Università
Ca'Foscari
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Master's Degree

In Sustainable Chemistry and Technologies

Final Thesis

Hydrogenation/hydrogenolysis of 5-(hydroxymethyl)furfural (HMF) catalyzed by Ru/C under multiphase and continuous flow conditions

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1. INTRODUCTION

1.1 Biomass

In the past two decades, the use of biomass has become increasingly popular for the sustainable production of fuels, energy and chemicals, as an alternative to conventional derivatives of fossil origin. Among renewable resources including hydroelectric, solar, geothermal and wind, biomass, especially that from the vegetable kingdom, is not only the most abundant one, but it is able to provide both energy and molecules as building blocks for a variety of applications such as plastics, fibres, solvents, fine chemicals, pharmaceuticals, etc.

This potential, however, is still highly underutilised if one considers that natural photosynthesis allows the growth of 170 billion metric tons/year of biomass, mostly comprised of carbohydrates (75%), of which only 3-4% is used by humans.[1,2]

One the most striking differences between renewable and not-renewable sources is related to the carbon management in terms of production of CO_2.[3] Figure 1 shows the carbon life cycle of chemical industry which is estimated at 10^6 years, meaning that all the CO_2 produced in the last 250 years since the industrial revolution, will take millions of years to be transformed in fossil sources and, at the same time, it will continue to accumulate in the atmosphere and in the environment. By contrast, if biomass is used as an energy source, emissions of CO_2 are absorbed by the vegetables during their growing process with a carbon lifecycle of only 1-10 years long.

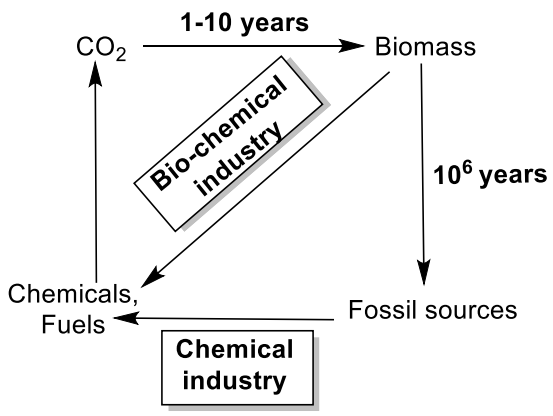


Figure 1. Global carbon cycling

Vegetable-derived biomass is often referred to as lignocellulosic biomass. Chemically speaking, it is comprised of:

- 40-50% cellulose and starch where glucose units are connected by 1,4-β-glycoside bonds and 1,4-α-glycoside bonds, respectively (Figure 2a). This structure is held together by strong hydrogen bonds and is therefore crystalline.
- 15-30% hemicellulose in which polysaccharides made of pentoses (xylose and arabinose), hexoses (glucose, mannose, galactose) and sugar acids form non-crystalline structures[4] (Figure 2b).
- 15-30% lignin, principally made of aromatics, conferring rigidity to plants (Figure 2c).

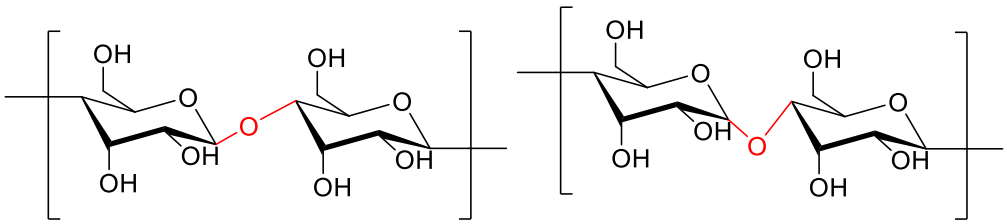


Figure 2a. Cellulose with 1,4-β-glycoside bonds and Starch with 1,4-α-glycoside bonds.

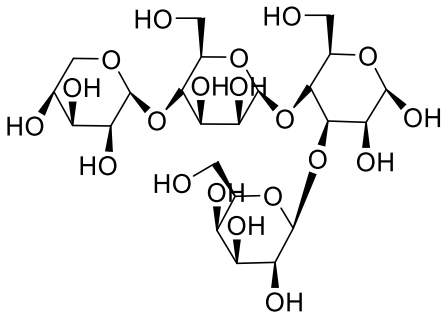


Figure 2b. Example of hemicellulose composed by xylose-β(1,4)-mannose-β(1,4)glucose-α(1,3)-galactose.

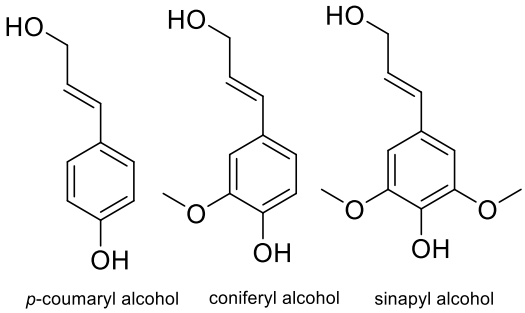


Figure 2c. Building blocks of lignin.

Moreover, other parts of plants such as seeds, fruits, leaves and trunks allow to extract natural oils (lipids) and bio-hydrocarbons.[5,6]

The interest in biomass has been originally driven by the synthesis of "first generation" biofuels which were obtained from agricultural resources, typically corn for bioethanol and oily seeds for biodiesel. Although these were efficient productive chains, over the years, ethics tended to prevail on economic reasons, since the depletion of feedstocks for food in favour of energy appeared unsustainable not only in term of the required (large) land usage, but mostly for its implications and incompatibility with the huge issue of the world hunger. Biorefinery plants have then been progressively upgraded towards the manufacture of "second generation" biofuels obtained from non-food biomass either lignocellulose as such or waste of processing of agricultural and forest feedstocks. In a further evolution of this concept, "third generation" biorefineries have been conceived – though not fully implemented yet – for the use of multiple inputs particularly based on microalgae as raw materials, that offer the advantage of being entirely renewable and cultured in the sea at low-cost compared to the energy required for their growth.[7]

Whatever the feedstocks and the processing method, biofuels come out as "low-value high-volume" products which in themselves do not guarantee competitiveness to biorefineries with respect to petro-refineries. Any techno-economic analysis has demonstrated that biomass can be conveniently exploited only if the biofuel production is integrated with the synthesis of "high-value low-volume" products, which in general terms implies the conversion of biomass into a range of derivatives , from bulk compounds (e.g., bioenergy) up to specialty chemicals. This scenario substantially follows that of a modern petroleum refinery where multiple fuels and chemicals are processed from oil, though the complexity of molecules that can be achieved from biomass makes rather challenging the technological progress of a biorefinery.

1.2 Top ten building blocks from biomass

Previous considerations highlight that when dealing with biomass, a not trivial issue is the identification of the most promising bio-based products or families of such compounds towards which research and investments should be addressed. In the past fifteen years or so, of the many analyses performed to sort out this complexity, the extensive work commissioned

by the US Department of Energy (DOE) in 2004 to the National Renewable Energy Laboratory (NREL) and the Pacific Northwest National Laboratory (PNNL) and its revision in 2010 continue to represent the best guidelines in this field.[8,9]

Starting from an initial inventory of over 300 candidates among bio-based molecules, US-DOE proposed a restricted list of compounds or building blocks, the so-called top platform chemicals (Figure 3), which were identified through several selection criteria including:

- Type of raw materials and their strategic fit into biorefinery
- Value of the building blocks and its derivatives for potential use and development in the market.
- Technical complexity of transformation and estimated processing costs and selling price of products (for example, sugars to building blocks and building blocks to derivatives)
- Potential to produce families or groups of similar derivatives.

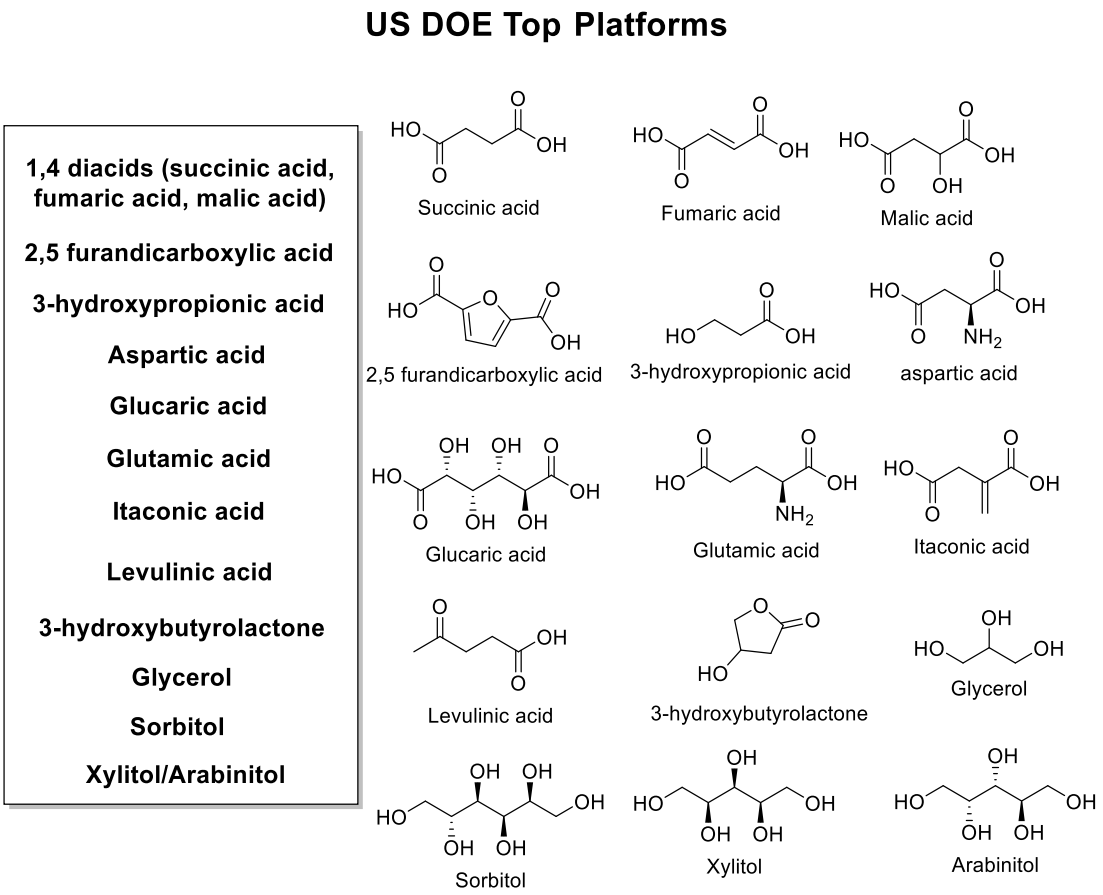


Figure 3. Top platform chemicals from US-DOE analysis.

In 2010, the above-quoted revision of the subject included further conditions, among which:

- The attention received to a compound in the literature
- The possibility to implement a technology to the synthesis multiple bio-based products on a high-volume scale, to enable direct substitution for existing petrochemicals.
- The potential of a platform compound to serve as a primary building block for biorefinery
- The availability of a compound as an (already existing) commercial product prepared at intermediate or commodity levels.

After these amendments, the list top-10 bio-based platform chemicals appeared as in Table 1.

Table 1. Top 10 renewable building blocks from the Bozell-Petersen analysis.

Entry	Name	Entry	Name
1	Ethanol	6	Succinic acid
2	Furans (Furfural, 5-Hydroxymethylfurfural, Furandicarboxylic acid)	7	Hydroxypropionic acid/ aldehyde
3	Glycerol derivatives	8	Levulinic acid
4	Bio-hydrocarbons (isoprene)	9	Sorbitol
5	Lactic acid	10	Xylitol

Authors clearly stated that such an analysis involved a degree of subjectivity due to the rapid change and expansion of the biorefining industry, but a peculiarity of the "revisited Top 10" with respect to the previous DOE report, was the enlargement of the family of furans which included furfural and 5-hydroxymethyl furfural (**HMF**) beyond 2,5-furandicarboxylic acid.

Although this approach was further refined over the years,[10] the furans trend was consolidated, particularly with HMF that emerged for its synthetic and market potential in the field of biofuels, fuel additives, pharmaceuticals, polymers, resins and solvents. [11,12]

Such an interest was confirmed by more than 10000 scientific articles and patents on HMF with approximately 1000 papers published annually in the past decade.[13] Notably, the molecule was named as "the sleeping giant" of sustainable chemistry.

For the specific interest of this Thesis work, the next paragraphs will briefly detail the synthesis and reactivity of HMF.

1.3 Synthesis of 5-hydroxymethylfurfural (HMF) from biomass

The majority of HMF is currently produced from cellulose and starch obtained by energy crops, *i.e.* cultivations destined to obtain biomass for energy purposes.[14] This strategy is showing an increasing interest also thanks to economic and environmental incentives.[15]

Technically speaking, the overall process is divided into four main steps (Figure 4 a,b,c,d):

1) Pre-treatment of biomass into cellulosic components.[16]

2) Hydrolysis of the glucan polymers to form monomers of glucose.

3) Isomerization of glucose into fructose by keto-enol tautomerism.[17]

4) Dehydration of fructose to HMF.[18]

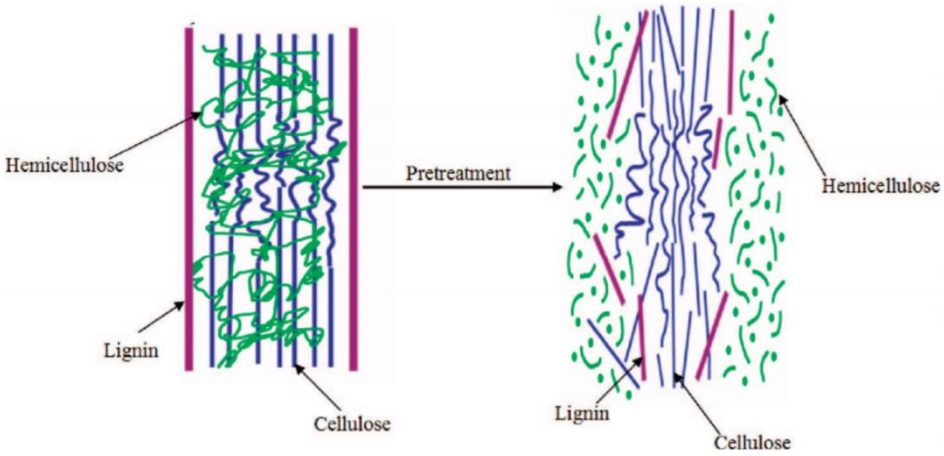


Figure 4a. Pretreatment of biomass

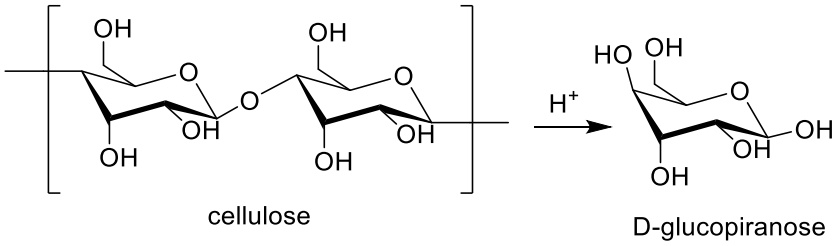


Figure 4b. Hydrolysis of cellulose to glucose

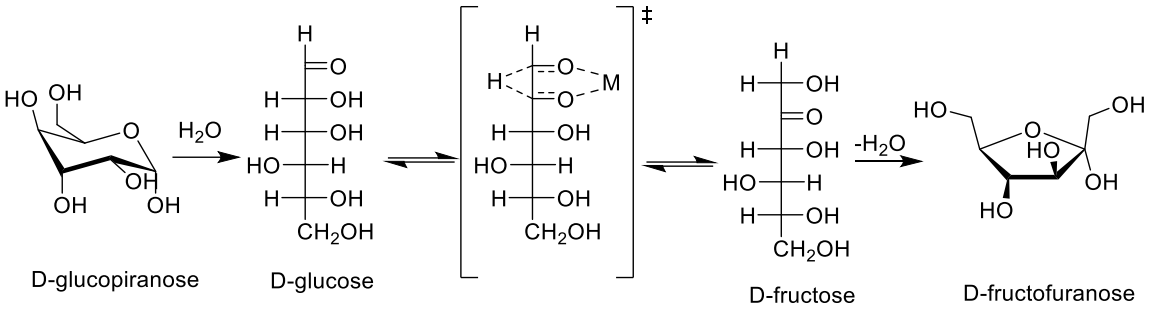


Figure 4c. Isomerization of glucose to fructose (acyclic route)

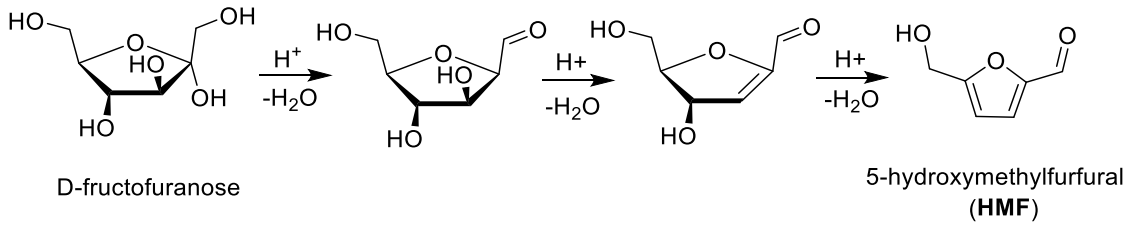


Figure 4d. Dehydration of fructose to HMF

The pre-treatment of biomass is aimed to destructurize the initial solid by partly removing its lignin content and disrupting the crystalline structure of cellulose. This step is more often divided into a physical or physicochemical pre-treatment such as chipping, grinding or milling and steam explosion respectively, and chemical pre-treatments.

Among chemical treatments it is worth mentioning: ozonolysis, that is able to degrade lignin reducing its content in the lignocellulosic wastes; acid hydrolysis, carried out mainly by H_2SO_4 (typically 4%), that is able to hydrolyse hemicellulose to xylose and other sugars, increasing the recovery of cellulose by hemicellulose removal. Typical acid pre-treatments are carried out at two different conditions: at temperature > 160°C in continuous-flow for low solids loadings (5-10% w/w substrate/solution) and at temperature < 160°C for high solids loadings (10-40% w/w).

Alkaline hydrolysis is also a valid pre-treatment for lignocellulosic materials, which can be carried out at ambient temperature and pressure although the times are longer than in other technologies (days instead of minutes). The most valid alkaline pre-treatment agent is $Ca(OH)_2$ (0,5% wt. in air or N_2 atmosphere at 25- 55°C).

Enzymatic oxidation with peroxidase in presence of H_2O_2 (2%, 30°C for 8h) is able to solubilize 50% of lignin and most of hemicellulose, achieving a 95% production of glucose from cellulose.[19]

Thereafter, hydrolysis of cellulose and dehydration of fructose reactions are mostly performed using either mineral or organic Brønsted acids as HCl, H_2SO_4 and HNO_3 or lactic acid and acetic acid, while the glucose-fructose isomerisation is promoted by Lewis acids based on metal salts.[20]

The latter process takes place through a ring opening reaction which requires the formation of complex between the catalytic metal and carbonyl/hydroxyl groups on C1 and C2, respectively, of glucose molecule. To this purpose, $AlCl_3$[21], $CrCl_3$,[22] $GaCl_3$, and $InCl_3$[23] have proven as the most active compounds, with yields of fructose (from glucose) in the range of 52-54%. The metal toxicity and the non-recyclability of salts and their hydroxide by-products pose however, significant issues. Safer alternatives have been proposed using solids acids as Sn-Beta zeolites (Figure 5), by which isomerization yields up to 34% have been achieved.[24, 25, 26]

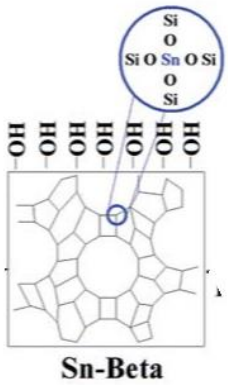


Figure 5. Example of Sn-Beta zeolite

It should be noted that the stable pyranose structure of glucose makes it comparatively less reactive than fructose: the reported activation energies for the dehydration glucose and fructose to HMF are 36.4 and 29.4 kcal mol^{-1}, respectively.[27] The efficiency of these reactions (both hydrolysis and dehydration) is also affected by the solvent that, due to the highly hydrophilic nature of carbohydrates obtained as products, is usually chosen among polar compounds as for example, water, alcohols, dipolar aprotic solvents, ionic liquids and water-organic biphasic systems.

Alternative syntheses of HMF have been conceived starting from fructose rather than lignocellulosic biomass. However, the most used/effective protocol to produce fructose is the enzymatic isomerisation of glucose which still suffers from several drawbacks such as the need of buffering solutions to control pH, a narrow range of operating temperature and the periodic

enzyme (xylose isomerase) deactivation.[1] This is why some analyses indicate that the resulting process and the cost of the final product are less convenient than the straightforward transformation of cellulose into HMF, shown in Figure 4. Whichever the case, examples discussed here will consider either cellulose or fructose as starting materials.

Both these substrates have been compared in a recent study demonstrating that in the presence of [BMIM][Cl] as an ionic liquid solvent: i) the reaction of fructose proceeded at 60 °C with H_2SO_4 as a catalyst, yielding high conversion (90–99%) and yield of HMF up to 80–90%; ii) the reaction of cellulose proceeded at 130 °C with $CrCl_3 \cdot 6H_2O$ as a catalyst, affording HMF in 43 % and >99.9 % yield and purity, respectively.[28]

Another investigation explored the activity of most common mineral acids as catalysts using a water-organic biphasic system (acetonitrile or γ-valerolactone) as the reaction medium.[29] Typical yields of HMF were 85-91% from fructose, and around 21% from cellulose.

Carbon-based solid acid catalysts containing $–SO_3H$, –COOH and phenolic –OH groups have also proven effective for the reaction. Catalysts (CCC) were prepared by thermal treatment (100 °C for 24 h and 400 °C for 1 h) of cellulose, glucose or starch followed by impregnation of carbonized solids with concentrated sulfuric acid (180 °C, 5 h). At 140 °C, in the presence of CCC and [BMIM]Cl as a solvent, the reaction of fructose, starch and cellulose produced HMF in 81, 46, and 45% yields, respectively.[30]

With the aim of performing a one-pot conversion of cellulose, starch, or even glucose to HMF, a different approach has been conceived using bifunctional catalysts bearing both Brønsted and Lewis acid sites active simultaneously for hydrolysis/dehydration and isomerization reactions. Two such cases have been described with $SnCl_4$ and H-ZSM-5 catalysts by which HMF was isolated in 21% and 42% yield starting from bread waste (one the most abundant household food waste) and glucose, respectively.[31, 32] In analogy to these studies, recent works have contemplated mechanical combinations of Brønsted and Lewis acids: from cellulose, a 40% yield of HMF was obtained using a mixture of Amberlyst 15 and $CrCl_3$ in ionic liquid [BMIM][Cl] as the solvent (110°C for 4 hours, 50 mg of cellulose, 0.1 equivalents $CrCl_3$, 0.5 equivalents Amberlyst in 0,5 g [BMIM][Cl]).[33]

The dehydration of fructose has been investigated also using non-toxic and renewable organic acids, as for example, lactic acid, formic acid and acetic acid. By these systems, the HMF yield was reported in the range of 48-61%.[34] Levulinic acid (LA) – a derivative of HMF - has been

considered as another potential catalyst: LA however, was effective only at very high temperatures (>180°C). [35]

Interestingly, a screening study on the activity of several Lewis acids proved that $SnCl_4$ was one of the best performing catalysts for the conversion of glucose to HMF. In a biphasic system comprised of a 1:1 mixture of water and *n*-butanol, conversion and HMF selectivity were 75 and 69%, respectively, after 5 h at 140 °C. [36] A close inspection of the products distribution indicated that no fructose was formed, *i.e.* no glucose isomerization took place under the investigated conditions. This unusual behaviour was explained considering that the hydrolysis of $SnCl_4$ generated both aquachlorotin(IV) $[SnCl_x(H_2O)_{6-x}]^{(4-x)+}$and hexaaquatin(IV) $[Sn(OH)_y(H_2O)_{6-y}]^{(4-y)+}$complexes. Moreover, the latter compounds undergo further hydrolysis, releasing a proton for each reaction stage (Scheme 1).

$$[Sn(H_2O)_6]^{4+} + H_2O \rightleftharpoons [Sn(OH)(H_2O)_5]^{3+} + H_3O^+$$

Scheme 1. Hydrolysis of hexaaquatin (IV) complexes.

Accordingly, the increased Brønsted acidity of the aqueous reaction environment made the ketose dehydration competitive with the isomerization of glucose.

As mentioned above, also the choice of solvents plays a critical role in the synthesis of HMF.[37] Water has been among the first solvents used: in the subcritical state (100 bar and 374 °C), it was demonstrated that both fructose and glucose were converted into HMF with 46% and 30% yields, respectively, without the need of any catalyst.[38]

These conditions, however, were much less effective when cellulose was used. Not only the yield was limited (4-12%), but the HMF product underwent a partial rehydration which generated other derivatives as levulinic acid, and reduced selectivity.[36,39] The combined use of water and water-miscible organic solvents as for example, tetrahydrofuran (THF), methyl tetrahydrofuran (MTHF), γ-valerolactone (GVL) and methyl isobutyl ketone (MIBK), has also proved advantageous.[26,40]

THF was able to increase the capability of hydrolysing cellulose and if a salt was added (NaCl),[41] the formation of two phases was noticed. HMF was produced in the water solution, and thereafter extracted in the organic solvent.[42] A drawback/limitation, however, was the degradation of THF at temperatures higher than 180 °C.

In the presence of dilute acid (0,05 wt % of H_2SO_4), a two-steps protocol using a mixture of water/GVL allowed to isolate HMF in 60% yield from corncob.[43] Glucan polymers were hydrolysed into C_6 sugars in the first step, then a salt, (NaCl) or liquid CO_2, were added to separate the aqueous from the organic phase, and the carbohydrates could be recovered in the aqueous phase where they could be upgraded to HMF with $AlCl_3$ as a catalyst for the isomerization. The reaction system is illustrated in Figure 6.

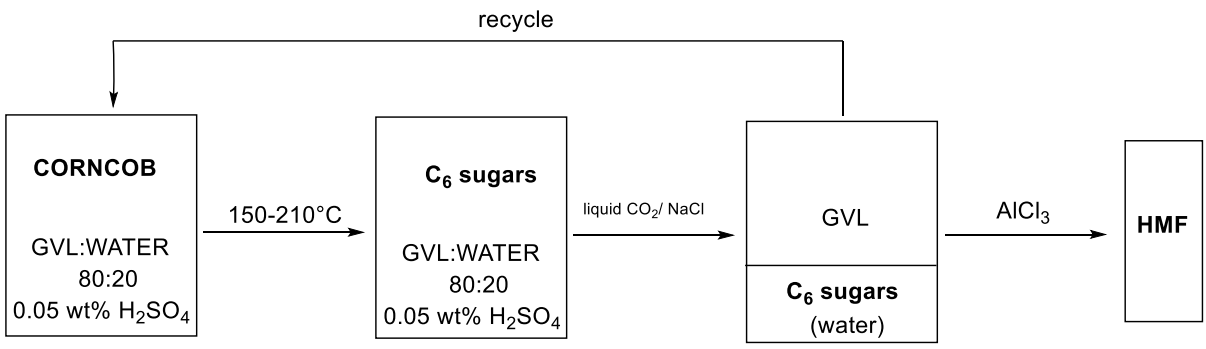


Figure 6. The synthesis of HMF from corncob in a water/GVL mixture

Dimethyl sulfoxide (DMSO) and water was also a good binary mixture for the conversion of glucose to HMF. Yields up to 90% were achieved in the reaction catalysed by $CrCl_3$.[44]

Ionic liquids have been also reported as excellent solvents for both cellulose and carbohydrates due to the strong hydrogen bonding ability with hydroxyl groups. Besides the above described examples, in the presence of $CrCl_2$ as a catalyst, several other mixtures of ionic liquids including imidazolium based like the ones shown in Figure 7, were successfully used as solvents, to reach HMF yields up to 90% and 32% starting from glucose and cellulose, respectively.[45]

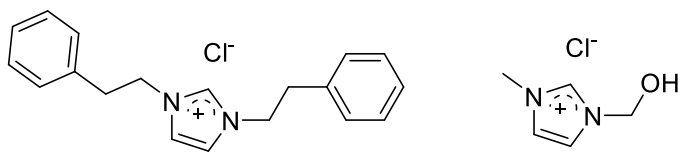


Figure 7. Imidazolium based ionic liquids used as solvents for HMF production from glucose and cellulose.

