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Sustaining the transition from petro- to biobased chemical industry with flow chemistry

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Sustaining the transition from petro- to biobased chemical industry with flow chemistry

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Abstract

In the current context of transitioning toward more sustainable chemical processes, upgrading of biobased platform molecules, *i.e.* the chemical transformation of widely available low molecular weight entities from biomass, gains significant attention, in particular when combined with enabling continuous flow conditions. The success of such combination relies mostly on the possibility to explore new process conditions and the perspective of seamless scalability while keeping a low overall footprint. This review gathers representative continuous flow processes utilizing a selection of current hot platform molecules targeting industrially relevant building blocks including (a) commodity chemicals, (b) specialty and fine chemicals and (c) fuels and fuel additives.

Keywords

Flow chemistry – continuous processes – upgrading – biobased platforms – intensification – heterogeneous catalysis

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1. Introduction

One of the main challenges of the 21st century concerns the progressive transition from a petrobased chemical industry toward biobased alternatives. Fourteen years ago, the US Department of Energy (DoE) issued of a list of the most promising biobased molecules (named "platforms") for defining a new era for the chemical industry.[1, 2] Biobased platforms are defined as widely available compounds of low molecular mass derived from biomass. Platform molecules are typically oxygenated compounds of low molecular complexity, yet upon the appropriate combination of a few chemical steps, they can be transformed into a large variety of smaller (defunctionalization processes) or larger molecular mass entities (functionalization processes). Biobased platforms are used as building blocks for the synthesis of value-added chemicals for industrial applications, and are intended to be potential alternatives for partially replacing petroresources.[3, 4]

Such context has stimulated intensive research efforts aiming both at developing new chemistries and new technologies for developing processes that increase the value of platform molecules. Continuous flow chemistry is now widely adopted as an enabling technology in the chemist's toolkit, and many reports have emphasized its assets for improving chemical processing.[5, 6] The contribution of continuous flow chemistry for designing safer and more reliable chemical processes using facilities with a low environmental footprint is now well established.[7–11] Despite the emergence of shale gas, the progressive depletion of fossil resources has contributed a lot to the development of biobased continuous flow processes.[5, 12–14]

The implementation of continuous flow technology in various fields, including the pharmaceutical industry, has triggered intense research efforts and is currently used in various commercial processes.[15] The same level of maturity has not been reached yet for the valorization of biobased platform molecules. One of the most challenging aspects of dealing with biobased molecules relates to the availability and variability of the quality of these biobased platforms as composition of the initial biomass may vary depending on, for instance, the location of fields or on the meteorology. Biobased processes are economically attractive as long as efficiency and robustness are guaranteed, and that includes the availability of sustained feedstocks as a well as low waste generation.

This review gathers a selection of representative continuous flow processes using current hot platform molecules (Figure 1) that are industrially relevant including (a) commodity chemicals, (b) specialty and fine chemicals and (c) fuels and fuel additives. This review only considers liquid and solid platform molecules.[16–18] Studies related to the upgrading of ethanol, formic and acetic acid, which have been already extensively reviewed, are not included.[19–22] Most of the examples described herein deal with alternative continuous flow processes starting from platforms toward traditionally petrobased chemicals. Some examples illustrate the emergence of new, exclusively

biobased chemicals taking full advantage of the specificity of the biobased building blocks compared to the ones derived from oil. The main classes are then divided into subcategories illustrating the most common end-use of the target chemicals (*i.e.* solvents, monomers, building blocks for active pharmaceutical ingredients, fuels, etc.).

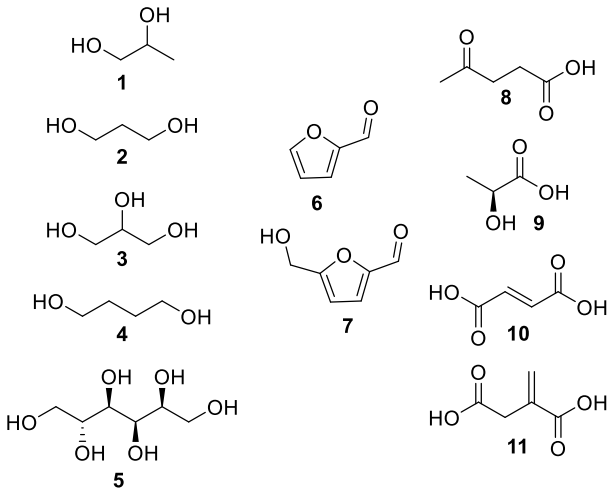

Figure 1. Selection of hot biobased platform molecules.

2. Commodity and other large scale industrially relevant building blocks

2.1 Solvents

2.1.1 Alkanes

Alkanes are benchmark commodity chemicals derived from fossil resources. The largest fraction of alkane's global production is used as fuel, but low-boiling point liquid alkanes also have applications as solvents for extractions or chemical reactions.[23, 24] Alternative routes for the production of alkanes from renewable resources include biomass gasification coupled to Fischer-Tropsch synthesis and direct deoxygenation of platform molecules derived from biomass.[25] In the latter strategy, selective C-O bond cleavage is required to remove oxygen while C-C bonds cleavage must be avoided for preserving the carbon backbone. In a representative example, Wang and colleagues reported a highly selective continuous flow process for the conversion of sorbitol (**5**) into *n*-pentane (**12**) and *n*-hexane (**13**, Figure 2). Ruthenium-molybdenum supported on carbon nanotubes (CNT) was used as heterogeneous catalyst in a fixed-bed reactor under high temperature (280 °C) and H_2 pressure (40 bar). *n*-Pentane and *n*-hexane were produced in a 1:2 ratio continuously for 7 days without any catalyst deactivation being noticed.[26]

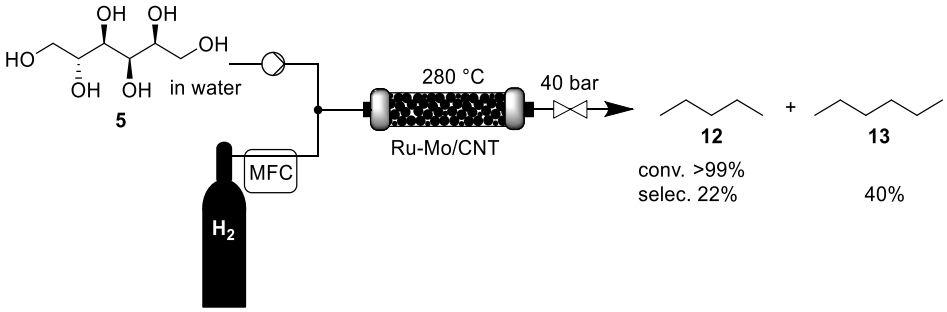

Figure 2. Simplified flow chart for the continuous flow conversion of sorbitol (**5**) into alkanes.

2.1.2 Alcohols

The continuous flow conversion of biomass-derived molecules into common alcoholic solvents is well documented in the literature. Hutchings *et al.* reported a straightforward, yet efficient process for the transformation of glycerol (**3**) into methanol. Water was used both as solvent for the glycerol feedstock solution and as hydrogen source for the reaction. Cheap and widely available oxides such as MgO, CaO and CeO_2 were assessed as heterogeneous catalysts, and the best results were obtained with ceria (quantitative glycerol conversion, 65% selectivity toward methanol) at 340 °C under atmospheric pressure. Most notably, similar results were obtained upon operation of the continuous reactor with crude or refined glycerol.[27]

Another literature report described the preparation of propanols from glycerol (**3**). The optimized process consisted in reacting an aqueous solution of **3** with hydrogen over a $Pt/TiPO_4$ heterogeneous catalyst at 220 °C under atmospheric pressure. Glycerol was quantitatively converted into a 9:1 mixture of 1- and 2-propanol with a 97% combined selectivity. The catalyst maintained its activity for 15 h time-on-stream, and deactivated for longer operation time.[28] Similarly, Zhu *et al.* obtained a selective conversion of 1,2- and 1,3-propanediols into 1-propanol (**14**) using a fixed-bed continuous reactor packed with a mesoporous copper-ceria catalyst (Figure 3). A moderate temperature (180 °C) and a high H_2 pressure (50 bar) enabled the preparation of *n*-propanol in >90% yield.[29]

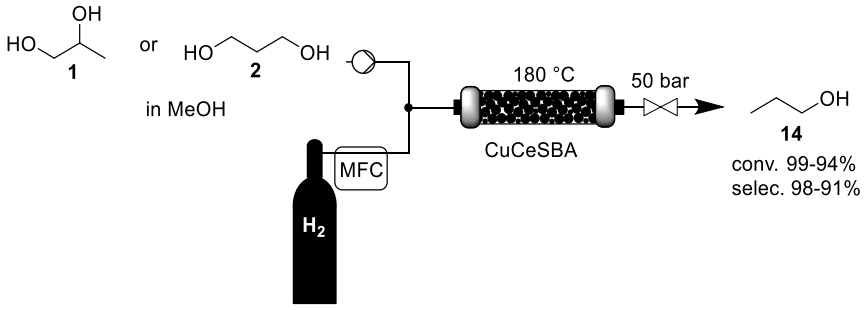

Figure 3. Continuous flow hydrogenolysis of propanediols (**1**, **2**) into *n*-propanol (**14**).

The progressive transition from a petro- to a biobased chemical industry has triggered the emergence of new classes of solvents that would have been otherwise too expensive or difficult to produce from fossil resources. Typical examples include solvents derived from furfural (**6**) and HMF (**7**), such as 2-methyltetrahydrofuran (see section 2.1.3) and tetrahydrofurfuryl alcohol (**16**). The main challenge in the development of continuous flow processes for the reduction of **6** into **16** is that the catalyst and operating conditions must be selective for the reduction of the alkene and aldehyde moieties, without triggering decarbonylation, hydrogenolysis or ring-opening toward products such as furan, 2-methylfuran (**18**) and 1,5-pentanediol. In a recent example, Guan and colleagues devised a two-step continuous flow procedure for the preparation of tetrahydrofurfuryl alcohol from furfural (Figure 4). Supported Pd and Ru catalysts were first assessed separately but gave low selectivities for the target compound. On the other hand, a fixed-bed reactor packed with two distinct layers of supported Pd and Ru catalysts, respectively, gave almost quantitative yield in tetrahydrofurfuryl alcohol (**16**) at low temperature (50 °C) and H_2 pressure (10 bar). Indeed, the Pd-based catalyst reduced furfural (**6**) into tetrahydrofurfural (**15**), which was then further reduced toward the corresponding alcohol **16** over the Ru-based catalyst.[30] Continuous flow processes featuring a single catalytic bed were also reported. For instance, Luque and coworkers assessed various Pd- and Pt-based heterogeneous catalysts in an H-Cube Pro reactor. 10% Pd/C gave promising results, with 98% furfural conversion and 83-64% selectivity for **16** over a 26 h run, without any Pd leaching observed. Process conditions involved pumping a solution of furfural in ethyl acetate over the catalytic bed operated at 150 °C and under 50 bar H_2.[31]

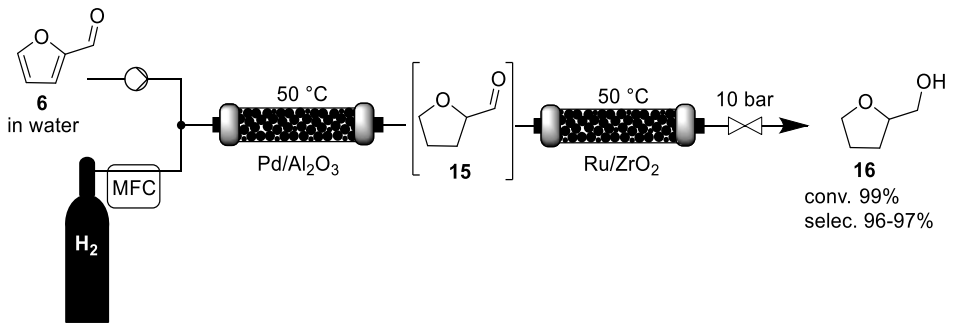

Figure 4. Two-step continuous flow procedure for the reduction of furfural (**6**) into tetrahydrofurfuryl alcohol (**16**).

