of the hydroformylation reactions started to rely uniquely on rhodium [94]. Rhodium has a better tolerance towards different functional groups than cobalt [95]. Similarly as cobalt, the active specie in rhodium-catalyzed hydroformylation is the mononuclear hydridocomplex, HRh(CO)₄ [96, 97].

The catalytic complex can be schematized as HMe(CO)ₙLₘ, where Me is the metal and L is the ligand. Ligands are necessary to enhance the selectivity of the reaction, in spite of a lower catalytic activity. Rhodium has a higher activity than cobalt, due to its larger atomic radius, but a lower selectivity, due to the steric effects of the groups bound to the metal center. Bulky ligands have been then added to rhodium catalysts, to enhance selectivity, like tributylphosphine, triphenylphosphine (TPP), and sulfonated triphenylphosphine (TPPS), which gives the complex water solubility (Figure 20).

Figure 20. Structure of a Rh(I) complex used in the hydroformylation complex
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Water solubility has been a crucial point in the improvement of hydroformylation reactions, to widen the applicability of the reaction itself and to facilitate the separation of the products from the reaction media. One of the major drawbacks of an aqueous media is the poor solubility of long-chain alkenes, which can be improved adding phase-transfer catalysts, cosolvents, and surfactants.

The first generation of catalyst was entirely based on cobalt as metal core, and resulted in poor product separation, poor chemo- and regioselectivity, higher reaction temperature, and a lower catalytic activity [89, 90]. The innovation in the second generation of hydroformylation catalyst has been mainly substituting cobalt with rhodium, along with a coordination with triphenylphosphine (TPP), which made the overall process capable of operating at a lower temperature (LPO, Low Process Oxo). Moreover, selectivity towards the formation of the linear aldehyde increased [94, 95]. The major drawbacks of this class of catalyst are the lower thermal stability of the complex, which increased the loss of the precious metal during the separation process (rhodium price is 740 dollars per troy ounce, while cobalt price is approximately 10 dollars per pound). To prevent this huge economical loss, water soluble ligands, such as TPPS (sulfonated triphenylphosphine), have been developed and represent the third generation catalysts for hydroformylation [98] (Figure 21). The Rh-TPPS complex is stable in reaction conditions and water soluble and non-miscible in most common organic solvents, where it is possible to concentrate the products [99]. The two phases can be easily separated by decantation: while the aqueous phase is recycled and used again for a new catalytic cycle, the organic phase undergoes product purifications. In industry, water-soluble catalytic complex base on TPPTS have been commercialized in the ‘80s, and used for the production of C4 aldehydes by Ruhrchemie AG. This process
yields 95% propylene conversion and a 92-97% conversion towards the linear aldehyde 1-butanal [100].

Recently, Beller and coworkers used different transition metals (ruthenium, iridium, palladium, platinum and iron) as catalysts in hydroformylations, highlighting lower productivity and activity towards the traditional rhodium-based catalysts [101].

Nowadays, industrial hydroformylations are carried out with Rh(I) triarylphosphine catalysts, that lead to high regioselectivities (usually towards the preferred linear aldehydes), high tolerances towards many functional groups and minimal problems with side reactions, like hydrogenations [102, 103].
Catalytic cycle

Scheme 4. Rhodium-catalyzed hydroformylation, according to Heck and Brezlow mechanism

Scheme 4 represents the catalytic cycle of a rhodium-catalyzed hydroformylation of ethene, according to the model proposed by Heck and Brezlow [104, 105]. This pathway has been accepted as the one that most of hydroformylation reactions follow. At the beginning, the active form of the catalyst (6), forms a complex with the olefin (6 → 7), while expelling a molecule of carbon monoxide (CO), which is then recovered, once
the olefin double bond has been bound to the metal center (8). Another molecule of CO is then added (9): after being bound to the alkyl chain, a molecule of the aldehyde (propanal) is released (12 → 6), under the action of a molecule of hydrogen. The catalyst is back to its original form and can start another catalytic cycle [106].

A biphasic system is present when a water-soluble rhodium complex is used as catalyst. In this case, the hydroformylation reaction occurs at the interphase between the organic and the aqueous phase. The products will then be recovered by distillation of the organic phase [100].

**Application**

New stereocenters can be formed with hydroformylations, when prochiral alkenes or chiral phosphine ligands are used in the reaction [107].

The Ruhrchemie/Rhone-Poulenc process is a good example of industrial application of hydroformylation. It consists of a rhodium catalyst over TPPTS (sulphonated triphenylphosphine), for the hydroformylation of propene (propene, catalyst, syngas, in a 1:1:1 ratio) [108]. The final products are the two expected aldehydes (1-butyraldehyde and isobutiraldehyde, in a 96:4 ratio), plus some alcohols as by-products (99% selectivity of the process for C4 aldehydes). In this process, the catalyst is immobilized, so that the loss of the metal is in ppb range: in the first ten years, with an esteemed 1-butanal production of 2 million metric tons, the leach of rhodium will be less than 2 kg. The catalyst inactivation is determined by the oxidation of the excess TPPTS ligand.
Longer-chain-aldehydes production has a smaller impact on the market (1 million metric tons). The main drawback of this process is the lower water solubility of both olefins and the produced aldehydes. Solubility problems are bypassed by using amphiphilic phosphine ligands, surfactants, and mass transfer additives (Figure 22) [109, 110, 111].

Figure 22. Tools for aqueous phase hydroformylation of higher carbon chain (C>5) alkenes.
1.4.2 Methanol carbonylation

The carbonylation of methanol is a reaction that follows the Reppe chemistry \[112\]. It is widely used in the chemical industry, to produce acetic acid. Important examples are the Monsanto and the Cativa processes, where methanol is carbonylated to acetic acid, using a rhodium and an iridium catalyst, respectively \[113, 114\] (Scheme 5). Recently the Cativa process has almost completely supplanted the Monsanto, since the presence of iridium allows the use of less water and the formation of less byproducts (such as propionic acid), making the overall process more environmental friendly.

$$\text{CH}_3\text{OH} + \text{CO} \xrightarrow{\text{HI, } \text{H}_2\text{IrCl}_6 \text{ promoter, H}_2\text{O}} \text{CH}_3\text{COOH}$$

Scheme 5. Carbonylation of methanol with the Cativa process.

Recently, Reppe chemistry has been applied for the production of dimethylcarbonate (DMC), a carbonate ester, used as a mild and green methylating agent, as a solvent, and especially as a fuel additive (O\(_2\) content 53.3% wt), to reduce CO\(_2\) and soot production during the burning of the fuel. DMC was historically prepared from phosgene and methanol: this synthesis has been replaced, due to the high toxicity of phosgene and the large amount of hydrochloric acid produced. Nowadays, DMC can be produced either by transesterification of ethylene and propylene carbonate with methanol, or by direct
carbonylation of methanol, in an oxidative atmosphere (Enichem synthesis, Scheme 6) [115].

\[
2\text{CH}_3\text{OH} + \frac{1}{2}\text{O}_2 + \text{CO} \xrightarrow{\text{Cu salts}} \text{CH}_3\text{OCOOCH}_3 + \text{H}_2\text{O}
\]

Scheme 6. Enichem synthesis of DMC [116].

### 1.4.3 Decarbonylation

Decarbonylation is that process where a molecule of carbon monoxide (CO) is selectively removed (Scheme 7). Thus, aldehydes, ketones, carboxylic acids, and esters are some of the chemical classes that may be involved in this reaction.