On a concluding note in this paragraph, some recent studies have confirmed that the degree of purity of HMF is critical for the preservation of its structure. Most of the times the product is obtained as an oily compound with 97–99% purity which should be considered high enough

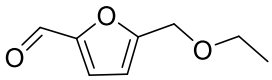
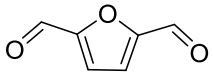
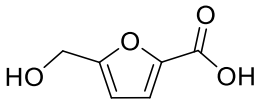
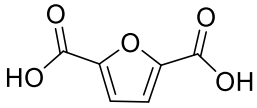
for further applications. Indeed, it has been demonstrated that traces of acidic impurities coming from the catalytic transformations used in the synthesis of HMF, may be responsible for a rapid aging of the product through oligomerization processes.[46] Apparently, the only way to prevent these degradation side-reactions is to obtain HMF in a crystalline form with purity >99.9%, in which molecules are involved in an extended intermolecular hydrogen bonding network, where a restricted mobility improves stability.[47]

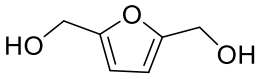
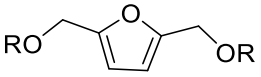
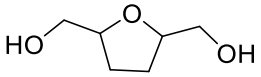
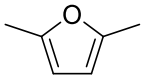
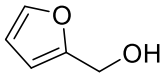
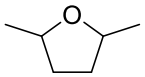
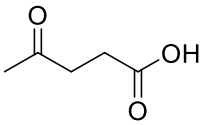
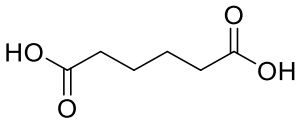
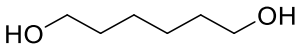
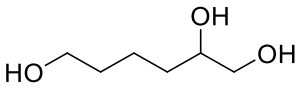
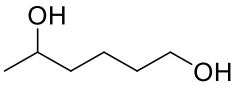
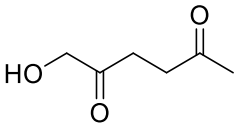
1.4 Major derivatives of HMF

HMF exhibits a flexible reactivity due to the simultaneous presence of multiple sites/functionalities such as the hydroxyl group, the aldehyde group, and the aromatic furan ring. Table 2 summarizes some of the most important derivatives of HMF along with their major applications.[12]

These compounds are obtained through a variety of transformations, the most common of which include oxidation and hydrogenation/hydrogenolysis processes commented below.

Table 2. Principal products from HMF

Name	Abbreviation	Applications
 Formic acid	FA	Commodity, chemical, textile, catalyst, solvent, fuel cells.
 5-ethoxymethyl furfural	EMF	Biofuels
 2,5-diformylfuran	DFF	Pharmaceuticals, polymers, fungicides, resins
 5-hydroxymethyl furoic acid	HFC	Polymers
 2,5-furandicarboxylic acid	FDCA	Polymers (polyethylene furanoate)

 2,5-bis(hydroxymethyl)furan	BHMF	Solvents, polymers
 ethers of BHMF	/	Fuel additives
 2,5-bis(hydroxymethyl)tetrahydrofuran	BHMTHF	Solvent, monomer
 2,5-dimethylfuran	DMF	Biofuel
 furfuryl alcohol	FA	Resins, solvents
 2,5(dimethyl)tetrahydrofuran	DMTHF	Solvent
 levulinic acid	LA	Platform chemical
 adipic acid	AA	Polymers (Nylon 6,6)
 1,6-hexanediol	1,6HD	Polymers (polyesters, polyurethanes)
 1,2,6-hexanetriol	1,2,6HT	Polymers
 1,5-hexanediol	1,5HD	Polymers
 1-hydroxyhexane-2,5-dione	HHD	New platform molecule

1.5 HMF oxidation

HMF can be oxidized to DFF, FFCA and FDCA, that have importance as building blocks for polymers, resins, foams, sealants, pharmaceuticals and solvents.[48]

FDCA is attracting an increasing interest due its similarities to (fossil-derived) terephthalic acid (TA), which is a key intermediate for the polymer industry, particularly for the production of the well-known polyethylene terephthalate (PET), the raw material for plastic soda bottles.[49] Indeed, the reaction of FDCA and ethylene glycol produces polyethylene furanoate (PEF) which shows similar, if not better, properties than PET in terms of gas barrier for oxygen, carbon dioxide and water vapor, and it can be used as 100% renewable packaging for alcoholic beverages, juices, soft drinks and water.

BASF and Avantium are designing the first large scale-plant for the production of FDCA via the reactions shown in Figure 8.

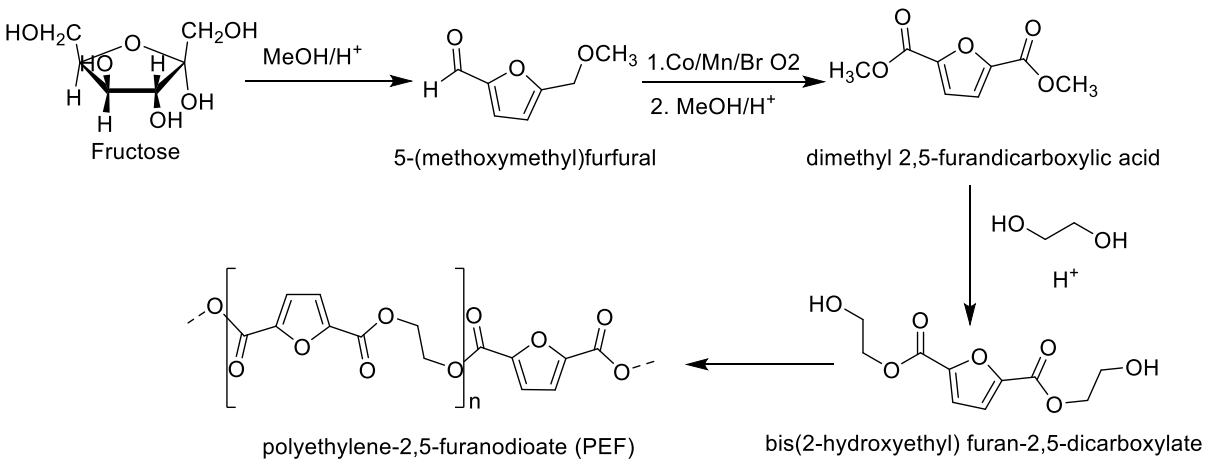


Figure 8. Avantium's Process to polyethylene furandioate via 5-methoxymethylfurfural.

Many other protocols have been described for the catalytic oxidation of HMF to FDCA with very high yields (>99%). The reaction usually takes place with O_2 (1-3 bar) or air (40 bar) in a range of temperature and time from 60 to 140°C and from 2 to 12 hours respectively and in the presence of a stoichiometric base. Most used catalysts are based on Pt, Pd and Au promoted by Bi to prevent the poisoning of the active surface by oxygen.[1] Different typologies of catalytic supports including carbon, Al_2O_3 and ZrO_2, and bases such as NaOH, $NaHCO_3$, Na_2CO_3, KOH, $KHCO_3$, and K_2CO_3, have been reported.

Among other catalysts, also Ru on activated carbon has been described, by which a quantitative transformation is observed with an excellent selectivity (93%), at 40 bar O_2, 100 °C, and using 4 molar equivs. of $NaHCO_3$ (with respect to HMF). An inconvenient however, is the long reaction time required, up to 48 h.[50] A recent improvement of the reaction catalysed by Ru/C has been achieved under base-free conditions: at 20 bar (O_2) and 120 °C, FDCA has been isolated in a 88% yield after 10 h.[51]

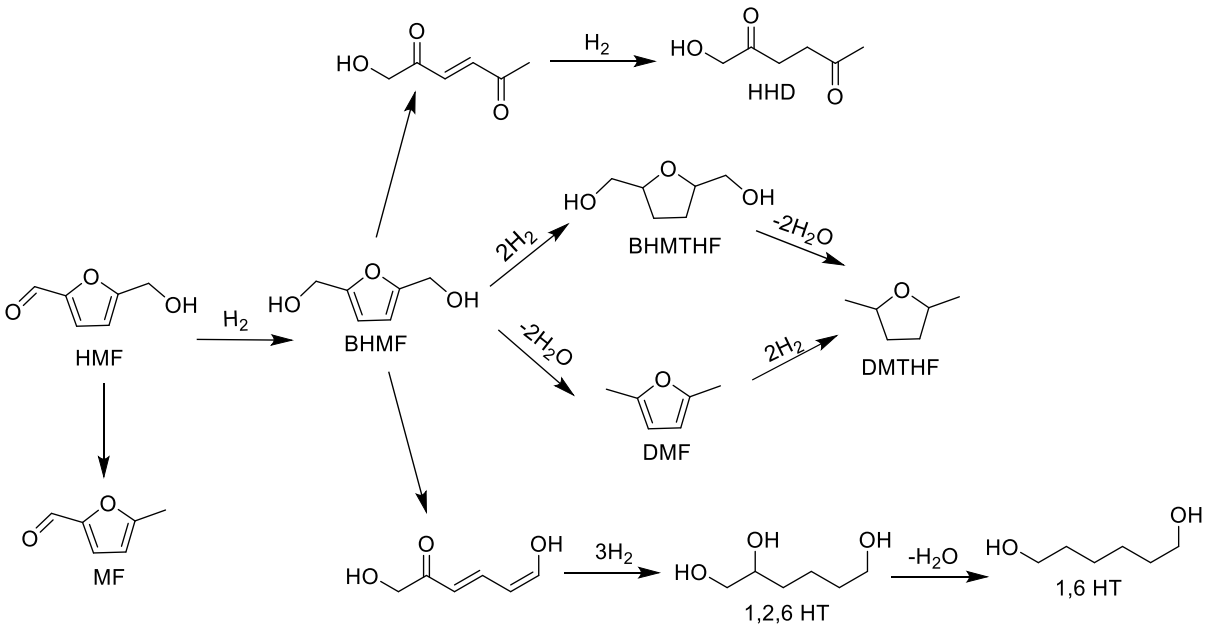
Other base-free processes have also been reported as for example, the base-free oxidative esterification of HMF carried out in methanol in the presence of Au supported on sulphated zirconia as a catalyst.[52] Although this is a potentially valuable approach, the reaction is not yet optimised and yields of FDCA are still relatively low (19-32 % yield).
Finally, the oxidation HMF has been accomplished using enzymes.[53] This strategy, however, is currently not competitive to chemical protocols, mostly due to the need of rigorous control of pH and a very long reaction time.

1.6 HMF hydrogenation/hydrogenolysis

The catalytic hydrogenation of HMF is one of the most studied reactions for the transformation of bio-based platform chemicals. The process may lead to several different products whose distribution is primarily steered by the nature of catalysts, the temperature and the pressure (Scheme 2). In the presence of several conventional catalysts including both homogeneous and heterogeneous systems as Ru, Ir or Rh complexes with bidentate N-heterocyclic carbenes (NHCs) and primary amine moieties, gold sub-nanoclusters, copper doped with Ru metal oxide (MgAl types), Pd, Pt Ru, Ni on C, Pd on SiO_2, Al_2O_3, TiO_2, the reaction easily affords 2,5-bis(hydroxymethyl)furan (BHMF) with high selectivity. [54,55,56,57,58]

Typical operating T and p are in the range of 50 - 80 °C and 10 – 50 bar. The ring hydrogenation of BHMF to obtain 2,5-bis(hydroxymethyl)tetrahydrofuran (BHMTHF) requires to force the experimental conditions by increasing either T and p up 100°C and 80 bar [59,60] while further catalyst optimization is necessary to obtain linear diols and triols. For example, the conversion of HMF to 1,2,6-HT (hexanetriol) has been reported to proceed with a 64.5% yield over a Ni-Co-Al mixed oxide catalyst (120 °C, 40 bar H_2), [61] whereas 1,6-HD (hexanediol) was prepared with 73% selectivity by the direct hydrodeoxygenation of 1,2,6-HT in water, using a Rh–ReO_x/SiO_2 catalyst (180 °C, 80 bar H_2, 20 h). [62] Notably, 1,6-HD (43% yield) was obtained also

from the hydrogenolytic ring opening of HMF: in this case however, the reaction was carried out with formic acid as a hydrogen source and Pd/zirconium phosphate (ZrP) as a catalyst (140 °C, 1 atm).[63,]



Scheme 2. Different pathways for HMF hydrogenation/hydrogenolysis

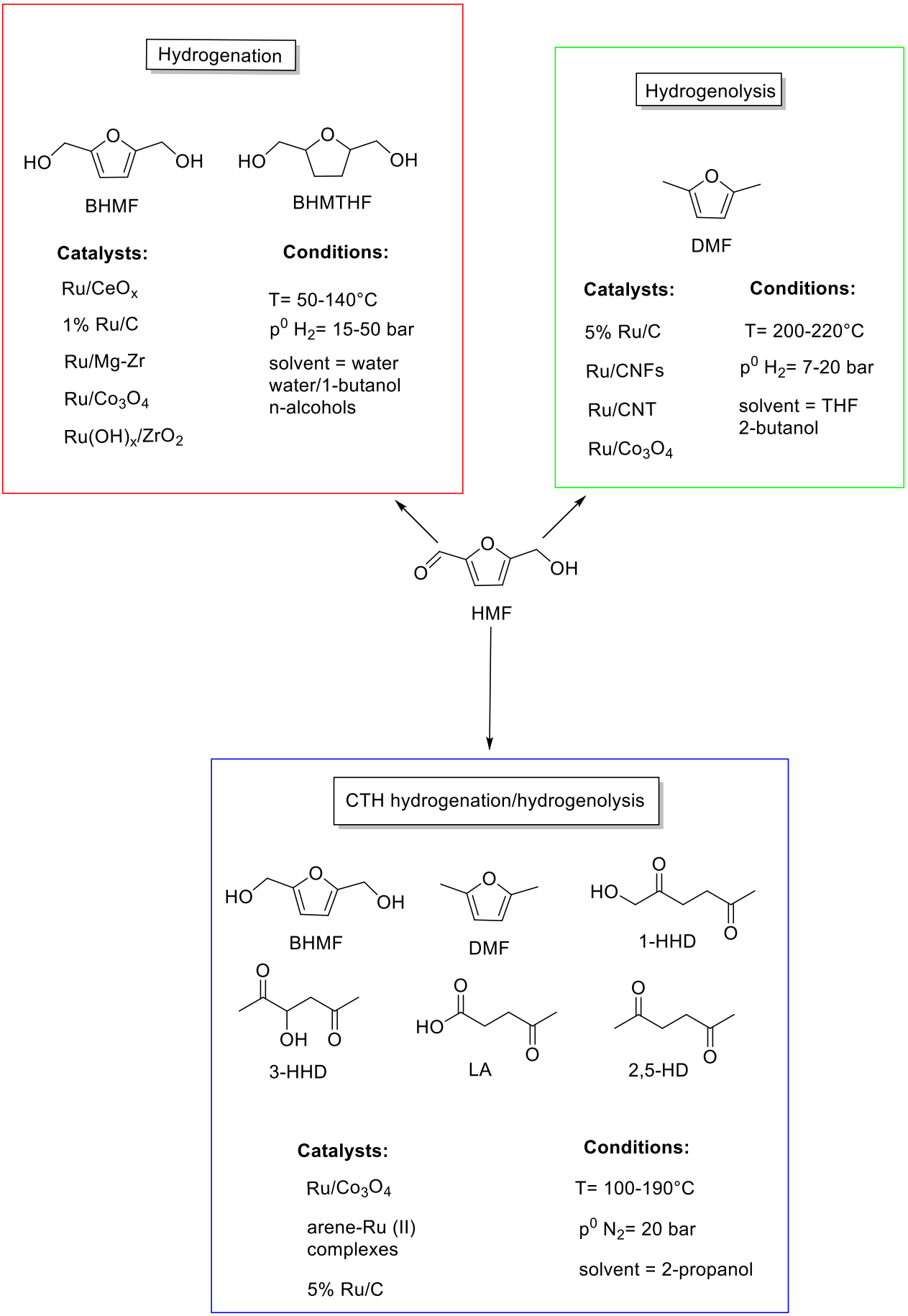
Multiple hydrogenolysis processes may take place competitively to hydrogenation reactions of HMF. Three major products as 2,5-dimethylfuran (DMF), 5-methylfurfural (MF), and 2,5-dimethyltetrahydrofuran (DMTHF), have been described. For example, DMF was obtained directly from HMF in 85-100% yields using either 5 wt% Pd/C under a combined atmosphere of CO_2 (100 bar) and H_2 (10 bar) at 80 °C,[64] or a bimetallic catalyst comprised of a Lewis-acidic Zn(II) and Pd/C at 150 °C and 22 bar of H_2;[65] while, a 97% yield of DMTHF was achieved by the hydrogenolysis of HMF carried out at 180 °C and 12 bar of H_2 in the presence of a Ni-Al_2O_3 catalyst derived from a hydrotalcite-like precursor.[60] MF was recently obtained with 80% yield using a Pd nanoparticles catalyst supported on carbon at 200°C and 5 bar of N_2 using formic acid as hydrogen donor, in THF. Authors compared this results with the use of commercial Pd/C, with which the yield was zero, emphasizing the importance of nanoparticle structure.[66] Additionally, an emerging product from the arena of the hydrogenolysis pathways of HMF is 1-hydroxyhexane-2,5-dione (HHD). Representative protocols for the HMF → HHD transformation have reported the following conditions/results: i) a 90% selectivity using Pd

supported on acidic Nb_2O_5 at 140 °C and 40 bar H_2;[67] ii) a 84% yield using a bipyridine coordinated Cp-Iridium(III) half-sandwich complex (Cp=1,2,3,4,5-pentamethylcyclopenta-1,3-diene (120 °C; 5 bar H_2);[68] iii) a 77% yield using a 7.5 wt % Pd/C at 120 °C, under a pressure of H_2 and CO_2 of 10 bar and 30 bar, respectively.[69] However, the first isolation procedure for HHD has been described only very recently by de Vries et al. who achieved 1-hydroxyhexane-2,5-dione in a 69% (isolated) yield after the reaction of aq. HMF carried out with the half-sandwich [Cp*Ir(dpa)Cl]Cl (dpa = dipyridylamine) catalyst at 120 °C and 10 bar H_2.[70] Results lead to conclude that the conversion of HMF from HHD still represents a largely unexplored area and effective synthetic methods remain a major challenge.

1.7 Heterogeneous Ru-based catalysts for HMF hydrogenation/ hydrogenolysis reactions.

Of the catalytic metals used for the hydrogenation/hydrogenolysis of HMF, ruthenium-based systems, more often heterogenous ones, have received a special attention both for their activity and their capability to tune the products distribution.

Scheme 3 summarizes the use of Ru-based catalysts for the hydrogenation/hydrogenolysis of HMF.



Scheme 3. Hydrogenation/hydrogenolysis of HMF catalyzed by Ru-systems

One of the first seminal works comparing the performance of Ru, Pd, and Pt catalysts supported on a variety of materials such as ceria, magnesia–zirconia, γ-alumina, carbon, and silica, demonstrated that Ru/CeO_x and Ru/Mg-Zr were the best systems: at 130 °C and 30 bar of H_2, in a 2:1 bi-phase 1-butanol/water batch reactor, HMF was quantitatively converted yielding either its partially hydrogenated derivative (BHMF) or its fully hydrogenated derivative (BHMTHF) with 94% and 91% selectivity, respectively.[71] Authors explained the role/benefits of oxide based supports with high isoelectric points and of the biphasic reaction medium (with respect to water alone) in the prevention of acid-catalyzed degradation reactions of HMF, particularly those forming linear hexane-polyols (1,2,5-HT, 1,2,5,6-HT, and 1,2,6-HT) from BHMF. A 99%-yield synthesis of BHMF was also described through the hydrogenation of HMF catalyzed by a heterogeneous zirconia-supported ruthenium ($Ru(OH)_x/ZrO_2$). [72] The reaction was carried out at 120 °C and H_2 15 bar, in the presence of different *n*-alcohol as solvents (ROH: R=Me, Et, Pr, and Bu). It was concluded that the strong (H-bonding) interactions between carbonyl functions of HMF and the solvent, and the simultaneous occurrence of –OH groups and coordinative unsaturated acidic–basic Zr^{4+}–O^{2-} pairs on the catalyst surface were critical to induce the selective formation of BHMF.

In another approach, a screening investigation of a series of commercial C-supported metals (5 wt%) including Pd/C, Pt/C, Rh/C, and Ru/C, and Raney-Ni proved that a complete HMF conversion and a 95% selectivity towards the hydrogenolysis product DMF were obtained at 200 °C and 20 bar H_2, in THF solution, using the Ru-based catalyst. [73]

By contrast, the amount of DMF ranged from 9 to 16% using other metals. The same hydrogenolysis process was also achieved by drastically reducing the Ru loading to 0.56 wt% on condition that a mixed Mg/Al (3:1 mol/mol) oxide was used as a support: at 220 °C and 10 bar H_2, the reaction of a 2-propanol solution of HMF afforded DMF in a 58% yield. [74] The mechanistic investigation indicated that the reaction initially formed 5-methylfurfural. This was as a quite reactive intermediate from which two consecutive transformations, *i.e.* the hydrogenation to 5-methylfurfuryl alcohol and the hydrogenolysis of MFA to DMF, took place in a rapid sequence.

Other active Ru-catalysts for the production of DMF were obtained using either activated carbon (AC) and carbon nanofibers (CNFs) as supports: [75] at 150 °C and 20 bar of H_2, the hydrogenolysis selectivity was 77% in the presence of 2-butanol as a solvent. It was confirmed that the reaction medium (BuOH) assisted the conversion of intermediate species such as

DHMF and MFA, to the final product. Relatively mild conditions (130 °C, 7 bar H_2) for the conversion of HMF into DMF (93% yield) were described using Ru/Co_3O_4 as a catalyst. The study proved that Ru was responsible for hydrogenation, while CoO_x species were involved in the hydrogenolysis of hydroxyl groups of HMF.[76]

Interestingly, a study on the effects of C-supports demonstrated that a Ru-catalyst supported on carbon nanotubes (CNT) showed a hydrogenolysis activity over 40 times higher that of the corresponding system supported on activated carbon (AC):[77] at 150 °C and 20 bar H_2, TOF and DMF yields were 820 h^{-1} and 84%, and 36 h^{-1} and 80%, for Ru/CNT and Ru/AC, respectively. The result was ascribed to a superior accessibility of pores in carbon nanotubes.

One last representative work compared the performance of Ru/C, Pd/C and Pt/C with low-metal loading (1 wt%) in the reaction of aqueous solutions of HMF (2–3 wt%), under H_2 pressure.[78] Notably, authors were able not only to tune the conditions towards the selective hydrogenation (with no side-reactions of hydrogenolysis) of HMF, but to demonstrate that Ru/C was the most effective catalyst to this purpose. Optimized yields of 93% for BHMF and 95% for BHMTHF were obtained at T/p of 50 °C/30 bar H_2 and 100 °C/50 bar H_2, respectively.

To conclude this paragraph, catalytic transfer hydrogenation/hydrogenolysis (CTH) reactions promoted by Ru are briefly mentioned. A quantitative conversion of HMF with 81% selectivity towards DMF (hydrogenolysis product) was achieved at 190 °C and N_2 pressure of 20 bar, in the presence of commercial 5 wt% Ru/C as a catalyst and 2-propanol as a hydrogen donor.[79] Under similar conditions (190 °C, 2-propanol) however, a recent work reported that the reaction of HMF catalyzed by Ru/Co_3O_4 proceeded through a transfer hydrogenation process, producing BHMF in a 82% yield. [80]

Authors highlighted major advantages of 2-propanol as a hydrogen donor, including its role as both reactant and solvent, and the easy recycle of acetone originated from its dehydrogenation reaction.

An alternative CTH route proposed the combined use of water soluble arene–Ru(II) complexes containing ethylenediamine-based ligands and formic acid as a hydrogen donor.[81] In this case, the acidic environment favored the ring-opening CTH of HMF to provide linear ketoacids and diketones such as 1-hydroxyhexane-2,5-dione (1-HHD), 3-hydroxyhexane-2,5-dione (3-HHD), levulinic acid, and hexane-2,5-dione (2,5-HD) with selectivities of 41, 36, 18, and 5 %, respectively (100 °C, conv. 92%).

From the above-described examples and the Scheme 3, the nature of the Ru-based catalysts plays the most critical role to steer the products distribution of reactions of HMF. However, the temperature and to a minor extent, the pressure of H_2, have also remarkable effects. Hydrogenation processes of HMF typically take place in the range of 50-140 °C, while hydrogenolysis reactions become predominant from 150 to 220 °C. The operative pressure largely depends by the hydrogen solubility in the reaction solvent, though it must be not below 10 bar and more often, above 15-20 bar regardless the studied transformation (hydrogenation or hydrogenolysis).

2. SCOPE AND SUMMARY OF THE THESIS

This thesis work was focused on the hydrogenation/hydrogenolysis of HMF carried out either under batch multiphase (MP) conditions or in the continuous-flow (CF) mode. The most part of experiments were performed at Ca' Foscari University where MP-reactions were investigated, while the study of CF-processes was done during a three-months Erasmus stage at the University of Cordoba (Spain). This section briefly introduces some representative cases from the literature of both MP and CF-reactions of HMF, followed by a summary of the experimental conditions implemented in this Thesis and the major results achieved.

2.1 Multiphase systems for the conversion of HMF

Multiphase (MP) catalytic hydrogenolysis/hydrogenation processes have been extensively reported for the conversion of a variety of renewable feedstocks including bio-oils, glycerol, sorbitol, xylitol, levulinic acid, etc.[82] MP-protocols, however, have been seldom described for the reactions of HMF. One of such examples has been mentioned in the previous paragraph, with reference to the use of a 1-butanol/water mixture for the hydrogenation of HMF under conditions mimicking those employed for fructose dehydration.[83] In another configuration, the synthesis of BHMTHF was accomplished in a water/cyclohexane system, starting from fructose that generated HMF as an intermediate. A conventional hydrogenation catalyst as Ru/SiO_2 was hydrophobized by treatment with trimethylchlorosilane to make the reaction proceed in the organic phase.[84]

Due to the long-standing interest of our research group for green organic synthesis under multiphase catalysis,[85,86] a relevant part of this Thesis work was focused on the design of batch multiphase conditions for the catalytic hydrogenation/hydrogenolysis of HMF. The study took inspiration mainly from two papers reporting on the selective MP-hydrogenation of levulinic acid to γ-valerolactone (GVL) carried out using a water/iso-octane biphasic system, either with or without an ionic liquid (IL), in the presence of a commercial Ru/C catalyst.[87,88]

This reaction configuration not only allowed an excellent selectivity (>99% at complete conversion), but it proved suitable to confine the product (GVL) in the water solution and the catalyst in the IL or the hydrocarbon medium where it could be recycled.

