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Continuous Flow Upgrading of Selected C2-C6 Platform Chemicals Derived from Biomass

Journal:	<i>Chemical Reviews</i>
Manuscript ID	cr-2019-00846k.R1
Manuscript Type:	Review
Date Submitted by the Author:	07-May-2020
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Continuous Flow Upgrading of Selected C₂-C₆ Platform Chemicals Derived from Biomass

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ABSTRACT

The ever increasing industrial production of commodity and specialty chemicals inexorably depletes the finite primary fossil resources available on Earth. The forecast of population growth over the next 3 decades is a very strong incentive for the identification of alternative primary resources other than petro-based ones. In contrast with fossil resources, renewable biomass is a virtually inexhaustible reservoir of chemical building blocks. Shifting the current industrial paradigm from almost exclusively petro-based resources to alternative bio-based raw materials requires more than vibrant political messages; it requires a profound revision of the concepts and technologies on which industrial chemical processes rely. Only a small fraction of molecules extracted from biomass bears significant chemical and commercial potentials to be considered as ubiquitous chemical platforms upon which a new, bio-based industry can thrive. Owing to its inherent assets in terms of unique process experience, scalability and reduced environmental footprint, flow chemistry arguably has a major role to play in this context. This review covers a selection of C₂ to C₆ bio-based chemical platforms with existing commercial markets, including polyols (ethylene glycol, 1,2-propanediol, 1,3-propanediol, glycerol, 1,4-butanediol, xylitol and sorbitol), furanoids (furfural and 5-hydroxymethylfurfural) and carboxylic acids (lactic acid, succinic acid, fumaric acid, malic acid, itaconic acid and levulinic acid). The aim of this review is to illustrate the various aspects of upgrading bio-based platforms molecules toward commodity or specialty chemicals using new process concepts that fall under the umbrella of continuous flow technology.

1. Introduction

1.1. A Brief Historical Overview of the Sourcing of Chemicals

The successful identification of primary sources for the preparation of valued-added organics has driven the development of Mankind since its earliest stages.¹⁻⁷ From about 300000 BCE to

the dawn of the 19th century, most of the raw organic chemicals were extracted from renewable natural resources including dead or alive organisms or the products of their metabolisms, hence providing Humanity with the first medicines, dyestuff materials, fuels and other commodity chemicals. With the increasing level of technology, a progressive transition from simple extraction to more advanced protocols for the transformation of raw organics toward added-value chemicals became commonplace. Even in the pre-modern era, availability, robustness and relative simplicity were key concepts for the large-scale transformation of organic matter. The further rise of scientific maturity and the progressive disappearance of Vitalism opened new perspectives for the production of value-added organics from resources other than directly related to biological organisms, including the various grades of coal.⁸ The 19th century is often presented as pivotal for the development of large scale industrial processes with the thriving of coal-based industrial processes to its apogee during the first half of the 19th century.^{8,9} The second half of the 19th century has witnessed the emergence of an almost exclusively petro-based industrial chemistry, crude oil being much more versatile than coal for feeding the diversity of commercial applications relying on organics.^{8,10} Only niche commercial applications such as for the perfume industry remained reminiscent of the exclusively bio-based past of valued-added organics.¹¹ The hegemony of the fossil-based economy lasted through the 20th century and is still flourishing through the 21st century.^{9,12}

According to UN, “*the world’s population is expected to increase by 2 billion persons in the next 30 years, from 7.7 billion currently to 9.7 billion in 2050 and could peak at nearly 11 billion around 2100*”.^{13,14} Such a raise in population over the next few decades will be accompanied with an exponentially increasing demand for Earth’s primary resources.¹⁴ These facts thus resonate with the finite nature of the fossil resources, regardless of the development of new extraction technologies, the identification of new potential oil reservoirs and

commercially exploitable sources of alternative fossil resources such as oil and shale gas from the beginning of the 21st century.¹⁵ One unavoidable question thus remains: how is Humanity going to sustain its current quality of life standards for an ever increasing population?

By contrast with fossil resources, renewable biomass is virtually inexhaustible and relies mostly on terrestrial plants with an estimated global production of $1.7 \cdot 10^{11}$ tons per year.^{16,17} Biomass is defined as a “*material of biological origin excluding material embedded in geological formations and/or fossilized*” that can be used for the production of energy or as starting material for the production of various commodity and specialty materials.¹⁸ The composition of biomass is much more diverse and complex than raw oil, hence imposing significant differences between a petroleum refinery and a biomass refinery (also known as biorefinery).^{17,19} Various types of biomass can be used as feedstock, mostly terrestrial biomass, including lignocellulosic material (cellulose, lignin and hemicellulose) typically from forestry, agriculture-derived feedstock (sugar, starch and oil), waste products (e.g. from the pulp industry, animal fat from the food industry) as well from marine biomass.^{17,20–25} While crude oil is typically rich in gaseous, liquid and solid hydrocarbons with high C/O ratio, biomass typically contains complex biomacromolecules with a much lower C/O ratio (Figure 1).^{17,21–26}

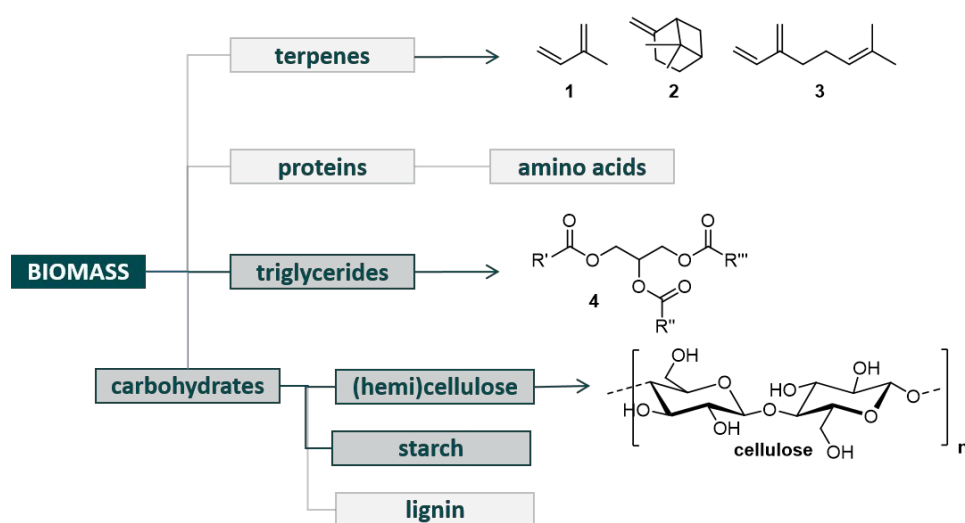


Figure 1. Main types of bio-based feedstock from biomass. This review essentially concerns bio-based chemical platforms obtained from triglycerides and carbohydrates (dark green).

Starting from biomass as a primary resource, the first steps including mechanical processes, (thermo)chemical and biochemical processes typically aim at decreasing the molecular complexity and increasing the C/O ratio toward smaller chemical building blocks. The latter are named bio-based chemical platforms and are defined by the US Department of Energy (US DoE) as “*molecules with multiple functional groups that possess the potential to be transformed into new families of useful molecules*”.²⁶ This further transformation of bio-based platforms to value-added chemicals is referred to here as upgrading.^{27,28} Processing of raw biomass toward bio-based platforms typically comes with much higher Environmental Factor (E-factor, a popular metric for green chemistry introduced by Sheldon, which is defined as the ratio of the mass of waste per mass of product) than petro-based processes.^{16,21,29}

Among bio-based chemical platforms, several additional subclasses are considered including drop-in, smart drop-in and dedicated bio-based chemicals (Figure 2).³⁰ Drop-in bio-based chemicals, such as bio-based ethylene, are defined as structurally identical to their petro-based counterparts with well-established commercial processes and markets.³⁰ Smart drop-in bio-based compounds answer the same definition, with the nuance that their bio-based production offers major assets compared to the existing petro-based processes.³⁰ Glycerol, 1,3-propanediol, 1,4-butanediol and succinic acid for instance fall all under the umbrella of smart drop-in.³⁰ Compounds belonging to this class are the most straightforward to implement commercially within a context of transitioning from an exclusively petro- to an alternative bio-based scheme. Other bio-based platform chemicals usually belong to the dedicated bio-based chemicals subclass; these are compounds produced through independent bio-based processes, non-related to existing fossil technologies or facilities.³⁰ Dedicated bio-based chemicals combine both

significant assets and potential disadvantages compared to drop-in bio-based chemicals. These compounds, such as 3-hydroxypropionic acid, itaconic acid, furfural, 5-hydroxymethylfurfural and its derivatives, bear significant potential since they offer unique opportunities for the design of novel commercial products, while they suffer from the lack of well-established commercial processes and markets.³⁰

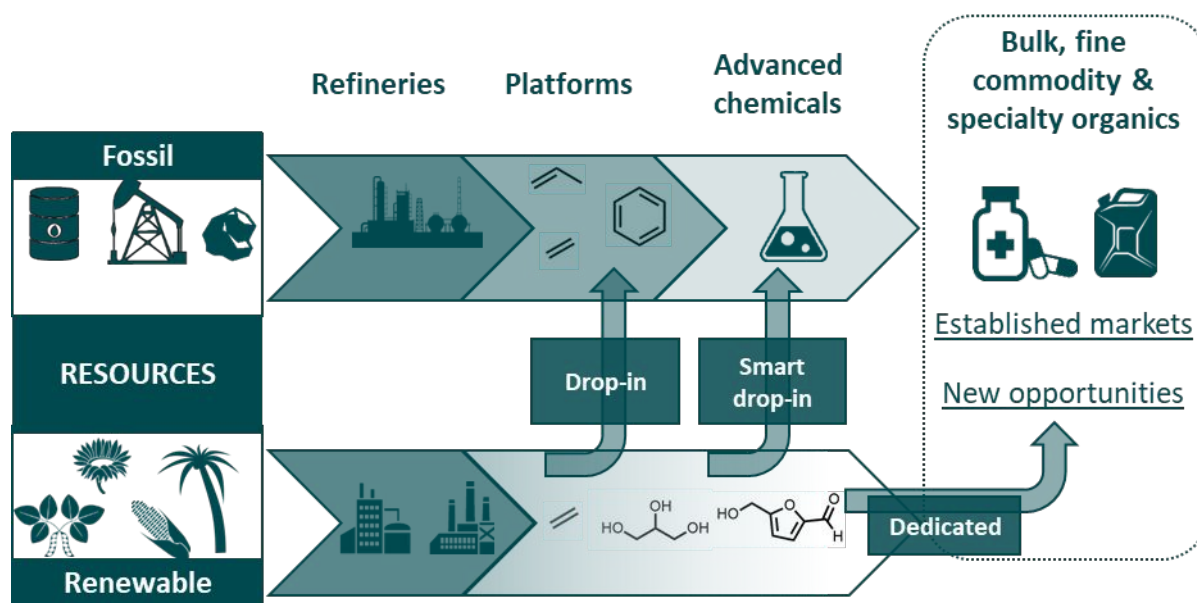


Figure 2. Simplified petro- and bio-based strategies for the commercial production of value-added chemicals.

The interest in a bio-based economy is not new and raised again when it became a societal and political concern in the late 1980's. Sustainable development and bio-based economy are arguably born to the world as a strong political message in 1987 in a report from the World Commission on Environment and Development.³¹ Europe and the US have launched ambitious programs over the next decades to support the development of a dedicated bio-based economy.^{20,32–36} The EU aims at a reduction of 40% of greenhouse gas and at an overall 25% bio-based chemicals and materials by 2030.^{37,38} With such strong ambitions for the thriving of more bio-based oriented economy,^{33,38} EU advocates a long term holistic strategy relying on

public and private partnerships with multiple aims: “(a) *Improving and securing access to renewable raw materials for industrial use; (b) Supporting targeted research, training and innovation programs; (c) Developing technologies and bridging the gap between research and the market; (d) Stimulating market demand for bio-based products and (e) Improving awareness via efficient communication and education*”.^{37,39} In the US, the ambition aims at developing a billion ton biomass economy that will feed emerging bio-based industries and products by 2030, a measure that mainly concerns the transportation market with a 30% penetration of biomass carbon in the form of bioethanol and biodiesel.^{40,41}

A list of highly potent bio-based chemical platforms that can be produced on commercial scale and that can be converted into high value bio-based chemicals was published in 2004 by the US DoE.²⁶ The original list included glycerol, 3-hydroxypropionic acid, aspartic acid, 3-hydroxybutyrolactone, succinic acid, fumaric acid, malic acid, glutamic acid, levulinic acid, itaconic acid, 2,5-furandicarboxylic acid, xylitol, arabinitol, glucaric acid and sorbitol.²⁶ The original list was next updated in 2010 by Bozell and Petersen, who proposed 13 chemicals that were pointed out as a “*top chemical opportunities*”.⁴² The updated list included ethanol, furfural, 5-hydroxymethylfurfural, isoprene and lactic acid. Each of these bio-based chemical platforms but glycerol and isoprene can be sourced from carbohydrate feedstock.⁴²

1.2. Flow Chemistry as an Enabling Tool for Processing Bio-based Chemicals

Apart from the upstream processes operated in petrorefineries, most industrial facilities are still equipped with large scale batch reactors that struggle to meet new regulatory constraints in terms of efficiency, small footprint and reduced chemical hazards.^{43,44} Batch reactors rely on large internal dimensions that define a finite internal volume.⁴³ Macroscopic batch reactors are being utilized since the early history of the production of valued-added chemicals.⁹ They are

typically associated with a simple yet robust design, are relatively versatile and easy to operate.⁴³ Their omnipresence in the industry has somehow conditioned the current scheme of centralized, stepwise mass production.

Since the early 2000's, other process technologies have progressively emerged from lab curiosity to robust alternatives.⁴⁵ Continuous flow chemistry, that was originally mostly confined to microfluidics (*i.e.* reactors within submillimetric dimensions) with small scale and high-end applications has come to age and is now widely accepted in the chemistry toolbox. Today, continuous flow chemistry is not anymore in its infancy and is considered as one of the technologies that will change the world. The International Union of Pure and Applied Chemistry (IUPAC) concluded that flow chemistry has the potential “*to make our planet more sustainable*”.⁴⁶ The contribution of flow chemistry for designing safer and more reliable chemical processes using facilities with a low environmental footprint opens up new perspectives for developing greener, more sustainable and safer chemical processes. In addition, the use of flow chemistry appears to be economically more interesting for emerging products as for well-established processes. In this context, the assets of flow chemistry are very supportive for the transition toward a bio-based, sustainable chemical industry.^{27,28,47,48}

Flow chemistry is a term widely used to describe the performance of a reaction in a continuous manner, in micro- and mesofluidic reactors.^{45,49,50} Such reactors are typically defined by a narrow channel in which chemicals circulate under strictly controlled conditions of temperature, pressure and stoichiometry.⁴⁵ Most of the inherent assets of flow reactors are related to their high surface/volume ratio. The typical dimensions of a continuous flow reactor defined within the context of flow chemistry (thus excluding macroscopic flow reactors used in the petrochemical industry) range from a few hundred micrometers to several millimeters and internal volumes ranging from hundreds of microliters to dozens of milliliters.⁴⁵ Microfluidics

typically apply to reactors whose internal dimension is in the range 250-800 μm and internal volumes of a few hundred microliters, while mesofluidics apply to larger internal dimensions and volumes.^{27,45} Typical flow reactors consist of a reaction channel with specific dimensions that might be embedded with static mixing elements and a heat exchanger (see Figure 3 for the conventions used within this manuscript). Capillaries, tubes, monoliths,^{51,52} and columns hence also fall under the definition of a flow reactor.⁴⁵ Columns can be packed with a solid material, either inert or chemical active (supported reagents or catalysts) thus providing convenient flow setups (*i.e.* packed-bed reactors) for chemical operations under heterogeneous conditions.^{53–57} Upon operation, the flow reactor is continuously fed through high accuracy pumps (for liquids and slurries) and/or with mass flow controllers (for gaseous feeds).⁴⁵ Specific designs ensure high mass transfer for immiscible fluids.^{58–61} Downstream processing can feature, besides simple collection of the reactor effluents and off-line analysis, a variety of in-line operations including in-line analysis, in-line purification or additional steps.^{45,62–65} The implementation of several steps within the same uninterrupted flow reactor network is referred to as process telescoping or concatenation (Figure 4).⁶⁶ Despite a rapidly overwhelming complexity for multiple step processes, concatenation is often seen as the quintessence of flow chemistry.^{66–69} Fully concatenated processes usually exploit all assets of flow chemistry and enable the processing of unstable or hazardous chemicals that are generated upstream and directly consumed within the next steps, hence avoiding any safety issues related to storage, handling and accumulation of such chemical species.^{66,70,71} Besides, concatenation is a fundamental concept that provides very low footprint reactors and facilities. Concatenation in flow relies on various engineering tools for connecting the various reaction modules.