2.1.3 Ethers

Tetrahydrofuran (THF, **17**) is widely used as a water-miscible organic solvent. It is already produced at industrial scale from potentially renewable 1,4-butanediol (**4**).[32] Cheap and widely available oxides bearing acidic sites catalyze the cyclodehydration of **4** into **17**. For instance, Sato and coworkers reported the formation of THF in 97% yield when neat 1,4-butanediol and nitrogen were

co-fed in a fixed-bed reactor packed with Al_2O_3 or ZrO_2 at 325 °C under atmospheric pressure.[33] A continuous flow procedure in rupture with the gas-phase process was also described, where supercritical water was used as an alternative reaction medium (Figure 5). An aqueous solution of 1,4-butanediol (**4**) was co-fed with an aqueous solution of carbon dioxide, the latter acting as an acid catalyst. THF (**17**) was obtained in 83% yield for 60 min of residence time at 300 °C.[34]

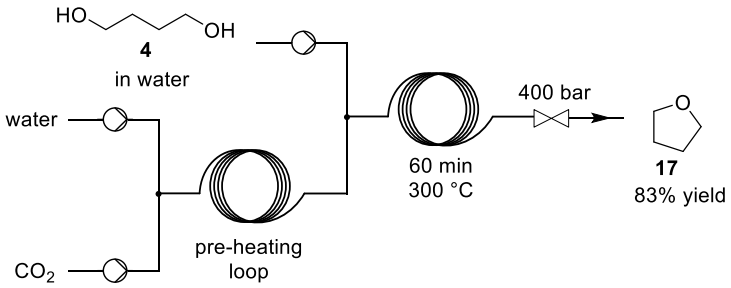

Figure 5. Continuous cyclodehydration of 1,4-butanediol (**4**) toward THF (**17**) under supercritical conditions.

2-Methyltetrahydrofuran (MeTHF, **19**) is an aprotic solvent that is exclusively biobased. By opposition to THF, it has a low solubility in water, and has been highlighted as a valuable alternative to replace THF in many instances.[35] Poliakoff *et al.* devised a two-step continuous flow reactor working under supercritical CO_2 regime for the conversion of furfural (**6**) into either furfuryl alcohol, 2-methylfuran (**18**), tetrahydrofurfuryl alcohol (**16**), furan (**48**) or MeTHF (**19**), depending on the reactions conditions. Two fixed bed reactor were fluidically connected in series, fed with hydrogen and packed with copper chromite and a 5%Pd/C catalyst, respectively (Figure 6 (a)). Upon operation of the first bed at 240 °C, furfural (**6**) was converted into 2-methylfuran (**18**). The second catalytic bed was operated at 300 °C for the reduction of the furanyl ring, affording MeTHF with quantitative furfural conversion and 82% selectivity.[36] Another emerging route for the preparation of MeTHF starts from levulinic acid (**8**) as substrate (Figure 6 (b)). Upare *et al.* described that at very high copper loading, a Cu/SiO_2 catalyst was selective for MeTHF production. Quantitative levulinic acid conversion and 89% selectivity for MeTHF were maintained for 320 h of operation over a nickel-doped copper catalyst. Most notably, no metal leaching or sintering could be evidenced.[37]

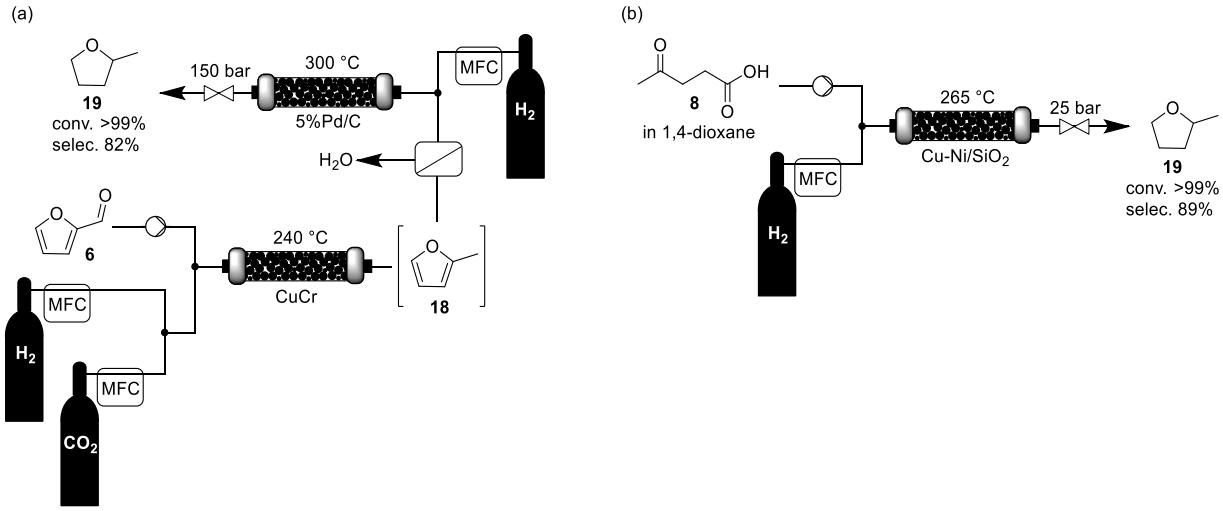

Figure 6. Continuous flow procedures for the preparation of 2-methyltetrahydrofuran (**19**) from (a) furfural (**6**) and (b) levulinic acid (**8**).

2.1.4 Lactones

Similarly to THF (see section 2.1.3), γ-butyrolactone (GBL, **20**) is already produced at an industrial scale from potentially renewable 1,4-butanediol (**4**). GBL has applications as an aprotic polar solvent or as a building block for the preparation of *N*-methylpyrrolidone.[38] Copper-based catalysts are known to trigger the oxidative cyclization of **4** into GBL in the gas-phase with high yield. For instance, 99% conversion and 99% selectivity were maintained for a 400 h time-on-stream over a copper-silica catalyst operated at 250 °C (Figure 7).[39] Co-Cu supported on MgO gave similar performances, with 95% conversion and 98% selectivity at 250 °C.[40]

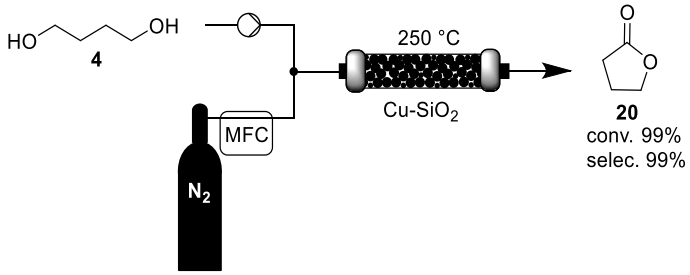

Figure 7. Continuous flow oxidative cyclization of 1,4-butanediol (**4**) toward γ-butyrolactone (**20**).

γ-Valerolactone (GVL, **21**) has a bright forecast as a solvent, but also as a fuel additive or fuel precursor (see section 4.2).[41] Intense research efforts were dedicated to the continuous flow upgrading of levulinic acid (**8**) into GVL. For instance, Moreno-Marrodan and Barbaro developed a sulfonated resin embedded with Ru nanoparticles as bifunctional heterogeneous catalyst for the H_2-mediated reduction of **8** toward GVL. [42] Excellent conversion (90-95%) and quantitative selectivity

were obtained at moderate temperature (70 °C) and pressure (5 bar) upon feeding an aqueous solution of levulinic acid and a stream of H_2 to the reactor. The catalyst maintained its activity for up to 32 h of operation.[42] Precious metal-free catalysts are also efficient for the reaction, such as molybdenum carbide supported within carbon nanotubes, which was stable for 24 h time-on-stream and gave quantitative conversion and 90% selectivity in GVL at 200 °C and under 30 bar of H_2.[43] Industrial grade molecular hydrogen is however currently obtained from fossil resources and its use requires dedicated equipment. Alternative hydrogen sources were thus assessed as well, such as formic acid and isopropanol (*i*PrOH). Chuah *et al.* developed a zirconium-β zeolite catalyst to promote the *i*PrOH-mediated continuous flow reduction of **8** into GVL. The catalyst featured Lewis acidic sites of moderate strength, and a very low amount of basic sites. Levulinic acid was pumped within the reactor as a solution in *i*PrOH. The catalyst was stable for 87 h of operation at 250 °C, and afforded quantitative yield in GVL. The catalyst then started to deactivate, but regeneration by aerobic calcination was possible.[44] Tadele *et al.* developed a catalyst based on palladium and silver nanoparticles supported on a graphitic carbon nitride surface for the conversion of levulinic acid into GVL using formic acid as H-donor (Figure 8). The catalyst was pumped as a suspension in a feedstock solution of **8** and formic acid, and quantitative yield in GVL was obtained for a 50 min residence time at 70 °C in a coil reactor.[45]

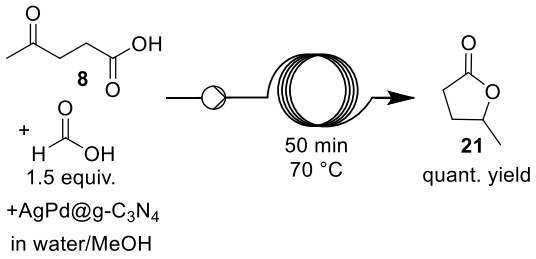

Figure 8. Continuous flow upgrading of levulinic acid (**8**) into γ-valerolactone (**21**) using formic acid as H-source.

2.1.5 Cyclic carbonates

Cyclic carbonates are widely used as polar aprotic solvents, building blocks for polymers, and electrolytes carriers in batteries. They are endowed with a low toxicity profile and a low volatility.[46] These scaffolds can be constructed from renewable polyols, such as ethylene glycol, 1,2-propanediol (**1**) and glycerol (**3**). Glycerol carbonate (**22**) has been recently highlighted as one of the most promising target to be produced in a glycerol biorefinery from both an economical and an environmental points of view.[47] Its synthesis from glycerol and dimethyl carbonate (DMC) can be efficiently catalyzed by strongly basic heterogeneous catalysts.[48] Selva and coworkers studied the synthesis of cyclic organic carbonates using dimethyl carbonate (DMC) as carbonation agent. Various renewable polyols were assessed such as ethylene glycol, 1,2- and 1,3-propanediol (**1**, **2**), 1,4-

butanediol (**4**) and glycerol (**3**). The reactions were optimized in catalyst-free and superheated conditions in an autoclave and translated to microfluidic conditions. Continuous conditions involved pumping an homogeneous feed of DMC and the diol, and reacting it at elevated temperature (230-250 °C) and pressure (50 bar) for about 15 min. Major differences were found as a function of the product ring size. The formation of five-membered rings from 1,2-diols occurred with high conversions (78-99%) and selectivities (82-95%), while selectivities of 14 and 0% were obtained for the formation of the six- and seven-membered rings derived from **2** and **4**, respectively.[49] Urea can also be used as a CO_2-based, cheap and widely available carbonation reagent. However, continuous removal of NH_3 is required to shift the equilibrium toward the products. Pérez-Ramírez *et al.* studied the reaction using a hydrotalcite-derived Mg-Al oxide catalyst packed in a fixed-bed reactor (Figure 9). GBL (**20**) was utilized as solvent for the glycerol-urea feedstock solution, and a gas/liquid separator connected to a vacuum line was inserted downstream the reactor to enable continuous ammonia removal. During a 100 h run, glycerol carbonate (**22**) yield decreased from 60% to 40%. The catalyst could however be reactivated by calcination.[50]

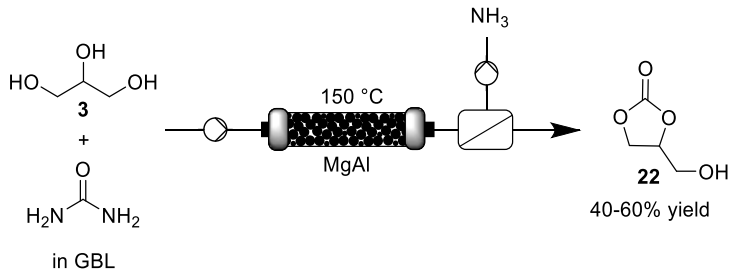

Figure 9. Continuous carbonation of glycerol (**3**) with urea toward glycerol carbonate (**22**).