A similar design was investigated in this Thesis. The aim was to integrate the catalytic synthesis of hydrogenation/hydrogenolysis derivatives of HMF with an efficient catalyst/products separation procedure for the recycling of the catalyst. In particular, the conversion of HMF to BHMF and HHD was explored using mutually immiscible aqueous/hydrocarbon phases in the presence and in the absence of selected ILs as trioctylmethyl phosphonium bis-(trifluoromethane)sulfonimide ([P_{8881}][NTf_2]).

BHMF was obtained with a 92 % yield at 60°C with a p^0H_2 of 30 bar for 18 hours. The reaction was carried on in a system made of an aqueous solution of HMF 0.2 M and 50 mg of Ru/C.

HHD was obtained selectively with a 99% yield at 100°C, a p^0H_2 of 50 bar for 18 hours. The reaction was carried on in a multiphasic system made of 10 mL of the aqueous phase containing HMF 0.05 M, 650 mg of [P_{8881}][NTf_2], 5 mL of *iso*-octane and 50 mg of Ru/C.

2.2 Continuous-flow hydrogenation of HMF

Several protocols have been described for the continuous-flow (CF) hydrogenation of HMF. Conventional continuous bench-scale fixed bed reactors have been used to test a variety of catalytic beds including for example, commercial carbon-supported metals (Pt, Pd, Ir, Ru, Ni, and Co)[89] and Pd/SiO_2,[90] and *ad-hoc* prepared systems such as noble (Pt and Ru) and non-noble (Ni and Cu) metal catalysts supported on acid ($HYAl_2O_3$ and Al_2O_3) and basic (ZrO_2 and TiO_2) supports,[91] or a combination of ZrO_2/SBA-15 and Pt/C.[92] In the range of 180-200 °C and 15-30 bar H_2, both hydrogenation and hydrogenolysis of HMF were observed with variable selectivities towards BMTHF (50-100%) and DMF (61-78%), respectively.

A different approach for the CF-hydrogenation of HMF has been recently proposed using H-Cube® a fixed-bed bench-top continuous-flow hydrogenation reactor developed by ThalesNano Inc (Figure 9).[93]

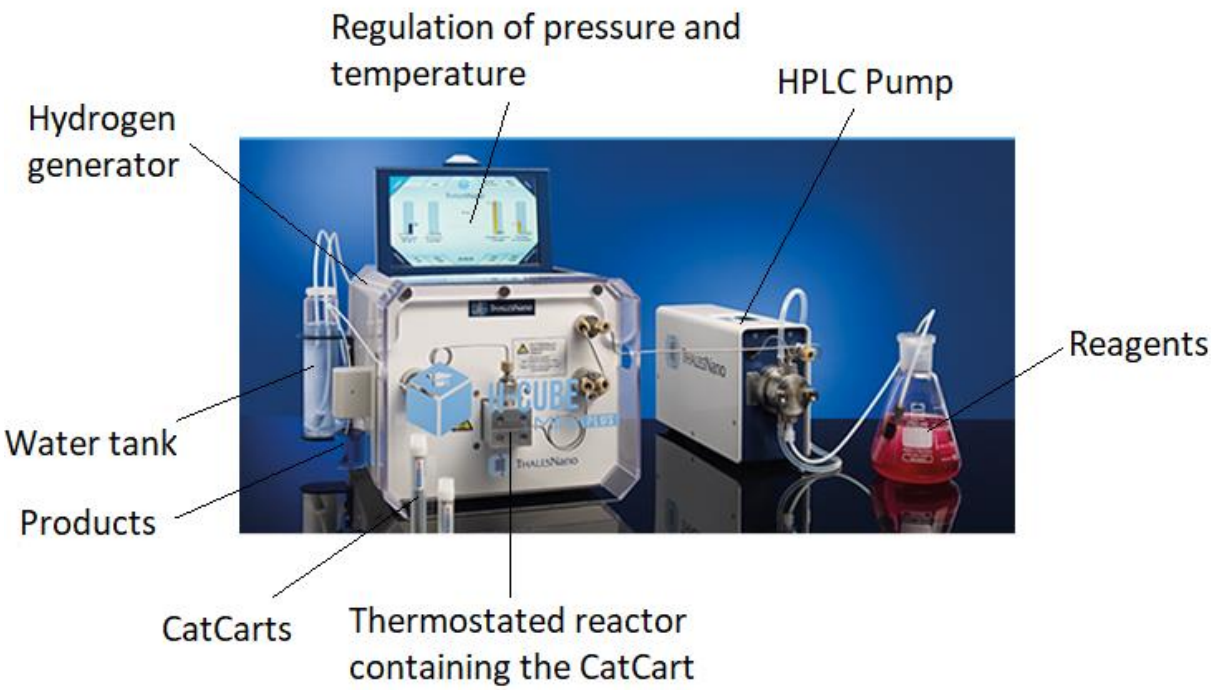


Figure 9. The H-Cube® MINI PLUS apparatus. (H-Cube® = cartridge containing the catalyst).

In two model cases, starting from either aqueous or ethanol solutions of HMF, this reaction setup allowed a selective hydrogenation to BHMF in a 92% yield using RANEY® Cu as a catalyst (90 °C, 90 bar H_2, flow rate: 0.05 mL/min),[94] or alternatively, the full conversion of HMF into its hydrogenolysis derivative DMF (ca 90% selectivity at 150 °C, 6 bar H_2, flow rate of 0.5-1 mL/min) using metal Ni dispersed on a porous carbon support obtained from a squaric acid (SA)-Zn complex.[95] Authors highlighted how some of the features of support, particularly the high pore volume (1.55 cm^3 g^{-1}), the large pores, and its homogeneous micrometric morphology were critical to minimise the pressure drop in the flow system.

The continuous flow system was very recently used to perform also the catalytic transfer hydrogenolysis (CTH) of HMF in the presence of Cu-Pd bimetallic catalysts incorporated on graphene oxide (RGO) and 2-propanol as a hydrogen donor. Under optimised conditions (0.05 M HMF in 2-propanol, 200 °C, 0.2 mL/min, and 30 bar), 10Cu- 1Pd/RGO system exhibited 96% HMF conversion with 95% DMF yield. It was suggested that the occurrence of Pd/Cu interactions enhanced the catalytic activity and prevented the catalyst deactivation by minimising the aggregation/leaching of the active Cu phase. [96] This last paper was published by the group led by Prof. Rafael Luque at the University of Cordoba (Spain) where part of this Thesis work was carried out.

The study presented here was focused on the hydrogenation of HMF using Ru/C as the catalyst with molecular hydrogen, generated in situ by H-Cube®. The reaction was studied in different solvents, such as ethyl acetate, tetrahydrofuran and ethanol.

BHMTHF could be produced as the main product with a yield of 80-90% for two hours at 100°C, a p^0H_2 of 50 bar, a flow rate of 0.1 mL/min and ethyl acetate as the solvent.

3. RESULTS AND DISCUSSION

3.1 HMF hydrogenation/hydrogenolysis in multiphasic batch system

3.1.1 Foreword

Some preliminary considerations are offered here to discuss on the choice of the solvent and the catalyst for this study. Most of the published papers report the use of tetrahydrofuran, 1,4-dioxane, alcohols, or ionic liquids as solvents for the reactions of HMF. These compounds, however, are often expensive, toxic, and non-renewable derivatives. In this work, with the aim of integrating the green chemistry principles in the development of sustainable synthetic protocols, water has been the preferred solvent. In addition, since HMF is supplied as an aqueous stream from the biorefining of sugars, it follows that the upgrading of HMF in water is of practical importance in view of avoiding unnecessary purification steps.
Commercial carbon-supported metal catalysts remain the preferred choice for hydrogenation reactions, because of their low cost, high surface area, chemical inertness, and thermal stability in non-oxidizing atmospheres.[97] More specifically, Ru is among the most frequently selected metals for the hydrogenations of various biomass derived compounds.[77] 5% Ru/C sourced by Aldrich was therefore used for this investigation.

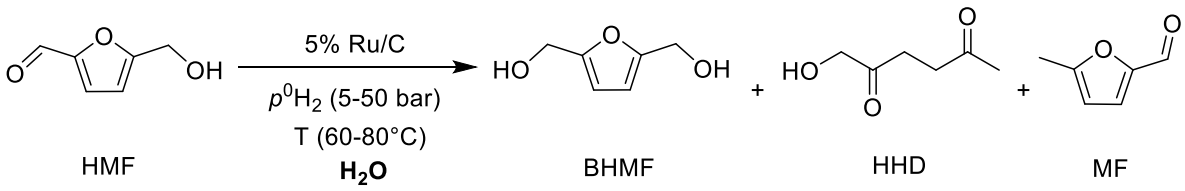
One last remark concerns intrinsic limitations due to the stability and the purity of the reagent (HMF) and its hydrogenation/hydrogenolysis products. In this work, it was noticed that: i) even if stored at 4 °C, commercial HMF underwent spontaneous oxidation yielding variable amounts of the corresponding dialdehyde (2-16%), after few weeks from the first use; ii) different batches of HMF sourced from the same supplier (Aldrich), came with variable contents of acid impurities (see later on this chapter). Moreover, the isolation of pure HMF derivatives, particularly BHMF and HHD, from aqueous solutions was tricky.

3.1.2 The batch reactions of HMF in water solution: effects of T and p

A protocol for the catalytic hydrogenation of aq. HMF recently reported by Raspolli Galletti *et al*.[78] was taken as a reference to begin the study. Accordingly, the same experimental procedure was used here, except for the adjustment (decrease) of the reaction volume to fit

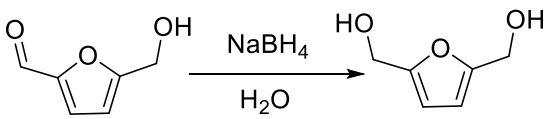
the reactors available in our laboratory. Tests were carried out using an aqueous solution of HMF (0.2 M, 10 mL) in the presence of 5% Ru/C (50 mg; Ru:HMF= 1 wt%). This suspension was set to react under stirring in a stainless-steel autoclave at different temperatures and pressures of H_2 in the range of 60-80 °C and 5-50 bar, respectively. A stirring rate as high as 1300 rpm was used. In a previous study of our group on the hydrogenation of aq. LA,[88] it was demonstrated that with the same experimental setup described here, a vigorous agitation of the reaction mixture (suspension) avoided mass transfer limitations.

The preferred, substantially exclusive, formation of BHMF as a product of the hydrogenation of carbonyl in HMF, was observed. Minor amounts of hydrogenolysis products as MF and HHD were also detected (Scheme 4).



Scheme 4. Hydrogenation/hydrogenolysis of HMF with 5% Ru/C at 5-50 bar, 60-80°C in water.

The structure of these compounds was assigned by GC/MS and NMR and confirmed by either independent syntheses or comparison to literature data. For example, BHMF was obtained by the stoichiometric reduction of HMF with $NaBH_4$ according to a reported procedure (Scheme 5).[107]



Scheme 5. The stoichiometric reduction of HMF with $NaBH_4$

Results are reported in Figure 10 where the trend of conversion and products distribution are shown as a function of T and p, after 6 h reactions.

The conversion of HMF was determined by calibration with standard solutions, using the following equation[77]:

$$Conversion\ (\%) = \frac{moles\ of\ substrate\ reacted}{initial\ moles\ of\ substrate} x100$$

Attempts to obtain pure reaction products in amounts enough for a GC-calibration procedure, failed and the selectivities of such compounds were calculated from their GC-responses as area %. Although aware of the limitations of this approach, the results were corroborated by the comparison with the above-quoted work taken as a reference (see Scheme 6, later in this paragraph).

All tests were run in duplicate to ensure reproducibility. Data (conversion and selectivity) of experiments repeated under the same conditions, differed by less than 5 % from one reaction to another (further details are in the experimental section).

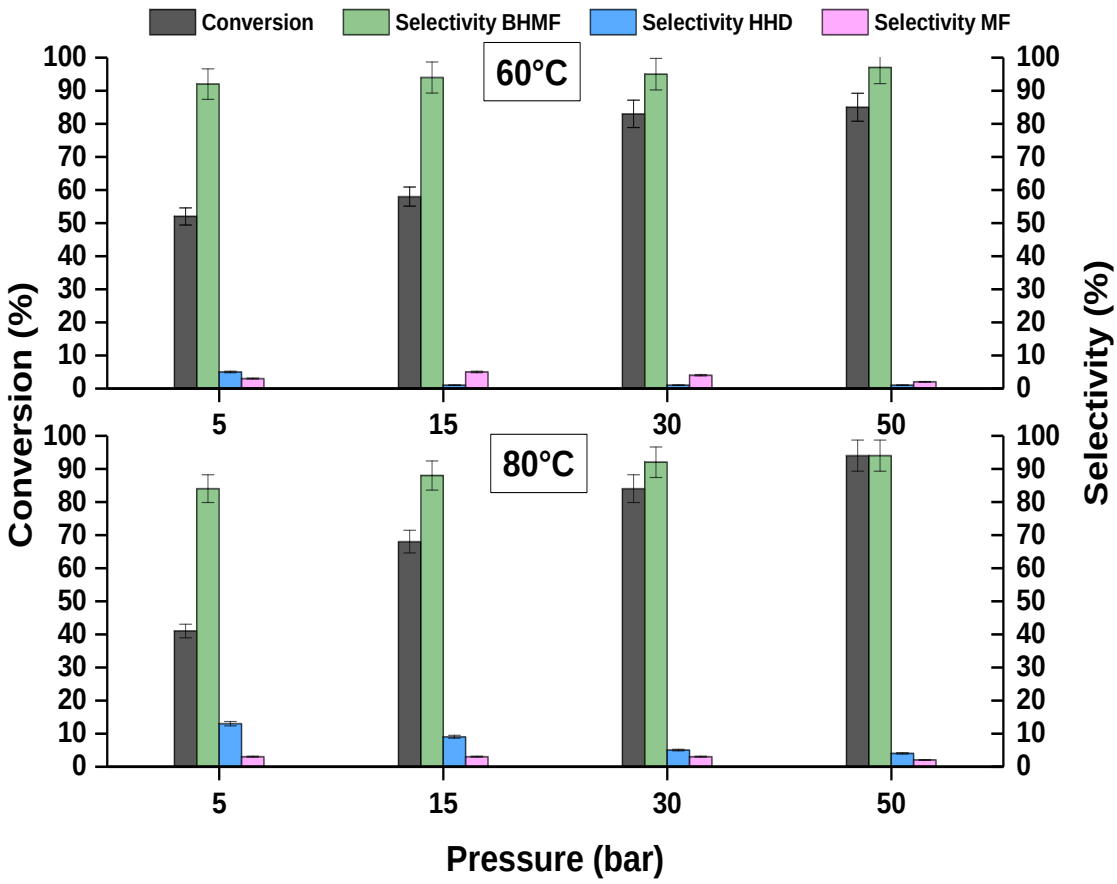
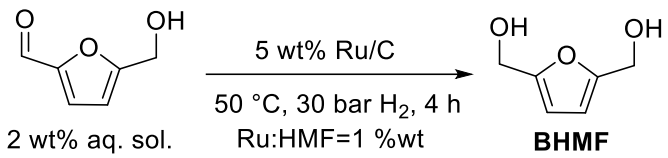


Figure 10. Comparative effects of T and H_2 pressure on the hydrogenation of HMF performed in a batch reactor (autoclave). Top: T = 60 °C, pressure from 5 to 50 bar. Bottom: T = 80 °C, pressure from 5 to 50 bar. Other conditions: t = 6 h, [HMF] = 0.2 M (10 mL) in deionized water, 5% Ru/C (50 mg). Conversion of HMF and product selectivity were obtained, upon calibration, by GC-FID analysis.

At 60 °C, increasing the pressure of H_2 from 5 to 50 bar, resulted in a significant increase of the conversion from 51% to a plateau value of 84%, and in a slight, but appreciable improvement of the BHMF selectivity from 92% to 97% (Figure 10, top). The combined increase of T to 80 °C and p in the interval of 15-50 bar, had similar consequences: it mostly affected the conversion which was enhanced from 68% up to 94%, while the BHMF selectivity ranged from 88% to 94% (Figure 10, bottom). These trends were likely determined by the effects/increase of the temperature and the pressure that favoured the reaction kinetics and the H_2 solubility in water. In any case, benefits on conversion and selectivity, if any, were rather limited above 30 bar.

Unexpectedly, compared to the process at 60 °C, the reaction run at 80 °C and 5 bar proceeded with a lower conversion and BHMF selectivity (41% and 84%, respectively), and a concurrent not negligible formation of HHD (12%) (Figure 10, bottom, left). The reasons for this behaviour were unclear. We hypothesised that the combined effect of the higher T and the modest availability of H_2 (in the aqueous reactant solution) at 5 bar, plausibly allowed the onset of the competitive hydrolytic ring opening of HMF (yielding HHD) rather than its hydrogenation to BHMF. Further considerations on this aspect will follow later in this section.

The results of Figure 10 however, were consistent with those of the reference work used for this study.[78] This was confirmed by a further test aimed to compare the reaction carried out in exactly the same experimental conditions (4 h, 50 °C, 30 bar), as shown in Scheme 5.



Conv.'n (%)	Selectivity (%)	
100	93	From ref 78
75	95	This work

Scheme 6. Replica of the hydrogenation of aq. HMF under the conditions of ref. 78.

Although both reactions used a commercial 5% Ru/C sourced from Aldrich, our catalyst batch was less effective yielding a 75% conversion (line 2) rather than a quantitative process (line 1) as reported by the literature work. Several reasons could account for this discrepancy including protocols for the catalyst preparation, use of different C-supports or different samples of HMF, etc. Importantly however, experiments proceeded with a comparable

selectivity (93-95%) towards BHMF, thereby making the above described method to determine the products distribution (area %, by GC) plausible.

To further investigate the performance of the catalyst and the effect of the temperature, the study was continued by carrying out two additional experiments at 40 and 100 °C. Other conditions were those of Figure 10 with the H_2 pressure set to 30 bar. Results are reported in Figure 11 in which, for a complete view, the outcome of reactions run at 60 and 80 °C and 30 bar (previously illustrated in Figure 10) is also shown. Products were those indicated in Scheme 4 and conversion and products distribution were determined as previously described.

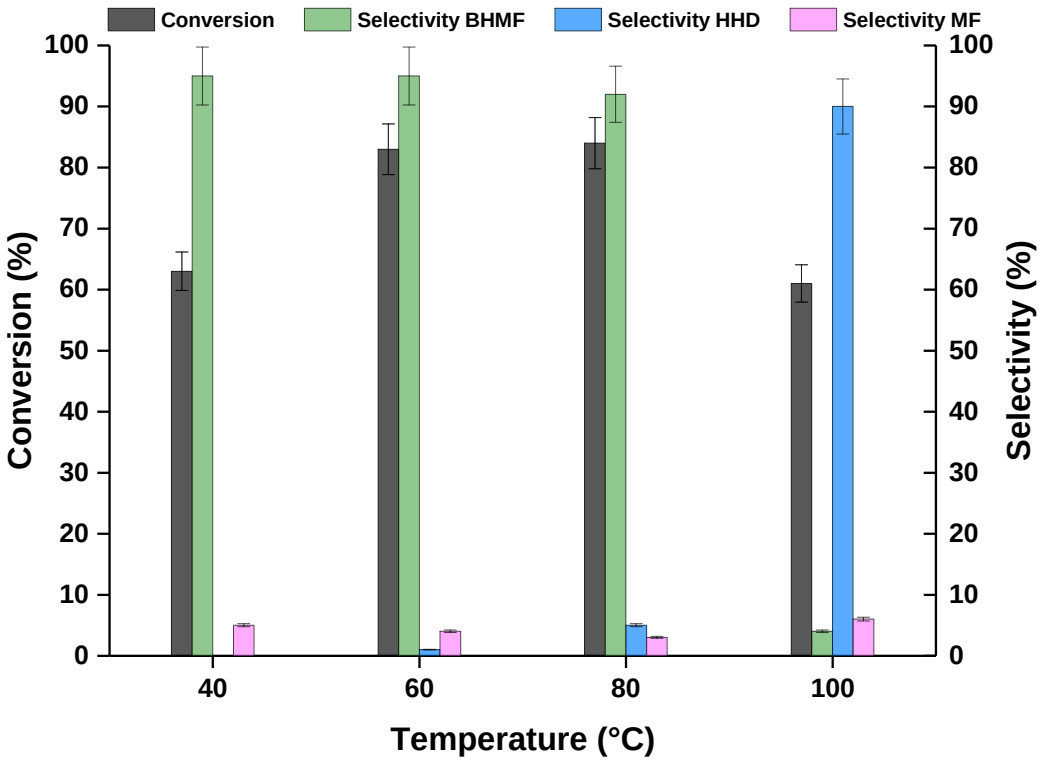
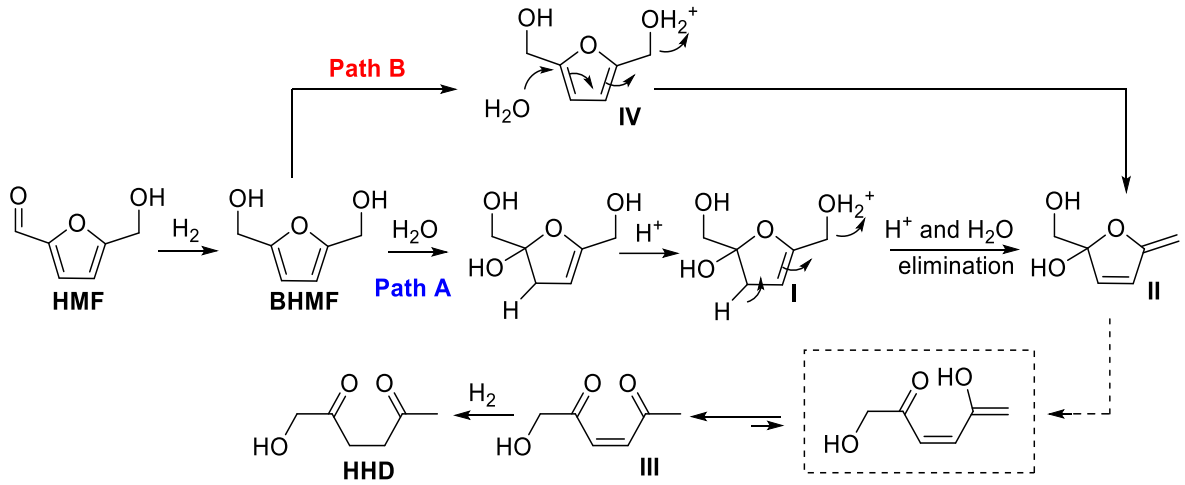


Figure 11. Detailed effect of the temperature on the hydrogenation of HMF performed in a batch reactor (autoclave). Conditions: p^0 H_2= 30 bar, t= 6 h, [HMF]= 0.2 M (10 mL) in deionized water, 5% Ru/C (50 mg). Conversion of HMF and product selectivity were obtained, upon calibration, by GC-FID analysis.

The most striking effect was the change in the products distribution. BHMF was steadily the major product (92-95%) at 40-80 °C. However, by increasing the temperature from 80 °C to 100 °C, the selectivity dramatically shifted to 90% towards HHD. Interesting was also the trend of HMF conversion. After an initial enhancement from 40 to 60 °C, it (conversion) levelled off to ca 85% at 80 °C, and finally dropped to 62% despite the rise of T to 100 °C. Apparently, the

HMF conversion was: i) no longer improved by the temperature as soon as HHD started to form in appreciable amounts (6%, 80 °C), and ii) even disfavoured when HHD became the predominant product at 100 °C.

As mentioned in the introduction, HHD is emerging product among those accessible from the reaction of HMF under reductive conditions. A common observation reported by already available studies for the conversion of HMF into HHD,[67-70] is that the reaction occurs on conditions that a metal catalyst active for hydrogenation (e.g. Pd or Ir) is assisted by an acidic environment provided by either the catalyst support (e.g. Nb_2O_5) or the catalytic activation of H_2 (e.g. Ir(III) + H_2 → Ir(III)-H + H^+), or the external supply of CO_2 for the *in situ* formation of carbonic acid. Indeed, a mechanistic pathway accepted for the formation of HHD, is shown in Scheme 6:



Scheme 7. A plausible mechanism for the hydrolytic ring opening of HMF to HHD

The formulation is based on the mechanism for the acid catalyzed conversion of HMF to levulinic acid, originally proposed by Horvat *et al*, and then adapted to HHD.[98] The initial step is the hydrogenation of HMF to BHMF. Thereafter, according to path A, a regioselective 2,3-addition of water and OH-protonation occur to provide the intermediate **I**. This in turn, undergoes a concerted elimination to provide the cyclic diene **II**. The same intermediate (**II**) is achieved by path B through an OH protonation of BHMF to yield **IV** and a subsequent one-step hydrolysis. Once **II** is formed, a ring opening reaction plausibly affords an enol species (dashed box, hypothesized compound) that tautomerizes to a α,β-unsaturated carbonyl compound (**III**). The final hydrogenation of **III** provides HHD. Further details on the energetics

of water addition/protonation to/of furan rings in acid water solutions have been described in a recent paper.[99]

The need for an acidic environment to assist both the addition of water and the hydrolytic ring opening of HMF prompted us to investigate whether a source of acidity was available even under the conditions of Figure 11. A response was readily obtained after the analysis of the aq. HMF solution (0.2 M) used for the reactivity tests of this study: the corresponding pH (measured by a portable pH meter using a glass electrode) was 3. The acid contamination of HMF, likely derived from the processing of sugars during the synthesis of commercial samples,[100] was previously reported by other papers:[71] authors further noticed that after removal of (acid) impurities by treatment with a basic ion-exchange resin, the selectivity of the hydrogenation of HMF to BHMTHF catalysed by Ru-black, was improved.

In our case, as an additional minor contribution to acidity in solution, previous characterisation test carried out by our group,[88] indicated that different oxygen-bearing groups were present on the surface of the catalyst used in this study. TPD analyses and Boehm titrations proved that functionalities including carboxylic, lactones, and phenol-like ones, imparted a total surface acidity of 140 μeq/g.

Another aspect emerging from Figure 11 was that the ring opening of HMF occurred to a very small extent below 100 °C. The same observation was reported also in the investigation of the hydrogenation/hydrogenolysis of HMF catalyzed by a Ni-Co-Al Mixed Oxide system,[61] where the formation of linear di- and poly-ols was noticed from 120 °C on. Such results were apparently supported also by a DFT investigation on the competition between the hydrogenation and the ring-opening of furan on Pd(111):[101] the comparison of the activation energies of elementary reaction steps and the kinetic analysis proved that at high temperatures, 1-butanol (from ring opening) was the thermodynamically favored product, while at a test temperature of 100 °C, the ratio between the rate constants of hydrogenation (to THF) and ring aperture was ∼6.

This led us to hypothesize that if BHMF and HHD were the kinetic and thermodynamic products, respectively, of our experiments, the longer the reaction time the higher the formation of the linear diketoalcohol. Additional prolonged experiments were then designed at 60-80 °C.

3.1.3 The batch reactions of HMF in water solution: effects of the reaction time

The reaction of HMF was investigated under the conditions of Figure 10 by limiting the temperature range from 60 to 80 °C, and by concurrently exploring an extended range of time from 2 to 40 h. Results are reported in Figure 12 for experiments carried out at 2, 6, 18, and 40 h at 60 ° C (top) and 80 °C (bottom), respectively.