The contribution of flow chemistry to the design of more sustainable conditions has been amply documented over the last few years.^{27,72–74} However, it must be stated that running a process

under continuous flow conditions does not make it sustainable *per se* if just taken as a copycat of a batch process. The combination of revised chemical strategies in conjunction with continuous flow conditions enables unique process experiences that rely on the inherent properties of micro- or mesofluidic reactors.⁵⁰ The specific design of micro- and mesofluidic reactors accounts for the possibility to explore new horizons for process conditions outside the boundaries imposed by conventional process equipments, as well as new perspectives for process intensification.^{75–79} The combination of flow chemistry with advanced automation and Artificial Intelligence (A.I.) is often seen as a revolutionary approach that will profoundly change the organic synthesis mindset.^{80,81} Many reports in the literature have documented that flow conditions accelerate the lab-to-market transition, also leading to processes with a significantly reduced environmental footprint.^{82,83} Flow chemistry has notably enabled the re-introduction of conditions or chemicals that were banned through increasingly restrictive legislations,^{70,84} as well as process conditions that were thought to be difficult to bring toward commercial production (such as photochemistry^{58,85–89} and electrochemistry^{90–92}). The fast development and generalized adoption of flow chemistry is strongly supported by increasing safety and environmental concerns related to commercial scale chemical processes.^{54,70}

Flow chemistry has been extensively applied to preparative organic chemistry and in particular to pharmaceutical organic chemistry,²⁷ both for R&D^{74,93–95} and production purposes.^{9,80,93,96–100} Such generalized adoption is strongly supported by the regulatory authorities.^{101,102} Chemists have adopted flow reactors to feed upstream the process of discovery in medicinal chemistry with the development of new and robust methodologies.^{27,93} Countless flow procedures have been reported over the last years for the preparation of libraries of complex molecules with improved selectivity and throughput while exploring pristine chemical spaces.^{103,104}

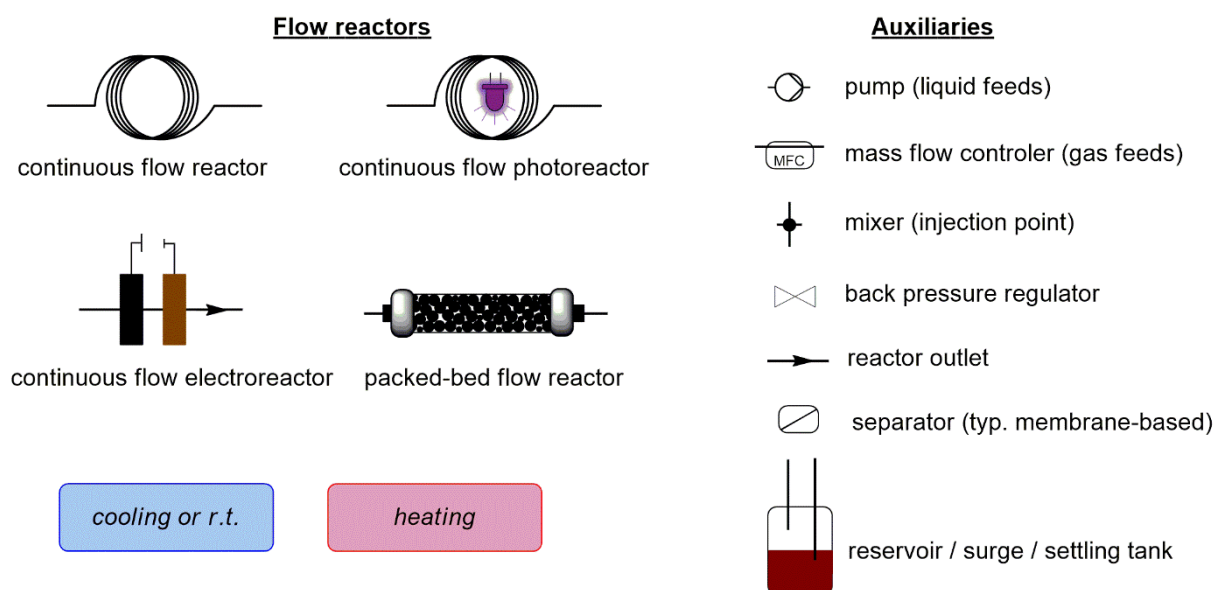


Figure 3. Conventions utilized in this review for the various reactor types and auxiliaries.

The upgrading of bio-based chemicals using flow technology is a much less developed area of research than for pharmaceutical applications.^{27,28,105–109} The application of flow chemistry to bio-based chemical platforms is typically more complex to implement in the sense that the bio-based platform chemical substrates are usually either sensitive compounds, viscous or poorly soluble materials difficult to process under flow conditions. Yet, chemists and chemical engineers are increasingly considering flow technology in conjunction with the valorization of bio-based chemicals.²⁷ The ability to control with high accuracy and reproducibility process conditions involving unconventional pressures and temperatures on sensitive substrates certainly appears as a major asset. To date, examples of full commercial continuous flow processes for the upgrading of bio-based platform molecules are still scarce, although a growing number of pilot-scale flow processes are encountered in the literature.

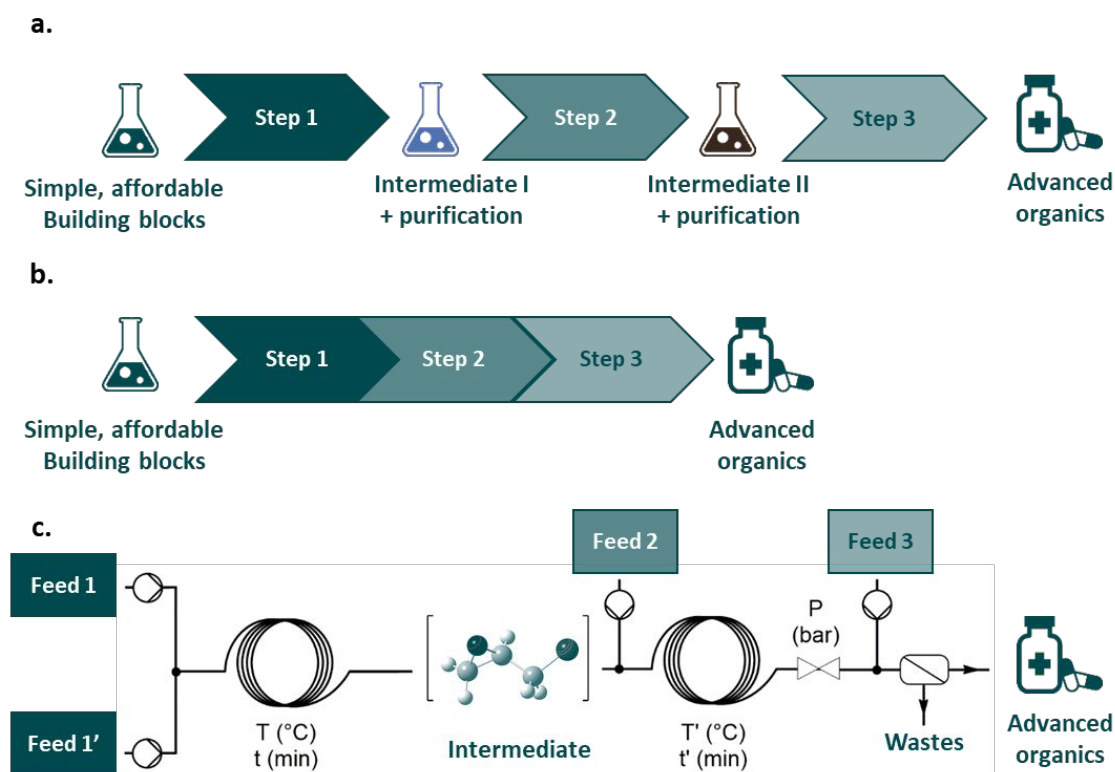


Figure 4. (a) Typical stepwise process (batch or flow) and (b) process concatenation with the integration of multiple steps, including purification, for the transformation of simple building blocks into advanced chemicals. Reaction concatenation in flow is particularly popular for processes involving unstable or toxic intermediates, hence alleviating their handling and isolation. (c) Hypothetical example of concatenated multistep process under continuous flow conditions (T , T' are process temperatures; t , t' are residence times and P is the back pressure).

Processing chemicals in flow under such intensified conditions often boosts productivity by comparison to corresponding batch processes, while concomitantly reducing the footprint of the reactor.²⁷ To support this argument, the space-time yield (the productivity normalized by the reactor internal volume) of batch and flow procedures for the upgrading/preparation of platforms is reported in Table 1. These selected examples of the primary literature are detailed later in the review within the appropriate sections.

Table 1. Comparison of batch and flow procedures for selected examples of bio-based platforms upgrading/preparation.

Ref.	Reaction	Substrate ^a	Product ^a	Reactor	Conditions	Yield (%)	Space-time yield (kg _{product} L _{reactor} ⁻¹ day ⁻¹)
110	homogeneous carbonation	1,2-PDO	propylene carbonate	batch	150 °C, 5 h, 5 equiv. of dimethyl carbonate	95	0.016
				flow	240 °C, 15 min, 5 equiv. of dimethyl carbonate	89	18.6
111,112	homogeneous nitration	GL	nitroglycerine	batch	0-10 °C, 30 min, 3.3 equiv. of N ₂ O ₅	99	3.9
				flow	20 °C, 17 s, 3.3 equiv. of N ₂ O ₅	90	314
113	electrocatalytic reduction	FU	furfuryl alcohol	batch	2.2V, 300 min, 0.5 equiv. of EtOK	31	6.1 x 10 ⁻⁴
				flow	2.2 V, 10 min, 0.5 equiv. of EtOK	90	1.27
114	Amberlyst 15 catalyzed hydroxymethylation	FU	HMF	batch	90 °C, 15 h, CH ₂ O _{aq} 37%, 200 g _{cat} mol _{FU} ⁻¹	43	0.017
				flow	90 °C, CH ₂ O _{aq} 37%, 6 x 10 ⁻⁴ mol _{FU} h ⁻¹ g _{cat} ⁻¹	36	0.26
115	biphasic dehydration	fructose	HMF	batch	180 °C, 60 min, HCl 0.025 M	68	0.31
				flow	180 °C, 4 min, HCl 0.025 M	93	1113

^aThe nomenclature of bio-based platforms is detailed on Figure 5.

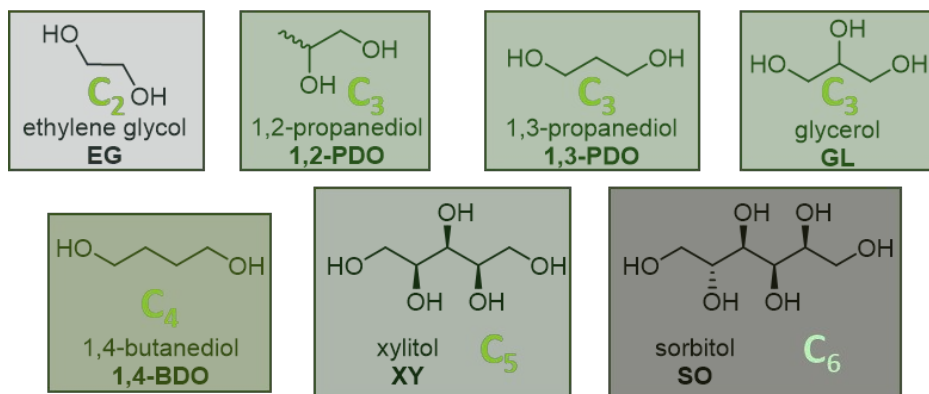
1.3. Scope and Organization of the Review

This review aims at providing a thorough and up-to-date overview of a hot topic that relates to one of the main challenges of the 21st century, which is, providing tools and technologies to support the transition from a mostly petro-based to an alternative bio-based chemical industry. Increasing research efforts are reported for the upgrading of bio-based molecules under flow conditions toward applications ranging from commodity to specialty chemicals. Probably one of the most challenging aspects of dealing with bio-based molecules relates to the variability of

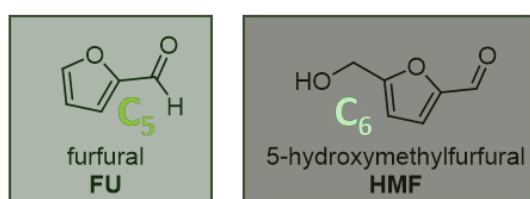
1
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3 the purity of these starting chemical building blocks. In addition, bio-based processes are
4 economically attractive as long as efficiency and robustness are guaranteed, and that includes
5 the availability of sustainable feedstocks as a well as low waste generation.
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10 This review covers continuous flow strategies (including micro- and mesofluidic processes
11 relying on reactors with internal diameters/dimensions below 10,000 μm , including packed-bed
12 reactors) involving current bio-based platform molecules. The reports covered in this review
13 were issued in the last twenty years (2000-2020) in the primary literature. Only liquid and solid
14 platform molecules are considered, and gaseous feedstock obtained from the pyrolysis of
15 biomass such as CH_4 , C_2H_6 , as well as C_1 platforms such as CO_2 are excluded. The upgrading
16 of ethanol, formic and acetic acid is not included. Aromatics that are sourced from the
17 depolymerization of lignin are not considered. This review covers a selection of C_2 to C_6 bio-
18 based chemical platforms with existing commercial markets (see section 1.4), including polyols
19 (ethylene glycol, 1,2-propanediol, 1,3-propanediol, glycerol, 1,4-butanediol, xylitol and
20 sorbitol), furanoids (furfural and 5-hydroxymethylfurfural) and carboxylic acids (lactic acid,
21 succinic acid, fumaric acid, malic acid, itaconic acid and levulinic acid) (Figure 5), thus
22 including C_2 to C_6 building blocks. The aim of this review is to provide the reader with a
23 substantial overview of the primary literature dealing with continuous processes for the
24 upgrading of bio-based platforms into higher value-added commodity and fine chemicals.
25 Therefore, their conversion into hydrogen, syngas, fuel and other low-value added compounds
26 was not considered.
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Polyols



Furanoids



Carboxylic acids

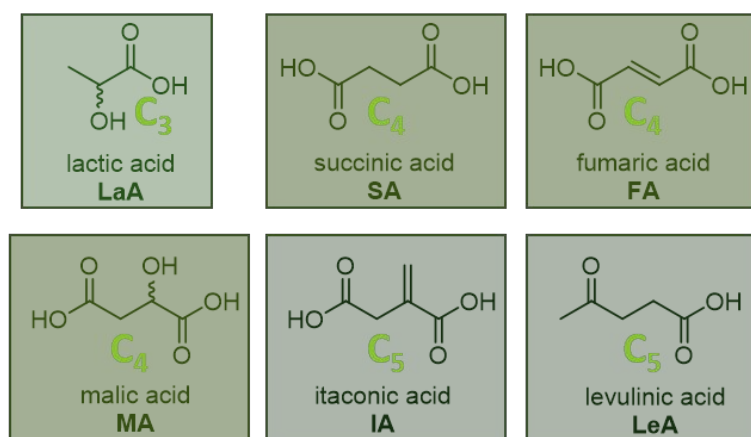


Figure 5. Selection of bio-based platform polyols (ethylene glycol, 1,2-propanediol, 1,3-propanediol, glycerol, 1,4-butanediol, xylitol and sorbitol), furanoids (furfural and 5-hydroxymethylfurfural) and carboxylic acids (lactic acid, succinic acid, fumaric acid, malic acid, itaconic acid and levulinic acid) for which flow processes are documented. The various shades of green reflect the number of carbons (C₂-C₆ building blocks).