2.1.6 Aromatics

Similarly to alkanes (see section 2.1.1), carboaromatics are flagship bulk chemicals obtained from fossil sources. Various alternative strategies were devised to access benzene (**23**), toluene (**24**) and xylene (**25**) (BTX) from biomass-derived chemicals. Cheng and Huber reported a cascade process involving the decarbonylation of furfural (**6**), a Diels-Alder cycloaddition with propene and a final dehydration for the preparation of BTX in the gas phase under continuous flow conditions (Figure 10 (a)). A packed-bed reactor was charged with ZSM-5 zeolite, heated at 600 °C and fed with furfural and propene. Quantitative furfural conversion was obtained with 9%, 25% and 6% selectivity for **23**, **24** and **25**, respectively.[51] Another study evaluated the pyrolysis of HMF (**7**) at 600 °C over ZSM-5, but in the absence of propene (Figure 10 (b)). 96% HMF conversion was obtained with 2%, 21% and 3% selectivity for **23**, **24** and **25**, respectively.[52] Similarly, the pyrolysis of glycerol (**3**) was reported over Zn-modified HZSM-5 zeolite for the preparation of BTX (Figure 10 (c)). Zinc promoted

dehydration reactions, thus improving the conversion toward carboaromatics. Elevated yields of benzene (10%), toluene (35%) and xylene (20%) were obtained at 400 °C and 20 bar of counter-pressure.[53]

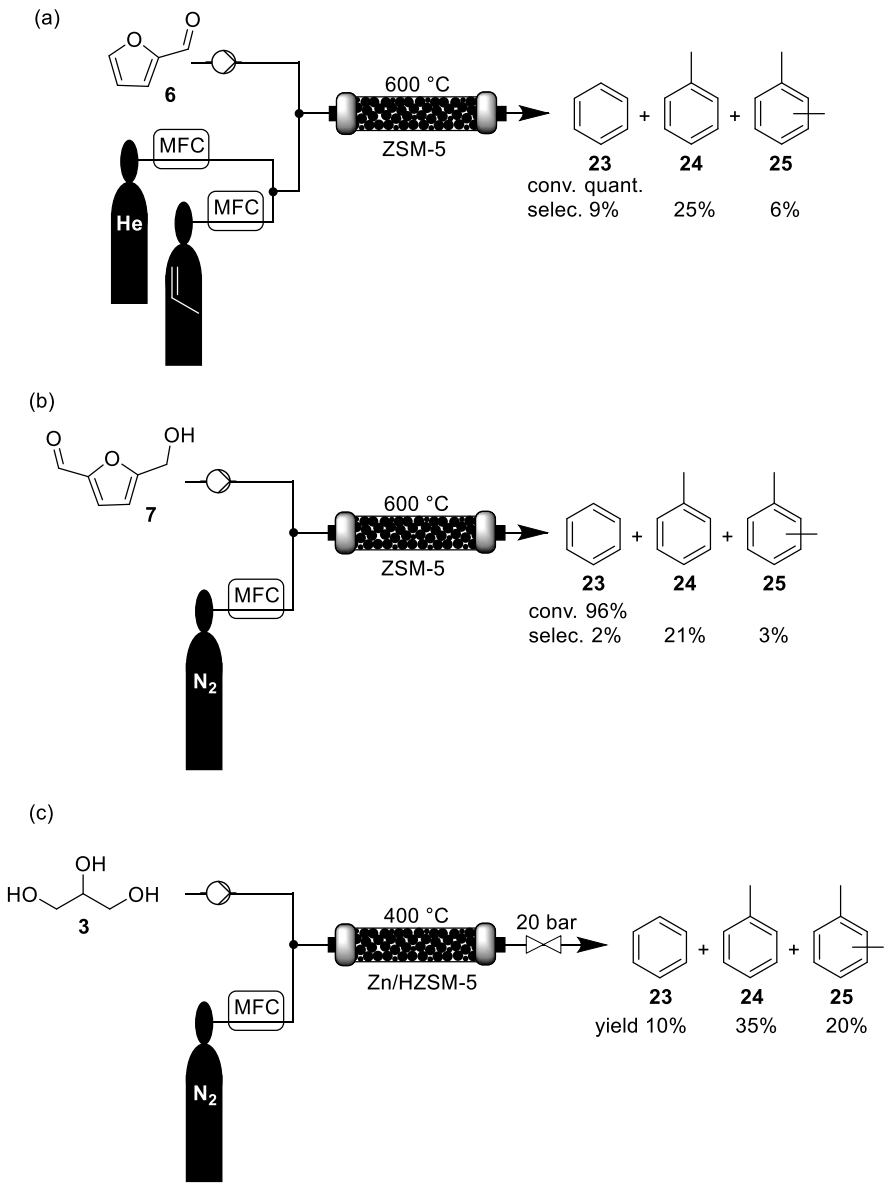

Figure 10. Continuous flow strategies for the preparation of benzene (**23**), toluene (**24**) and xylene (**25**) from (a) furfural (**6**), (b) HMF (**7**) and (c) glycerol (**3**).

2.2 Monomers

2.2.1 Olefins

Propene is one of the most important bulk chemical derived from fossil resources, being the starting material for the preparation of polypropylene and monomers such as propylene oxide, acrylonitrile (**27**), and acrylic acid (**28**).[54] Mota and coworkers reported a high-yielding continuous flow procedure for the transformation of glycerol (**3**) into propene. A highly concentrated aqueous

feedstock solution of **3** (90% vol.) was mixed with a stream of molecular hydrogen and fed to a fixed bed reactor operated at 300 °C. Up to 90% propene selectivity and a quantitative glycerol conversion were obtained over a Fe/Mo heterogeneous catalyst supported on carbon. In addition, no deactivation was observed during 24 h of operation. The proposed mechanistic pathway involved hydroxyacetone, 1,2-propanediol (**1**) and 2-propanol as reaction intermediates.[55]

Acrylonitrile (**27**) is widely used as monomer for the preparation of polyacrylonitrile and acrylonitrile-butadiene-styrene (ABS) copolymer, as well as for the synthesis of acrylamide. It is industrially manufactured *via* the ammoxidation of petrobased propene.[56] Guerrero-Pérez and Bañares studied an alternative cascade continuous flow process involving the dehydration of glycerol (**3**) into acrolein (**26**) followed by its ammoxidation into acrylonitrile (**27**). V-Sb-Nb oxide supported on alumina triggered the formation of **27** upon feeding the reactor with **3**, oxygen and ammonia, and operating the system at 400 °C at atmospheric pressure. 83% glycerol conversion and 58% acrylonitrile selectivity were obtained after 30 min of operation, but the catalyst deactivated after 2 h.[57] On this basis, Paul and colleagues developed a two-step continuous procedure including glycerol dehydration into acrolein over a WO_3/TiO_2 catalytic bed operated at 280 °C, followed by acrolein ammoxidation at 400 °C triggered by a Sb-Fe oxide catalyst (Figure 11). The process was conducted at atmospheric pressure, and an aqueous solution of acetic acid was injected downstream to quench the reactor effluents. Deactivation of the catalyst after about 24 h resulted in an overall yield drop from 36% to 26%.[58]

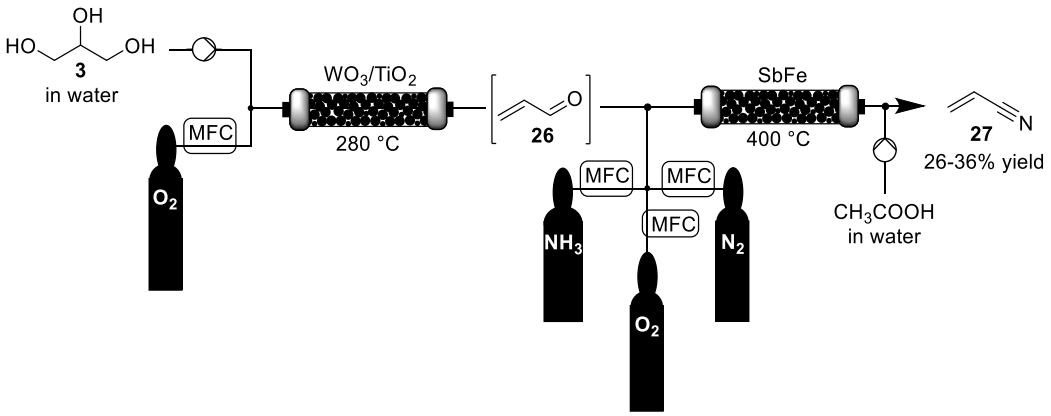

Figure 11. Two-step continuous flow procedure for the synthesis of acrylonitrile (**27**) from glycerol (**3**).

By analogy to acrylonitrile, acrylic acid (**28**) is currently produced from propene, and is widely used for the preparation of polyacrylic acid and ester derivatives.[59] Alternative emerging biobased strategies for the preparation of acrylic acid use glycerol (**3**) or lactic acid (**9**) as starting materials. In the former case, acrylic acid is produced in two steps from dehydration of **3** into acrolein (**26**)

followed by its subsequent oxidation.[59] These successive reactions can be conducted either in cascade using a single bifunctional heterogeneous catalyst or sequentially using two monofunctional heterogeneous catalysts. For instance, Cavani *et al.* developed a W-Mo-V oxide bifunctional catalyst, where tungsten was involved in dehydration sites, vanadium in oxidation sites and molybdenum modulated the strength of the oxidation sites to avoid overoxidation toward CO_2. The material was packed in a fixed bed reactor heated at 290 °C, operated at atmospheric pressure and fed with aqueous glycerol and oxygen. The yield in **28** decreased from 51% to 42% after 28 h of operation, but then remained steady for the next 40 h.[60] A bifunctional $Cs(VO)_{0.2}(PMo)_{0.25}(PW)_{0.75}$ catalyst was reported by Li and Zhang and gave excellent results at 340 °C under atmospheric pressure. Aqueous **3** and oxygen were continuously fed into the reactor and gave an initial yield of 60% for **28**, which however started to decrease after 10 h time-on-stream to reach 38% after 56 h of operation.[61] A sequential continuous flow setup enabled the preparation of acrylic acid from glycerol in 75% yield, with up to 70 h of stability (Figure 12 (a)). Aqueous glycerol was fed with oxygen over $Cs_{2.5}H_{0.5}PW_{12}O_{40}$ supported on Nb_2O_5 as first dehydration catalyst. The catalytic dehydration bed was operated at 300 °C under atmospheric pressure. Acrolein (**26**) was produced in 80% yield before entering the second catalytic bed, featuring an oxidation catalyst based on V-Mo oxide supported on silicon carbide, and operated also at 300 °C and atmospheric pressure.[62]