Decarbonylation proceeds through metal acyl hydrides. The first reported example is the decarbonylation of cinnamaldehyde to obtain styrene, performed by Tsuji and Ono in 1965, using Wilkinson catalyst RhCl(TPP)_3 [117, 118] (Scheme 8).

\[
\begin{align*}
\text{R} & \xrightarrow{\text{cat.}} \text{R}X + \text{CO} \\
\end{align*}
\]

Scheme 7. A general scheme for decarbonylation, where X can be either hydrogen or halides.
Decarbonylation proved to be tolerant towards a wide range of functional groups, when employed in total synthesis: stereochemistry is maintained, when chiral aldehydes are treated with Wilkinson catalyst [119]. Later new ligands, from simple phosphines (like trimethylphosphine, PMe₃), to large chiral ones (like (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl), BINAP), have been tried and proved to be highly efficient. Recently, other transition metals, especially iridium and palladium, have demonstrate to be valid alternatives than rhodium [120].

Since its inner great tolerance, decarbonylation is a valid instrument for reactions where susceptible functional groups are present in the molecule. For example, decarbonylation of 5-hydroxymethylfurfural (HMF, a key intermediate in the dehydration of hexoses) [121], leads to furfuryl alcohol, a useful chemical, which can be further hydrogenated to tetrahydrofurfuryl alcohol (THFA), which is used in agriculture as a non-hazardous solvent. Recently, Rauchfuss et al. reported a decarbonylation of HMF to furfural in dioxane, using palladium over a carbon support as a catalyst, leading to more than 95% of selectivity and conversion [122], as it can be seen in Scheme 9.
1.4.4 Hydroxy- and alkoxy carbonylation

In the Sixties, Reppe’s work on carbonylation of alkynes has been of crucial importance for the understanding and development of the chemistry of carbon monoxide [112]. Methyl acrylate has been produced in the industry following the Shell process (Scheme 10). Recently this reaction is no longer operating, due to the high price of acetylene [123].

Hydroxycarbonylation

The first hydroxycarbonylation (occasionally called hydrocarboxylation, when related to the couple H₂/CO₂), has been reported by BASF in 1969: a terminal alkene was
treated with palladium and a phosphine complex [124]. Later, the reaction was optimized to consolidate good yields, selectivity towards the linear esters, and better conversion rates [125]. Alper et al. discover that the reaction outcome can shift towards the branched ester, by adding CuCl$_2$ and HCl to the catalyst [126], as displayed in Scheme 11.

Scheme 51. Hydroxycarbonylation of alkenes.

Hydroxycarbonylation is also possible on alkynes [127, 128].

**Alkoxycarbonylation**

Alkoxycarbonylation is a reaction between an alkene, carbon monoxide and an alcohol, to produce an ester. BASF and other companies investigated and developed a method for the production of dimethyladipate, a plasticizer used in PVP (polyvinylpyrrolidone) production, via a double methoxycarbonylation reaction [129, 130, 131] (Scheme 12).
The first reported example of alkoxy carbonylation date back from James and Stille, who found out that two carboxymethyl groups were incorporated into a molecule of norbornene, when a Pd-Cu catalyst were used [132, 133] The double methoxycarbonylation of norbornene is reported in Scheme 13.

Further studies by Inomata, showed that the reaction can be directed towards the monoester, when Cu(II) is used, or the diester, when Cu(I) is used [134].

Later, phosphines and SnCl₂ have been added to the reaction mixture, improving the yields and making the reaction conditions milder. These conditions were used
for the synthesis of esters coming from terpenes, such as limonene, that are very important in the pharmaceutical and flavor industry [135, 136].

At the beginning, it was believed that monodentate phosphines (like TPP), favored the formation of linear esters, while bidentate ligands favored the formation of poliketones [137]. Later, it has been proved that the formation of the linear ester can be greatly enhanced when a bulky phosphate ligand, such as 1,2-bis(di-tert-butylphosphinomethyl)benzene (DTBPMB) (the latter being chosen as the best ligand for methoxycarbonylation reactions) [138], or bis(phosphoadamantyl)diphosphines [140], are used.

Scheme 64. Two possible catalytic cycles for the methoxycarbonylation of ethylene.

Scheme 14 highlights the two possible catalytic cycles for the methoxycarbonylation of ethylene. Route A shows the Hydride-cycle, where a Pd-hydride...
complex (14) is formed. Afterwards, coordination of the alkene and insertion into the [Pd]-H gives the alkyl complex (21). Migratory insertion of a molecule of carbon monoxide, form an acyl complex (15). Nucleophilic attack of methanol gives the final product, methylpropanoate (16), and the reformed Pd-hydride complex (14) [140- 142].

The Methoxy-mechanism (B) implies the formation of a methoxycarbonyl complex. The migratory insertion of CO into the Pd-OMe (17) bond is followed by the coordination and the insertion of the alkene. Final methanolysis gives the desired product and the recycled catalyst [143].

Since a nucleophilic attack from the alcohol is needed, alkoxy carbonylation is usually performed only in methanol, the most nucleophilic alcohol. Furthermore, methyl esters are the most widely produced in the industry.
1.5 Objectives

Over the last century, the world has become increasingly dependent on oil as its main source of chemicals and energy. In this sense, biomass is the one of the most attractive alternative feedstock for chemicals and energy production, as it is the only widely available carbon source apart from oil and coal.

Recently, biomass achieved resounding success in the last years, since it can be used for producing either already known chemical or chemicals with a great potential, like HMF (5-hydroxymethylfurfural), or lactic acid. The most positive aspect of biomass is that it is CO₂ neutral, since the CO₂ released during the use of biomass is used for the production of biomass itself.

The aim of this thesis is to develop a new catalytic route, where it is possible to match the decarbonylation of biomass with the methoxycarbonylation of an alkene with the biomass-produced CO. The focus of this work will be held on the catalytic parameters and their optimization, to better understand the behavior of the reactions, and to increase the yields of the reaction itself. In particular, methoxycarbonylation will be studied and optimized much deeply, due to its lower presence in the literature.

Hereby, we introduce a new one-pot methodology, which is able to join successfully the process of decarbonylation of a biomass-derived molecule, and methoxycarbonylation with an alkene.

The points of the present work can be summarized as follows:
• Improving the catalytic activity and yields, by understanding the behavior and the role of the different parameters;

• Screen different substrate, to comprehend how the latter can influence the progress of the reaction

Scheme 15 shows a model methoxycarbonylation reaction, where HMF, 5-(hydroxymethyl)furfural, is the substrate and 1-hexene is the alkene.

Scheme 15. Methoxycarbonylation of hexene with HMF as CO source.
Chapter 2.

Experimental

2.1 General comments

2.1.1 Materials

All chemicals were purchased from Sigma-Aldrich and used without further purification, unless otherwise noted. Argon (grade 5.0, Air Liquide) was used when an inert atmosphere was needed.

2.1.2 Characterization Techniques

The catalytic yield was monitored using a GC-FID, with a HP 5890 Series II chromatograph equipped with a SGE BP1 non-polar 100% dimethyl polysiloxane capillary column (50 m x 0.32 mm x 0.25 mL), N₂ as carrier gas. GC-MS is Agilent, 6850N with HP-5 capillary column (Agilent, J & W), N₂ as carrier gas, bearing the same column as the GC-FID. HPLC is Agilent 1200 Series instruments equipped with an Aminex HPX-87H column (Bio-Rad), by using 0.005 M aqueous sulfuric acid as the eluent, at a flow rate of 0.6 mL/min.
and a column temperature of 80°C. Standard curves were used to quantify the conversion and product yield.
2.2 Methoxycarbonylation reactions

General procedure for methoxycarbonylation of HMF with 1-hexene

Catalytic experiments were performed in a 10 mL ACE pressure tube, or alternatively in a 10 mL Fisher-Porter tube.