At 60 °C, the increase of the reaction time from 2 to 18 h resulted in an enhancement of the conversion from 62 to 96%, while the selectivity to BHMF was always steady to a very high value (≥95%). However, when the reaction was further prolonged up to 40 h, the process was still quantitative, but a significant presence of HHD (32%) was observed at the expenses of BHMF (64%). This indicated that not only the HMF ring opening was allowed at the lowest investigated temperature, but it also corroborated the role of BHMF as an intermediate on the formation of HHD, in line with the mechanism of Scheme 5.

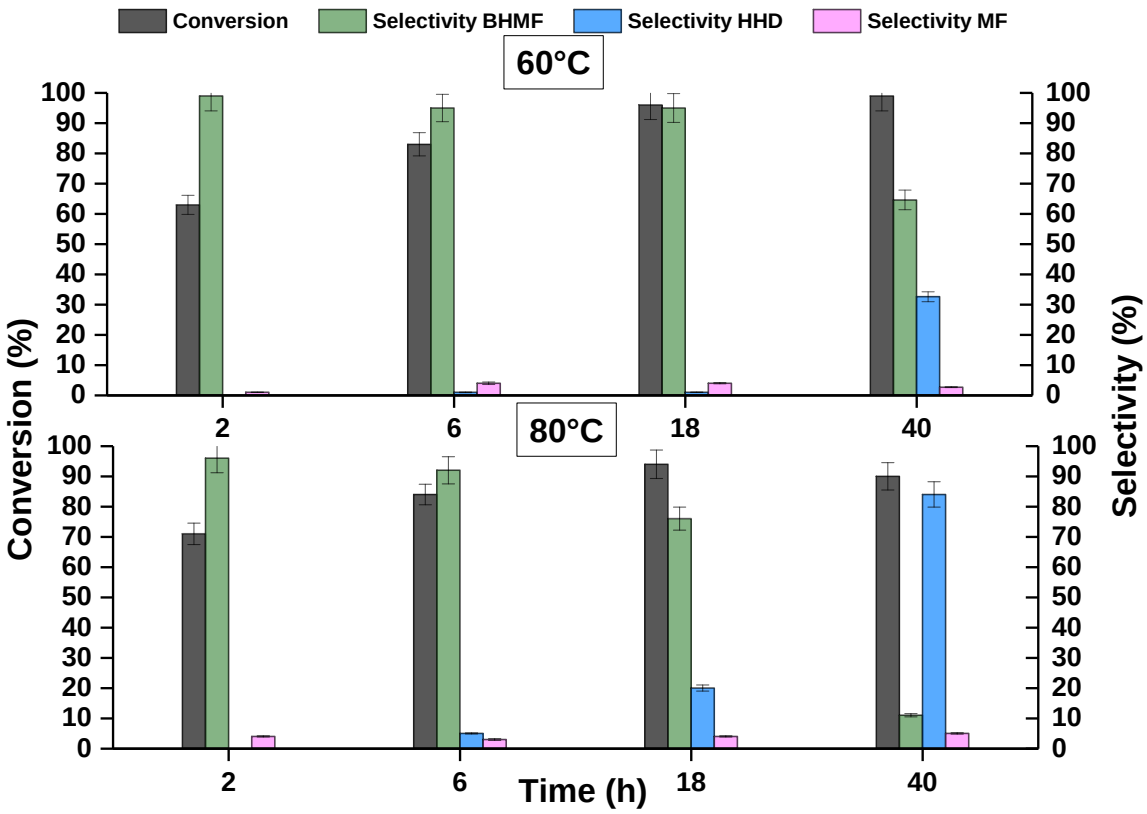


Figure 12. Effect of time on the hydrogenation of HMF performed in a batch reactor (autoclave). Conditions: $p^0 H_2$ = 30 bar, [HMF]= 0.2 M (10 mL) in deionized water, 5% Ru/C (50 mg). Top and bottom: 60 °C and 80 °C, respectively. Conversion of HMF and product selectivity were obtained as described for Figure 10.

Similar considerations applied to the second set of experiments at 80 °C, though appreciable amounts of HHD were already noticed after 18 h. When reactions were prolonged from 2 to 18 h, the conversion increased from 71 to 94%, while the selectivity towards BMHF and HHD decreased and increased from 94 to 76% and from 0 to 20%, respectively. The final experiment carried out for 40 h proved that HHD could be obtained as a major product (84%) at 90% conversion. Notably, compared to the literature results, this was one of the best achievements for the preparation of HHD, made possible under mild conditions by exploiting the presence of acid impurities in the HMF reagent.

Figure 12 supported our initial hypothesis: even at moderate temperature (80 °C), on condition that the supplied energy was enough to trigger the ring opening of HMF, the reaction mixture equilibrated with time towards the thermodynamically favoured product HHD at the expenses of the kinetic derivative BHMF. In analogy to the trend of Figure 11, albeit less pronounced, Figure 12 also showed a slight drop of the reaction conversion from 18 to 40 h, as the formation of HHD increased. The reasons for this behaviour are still unclear, but apparently, the onset of the hydrolytic aperture of the furan species affects the adsorption of the same compounds over the catalyst surface during the hydrogenation step.

3.1.4 Multiphase (MP) conditions for the hydrogenation/ hydrogenolysis of HMF: products/catalyst separation

The cost of the catalyst in a liquid-phase reaction may represent up to one third of the total cost of the process, implying that its loss, for example, by leaching, can be critical, and its recovery and reuse are imperative. Particularly, the separation of C-supported catalysts from organic/aqueous solutions is a well-documented issue also in industry, where conventional techniques of filtration and centrifugation often become expensive, if not impracticable, for fine powdered carbons with low particle sizes (the most active supports).[97,102] This subject has been part of this Thesis work and will be examined in the following paragraphs.

The commercial sample of 5% Ru/C (Sigma Aldrich, lot MKBW5890V) used in this study was previously employed by our research group to investigate the hydrogenation of levulinic acid (LA) to γ-valerolactone.[88] As mentioned in the introduction, it was discovered that in the presence of two mutually immiscible phases as water and iso-octane, the catalyst could be perfectly segregated in the hydrocarbon medium providing that the aqueous phase was

always acid (2.5≤pH≤5). The aqueous acidity was sourced by either LA or any other mineral acid as for example, HCl or H_2SO_4. After vigorous stirring for 60-90 min at room temperature, the multiphase mixture appeared as shown in Figure 13.

Figure 13. A multiphase mixture of iso-octane (5 mL), acid water (10 mL, aq. HCl $3x10^{-3}$ M), and 5% Ru/C (50 mg). The catalyst, Ru/C, was visibly segregated in top iso-octane layer.

The extensive characterisation study (N_2 adsorption, temperature-programmed desorption (TPD), Raman and infrared spectroscopy methods including DRIFTS, SEM coupled with energy-dispersive X-ray analysis (EDX), and chemical titration methods) carried out to inspect both the surface and the morphological/textural properties of the catalyst, did not allow to draw definitive conclusions to explain the behaviour of Figure 13. The presence of non-negligible quantities (0.1–0.2 %) of Na-based impurities combined to a moderate surface acidity of the commercial Ru/C sample could play a role. Overall, although the segregation phenomenon was far from being understood, the multiphase system offered an original solution to separate the reaction products from the catalyst in a semi-continuous mode. By tuning the relative volumes of water and hydrocarbon and the concentration of reactants in the aqueous solution, Ru/C was confined, without aqueous leaching, and recycled as a suspension in the hydrocarbon medium, whereas the organic product was recovered from the water solution, free of any cross-contamination.

The versatility of this MP protocol prompted us to investigate whether it could be successful also for the reaction of aq. HMF investigated in this Thesis. The presence of acid impurities in the starting reactant (see above, formation of HHD) could have been of help to the purpose.

The second part of this work was therefore dedicated to design reaction conditions aimed at allowing the hydrogenation/hydrogenolysis of HMF with the concurrent *in-situ* recycle of the catalyst.

3.1.5 Ru/C-catalysed reactions of HMF in an *i*-octane/aqueous biphase system

Experiments were carried out under the same set of conditions previously described for the conversion of aq. HMF into BHMF (30-50 bar; 60-80 °C; 6h; [HMF]= 0.2 M, 10 mL; 5% Ru/C, 50 mg), making sure to add iso-octane (5 mL) to each reaction mixture. Some representative results are summarised in Table 3. Products were those indicated in Scheme 4 and conversion and products distribution were determined as previously described.

Table 3. The MP-reaction of HMF in a water-isooctane system. Conditions: $p^0 H_2$= 30-50 bar, T= 60-80°C, t= 6 h, [HMF]= 0.2 M (10 mL) in deionized water, iso-octane (5 mL), 5% Ru/C (50 mg).

Entry	T/p/t (°C/bar/h)	Conv. (%)	Products (selectivity, %)		
			BMHF	MF	HHD
1	60/30/6	77	90	8	2
2	60/50/6	85	91	7	2
3	80/30/6	68	90	6	4
4	80/50/6	81	86	6	8

Compared to the experiments performed using only aq. HMF solutions (Figures 10-11), the addition of isooctane did not significantly alter the reaction outcome, except for a slight decrease of the conversion. This was consistent with the partitioning of the catalyst in the hydrocarbon phase, where HMF was not soluble. The expected segregation of Ru/C, however, was never observed and any attempt to induce the separation by further acidifying the final reaction mixtures with extra aq. HCl (until a pH=2 was reached) was unsuccessful.

As an example, Figure 14 shows some pictures of the multiphase system as recovered once the reaction of entry 1 of Table 3 was complete (A), and during and after acidification with HCl (B and C). Although the acidification helped the preferential partitioning of the catalyst in the hydrocarbon phase (C, top layer), a substantial amount of Ru/C was still suspended in water, making the desired separation ineffective.

A slightly better situation (separation), yet not satisfactorily, was achieved by lowering the amounts of both HMF and Ru/C. Figure 14 D exemplifies the case when the HMF concentration

was reduced by a factor of 4 (0.05 M) and the quantity of Ru/C was halved (25 mg) with respect to the above described reaction conditions.

Contrarily to the case of levulinic acid, it became clear that in no way could the catalyst be segregated when HMF or its hydrogenated derivative (BHMF) were present in the aqueous/isooctane biphase. The occurrence of strong interactions (H-bonding) of HMF and its products with the surface groups on the carbonaceous support of the catalyst were likely responsible for the result.

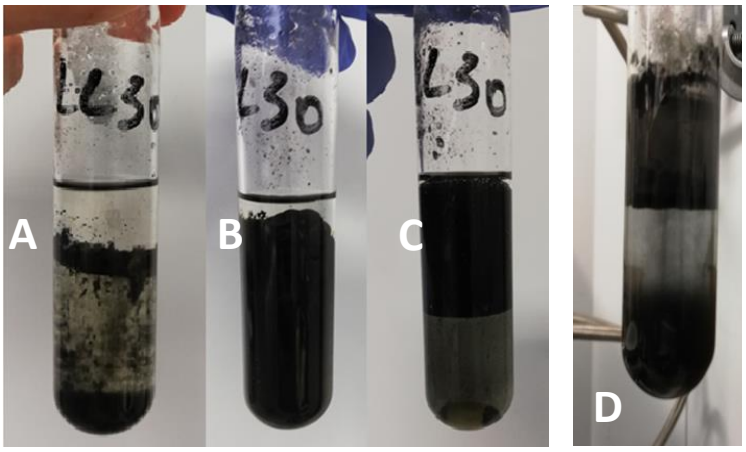


Figure 14. A: the MP-mixture as recovered once the experiment of entry 1 of Table XX was complete (conditions: aq. [HMF]= 0.2 M, 10 mL; iso-octane, 5 mL; Ru/C, 50 mg; 60 °C, 30 bar, 6 h.
B and C: during and after acidification of the same mixture with conc.d HCl (37%) until pH=2 was reached.
D: appearance of a MP-mixture comprised of aq. [HMF (0.05 M, 10 mL), iso-octane (5 mL), Ru/C (25 mg), after acidification with conc.d HCl (37%) until pH=2 was reached.

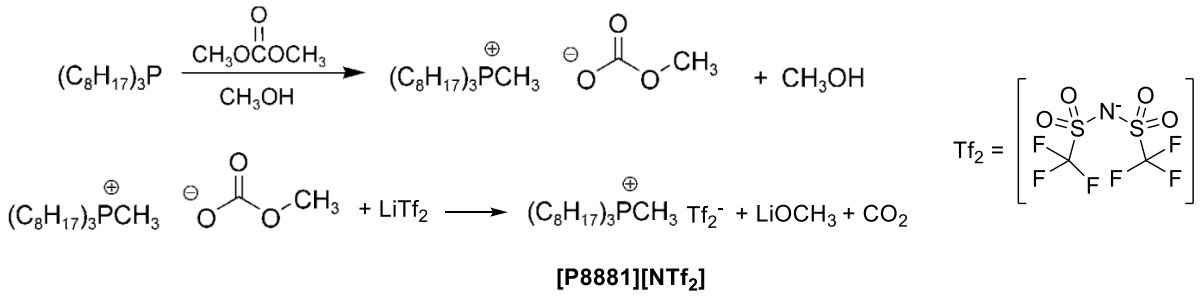
A different approach was therefore conceived using ionic liquids (ILs)-based MP-systems.

3.1.6 Ru/C-catalysed reactions of HMF in an *i*-octane/aqueous/ionic liquid multiphase system

In a previous work of our research group,[87] the model reaction of conversion of levulinic acid (LA) to γ-valerolactone was investigated in the presence of MP-systems whose formation was assisted by the presence of ionic liquids (ILs). The screening of several of such ILs indicated that phosphonium salts, particularly trioctylmethylphosphonium bis(trifluoromethane)sulfonimide ([P_{8881}][NTf_2]) was effective to the purpose. Phosphonium salts were not only more thermally stable than the corresponding ammonium and imidazolium salts (a relevant requisite to design reactions operating at T ≥100 °C),[103] but the lipophilic nature of the [NTf_2] anion reduced the IL miscibility with water. It was noticed that a MP-system comprised of two mutually immiscible media as water and isooctane, and ([P_{8881}][NTf_2]) as an ionic liquid was

suitable for the conversion of LA to GVL and importantly, it allowed the perfect segregation of the hydrogenation catalyst (5% Ru/C) in the IL phase, thereby ensuring its *in situ* recovery and reuse.

The same MP-system was used to explore the hydrogenation/hydrogenolysis reactions of HMF in this thesis work. $[P_{8881}][NTf_2]$ was synthesised according to a procedure reported by our group and illustrated in Scheme 8.[109]



Scheme 8. Protocol for the synthesis of $[P_{8881}][NTf_2]$

The quaternarization of *n*-trioctylphoshine with dimethyl carbonate ($MeOCO_2Me$) provided methyltrioctylphosphonium methyl carbonate (top). This salt was subjected to a metathetic anion exchange with an aq. $LiTf_2$. The lypophilic character of the NTf_2 anion, allowed the precipitated of the desired ionic liquid ($[P_{8881}][NTf_2]$) out of the aqueous solution.

Several tests were then performed to optimise the phase separation in the MP system with $[P_{8881}][NTf_2]$. Accordingly, the HMF:catalyst molar ratio (W) was varied from 100:1 (aq. HMF: 0,2 M, 10 mL; 5% Ru/C: 50 mg) to 50:1 (HMF: 0.05 M, 10 mL; 5% Ru/C, 25 mg), and the quantity of the IL (Q) was changed between 355 to 657 mg corresponding to ca 0.6 and 1 mmol, respectively. A good result was finally achieved at W=50 and Q=657 mg (Figure 15). The substrate (HMF) and the catalyst were fully confined in the aqueous and in the IL phases, respectively. Albeit the role of *i*-octane was inconsistent as a solvent for the chemical species, it was necessary, however, to obtain phase separation and catalyst segregation.

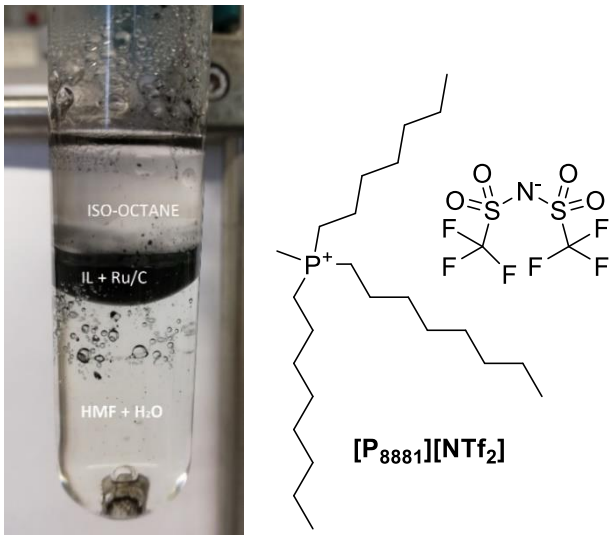


Figure 15. Appearance of a MP-mixture comprised of aq. [HMF (0.05 M, 10 mL), iso-octane (5 mL), Ru/C (25 mg), and $[P_{8881}][NTf_2]$ as an ionic liquid (650 mg).

This system was used to explore the hydrogenation/hydrogenolysis of HMF under MP conditions. Two initial sets of experiments were carried out at 60 and 80 °C for 6, 18 and 40 h in each case. The pressure of H_2 was set to 50 bar to ensure/favour the gas solubility in the involved phases, particularly in the viscous IL.

Results are reported in Figure 16. Products were those indicated in Scheme 4 and conversion and products distribution were determined as previously described.

Although conditions (particularly the HMF concentration and the catalyst amount) were not strictly comparable to those used for reactions carried out only in water, the use of the MP-system brought about a decrease of the conversion and most importantly, a significant alteration of the products distribution. At 60 °C, the HMF conversion was slightly enhanced from 50 to 75% when the reaction time was increased from 6 to 40 h.

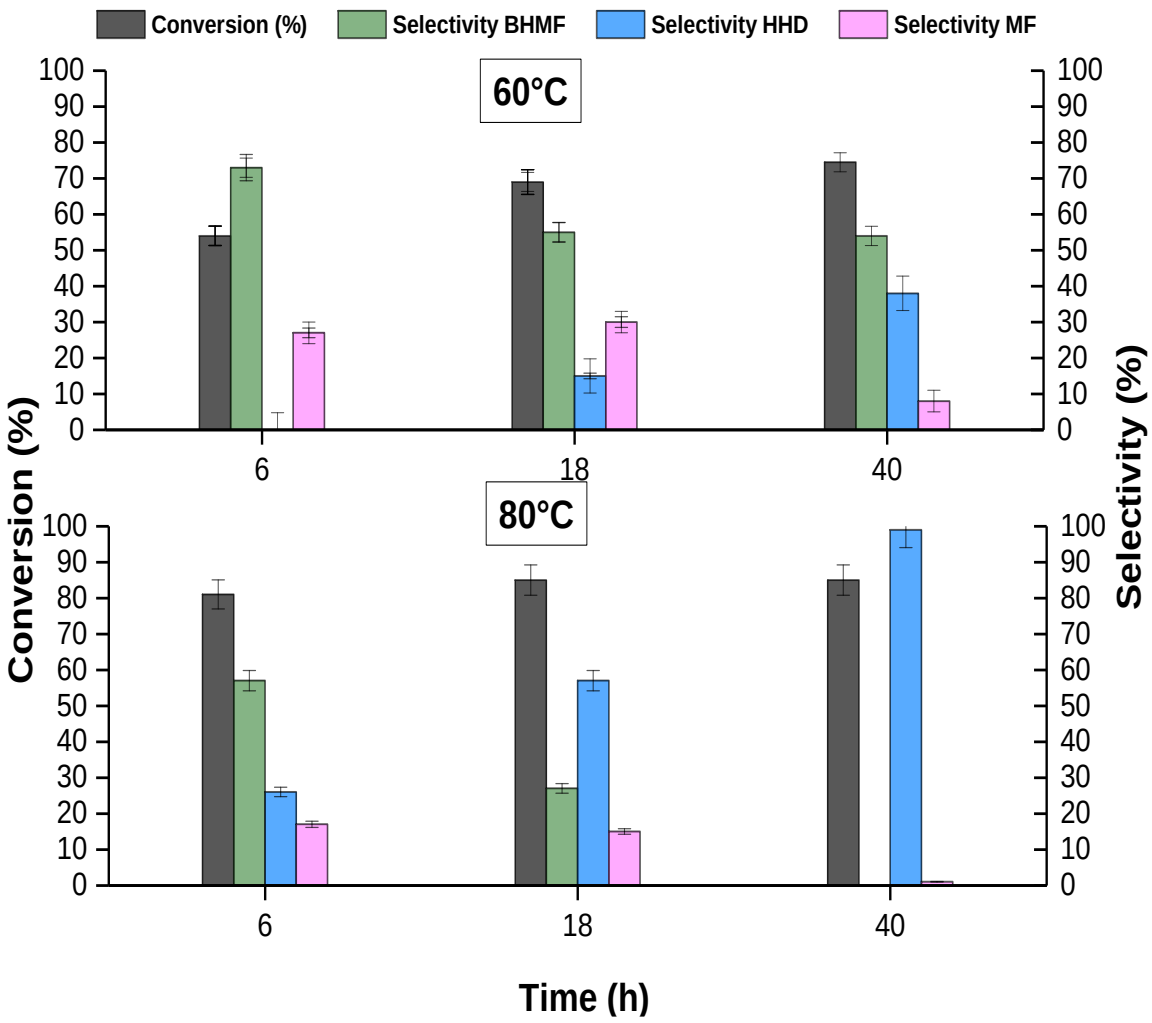


Figure 16. Effects of temperature and time for reactions performed in a multiphase system comprised of aqueous HMF (0.05 M, 10 ml), iso-octane (5 mL), Ru/C (25 mg), and $[P_{8881}][NTf_2]$ (650 mg). Other conditions: $p^0 H_2$ = 50 bar, 60 °C (top) and 80 °C (bottom). Conversion of HMF and product selectivity were obtained as described for Figure 10.

Products from hydrogenolysis and ring opening reactions were obtained in comparatively high amounts, though widely variable with time: the selectivities towards MF and HHD were 28% and 0% after 6 h, and 7% and 39% after 40 h, respectively. By contrast, using water alone, substantially quantitative reactions with the almost exclusive formation of BHMF were noticed at 60 °C (except after 40 h, cfr Figure 12).

The trend was more pronounced at 80 °C, where the conversion reached ca 85% after 18 h, and it did not further improve even for the experiment prolonged to 40 h. Simultaneously, HHD became the predominant (58%) and then, the sole product (99%) after 18 h and 40 h, respectively.

The observed behaviour was ascribable to the presence of the IL-phase. Several previous investigations by our group and by others, clearly demonstrated that the performance of

different active metals (Pd/C, Pt/C, Ru/C, and Raney-Ni) were significantly affected by their confinement in ionic liquids media.[85] The occurrence of polar interactions between the catalyst (mostly through its support) and the IL were claimed responsible for the embodiment of the metal in a dense-viscous environment. Therefore, when a MP-system as that above described, was subjected to energic stirring, the IL acted concurrently as a catalyst-philic phase in close proximity of the active metal sites and as an interfacial boundary layer which mediated the migration of the (liquid and gaseous) reagents and products to and from the catalyst. A pictorial view of this arrangement is shown in Figure 17.

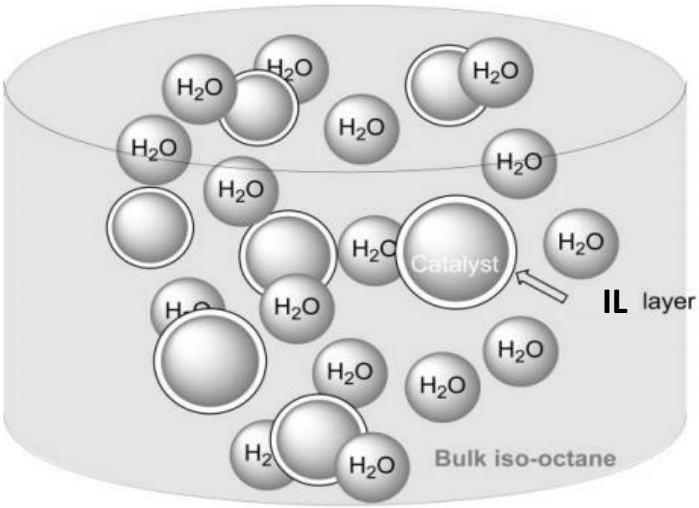


Figure 17. Pictorial view of iso-octane/water/IL multiphase system under stirring (from ref 85)

Under such conditions, the IL was able to influence the adsorption/desorption modes of all reactive species on the catalyst surface, thereby impacting on the reaction outcome in terms of both conversion and products distribution. The better the stirring, the high the interfacial area achieved, the lower the mass transport limitations.

Whatever the mechanism behind the results of our experiments, it should be noted that the hydrolytic ring opening of HMF to HHD was by far more selective under MP-conditions rather than when only aqueous solutions were used (cfr Figure 12, at 80 °C). The synthetic value of this finding prompted us to further investigate the effect of the temperature by designing additional experiments at 100 and 120 °C, respectively, while keeping all other conditions unaltered (aq. HMF: 0,05 M, 10 mL, iso-octane: 5 mL), $[P_{8881}][NTf_2]$: 650 mg; 50 bar of H_2) with respect to Figure 16. Results are summarised in Table 4.

Table 4. The MP-reaction of HMF in water/isooctane system/IL multiphase conditions.
Entries 1-2: reactions were carried out using a multiphase system comprised of an aq. solution of HMF (0.05 M, 10 mL), isooctane (5 mL), and [P_{8881}][NTf_2] (650 mg). The H_2 pressure was 50 bar. Entry 3: same conditions of lines 1-2, except for the catalyst amount, which was doubled. Conversion of HMF and product selectivity were obtained as described for Figure 10.

Entry	T (°C)	t (h)	Cat. (mg)	Conv. (%)	Products (selectivity %)	
					HHD	MF
1	120	18	25	>99	99	1
2	100	18	25	83	99	1
3	100	18	50	>99	99	1

The rise of T to 120 °C brought about the desired enhancement of the conversion, with no side-effects on the selectivity. The reaction was quantitative, and it proceeded with the exclusive formation of HHD after 18 h (entry 1). Under such conditions, however, the catalyst did not appear neatly confined in the IL-phase and the end of the experiment. The reasons for this behaviour were not investigated, but a partial degradation of the IL due to the combined (and prolonged) action of the temperature and the acid environment , was not ruled out.[104]

Further optimisation tests were then carried out at 100 °C where the catalyst separation in the MP-system was excellent before and after the reaction. The best result is shown in Table 4, line 3: full conversion and 99% selectivity to HHD were achieved after 18 h, providing that the catalyst amount was doubled (50 mg).

Encouraged by this excellent outcome, the conclusive part of this study was focused on exploring the potential of MP-conditions for the recycling of the catalyst and the isolation of the product. It should be noted that one of the synthetic challenges reported by the (few available) methods for the preparation of HHD is its extraction/purification from aqueous solutions.[70]

3.1.7 Recycle and leaching tests of Ru/C in the multiphase system

Tests for the recycling and reuse of the catalyst were designed under the conditions of line 3 of Table 4 ([HMF]= 0.05 M, 50 mg Ru/C, 50 bar, 100°C, 18 h). The following procedure was used: once a first reaction was complete (run 0), the aqueous solution was removed, and the remaining phases of IL (with the confined catalyst) and isooctane were washed with milli-Q water (2x10 mL). Thereafter, a fresh aqueous HMF solution (0.05 M, 10 mL) was added to the system and a second reaction was started at 100 °C and 50 bar. Four subsequent runs were

performed in this way (further details are in the experimental section). The results are reported in Figure 18.