Both liquid- and gas-phase reactions are discussed. Since most processes described here rely on catalysis, an important aspect of the review relates to the description of the homogeneous,

heterogeneous and sometimes enzymatic catalysts used in such flow processes. Specific aspects of downstream processing are presented as well with perspectives on the integration of purification in flow.

1.4. Presentation of the Selected Bio-based Platform Chemicals

This section introduces the various bio-based platform molecules that have benefited from significant research efforts for their upgrading under continuous flow conditions, either on lab or pilot scales. Current commercial routes, major players as well as the main markets for selected bio-based platform polyols (ethylene glycol, 1,2-propanediol, 1,3-propanediol, glycerol, 1,4-butanediol, xylitol and sorbitol), furanoids (furfural and 5-hydroxymethylfurfural) and carboxylic acids (lactic acid, succinic acid, fumaric acid, malic acid, itaconic acid and levulinic acid) are detailed in the appropriate sections of the review.

Among the selected bio-based chemical platforms, significant differences can be spotted from Figure 6. Simple polyols such as ethylene glycol and glycerol that both belong to the smart drop-in subclass, have clearly well established and huge markets are available at a low price (< \$1500 per ton). Xylitol is another bio-based polyol yet at the other antipode in terms of production cost that remain higher than the \$3000 per ton threshold. Apart from xylitol, all polyols considered in this review are rather in the \$1000-3000/ton production cost range^{116,117} (which is taken here as a safe margin for profitable commercial production). The two furanoids considered in this review have very different profiles. Furfural, a C₅ building block, can be produced at reasonable costs and already benefits from a significant market volume. 5-Hydroxymethylfurfural (HMF), a C₆ building block, still suffers from prohibitive production costs and a very narrow market. All bio-based carboxylic acids considered within this review have acceptable production costs below the \$3000 threshold and established markets.^{116,117} Some of these bio-based chemical platforms have promising forecasts. Large market expansion

depends on several up- and downstream factors.^{116,117} Upstream factors are typically related to the development of more effective processes from the starting biomass feedstock or alternative non-food bioresources.^{116,117} Downstream factors include tedious purification processes, stability issues and the lack of demand. It is expected that the development of new process technologies for the upgrading of bio-based chemical platforms toward value-added chemicals will stimulate commercial applications and will hence help increasing market volumes.^{116,117}

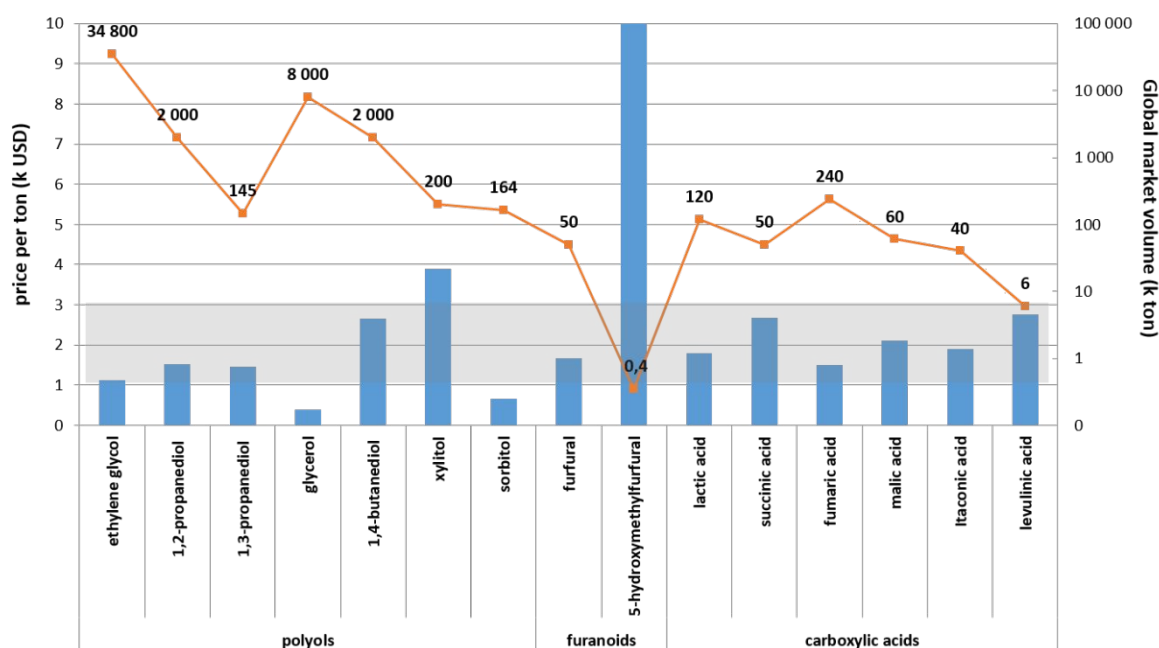


Figure 6. Overview of the current commercial status for selected bio-based platform molecules including polyols (ethylene glycol, 1,2-propanediol, 1,3-propanediol, glycerol, 1,4-butanediol, xylitol and sorbitol), furanoids (furfural and 5-hydroxymethylfurfural) and carboxylic acids (lactic acid, succinic acid, fumaric acid, malic acid, itaconic acid and levulinic acid).^{116,117} Prices per ton (average, $\times 10^3$ USD, data from 2015-2019) are displayed in blue and the estimated global market volumes ($\times 10^3$ ton, data from 2015-2019) are displayed in orange. The gray area shows the typical cost for primary chemicals in order to sustain profitable commercial exploitation.

2. Upgrading of Polyols

2.1. Ethylene Glycol

2.1.1. Presentation and Markets

Ethane-1,2-diol (ethylene glycol, EG, CAS 107-21-1) is the simplest diol that was first synthesized by Wurtz in 1859.¹¹⁸ EG is a very important industrial building block with a market volume of 34.8 million tons per year (\$1114 per ton) and a global market of \$28.58 billion.¹¹⁶ EG is essentially used for antifreeze formulations (~50%) and for the manufacture of polyesters (~40%). Some niche applications concern for instance the upgrading toward other molecules such as 1,4-dioxane and the reversible protection of aldehydes and ketones in organic synthesis.¹¹⁸ The main commercial routes, emerging continuous flow alternatives and major producers of EG are detailed in section 2.5.5.

2.1.2. Intra- and Intermolecular Etherification

Ethylene oxide. Ethylene oxide is the simplest epoxide, and a very important C₂ building block for the chemical industry. As a gaseous alkylating agent, it is also strongly toxic to life, and used directly as a sterilizing/disinfecting agent. It is currently produced from the oxidation of petro-based ethylene.¹¹⁹ Yi and coworkers alternatively converted 36% of ethylene glycol into a mixture of ethylene oxide (38%) and acetaldehyde (47%).¹²⁰ Process conditions involved pumping an aqueous solution of ethylene glycol along with N₂ over a strongly basic Cs/SiO₂ catalyst loaded in a gas-phase fixed-bed reactor (400 °C, atmospheric pressure). The paper was mostly dedicated to the epoxidation of 2,3-butanediol, and no further optimization on ethylene glycol was attempted.

2-Methoxyethanol. EG was etherified under continuous flow conditions, using supercritical methanol both as reaction medium and alkylating agent.¹²¹ In the report, Cs-P-Si mixed oxide was evaluated as heterogeneous catalyst, which selectively afforded 2-methoxyethanol (76% selectivity), at low ethylene glycol conversion (23%). The selective monomethylation was explained by a tethering effect between one of the hydroxyl group of ethylene glycol and the surface of the catalyst.

1,2-Dimethoxyethane. Lu and colleagues studied the etherification of ethylene glycol with methanol in a gas-phase fixed-bed reactors over various acidic zeolites (HZSM-5, HY, H- β , SAPO-11, SAPO-34).¹²² The best results for the formation of dimethoxyethane (**5**) were obtained with microporous SAPO-34, and were rationalized by the presence of (1) strong acid sites in high concentration and of (2) small micropores, which promoted the selective methylation of ethylene glycol over its dimerization into 1,4-dioxane. Indeed, the kinetic diameter of dioxane was estimated to be larger than the pore size of SAPO-34, decreasing the likeliness of its formation. During 5 h of continuous operation, the catalyst gradually deactivated with the accumulation of coke. Both ethylene glycol conversion (97-60%) and dimethoxyethane selectivity (83-70%) were affected (Figure 7). Its activity could not be regenerated by air calcination.

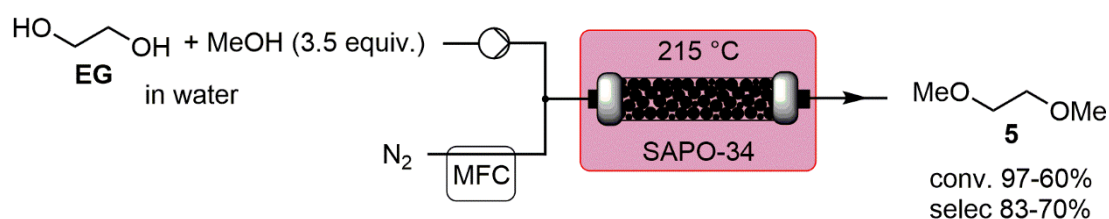
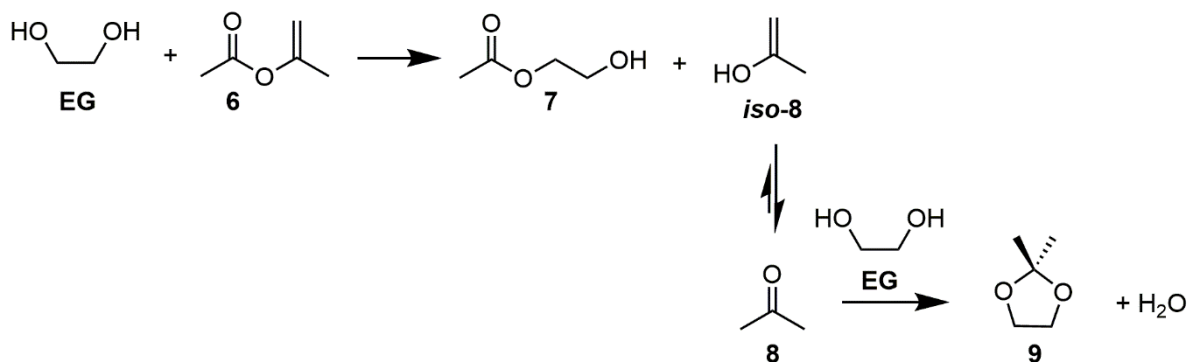


Figure 7. Gas-phase continuous flow process for the synthesis of dimethoxyethane using methanol as methylating agent.¹²²

2.1.3. Esterification and Ketalization

Ethylene glycol monoacetate and 2,2-dimethyl-1,3-dioxolane. Selva and coworkers reported a cascade reaction in a fixed-bed reactor between diols, including EG, and isopropenyl acetate (**6**).¹²³ The process was triggered under heterogeneous acidic organocatalysis conditions using Amberlyst 15. In this tandem reaction, 1 equiv. EG reacted with 1 equiv. of isopropenyl acetate to yield 1 equiv. of ethylene glycol monoacetate (**7**) and 1 equiv. of propene-2-ol (*iso*-**8**). The latter alcohol underwent keto-enol tautomerization into acetone, which subsequently reacted with another equiv. of ethylene glycol to form 2,2-dimethyl-1,3-dioxolane (**9**, Figure 8a). The process is virtually 100% carbon economic, since only water was formed as by-product of the reaction. With 1,2-propanediol as the substrate, a 50:50 selectivity for monoester/ketal could be obtained under optimized conditions. Poorer results were obtained with ethylene glycol owing to a faster esterification reaction (31% selectivity for ketal **9** under optimized conditions, Figure 8b).

(a)



(b)

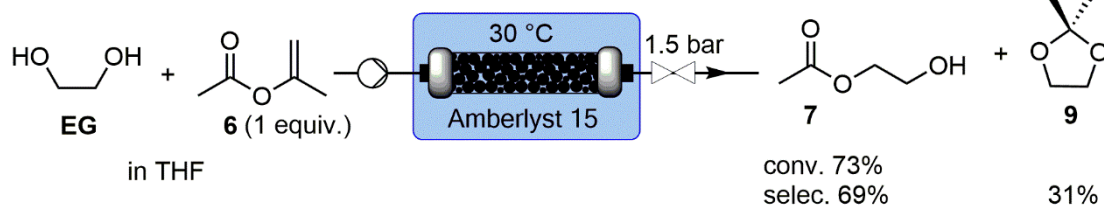


Figure 8. Tandem reaction for the monoesterification and ketalization of ethylene glycol. (a) Reaction sequence and (b) detailed flow process.¹²³

2.1.4. Carbonation into Ethylene Carbonate

Selva and coworkers prepared ethylene carbonate (**10**) from ethylene glycol and dimethyl carbonate (DMC) in a microfluidic reactor under superheated conditions.¹¹⁰ DMC was used both as carbonating agent and solvent in the feed, and 82% yield was obtained by heating the mixture at 240 °C for 15 min, under a pressure of 50 bar in catalyst-free conditions (Figure 9). Monbaliu and coworkers reported a homogeneous continuous flow process relying on DMC and solvent-free conditions as well.¹²⁴ *tert*-Butyl-tetramethylguanidine was used as organocatalyst (1 mol%), affording good ethylene glycol conversion (82%) and ethylene carbonate selectivity (79%) under mild conditions (135 °C, 7 bar, 2 min of residence time). In a follow-up paper, ethylene carbonate was obtained in 88% yield upon reacting DMC and ethylene glycol in the presence of 3.5 mol% of tetrabutylammonium bromide as an inexpensive homogeneous catalyst.¹²⁵ The procedure involved solvent-free conditions and 3 min of residence time at 180 °C. Implementation of an in-line NMR spectrometer enabled real-time qualitative monitoring of the reaction.

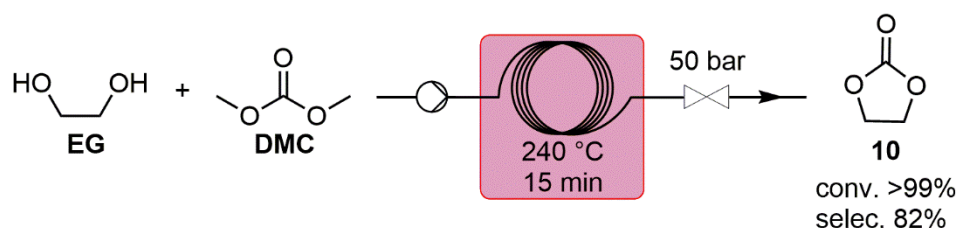


Figure 9. Catalyst-free continuous flow synthesis of ethylene carbonate.¹¹⁰

2.1.5. Aromatization into 2-Methylquinoline and Derivatives

In an early report, the group of Vaccari investigated the gas-phase preparation of *N*-heterocyclic compounds in a continuous flow reactor, from the reaction of ethylene glycol with 2-ethylaniline.¹²⁶ 2-Methyl-8-ethylquinoline was obtained in 41% yield when the reaction was carried out over an acid-treated K10 montmorillonite, at 330 °C and using N₂ as carrier gas. It was shown that the presence of a combination of Lewis and strong Brønsted acid sites on the surface of the catalyst favored the process. The reaction mechanism proposed involved the dehydration of ethylene glycol into acetaldehyde, which underwent self-aldol condensation into crotonaldehyde. Crotonaldehyde was then condensed with 2-ethylaniline through Michael addition, followed by cyclization and dehydrogenation into the corresponding quinoline. Alternatively, when these reactants were pumped over copper chromite as catalyst, 7-ethylindole could be obtained in up to 39% yield under optimized conditions. This alternative reaction was favored by the presence of weak Lewis acid and dehydrogenation sites on the catalyst, and at lower temperatures. The mechanism most probably proceeded through EG oxidation into glycolaldehyde, which underwent imination with 2-ethylaniline followed by cyclization toward the indole core. 2-Methylquinoline (**12**) was more recently obtained in 56% yield from the gas-phase reaction between EG and aniline (**11**) in a fixed-bed reactor embedded with acid-treated ZnCl₂/Ni-USY (Figure 10).¹²⁷ The enhanced yield was related to the high Lewis acidic character of the zeolitic material, as well as its large pore size.