In a typical experiment, palladium(II) acetate (5.6 mg, 0.02 mmol, 0.25%), or palladium(II) acetylacetonate (7.7 mg), 1,2-bis(di-tert-butylphosphinomethane)-benzene (DTBPMB, 49.0 mg, 0.125 mmol, ligand/Pd molar ratio of 5), 5-(hydroxymethyl)furfural (126.0 mg, 1 mmol), 1-hexene (100 μL, 0.80 mmol), methansulphonic acid (80 μL, 1.05 mmol) and 5 mL of methanol were introduced in the pressure tube directly. The pressure tube was then immersed in an oil bath, previously pre-heated at 120°C, for 20 h. After the reaction the pressure tube was cooled down and then naphthalene (12.8 mg, 0.1 mmol), was added and the reaction mixture stirred for 10 more minutes. Afterwards the solution was filtered and analyzed by GC, GC-MS and HPLC, using naphthalene as internal standard.

General procedure for methoxycarbonylation of HMF with alkenes

In a typical experiment, palladium(II) acetate (5.6 mg, 0.02 mmol, 0.25%), or palladium(II) acetylacetonate (7.7 mg), 1,2-bis(di-tert-butylphosphinomethane)-benzene (DTBPMB, 49.0 mg, 0.125 mmol, ligand/Pd molar ratio of 5), 5-(hydroxymethyl)furfural
(126.0 mg, 1 mmol), the chosen alkene (0.80 mmol), methansulphonic acid (80 μL, 1.05 mmol) and 5 mL of methanol were introduced in the pressure tube directly. The pressure tube was then immersed in an oil bath, previously pre-heated at 120°C, for 20 h. After the reaction the pressure tube was cooled down and then naphthalene (12.8 mg, 0.1 mmol), was added and the reaction mixture stirred for 10 more minutes. Afterwards the solution was filtered and analyzed by GC, GC-MS and HPLC, using naphthalene as internal standard.

**General procedure for alkoxy carbonylation of HMF with alcohols**

In a typical experiment, palladium(II) acetate (5.6 mg, 0.02 mmol, 0.25%), or palladium(II) acetylacetonate (7.7 mg), 1,2-bis(di-tert-butylphosphinomethane)-benzene (DTBPMB, 49.0 mg, 0.125 mmol, ligand/Pd molar ratio of 5), 5-(hydroxymethyl)furfural (126.0 mg, 1 mmol), 1-hexene (100 μL, 0.80 mmol), methansulphonic acid (80 μL, 1.05 mmol) and 5 mL of the chosen alcohol were introduced in the pressure tube directly. The pressure tube was then immersed in an oil bath, previously pre-heated at 120°C, for 20 h. After the reaction the pressure tube was cooled down and then naphthalene (12.8 mg, 0.1 mmol), was added and the reaction mixture stirred for 10 more minutes. Afterwards the solution was filtered and analyzed by GC, GC-MS and HPLC, using naphthalene as internal standard.

**General procedure for methoxycarbonylation of sugars with 1-hexene**
In a typical experiment, palladium(II) acetate (5.6 mg, 0.02 mmol, 0.25%), 1,2-bis(di-tert-butylphosphinomethane)-benzene (DTBPMB, 49.0 mg, 0.125 mmol, ligand/Pd molar ratio of 5), hexoses (180.0 mg, 1 mmol), 1-hexene (100 μL, 0.80 mmol), methansulphonic acid (80 μL, 1.05 mmol) and 5 mL of methanol were introduced in the pressure tube directly. The pressure tube was then immersed in an oil bath, previously pre-heated at 120°C for, 20 h. After the reaction the pressure tube was cooled down and then naphthalene (12.8 mg, 0.1 mmol), was added and the reaction mixture stirred for 10 more minutes. Afterwards the solution was filtered and analyzed by GC, GC-MS and HPLC, using naphthalene as internal standard.
Chapter 3.

Results and Discussion

Due to the nature of this thesis, the result and discussion part is divided into two parts. The first one, where HMF is the main substrate, and the second one, where different sugars are the reagent.

3.1 From HMF to MH and GVL

GVL, γ-valerolactone, is a natural occurring chemical in fruits and a frequently used food additive [144]. It is renewable and it has also potential use as a monomer for polyester production. It exhibits the most important characteristics of an ideal sustainable liquid, since it is convertible to both energy and carbon-based consumer products. Methyl heptanoate (MH) is a fruity orris smelling ester, similar to hexyl acetate, which is naturally found in some fruits and used in the food industry as additive for human consumption.

Dehydration of HMF is a well-studied reaction, as well as methoxycarbonylation of alkenes. This is the reason why we decided to proceed developing a catalytic system, optimizing the conditions of both dehydration of HMF and methoxycarbonylation of 1-hexene, at the same time [102, 146]. At the same time, HMF possesses an abundantly
studied chemistry; therefore, it represents a key compound, which stands between sugars and levulinic acid and can connect the two latter.

To achieve the products, dehydration of HMF (23) occurs first, followed by methoxycarbonylation of 1-hexene, to give methyl heptanoate (MH, 27), and the contemporary reduction of methyl levulinate (ML, 25), to yield γ-valerolactone (GVL, 29). An overview of the whole work is depicted in Scheme 16.

We decided to combine HMF and sugar dehydration along with methoxycarbonylation of alkenes and hydrogenation of levulinic acid, in order to boost biomass processing. Methoxycarbonylations and hydrogenations represent two of the most atom-efficient reactions, so they perfectly match the need to reduce the waste in biomass treatment, which is usually extremely high [48].

With this work, we state how it is possible to achieve biomass upgrading to simpler and industrially useful compounds, without the need of costly and time-consuming separation and purification steps [148, 149, 150, 151].
Fructose Dehydration and HMF Decarbonylation

Fructose (22) → HMF (23) → Furfuryl Alcohol (24) → Methyl Levulinate (25)

Levulinic Acid Formation

HMF (23) + 2MeOH → Methyl Levulinate (25) + Methyl Formate (26)

Hexene Methoxycarbonylation

Methyl Formate (26) → CO + H2 + MeOH → Methyl Heptanoate (27)

Methyl Levulinate Hydrogenation

Methyl Levulinate (25) → Methyl 4-hydroxypentanoate (28) → GVL (29)

Scheme 7. Overview of the Ph.D. work.
CHAPTER 3. RESULTS AND DISCUSSION

We used gas chromatography (GC-FID), mass spectrometry combined with gas chromatography (GC-MS), and high-performance liquid chromatography (HPLC) to process the samples and analyze the data.

The yields of methyl heptanoate are calculated taking into account the production of a single mole of CO from the decarbonylation of HMF. As mentioned later in the paper, we proved that decarbonylation of HMF could occur on both the aldehydic moiety and on the hydroxymethyl group, leading to the production of two theoretical moles of carbon monoxide. Thus, yields above 100% are possible, when calculated with this methodology.