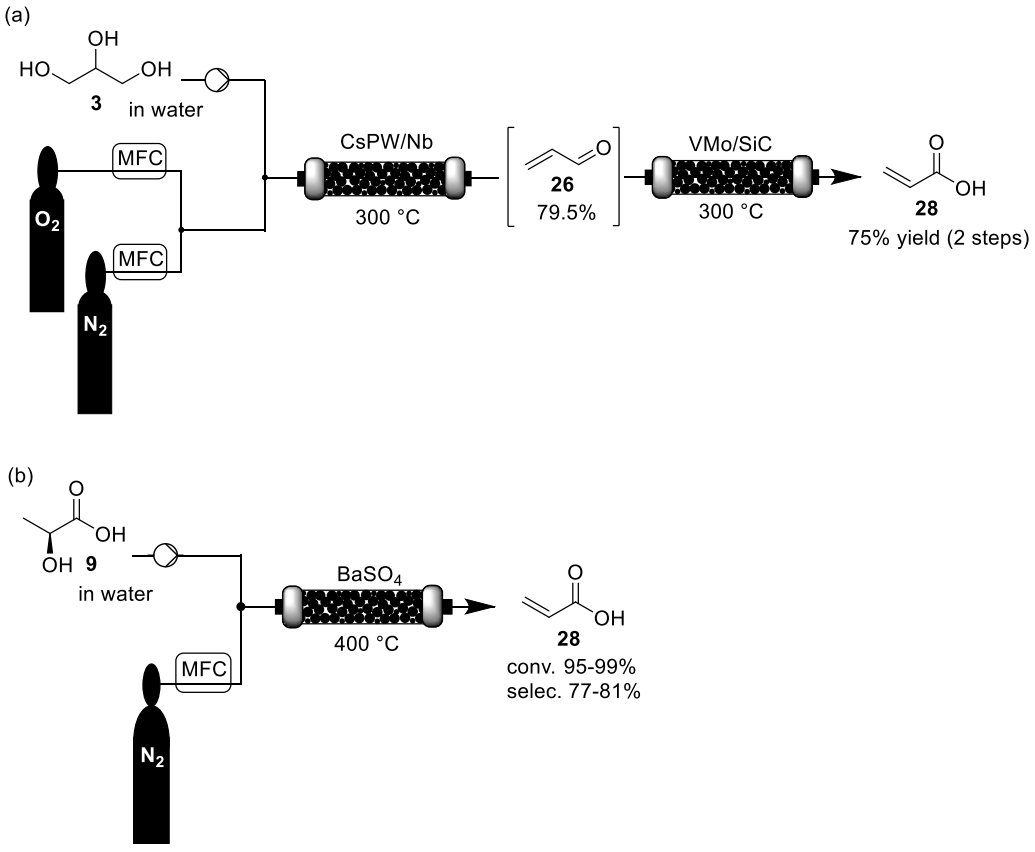

Figure 12. Biobased continuous flow strategies toward acrylic acid (**28**) using (a) glycerol (**3**) and (b) lactic acid (**9**) as substrates.

The lactic acid route involves a single step process consisting in a catalytic dehydration.[63] In a representative example, barium sulfate gave promising results because of its moderate acidity, preventing the formation of side-products such as acetaldehyde (see section 3.2.1).[64] In a follow-up paper, the authors of the study improved the preparation of the catalyst, promoting even further the formation of **28** (Figure 12 (b)). 81% yield was initially obtained at 400 °C under atmospheric pressure, with only mild deactivation noticed after 24 h time-on-stream. Major deactivation was obtained for longer operation time, but elimination of the carbonaceous deposits on the surface of the catalyst by calcination fully regenerated the activity.[65]

Maleic anhydride (**29**) is industrially manufactured from the catalytic oxidation of benzene (**23**) or *n*-butane. It is an important bulk chemical with various applications ranging from the preparation of unsaturated polyesters, to more specialized chemicals such as agrochemicals and surfactants.[66] Chemists engineered an alternative biobased process which uses furfural (**6**) as starting material (Figure 13). The oxidation of **6** toward **29** can be triggered with air using a vanadium phosphorus oxide catalyst. The reaction pathway likely involves the oxidation of furfural into 2-furoic acid, followed by decarboxylation and further oxidation toward the product. Stable catalytic activity could be obtained during a 25 h run at 350 °C under atmospheric pressure, with 92-99% conversion and 90-95% selectivity. Pure and solid maleic anhydride condensed downstream the gas-phase reactor.[67]

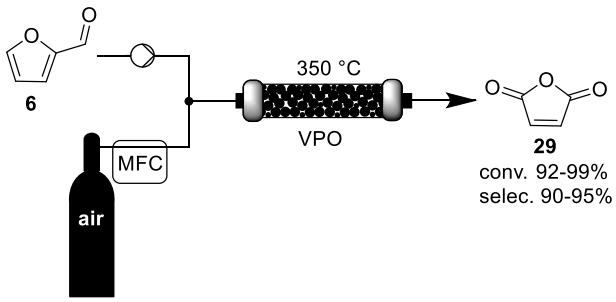

Figure 13. Gas-phase catalytic conversion of furfural (**6**) into maleic anhydride (**29**).

2.2.2 Diols

Diols are starting materials for the preparation of polyesters and polycarbonates. Many diols can be derived directly or indirectly from biomass resources through enzymatic or chemical methods. Typical examples include ethylene glycol, propanediols (**1, 2**), 1,4-butanediol (**4**), 1,6-hexanediol (**32**) and isosorbide (**33**). Additionally, in the context of growing concerns regarding plastic pollution,

polyesters and polycarbonates have been highlighted as green polymers due to their biodegradability and potentially biobased nature.[68]

Research efforts focused on the continuous flow catalytic hydrogenolysis of glycerol (**3**) for the preparation of 1,3-propanediol (**2**). However, the development of selective catalysts is challenging as many side-products are often encountered, sometimes in large amounts. Typical examples of side-products include 1,2-propanediol (**1**), ethylene glycol, as well as 1- and 2-propanol. In a representative example, Pt-WO_x supported on alumina afforded **2** in 66% selectivity with a 64% conversion of glycerol (Figure 14). Aqueous glycerol and molecular hydrogen were co-fed to the fixed-bed reactor, which was operated under 50 bar of counter-pressure. The presence of Brønsted acidic sites on the catalyst favored the formation of **2**, while 1,2-propanediol (**1**) was promoted by Lewis acidic sites.[69]

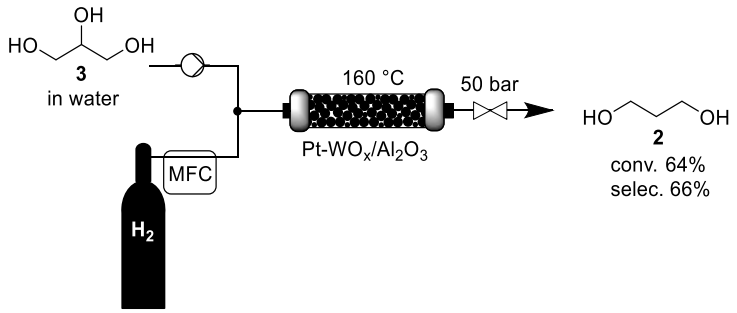

Figure 14. Continuous flow hydrogenolysis of glycerol (**3**) toward 1,3-propanediol (**2**).

Direct hydrogenation of levulinic acid (**8**) toward 1,4-pentanediol (**30**) was achieved using a continuous flow reactor and Rh-MoO_x/SiO_2 as a heterogeneous catalyst (Figure 15). While most of the research concerning the hydrogenation of **8** leads to the formation of γ-valerolactone (**21**, see section 2.1.4), the presence of molybdenum in the catalyst allowed the direct production of **30**. Quantitative conversion (>99%) and good selectivity (70%) were achieved at low temperature (80 °C) and high H_2 pressure (60 bar). **21** could be converted to 1,4-pentanediol as well, which most likely evidenced that γ-valerolactone is a reaction intermediate. Concerning the stability of the catalyst, no change of activity and/or selectivity could be evidenced after 30 h.[70]

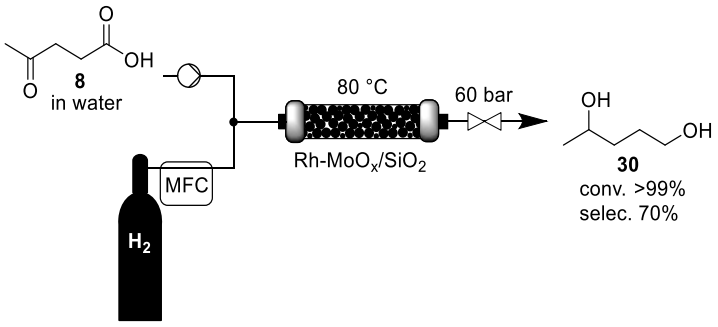

Figure 15. Liquid-phase continuous flow reduction of levulinic acid (**8**) toward 1,4-pentanediol (**30**).

HMF (**7**) was converted into 1,6-hexanediol (**32**) using a two-bed continuous flow setup at moderate temperature (100 °C) under high pressure in molecular hydrogen (70 bar, Figure 16). Pd supported on silica was loaded in the first bed and was selective for saturation of both the furan ring and the aldehyde moiety, resulting in selective 2,5-bis(hydroxymethyl)tetrahydrofuran (**31**) formation. The second heterogeneous catalyst, Ir-ReO_x supported on silica, triggered a ring-opening/hydrogenolysis reaction toward the formation of 1,6-hexanediol. The conversion increased fivefold, and the selectivity for 1,6-hexanediol was also enhanced, when the hydrogenolysis of **31** was transferred from batch to continuous flow conditions. High hydrogen pressure within the reactor inhibited over-reduction of **32** toward *n*-hexane (**13**), as hydrogen had a high affinity for the active sites, covering them and thus removing the target products from the catalyst. Progressive catalyst deactivation over a 24 h run resulted in a yield drop from 58% to 40%, and was ascribed to Re leaching. Lower yields were obtained upon utilization of a single Pd-Ir-ReO_x catalyst.[71]

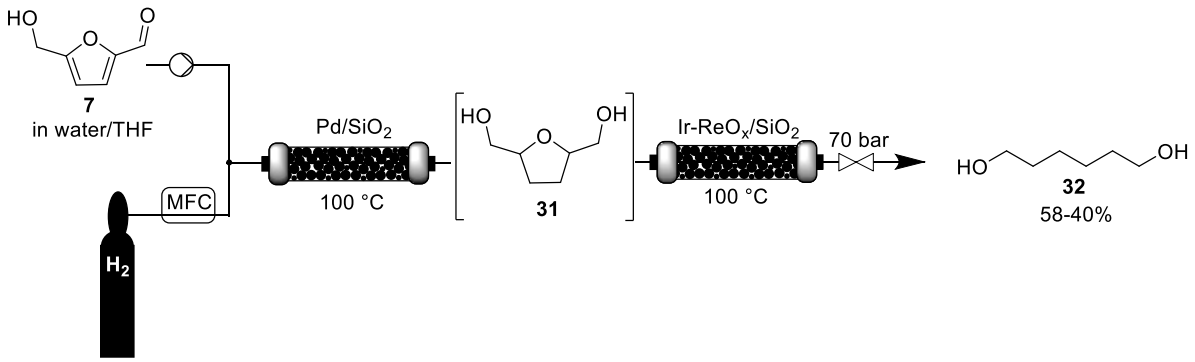

Figure 16. Two-step continuous flow procedure for the synthesis of 1,6-hexanediol (**32**) from HMF (**7**).

The dehydration of sorbitol (**5**) into isosorbide (**33**) is efficiently catalyzed by mineral acids such as HCl or H_2SO_4, but their utilization on a large scale is expensive since it involves dedicated equipment and demanding neutralization steps before disposal.[72] Huang and colleagues assessed the dehydration of sorbitol in a fixed-bed reactor packed with sulfated copper oxide (Figure 17). 68%

selectivity for the **33** at quantitative conversion were obtained at 200 °C under atmospheric pressure.[73]

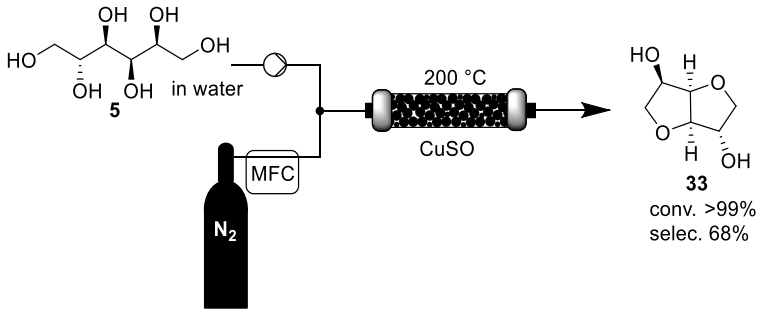

Figure 17. Continuous catalytic dehydration of sorbitol (**5**) into isosorbide (**33**).