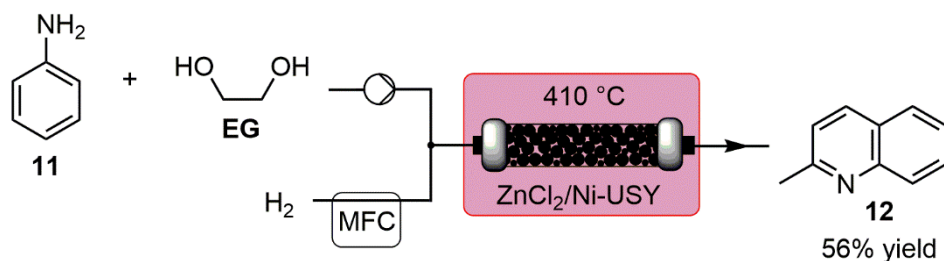


Figure 10. 2-Methylquinoline synthesis from ethylene glycol and aniline in fixed-bed flow reactor.¹²⁷

2.2. Propanediols

2.2.1. Presentation and Markets

1,2-Propanediol (propylene glycol, 1,2-PDO) is a diol bearing a stereogenic center. It exists as two enantiomers: *R*-(-)-1,2-PDO (CAS 4254-15-3) and *S*-(+)-1,2-PDO (CAS 4254-14-2), although most commercial processes produce the racemate ((*R,S*)-($\pm$)-1,2-PDO CAS 57-55-6). 1,2-PDO is an important industrial building block with a market volume of 2 million tons per year (\$1530 per ton) and a global market of \$3.91 billion.¹¹⁶ Its market is still expected to grow.¹¹⁶ The major part of 1,2-PDO's market concerns the production of polymers. It has also niche applications in the food, cosmetic and pharmaceutical industries. 1,2-PDO is also a common additive for electronic cigarettes.

1,3-Propanediol (1,3-PDO, CAS 504-63-2) is an important diol building block for the preparation of polymers. The global value of the 1,3-PDO market is estimated to reach \$620 million by 2021 with a global market demand of 225,900 tons by 2022.^{116,128} Almost the entire production of 1,3-PDO is utilized for the polymer industry for the preparation of polyesters, polyethers, and polyurethanes.¹¹⁶ 1,3-PDO is also utilized for niche applications, including the preparation of chemical building blocks, as humectant for personal care products, solvent, antifreeze agent and coolant.^{128,129}

The main commercial routes, emerging continuous flow alternatives and major producers of 1,2-PDO and 1,3-PDO are detailed in section 2.3.12.

2.2.2. Intra- and Intermolecular Etherification

Propylene oxide. Propylene oxide (**13**) is an important chemical building block, used as a starting material for the synthesis of polymers, solvents and industrial fluids.¹³⁰ It is currently produced at the industrial level according to various routes: through oxidation, chlorination or

as a by-product during the synthesis of other bulk chemicals.¹³⁰ However, all of these routes start from petro-based propene. An alternative emerging route starts from bio-based 1,2-PDO. It is noteworthy that for decades, the reverse reaction has been predominant, *i.e.* 1,2-PDO has been exclusively manufactured from the hydration of propylene oxide (see section 2.3.12 and Scheme 8). Similar conditions are used in all reports, that are, 1,2-PDO is pumped either neat or as an aqueous solution along with nitrogen as carrier gas. It is reacted over a heterogeneous catalyst in the gas phase at 400 °C and atmospheric pressure (Figure 11).^{120,131–133}

In their pioneering work, Liu and coworkers evaluated various silica-supported alkali catalysts, and the best results were obtained with K/SiO₂.¹³¹ It was claimed that the most efficient catalysts possessed only weak basic sites. By contrast, MgO, possessing medium-strength basic sites, triggered the selective formation of hydroxyacetone through dehydrogenation. Under optimized conditions, a conversion of 44% in 1,2-propanediol and a selectivity of 70% for propylene oxide (**13**) were obtained at TOS = 3 h (Figure 11). Inspired by these results, Yi and coworkers reported on a Cs/SiO₂ catalyst.¹²⁰ 45% glycerol conversion and 50% selectivity for propylene oxide were obtained. The main side-products included propanal (22%), acetone (9%) and allyl alcohol (8%). Miller and coworkers studied a silica-supported KOH catalyst.¹³² In this study, a mixture of 1,2-PDO, 1,2-propanediol monoacetate isomers and 1,2-propanediol diacetate (1:2:1 molar ratio) was used as the feedstock solution, since utilization of neat 1,2-PDO yielded mainly intermolecular etherification products. The authors showed that the catalyst underwent structural changes as the time-on-stream evolved, through the reaction of KOH with acetic acid generated by the epoxidation reaction. Potassium acetate was formed within the catalyst and further underwent a disproportionation reaction into K₂CO₃ as the stable catalytic active species, along with acetone as a volatile by-product. Under optimized conditions, up to 30% yield in propylene oxide could be obtained. Other supported potassium salts did not improve

the results. Independently, the group of Zhang reported on $\text{KNO}_3/\text{SiO}_2$ as catalyst for the reaction.¹³³ The catalyst underwent rapid deactivation after only 2 h of continuous operation, as the conversion of the starting material dropped from 71 to 19%, and the selectivity for propylene oxide from 82 to 59%. Coke deposition was incriminated as the main cause leading to deactivation.

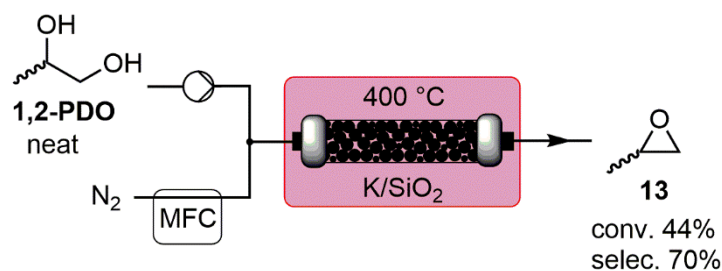


Figure 11. Gas-phase epoxidation of 1,2-propanediol.¹³¹

1-(Trityloxy)propan-2-ol. De Souza and coworkers reported a continuous flow procedure for the conversion of the primary alcohol function of 1,2-PDO into the corresponding trityl ether.¹³⁴ A classical Williamson ether synthesis was utilized, with trityl chloride as etherification reagent, triethylamine as stoichiometric base and 10 mol% of 1,4-diazabicyclo[2.2.2]octane (DABCO) as organocatalyst. Up to 63% conversion was obtained under optimized conditions, but no information regarding selectivity was provided.

1,3-Dimethoxypropane and 3-methoxypropan-1-ol. Poliakoff *et al.* studied the methylation of 1,3-PDO using reagents that alleviated the use of toxic methylating agents such as methyl iodide or dimethyl sulfate.¹³⁵ For instance, they reported that depending on the internal pressure of a fixed-bed reactor, 1,3-PDO underwent selective mono- or dimethylation using methanol as reagent and Amberlyst 15 as acidic heterogeneous catalyst. Process conditions involved pumping a methanolic solution of 1,3-PDO within the system along with CO_2 . Upon utilization of a 50 bar counterpressure, the reaction yielded 68% of dimethyl ether **14** and 32% of

monomethyl ether. At 100 bar, 76% of monomethyl ether and 20% of dimethyl ether were obtained. This behavior was rationalized by a change in the phase state of the system as a function of the pressure: low pressures resulted in a biphasic (gas-liquid) system, while high pressures created a homogeneous medium. Under biphasic conditions, the residence time of the liquid reactants within the catalytic bed increased. Additionally, the presence of such liquid phase increased the wettability of the catalyst, accelerating the reaction rate. In a follow-up paper, various catalysts including Amberlyst 15, Amberlyst 70, Nafion SAC-13, Zeolite H-Beta and alumina; as well as various “green” methylating agent, such as MeOH, dimethyl carbonate and dimethyl ether were assessed on the model methylation of 1-octanol.¹³⁶ The best results were obtained with acid-treated alumina as catalyst and DMC as methylating agent. The reaction was then extended to other substrates, including 1,3-PDO. 1,3-PDO dimethyl ether (**14**) was obtained in 68% yield at 270 °C and 100 bar, using a setup configuration similar to that of the previous report (Figure 12).

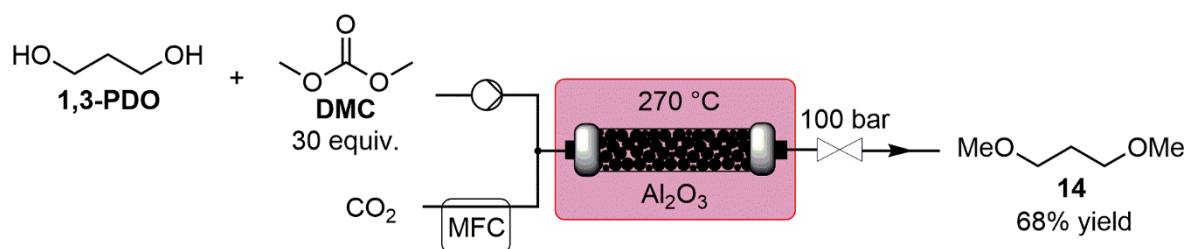


Figure 12. Methylation of 1,3-propanediol with dimethyl carbonate in supercritical CO₂.¹³⁶

2.2.3. Esterification and Ketalization

1,3-Propanediol diacetate. Acetic anhydride (Ac₂O) was utilized as acetylating agent under catalyst-free conditions, and using subcritical water (200 °C, 50 bar) as the reaction medium.¹³⁷ The procedure is appealing in the sense that it relied on a water-sensitive reagent, but was amenable to the use of water as the reaction solvent since short reaction times were utilized. In the report, the mono- or diacetate of 1,3-PDO could be prepared selectively upon varying the

molar excess of Ac_2O . With 1.1 equiv. of Ac_2O , 90% yield of 1,3-PDO monoacetate was obtained in 5.5 s residence time. Similarly, when 2.2 equiv. of Ac_2O were utilized, quantitative yield of 1,3-PDO diacetate was obtained in 9.9 s residence time.

1,2-Propanediol monoacetates and 2,2,4-trimethyl-1,3-dioxolane. Enol esters, and especially isopropenyl acetate (**6**), were evaluated in transesterification reactions with 1,2-propanediol under acidic heterogeneous organocatalytic (Amberlyst 15) conditions.¹²³ The main asset of using enol esters in transesterification reactions is the irreversibility of the reaction, since the enol by-product undergoes keto-enol tautomerization. In this report, the process was developed to consume acetone, the by-product of the esterification reaction, through a subsequent ketalization reaction. Thus, 2 equiv. of 1,2-PDO were converted into 1 equiv. of monoesters **15a,b** and 1 equiv. of ketal **16** through a “tandem” process. Control experiments in batch evidenced that with 1,2-propanediol, the ketalization reaction was much faster than the esterification reaction. This feature of the process enabled a 50:50 selectivity for monoesters/ketal under optimized conditions – thus corresponding to a 100% carbon efficiency (with water as the only by-product). In flow, the best results were obtained at 30 °C (Figure 13) and the catalyst maintained steady activity for 160 h TOS. Characterization of the spent catalyst evidenced no structural change or loss of acid sites.

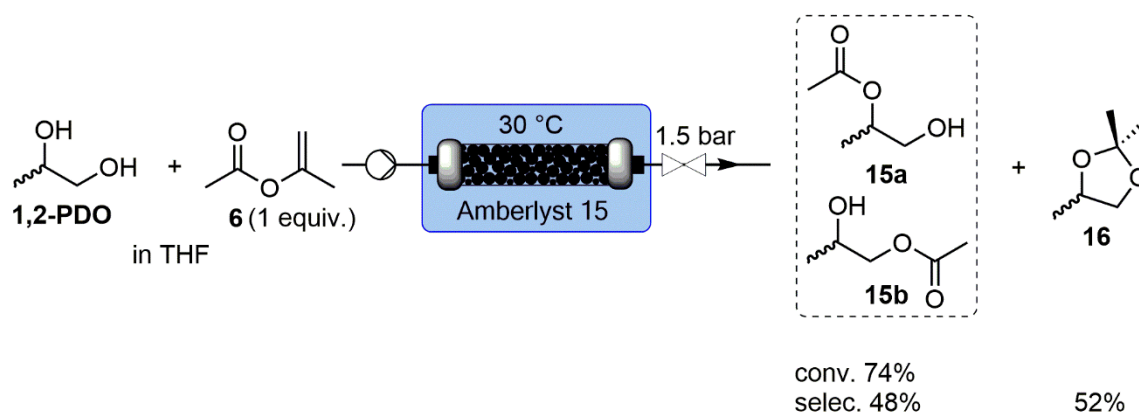


Figure 13. Tandem transesterification/ketalization reaction of 1,2-propanediol with isopropenyl acetate.¹²³

2.2.4. Carbonation into Propylene Carbonate

The Selva group transformed 1,2-PDO into propylene carbonate (**17**) using dimethyl carbonate (DMC) as carbonation reagent in a microfluidic reactor under superheated conditions.¹¹⁰ The reaction proceeded under catalyst-free conditions, and almost quantitative yield in **17** was obtained at 240 °C, with a counterpressure of 50 bar and about 15 min of residence time (Figure 14). The space-time yield of the continuous flow procedure was 3 orders of magnitude higher than an analog batch reaction (Table 1). De Souza described an alternative continuous flow protocol involving 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as homogeneous organocatalyst (10 mol% loading).¹³⁴ Starting from a homogeneous feed containing (*R*)-1,2-propanediol, DMC and the catalyst, the reaction yielded (*R*)-propylene carbonate in 94% conversion and quantitative selectivity under mild conditions (120 °C, 6 bar), but required 60 min of residence within the reactor. Similarly, Monbaliu and colleagues reported the use of *tert*-butyl-tetramethylguanidine (1 mol% loading) as organocatalyst for the carbonation reaction of 1,2-PDO.¹²⁴ The catalyst was loaded in a DMC feedstock solution, and reacted with neat 1,2-PDO for 2 min at 135 °C and 7 bar. Excellent 1,2-PDO conversion (94%) and **17** selectivity (85%) were obtained. In a follow-up paper, tetrabutylammonium bromide was evaluated as homogeneous catalyst (3.5 mol%) for the same reaction.¹²⁵ The procedure was also solvent-free, but more demanding reaction conditions were utilized (180 °C, 3 min, 11 bar), affording propylene carbonate in 93% yield. The efficiency of in-line NMR for real-time quantitative monitoring of the reaction was demonstrated.

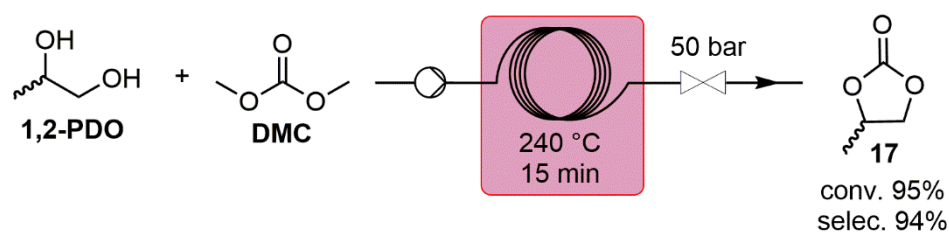


Figure 14. Preparation of propylene carbonate from propylene glycol in a microfluidic reactor.¹¹⁰

2.2.5. Oxidation into Acetol and Methylglyoxal

Acetol. Hydroxyacetone, also known as acetol, is a compound used in the textile, cosmetic and food industries, as well as an intermediate for the preparation of other bulk chemicals.¹³⁸ Sato *et al.* reported that 1,2-PDO underwent dehydrogenation into acetol when it was pumped as an aqueous solution over a fixed bed of Cu/Al₂O₃.¹³⁹ The reactor was operated at 250 °C and under atmospheric pressure, and 71% selectivity for acetol at 61% 1,2-PDO conversion were obtained.