The handling of carbon monoxide represents the reason why we decided to replace this hazardous chemical with a CO-releasing molecule, such as HMF, taking into account a lower atom efficiency, which is maximum when CO is used as carbonylating agent. Previous studies proved HMF capable of releasing formic acid, known as a CO-releasing molecule when transition metals (Ru, Pd) are used as catalysts, with only molecular hydrogen as byproduct [152, 153, 154]. Another reactant, hydrogen in our case, which could have been a problem, increasing the number of byproducts in the final mixture, turned out to be a viable mean to obtain GVL from direct reduction of 4-hydroxypentanoic acid.

Moreover, due to the impossibility of the human body to detect carbon monoxide, we increased the safety of the overall process at the same time.
3.1.1 Activation of the catalyst

Gas-chromatography analysis have been carried out after filtration of the samples, to quantify the desired and undesired products, according to calibration, previously done with standards. GC-MS is used to crosscheck the results obtained from the GC-FID, and verify whether there are further notable byproducts or not. HPLC is necessary to quantify the conversion of sugars and HMF.

The activation of the catalyst was initially performed, following known procedure reported in the literature [155], stirring the palladium precursor with the ligand in 4 mL of methanol for 2 h under an inert (argon) atmosphere. Subsequently a solution containing HMF, MSA and methanol was added under a stream of argon.

Alternatively, a quicker and simpler one-pot methodology has been used, leading to better results, which highlighted that an argon atmosphere it is not necessary. In all the reactions, Pd(OAc)₂ was selected as the catalyst precursor in combination with the diphosphine ligand 1,2-bis(di-tert-butylphosphinomethyl)benzene (DTBPMB), which has been reported to result in highly selective and active methoxycarbonylation systems for MP production, in a recent publication of our group, from Dr. García-Suarez and Dr. Khokarale [4].
3.1.2 Influence of the acid concentration

Our research started by choosing the best acid co-catalyst to use in the reaction. We performed a quick screening among four different Brønsted (protic) acids, with different characteristics: H₂SO₄ and methanesulfonic acid (MsOH, or MSA), are liquids and allow working in a homogeneous environment; p-toluenesulfonic acid (TsOH, or PTSA), and the zeolite H-ZSM-5, are solids, and they would allow a better and easier work up at the end of the reaction. Furthermore, they would direct the overall process towards a more feasible industrial application [155]. The choice of MSA has been done following the work of Dr. García-Suarez and Dr. Khokarale [4], then, sulfuric acid has been chosen since it has a similar methanol solubility, and a similar pKₐ. Afterwards, we decided to check whether solid acids, such as PTSA and the zeolite H-ZSM-5 were able to catalyze the overall process. Despite their well-assessed capability towards carbohydrates dehydrogenation [38, 43], solid acids have a lower coordination capability, which is supposed to interfere with the methoxycarbonylation reaction.

According to the data that we collected, that are displayed in Table 1, MSA showed to be the best for conversions and yields (entry 1), along with sulfuric acid (2). Nevertheless, we chose MSA in spite of H₂SO₄, due to its lower volatility. The low amounts of methyl heptanoate when a solid acid is used can be explained by the pKₐ of the acids that seems to be insufficient to carry out the dehydration of HMF. Moreover, a solid acid could exploit a more difficult coordination of the palladium core.
Table 1. Screening of the acid promoter.

Subsequently, the amount of the chosen acid promoter (MSA) for the dehydration reaction has been investigated. The obtained results are shown in Table 2.

Table 2. Methyl heptanoate dehydration reaction using different acid promoters.
TABLE 2. Reaction conditions: 0.025 mmol Pd(OAc)$_2$, 1 mmol HMF, diphosphine ligand 0.125 mmol, naphthalene after reaction 12% (0.12 mmol), MeOH 5 mL, 1-hexene (approx. 1.8 mmol), temperature 120° C, reaction time 20 hours.

The graphic clearly shows that a linear trend between the volume of acid and the amount of the products is evident. The maximum yield of methyl heptanoate and GVL is reached when 80 μL of MSA (1.05 mmol), are used in the reaction. These results could be explained with both a major stabilization of the metal center for the methoxycarbonylation reaction (carried out by the acidic protons) and for the increased speed in the dehydration of HMF. Higher volumes of acid lead to a decrease of the valuable products, since the side reaction for the formation of unreactive humins is favored.

GVL is produced only when a significant amount of acid is used, at least 30 μL (~0.40 mmol of MSA). It is notable how the amount of methyl levulinate and GVL are
inversely proportional. This is because hydrogenation of ML leads to GVL production, so when the first reacts, the second increases.

It is possible to observe the complete conversion of HMF when at least 50 µL (0.656 mmol) of the acid are used.

### 3.1.3 Time study

Stating the ideal reaction time has been a crucial point, not only to optimize the catalytic system, but also to understand the kinetic of the reaction, both under the point of view of conversions and also the production of the products.

As Table 3 shows, the highest percentages of valuable products are obtained when a reaction time of 20 h is employed (entry 5). The amount of MH tends to increase when reaction time is increasing and, at the same time, the percentage of ML tends to decrease considerably.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Time (h)</th>
<th>Methyl heptanoate (%)</th>
<th>Methyl levulinate (%)</th>
<th>GVL (%)</th>
<th>Conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1)</td>
<td>2</td>
<td>0.11</td>
<td>65.13</td>
<td>3.21</td>
<td>78</td>
</tr>
<tr>
<td>(2)</td>
<td>4</td>
<td>7.37</td>
<td>64.36</td>
<td>6.59</td>
<td>84</td>
</tr>
<tr>
<td>(3)</td>
<td>8</td>
<td>38.36</td>
<td>48.43</td>
<td>20.93</td>
<td>91</td>
</tr>
<tr>
<td>(4)</td>
<td>16</td>
<td>80.97</td>
<td>6.88</td>
<td>54.64</td>
<td>100</td>
</tr>
<tr>
<td>(5)</td>
<td>20</td>
<td>81.29</td>
<td>8.89</td>
<td>55.06</td>
<td>100</td>
</tr>
<tr>
<td>(6)</td>
<td>48</td>
<td>84.96</td>
<td>10.42</td>
<td>54.01</td>
<td>100</td>
</tr>
</tbody>
</table>
Table 3. Reaction conditions: 0.025 mmol Pd(acac)$_2$, 1 mmol HMF, 1.05 mmol of MSA, diphosphine ligand 0.125 mmol, naphthalene after reaction 12% (0.12 mmol), MeOH 5 mL, 1-hexene (approx. 1.8 mmol), temperature 120° C.

This means that the reaction environment, at that point, favors the hydrogenation of methyl levulinate that leads to GVL production.

The low amount of MH at lower times exhibits how the first reaction that has to occur is the dehydration of HMF.

Longer times do not provide considerably better results: only a slight increase for methyl heptanoate and GVL is registered when the reaction time is doubled (6) and tripled (7).
3.1.4 Catalyst loading

Different amounts of the metal precursor have then been examined in order to state the optimal quantity of palladium to employ in the reaction.

Table 4 shows the results. The best ones are obtained when 0.025 mmol of the metal precursor, Pd(acac)$_2$ (palladium acetylacetonate) in this case, are used (entry 2). Lower concentrations lead to lower MH yields and to high amounts of ML, since there is not enough catalytic complex to achieve the decarbonylation of HMF and the subsequent methoxycarbonylation of 1-hexene.