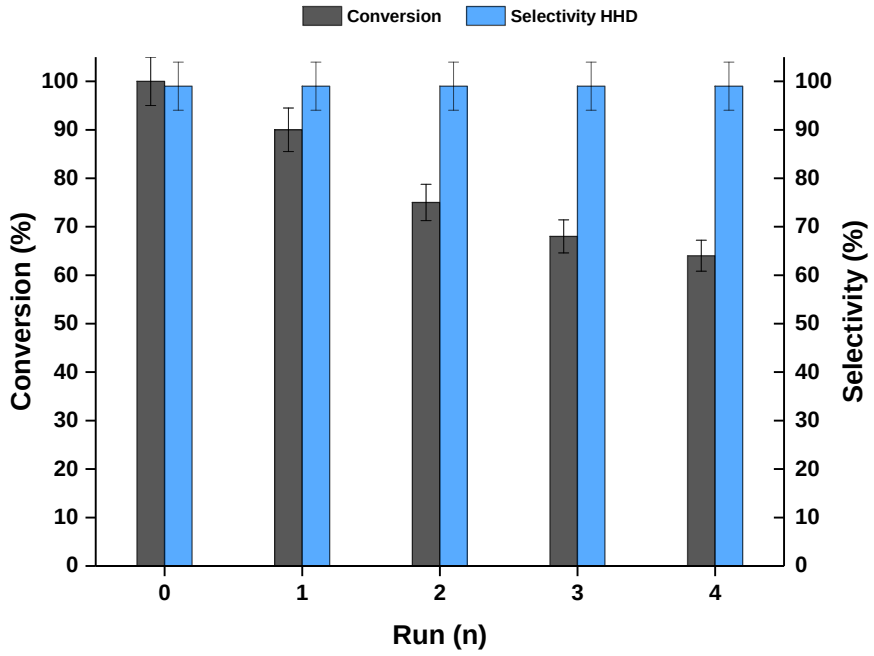


Figure 18. Recycle of Ru/C in five subsequent runs in the hydrogenation of HMF. Conditions: [HMF]= 0.05 M in 10 mL of deionized water, Ru/C= 50 mg, $[P_{8881}][NTf_2]$= 650 mg, iso-octane= 5 mL, T= 100°C, p^0H_2= 50 bar, t= 18h. Conversion of HMF and product selectivity were obtained as described for Figure 10.

The catalyst appeared steadily segregated in the IL-phase at the end of each test. After the first quantitative reaction (run 0), the conversion of HMF progressively decreased to 64%, during the recycling tests, clearly indicating that the catalyst was subjected to a partial deactivation from one (re)use to another. The selectivity toward HHD however, remained steady at 99%. This trend was not observed in previous investigations of our group of different multiphase reactions including the hydrogenation of levulinic acid, the hydroformylation of alkenes, or the hydrodechlorination of aromatics, catalysed by Ru/C, Pd/C and Pd- or Rh-nanoparticles.[85,86,87,105,106] In all these cases, recycling and reuse of active metals confined/stabilised by an IL (based on onium salts as for example, trioctylmethylammonium chloride or trioctylmethylphosphonium bistriflimide), were effective without any loss of their performance.

To verify whether the drop of the catalytic activity was due to metal leaching, the aqueous phases recovered after at the end of experiments of lines 2 and 3 of Table 4, were analysed by ICP (MP-AES; details are in the experimental section). Results are summarized in Table 5.

Table 5. ICP-analysis of spent aqueous phases recovered after multiphase reactions of HMF. [a] Weight % of metal dissolved in water with respect to the amount of Ru in the catalyst used for the reactivity tests.

Entry	Reaction parameters	Ru (ppm)	% wt[a] Ru
1	Ru/C= 25 mg, 50 bar H_2, 60°C, 40 h	0,21	0,17
2	Ru/C= 25 mg, 50 bar H_2 100°C, 18 h	0,15	0,12
3	Ru/C= 50 mg, 50 bar H_2 100°C, 18 h	0,02	0,01

A not-negligible variability was noticed between the two analysed solutions with results differing by an order of magnitude from each other. Notwithstanding this inconsistency, the amount of leaching was so small, from 0.01 to 0.2 wt % of the total Ru, that the above-described decrease of catalytic activity was hardly imputable to a loss of the active metal. We rather suspected that the effect was due to the presence of poisoning impurities in the reactant HMF which co-adsorbed on the catalyst surface. This will the subject of future studies.

3.2 Hydrogenation of HMF in the continuous flow mode

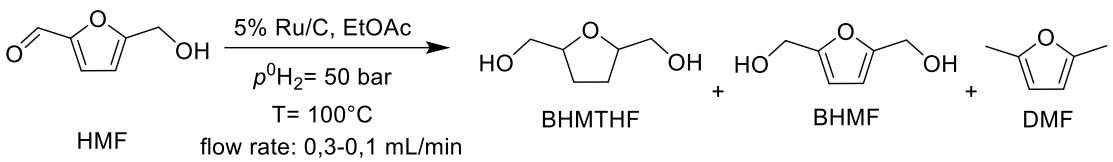
This part of the Thesis work was carried out during a 3-months stage at the University of Cordoba (Spain) under the supervision of Prof. Rafael Luque. Experiments were all performed using an H-Cube® apparatus whose features have been described in the introduction and in the experimental sections.

3.2.1 Initial screening test: effect of the flow rate

The continuous-flow (CF) hydrogenation/hydrogenolysis of HMF was explored under conditions as close as possible to those used in the batch mode, in order to compare the two methodologies. Initial tests were run at 100°C, p^0H_2= 50 bar, using a solution of HMF in ethyl acetate (EtOAc; 0.05 M) that was delivered at two flow rates (F) of 0.1 and 0.3 mL/min, respectively, to a catalytic bed of 5% Ru/C (0.3 g). The catalyst was loaded in a 70 mm cartridge

(CatCart®) which was an essential component of H-Cube® (Figure 19Figure 9). The selection of CF-conditions also took advantage from previous recent work of the Cordoba group on the hydrogenation of HMF derivatives as 5-methoxymethylfurfural (MMF).[110] Unfortunately, water could not be as a solvent because it was not compatible with the available analytical equipment (GC and GC/MS).

The CF-reaction provided BHMF and BHMTHF as products from the hydrogenation of the carbonyl and both the carbonyl and the furan ring respectively, and DMF coming from the hydrogenation/hydrogenolysis of the alcohol groups from HMF (Scheme 9).



Scheme 9. The CF-hydrogenation/hydrogenolysis of HMF at 100 °C and 50 bar in EtOAc as a solvent

Figure 19 reports the results by showing the effect of the time-on-stream on the conversion and selectivity to BHMTHF, BHMF and DMF. Both conversion and selectivity were calculated from GC-analyses, as described for batch reactions in previous paragraphs.

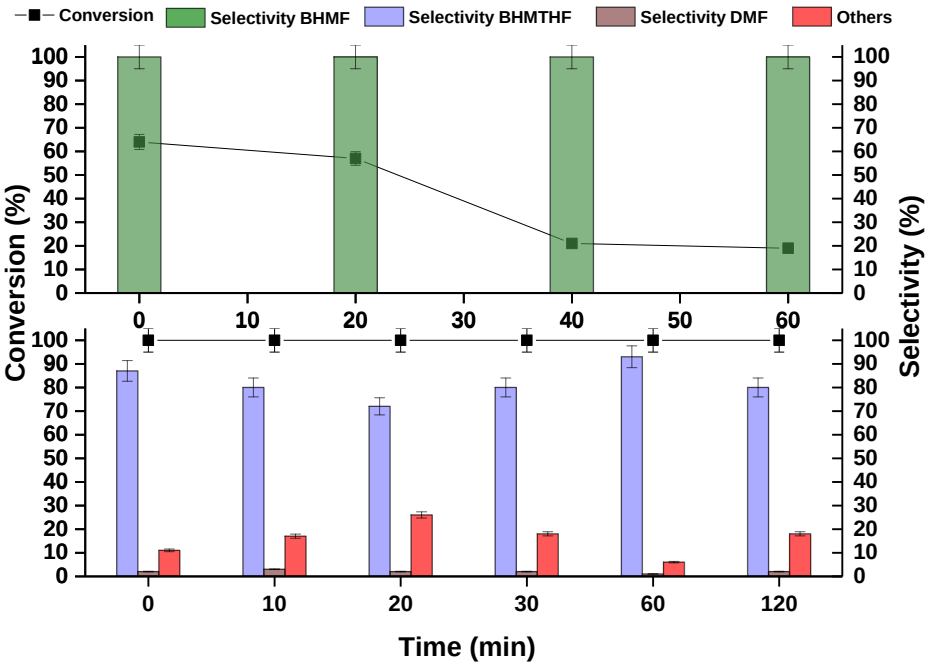


Figure 19. HMF hydrogenation in continuous flow mode. Conditions: $p^0 H_2$ = 50 bar, T= 100°C, HMF in EtOAc (0.05 M), Ru/C (0.3 g) in a CatCart® capsule. Top: flow rate= 0.3 mL/min; bottom: flow rate= 0.1 mL/min.

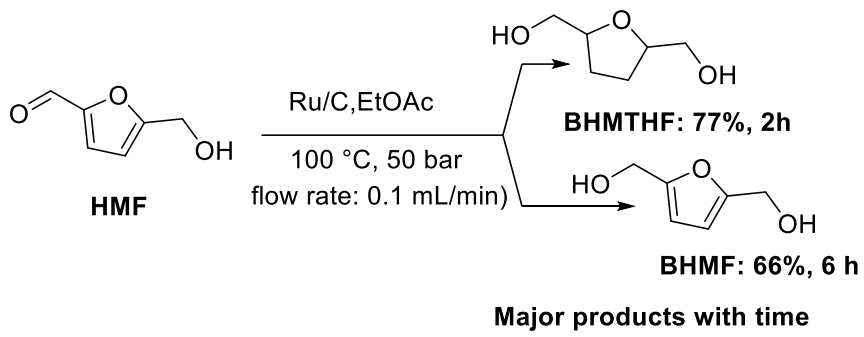
At F=0.3 mL/min, a rapid decreased of conversion with time, from 65% at t_0 (when the first sample was collected at the outlet of H-Cube® after ca 18 min from the start of flowing the mixture in the apparatus), to less than 20% at t_{60}, after 1 h of reaction. By contrast, the selectivity to BHMF was 100% throughout the experiment (top; other details on the sampling of the reaction mixture are reported in the experimental section).

By reducing the flow rate to 0.1 mL/min, a steady quantitative conversion was obtained for 120 min. However, as a result of the higher contact time, the onset of hydrogenolysis reactions of HMF brought about the formation of dimethylfuran (DMF: 5%) along with the hydrogenation product, BHMTHF, which became under these conditions the major derivative (75-90%; bottom). Minor unidentified side-compounds were also detected.

3.2.2 The effects of time-on-stream and HMF concentration

With the aim of exploring the effect of time-on-stream, prolonged CF-experiments were carried out for 6 h under the conditions of Figure 19 (bottom: F=0.1 mL/min). Figure 20 shows the results.

Albeit the conversion continued to remain quantitative, the products distribution completely changed after 6 h compared to the previous results achieved at 2 h. Particularly, the less hydrogenated derivative BHMF (66%; from reduction of HMF carbonyl function) was observed at the expenses of BHMTHF whose selectivity dropped to 18% (Scheme 10). The relative amount of side-products indicated as "others" did not vary appreciably with time, oscillating in the range of 12-18%. This trend highlighted a diminishing of the hydrogenation performance of the catalyst, thereby indicating that saturation or deactivation phenomena were plausible in the long run.



Scheme 10. Products distribution of HMF hydrogenation in the continuous flow mode at F= 0.1 mL/min at 2 and 6 hours.

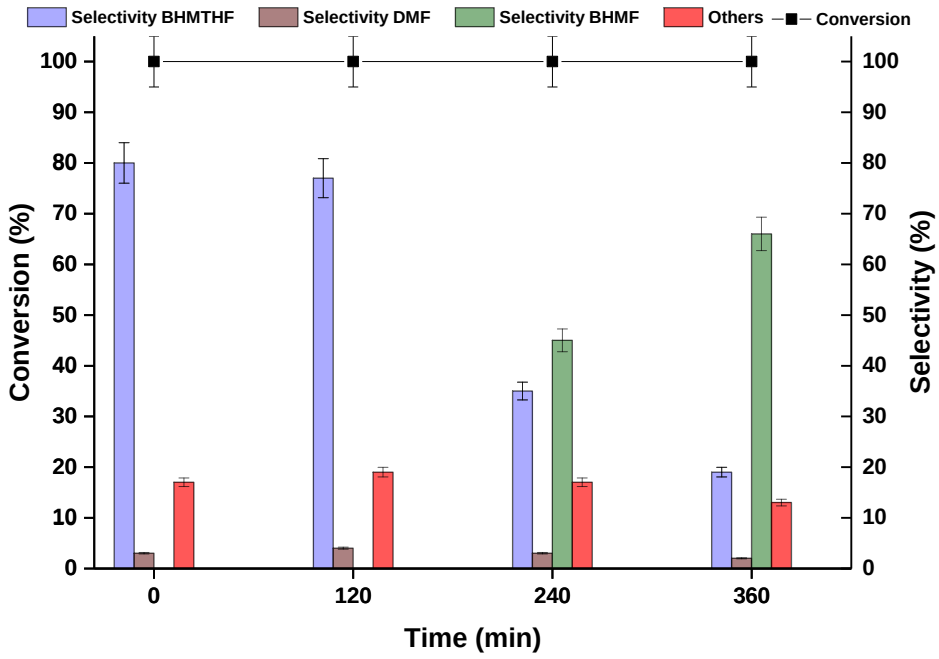


Figure 20. HMF hydrogenation in the continuous flow mode. Conditions: $p^0 H_2$ = 50 bar, T= 100°C, HMF in EtOAc (0.05 M), Ru/C (0.3 g) in a CatCart® capsule, flow rate= 0.1 mL/min. The cConversion of HMF was obtained with a calibration curve from GC-FID analysis, while the products selectivity was calculated from % area response by GC.

Experiments carried out by halving the HMF concentration (0.025 M) and varying the flow rate between 0.1 and 0.3 mL/min, led to the same conclusions. Results are illustrated in Figure 21. At F=0.1 mL/min, the progress of the reaction was comparable to that previously observed (at [HMF] = 0.05 M). The fully hydrogenated product, BHMTHF, was the major product up to 79%, for the first 3 h. Then, BHMF started to form and its amount gradually increased to 35% after 6 h. The conversion was quantitative throughout the test.

When the flow rate was increased to 0.3 mL/min, not only the conversion rapidly dropped from 100 to 65% after 120 min, but in the same time interval, the selectivity changed in favour of the less hydrogenated BHMF which became the predominant product (90%). Again, results suggested a deactivation/saturation of the catalyst with time.

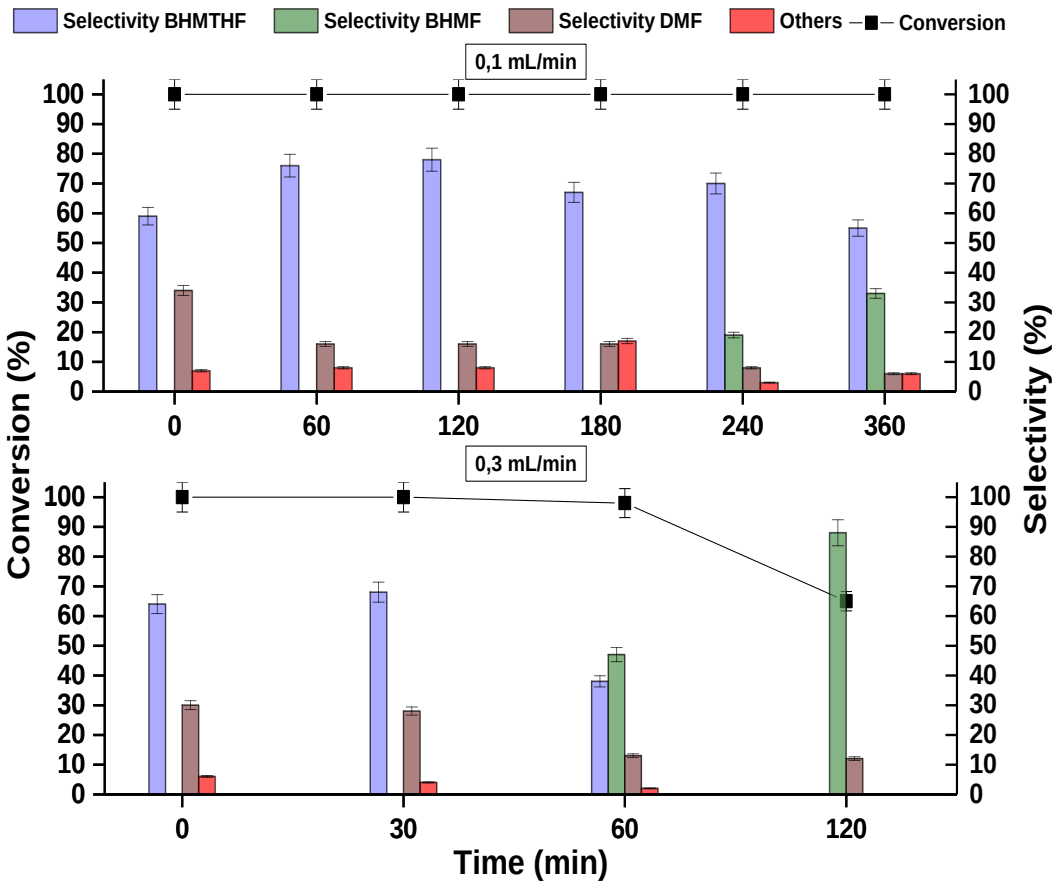


Figure 21. HMF hydrogenation in the continuous flow mode. Conditions: $p^0 H_2$ = 50 bar, T= 100°C, HMF in EtOAc (0.025 M), Ru/C (0.3 g) in a CatCart® capsule, flow rate= 0.1 mL/min (top); flow rate= 0.3 mL/min (bottom). The conversion of HMF was obtained with a calibration curve from GC-FID analysis, while the products selectivity was calculated from % area response by GC.

3.2.3 Effect of the solvent

Tetrahydrofuran (THF) and ethanol were considered as alternative solvents for the CF-reaction of HMF. Tests were carried out under conditions by which our previous experiments showed complete conversion for a relatively long reaction time (up to 6 h) and a moderate formation of by-products. Accordingly, reactions were run at 100 °C and 50 °C for 6h, F= 0.1 mL/min, and using 0.05 M solutions of HMF in both THF or EtOH, respectively, in place of ethyl acetate. Results are reported in Figures 22 and 23 for THF and EtOH, respectively.

In the presence of THF as the solvent, the formation of BHMTHF gradually increased, with a selectivity ranging from 57% at t_0 to a steady value of ca 80 at t_{360}. The conversion however, significantly decreased from 100% to 48% in the same time interval.

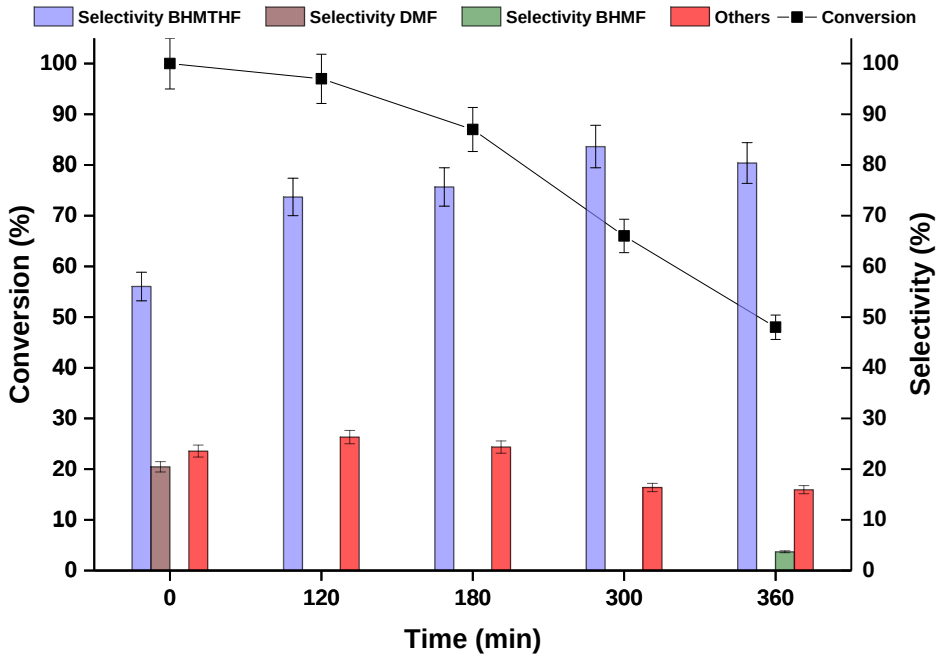


Figure 22. HMF hydrogenation in the continuous flow mode. Conditions: $p^0 H_2$ = 50 bar, T= 100°C, HMF in THF (0.05 M), Ru/C (0.3 g) in a CatCart® capsule, flow rate= 0.1 mL/min. The conversion of HMF was obtained with a calibration curve from GC-FID analysis, while the products selectivity was calculated from % area response by GC.

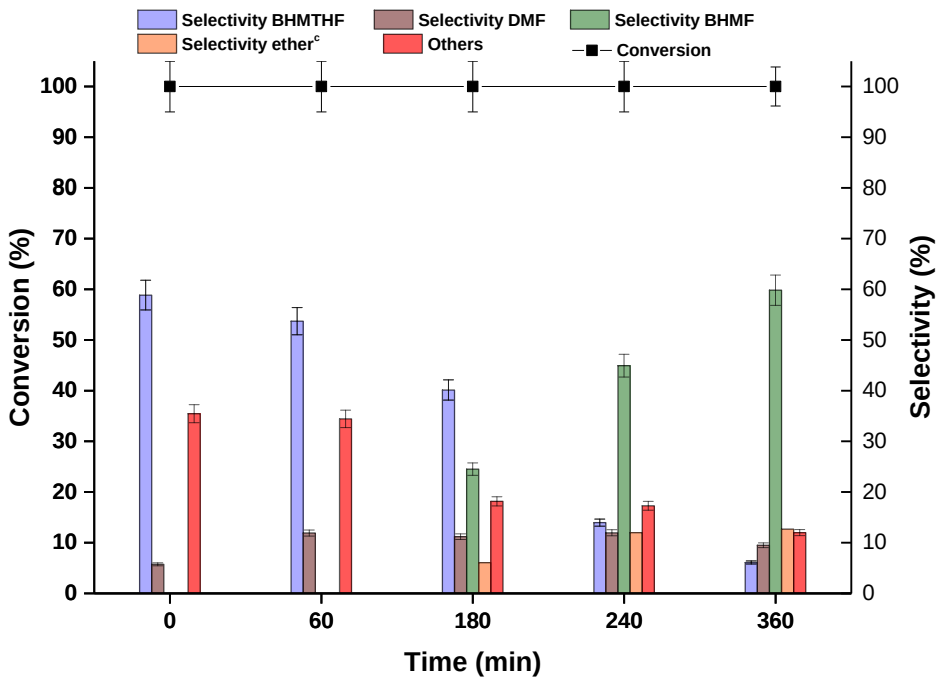


Figure 23. HMF hydrogenation in the continuous flow mode. Conditions: $p^0 H_2$ = 50 bar, T= 100°C, HMF in EtOH (0.05 M), Ru/C (0.3 g) in a CatCart® capsule, flow rate= 0.1 mL/min. The conversion of HMF was obtained with a calibration curve from GC-FID analysis, while the products selectivity was calculated from % area response by GC.

The use of ethanol as the solvent resembled that of ethyl acetate, albeit some differences were appreciated. The conversion of HMF was always quantitative during the explored time interval. BHMTHF was the initial major product (55-58%), though its formation was accompanied by the presence of a relative high amounts of side-products ("others": ca 35%). After the first 3 h, both BHMTHF and "others" decreased in favour of the less hydrogenated derivative BHMF whose selectivity raised up to 60% at 6 h. Notably, under this conditions, BHMF underwent a partial etherification with ethanol yielding 2-(hydroxymethyl)-5-(ethoxymethyl)furan (13%, Figure XX), which was identified among products in the reaction mixture.

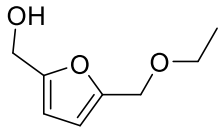


Figure 24. 2-(hydroxymethyl)-5-(ethoxymethyl)furan

No further investigations of the CF-reaction of HMF were carried out using the H-Cube® system. Although only preliminary results were obtained, some conclusions could be drawn. The formation of partially hydrogenated products, particularly BHMF, was preferred at the low residence time (τ=2.6 min) achieved with a flow rate of 0.3 mL/min. These conditions favoured also side reactions of hydrogenolysis yielding comparably high amounts of undesired compounds ("others"). As expected, when τ was increased (8 min at 0.1 mL/min), the fully hydrogenated product, BHMTF, was predominant. The solvent also induced significantly different reaction outcomes with ethyl acetate and ethanol that allowed a steady conversion compared to THF, but a quicker change of selectivity as well.

Varying the HMF concentration in the range of 0.025-0.05 M did not result in significant improvements in the reaction outcome, except for increasing (at 0.05 M) or decreasing (at 0.025 M) the time at which the products distribution changed in the direction of favouring partially hydrogenated derivatives. Indeed, this variation of the selectivity was the major issue of the CF-reaction, consistent with a plausible loss of hydrogenation activity of the catalyst.

At our present stage of knowledge of the process, it is difficult to formulate any explanation for the observed behaviour, though degradation of HMF or its derivatives and the formation of carbonaceous deposits on the catalyst surface might play a role. Future studies will work on this hypothesis.

4. CONCLUSIONS

The poor stability of HMF, plausibly responsible for the variable purity of commercial samples, together with the presence of acid impurities are major issues when studying the reactivity of this compound. Moreover, also hydrogenation derivatives of HMF prove sensitive to chemical modifications with time, and their isolation is often complicated. These drawbacks were encountered in this study and it was not always possible to find proper solutions. One example has been the determination of the reaction selectivity, and consequently, of the carbon balance. Although the comparison to literature works, made plausible the choice of using GC-responses as area % to calculate the products distribution in this Thesis work, a standard GC-calibration procedure was not implemented because reaction products as BHMF, could not be obtained in a pure form and/or in high enough amounts. In addition to the many attempts already carried out, further strategies will be designed in the future to overcome this difficulty. Notwithstanding these aspects, the investigation has highlighted some salient features of the reaction of aqueous solutions of HMF under a H_2 pressure and with a commercial 5% Ru/C as a catalyst. It has been demonstrated how the selective formation of two different products as BHMF and HHD can be tuned by the reaction conditions, and interestingly, for the first time, the synthesis of HHD has been described in an ionic liquid assisted multiphase system.