Methylglyoxal. Shen *et al.* reported a procedure for the preparation of an Ag-based catalyst that was evaluated for the gas-phase aerobic continuous oxidation of 1,2-PDO into 2-oxopropanal, also known as methylglyoxal (**18**).¹⁴⁰ The catalyst was prepared by electrodeposition of Ag on a copper grid covered with a thin zeolite film. The zeolitic framework prevented agglomeration of metallic Ag during the synthesis of the catalyst. As a result, the high dispersion of small Ag particles enabled excellent conversion (92-88%) and selectivity (76-72%) for a prolonged operation time (190 h, Figure 15). Hydroxyacetone was the main side-product (~10%). Fifteen years later, Vodyankina *et al.* studied iron-molybdenum oxides supported on silica as heterogeneous catalysts.¹⁴¹ Molecular oxygen served as oxidant, and the reactor was operated at 350 °C and atmospheric pressure. The highest selectivity (55%)

for the target compound was obtained with a Mo/Fe ratio of 3. Progressively decreasing this ratio to 0.5 rather yielded compounds resulting from C-C cleavage, such as acetaldehyde and CO_x, but also increased the conversion from 5% to 33%. The best balance between conversion (15%) and selectivity (38%) was obtained at the intermediate ratio of 1. Hydroxyacetone, a reaction intermediate, was also detected in the effluents of the reactor, indicating that the dehydrogenation of the secondary alcohol of 1,2-PDO is much more favorable than that of the primary one.

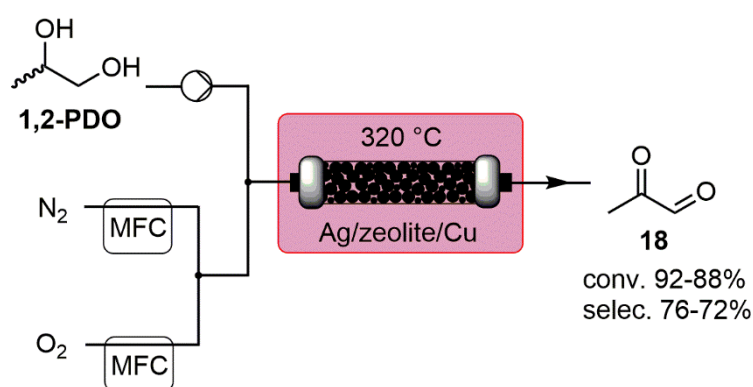


Figure 15. Continuous oxidation of 1,2-propanediol into methylglyoxal.¹⁴⁰

2.2.6. Dehydration (and Oxidation) into Allyl Alcohol, Propanal and Propanoic acid

Allyl alcohol. Allyl alcohol (**19**) is widely used as a monomer, or as a building block for the preparation of other monomers such as allyl ethers, allyl esters and glycidol, as well as a precursor of acrolein and acrylic acid.^{142–144} It is manufactured at the industrial scale from the hydration of allyl chloride or from the isomerization of propylene oxide. The raw material on which both routes rely is petro-based propene.¹⁴² Lange and colleagues developed a sequential continuous flow process for the conversion of 1,2-PDO into acrylic acid (**20**), with allyl alcohol (**19**) as intermediate.¹⁴⁵ 1,2-PDO was first dehydrated into allyl alcohol over a K-doped ZrO₂ catalyst in a gas-phase fixed-bed reactor (Figure 16). After purification, **19** was then oxidized

into **20** over a Mo-V-W oxides catalyst, using oxygen as the oxidant and in a gas-phase fixed-bed reactor as well. In the dehydration reaction, low K loadings on ZrO_2 resulted in the formation propanal, hydroxyacetone and 1-propanol as the main reaction products. This reaction profile suggested that Lewis acid sites catalyzed a dehydration of 1,2-PDO into propanal (see below), and then an H-transfer reaction from propanediol to propanal, yielding hydroxyacetone and 1-propanol.

With 1,3-PDO as the substrate, the dehydration reaction toward allyl alcohol catalyzed by solid acid catalysts was reported to be unselective in most cases. However, when an aqueous feed of 1,3-PDO was injected over basic CeO_2 at 315 °C, an enhanced formation of allyl alcohol (**19**) was noticed.^{146–148} While 1,3-PDO conversion rapidly decreased from 81% to 50% during a 10 h run, the selectivity for **19** maintained steady and elevated values (88-91%).

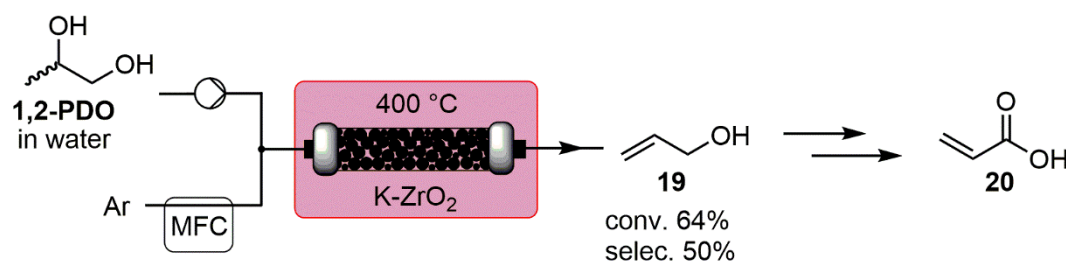


Figure 16. Continuous dehydration of propanediol toward allyl alcohol.¹⁴⁵

Propanal. Propanal (**21**) is used as intermediate in the manufacturing of various commodity chemicals.¹⁴⁹ It is mainly produced at an industrial level from the hydroformylation of ethylene with CO and H_2 over rhodium catalysts, and therefore relies on non-renewable fossil resources.¹⁴⁹ Alternatively, **21** could be produced from the continuous flow catalyzed dehydration of propanediols.^{139,148,150–155}

With 1,3-PDO as the substrate, catalysts possessing metallic sites were selective for propanal formation. For instance, at 250 °C and atmospheric pressure, 1,3-PDO was pumped as an

aqueous solution over Cu/Al₂O₃ embedded in a fixed-bed continuous reactor, and **21** was obtained in 66% yield.¹³⁹

With 1,2-PDO as the substrate, aqueous solutions were typically reacted in the gas-phase over solid acid catalysts loaded in fixed-bed reactors (Figure 17). As propanal formed, it often reversibly reacted with the diol substrate to yield the ketal condensation product **22** and water.^{151–154} Utilization of water as the solvent was thus appropriate to inhibit the formation of side-product **22**.^{151,154} Representative catalysts and optimized conditions for the gas-phase dehydration of 1,2-PDO are reported in Table 2. Deactivation was often associated with strong acid sites that tend to trigger coking.^{148,152}

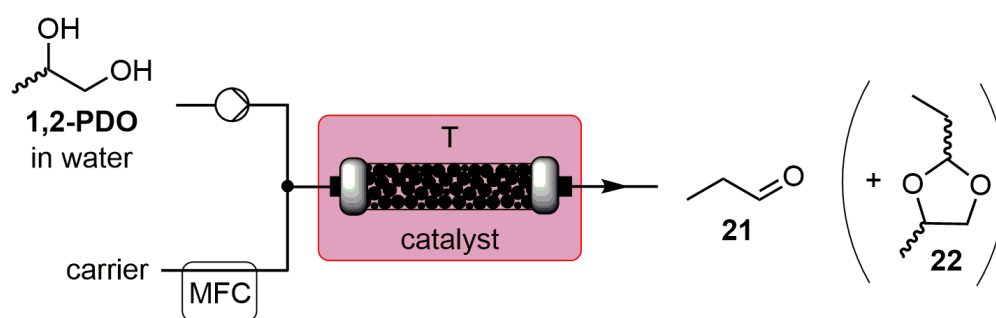


Figure 17. Representative flow process for the gas-phase dehydration of 1,2-propanediol into propanal.

Table 2. Catalysts and optimized conditions for the gas-phase dehydration of 1,2-propanediol into propanal.

Entry	Catalyst	Carrier	T (°C)	Space velocity	TOS (h)	Conv. (%)	Selec. (%)	Ref.
1 ^a	Ag/SiO ₂ -Al ₂ O ₃	H ₂	300	W/F = 0.077 g h mL ⁻¹	0.5-4.5	>99	68-69	152
2	BPO ₄	H ₂	220	W/F = 27 g h mol ⁻¹	1-10	>99	95-70	154
3	H ₄ SiW ₁₂ O ₄₀ /SiO ₂	N ₂	200	W/F = 0.529 g h mL ⁻¹	1-5	>99	94	151
4	SAPO-34	- ^b	315	GHSV = 400 h ⁻¹	2-10	90-83	63-67	148
5	WNbO	O ₂ + N ₂	240	W/F = 1.67 × 10 ⁻⁴ g h mL ⁻¹	1	>99	86	153

^aSolvent-free. ^bNo carrier gas.

Sato *et al.* improved the selectivity and stability of a silica-alumina catalyst by modification with silver.¹⁵² A decrease in concentration of strong and medium acid sites, along with an increase in concentration of weak acid sites, accounted for the better performance of Ag/SiO₂-Al₂O₃ by comparison to the bare mixed oxide. A stable 68-69% selectivity at quantitative conversion was maintained for 4 h of operation (Table 2, entry 1). A peculiar observation was made over various metal phosphate catalysts.¹⁵⁴ Boron phosphate gave indeed better results than phosphates of Al, Fe, Ni and La, despite lower surface area and acidity. Quantitative conversion was maintained during a 10 h run, while selectivity decreased from 95 to 70% (entry 2). The group of Sato evaluated supported heteropoly acids, and the best results were obtained with H₄SiW₁₂O₄₀/SiO₂.¹⁵¹ It was noticed that the presence of mesopores larger than 6 nm in the silica support favored the reaction. 94% yield was obtained under optimized conditions (entry 3). Xu and coworkers studied the dehydration of 1,2-PDO over a wide range of heterogeneous acid and base catalysts.¹⁴⁸ The best results were obtained when an aqueous solution was pumped over acid catalysts including microporous molecular sieve materials such as SAPO-34. 1,2-PDO conversion decreased from 90 to 83% during a 10 h run, while **21** selectivity slightly increased from 63 to 67% (entry 4). The authors proposed that the reaction proceeds through elimination of the secondary alcohol of 1,2-PDO, affording 1-hydroxy-1-propene, which then undergoes tautomerization into propanal. They also claimed that dehydration of the secondary OH was favored over Brønsted acid sites of the catalyst. Cavani and colleagues reported up to 86% yield in propanal upon reacting an aqueous feed of 1,2-PDO in the presence of O₂/N₂ as the carrier gas, over a catalytic bed of WNb oxides operated at 240 °C (entry 5).¹⁵³

Vogel and coworkers alternatively evaluated the reaction in sub- and supercritical water and in the presence of an homogeneous catalyst.¹⁵⁰ ZnSO₄ (400 ppm) was loaded in the aqueous feed

of 1,2-PDO, and the mixture was superheated for 1 min at 360 °C and 340 bar in a continuous flow reactor, affording 90% yield in **21**.

Propanoic acid. Propanoic acid (or propionic acid) is used in plastic dispersions and herbicides, and for the manufacturing of cellulose esters. It is produced at the industrial level from the oxidation of propanal (**21**).¹⁵⁶ Cavani and colleagues evaluated W-V-O and W-Mo-V-O catalysts in fixed-bed reactors, for the one-pot dehydration of 1,2-PDO into propanal and its subsequent oxidation toward propanoic acid.¹⁵³ Such catalysts are efficient for the analog one-pot dehydration of glycerol into acrolein, followed by its subsequent oxidation into acrylic acid (see section 2.3.9.). However, a maximum yield of only 13% in propanoic acid was obtained. Indeed, significant side-reactions were observed, such as (1) oxidative cleavage of 1,2-PDO and **21** into acetaldehyde and formaldehyde, (2) acetalization of the corresponding aldehydes with unconverted 1,2-PDO and (3) over-oxidation of propanal toward CO_x species.

2.2.7. Hydrogenolysis into 1-Propanol

1-Propanol is manufactured at the industrial level from the reduction of propanal (**21**), itself produced from the hydroformylation of petro-based ethylene. It comes with a broad range of applications, including its use as a solvent.¹⁵⁷ Zhu and coworkers demonstrated both the selective conversions of 1,2-PDO and 1,3-PDO into 1-propanol over a Cu-Ce-SBA catalyst.¹⁵⁸ A methanolic solution of 1,2- or 1,3-propanediol was co-fed with H₂ over a catalytic bed operated at 180 °C and 50 bar. With 1,2-PDO, quantitative conversion and 91% selectivity were obtained, with 2-propanol as main side-product (8% selectivity). Upon utilization of 1,3-PDO, almost quantitative conversion (94%) and excellent selectivity (98%) were obtained as well. In the context of a research program aiming at the hydrogenolysis of glycerol (see section 2.3.12), Ding and coworkers performed control experiments with 1,3-PDO as the substrate.¹⁵⁹ The diol

was pumped as a concentrated aqueous solution (80 wt%), along with molecular hydrogen, in a fixed-bed reactor loaded with a catalyst based on egg-shell Ir-ReO_x. Operation at 130 °C and 80 bar yielded 1-propanol with 96% selectivity at 43% propanediol conversion. A procedure that did not require external H₂ co-feeding was described by Mu and coworkers.¹⁶⁰ An aqueous solution of 1,2-PDO was diluted with N₂ and reacted at 290 °C and atmospheric pressure in a fixed-bed reactor loaded with Nb₂O₅/ZrO₂ as the heterogeneous catalyst. 39% selectivity for 1-propanol was obtained at 85% 1,2-PDO conversion. The presence of propanal (27%) and acetol (22%) as the main side-products suggested a mechanism where 1,2-PDO is first dehydrated into propanal (**21**), and then a H-transfer reaction between 1,2-PDO and **21** yields 1-propanol and acetol. The rather low selectivity for acetol, and control experiments with propanal as the substrate, indicated that H-transfer with 1,2-PDO was however not the only reaction pathway involved.

2.2.8. Aromatization into *N*-heterocycles

2-Methylpyrazine. 2-Methylpyrazine (**24**) was prepared from the gas-phase dehydrocyclization of 1,2-PDO in the presence of a stoichiometric amount of ethylenediamine (**23**) in fixed-bed flow reactor. In most cases, nitrogen was utilized as diluting carrier gas (Figure 18). Zn- or Co-based heterogeneous catalysts such as supported or mixed oxides^{161–166} and modified zeolites^{167,168} were assessed for the reaction, and the corresponding optimized conditions are reported in Table 3.

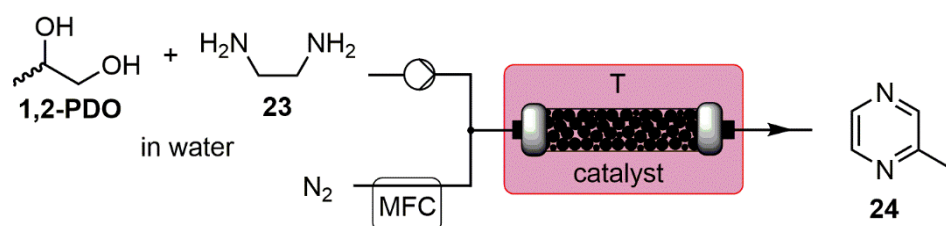


Figure 18. General flow procedure for the gas-phase dehydrocyclization of 1,2-propanediol and ethylenediamine into 2-methylpyrazine.

Table 3. Catalysts and optimized conditions for the gas-phase dehydrocyclization of 1,2-propanediol and ethylenediamine into 2-methylpyrazine.