Blank experiments without palladium (entry 5) proved that no methyl heptanoate is produced when the metal is not involved in the reaction. The absence of GVL proves that the palladium complex may also be able to catalyze the hydrogenation of methyl levulinate to the lactone.

Furthermore, it is notable how the maximum amount of methyl levulinate we could obtain is ~92%. The rest is lost in humins and non-detectable products.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd (mmol)</th>
<th>Methyl Heptanoate (%)</th>
<th>Methyl</th>
<th>GVL (%)</th>
<th>Conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1)</td>
<td>0.050</td>
<td>102.03</td>
<td>19.21</td>
<td>57.56</td>
<td>100</td>
</tr>
<tr>
<td>(2)</td>
<td>0.025</td>
<td>81.29</td>
<td>8.89</td>
<td>55.06</td>
<td>100</td>
</tr>
<tr>
<td>(3)</td>
<td>0.012</td>
<td>61.94</td>
<td>31.54</td>
<td>33.83</td>
<td>100</td>
</tr>
<tr>
<td>(4)</td>
<td>0.006</td>
<td>12.37</td>
<td>69.84</td>
<td>7.63</td>
<td>100</td>
</tr>
</tbody>
</table>
Different sources of palladium and different phosphine ligands have been then tested to find the best candidate for the methoxycarbonylation reaction.

The ligand has a crucial importance in the correct development of the catalytic reaction. It has been reported that the diphosphine ligand 1,2-bis(di-tert-butylphosphinomethane)-benzene (DTBPMB, 30) is the best ligand to accomplish the
highest yields for this process, so we took into account this ligand for our tests [4]. The major drawback of DTBPMB is its extremely high cost, almost 300€/g. Since the ligand is commonly used in excess (5:1 equivalents, in our case), and would then heavily affect the overall cost for the process, we decided to proceed with some trials with cheaper and simpler phosphines (Figure 23). Triphenylphosphine, a monophosphine ligand (TPP, 31, ~20 €/g), and the diphosphine ligand 1,3-bis(diphenylphosphino)propane (dppp, 32, ~40 €/g), ligands that are unexpensive and commonly used in catalysis, leaded to no valuable results (no methyl heptanoate at all), so we decided to keep going with the DTBPMB. The results are summarized in Table 5.

Then, we decided to try different sources of palladium, as palladium precursors (Figure 24): palladium (II) acetate (33), palladium (II) acetylacetonate (34), and palladium (0) dibenzylidenacetate (35). These are commonly used palladium source, with approximately the same cost (119 €/g, 65€/g, and 76 €/g, respectively).
As we can see from Table 5, we obtained the best results when Pd(acac)$_2$ is used (entry 3), followed by Pd(OAc)$_2$ (1), which gave only slightly lower yields. When Pd$_2$(dba)$_3$ (dibenzylidenacetate) is employed the results are considerably worst, though (entry 2). This is probably because, in this case, palladium is in the (0) oxidation state and has to be oxidized to enter the catalytic cycle of methoxycarbonylation, slowing down the entire chemical process.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd source</th>
<th>Methyl heptanoate (%)</th>
<th>Methyl</th>
<th>GVL (%)</th>
<th>Conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1)</td>
<td>Pd(OAc)$_2$ + DTBPMB</td>
<td>73,38</td>
<td>4,14</td>
<td>38,09</td>
<td>100</td>
</tr>
<tr>
<td>(2)</td>
<td>Pd$_2$(dba)$_3$ + DTBPMB</td>
<td>48,21</td>
<td>1,16</td>
<td>14,12</td>
<td>100</td>
</tr>
<tr>
<td>(3)</td>
<td>Pd(acac)$_2$ + DTBPMB</td>
<td>81,29</td>
<td>8,89</td>
<td>55,06</td>
<td>100</td>
</tr>
<tr>
<td>(4)</td>
<td>Pd(acac)$_2$ + TPP</td>
<td>-</td>
<td>70,67</td>
<td>-</td>
<td>100</td>
</tr>
</tbody>
</table>

Figure 24. Different palladium sources.
STating the optimal operating temperature has been the last step during the optimization of the process and its catalytic conditions. While it is known that the higher the temperature, the better the dehydration of HMF occurs, the optimum temperature for methoxycarbonylation was an issue.

Table 5. Reaction conditions: 0.025 mmol Pd, 1 mmol HMF, 1.05 mmol MSA, diphosphine ligand 0.125 mmol, naphthalene after reaction 12% (0.12 mmol), MeOH 5 mL, 1-hexene (approx. 1.8 mmol), reaction time 20 hours, temperature 120° C.
It is evident from Table 6 that lower temperatures then 120°C lead to considerably lower yields of every product. This is presumably due to both a non-activation of the palladium catalyst (responsible of the methoxycarbonylation) and to a decreased activity of the acid, responsible of the dehydration of HMF.

A higher temperature, on the other hand, leads to a decrease of the yields. In this case, probably the catalytic complex undergoes thermal decomposition and HMF tends to aggregate and self-react to form humins and other non-valuable byproducts.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature (°C)</th>
<th>Methyl Heptanoate (%)</th>
<th>Methyl Levulinate (%)</th>
<th>GVL (%)</th>
<th>Conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1)</td>
<td>80</td>
<td>5.95</td>
<td>17.89</td>
<td>-</td>
<td>68</td>
</tr>
<tr>
<td>(2)</td>
<td>100</td>
<td>25.64</td>
<td>11.13</td>
<td>14.03</td>
<td>87</td>
</tr>
<tr>
<td>(3)</td>
<td>120</td>
<td>81.29</td>
<td>8.89</td>
<td>55.06</td>
<td>100</td>
</tr>
<tr>
<td>(4)</td>
<td>140</td>
<td>69.20</td>
<td>8.66</td>
<td>31.36</td>
<td>100</td>
</tr>
</tbody>
</table>
Table 6. Reaction conditions: 0.025 mmol Pd(acac)$_2$, 1 mmol HMF, 1.05 mmol MSA, diphosphine ligand 0.125 mmol, naphthalene after reaction 12% (0.12 mmol), MeOH 5 mL, 1-hexene (approx. 1.8 mmol), reaction time 20 hours.

It is clear how a higher temperature strengthens the acid capability. Thereof, it can be understood why dehydration of HMF occurs completely only with a higher temperature than 80°C, and the faster the more the temperature is risen.

The TON of the reaction when all the conditions are optimized resulted to be 32,51 for MH and 22,004 for GVL. The TOF of the catalytic system is 1,6255 h$^{-1}$ for MH and 1,1002 h$^{-1}$ for GVL. The numbers are not very encouraging, but we have to consider that this is a brand new reaction that needs to face further developments in the future, especially for which it concerns the recycling part, that has not been considered intentionally.
3.1.7 Substrate screening

Once optimized all the reaction conditions we proceeded with a screening of several HMF-related compounds, in order to state possible reaction mechanisms. Furfural (36) and furfuryl alcohol (24) were chosen due to their chemical affinity with the HMF molecule: it has been then possible to study how the two different functional groups present on HMF behave in the presence of our catalytic complex. Then, we decided to use the methylated analogues of the two latter molecules, 5-methylfurfural (37) and (5-methyl-2-furyl)methanol (38) to state whether a small steric hindrance could affect the overall process, in particular the decarbonylation step. The compounds are shown in Figure 25.

The operating conditions we used were 0.025 mmol of Pd(acac)$_2$, 0.125 mmol of DTBPMB, 1.05 mmol of MSA, naphthalene after reaction 12% (0.12 mmol), 5 mL of MeOH, 1-hexene (approx. 1.8 mmol), 120°C, and 20 hours of reaction.