The reaction temperature is the most critical parameter to steer the conversion/selectivity, while the pressure of H_2 has a less impact providing that it is above 30 bar. In line with the many reported papers on the subject, BHMF has been obtained as an almost exclusive product (95%) from the partial hydrogenation of aq. solutions of HMF at 40-80 °C. However, it has been noticed that the increase of T to 100-120 °C favoured the hydrolytic ring opening of HMF yielding HHD as the sole derivative at complete conversion. A further analysis of the reaction system has proved that the selectivity shift from BHMF to HHD was likely due to the combined effects of the temperature and acid impurities in the reactant HMF. This hypothesis, though plausible, will be investigated in the future to clarify the acidity level of aqueous HMF solution necessary for the reaction to occur. Whatever the role of acidity, the result has prompted us to transfer the process from a single aqueous solution to a multiphase system comprised of three immiscible phase including water, isooctane and an ionic liquid (trioctylmethylphosphonium bis(trifluoromethane)sulfonimide: $[P_{8881}][NTf_2]$). The multiphase

system has proven excellent not only to achieve the same high conversion and selectivity observed in the aqueous solution alone, but to allow the catalyst/product separation, being Ru/C and the product (HHD) perfectly segregated in the IL and water, respectively. At the present stage, however, recycling of the catalyst showed a partial drop of its performance after few (5) repeated reactions. This will be another subject for future studies.

The hydrogenation/hydrogenolysis of HMF has been studied also in the continuous-flow mode using a H-Cube® apparatus. The very preliminary results achieved so far, suggest that the catalytic bed (Ru/C on a preformed cartridge specifically supplied for the H-Cube®), undergoes deactivation in a few hours (6 h) at 100 °C and 50 bar of H_2. Any hypothesis for this behavior would be conjectural due to the few data available.

5. EXPERIMENTAL PART

5.1 Materials and instruments

Part of the work carried out at Ca' Foscari University, Venice, Italy

All chemicals were purchased from Sigma Aldrich and used without any further purifications. Water was milli-Q grade. H_2 and N_2 gases were purchased from SIAD, Italy.

GC/MS (electron ionization, EI, 70 eV) and GC-FID (flame ionization detector) analyses were performed with a Perkin Elmer Elite 624 column, (L= 30 m, ø= 0,32 mm, film= 1,8 µm).

The same method was used for both the instruments: 50 °C for 2 min., 25°C/min, 150°C for 15 min., 20°C/min, 240°C for 2 min.

^{1}H NMR spectra were recorded at 400 MHz and 300 MHz, ^{13}C NMR were recorded at 100 MHz and ^{31}P NMR were recorded at 161 MHz. Chemical shifts are reported downfield from tetramethyl silane (TMS) and $CDCl_3$ or DMSO-d_6 were used as the solvents.

ICP analysis were performed with Agilent 4210 MP-AES at λ= 372.8 nm.

pH measure was performed with Microprocessor pH meter pH 211 HANNA instruments equipped with a glass electrode, at 19.4°C, after a calibration with buffer solutions at ph= 7, 4 and 10.

Part of the work carried out at Cordoba University, Cordoba, Spain

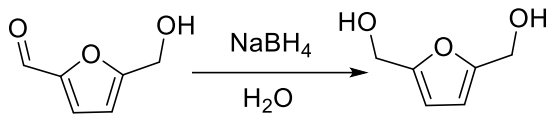
All chemicals were used without any further purification. Hexane, ethyl acetate, tetrahydrofuran and methanol were purchased from Panreac. HMF and BHMTHF were purchased from Sigma Aldrich. Pd/C and Ru/C CatCart® were purchased from ThalesNano.

Continuous flow hydrogenation reactions of HMF were carried out in a ThalesNano H-Cube® Mini Plus.

GC-FID analyses were performed with an HP-5 capillary column (L=30 m, ø= 0,32 mm, film= 0,25 µm) with the method: 105°C for 2 min., 20°C/min, 150°C for 3 min., 25°C/min, 210°C for 3 min.; and Restek Rt®-yDEXsa (L=30 m, ø= 0,25 mm, film= 0,25 µm) with the method: 60°C for 3 min., 20°C/min, 170°C for 10 min.

GC/MS analyses were performed with an HP-5 MS ultrainert (L= 30 m, ø= 0,25 mm, film= 0,25 0,25 µm) with the method: 50°C for 1 min., 10°C/min, 230°C for 10 min.

5.2 Synthesis of 2,5-bishydroxymethylfurane (BHMF)



BHMF was at first synthetized with a stoichiometric reductant following the procedure reported in literature[107] to use it as standard for the following experiments. 1,26 g (10 mmol) of HMF were dissolved in 20 mL of H_2O mQ in a round bottom flask. A solution of 0,38 g (10 mmol) of $NaBH_4$ in 4 mL of H_2O was prepared and then added dropwise to the HMF solution under vigorous stirring, keeping the reaction in a water bath at room temperature for 2 hours (the reaction is exothermic).

The product was extracted with 50 mL of ethyl acetate (EtOAc) in four times and the organic solution was analysed at GC-FID. The conversion resulted complete.

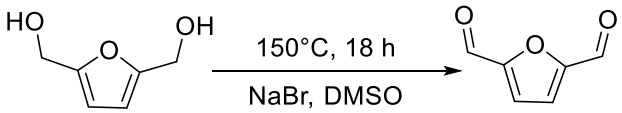
EtOAc was removed by rotary evaporation and then with vacuum pump and a white solid was obtained (yield 50%).

The isolated product was analysed by GC-MS and NMR spectroscopy:

GC/MS (relative intensity, 70 eV) m/z: 128.0 (55), 111.0 (15), 109.0 (28), 97.0 (100), 69.1 (22), 55.0 (16), 53.1 (13), 44.0 (11), 41.0 (28).

^{1}H NMR in $CDCl_3$ (400 MHz) δ(ppm): 9,57 (s, 1H, CHO), 7,22-7,21 (d, J (H,H) 3,7 Hz, 1H), 6,52-6,50 (d, J (H,H) 3,6 Hz, 1H), 4,71 (s, 2H), 2,58 (s, 1H, OH).

5.3 Synthesis of 2,5-diformylfurane (DFF)



DFF was synthetized[108] to have a standard of the oxidation product, in order to verify its presence during the following experiments.

0,126 mg (0,1 mmol) of 2,5-hydroxymethylfurfural (HMF) were dissolved in 2 mL of dimethyl sulfoxide (DMSO) in a round bottomed flask provided with a magnetic stirrer and a reflux condenser.

0,34 mg (0,3 mmol) of NaBr were added to the reaction mixture. The solution was heated at 150°C with an oil bath for 18 h, vigorously stirring. At the end of the reaction time the mixture assumed a strong brown colour and an intense sulfuric smell.

After cooling the reaction to room temperature, 50 mL of EtOAc were added. The products were extracted with water (20 ml for three times) to separate them from DMSO sub products (dimethyl sulphide) and then again extracted with EtOAc from the aqueous phase to eliminate the residual salts.

The organic phase was analysed at GC-FID and GC-MS.

DFF was isolated from flash chromatography using SiO_2 and petroleum ether:EtOAc, 60:40, as an eluent. It was then characterized by ^1H spectroscopy.

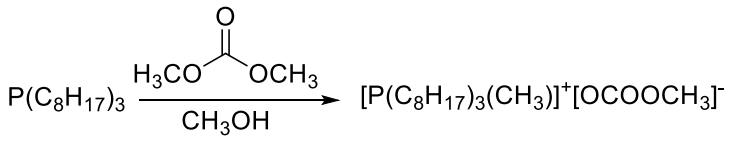
GC/MS (relative intensity, 70 eV) m/z: 125,0 (7,0), 124,0 ([M^+] 100,0), 123,0 (60,0), 95,0 (26,0), 39,1 (25,0), 38,1 (12,0), 37,1 (7,0).

^{1}H NMR in CDCl3 (400 MHz)δ(ppm): 9,87 (s, 2H, CHO), 7,33 (s, 2H).

5.4 Synthesis of Ionic Liquid Trioctylmetilphosphonium bis(trifluoro-methane)-sulfonimide ([P_{8881}][NTf_2])

The synthesis is divided into two steps[109]: 1) the synthesis of trioctylmethyl phosphonium methyl carbonate and 2) the anion exchange with lithium bis(trifluoromethane)sulfonimide salt.

5.4.1 Quaternarization of trioctyl phosphine with dimethylcarbonate to [P_{8881}][MC]



25 mL (20,8 g, 56 mmol) of trioctyl phosphine, 30 mL (32,1 g, 356 mmol) of dimethylcarbonate and 30 mL of methanol were added to a 200 mL jacketed sealed steel autoclave provided with a magnetic stirrer.

The autoclave was closed and purged with three cycles of freeze-pump-thaw: it was firstly immersed in a dewar filled with liquid nitrogen.

When the liquid inside of it was completely frozen, it was purged with three nitrogen-vacuum cycles, leaving it under vacuum. The liquid was then thawed by immersing the autoclave in hot water, and the gases dissolved into the liquid occupied again the empty volume of the autoclave.

After freezing again, the liquid phase, the residual gases were once more extracted.

This procedure was repeated for three times, leaving at the end the autoclave under nitrogen atmosphere.

This methodology is very important because trioctyl phosphine is an air sensitive compound and it can be easily oxidized to trioctyl phosphine oxide.

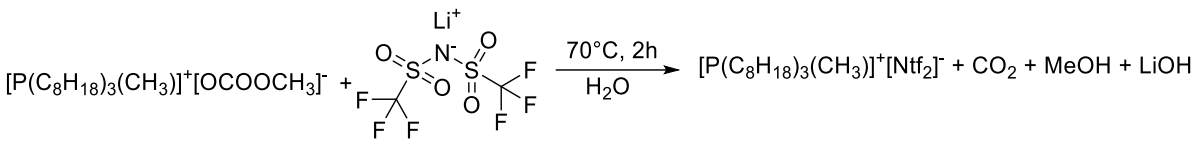
The system was therefore heated by oil circulation at 140°C for 20 h. After cooling it at room temperature, the mixture was transferred to a round bottom flask and the residual of DMC and methanol was removed by rotary evaporation and then by high vacuum pump.

Before proceeding with the anion exchange the product was analysed by NMR spectroscopy.

^{1}H NMR in DMSO-d_6 (400 MHz) δ(ppm): 3,171 (s, 3H, CH_3-OCOO), 2,152 (m, 6H), 1,799-1,764 (d, J (P,H)= 14,0 Hz, 3H, CH_2-P), 1,466 (m, 6H), 1,373 (m, 6H), 1,274 (br m, 24H), 0,86 (t, 9H, CH_3).

^{31}P NMR in DMSO-d_6 (161 MHz) δ(ppm): 32,30 (s, 1P).

5.4.2 Anion Exchange with $LiNTf_2$



26,84 g (0,058 mol) of $[P_{8881}][MC]$ were dissolved in 150 mL of H_2O mQ; 16,725 g (0,058 mol) of $LiNTf_2$ were dissolved in 100 mL of H_2O mQ and it was added to the ionic liquid solution in a 500 mL round bottom flask.

The reaction mixture was heated at 70°C and kept under stirring for two hours. The mixture becomes white while the new ionic liquid, insoluble in water due to the lipophilic character of NTf_2, is forming.

After cooling the reaction to room temperature, $[P_{8881}][NTf_2]$ was extracted with CH_2Cl_2 several times until the water phase appeared clear.

The organic solvent was then removed with rotary evaporation and in high vacuum pump.

$[P_{8881}][NTf_2]$ appeared as a transparent viscous liquid was then characterized by NMR spectroscopy.

^{1}H NMR in $CDCl_3$ (400 MHz) δ(ppm): 2,12 (m, 6H, CH_2-P), 1,81-1,77 (d, J(P,H)= 13,2 Hz, 3H, CH_3-P), 1,48 (m, 12H), 1,27 (br m, 24H), 0,88 (t, 9H, CH_3).

^{31}P NMR in $CDCl_3$ (161 MHz) δ(ppm): 31,39 (s, 1P).

5.5 General procedure for hydrogenation of Hydroxymethyl Furfural (HMF) in multiphasic batch system

The proper amount of 5% wt. Ru/C (50 or 25 mg) was weighed and added to a 25 mL tubular reactor of borosilicate glass (Pyrex) equipped with a magnetic stirrer. It was then charged with an aqueous solution of HMF with the proper concentration (0,2 or 0,05 M). When the biphasic

system was employed, 5 mL of iso-octane were added and when the multiphasic system was used, also 0,65 g (1 mmol) of $[P_{8881}][NTf_2]$ were charged to the mixture.

The reactor was closed with a pierced lid and the vessel was placed in a jacketed steel autoclave equipped with a manometer and two needle valves by which, at room temperature, H_2 was admitted at the desired pressure (5-50 bar). The autoclave was then heated at the desired temperature by oil circulation (40-120°C) and the mixture was stirred at 1300 rpm.

After the proper time the autoclave was cooled at room temperature immersing it in a cool water bath and then purged.

0,5 mL of the aqueous phase was collected, after the filtration on Celite®545 to avoid the passage of Ru/C particles and then added to 0,5 mL of a 0,01 M aqueous solution of diethylene glycol dimethyl ether (diglyme) used as an external standard.

The mixture was analysed by GC-FID to determine the conversion of HMF and the selectivity toward the products. The conversion of HMF was determined by calibration with standard solutions (Figure 40).

To qualitatively identify the products, GC/MS was used.

5.5.1 Isolation and identification of HHD

The mixture of products obtained from HMF hydrogenation in batch system at the proper condition to reach the maximum value of HHD (deduced from GC-FID analysis) was firstly extracted with EtOAc, then dried with rotary evaporation. The solid residual was eluted on a flash column made of SiO_2 with diethyl ether (Et_2O) as the eluent.

HHD was so isolated and identified at GC/MS and NMR spectroscopy.

GC/MS (relative intensity, 70 eV) m/z: 99,1 (100,0), 71,0 (16,0), 43,1 (98,0).

^{1}H NMR in $CDCl_3$ (400 MHz) δ(ppm): 4,33 (s, 2H), 2,84 (t, 2H), 2,63 (t, 2H), 2,19 (s, 3H).

^{13}C NMR in $CDCl_3$ (100 MHz) δ(ppm): 208,64 (s, 1C, C=O), 206,55 (s, 1C, C=O), 68,35 (s, 1C), 37,02 (s, 1C), 31,87 (s, 1C), 29,83 (s, 1C).

5.5.2 Catalyst recycle procedure

At the end of the reaction the glass reactor containing the multiphase system (aqueous solution/IL + Ru/C/*iso*-octane) was extracted from the autoclave and the pierced lid was replaced with a septum. A long needle (A) was inlaid to the septum, until the bottom of the

reactor, in order to touch only the aqueous phase. A second (shorter) needle (B) was inlaid and connected to a N_2 valve with a tube. A third needle (C) was inlaid and let open, used as a relief valve. Needle A was bent (Figure 25) in order to collect the solution coming out of it. N_2 valve was opened and thanks to the pressure, the aqueous phase started to go up the needle A. When all the aqueous phase was subtracted to the system, a fresh amount of water mQ (2x10 mL) was added from needle A with the help of a syringe. The system was stirred in order to wash the catalyst and to recover the rest of the previous reaction, for one hour. After the separation of the phases, the water was removed with the same method and a fresh amount of HMF solution (10 mL) was added with the syringe. The needles were removed, and needle A was cleaned from Ru/C residues in the *iso*-octane phase. The reactor was closed with the pierced lid and placed in the autoclave, charged with H_2 and heated at the desired temperature for the proper amount of time.

Figure 25. The system employed to recycle the catalyst.

5.5.3 Leaching tests

Leaching tests were performed using an Agilent 4210 MP-AES Microwave Plasma Atomic Emission Spectroscopy. The primary ionization excitation wavelength signal centred at λ= 372.8 nm. was selected to detect Ru.

A calibration curve (Figure 41) was obtained using seven standard solution containing 0, 0.05, 0.1, 0.25, 0.5, 1, 2.5 ppm of Ru in a 10% HCl aqueous solution. The solutions were prepared by dilution of a 1000 mg/L standard solution of $RuCl_3$ in HCl 10%. Each analysis was repeated five times.

The linear fit was automatically calculated by the software resulting with intercept= 8,54854, slope= 18406,12114 and correlation coefficient= 0,99995.

Samples of two different reaction mixtures were analysed. The reactions were conducted with the water/IL/*iso*-octane multiphasic system and the samples were collected with the system described in "catalyst recycle procedure" section. The reaction parameters in particular for each sample are:

1) HMF 0,05 M, Ru/C 25 mg, 100°C, 50 bar H_2, 18h.
2) HMF 0,05 M Ru/C 50 mg, 100°C, 50 bar H_2, 18 h.

A solution of HMF 0,05 M was analysed and used as blank.

The value of Ru recorded for each analysis was the average of five subsequent acquisitions.

5.6 Hydrogenation of HMF in continuous flow reactor

H-Cube® Mini Plus reactor (Figure 9) is made of:

- An hydrogen generator
- An HPLC pump that introduces the solvents or the mixtures inside the reactor, where they are mixed with hydrogen
- A computer that sets the reaction temperature, the flow rate and the hydrogen pressure
- A packed column (CatCart®) containing the solid catalyst, where the reaction takes place.
- A vial to collect the products

In a typical experiment[110] H-Cube® Mini Plus, with a 70 mm CatCart® containing 0.3 g of 5% Ru/C was firstly flushed with methanol (MeOH) and then with the solvent used for the reactions (EtOAc, THF, EtOH), (0,1 mL/min for 1h at room temperature). After the washing, a

solution of HMF at the proper concentration, with cyclohexane as an internal standard, was pumped through the instrument to rinse it, then the desired conditions of temperature, pressure and flow rate were set up. Once the system was stable, and after waiting the time corresponding to the dead volume of the instrument, so that the solution sampled could pass through the catalyst at the right conditions, the sampling began.

The samples were then analysed at GC-FID. The conversion of HMF was determined by calibration with standard solutions (Figure 38 and 39). The principal products could be identified with GC-MS and confirmed with standards (BHMF, DMF, BHMTHF). Other products could not be identified and will be represented as *others* in the "Results" section.

After the reaction was complete, both the system and catalyst were washed thoroughly with the reaction solvent and methanol and the system was subsequently rinsed again with methanol using a CatCart® containing inert material. The CatCart® containing the catalyst was then dried in a stove a 80°C overnight.

6. APPENDIX

6.1 NMR

6.1.1 [P_{8881}][MC]

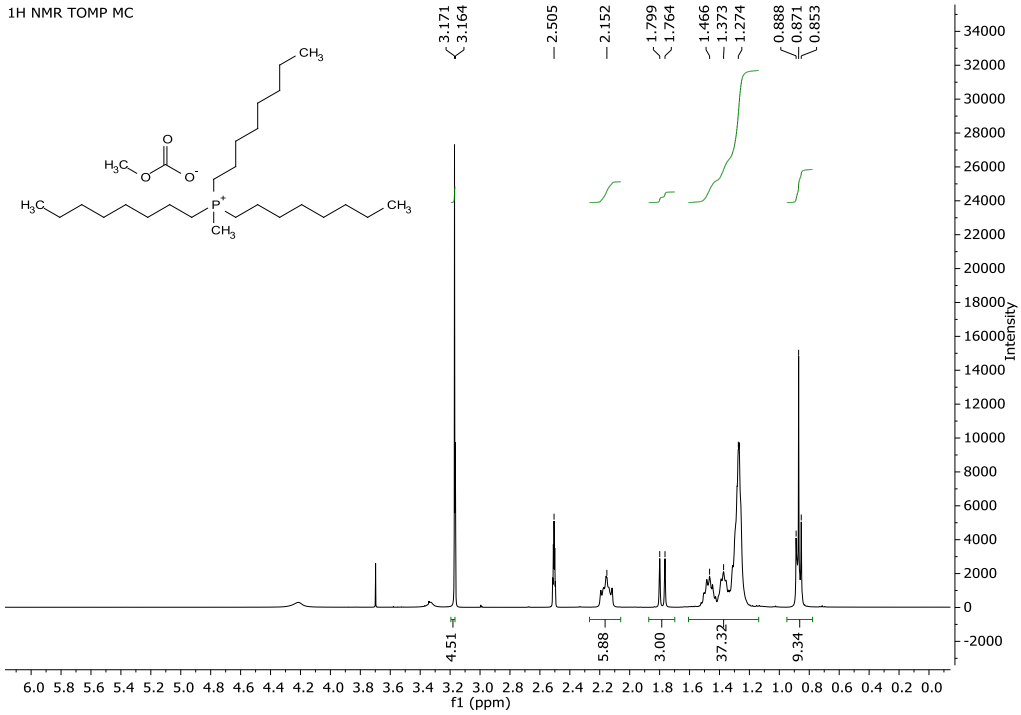


Figure 26. ^{1}H NMR in DMSO-d_6 (400 MHz) δ(ppm): 3,171 (s, 3H, CH_3-OCOO), 2,152 (m, 6H), 1,799-1,764 (d, J (P,H)= 14,0 Hz, 3H, CH_2-P), 1,466 (m, 6H), 1,373 (m, 6H), 1,274 (br m, 24H), 0,86 (t, 9H, CH_3).

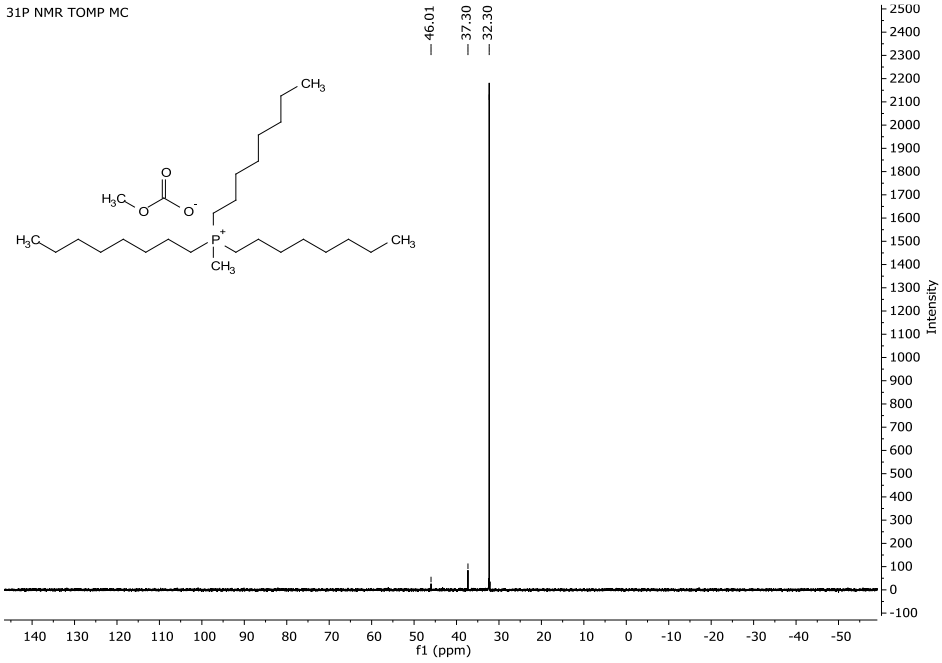


Figure 27. ^{31}P NMR in DMSO-d_6 (161 MHz) δ(ppm): 32,30 (s, 1P)

6.1.2 [P_{8881}][NTf_2]

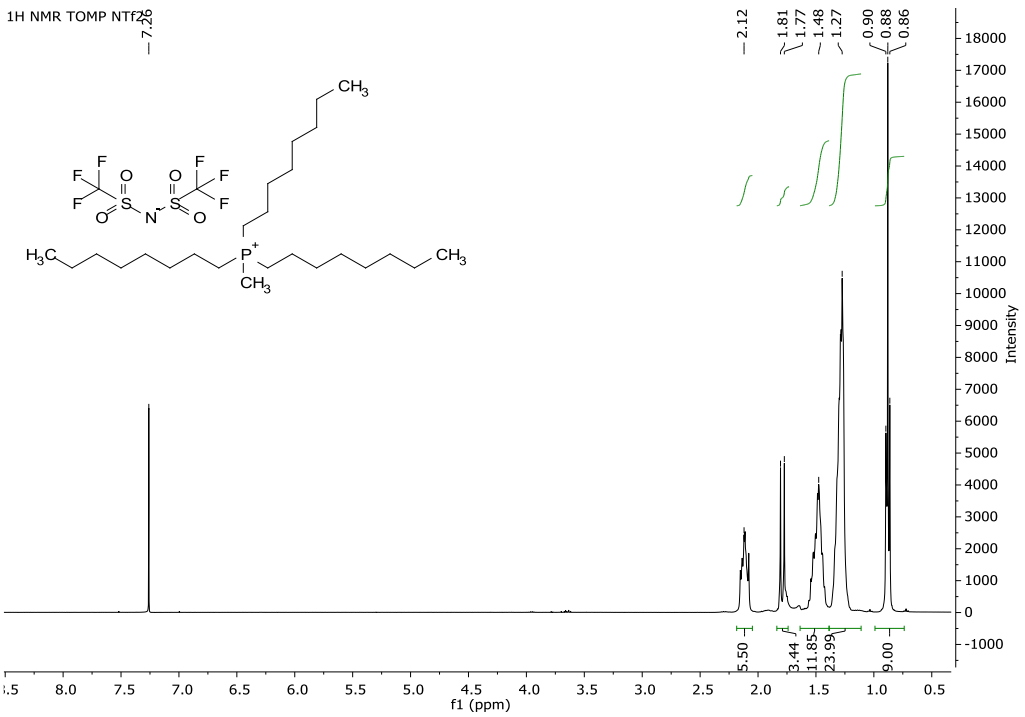


Figure 28. ^{1}H NMR in $CDCl_3$ (400 MHz) δ(ppm): 2,12 (m, 6H, CH_2-P), 1,81-1,77 (d, J(P,H)= 13,2 Hz, 3H, CH_3-P), 1,48 (m, 12H), 1,27 (br m, 24H), 0,88 (t, 9H, CH_3).

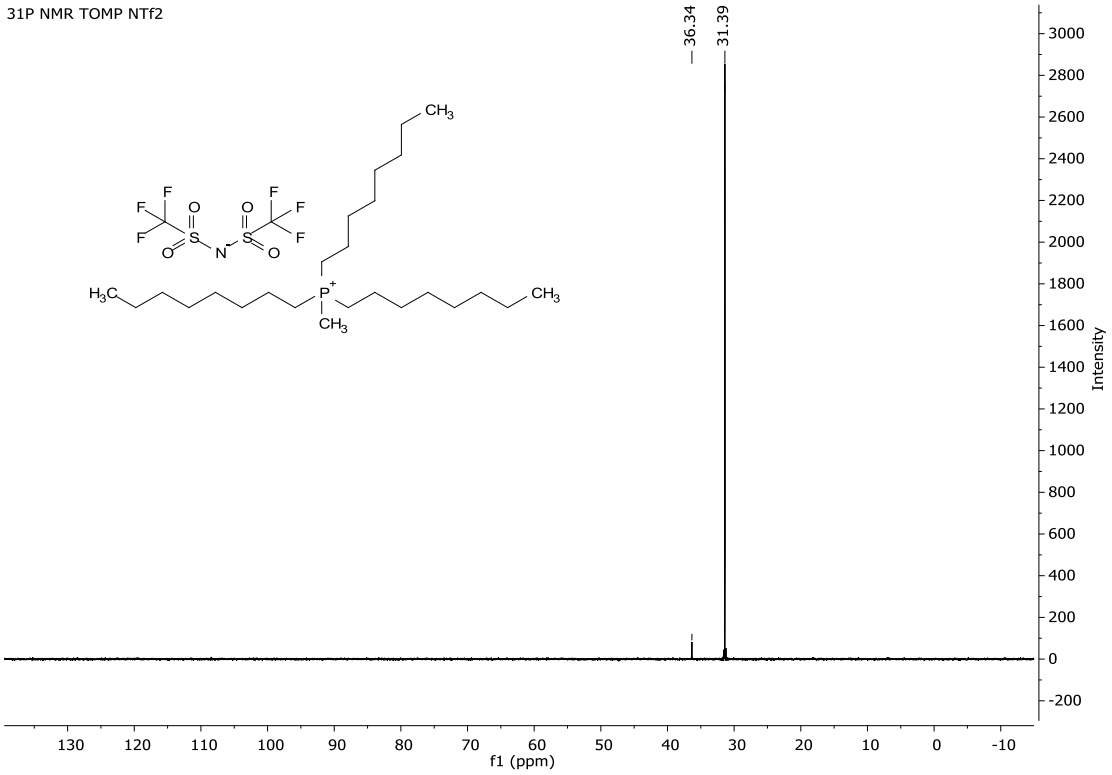


Figure 29. ^{31}P NMR in $CDCl_3$ (161 MHz) δ(ppm): 31,39 (s, 1P).