Entry	Catalyst	T (°C)	Space velocity	TOS (h)	Conv. (%)	Selec. (%)	Ref.
1	Co ₃ O ₄ /ZnO/SiO ₂	360	- ^a	- ^a	>99	82	161
2	CuCoAl	400	- ^a	- ^a	85	57	162
3	CuZnAl	380	- ^a	- ^a	96	88	163
4	CuO/ZnO/SiO ₂	360	- ^a	50-350	99	90-85	164
5	Cu-Zn-Cr/Al ₂ O ₃	380	LHSV = 1 h ⁻¹	2-10	98-90	86-80	165,166
6 ^b	ZnO-ferrierite	400	WHSV = 0.66 h ⁻¹	2	>99	43	167
7 ^b	ZnO-ZSM-5	450	WHSV = 1 h ⁻¹	2	>99	64	168

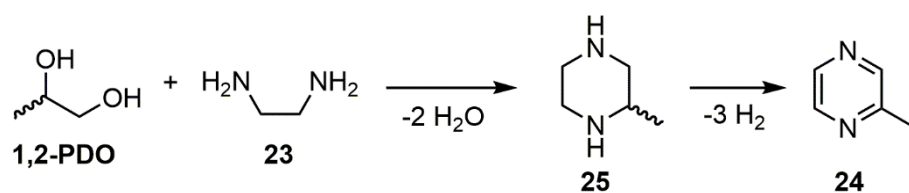
^a Unclear. ^b No carrier gas.

The reaction proceeded in general with excellent yields, although poorer results were obtained over zeolite-based systems (Table 3, entries 6-7).^{167,168} The highest prolonged yield was reported over CuO/ZnO/SiO₂, where about 99% conversion was maintained for 350 h TOS, with only a mere decrease in selectivity from 90 to 85% (entry 4).¹⁶⁴

The catalysts require bifunctional acid and metallic sites to promote the formation of 2-methylpyrazine (**24**). Indeed, the reaction mechanism involves a dehydrative cyclization of 1,2-PDO and ethylenediamine, catalyzed by acid sites, followed by a subsequent dehydrogenation of the intermediate 2-methylpiperazine (**25**), triggered by metallic sites (Scheme 1). It was reported that over unmodified ZnO/SiO₂ catalyst, a large amount (about 20%) of 2-methylpiperazine, was present in the reactor effluents.¹⁶¹ Thus, the catalyst was modified with CuO or Co₃O₄ to improve the dehydrogenation activity, and the selectivity for 2-methylpiperazine was dramatically reduced below 1.5%. However, 8-12% of pyrazine was

obtained over such systems, and the formation of this side-product was rationalized by dimerization of ethylenediamine over the metallic sites of the catalyst. Similarly, SiO₂-supported ZnO, CuO or CuO/ZnO were assessed independently.¹⁶⁴ It was found that the zinc-based material showed enhanced activity toward dehydration, while the copper catalyst promoted dehydrogenation. A combination of both oxides was thus preferred for the selective formation of **24**. Hou *et al.* compared different CuMAI materials (M = Cr, Mn, Zn and Co), and established a linear relationship between the acid site density and the conversion of both 1,2-propanediol and ethylenediamine.¹⁶² In this example as well, a relationship between the dispersion of metallic Cu and 2-methylpyrazine selectivity was observed.

Scheme 1. Reaction sequence toward 2-methylpyrazine.



2-Ethyl-3-methylquinoline. Chao *et al.* prepared 2-ethyl-3-methylquinoline from the gas-phase reaction of aniline and 1,2-PDO in a fixed-bed reactor packed with acid-treated ZnCl₂/Ni-USY zeolite.¹²⁷ A solution of both reactants with a threefold molar excess in the diol was pumped along with H₂ as carrier gas in the continuous flow setup. The reaction took place at 410 °C and atmospheric pressure in the presence of the catalyst, but only a moderate 30% yield in the target compound was obtained.

2.3. Glycerol

2.3.1. Presentation, Producers, Current Commercial Routes and Markets

1,2,3-Propanetriol (glycerol, GL, CAS 56-81-5) is a widely available biomolecule found as the common backbone of glycerides.¹⁶⁹ GL was included on the original 2004 list of most

promising chemicals from biomass issued by the US Department of Energy.²⁶ It was discovered by Scheele in 1779, and its first industrial use dates back to 1866 with the preparation of nitroglycerin by Nobel. GL market was estimated at \$2.19 billion in 2015.^{169,170} The global production of GL is expected to reach 8 million tons by 2025, mainly as a by-product of biodiesel production.^{117,171} The price of glycerol has dramatically decreased over the last decade (\$385 per ton for crude glycerol; \$660 per ton for refined glycerol.¹⁷² Europe and South-East Asia are the biggest consumers of glycerol (55% of the demand worldwide), while Asia is the biggest producer (35% of supply worldwide).¹¹⁷

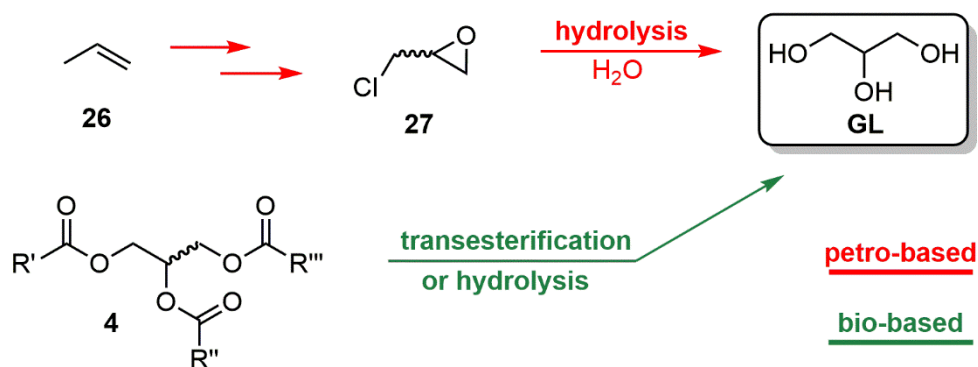
GL can be produced either from petro-based chemicals or from bioresources. The petro-based process typically starts from the oxidation of propene (**26**) to epichlorohydrin (**27**) and its subsequent hydrolysis to glycerol (Scheme 2).¹⁶⁹ Despite a much higher cost, the petro-based process is sometimes preferred for the preparation of high purity GL for specialty applications.¹⁶⁹ GL is mostly produced from the commercial utilization of triglycerides (**4**) from vegetable oils or animal fats for the agrochemical and biodiesel industries (Scheme 2).¹⁶⁹

The volume of glycerol obtained through the biodiesel industry is significant, and it accounted for 62% of the total volume of glycerol worldwide in 2013.¹¹⁷ Just in the US for instance, which is the largest producer of biodiesel worldwide, about 600 million liters of biodiesel were produced in 2019 (5.4 billion liters in Brazil in 2018).¹⁷³ The most common biodiesel processes rely on the transesterification of triglycerides with lower alcohols (MeOH or EtOH) in the presence of a homogeneous acid or basic catalyst, and both processes have reached full commercial development. GL obtained accordingly is typically impure and referred to as crude bio-based GL; it contains various impurities including mostly water, lower alcohols, carboxylic acids and inorganic salts in variable amounts.¹⁷⁴ The purification of crude GL is energy and resource intensive.^{169,170} Alternative processes including enzymatic catalysis or supercritical

conditions, as well as alternative non-food resources,¹⁷⁰ are studied yet still with a low to intermediate maturity. GL can also be produced through the fermentation of sugar or hydrogenolysis of carbohydrates, but these processes have a low maturity and are restricted to lab and small scale prototypes.¹⁶⁹

The main producers of biodiesel, which are *de facto* the main producers of glycerol, are NESTE with an overall capacity of 2,7 million tons per year of biodiesel (facilities in the Netherlands, Finland and Singapore), Total (France) with an overall capacity of 500,000 tons per year of biodiesel and Diamond Green Diesel (USA) with an overall capacity of 800,000 tons per year of biodiesel.

Scheme 2. Simplified chemical processes for the preparation of glycerol from petro-based or bio-based feedstock.



There is an important market (65% of the total production) for the direct utilization of GL in the food industry,¹¹⁷ for pharmaceuticals and personal care products, mainly as a lubricant or moisturizer.^{169,170} GL can also be transformed in a wide range of value-added chemicals such as glycidol, epichlorohydrin, allyl alcohol, acrolein, 1,2- and 1,3-PDO, ethylene glycol, glycerol carbonate and 3-hydroxypropionic acid.^{77,116,129,171,175–180} Epichlorohydrin represents the most important volume of glycerol (11%) converted to valued-added chemicals.¹¹⁷ Other

applications concern tobacco products, explosives, fuel additives alkyd resins, cellophane and detergents.^{169,170,181}

2.3.2. Intramolecular Etherification into Glycidol

Glycidol (**28**) is a very important chemical building block, notably for the preparation of branched polymers.¹⁸² It is commonly synthesized from the epoxidation of allyl alcohol (**19**).¹⁸³ A recent study reported the one-step conversion of glycerol into glycidol over Cs/HZSM-5 in a gas-phase fixed-bed reactor (Figure 19a).¹⁸⁴ With the best catalyst, the conversion of GL increased sharply at a maximum of 86% at TOS = 3 h, but then dropped at longer operation time (Figure 19b). On the other hand, **28** selectivity increased steadily from 41% to 64% over 27 h of operation, probably due to progressive coking of the nonselective active sites. Deactivation of the catalyst occurred both through CsNO₃ decomposition and coke accumulation. The procedure is clearly not synthetically viable in its current form, but potentially opens new avenues for the preparation of this expensive building block from cheap glycerol. Another continuous-flow preparation of glycidol from glycerol was described, but it relies on a two-step hydrochlorination/etherification procedure, and is thus detailed in section 2.3.16.

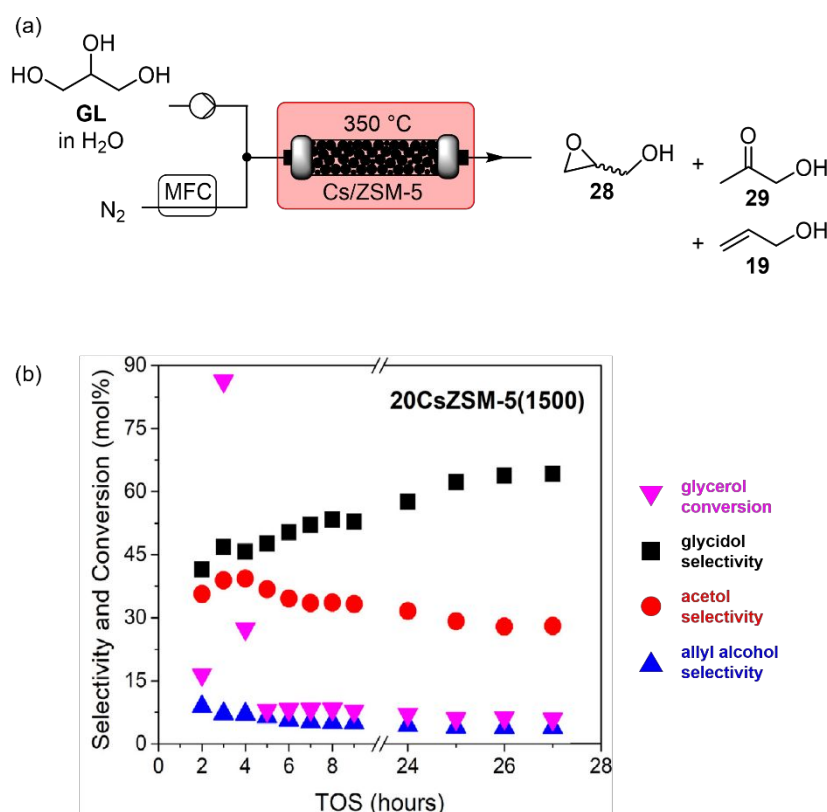


Figure 19. Intramolecular etherification of glycerol into glycidol over CsNO₃-modified zeolite.

(a) Process utilized and (b) results obtained over operation time.¹⁸⁴ Reproduced with permission from ref 184. Copyright 2020 Elsevier.

2.3.3. Ketalization and Intermolecular Etherification

Solketal. The ketalization of GL with acetone was studied in continuous flow reactor, using either homogeneous¹⁸⁵ or heterogeneous^{186–197} (Table 4) acid catalysts. The formation of the 5-membered ring, 4-hydroxymethyl-2,2-dimethyl-1,3-dioxolane (solketal, **30**), was always favored and the 6-membered ring **31**, resulting from the capping of the two primary alcohols of glycerol, was detected only in traces (typically 1%, Figure 20).¹⁹⁸ Ketal **30** has the potential to be used as an oxygenated fuel additive since it reduces gum and particle formation and increases octane number.¹⁹⁹ The most relevant continuous flow processes in fixed-bed reactor for solketal

are summarized in Table 4. Acetone is not miscible with glycerol, and solvents were utilized in most cases to prepare a homogeneous feedstock solution.

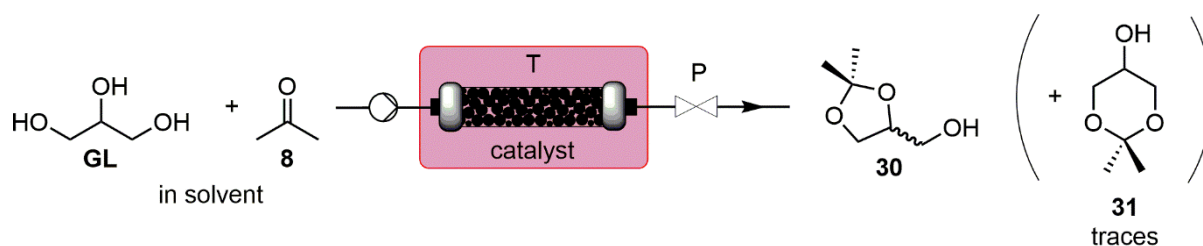


Figure 20. General flow procedure for the ketalization of glycerol into solketal.

Table 4. Catalysts and optimized conditions for the continuous synthesis of solketal.

Entry	Catalyst	Solvent	Acetone (equiv)	T (°C)	P (bar)	Space velocity	TOS (h)	Conv. (%)	Selec. (%)	Ref.
1	Amberlyst 15	DMF	20	50	^a	^b	0.2	92	96	186
2	Amberlyst 36	EtOH	6	40	41	WHSV = 4 h ⁻¹	4	88 ^d		187
3	Amberlyst 36	MeOH	4	25	35	WHSV = 2 h ⁻¹	2-24	94-89 ^d		190
4	C-SO ₃ H	^c	8	57	^a	WHSV = 2.9 h ⁻¹	0.1-5	>99	>99	191
5	C-SO ₃ H	EtOH	6	50	^a	^b	1-90	82-85	>99	192
6	Purolite PD206	EtOH	5	20	120	^b	1-8	95-92 ^d		193
7	AlF ₃ ·3H ₂ O	^e	4	100	10	WHSV = 2 h ⁻¹	24	78	>99	194
8	β-zeolite	MeOH	3	50	^a	WHSV = 3.4 h ⁻¹	1-24	90-88	98	188
9	HZSM-5	MeOH	3	50	^a	WHSV = 3.4 h ⁻¹	1-24	93-89	98	188
10	HZSM-5 ^f	^c	8	50	^a	res. time = 172 s	1-100	63 ^d		189
11	SBA-15-Sn-OH	<i>t</i> -BuOH	1	80	^a	^b	1-50	55-49	97-99	195

^a Atmospheric pressure. ^b Unclear. ^c No solvent, two separate feeds. ^d Yield. ^e No additional solvent, crude glycerol contaminated with water/MeOH. ^f Walls of a capillary microreactor functionalized with the catalyst.