![Figure 225. Substrates used in this study](image)
Firstly, we decided to investigate the origin of the CO molecule, which is necessary for the carbonylation of the alkene (1-hexene), to produce methyl heptanoate.

This molecule could indeed derive from both a direct decarbonylation of the aldehyde moiety (Scheme 17) or, on the other hand, it could follow the dehydrogenation of the alcoholic functionality, as illustrated in Scheme 18: here, HMF could undergo dehydrogenation first, followed by the decarbonylation of one of the two aldehydic moiety.

![Scheme 17. Proposed mechanism: direct decarbonylation.](image1)

![Scheme 18. Proposed mechanism: dehydrogenation of the alcohol with further decarbonylation.](image2)

Therefore, we decided to make a quick screening of different substrates, in order to state the provenience of the CO molecule.

We decided to use furfural (furan-2-carbaldehyde, 36), and furfuryl alcohol (2-furanmethanol, 24), since they bear the two different functional groups of HMF, but divided into two separate molecules. This allows an easier study of the kinetic of the reaction.
Furfural gives, as expected, considerably high yields of both methyl heptanoate and GVL (58% and 22%, respectively), confirming the first proposed pathway. Unexpectedly, the data gathered after the reaction of furfuryl alcohol, show that also this substrate is able to form carbon monoxide, even if in a smaller amount (30% of methyl heptanoate). The lower reactivity of furfuryl alcohol is probably because the carboxylation is completed after two sub-reactions: the dehydrogenation of the alcoholic moiety, which occurs first, and the decarbonylation of the obtained aldehyde (see Scheme 2).

At a later stage, we decided to use the methylated analogues of furfural and furfuryl alcohol, 5-methyl furfural (37) and 5-(methyl-2-furyl)-methanol (38) respectively, in order to check whether the steric hindrance of a methyl group could influence the decarbonylation (and the following methoxycarbonylation) of the furanic core. The results, shown in Table 7, demonstrate that the methyl group does not constitute an obstacle for the decarbonylation.
Table 7. Reaction conditions: 0.025 mmol Pd(acac)$_2$, 1 mmol substrate, 1.05 mmol MSA, diphosphine ligand 0.125 mmol, naphthalene after reaction 12% (0.12 mmol), MeOH 5 mL, 1-hexene (approx. 1.8 mmol), reaction time 20 hours, temperature 120° C.

![HMF dehydration - Substrate screening](image)

We finally decided to check whether CO can be formed from methyl levulinate (ML), which is a valuable chemical itself, but it can be also considered as a byproduct in this particular reaction. When methyl levulinate is used as a substrate, alone or along with methyl formate (MF), methyl heptanoate was formed anyway, proving that an equilibrium is existing and ML cannot be considered as a final product (the final percentage was 0%).

The presence of GVL in the final mixture proves that our catalyst is also able to let formic acid, coproduced in equimolar amounts with levulinic acid, undergo transfer hydrogenation. The formed hydrogen is then able to reduce levulinic acid to 4-
hydroxypentanoic acid (4-HPA, 28). This product cannot be isolated in our catalytic environment, since it will spontaneously undergo esterification to give γ-valerolactone, because of the acidity of the system catalyze the cyclization (Fischer esterification).

Subsequently, we investigated the provenience of the hydrogen molecule. The most obvious solution is methyl formate (26). Methyl formate can be dismantled into hydrogen and carbon monoxide and undergo transfer hydrogenation, as previously mentioned. Otherwise, methyl formate can decompose naturally, just by heating it. A reaction carried out without any catalytic complex, leaded to no GVL at all, proving that a metal center is necessary to obtain the hydrogenation of methyl levulinate. Finally, a blank reaction with just methanol and the catalytic complex, in order to state whether hydrogen could come also from the solvent, has been run, but leaded to no results. Thus, we proved that hydrogen, in our reaction conditions, could come only from methyl formate.

3.1.8 Alkene and alcohol screening

As the final part of this work, we decided to carry out a small screening among different alcohols and different alkenes, in order to check the possibility of expanding this catalytic system towards different substrates.

We chose to use ethanol (EtOH) and benzyl alcohol (BnOH), as solvents-reactants, since they are commonly used and are non-expensive alcohols. Plus, the predicted products would have a certain industrial relevance. The use of more nucleophilic alcohols, such as trifluoroethanol (2,2,2-trifluoroethanol, CF₃CH₂OH) would be costly and of no industrial importance, so we decided not to proceed this way. Anyway, there is no reason
to think that a nucleophilic alcohol won’t be able to react to give the alkoxy carbonylated alcohol.

After 20 hours of reaction, we could observe almost 10% of ethyl heptanoate (39) (8.21%) and 65% of GVL, when ethanol is used as a solvent. The low yield of the alkoxy carbonylated product is because ethanol is a less nucleophilic alcohol than methanol. When benzyl alcohol is used, we could see no alkoxy carbonylated (45) products at all. This is because benzyl alcohol is not reactive enough to allow the migratory insertion of the CO molecule into the Pd-OMe bond. The results are shown in Table 8.

Table 8. Alkene and alcohol screening. Reaction conditions: 0.025 mmol Pd(OAc)$_2$, 1 mmol HMF, 1.05 mmol MSA, diphosphine ligand 0.125 mmol, naphthalene after reaction 12% (0.12 mmol), ROH 5 mL, alkene (approx. 1.8 mmol), reaction time 20 hours, temperature 120° C.
The following step has been testing different alkenes. We chose 1-octene, styrene, and acrylic acid, since they all have different chemical characteristics (longer chain alkene, an aromatic moiety, and a coordinated acidic moiety, respectively), they are cheap, industrially produced in bulk (more than 20 million tons per year, each), and could achieve interesting methoxycarbonylated products. These products are shown in Figure 26.

1-octene gave, as expected, lower yields in both the methoxycarbonylated product (methyl nonanoate, 43, 30%) and GVL (40%). Styrene yielded around the 50% of methyl-3-phenyl propanoate (42). The methoxycarbonylation could occur also on the benzylic carbon, to produce the branched product, methyl 2-phenylpropanoate, but no evidence of the presence of this substance was found. Perhaps a rearrangement occurs before insertion of the nucleophile.

Acrylic acid is a cheap chemical, derived from the treatment of biomass waste [156]. Furthermore, the product deriving from the methoxycarbonylation reaction would be dimethylsuccinate (DMS, 44), a bulk chemical used as precursor for polymers, as excipient in the pharmaceutical industry, and as acidity regulator in food beverages [6]. Dimethylsuccinate (DMS) is industrially produced by a double esterification reaction of succinic acid (SA, 46) with methanol, and it usually catalyzed by strong mineral acid, acidic ion exchange resins, but it is also autocatalyzed by succinic acid itself. This reaction creates an equilibrium between the monomethylated acid (MMS, monomethylsuccinate, 47), thanks to the presence of water, as expressed in Scheme 19.
Since a purity of more than 99% is required in industry, costly separation processes have to be used [157].

The reaction worked very well also with this substrate, leading to up to 60% of the desired product, dimethylsuccinate. Since acrylic acid is a Brønsted acid itself, we decided to try a trial reaction with no MSA, but it resulted in no products at all. This is probably because the $pK_a$ of acrylic acid is not sufficiently low, and the acid is not able to protonate the palladium center, during the methoxycarbonylation reaction. Moreover, it is reasonable to postulate that acrylic acid is not able to dehydrogenate HMF, for its weak acidity.
CHAPTER 3. RESULTS AND DISCUSSION

Figure 26. Products resulting from the screening. The alkene is highlighted in blue, while the alcohol in red.