6.1.3 DFF

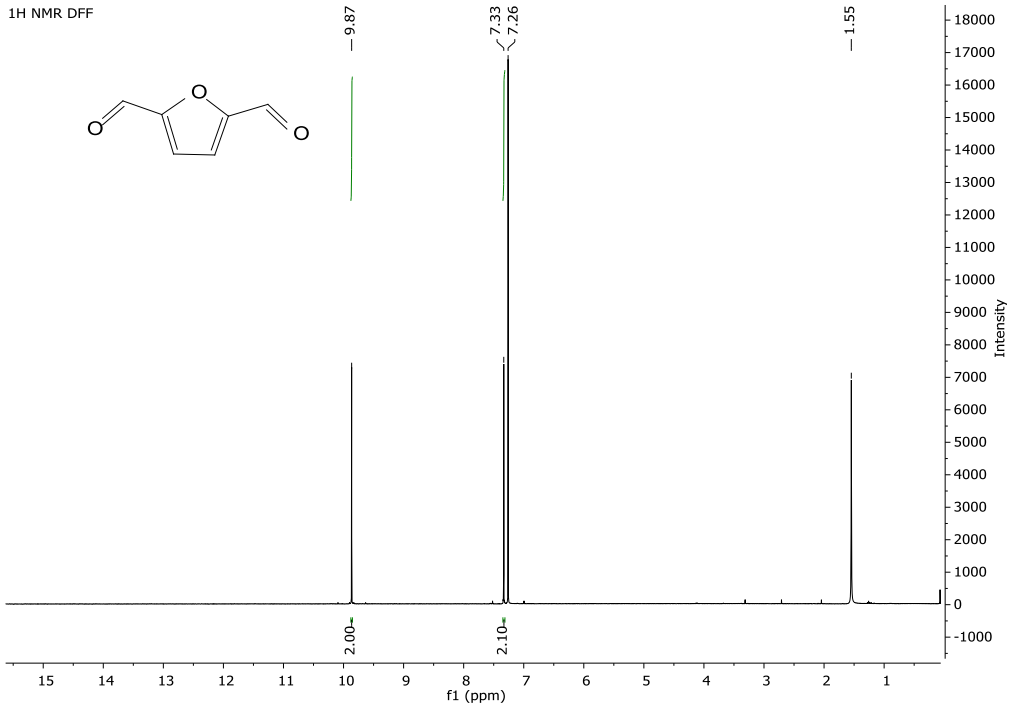


Figure 30. ^{1}H NMR in CDCl3 (400 MHz)δ(ppm): 9,87 (s, 2H, CHO), 7,33 (s, 2H).

5.1.4 HMF

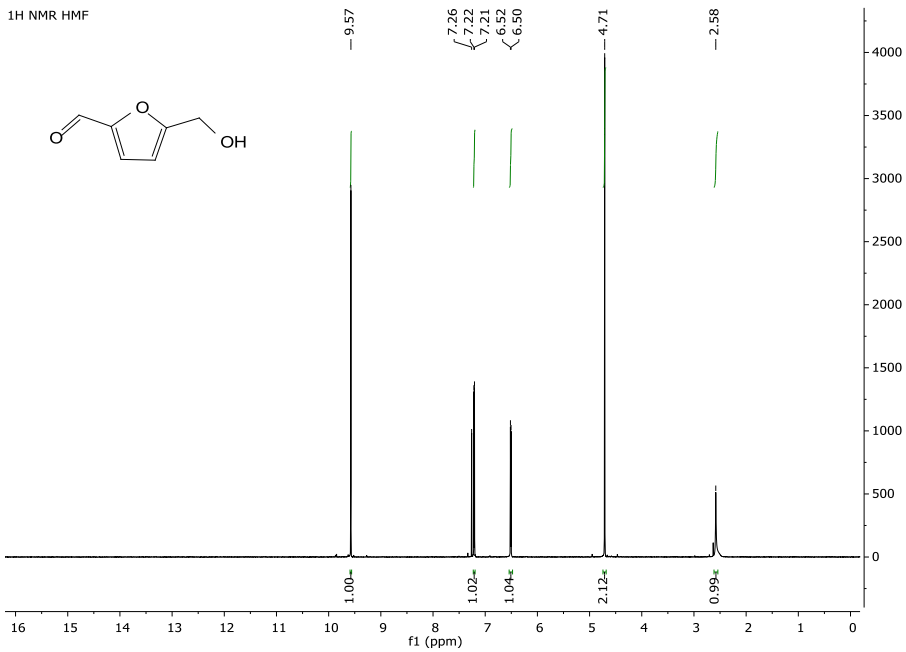


Figure 31. ^{1}H NMR in CDCl3 (400 MHz)δ(ppm): 9,57 (s, 1H, CHO), 7,22 (d, J_{HH}= 3,6Hz 1H), 6,52 (d, , J_{HH}= 3,6Hz 1H), 4,71 (s, 2H), 2,58 (s, 1H, OH).

6.1.5 HHD

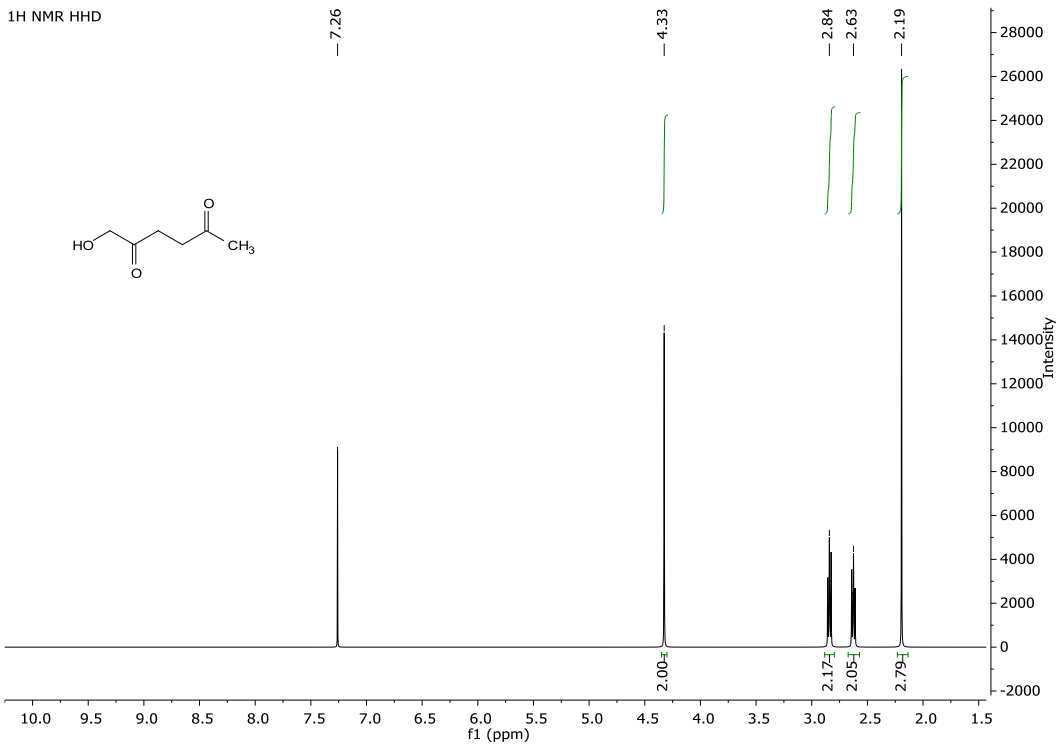


Figure 32. ^{1}H NMR in $CDCl_3$ (400 MHz) δ(ppm): 4,33 (s, 2H), 2,84 (t, 2H), 2,63 (t, 2H), 2,19 (s, 3H).

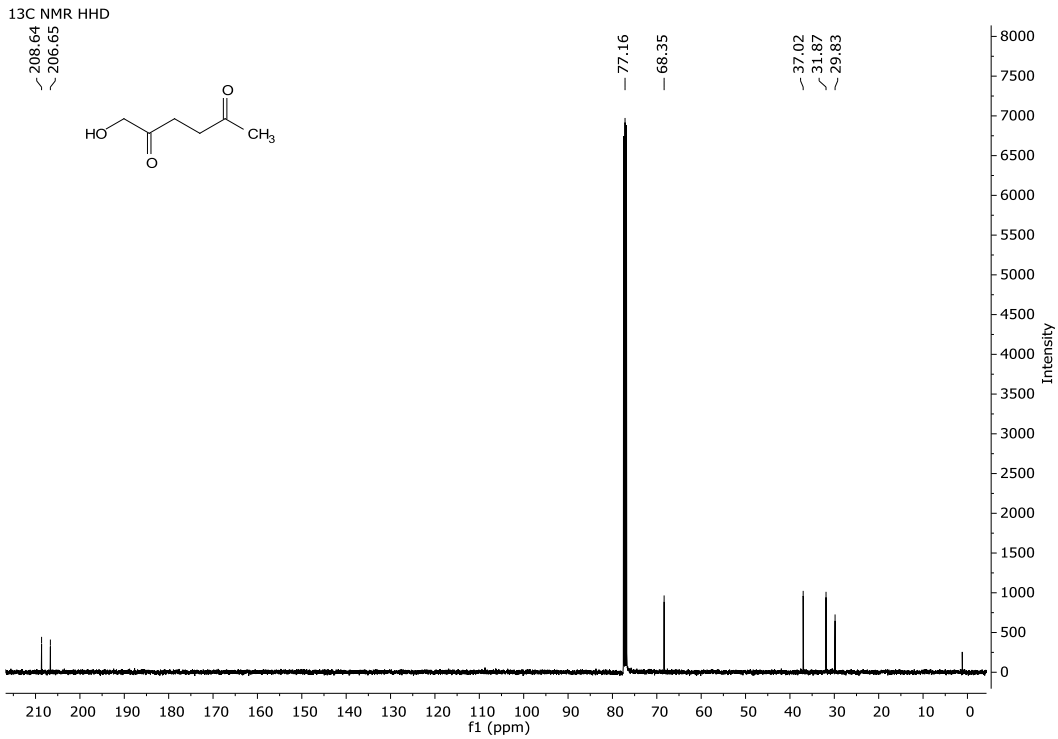


Figure 33. ^{13}C NMR in $CDCl_3$ (100 MHz) δ(ppm): 208,64 (s, 1C, C=O), 206,55 (s, 1C, C=O), 68,35 (s, 1C), 37,02 (s, 1C), 31,87 (s, 1C), 29,83 (s, 1C).

6.2 GC-MS

6.2.1 HHD

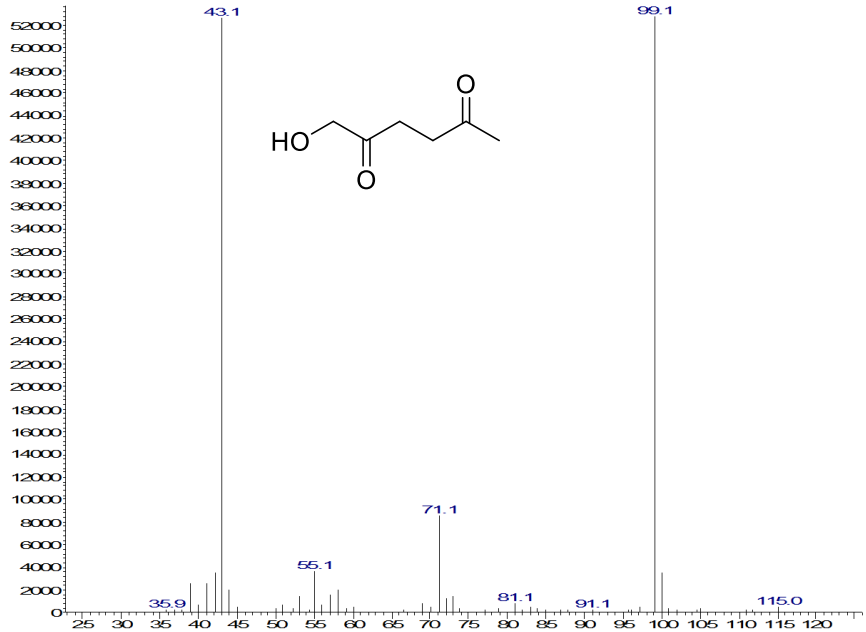


Figure 34. GC/MS (relative intensity, 70 eV) m/z: 99,1 (100,0), 71,0 (16,0), 43,1 (98,0).

6.2.2 BHMF

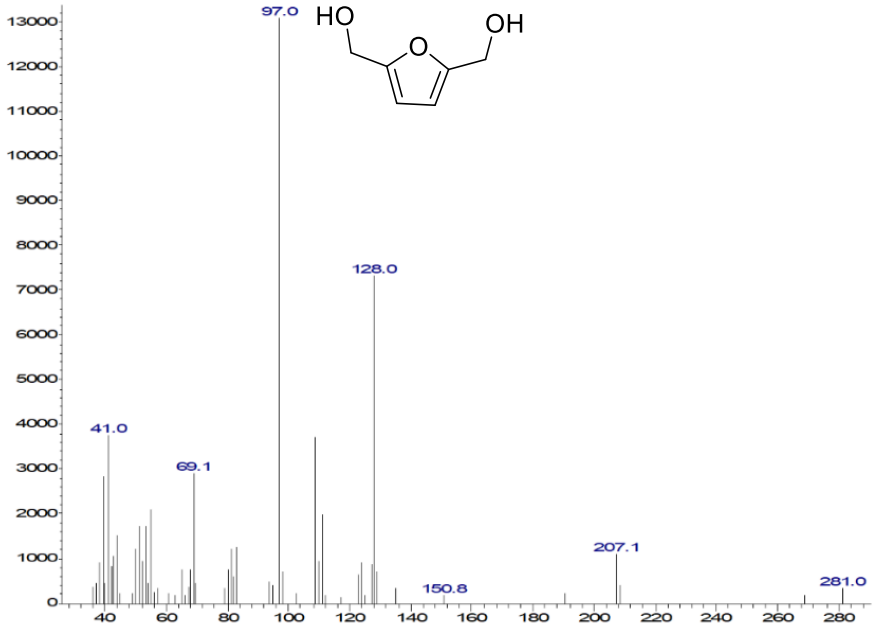


Figure 35. GC/MS (relative intensity, 70 eV) m/z: 128.0 (55), 111.0 (15), 109.0 (28), 97.0 (100), 69.1 (22), 55.0 (16), 53.1 (13), 44.0 (11), 41.0 (28).

6.2.3 BHMTHF

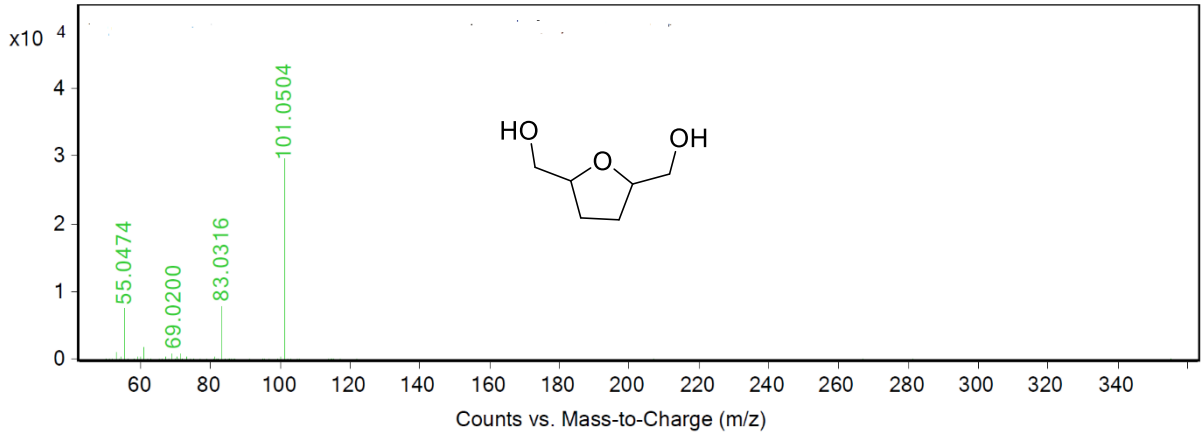


Figure 36. . GC/MS (relative intensity, 70 eV) m/z: 101 (100), 83 (26), 55 (25).

6.2.4 DMF

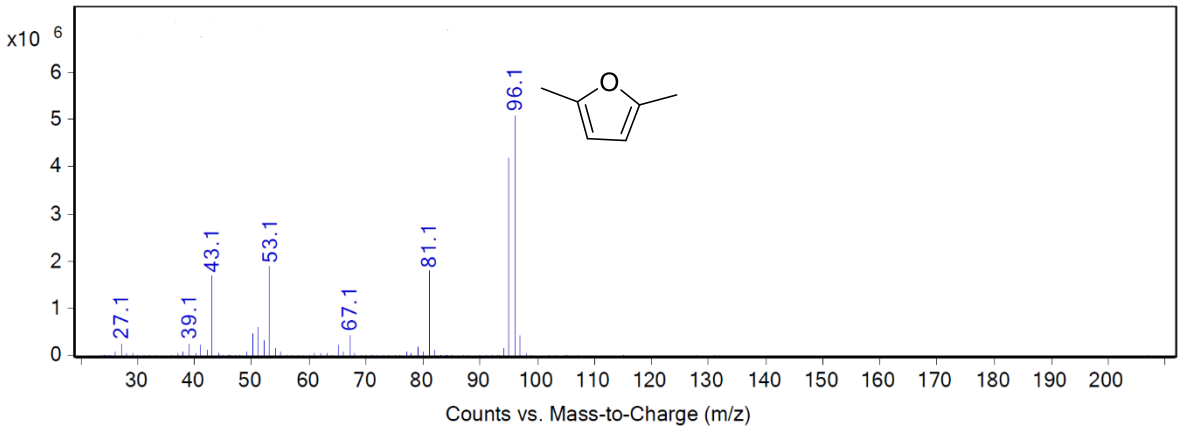


Figure 37. GC/MS (relative intensity, 70 eV) m/z: 96,1 (100), 95,1 (82,0), 81,1 (35,0), 53,1 (37,0), 43,1 (32,0).

6.3 Calibration curves

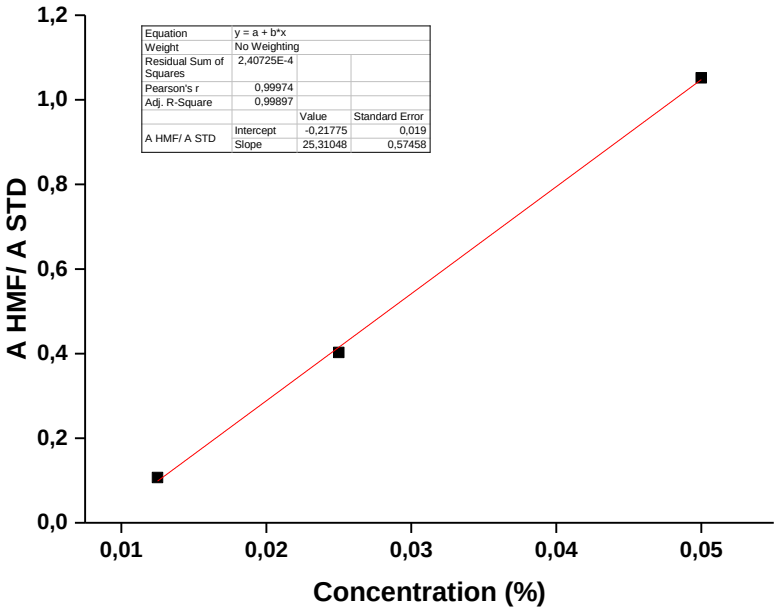


Figure 38. Calibration curve for the conversion of HMF with HP-5 capillary column (L=30 m, ø= 0,32 mm, film= 0,25 µm) with the method: 105°C for 2 min., 20°C/min, 150°C for 3 min., 25°C/min, 210°C for 3 min. Standard used: cyclohexane.

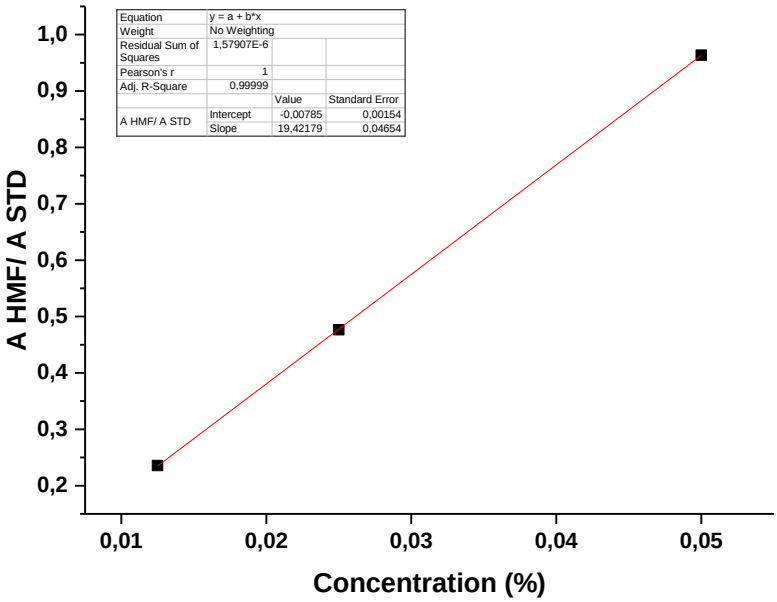


Figure 39. Calibration curve for the conversion of HMF with Restek Rt®-yDEXsa (L=30 m, ø= 0,25 mm, film= 0,25 µm) with the method: 60°C for 3 min., 20°C/min, 170°C for 10 min. Standard used: cyclohexane.

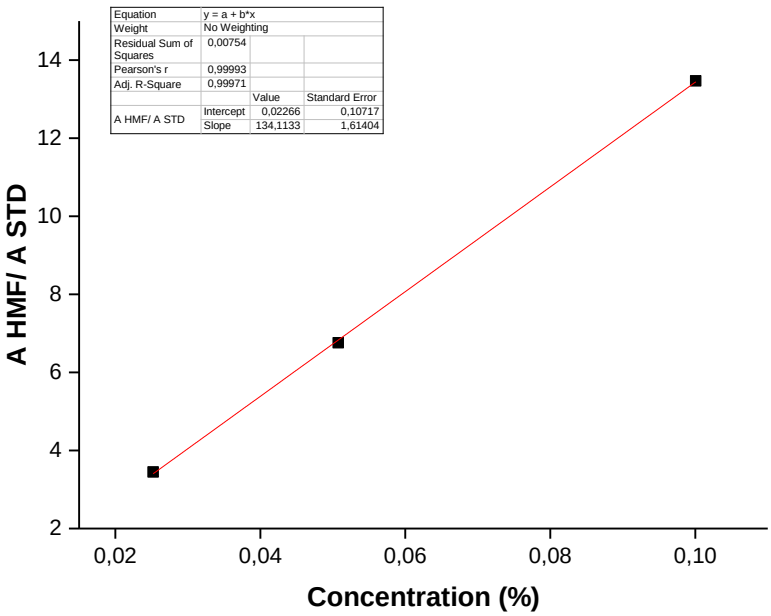


Figure 40. Calibration curve for the conversion of HMF with Perkin Elmer Elite 624 column, (L= 30 m, ø= 0,32 mm, film= 1,8 µm) with the method: 50 °C for 2 min., 25°C/min, 150°C for 15 min., 20°C/min, 240°C for 2 min. Standard used: diethyelene glycol dimethyl ether.

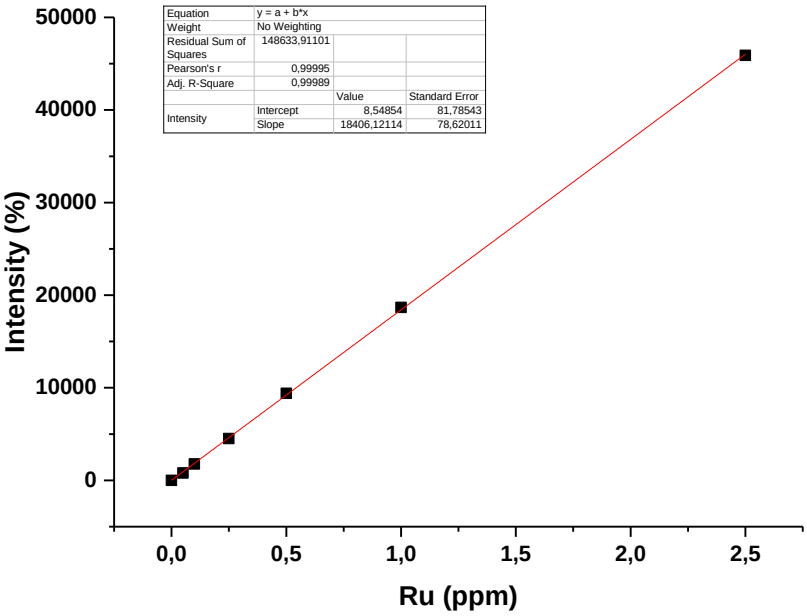


Figure 41. Calibration curve for Ru with MP-AES. Standard used: $RuCl_3$ in 10% HCl.

7. BIBLIOGRAPHY

[1] J.G. de Vries, Green syntheses of heterocycles of industrial importance. 5-Hydroxymethylfurfural as a platform chemical, *Adv. Heterocycl. Chem.*, **2016**, *121*.

[2] X. Ge, F. Xu, Y. Li, Solid-state anaerobic digestion of lignocellulosic biomass: recent progress and perspectives, *Bioresour. Technol.* **2016**, *205*, 239–249.

[3] J. Bozell, *Chemicals and Materials from Renewable Resources*, ACS Symposium Series, American Chemical Society: Washington, DC, **2001**.

[4] H. V. Scheller, P. Ulvskov, Hemicellulose, *Annu. Rev. Plant Biol.,* **2010**, *61*, 263–89.

[5] M.A. Asokan, S.S. Prabu, S. Kamesh, W. Khan, Performance, combustion and emission characteristics of dieselengine fuelled with papaya and watermelon seed oil bio-diesel/diesel blends, *Energy,* **2018**, *145*, 238-245.

[6] E. Lazzari, T. Schena, C.T. Primaz, G. Pereira da Silva Maciel, M.E. Machado, A. Lima Cardoso, R. Assis Jacques, E. Bastos Caramão, Production and chromatographic characterization of bio-oil from the pyrolysis of mango seed waste, *Ind. Crops Prod.*, **2016**, *83*, 529–536.

[7] J. Moncada, V. Aristizábal, M. C. Cardona, Design strategies for sustainable biorefineries, *Biochem. Eng. J.,* **2016**, *116*, 122-134.

[8] T. Werpy, G. Petersen, Top Value Added Chemicals From Biomass Volume I: Results of Screening for Potential Candidates from Sugars and Synthesis Gas, **2004**.

[9] J. Bozell, G.R. Petersen, Technology development for the production of biobased products from biorefinery carbohydrates—the US Department of Energy's "Top 10" revisited, *Green Chem.,* **2010**, *12,* 539–554.