Amberlyst 15 was assessed by Mota and coworkers for the reaction, and 92% glycerol conversion with 96% solketal selectivity were reported at 50 °C and atmospheric pressure.¹⁸⁶ Toxic DMF was used as solvent to prepare a homogeneous glycerol/acetone feed stock solution, negatively impacting the process (Table 4, entry 1). Xu and colleagues assessed Amberlyst 36, which gave up to 94% yield at room temperature, and this value decreased by only 5% after 24

h TOS, highlighting the stability of the catalyst and its suitability to sustain continuous production.^{187,190} However, the main drawback of this material was the poor tolerance to water and sodium chloride, which precluded direct utilization of crude GL (entries 2-3). The same group also studied Purolite PD206 as a catalyst packed in a fixed-bed reactor, and solketal was obtained in 95% yield in subcritical acetone at room temperature and 120 bar of pressure (entry 6).¹⁹³ Amberlyst 36 was evaluated by Selva and coworkers, and the authors similarly reported a deactivation of the catalyst in the presence of traces of NaCl, with a conversion decreasing from 82% to 4% after 24 h TOS.¹⁹⁴ Others also reported on Purolite CT275 as the acidic heterogeneous catalyst, which maintained its activity for 600 h of operation.¹⁹⁷ Konwar *et al.* prepared a strong Brønsted acidic meso-/macroporous catalysts from Na-lignosulfonate as precursor, by pyrolysis and ion exchange.¹⁹² The catalytic material was evaluated in a fixed-bed reactor, which was fed with a solution of acetone and glycerol in ethanol, and operated at 50 °C and atmospheric pressure. Elevated conversion (82-85%) with near quantitative selectivity for solketal (>99.5%) were maintained for 90 h TOS (entry 5). Moving away from (resin) organocatalysts, Selva and colleagues studied strong inorganic Lewis acids such as $\text{AlF}_3 \cdot 3\text{H}_2\text{O}$.¹⁹⁴ The latter reached a maximum activity at 100 °C, and was effective to process all glycerol grades containing methanol, water and salt, giving high conversions (71-84%) and selectivity (>99%) without any loss of activity after 48 h TOS. $\text{AlF}_3 \cdot 3\text{H}_2\text{O}$ was thus reported as an effective heterogeneous catalyst for the direct transformation of crude glycerol into **30**. In addition, no additional solvent other than acetone was utilized, since residual methanol and water present in the feed solution improved the miscibility of glycerol and acetone (entry 7). Kowalska-Kuś and coworkers prepared and evaluated hierarchical micro-/mesoporous zeolites by desilication of parent HZSM-5, β - and Mordenite zeolites.¹⁸⁸ Unmodified β - and Mordenite zeolites gave good activity and stability, while the parent HZSM-5 gave low conversion and

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3 stability, since conversion evolved from 35% to 10% during 6 h TOS. This was most likely
4 related to its channel size (5.3 x 5.4 Å) that is close to the molecular diameter of glycerol and
5 solketal (4.3-5.2 Å) and more prone to trap water. By contrast, desilicated HZSM-5 gave a
6 stable and elevated conversion (93-89%, entry 9) for 24 h of operation under identical
7 conditions. Good results were obtained over hierarchical β -zeolite as well (entry 8). A poorer
8 performance was however obtained with hierarchical Mordenite, most likely because of its
9 hydrophilic character, which tends to retain water molecules. Zhang and colleagues
10 functionalized the walls of a quartz capillary microreactor with a film of HZSM-5 zeolite using
11 a hydrothermal continuous flow synthetic process.¹⁸⁹ The catalytic reactor yielded 63% yield
12 in solketal under optimized conditions (entry 10). It was shown that the yield increased with
13 the thickness of the film, evidencing that the catalytic loading prevailed over the diffusion
14 resistance. Although the yield claimed is modest by comparison to other reports, the process is
15 robust since it proceeded without solvent and the catalytic microreactor did not deactivate
16 during a 100 h run. Wang *et al.* prepared mesoporous silica (SBA-15) grafted with Sn-OH
17 species, and evaluated the catalytic material in a fixed-bed flow reactor.¹⁹⁵ Cost-effective
18 conditions (80 °C, glycerol/acetone ratio of 1:1) were employed, and a steady solketal
19 selectivity of 97-99%, with a marginal decrease in glycerol conversion from 55% to 49%, were
20 observed during 50 h TOS. In the report, *tert*-butanol was utilized as solvent to prepare a
21 homogeneous feedstock solution (entry 11).
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47 Overall, high yields and catalytic stability were reported using mild process conditions, and
48 procedures were often associated with a low E-factor. In light of these results, we anticipate
49 that the production of solketal could be a viable pathway for the upgrading of GL on the
50 commercial scale.
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Glyceryl *tert*-butyl ethers. Few studies were dedicated to the etherification of glycerol in continuous flow reactors, despite a huge interest for glycerol ethers.²⁰⁰ These studies utilized alcohols^{201–205} or alkene²⁰⁶ as glycerol alkylating agents, and relied on heterogeneous acid catalysts such as zeolites and resins. The preparation of glyceryl 1,2- (**32a**) and 1,3-di-*tert*-butylethers (**32b**), as well as glyceryl tri-*tert*-butylether (**33**) stimulated intense research efforts since these compounds can be directly blended with fuels to improve engine performances.²⁰⁷ Dogu *et al.* assessed several commercial catalysts for the direct alkylation of glycerol with *tert*-butanol (*t*-BuOH), both in batch and flow reactors.^{201–203} The best results were obtained over Amberlyst 15 and Amberlyst 36 resins. The superiority of flow reactors was demonstrated for such processes, with high glycerol conversions obtained within short contact times, while prolonged reaction times were needed in batch reactors. For instance with Amberlyst 15 as the catalyst and under similar process conditions, a contact time of ~ 0.3 min was required in flow to reach ~ 50% conversion, while more than 100 min of reaction time was necessary in batch to reach a similar conversion. The difference in reaction time was explained by the improved mass transfer between reactants and catalysts in continuous flow reactors.²⁰¹ In one of the most advanced examples, 62% glycerol conversion and a moderate 35% combined selectivity toward **32a** and **32b** were obtained at 90 °C in the presence of Amberlyst 15 as a catalyst and Zeolite 4A as a dehydrating agent. Only trace amounts of **33** were detected in the reactor effluents.²⁰² The methodology was improved by Viswanadham and Saxena, using a fixed bed reactor packed with nano-BEA zeolite (Figure 21).²⁰⁴ 99% Glycerol conversion, along with 45% and 54% selectivity for diethers **32a,b** and triether **33**, respectively, were obtained at 110 °C. Additionally, the catalyst was stable since these values were maintained for 24 h TOS. The large pores of the catalyst promoted the formation of these hindered ethers. Alternatively, Uzun assessed the reaction with isobutene as alkylating agent, both in batch and flow reactors.²⁰⁶

Partially Na-exchanged Amberlyst 15 resins were assessed as heterogeneous organocatalysts and compared to the fully protic counterpart. Although the total amount of Brønsted acid sites was lower on the Na-exchanged materials, the strength of these acid sites was higher. DFT computations suggested that Na ions acted as Lewis acids that withdrew electron density from the neighboring Brønsted acid sites and thus increased their strength. In batch, a complete glycerol conversion was obtained and the Na-exchanged materials gave higher diethers/monoethers ratio than the parent Amberlyst 15 catalyst. The experiments under continuous flow conditions were conducted at high space velocity ($2\text{--}20\text{ mol}_{\text{glycerol}}\text{ mol}^{-1}_{\text{proton}}\text{ min}^{-1}$) to attain low glycerol conversion ($<3\%$) and gain insight on the reaction mechanism and kinetics.

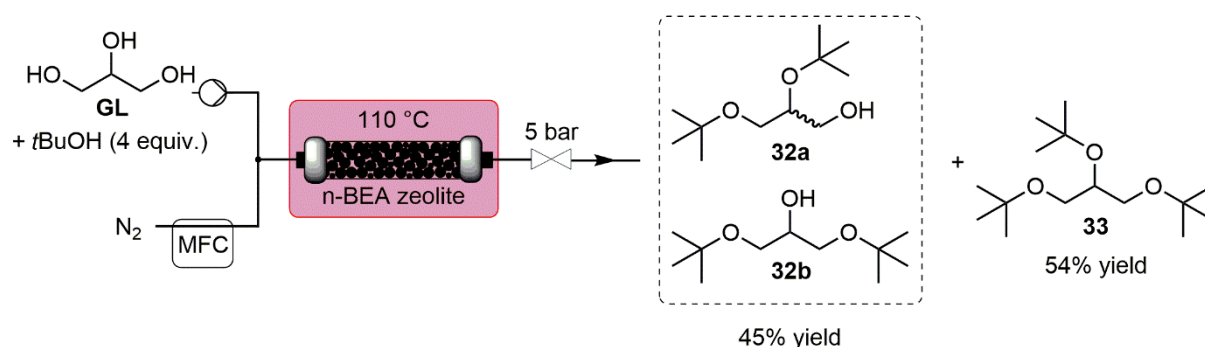


Figure 21. *tert*-Butylation of glycerol in a fixed-bed reactor containing nano-BEA zeolite.²⁰⁴

Glyceryl ethyl ethers. The ethanol-mediated alkylation of glycerol was also implemented in a flow reactor over Amberlyst 15, but a combined yield of only 13% was reported under optimized conditions.²⁰⁵

β -glucosylglycerol. A procedure in rupture for glycerol ethers reported by Nidetzky and coworkers involved a β -glycosidase immobilized within a continuous microreactor, and the condensation of glycerol and cellobiose was demonstrated in the setup.²⁰⁸ β -glucosylglycerol

was prepared accordingly, and the biocatalytic heterogeneous continuous flow system gave similar performance to the corresponding homogeneous batch process.

Solketal *tert*-butyl ether (STBE). The ketalization and etherification methodologies were applied to the preparation of solketal *tert*-butyl ether (STBE, **35**), using either a sequential¹⁸⁵ or a concerted²⁰⁹ process. STBE was reported as a promising fuel additive, which reduces the production of nitrogen oxides, carbon monoxide and particle emissions resulting from fuel combustion.²¹⁰ Maximov and coworkers studied the concerted reactions, where BEA zeolite catalyst was used in a fixed-bed reactor to promote simultaneously both ketalization with acetone and alkylation with *t*-BuOH.²⁰⁹ Various reaction species were involved in this one-pot process, *i.e.* glycerol (GL), solketal (**30**), glycerol di- (**32a,b**) and mono-*tert*-butylethers, as well as STBE (**35**). Therefore, a complex balance of parameters affected the formation of **35**. Under optimized process conditions, STBE was obtained in 36% selectivity with quantitative glycerol conversion. Solketal was the major side-product. Alternatively, Stevens and coworkers reported a sequential continuous process for the preparation of STBE (Figure 22) in a glass mesofluidic reactor of 56 mL internal volume.¹⁸⁵ The glass reactor was characterized by a high mixing efficiency to ensure fast mass transfer between immiscible reagents. Glycerol was first subjected to ketalization by acetone in the presence of a catalytic amount of sulfuric acid, to give solketal in 98% yield with a productivity of 11 kg h⁻¹. The etherification of **30** was next implemented in the reactor, with isobutene (**34**) as the alkylating agent and sulfuric acid as the catalyst. Isobutene was kept liquid under a moderate internal pressure to improve mass transfer, and conversion increased by comparison to a corresponding batch gas-liquid reaction. For instance, 83% conversion was obtained after 9 h in batch with more than 10 equiv. of gaseous isobutene, while only 2 equiv. of liquid isobutene were required in flow to reach complete conversion under 12 bar of counterpressure (41 s of residence time at 90 °C). To reduce its

oligomerization in the presence of sulfuric acid, multipoint injection of isobutene was considered. STBE was obtained accordingly in 85% yield with a 12 kg h⁻¹ productivity. The process afforded excellent yields, high process safety, significantly shorter reaction times and a virtual 90 t y⁻¹ production of STBE.

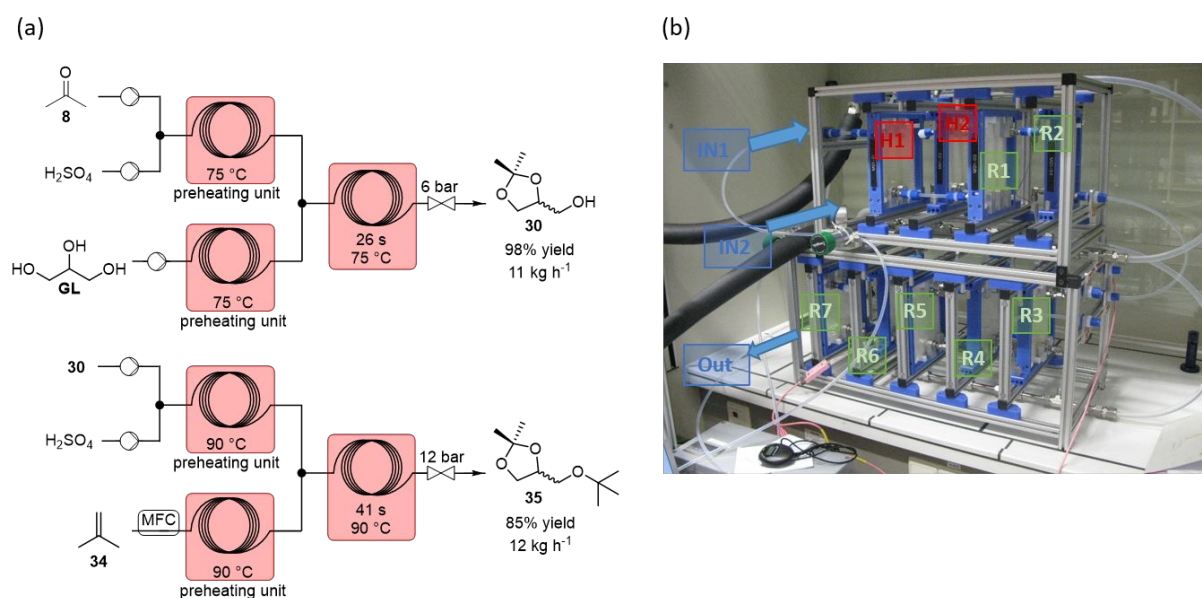


Figure 22. (a) Sequential synthesis of STBE catalyzed by H₂SO₄ in a glass mesofluidic reactor.¹⁸⁵ (b) Photograph of flow reactor utilized for the preparation of solketal and STBE, featuring 9 fluidic modules (~8 mL of internal volume each) connected in series. Modules 1 and 2 (H1-2) are used to preheat and premix either acetone/sulfuric acid and glycerol or solketal/sulfuric acid and isobutene. Modules 3-9 (R1-7) are utilized to increase the residence time (26 s for the preparation of solketal and 41 s for the preparation of STBE). Adapted with permission from ref 185. Copyright 2011 Elsevier.

2.3.4. Esterification

Depending on the acylation degree of glycerol and on the hydrocarbon chain length of the corresponding acyl moieties, glycerol esters find applications in various fields such as material,

fuel, healthcare and food sciences.^{211,212} As for the ethers, the preparation of esters derived from glycerol generally leads to mixtures of species, *i.e.* 1- and 2-monoacylglycerol, 1,2- and 1,3-diacylglycerol, as well as 1,2,3-triacylglycerol. Research efforts were therefore triggered by the need for selective preparation of such esters, depending on the final commercial application targeted. Flow reactors packed with immobilized lipases^{213–215} and resins^{216–218} as heterogeneous catalysts, as well as non-catalyzed continuous technologies,^{219–221} were reported as enabling tools for such selective syntheses.