Summary

The GC-FID and GC-MS results corroborated what was previously seen in the literature, namely that the ligand DTBPMB forms an excellent palladium complex for the methoxycarbonylation of alkenes [146], while other phosphinic ligands (TPP, dppp), turned out being inappropriate for this kind of reaction. Moreover, it appeared to be of pivotal importance the presence of palladium (II) in the metal precursor. A protic Brønsted acid
revealed its essential importance for the protonation of the metallic center. Running the reaction into an inert atmosphere, proved to be non-necessary, and might even decrease the product rate.

The novelty of the works lies in the combination of dehydration of carbohydrates (or carbohydrates-derived compounds, such as HMF), with the methoxycarbonylation of alkenes, in a one-pot methodology. An overview of the process is reported in Scheme 20.

It was further seen that the same catalytic palladium complex is able to complete the transfer hydrogenation of levulinic acid to γ-valerolactone (29), at the same reaction conditions. This is the first reported example of transfer hydrogenation with this
metal as catalyst. We highlighted the crucial importance of the temperature, which played a major role in the dehydration of the substrate and in the methoxycarbonylation reaction. While the higher the temperature, the faster dehydration occurs, for methoxycarbonylation the optimum temperature is reached at 120°C, since the catalytic complex undergoes decomposition at a higher degrees of temperature.

It was also shown how a screening of furan-based compounds proved our hypothesized system to be realistic. The catalytic complex is able to decarbonylate both the aldehydic and the hydroxymethylic moiety present on HMF molecule, since methyl heptanoate (27) is produced when both furfural (36) and furfuryl alcohol (24) are used as substrates. Steric hindrance resulted of no considerable importance, as the methylated analogues of the two latter compounds produced MH. The proposed mechanisms are reported in Scheme 21.

Scheme 21. Proposed reaction mechanism. (a) depicts the direct decarbonylation of the carbonylic moiety, while (b) depicts first the dehydrogenation of HMF, followed by the decarbonylation.
To conclude, a small screening of different alkenes and alcohols determined the practicability of our reaction on different substrates, to achieve different interesting products, such as dimethyl succinate (44) and ethyl heptanoate (39).
3.2 From sugars to MH and GVL

Once completed and optimized the dehydration/methoxycarbonylation of HMF to methyl heptanoate, we decided to radically change the substrate, using sugars. The reason why we took this decision is because sugars (in particular hexoses, C6 sugars), is that they are bulk chemicals, they are cheap substrates and they are ready available from a simple treatment of biomass [13, 32].

We focused our efforts on fructose and glucose, since they are the cheapest and the most abundant sugars on the planet. It has been demonstrated that HMF (23) is obtained from the dehydration of fructose (22), and that fructose is coming from the isomerization of glucose (48) [37, 102], as depicted in Scheme 22.
To summarize, the production of methyl heptanoate and GVL needs an isomerization reaction, a dehydration reaction and then a methoxycarbonylation (or a reduction), when the starting material is glucose.

### 3.2.1 Palladium precursor influence

Our investigation on the sugars started studying the influence of the palladium precursor. Taking into account the results obtained when HMF was the substrate, we
decided to limit the experimentation to only Pd(OAc)$_2$ and Pd(acac)$_2$. Fructose gave almost the same results for both MH (33% and 29%) and GVL (12% and 15%).

Surprisingly, for glucose the outcome of this investigation was the opposite of the previous one, with only palladium acetate yielding consistent amount of methyl heptanoate (22%). These results are probably due to the nature of the anion, with the acetate ion that may have a certain capability of helping to catalyze the isomerization of glucose to fructose (Table 9).

Table 9. Reaction conditions: 0.025 mmol Pd, 1 mmol sugar, 1.05 mmol MSA, diphosphine ligand 0.125 mmol, naphthalene after reaction 12% (0.12 mmol), MeOH 5 mL, 1-hexene (approx. 1.8 mmol), reaction time 20 hours, temperature 120° C.
3.2.2 Time study

We effected a time study in order to state the conversion of the hexoses and to better understand the kinetic of the reaction. The results for fructose are summarized in Tables 10 and 11.

![Fructose dehydration - Time study](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Time (h)</th>
<th>Methyl</th>
<th>Methyl</th>
<th>GVL (%)</th>
<th>Conversion (%)</th>
<th>Fructose (%)</th>
<th>HMF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Heptanoate</td>
<td>Levulinate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1)</td>
<td>1</td>
<td>0,92</td>
<td>5,48</td>
<td>-</td>
<td>18,39</td>
<td>81,61</td>
<td>7,86</td>
</tr>
<tr>
<td>(2)</td>
<td>2</td>
<td>3,73</td>
<td>13,21</td>
<td>1,34</td>
<td>54,46</td>
<td>45,54</td>
<td>13,55</td>
</tr>
<tr>
<td>(3)</td>
<td>4</td>
<td>8,58</td>
<td>12,65</td>
<td>3,98</td>
<td>80,94</td>
<td>19,06</td>
<td>24,71</td>
</tr>
</tbody>
</table>
CHAPTER 3. RESULTS AND DISCUSSION

Table 10. Reaction conditions: 0.025 mmol Pd(OAc)$_2$, 1 mmol fructose, 1.05 mmol of MSA, diphosphine ligand 0.125 mmol, naphthalene after reaction 12% (0.12 mmol), MeOH 5 mL, 1-hexene (approx. 1.8 mmol), temperature 120° C.

<p>| | | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
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<th></th>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>(4)</td>
<td>8</td>
<td>16,39</td>
<td>6,34</td>
<td>15,01</td>
<td>91,64</td>
<td>8,36</td>
</tr>
<tr>
<td>(5)</td>
<td>20</td>
<td>36,43</td>
<td>3,15</td>
<td>30,64</td>
<td>100</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 11. Results with the conversion of fructose.

The first graph shows the linearity between the formation of methyl heptanoate and GVL (which reach a maximum of 36% and 31%, respectively), and the inverse proportionality between the formation of the lactone and the amount of methyl levulinate still present in the reaction mixture. As expected, the conversion increases with the time,
reaching 100% after 20 hours (Table 10, entry 5). There is almost no trace of fructose after 8 hours (entry 4), so the substrate is completely consumed in the reaction.

Table 12. Reaction conditions: 0.025 mmol Pd(OAc)$_2$, 1 mmol Glucose, 1.05 mmol of MSA, diphosphine ligand 0.125 mmol, naphthalene after reaction 12% (0.12 mmol), MeOH 5 mL, 1-hexene (approx. 1.8 mmol), temperature 120° C.

The trend observed for fructose is respected when glucose is the substrate (Table 12). The yields are lower, due to the isomerization reaction that slows down the overall process, and the higher solubility of fructose in the reaction media (methanol).
The conversion proceeds slower for glucose because of the additional step of its isomerization into fructose, as it can be seen in Table 13. After 20 hours, the conversion of glucose is completed. However, it is still possible to observe small amounts of fructose, which indicates that the isomerization occurs slower than dehydration and methoxycarbonylation.