2.2.3 Lactide

L-Lactide (**34**) is exclusively biobased, and readily prepared at an industrial scale using mature processes. It is used for the synthesis of polylactic acid, a biodegradable polyester. **34** is commonly prepared according to a two-step process involving L-lactic acid (**9**) polymerization into polylactic acid oligomers, followed by its depolymerization into **34**. This method is energy-intensive, as high reaction temperatures and continuous water or lactide (**34**) elimination are required. Additionally, only a moderate selectivity is typically obtained.[68, 72] Alternatively, L-lactic acid can be directly converted into L-lactide. In a representative example, Chang *et al.* developed a selective continuous synthesis of optically pure **34** from **9** using a SnO_2-SiO_2 nanocomposite catalyst (Figure 18). The yield in L-lactide reached 94% at 240 °C under atmospheric pressure. This excellent result was related to the favorable adsorption of **9** and desorption of **34** on the catalyst surface. The catalyst gave an outstanding stability of 2500 h of operation without any significant deactivation being noticed.[74] In a recent development, Sels *et al* have proposed a gas-phase flow process for the direct conversion of methyl lactates into L-lactide. With the best TiO_2/MCM-41 catalyst working at 220-260°C, a high lactide selectivity (~90%) was maintained even at high conversion (limited to about 50% by the thermodynamic equilibrium).[75, 76]

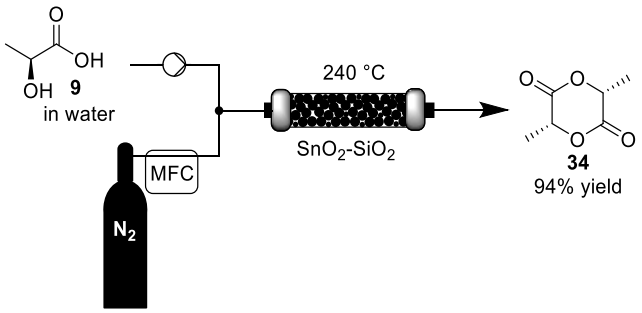

Figure 18. Continuous flow procedure for the direct synthesis of L-lactide (**34**) from lactic acid (**9**).

2.2.4 FDCA

2,5-Furandicarboxylic acid (**35**, FDCA) can be obtained either from furfural (**6**) or HMF (**7**), and has a bright forecast as renewable monomer for the polyester industry.[77] It is considered as a biobased alternative to terephtalic acid, which is widely used for the synthesis of polyethylene terephthalate (PET).[72] Researchers developed a cost-efficient continuous flow procedure using heterogeneous catalysis for the highly selective aerobic oxidation of **7** into **35** (Figure 19). Quantitative HMF conversion and 95-99% selectivity for FDCA were obtained over a Pt/C catalyst at moderate temperature (100 °C) and pressure (10 bar), under alkaline conditions and using air as an oxidant.[78]

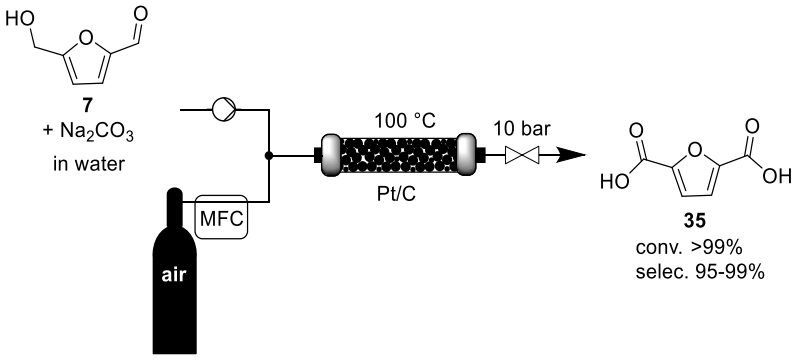

Figure 19. Continuous flow process for the air-mediated oxidation of HMF (**7**) into FDCA (**35**).

2.3 Other important olefinic building blocks

Acrolein (**26**) is used as starting material for the preparation of racemic methionine, pyridine bases, and can also be converted into acrylic acid (**28**, see section 2.2.1). **26** is currently manufactured from the oxidation of propene, although the gas-phase catalytic dehydration of aqueous glycerol (**3**) stimulated considerable research efforts in the last decade.[79, 80] The main challenge associated with the latter route is that some reaction intermediates tend to form carbonaceous deposits on the catalyst surface (coking), ultimately leading to its deactivation. The widely accepted mechanism for **26** formation involves a double dehydration of **3** on Brønsted acidic sites, while Lewis acidic sites tend to trigger the formation of hydroxyacetone.

Ueda *et al.* reported excellent results with an iron phosphate catalyst as packing material in a fixed-bed reactor. Elevated conversion (99-95%) and selectivity (96-90%) were maintained over 20 h of operation at 320 °C under atmospheric pressure.[81] A hierarchical meso-/macroporous silica functionalized with sulfonic acid moieties was developed by Yi and colleagues.[82] The hierarchical structure of the catalyst was beneficial for its catalytic stability, as pore clogging by coke deposition was reduced in such system. As a results, the catalyst remained stable for a 50 h run at 250 °C under atmospheric pressure, with quantitative glycerol conversion and a 73% selectivity in acrolein.[82] MCM-41 mesoporous molecular sieves were modified with heteropolyacids $H_3PW_{12}O_{40}$ and used as

heterogeneous catalysts by Shao and coworkers (Figure 20). The best results were obtained with Pd-$H_3PW_{12}O_{40}$/Zr-MCM-41, with glycerol conversions in the 87-97% range, and a selectivity for acrolein in the 80-85% range over 50 h of operation.[83] Hierarchical porous ZSM-5 zeolite were prepared and assessed for the reaction. The large mesopores enabled improved diffusion and therefore a more efficient removal of coke precursors from the catalytic sites. Quantitative glycerol conversion was maintained for 50 h of operation at 320 °C under atmospheric pressure, with a steady 82% acrolein selectivity.[84]

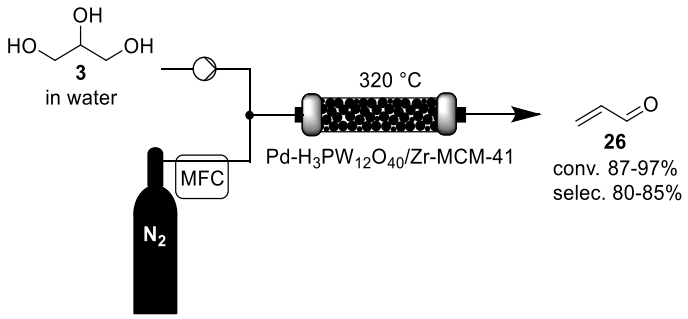

Figure 20. Catalytic dehydration of glycerol (**3**) into acrolein (**26**) in a gas-phase fixed-bed reactor.

Allyl alcohol (**36**) is a starting material for the preparation of important building blocks/monomers such as glycidol, allyl ethers and allyl esters.[85] Monbaliu *et al.* developed a metal-free deoxydehydration (DODH) of glycerol (**3**) into allyl alcohol under microfluidic conditions (Figure 21).[86] Triethyl orthoformate was used as DODH reagent in the presence of a catalytic amount of formic acid. The process relies on the formation of dynamic hybrid orthoesters. Allyl alcohol and its formate **37** were obtained in high combined yields (85-97%) for short residence times (1-6 min) at high temperatures (250-300 °C), with a major selectivity for the alcohol. The use of triethyl orthoesters enabled the processing of **3** containing various amounts of water, yet affording consistent results.[86]

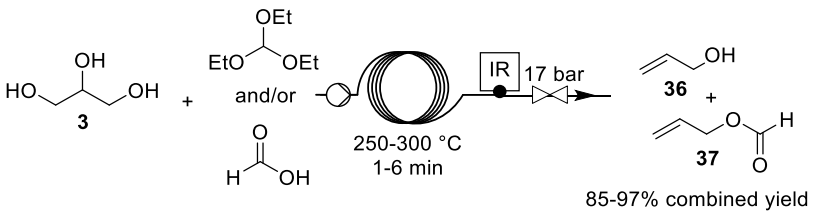

Figure 21. Microfluidic metal-free deoxydehydration of glycerol (**3**) toward allyl alcohol (**36**).

3. Specialty, fine and niche chemicals

3.1 Specialty monomers

Kappe and coworkers investigated the photocatalytic aerobic oxidation of HMF (**7**) for the preparation of 5-hydroxy-5-(hydroxymethyl)furan-2(5H)-one (**38**, Figure 22). The generation of singlet oxygen was performed using catalytic amounts of rose Bengal as photosensitizer. Solvent optimization revealed that an *i*PrOH/water mixture was the most suitable system to avoid acetalization, which was typically encountered when using methanol. Under optimized conditions, 98% yield in **38** was obtained in 20 min of residence time. Isomerization of the so-formed diol **38** was conducted in batch and gave 5-hydroxy-4-keto-pentenoic acid oligomers (**39**), highlighting the potential of **38** for the preparation of biobased polyesters.[87]

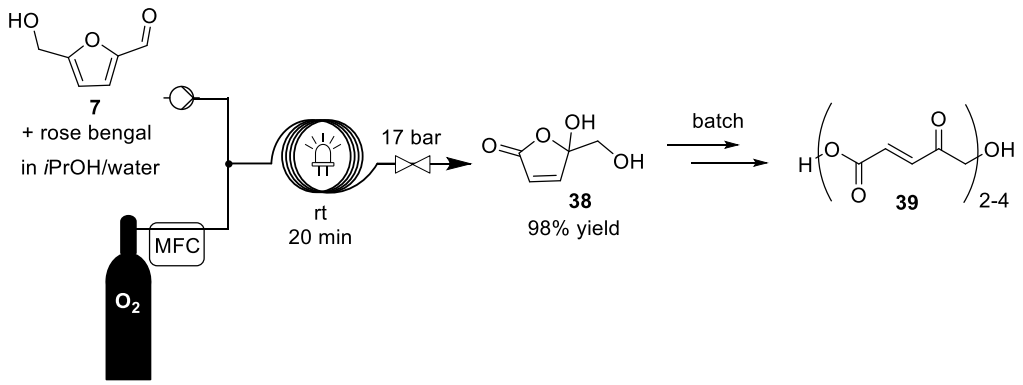

Figure 22. Flow photocatalytic oxidation of HMF (**7**).

3.2 Building blocks for the agrochemical and pharmaceutical industries

3.2.1 Carbonyls

Pyruvic acid (**40**) and its derivatives are useful synthons for the preparation of more elaborate scaffolds that are relevant for both the pharmaceutical and agrochemical fields. Examples include L-tyrosine and (*R*)-phenylacetylcarbinol, which are conveniently synthesized from pyruvate using biotechnologies. **40** can be prepared from the catalytic oxidation of lactic acid (**9**), although biochemical methods are also reported.[63] Hermans *et al.* reported a catalytic system based on silica-supported TEMPO for the aerobic oxidation of lactic acid to pyruvic acid.[88] A short contact time with the catalyst (15 s), as well as a mild process temperature (55 °C) and O_2 pressure (5 bar) enabled the preparation of **40** with 98% selectivity for a 98% lactic acid conversion. **9** was co-fed into the reactor, along with oxygen, as a dichloroethane solution in the presence of 5 mol% HNO_3 over the catalytic bed. Hensen and coworkers assessed MoO_3-TiO_2 as an oxide catalyst, and obtained **40** with up to 75% conversion and 80% selectivity at 200 °C and using air as oxidant (Figure 23). Different side-products were obtained upon utilization of the single oxide counterparts: TiO_2 gave mainly

methylsuccinic anhydride and propionic acid, while MoO_3 converted lactic acid into acetaldehyde and CO_2.[89]

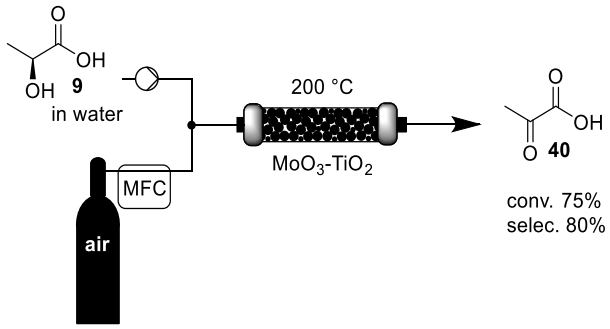

Figure 23. Continuous flow aerobic oxidative dehydrogenation of lactic acid (**9**) into pyruvic acid (**40**).