[10] T. J. Farmer, M. Mascal, Introduction to chemicals from biomass, *Wiley Online Library*, **2015**.

[11] C. Wang, H. Xu, R. Daniel, A. Ghafourian, J.M. Herreros, S. Shuai, X. Ma, Combustion characteristics and emissions of 2-methylfuran compared to 2,5-dimethylfuran, gasoline and ethanol in a DISI engine, *Fuel*, **2013**, *103*, 200–211.

[12] A. Mukherjee, M.J. Dumont, V. Raghavan, Review: Sustainable production of hydroxy-methylfurfural and levulinic acid: Challenges and opportunities, *Biomass and Bioenerg.*, **2015**, *72,* 143-183.

[13] K. Galkin, V. P. Ananikov, When Will 5-Hydroxymethylfurfural, the "Sleeping Giant" of Sustainable Chemistry, Awaken? *ChemSusChem* **2019**, *12*, 2976–2982.

[14]T. Kläusli, AVA Biochem: commercialising renewable platform chemical 5-HMF, *Green Process. Synth.,* **2014**, *3*, 235–236.

[15] C.O. Tuck, E. Pérez, I.T. Horváth, R.A. Sheldon, M. Poliakoff, Valorization of biomass: deriving more value from waste, *Science,* **2012**, *337*, 695–699.

[16] P. Kumar, D.M. Barrett, M.J. Delwiche, P. Stroeve, Methods for Pretreatment of Ligno-cellulosic Biomass for Efficient Hydrolysis and Biofuel Production, *Ind. Eng. Chem. Res.,* **2009**, *48*, 3713–3729.

[17] Y. Román-Leshkov, M. Moliner, J.A. Labinger, M.E. Davis, Mechanism of Glucose Isomerization Using a Solid Lewis Acid Catalyst in Water, *Angew. Chem.,* **2010**, *49*, 8954-8957.

[18] A.S. Amarasekara, L.D. Williams, C.C. Ebede, Mechanism of the dehydration of D-fructose to 5-hydroxymethylfurfural in dimethyl sulfoxide at 150°C: an NMR study, *Carbohyd. Res.,* **2008**, *343*, 3021–3024.

[19] Azzam, M. Pretreatment of cane bagasse with alkaline hydrogen peroxide for enzymatic hydrolysis of cellulose and ethanol fermentation. *J. Environ. Sci. Health B* **1989**, *24* (4), 421–433.

[20] P.K. Rout, A.D. Nannaware, O. Prakash, A. Kalra, R. Rajasekharan, Synthesis of hydroxymethylfurfural from cellulose using green processes: A promising biochemical and biofuel feedstock, *Chem. Eng. Sci.,* **2016**, *142*, 318-346.

[21] J. Tang, X. Guo, L. Zhu, C. Hu, Mechanistic study of glucose-to-fructose isomerization in water catalyzed by [Al(OH)2(at)]+, *ACS Catal.*, **2015**, *5*, 5097–5103.

[22] S.H. Mushrif, J.J. Varghese, D.G. Vlachos, Insights into the Cr(III) catalyzed isomerization mechanism of glucose to fructose in the presence of water using ab initio molecular dynamics, *Phys. Chem. Chem. Phys.*, **2014**, *16*, 19564–19572.

[23] H. Nguyen, V. Nikolakis, D.G. Vlachos, Mechanistic insights into Lewis acid metal salt-catalyzed glucose chemistry in aqueous solution, *ACS Catal.*, **2016**, *6*, 1497–1504.

[24] G. Li, E.A. Pidko, E.J. Hensen, Synergy between Lewis acid sites and hydroxyl groups for the isomerization of glucose to fructose over Sn-containing zeolites: a theoretical perspective. *Catal. Sci. Technol.*, **2014**, *4*, 2241–2250.

[25] Z. Shen, L. Kong, W. Zhang, M. Gu, M. Xia, X. Zhoub, Y. Zhang, Surface amino-functionalization of Sn-Beta zeolite catalyst for lactic acid production from glucose, *RSC Adv.*, **2019**, *9*, 18989-18995.

[26] C.M. Lew, N. Rajabbeigi, M. Tsapatsis, Tin-containing zeolite for the isomerization of cellulosic sugars, *Micropor. Mesopor. Mat.,* **2012**, *153*, 55–58.

[27] R. van Putten, J. C. van der Waal, E. de Jong, C. B. Rasrendra, H. J. Heeres and J. G. de Vries, Hydroxymethylfurfural, A Versatile Platform Chemical Made from Renewable Resources, *Chem. Rev*., **2013**, *113*, 1499–1597.

[28] Q. Cao, X. Guo, S. Yao, J. Guan, X. Wang, X. Mu, D. Zhang, Conversion of hexose into 5-hydroxymethylfurfural in imidazolium ionic liquids with and without a catalyst, *Carbohydr. Res*. **2011**, *346*, 956-959.

[29] P. Wrigstedt, J. Keskiväli, T. Repo, Microwave-enhanced aqueous biphasic dehydration of carbohydrates to 5-hydroxymethylfurfural, *RSC Adv.*, **2016**, *6*, 18973-18979.

[30] L. Hu, G. Zhao, X. Tang, Z. Wu, J. Xu, L. Lin, S. Liu, Catalytic conversion of carbohydrates into 5-hydroxymethylfurfural over cellulose-derived carbonaceous catalyst in ionic liquid, *Bioresour. Technol.*, **2003**, *148*, 501–507.

[31] I.K.M. Yu, D.C.W. Tsang, Conversion of biomass to hydroxymethylfurfural: A review of catalytic systems and underlying mechanisms*, Bioresour. Technol.,* **2017**, *238*, 716–732.

[32] M. Moreno-Recio, J. Santamaría-González, P. Maireles-Torres, Brönsted and Lewis acid ZSM-5 zeolites for the catalytic dehydration of glucose into 5- hydroxymethylfurfural, *Chem. Eng. J.*, **2016**, *303*, 22–30.

[33] K. I. Galkin, E. A. Krivodaeva, and V. P. Ananikov, *A catalytic system for the selective conversion of cellulose to 5-hydroxymethylfurfural under mild conditions*, Russ. Chem. Bull., Int. Ed., **2015**, *64*, 2954-2957.

[34] R.L. De Souza, H. Yu, F. Rataboul, N. Essayem, 5-Hydroxymethylfurfural (5-HMF) production from hexoses: limits of heterogeneous catalysis in hydrothermal conditions and potential of concentrated aqueous organic acids as reactive solvent system, *Challenges*, **2012**, *3,* 212–232.

[35] B. Seemala, V. Haritos, A. Tanksale, Levulinic Acid as a Catalyst for the Production of 5-Hydroxymethylfurfural and Furfural from Lignocellulose Biomass, *ChemCatChem*, **2016**, *8*, 640–647.

[36] K.R. Enslowab, A.T. Bell, SnCl4-catalyzed isomerization/dehydration of xylose and glucose to furanics in water, *Catal. Sci. Technol.*, **2015**, *5*, 2839-2847.

[37] M. Dashtban, A. Gilbert, P. Fatehi, Recent advancements in the production of hydroxymethylfurfural, *RSC Adv*., **2014**, *4*, 2037–2050.

[38] M. Möller, F. Harnisch, U. Schröder, Microwave-assisted hydrothermal degradation of fructose and glucose in subcritical water, *Biomass Bioenerg.* **2012**, *39*, 389–398.

[39] R. Parthasarathi, G. Bellesia, S.P.S. Chundawat, B.E. Dale, P. Langan, S. Gnanakaran, Insights into hydrogen bonding and stacking interactions in cellulose, J. *Phys. Chem. A,* **2011**, *115*, 14191–14202.

[40] Y. Román-Leshkov, J.N. Chheda, J.A. Dumesic, Phase Modifiers Promote Efficient Production of Hydroxymethylfurfural from Fructose, *Science,* **2006**, *312*, 1933-1937.

[41] E. Nikolla, Y. Romàn-Leshkov, M. Moliner, M.E. Davis, "One-Pot" Synthesis of 5-(Hydroxymethyl)furfural from Carbohydrates using Tin-Beta Zeolite, *ACS Catal.*, **2011**, *1,* 408–410.

[42] C.M. Cai, T. Zhang, R. Kumar, C.E. Wyman, THF co-solvent enhances hydrocarbon fuel precursor yields from lignocellulosic biomass. *Green Chem.,* **2013**, *15*, 3140–3145.

[43] J.S. Luterbacher, J.M. Rand, D.M. Alonso, J. Han, J. T. Youngquist, C.T. Maravelias, B.F. Pfleger, J.A. Dumesic, Nonenzymatic Sugar Production from Biomass Using Biomass-Derived *g*-Valerolactone, *Science*, **2014**, *43*, 277-280.

[44] S. Jia, Z. Xu, Z.C. Zhang, Catalytic conversion of glucose in dimethylsulfoxide/water binary mix with chromium trichloride: role of water on the product distribution, *Chem. Eng. J.,* **2014**, *254*, 333–339.

[45] S. Siankevich, Z. Fei, R. Scopelliti, P.G. Jessop, J. Zhang, N. Yan, P.J. Dyson, Direct conversion of mono-and polysaccharides into 5-hydroxymethylfurfural using ionic-liquid mixtures, *ChemSusChem*, **2016**, *9*, 2089–2096.

[46] K.I. Galkin, E.A. Krivodaeva, L.V. Romashov, S.S. Zalesskiy, V.V. Kachala, J.V. Burykina, V.P. Ananikov, Critical Influence of 5-Hydroxymethylfurfural Aging and Decomposition on the Utility of Biomass Conversion in Organic Synthesis, *Angew. Chem.*, **2016**, *55*, 8338 –8342.

[47] T. Shalumova, J. M. Tanski, 5-(Hydroxymethyl)furan-2-carbaldehyde, *Acta Crystallogr. Sect. E* **2010**, *66*, o2266.

[48] M.A. Lilga, R.T. Hallen, M. Gray, Production of Oxidized Derivatives of 5-Hydroxymethyl-furfural (HMF), *Top Catal*, **2010**, *53*, 1264–1269.

[49] S. Deiss, F. Gloeckner, H. Mueller, Process for production of polyethylene terephthalate pellets, United States Patent, **2015**, US 8, 557, 155 B2.

[50] F. Kerdi, H.A. Rass, C. Pinel, M. Besson, G. Peru, B. Leger, S. Rio, E. Monflier, A. Ponchel, Evaluation of surface properties and pore structure of carbon on the activity of supported Ru catalysts in the aqueous-phase aerobic oxidation of HMF to FDCA, *Appl. Catal. A,* **2015**, *506*, 206-219.

[51] G. Yi, S.P. Teong, Y. Zhang, Base-free conversion of 5-hydroxymethylfurfural to 2,5 furandicarboxylic acid over a Ru/C catalyst, *Green Chem.,* **2016**, *18*, 979-983.

[52] F. Menegazzo, M. Signoretto, D. Marchese, F. Pinna, M. Manzoli, Structure–activity relationships of Au/ZrO_2 catalysts for 5-hydroxymethylfurfural oxidative esterification: Effects of zirconia sulphation on gold dispersion, position and shape, *J. Catal.,* **2015**, *326*, 1-8.

[53] W.P. Dijkman, D.E. Groothuis, M.W. Fraaije, Enzyme-Catalyzed Oxidation of 5-Hydroxymethylfurfural to Furan-2,5-dicarboxylic Acid, *Angew. Chem. Int. Ed.*, **2014**, 53, 6515-6518.

[54] E. Jansen, L.S. Jongbloed, D.S. Tromp, M. Lutz, B. de Bruin, C.J. Elsevier, Ligand Effects on the Hydrogenation of Biomass-Inspired Substrates with Bifunctional Ru, Ir, and Rh Complexes, *ChemSusChem*, **2013**, *6*, 1737-1744.

[55] J. Ohyama, A. Esaki, Y. Yamamoto, S. Araic, A. Satsuma, Selective hydrogenation of 2-hydroxymethyl-5-furfural to 2,5-bis(hydroxymethyl)furan over gold sub-nano clusters, *RSC Adv.,* **2013**, *3*, 1033-1036.

[56] A.J. Kumalaputri, G. Bottari, P.M. Erne, H.J. Heeres, K. Barta, Tunable and Selective Conversion of 5-HMF to 2,5-Furandimethanol and 2,5-Dimethylfuran over Copper-Doped Porous Metal Oxides, *ChemSusChem*, **2014**, *7*, 2266 – 2275.

[57] H. Cai, C. Li, A. Wang, T. Zhang, Biomass into chemicals: One-pot production of furan-based diols from carbohydrates via tandem reactions, *Catal. Today*, **2014**, *234*, 59-65.

[58] N. Perret, A. Grigoropoulos, M., T.D. Manning, J.B. Claridge, M.J. Rosseinsky, Catalytic Response and Stability of Nickel/Alumina for the Hydrogenation of 5-Hydroxymethylfurfural in Water, *ChemSusChem*, **2016**, *9*, 521–531.

[59] Y. Nakagawa, K. Takada, M. Tamura, K. Tomishige, Total Hydrogenation of Furfural and 5-Hydroxymethylfurfural over Supported Pd−Ir Alloy Catalyst, *ACS Catal.*, **2014**, *4*, 2718−2726.

[60] X. Kong, R. Zheng, Y. Zhu, G. Ding, Y. Zhu, Y.-W. Li, Rational design of Ni-based catalysts derived from hydrotalcite for selective hydrogenation of 5-hydroxymethylfurfural, *Green Chem.*, **2015**, *17*, 2504-2514.

[61] S. Yao, X. Wang, Y. Jiang, F. Wu, X. Chen, X. Mu, One-Step Conversion of Biomass-Derived 5-Hydroxymethylfurfural to 1,2,6-Hexanetriol Over Ni−Co−Al Mixed Oxide Catalysts Under Mild Conditions, *ACS Sustainable Chem. Eng.,* **2014**, *2*, 173−180.

[62] T. Buntara, S. Noel, P.H. Phua, I. Melian-Cabrera, J.G. de Vries, H.J. Heeres, From 5-Hydroxymethylfurfural (HMF) to Polymer Precursors: Catalyst Screening Studies on the Conversion of 1,2,6-hexanetriol to 1,6-hexanediol, *Top Catal.*, **2012**, *55*, 612–619.

[63] J. Tuteja, H. Choudhary, S. Nishimura, K. Ebitani, Direct Synthesis of 1,6-Hexanediol from HMF over a Heterogeneous Pd/ZrP Catalyst using Formic Acid as Hydrogen Source, *ChemSusChem*, **2014**, *7*, 96-99.

[64] M. Chatterjee, T. Ishizaka, H. Kawanami, Hydrogenation of 5-hydroxymethylfurfural in supercritical carbon dioxide–water: a tunable approach to dimethylfuran selectivity, *Green Chem.*, **2014**, *16*, 1543-1551.

[65] B. Saha, C.M. Bohn, M.M. Abu-Omar, Zinc-Assisted Hydrodeoxygenation of Biomass-Derived 5-Hydroxymethylfurfural to 2,5-Dimethylfuran, *ChemSusChem*, **2014**, *7,* 3095 – 3101.

[66] G. Sun, J. An, H. Hu, C. Li, S. Zuo, H. Xia, Green catalytic synthesis of 5-methylfurfural by selective hydrogenolysis of 5-hydroxymethylfurfural over size-controlled Pd nanoparticle catalysts, *Catal. Sci. Technol.,* **2019***, 9*, 1238-1244.

[67] Y. Duan, M. Zheng, D. Li, D. Deng, L.F. Ma, Y. Yang, Conversion of HMF to methyl cyclopentenolone using Pd/Nb2O5 and Ca–Al catalysts via a two-step procedure, *Green Chem.*, **2017**, *19*, 5103-5113.

[68] Z. Xu, P. Yan, W. Xu, X. Liu, Z. Xia, B. Chung, S. Jia, Z.C. Zhang, Hydrogenation/Hydrolytic Ring Opening of 5-HMF by Cp*-Iridium(III) Half-Sandwich Complexes for Bioketones Synthesis, *ACS Catal.,* **2015**, *5*, 788-792.

[69] F. Liu, M. Audemar, K. De Oliveira Vigier, J.-M. Clacens, F. De Campo, F. Jérôme, Palladium/Carbon Dioxide Cooperative Catalysis for the Production of Diketone Derivatives from Carbohydrates, *ChemSusChem*, **2014**, *7*, 2089 – 2095.

[70] B. Wozniak, A. Spannenberg, Y. Li, S. Hinze, J.G. de Vries, Cyclopentanone Derivatives from 5-Hydroxymethylfurfural via 1-Hydroxyhexane-2,5-dione as Intermediate, *ChemSusChem*, **2018**, *11*, 356 – 359.

[71] R. Alamillo, M. Tucker, M. Chia, Y. Pagán-Torres, J. Dumesic, The selective hydrogenation of biomass-derived 5-hydroxymethylfurfural using heterogeneous catalysts, *Green Chem.*, **2012**, *14*, 1413-1419.

[72] J. Han, Y.-H. Kim, H.-S. Jang, S.-Y. Hwang, J. Jegal, J.W. Kim, Y.-S. Lee, Heterogeneous zirconia-supported ruthenium catalyst for highly selective hydrogenation of 5-hydroxymethyl-2-furaldehyde to 2,5-bis(hydroxymethyl)furans in various n-alcohol solvents, *RSC Adv.*, **2016**, *6*, 93394-93397.

[73] L. Hu, X. Tang, J. Xu, Z. Wu, L. Lin, S. Liu, Selective Transformation of 5-Hydroxy-methylfurfural into the Liquid Fuel 2,5-Dimethylfuran over Carbon-Supported Ruthenium, *Ind. Eng. Chem. Res.,* **2014**, *53*, 3056−3064.

[74] A.S. Nagpure, A.K. Venugopal, N. Lucas, M. Manikandan, R. Thirumalaiswamy, S. Chilukuri, Renewable fuels from biomass-derived compounds: Ru-containing hydrotalcites as catalysts for conversion of HMF to 2,5-dimethylfuran, *Catal. Sci. Technol*., **2015**, *5*, 1463-1472.

[75] S. Cattaneo, H. Naslhajian, F. Somodi, C. Evangelisti, A. Villa, L. Prati, Ruthenium on Carbonaceous Materials for the Selective Hydrogenation of HMF, *Molecules,* **2018**, *23*, 2007-2019.

[76] Y. Zu, P. Yang, J. Wang, X. Liu, J. Ren, G. Lu, Y. Wang Efficient production of the liquid fuel 2,5-dimethylfuran from 5-hydroxymethylfurfural over Ru/Co_3O_4 catalyst, *Appl Catal B: Environ* **2014**, *146,* 244–248.

[77] P. Priecel, N. A. Endot, P. D. Cara, J. A. Lopez-Sanchez Fast Catalytic Hydrogenation of 2,5-Hydroxymethylfurfural to 2,5- Dimethylfuran with Ruthenium on Carbon Nanotubes *Ind. Eng. Chem. Res.* **2018**, *57*, 1991-2002.

[78] S. Fulignati, C. Antonetti, D. Licursi, M. Pieraccioni, E. Wilbersb, H.J. Heeresb, A.M. Raspolli Galletti, Insight into the hydrogenation of pure and crude HMF to furan diols using Ru/C as catalyst, *Appl. Catal. A,* **2019**, *578,* 122–133.

[79] J. Jae, W. Zheng, R. F. Lobo, D.G. Vlachos, Production of Dimethylfuran from Hydroxymethylfurfural through Catalytic Transfer Hydrogenation with Ruthenium Supported on Carbon, *ChemSusChem*, **2013**, *6*, 1158 – 1162.

[80] T. Wang, J. Zhang, W. Xie, Y. Tang, D. Guo, Y. Ni, Catalytic Transfer Hydrogenation of Biobased HMF to 2,5-Bis-(Hydroxymethyl)Furan over Ru/Co_3O_4, *Catalysts,* **2017**, *7*, 92-99.

[81] A.D. Dwivedi, K. Gupta, D. Tyagi, R.K. Rai, S.M. Mobin, S.K. Singh, Ruthenium and Formic Acid Based Tandem Catalytic Transformation of Bioderived Furans to Levulinic Acid and Diketones in Water, *ChemCatChem*, **2015**, *7*, 4050 – 4058.

[82] R. V. Chaudhari, A. Torres, X. Jin, B. Subramaniam Multiphase Catalytic Hydrogenolysis/Hydrodeoxygenation Processes for Chemicals from Renewable Feedstocks: Kinetics, Mechanism, and Reaction Engineering *Ind. Eng. Chem. Res*. **2013**, *52*, 15226-15243.

[83] R. Alamillo, M. Tucker, M. Chia, Y. Pagán-Torres, J. Dumesic, The selective hydrogenation of biomass-derived 5-hydroxymethylfurfural using heterogeneous catalysts, *Green Chem.*, **2012**, *14*, 1413–1419.

[84] Y. Yang, Z. Du, J. Ma, F. Lu, J. Zhang, J. Xu, Biphasic Catalytic Conversion of Fructose by Continuous Hydrogenation of HMF over a Hydrophobic Ruthenium Catalyst, *ChemSusChem*, **2014**, *7*, 1352 – 1356.

[85] P. Tundo, A. Perosa, Multiphasic heterogeneous catalysis mediated by catalyst-philic liquid phases, *Chem. Soc. Rev*., **2007**, *36*, 532–555.

[86] M. Selva**,** A. Perosa, P. Canton Metal Nanoparticles stabilized in Liquid Multiphase Systems Mediated by Ionic Liquids *Curr. Org. Chem.*, **2017,** *21*, 2445-2454.

[87] M. Selva, M. Gottardo, A. Perosa, Upgrade of Biomass-Derived Levulinic Acid via Ru/C-Catalyzed Hydrogenation to γ-Valerolactone in Aqueous−Organic−Ionic Liquids Multiphase Systems, *ACS Sustainable Chem. Eng*., **2013**, *1*, 180−189.

[88] A. Bellè, T. Tabanelli, G. Fiorani, A. Perosa, F. Cavani, M. Selva, A Multiphase Protocol for Selective Hydrogenation and Reductive Amination of Levulinic Acid with Integrated Catalyst Recovery, *ChemSusChem*, **2019**, *12*, 3343 – 3354.

[89] J. Luo, L. Arroyo-Ramírez, J. Wei, H. Yun, C. B. Murray, R. J. Gorte Comparison of HMF hydrodeoxygenation over different metal catalysts in a continuous flow reactor *Appl Catal A: General* **2015**, *508*, 86–93.

[90] X. Tang, J. Wei, N. Ding, Y. Sun, X. Zeng, L. Hu, S. Liu, T. Lei, L. Lin Chemoselective hydrogenation of biomass derived 5-hydroxymethylfurfural to diols: Key intermediates for sustainable chemicals, materials and fuels *Renew Sustainable Energy Rev* **2017***, 77,* 287–296.

[91] A. Iriondo, A. Mendiguren, M.B. Güemez, J. Requies, J.F. Cambra 2,5-DMF production through hydrogenation of real and synthetic 5-HMF over transition metal catalysts supported on carriers with different nature *Catal Today* **2017**, *279*, 286–295.

[92] J. Luo, L. Arroyo-Ramìrez, R.J. Gorte, D. Tzoulaki, D.G. Vlachos Hydrodeoxygenation of HMF Over Pt/C in a Continuous Flow Reactor, *AlChE Journal*, **2015**, *61*, 590-597.

[93] https://thalesnano.com/

[94] S. Lima, D. Chadwick, K. Hellgardt Towards sustainable hydrogenation of 5-(hydroxymethyl)furfural: a two-stage continuous process in aqueous media over RANEY® catalysts *RSC Adv*., **2017**, *7*, 31401–31407.

[95] C. M. Mani, M. Braun, V. Molinari, M. Antonietti, N. Fechler A High-Throughput Composite Catalyst based on Nickel Carbon Cubes for the Hydrogenation of 5- Hydroxymethylfurfural to 2,5-Dimethylfuran C*hemCatChem* **2017**, *9*, 3388 – 3394.

[96] S. Mhadmhan, A. Franco, A. Pineda, P. Reubroycharoen, R. Luque, Continuous Flow Selective Hydrogenation of 5-Hydroxymethylfurfural to 2,5-Dimethylfuran Using Highly Active and Stable Cu−Pd/Reduced Graphene Oxide, *ACS Sustainable Chem. Eng.*, **2019**, *7*, 14210−14216.

[97] E. Auer, A. Freund, J. Pietsch, T. Tacke, Carbons as supports for industrial precious metal catalysts, *Appl Catal A: General,* **1998**, *173*, 259–271.

[98] J. Horvat, B. Klaic, B. Metelko and V. Sunjic, Mechanism of levulinic acid formation, *Tetrahedron Lett*., **1985**, *26*, 2111–2114.

[99] Xiao Liang, Brian S. Haynes, and Alejandro Montoya, Acid-Catalyzed Ring Opening of Furan in Aqueous Solution, *Energy Fuels,* **2018**, *32*, 4139−4148.

[100] F. Menegazzo, E. Ghedini, M. Signoretto, 5-Hydroxymethylfurfural (HMF) Production from Real Biomasses , *Molecules,* **2018**, *23*, 2201-2219.

[101] S. Wang, V. Vorotnikov, D. G. Vlachos, A DFT study of furan hydrogenation and ring opening on Pd(111), *Green Chem.,* **2014**, *16*, 736–747.

[102] D. S. Cameron, S. J. Cooper, I. L. Dodgson, B. Harrison, J. W. Jenkins, Organonickel catalyzed cross -coupling reactions, and synthetic studies toward cyclopeptide alkaloids via optically active oxazole intermediates, *Catal. Today* **1990**, *7*,113 –137.

[103]https://www.sigmaaldrich.com/chemistry/chemistry-products.html?TablePage=16255998

[104] D. Landini, A. Maia, A. Rampoldi, *J. Org. Chem.,* Stability of Quaternary Onium Salts under Phase-Transfer Conditions in the Presence of Aqueous Alkaline Solutions **1986**, 51, 16, 3187-3191.

[105] S. Paganelli, A. Perosa, M. Selva, Triphasic Liquid Systems for Improved Separations. Trioctylmethylammonium Chloride-Immobilised Rhodium Trichloride: A Phosphine-Free Hydroformylation Catalytic System, *Adv. Synth. Catal*. **2007**, 349, 1858 – 1862.

[106] A. Perosa, P. Tundo, M. Selva, P. Canton, Triphasic liquid systems: generation and segregation of catalytically active Pd nanoparticles in an ammonium-based catalyst-philic phase, *Chem. Commun*., **2006**, 4480–4482.

[107] F. A. Kucherov, K. I. Galkin, E. G. Gordeev, V. P. Ananikov, Efficient route for the construction of polycyclic systems from bioderived HMF, *Green Chem.,* **2017**, *19*, 4858–4864.

[108] C. Laugel, B. Estrine, J. Le Bras, N. Hoffmann, S. Marinkovic, J. Muzart, NaBr/DMSO-Induced Synthesis of 2,5-Diformylfuran from Fructose or 5-(Hydroxymethyl)furfural, *ChemCatChem,* **2014,** *6*, 1195–1198.

[109] M. Fabris, V. Lucchini, M. Noè, A. Perosa, M. Selva, Ionic Liquids Made with Dimethyl Carbonate: Solvents as well as Boosted Basic Catalysts for the Michael Reaction, *Chem. Eur. J.*, **2009**, *15*, 12273–12282.

[110] E. Pfab, L. Filiciotto, A.A. Romero, R. Luque, Valorization of Humins-Extracted 5-Methoxymethylfurfural: Toward High Added Value Furanics via Continuous Flow Catalytic Hydrogenation, *Ind. Eng. Chem. Res.,* **2019**, *58*, 16065−16070.