### 3.2.3 Sugar screening

The last step of our research has been proceeding with a screening of several sugars, of different natures, in order to prove the viability of our catalytic system with different kind of compounds.
The sugars we chose, represented in Figure 3, are aldoses (glucose, galactose, mannose), ketoses (fructose, sorbose), disaccharides (sucrose, cellobiose, lactose, maltose), pentoses (xylose and ribose), and polysaccharides (inulin and starch).

Figure 7. Carbohydrates used in this study
The sugars present few differences in the structures, which are clearly highlighted in the graph that follows below (Table 14).

The reactivity is similar for all the classes of sugars (aldoses, ketoses, and so on), with only small differences in the final yields, possibly due to the stereochemistry of the substrate, or the nature of the glycosidic bond, that influences the catalytic complex.

Table 14. Reaction conditions: 0.025 mmol Pd(OAc)$_2$, 1 mmol sugar, 1.05 mmol MSA, diphosphine ligand 0.125 mmol, naphthalene after reaction 12% (0.12 mmol), MeOH 5 mL, 1-hexene (approx. 1.8 mmol), reaction time 20 hours, temperature 120° C.

Some interesting remarks can be done analyzing Table 14.
If the trend for monosaccharides was expected (aldoses less reactive then ketoses), appealing consideration are to be done on disaccharides. The highest yields for methyl heptanoate and GVL are present when lactose (57) and sucrose (59), rather than cellobiose (56) and maltose (58), are used as a substrate. This pattern can be explained by staring at the nature of the sugars and at the type of the glycosidic bonds through which they are connected. Thus, lactose and sucrose result in being the most reactive, since a molecule of glucose composes them and they differ from one galactose unit and one fructose unit, respectively. Galactose (51) and fructose (22), as shown in the graph, are the most reactive hexoses of our screening and then they enhance the final amount of products. On the other hand, cellobiose and maltose are two glucose dimers, but bound in a different way: α(1→4) glycosidic bond the maltose and β(1→4) glycosidic bond the cellobiose. It is well assessed that the β(1→4) glycosidic bond is a very stable kind of bond and the breakage of the latter slows down the overall process. Cellobiose, in particular, is a very important product, since it represent the unit for the cellulose biopolymer. Cellulose itself constitutes up to 35% of lignocellulosic biomass and the reactivity of cellobiose, and thus cellulose, would open new interesting perspectives and insights on the valorization of the latter. Solubility problems would arise and might be solved by switching to a different system where cellulose shows being soluble, such as ionic liquids [158, 159], supercritical water [160, 161], or the system DMSO/TBAF (dimethyl sulfoxide and tetrabutylammonium fluoride) [162].

Notably, we proved that also polysaccharides, such as starch and inulin, are reactive in our catalytic system. Obviously, the low yields (~1% for both starch and inulin), constitute a major problem. On the other hand, the complete conversion of these carbohydrates are encouraging results.
Summary

The catalytic complex used for the dehydration-methoxycarbonylation of HMF proved to be active also when fructose or glucose are used as substrates, following the known path: glucose isomerization, fructose dehydration, HMF dehydration, and 1-hexane methoxycarbonylation [37]. While dehydration followed the paths reported in literature, methoxycarbonylation confirmed the results achieved for the methoxycarbonylation of HMF [31, 32]. An optimum reaction temperature of 120°C turned out to be the maximum operational allowed, because of the decomposition of both fructose (22) and glucose (48), which occurs at higher temperatures.

Glucose, in particular, gave considerable high yields of methyl heptanoate and GVL, despite its lower sensibility towards the catalytic complex. Longer reaction times are needed for glucose to obtain notable yields of products, since it has to isomerize first to fructose.

Different carbohydrates (monosaccharides, disaccharides and polysaccharides) have been tested and proved the adaptability of our reaction system to different and diverse substrates.
Chapter 4.

Conclusions

4.1 From HMF to MH and GVL

A brand new, one-pot methodology for the direct conversion of HMF (5-hydroxymethylfurfural) into valuable chemicals, such as methyl heptanoate (MH), methyl levulinate (ML) and γ-valerolactone (GVL), via methoxycarbonylation of 1-hexene has been developed. The use of the catalytic complex Pd plus the ligand 1,2-bis(di-tert-butylphosphinomethane)-benzene (DTBPMB) in the transfer hydrogenation for the production of GVL has been reported successfully for the first time: the involvement of this specific diphosphinic ligand represents a key factor for a positive development of the process. The presence of a protic, homogeneous Brønsted acid has proven to be of a crucial importance for the completion of the reaction. An inverse proportionality between ML and GVL has been discovered and explained in a mutual conversion of ML to GVL, via hydrogenation. Poor TON and TOF have been calculated, and are to be addressed to such a novelty that needs future developments in the future.

A small screening of HMF-related compounds, to understand the mechanistic insight of the reaction has been done. We proved the capability of our catalytic complex to decarbonylate both the aldehydic and the hydroxymethylic moiety present on the HMF molecule, since MH was produced when both furfural and furfuryl alchol has been used as
substrates. Evidence that a small steric hindrance does not affect the reaction pattern come
from the use of the methylated analogous of the latter, as substrate.

A small screening of different cheap alkenes and alcohols has been carried out.
It proved the viability of our reaction on different reagents, to yield different and interesting
products, such as ethyl heptanoate, or dimethylsuccinate.

Perspectives

Switching to a heterogeneous system would be meaningful in order to ensure
a possible evolution into an industrial process. The recyclability of the overall system should
also be taken into account.
4.2 From sugars to MH and GVL

The same methodology used for the dehydration/methoxycarbonylation of HMF has been tested with sugars as substrates. Fructose and glucose proved to be susceptible to the reaction conditions and gave considerably high yields of both MH and GVL. Glucose, in particular, yielded notable amounts of methyl heptanoate, despite its lower reactivity towards our catalytic complex. Time studies highlighted the slower pace that glucose has towards methoxycarbonylation, due to its need to isomerize to fructose, in the first place.

A screening of different carbohydrates of different natures (aldoses, ketoses, pentoses, disaccharides, and polysaccharides) proved out system to be active on all these kind of compounds. The structural differences demonstrated to be crucial for the dissimilarities in the yields of the final products.

Perspectives

Further experiments on polymers should be done, to expand this catalytic system to a broader amount of different compounds: it would turn the overall process in a comprehensive way of using biomass, minimizing the waste. An application of the catalytic system for the decarbonylation-methoxycarbonylation of lignin model compounds should be considered.
Appendix A

Publications

A1. Oral presentation

Catalytic Conversion of Biomass-Derived Carbohydrates into $\gamma$-Valerolactone in Ionic Liquids
D. Paolicchi, A. Riisager
11th European Congress on Catalysis, EUROPCAT XI, Lyon, 1-6 September 2013

A2. Poster presentation

Catalytic Conversion of Biomass-Derived Carbohydrates into $\gamma$-Valerolactone in Ionic Liquids
D. Paolicchi, A. Riisager
5th Congress on Ionic Liquids, COIL V, Algarve, 21-25 April 2013

Catalytic Conversion of Biomass-Derived Carbohydrates into $\gamma$-Valerolactone in Ionic Liquids
D. Paolicchi, A. Riisager
11th European Congress on Catalysis, EUROPCAT XI, Lyon, 1-6 September 2013
Methoxycarbonylation of alkenes with biomass-derived CO

D. Paolicchi, S. Saravanamurugan, E. J. García-Suárez, A. Riisager

16th Nordic Symposium on Catalysis, Oslo, 15-17 June 2014
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