3.2.2 *N*-Heterocycles

The pyridine scaffold is encountered in numerous biologically active compounds, and pyridine (**41**) is thus a useful synthon for the elaboration of pharmaceuticals and agrochemicals.[90] Pyridine (**41**) and methylpyridines (**42**) were prepared from glycerol (**3**) in a two-step continuous flow process involving fixed-bed reactors (Figure 24). The catalytic dehydration of glycerol into acrolein (**26**) was conducted over HZSM-22 zeolite at 400 °C in a first packed bed reactor. Gaseous ammonia was mixed with the reactor effluents containing **26**, and the mixture was redirected toward a second bed consisting of zinc oxide supported on HZSM-5 zeolite operated at 425 °C. Pyridine (**41**) and methylpyridines (**42**) were obtained in a steady 61-65% combined yield over 9 h of operation, but the yield dropped for longer time-on-stream.[91]

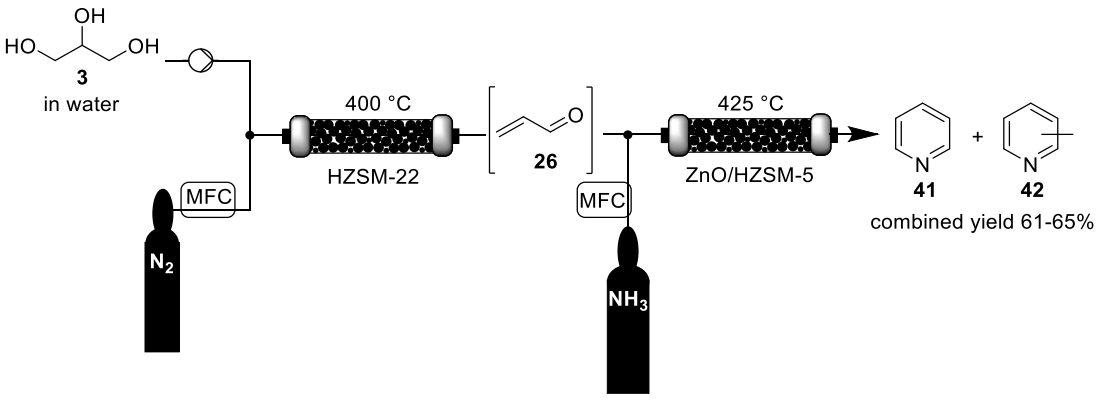

Figure 24. Two-step continuous flow synthesis of (methyl)pyridines (**41**, **42**) from glycerol (**3**).

A related strategy for the synthesis of quinoline (**44**) consisted in reacting aniline (**43**) and glycerol (**3**) in a fixed-bed reactor operated at 470 °C (Figure 25). There is however a main difference with the above-mentionned sequential process for the synthesis of pyridines. In the present example, the

dehydration of **3** into **26** was followed by a condensation with **43** toward **44** in cascade using a single nickel-modified mesoporous β-zeolite catalyst. The catalyst gave initially a good yield for quinoline (up to 71% after 2 h), which however decreased to 15% after 6 h. Catalyst regeneration by calcination was possible.[92]

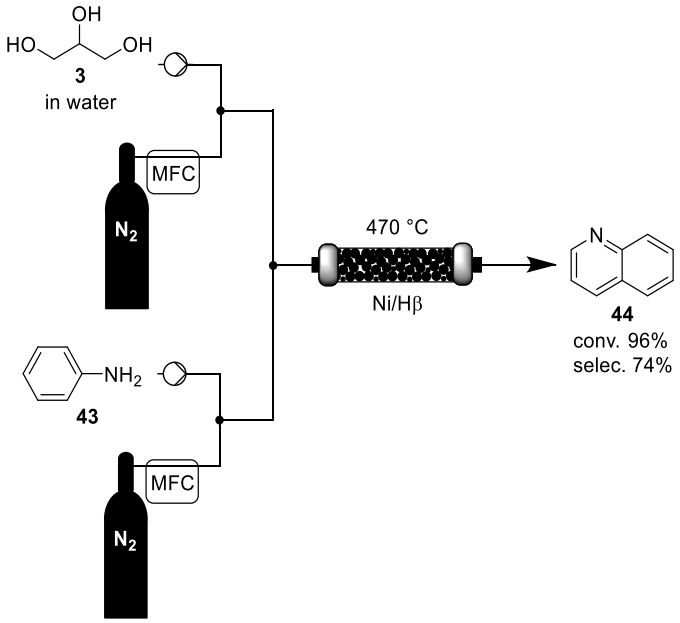

Figure 25. Gas-phase continuous flow synthesis of quinoline (**44**) from glycerol (**3**) and aniline (**43**).

Similarly to pyridine, the indole moiety is frequent in biologically active molecules. Synthetic methodologies for the functionalization of this heterocycle are abundant and many drugs and agrochemicals bear the indole scaffold.[93] Fu and coworkers reported a direct synthesis of indole and methylindoles (**45**) based on the pyrolysis of furfural (**6**) in the presence of ammonia (Figure 26). The reaction took place in a fixed-bed reactor packed with HZSM-5 zeolite and operated at 600 °C under atmospheric pressure. Up to 33% combined yield was obtained with furfural as feedstock, while the use of HMF (**7**) resulted in only 7% combined yield.[94]

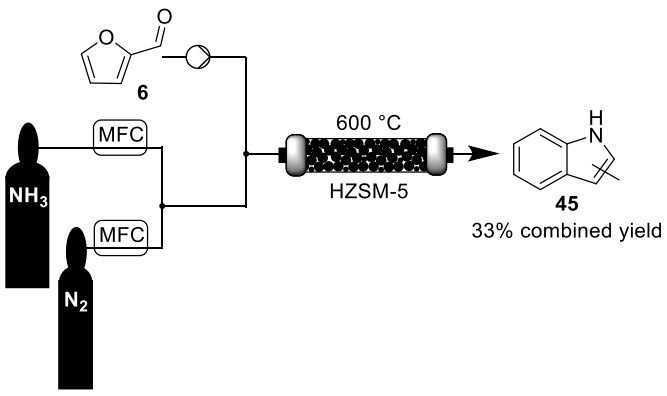

Figure 26. Gas-phase continuous pyrolysis of furfural (**6**) into (methyl)indoles (**45**).

2-Methylpyrazine (**47**) is the starting material for the synthesis of pyrazinamide, an antituberculosis drug listed on the World Health Organization's List of Essential Medicine. Venugopal and colleagues evaluated a $ZnO\text{-}ZnCr_2O_4$ catalyst for the continuous preparation of 2-methylpyrazine through the dehydrocyclization of glycerol (**3**) in the presence of a stoichiometric amount of ethylenediamine (**46**, Figure 27). During a 48 h run under optimized conditions, the conversion in glycerol was maintained constant at 96%, and selectivity in **47** remained at a steady 74%. It was shown that a combination of both weakly acidic and strong basic sites is desirable to promote the dehydrocyclization reaction.[95]

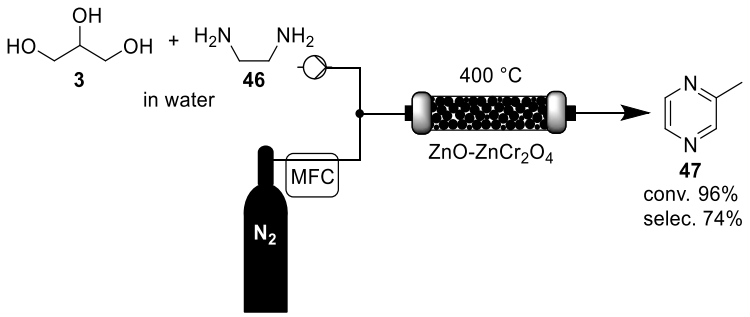

Figure 27. Continuous flow synthesis of 2-methylpyrazine (**47**) from glycerol (**3**) and ethylenediamine (**46**).

3.2.3 *O*-Heterocycles

Furan (**48**) is already manufactured at an industrial scale *via* the decarboxylation of furfural (**6**) decarbonylation over Pd-based catalysts.[96] Zheng and colleagues evaluated the gas-phase continuous reaction on Pd nanoparticles supported on silicalite-1 zeolite. Quantitative yield could be achieved at 250-275 °C depending on the proper tuning of the zeolite wettability. The enhanced performances were ascribed to an appropriate control of diffusion within the catalyst, where **6** and by-products adsorption and **48** desorption, were favored. A prolonged run conducted at 200 °C evidenced mild deactivation of the catalyst after 45 h time-on-stream (Figure 28). Catalyst coking was pointed out as deactivation mechanism, but complete regeneration of the catalytic activity was possible by calcination. Pd leaching or sintering remained negligible.[97]

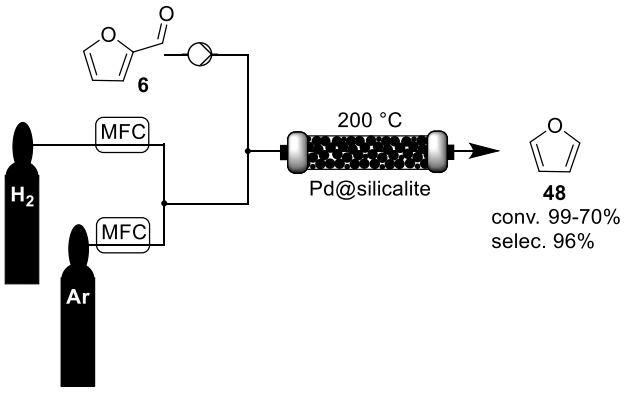

Figure 28. Gas-phase continuous decarbonylation of furfural (**6**) into furan (**48**).

3.3 Other high value-added targets

Tsupova *et al.* prepared phenols from HMF (**7**) using batch and continuous flow processing (Figure 29).[98] Propargyl ether **49** was synthesized under continuous flow conditions. The reaction took place in ethyl acetate, which also reacted with **7** and gave about 15% of ethoxymethylfurfural. Good yield toward **49** was obtained using a fixed bed reactor loaded with Amberlyst 15, and up to ten 20-minute runs were possible using the same catalytic bed, without any deactivation. Then, after derivatization of the aldehyde in batch, a gold-catalyzed transformation afforded phenol derivatives, such as **50**.

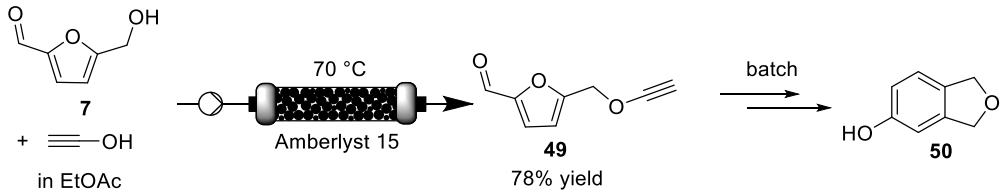

Figure 29. Combined batch and flow approach for the upgrading of HMF (**7**) into phenol **50**.

Monbaliu *et al.* studied the photoaddition of alcohols onto fumaric (**10**) and itaconic (**11**) acids, affording γ-butyrolactones (**52**, **53**) in 47-76% isolated yield. Process conditions involved pumping an alcoholic solution of **10** or **11** and of a photosensitizer, such as benzophenone (**51**), into a glass photoreactor irradiated at 365 nm. The sequence of reactions involved alcohol-derived radical formation, Michael addition-type reaction, and lactonization. In-line NMR monitoring was implemented downstream the reactor, and ensured rapid optimization of the process. The optimized process was further scaled-out in a pilot-scale continuous flow photoreactor, affording a productivity of 83 g day^{-1} for terebic acid.[99]

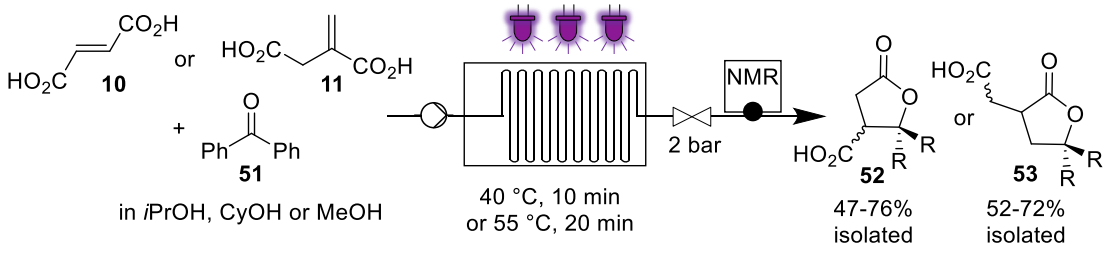

Figure 30. Continuous flow photocatalytic addition of alcohols to fumaric (**10**) and itaconic (**11**) acids toward butyrolactones **52, 53**.

Cantillo and Kappe described the conversion of levulinic acid (**8**) into 4-oxo-pentanitrile (**54**) using a direct acid-nitrile exchange reaction triggered in supercritical acetonitrile (T_c = 275 °C, P_c = 48 bar).

85% isolated yield in **54** was obtained in 25 min of residence at 350 °C under 65 bar of counter-pressure (Figure 31).[100]

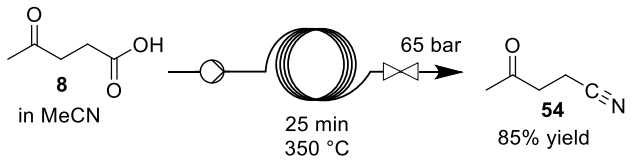

Figure 31. Supercritical acid-nitrile exchange under flow conditions.

4. Fuels and additives

4.1 Derivatives of glycerol

Glycerol-derived esters, ethers and ketals have emerged as promising biobased fuel additives.[101] Fuel additives are blended with gasoline or diesel for different purposes, *i.e.* increasing engine and fuel performances, reducing harmful gases and particles emission, protecting engine toward corrosion.

Glycerol acetates **55** and **56** were prepared from the reaction between glycerol (**3**) and acetic acid in supercritical CO_2 conditions within a fixed-bed reactor packed with Amberlyst 15 (Figure 32). Under optimized conditions, quantitative selectivity for **56** was initially obtained at 110 °C under 200 bar of counter-pressure. A 25 h run was conducted, and the selectivity for **56** decreased from quantitative to 60% in favor of **55** during the first 5 h, and then stabilized for the remaining 20 h. Noteworthy, this decrease in **56** selectivity was accompanied by a **55** and **56** combined yield increase from 40% to 80%.[102]

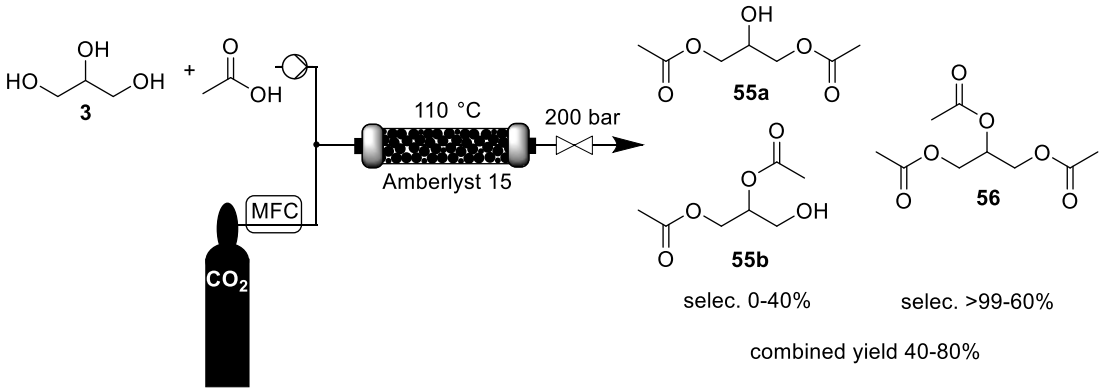

Figure 32. Continuous esterification of glycerol (**3**) in supercritical CO_2.

Glycerol *tert*-butyl ethers are typically prepared from the reaction of glycerol (**3**) with isobutene, but an emerging alternative route uses *tert*-butanol as reagent instead. Viswanadham and Saxena

studied the reaction in batch and continuous flow reactor (Figure 33).[103] Nano-BEA zeolite was depicted as the most efficient acidic catalyst to trigger the reaction. Its acidity was not the only key parameters to rationalize the overall high selectivity obtained as physical properties such as the large pore volumes and sizes were also critical. A higher selectivity for **58**, in detriment to glycerol-derived monoethers, was obtained in flow. It was proposed that water released by the reaction was not efficiently removed from the catalyst in the batch reactor, thus decreasing the selectivity toward **58**. Under optimized conditions, 45% and 54% selectivity for **57** and **58**, respectively, were obtained for a quantitative glycerol conversion. The catalyst activity was maintained for 24 h without any noticeable decrease in activity.

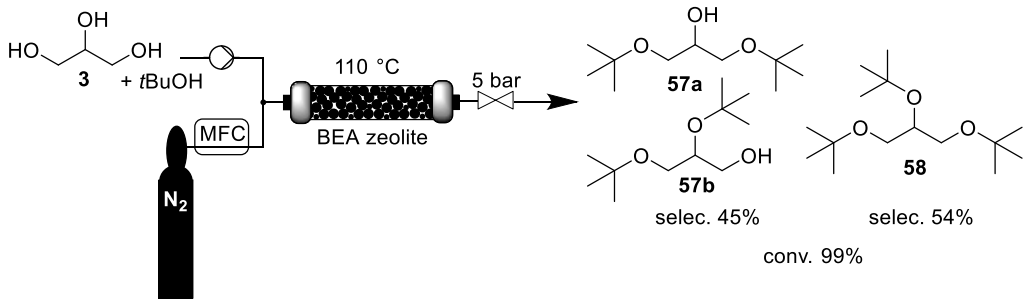

Figure 33. Continuous flow etherification of glycerol (**3**) using tert-butyl alcohol as reagent.

Solketal (**59**), the ketal derived from glycerol (**3**) and acetone, was prepared over $AlF_3 \cdot 3H_2O$ in a fixed-bed reactor (Figure 34).[104] The best results were obtained at 100 °C, and the catalyst was able to process all glycerol grades, containing water, methanol and sodium chloride as impurities. High glycerol conversion (71-84%) and quantitative selectivity for **59** were obtained without any loss of activity over 48 h of operation. No catalyst leaching was reported. The scope of the process was extended to the acetalization of 2-butanone, which also gave promising results.

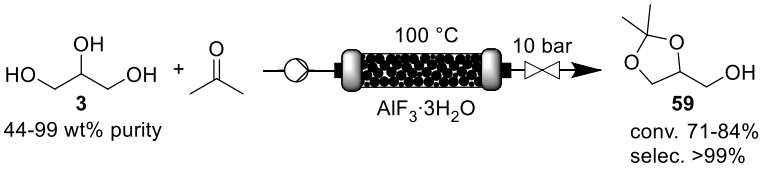

Figure 34. Ketalization of glycerol (**3**) into solketal (**59**) in fixed-bed flow reactor.

Solketal *tert*-butyl ether (**60**, STBE) was synthesized by Stevens and colleagues according to a two-step sequential process (Figure 35).[105] The glass mesofluidic reactor was devised for pilot-scale production, and had an internal volume of 56 mL. **59** was first prepared in the presence of a catalytic amount of sulfuric acid. 98% yield and a productivity of 11 kg h^{-1} were obtained in 26 s of residence

time at 75 °C. In the second step, solketal (**59**) was reacted with isobutene in the presence of catalytic amount of sulfuric acid. To avoid oligomerization of isobutene, multipoint injections were implemented. STBE was obtained in 85% yield with a 12 kg h^{-1} productivity, in 41 s of residence time at 90 °C. The setup sustained a virtual productivity of 90 t y^{-1} of **60**.

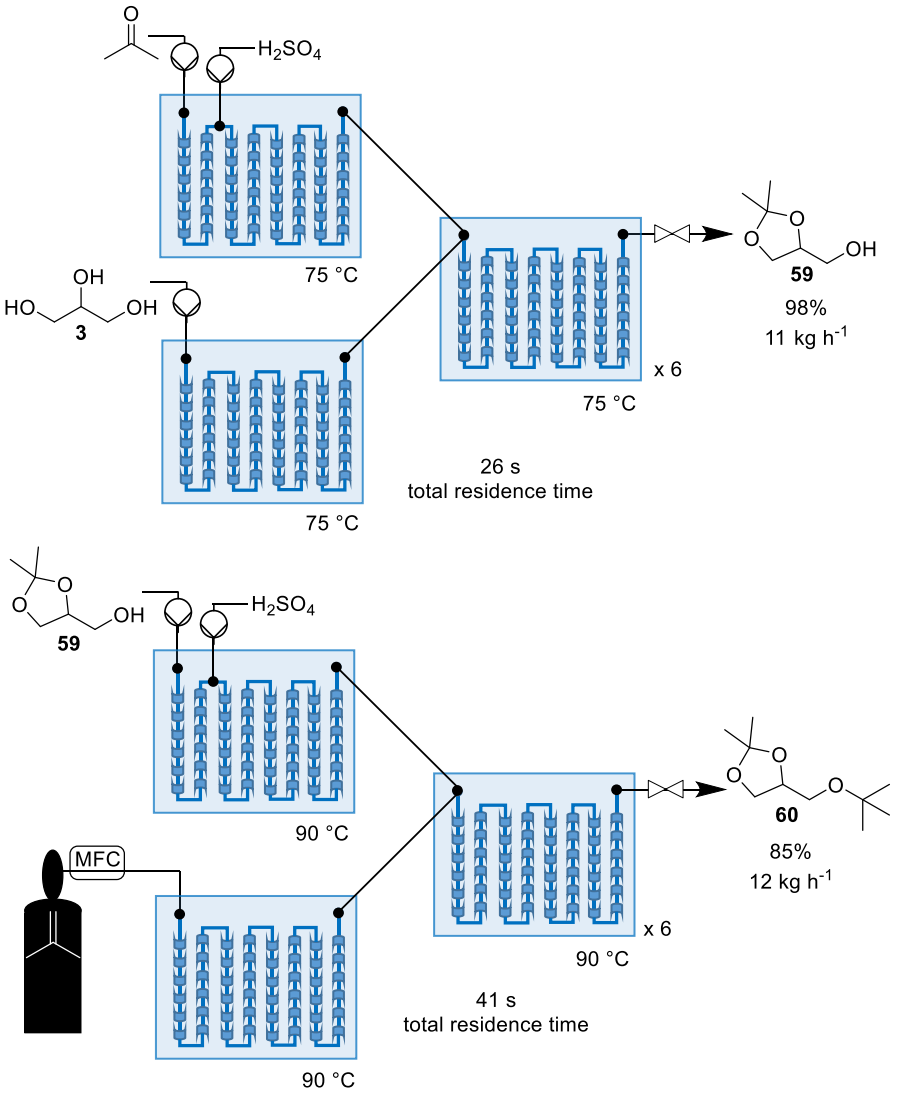

Figure 35. Two-step sequential continuous flow process for the synthesis of solketal *tert*-butyl ether (**60**).

4.2 Derivatives of levulinic acid

Alkyl levulinates raise a strong interest as biobased fuel additives. They also have potential applications in the perfume and flavor industries.[106] Kong *et al.* evaluated cerium salt of phosphotungstic acid supported on silica gel pellets as heterogeneous catalysts for the continuous flow esterification of ethanol with levulinic acid (**8**). **8** was injected as an ethanol solution and quantitative selectivity and 99% conversion were maintained for 50 h upon operation of the catalytic

bed at 160 °C under atmospheric pressure.[107] Similarly, Vaccaro and colleagues studied the continuous flow synthesis of alkyl levulinates using various sulfonic acid-based resins (Figure 36).[108] Among the various acidic catalysts, the best results were obtained over Aquivion mP98, bearing $-CF_2CF_2SO_3H$ functional groups, partially due to its non-porous structure which prevents water adsorption. Preliminary attempts were performed in batch with 1-pentanol (**61**) as reagent and various other alcohols were then assessed as well. Conversions in the 50-84% range were obtained. Finally, the process was tested under continuous flow conditions, affording a 4.8 g h^{-1} productivity for **62** at quantitative **8** conversion under optimized conditions.

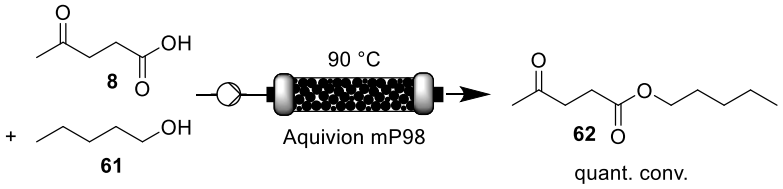

Figure 36. Esterification of *n*-pentanol (**61**) with levulinic acid (**8**) in fixed-bed flow reactor.

Alkyl esters of valeric (pentanoic) acid, commonly called "valeric biofuels", can be blended at high volume percentage both with gasoline and diesel, and give satisfactory fuel properties. Lange *et al.* studied their preparation, and evaluated their performances over a successful 250 000 km road trial.[109] Valeric biofuels are typically prepared in a three-step process from levulinic acid (**8**) including hydrogenation into γ-valerolactone (**21**, see section 2.1.4), **21** hydrogenation into valeric acid (**63**) followed by a final esterification toward alkyl valerates. Li and colleagues developed a cascade process featuring a single bifunctional Ni-K/HZSM-5 catalyst for the direct conversion of **8** into a mixture of valeric acid (**63**) and ethyl valerate (**64**, Figure 37).[110] Potassium-doping of the Ni/HZSM-5 catalyst improved its performances in terms of yield and stability through acidity regulation. Optimized process conditions consisted in co-feeding an EtOH solution of **8** and hydrogen over the fixed bed reactor operated at 240 °C under 30 bar of counter-pressure. Quantitative conversion and >90% combined yield for **63** and **64** were almost maintained for 80 h of operation.

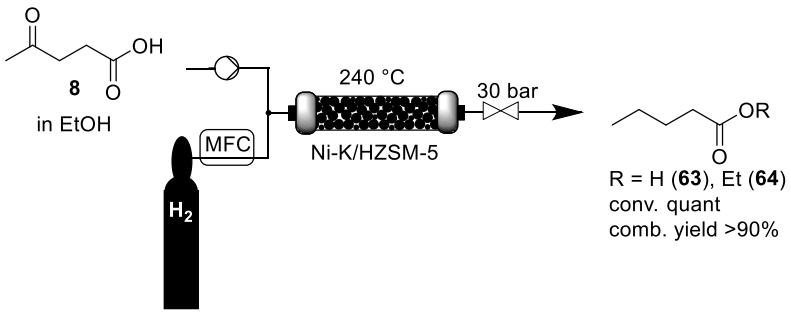

Figure 37. Continuous flow cascade process for the upgrading of levulinic acid (**8**) into valeric biofuels.

4.3 Derivatives of HMF and furfural

2-Methylfuran (MF, **18**) and 2,5-dimethylfuran (DMF, **65**) are prepared from the hydrogenolysis of furfural (**6**) and hydroxymethylfurfural (**7**), respectively. They have been highlighted as promising biofuels, having an energy density (28.5-29.3 MJ/L) higher than ethanol (21 MJ/L) and slightly inferior to gasoline (31.9 MJ/L), and showing excellent properties as fuels and fuel additives. Experts however anticipated that the production of **18** and **65** is still too challenging and thus expensive, to make them commercially viable.[111, 112]

In a representative example disclosing the continuous flow hydrogenolysis of furfural into MF, Zhua *et al* reported copper supported on silica as a catalyst (Figure 38). Quantitative conversion and 90% selectivity were steadily obtained over 210 h of operation at 220 °C under atmospheric pressure. The high interaction between metallic copper active sites and the support accounted for these excellent results.[113]

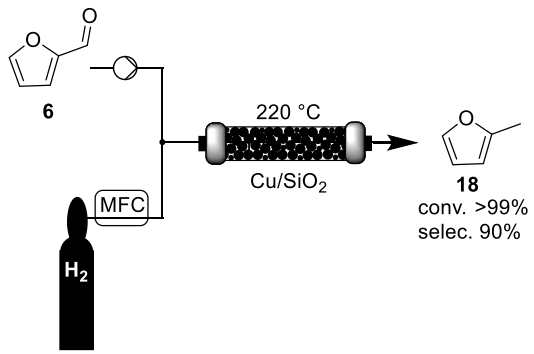

Figure 38. Hydrogenolysis of furfural (**6**) toward 2-methylfuran (**18**) in fixed-bed reactor.

Dumesic and coworkers pioneered the preparation of DMF in 2007 (Figure 39).[114] The H_2-mediated hydrogenolysis of a crude HMF solution in *n*-butanol, prepared though dehydration of fructose, was preliminary assessed in batch. Copper-ruthenium supported on carbon was developed as efficient catalyst. The reaction was then translated to gas-phase continuous flow conditions, affording 72% yield in DMF at 220 °C. By comparison to the batch process, the continuous procedure benefited from a reduced formation of by-products, and enabled straightforward *in situ* regeneration of the catalyst after deactivation. Deactivation was observed only for highly concentrated feedstock solutions of HMF. Finally, DMF was separated from the crude reactor effluent by distillation, and co-evaporated with water. It was then readily recovered as it is not miscible with water.

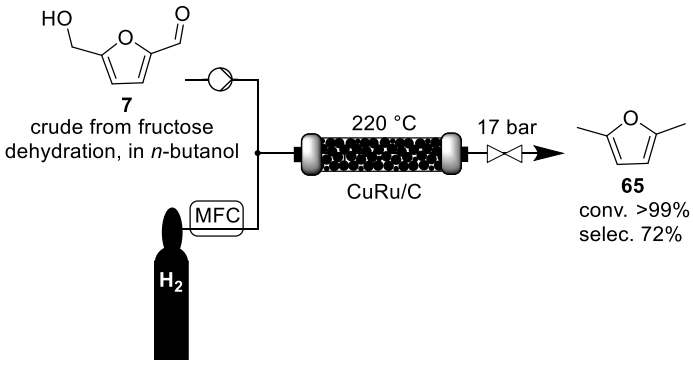

Figure 39. Continuous hydrogenolysis of HMF (**7**) for the preparation of 2,5-dimethylfuran (**65**).

Recent technological developments for the continuous flow hydrogenolysis of HMF toward DMF involves new catalysts and H_2-free alternative reductants. For instance, a HMF and cyclohexanol solution in dioxane was co-fed with N_2 over a Ni-Cu catalyst operated at 240 °C under atmospheric pressure. 99% conversion were reported for both cyclohexanol and HMF. DMF and phenol were obtained with 99% and 98% selectivity, respectively. The catalyst remained stable for 160 h of operation, despite a mild catalyst leaching.[115] Aliphatic alcohols were reported as efficient reductants as well. *i*PrOH provided DMF in 72% yield at 180 °C and 25 bar of counter pressure over a Pd/Fe_2O_3 catalyst.[116] 1,4-butanediol (**4**) gave DMF in 72% yield using a catalyst based on copper nanoparticles dispersed in AlO_x, which was operated at 220 °C and 16 bar. γ-Butyrolactone (**20**) was concomitantly formed from 1,4-butanediol lactonization (see section 2.1.4).[117]

The reaction of furfural (**6**) with ketones through aldol condensation, followed by hydrogenation/hydrogenolysis to remove oxygen and saturate double bonds, is a promising route for increasing the carbon-chain length of furfural-based biofuels. The so-formed long-chain hydrocarbons have the potential to be blended with diesel or used as fuels.[111] Zhu and coworkers studied the aldol condensation of furfural (**6**) with various ketones **66** and catalyzed by 1,5,7-triazabicyclo[4.4.0]dec-5-ene (**67**, Figure 40). Preliminary experiments were performed with 3-pentanone in batch, and then the process was translated to continuous flow conditions. The flow reactor appeared to be more efficient than the batch system to perform the single or double condensation reaction as reaction times were reduced from 2-4 h to 20 min, and yet 87-91% yield were obtained. The catalyst could be removed downstream by a straightforward liquid-liquid extraction. The scope of the methodology was finally extended to single and double aldol condensation with acyclic symmetrical and unsymmetrical ketones, as well as cyclic ketones, giving he corresponding enones **68** and **69** in 72-92% yield.[118]

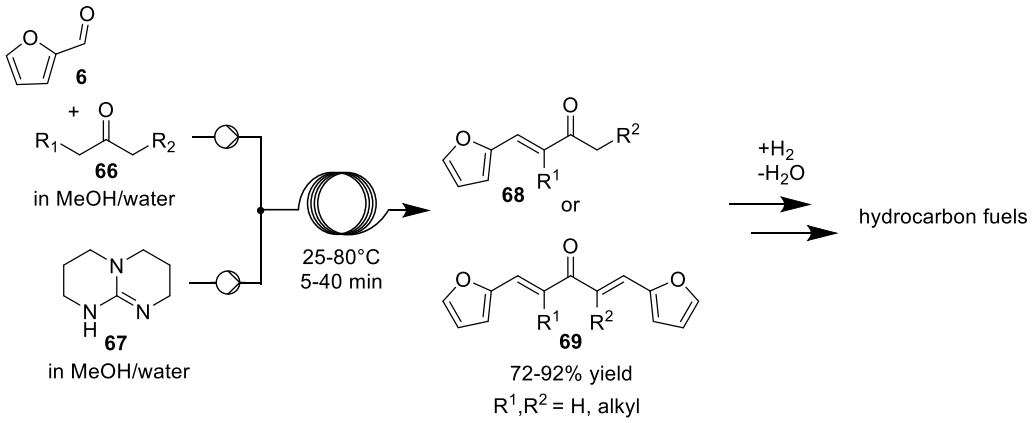

Figure 40. Homogeneous continuous flow aldol condensation toward furfural-based fuel precursors.

5. Conclusion and Perspectives

Intense research efforts are currently dedicated to assess continuous flow technology for upgrading of biobased platforms. Given the steady increase in reports both from the primary and the patent literatures, it can be foreseen that it will become a blooming research area in the near future. Future developments will most likely rely on two main aspects of flow chemistry, namely, the possibility to explore new process windows and the perspective of seamless scalability while keeping a low global footprint for the process. There are, however, still major challenges to be dealt with in this research area. These challenges concern both the specific chemistry forupgrading biobased platforms and the development of appropriate continuous flow technologies for such processes. Upgrading biobased platforms at the industrial level is economically attractive as long as the process conditions are robust enough to sustain long operation campaigns with minimal maintenance, and as long as the process ensures low waste generation and straightforward downstream purification. Robust process conditions rely on the development of cheap, readily available and selective catalysts that are operated at lower temperature to prevent coking and/or deactivation. Besides, since biobased platforms suffer from an inherent variability of their quality, processes for their upgrading must be somewhat accommodating. Low waste generation not only concerns the use of additives or reaction selectivity, but also relates to the use of solvents. Since most of biobased platform molecules are either viscous liquids or solids, their successful use for commercial applications under continuous conditions requires solvents and/or additives to improve processability in most instances, thus negatively impacting the overall footprint of the process. Recent developments in the integration of innovative downstream technologies

such as membrane separation or pervaporation will likely support the further development of this research area.

Acknowledgements

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