Glycerol acetates (Acetins). Ghaziaskar and colleagues reported the acylation of glycerol with acetic acid under catalyst-free flow conditions.²¹⁹ Monoacetins (glycerol monoacetates) were prepared accordingly in 93% selectivity and 53% glycerol conversion, at 100 °C under atmospheric pressure and with an equimolar ratio of acetic acid and glycerol. Using identical temperature and pressure, they also reported the preparation of monoacetins, diacetins (**36a,b**) and triacetin (**37**) with 43%, 44% and 13% selectivities, respectively, at quantitative glycerol conversion.²¹⁶ In the latter case, the formation of di- and triacetins was promoted by increasing the acetic acid/glycerol ratio to 7 in the feed, and by catalyzing the reaction with Amberlyst 36 in a fixed-bed flow reactor. The catalyst maintained maximal activity during a 25 h continuous run. In an advanced example, they could suppress the formation of monoacetin under supercritical CO₂ conditions (Figure 23).²¹⁷ A glycerol feed with 24 equivalents of acetic acid was heated at 110 °C under 200 bar of carbon dioxide pressure, over an Amberlyst 15 heterogeneous catalyst, and **37** was produced with quantitative selectivity. However, this selectivity rapidly decreased to 60% after 5 h TOS, and then remained steady for the next 20 h. This decrease in selectivity was due to an increase in **36a,b** formation, and combined yields evolved from about 40% to 80% during the 25 h run. Selva and coworkers reported a catalyst-free continuous flow procedure for the selective synthesis of triacetin from glycerol.²²¹ With

methanol as the acyl donor, a mixture of mono-, di- and triacetins was obtained. Remarkably, isopropenyl acetate (**6**) enabled the preparation of triacetin (**37**) in quantitative yield at 300 °C and 50 bar. The main asset of using enol esters in transesterification reactions is the irreversibility of the reaction, since the enol by-product undergoes keto-enol tautomerization. The main drawbacks of the procedure were however the utilization of (1) diglyme as the reaction solvent to prepare a homogeneous feedstock solution, (2) an isopropenyl acetate/glycerol molar ratio of 20, and (3) a very long residence time within the reactor (5 h).

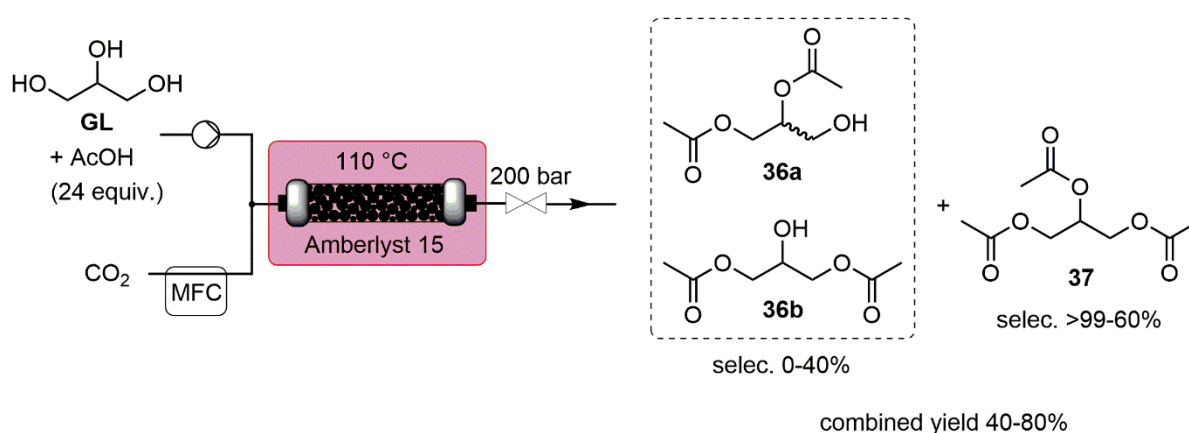
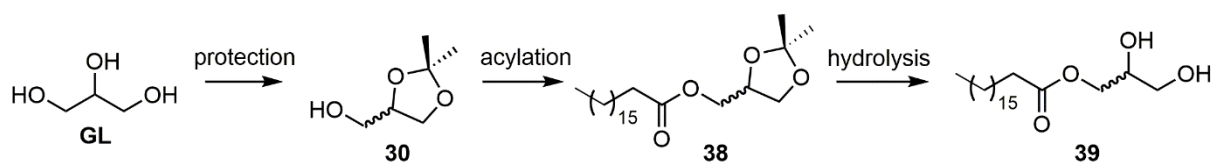


Figure 23. Di- and triacetin preparation in a supercritical CO₂ fixed-bed flow reactor.²¹⁷

The de Souza group studied the biocatalyzed preparation of di- and triacetins from various acetyl donors, such as vinyl and ethyl acetate, in batch and flow reactors.²¹³ Although the batch methodology gave access to diacetin in high yield (92%), a long reaction time (1 h) was necessary. Under continuous flow conditions, high diacetin yields were obtained irrespective of the residence time (0.8-6 min), the acyl donor and the temperature (25-60 °C) utilized. Crude glycerol obtained from the biodiesel industry, containing *ca.* 35% w/w water, could even be esterified under mild heating (60 °C) and using vinyl acetate as acetyl donor. Precise control of the residence time ranging from 1.6 to 4.8 min, enabled the preparation of diacetin and triacetin in 70% and 84% yields, respectively. The lipase-catalyzed flow methodology was extended to

the regioselective 1-monoacylation of glycerol (Scheme 3).²¹⁴ At first, solketal (**30**, see section 2.3.3) was prepared in 87% yield from glycerol protection with acetone at 55 °C, in a fixed-bed flow reactor packed with H₂SO₄-treated silica. The hydroxyl group of **30** was then acylated at 60 °C with stearic acid, using a packed bed of immobilized lipase, and **38** was obtained in 90% yield. Finally, ketal deprotection was conducted in the presence of water over the same H₂SO₄/SiO₂ catalyst at 55 °C. The relevance of flow reactors for the deprotection step was evidenced, as the precise control of the residence time enabled the selective hydrolysis of the ketal group of **38** without hydrolysis of the ester bond. 1-Monoacyl glycerol **39** was obtained accordingly in 87% yield. The acylation and deprotection steps could be concatenated in the final part of the work, but off-line solvent swap from acetone to heptane had to be performed between the protection and esterification steps.

Scheme 3. Reaction sequence for the regioselective 1-monoacylation of glycerol in fixed-bed flow reactors.²¹⁴



Other glycerol esters. Concerning the direct acylation of glycerol with fatty acids, the immiscibility of reactants was circumvented by addition of *t*-BuOH in the feed.²²⁰ In another example, Hill *et al.* took advantage of their immiscibility to improve the efficiency of the flow process.²¹⁵ Glycerol and fatty acid were co-fed separately through a Y-mixer to create a segmented-flow, and the latter was next passed through a packed bed of immobilized lipase. The hydrophilic glycerol phase acted as reactant, but also as drying agent, to shift the equilibrium toward acylated glycerol products by continuous elimination from the lipophilic phase of the water formed upon esterification. In addition, the lipophilic phase, containing

acylglycerols and unreacted fatty acid, could be separated from the hydrophilic phase by simple phase separation (decantation) at the end of the process, enabling glycerol recycling for further runs. The internal diameter of the tubular-flow reactor packed with enzymes had a dramatic impact on the reaction, with linoleic acid conversion increasing from about 25% to 50%, when the reactor diameter was reduced from 5/16" to 1/8". A higher interfacial area between the two immiscible phases, and thus an improved mass transfer, accounted for the better conversion value obtained in the thinner reactor. A long residence time (1 h) at moderate temperature (50 °C) was necessary to obtain linoleic acid conversion of 88-90%, which was maintained for 12 days TOS, with a steady 70% combined selectivity for 1,2- and 1,3-diacylglycerol.

Instead of carboxylic acids, esters and anhydrides, aldehydes could be utilized as alternative acylating agents, under oxidative NHC-catalysis conditions (Figure 24).²¹⁸ *N*-Heterocyclic carbenes (NHC) were generated *in situ* from a supported triazolium salt precatalyst that reacted with a homogeneous organic base, and tetra-*tert*-butyldiphenoquinone (**40**) served as the oxidant. With model compound 2-naphtaldehyde (**41a**), >95% conversion and >95% selectivity were maintained for 120 h of continuous operation, and then conversion slightly decreased to ~70% at TOS = 200 h. The substrate scope was extended to bio-based aldehydes, such as citronellal (**41b**), vanillin (**41c**), furfural and HMF. The target glycerol esters **42a-e** were obtained in excellent conversion and selectivity.

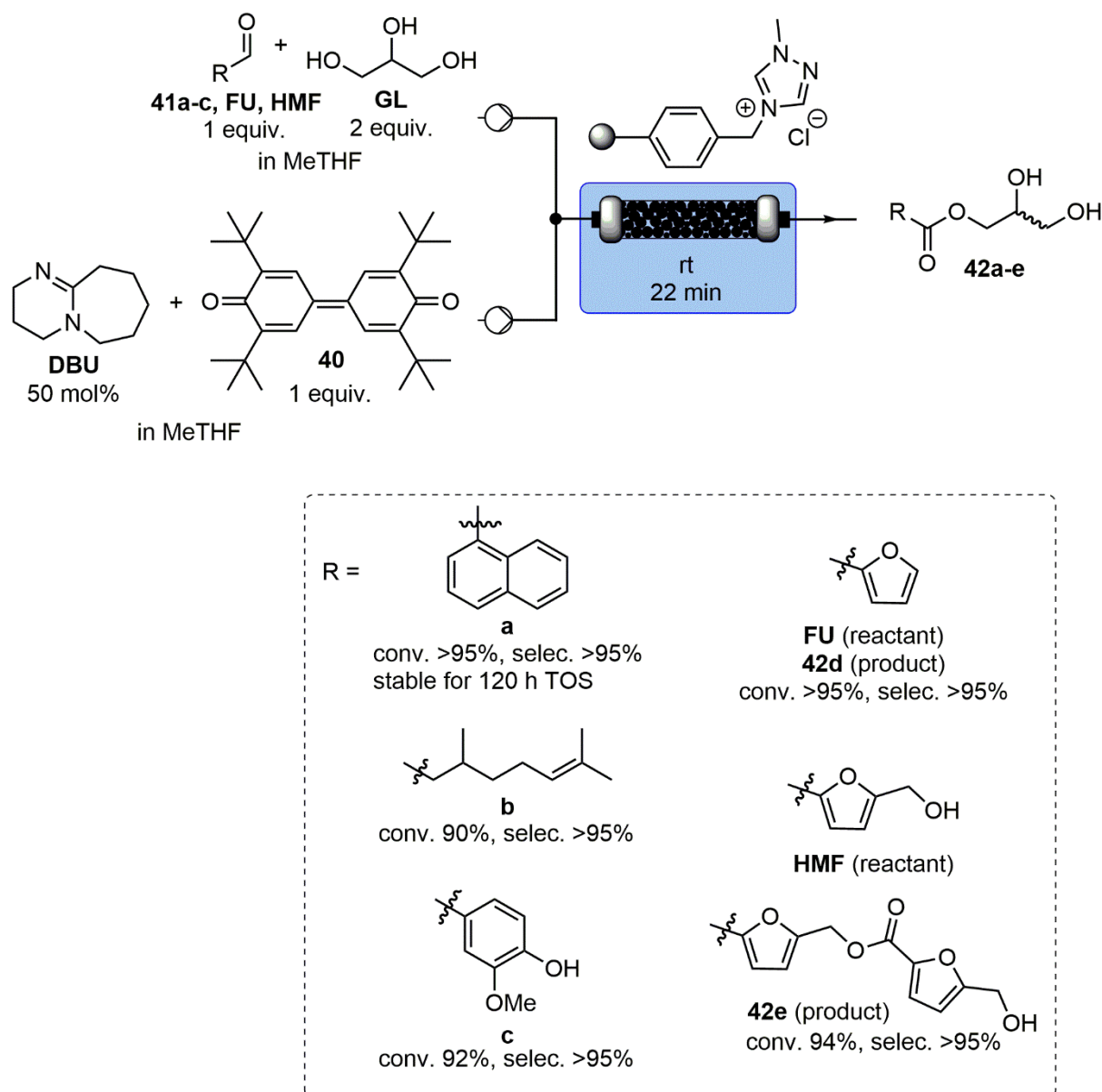


Figure 24. Oxidative NHC-catalyzed esterification of glycerol with aldehydes in a packed-bed reactor.²¹⁸

2.3.5. Carbonation into Glycerol Carbonate

Glycerol carbonate. 4-(Hydroxymethyl)-1,3-dioxolan-2-one, or glycerol carbonate (**43**) is a non-toxic, non-flammable, non-volatile, biodegradable and water-miscible compound, which has numerous applications as solvent, lubricant, additive, formulating agent and chemical

building block.^{179,222–224} It was recently pointed out that glycerol carbonate would be one of the most promising targets to be produced in a glycerol biorefinery from environmental and economic standpoints.^{177,225} Carbonate **43** can be prepared from glycerol and various carbonating agents such as phosgene, alkyl chloroformates, carbonyldiimidazoles (CDI), carbon monoxide in combination with an oxidant, urea, diphenyl carbonate and alkylene/dialkyl carbonates.^{222–224,226–228} Similarly to solketal (**30**, see section 2.3.3.), the 5-membered ring isomer of glycerol carbonate is always selectively formed over the 6-membered ring isomer. Glycerol carbonate was prepared under continuous flow conditions from the reaction of glycerol with dialkyl carbonates or urea, and using homogeneous^{124,125,229,230} or heterogeneous catalysts,^{124,230–234} as well as catalyst-free conditions.¹¹⁰ The most relevant homogeneous (Figure 25) and heterogeneous (Figure 27) processes are summarized in Table 5 and 6, respectively. Homogeneous processes involved only dimethyl carbonate (DMC) as carbonation reagent, while urea, DMC or diethyl carbonate (DEC) were typically utilized in the heterogeneous processes. It is noteworthy that dimethyl and diethyl carbonates are liquid compounds that are not miscible with glycerol, while urea is a solid that cannot be dissolved in a stoichiometric amount in glycerol. Therefore, solvents were commonly used in most reports to prepare a single homogeneous feedstock solution.

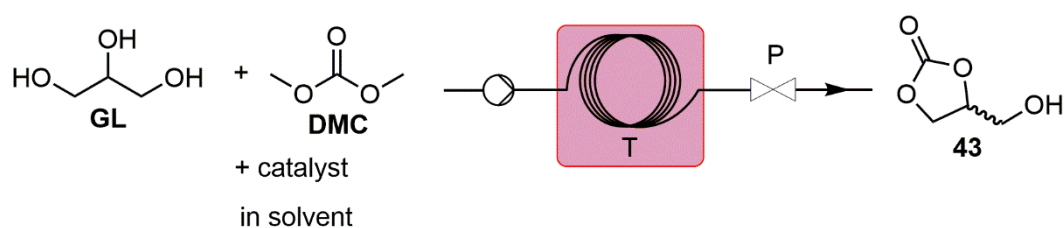


Figure 25. General homogeneous flow procedure for the carbonation of glycerol with DMC.

Table 5. Homogeneous continuous flow processes for the carbonation of glycerol with dimethyl carbonate.

Entry	Catalyst	Solvent	DMC (equiv)	T (°C)	P (bar)	Residence time (min)	Conv. (%)	Selec. (%)	Ref.
1	none	MeOH	10	230-250	50	15	78-94	83-92	110
2	DBU (1.5 mol%)	- ^a	3	120	7	8	80	82	229
3	NBu ₄ Br (3.5 mol%)	- ^a	2.25	180	11	3	95	79	125
4	Phosphazene P ₁ - <i>t</i> -Oct (1 mol%)	- ^a	3	135	7	2	95	83	124
5	<i>tert</i> -Butyl-tetramethylguanidine (1 mol%)	- ^a	3	135	7	2	94	87	124
6	Tetraethylammonium pipicolinate (3 wt%)	EtOH	3.5	140	17	30	90	85	230

^aNo solvent, glycerol and DMC were pumped as separate feeds.

Selva and coworkers prepared glycerol carbonate under catalyst-free continuous flow conditions (Table 5, entry 1).¹¹⁰ Methanol enabled the preparation of a homogeneous glycerol/DMC feed, which was then superheated under 50 bar for 15 min within the flow reactor. 78% and 94% glycerol conversion, along with **43** selectivity of 92% and 83% were obtained at 230 °C and 250 °C, respectively. A high pressure within the reactor was mandatory for a good selectivity: at 5 bar, **43** underwent the extrusion of 1 equiv. of CO₂ to form 2,3-epoxy-1-propanol (also known as glycidol, **28**), with a 83% selectivity. However, the synthetic viability of this methodology could not be further assessed, as polymerization and clogging occurred. de Souza and colleagues studied the carbonation of glycerol with dimethyl carbonate and investigated various amines as homogeneous catalysts in a microwave batch reactor.²²⁹ 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) was reported as the most promising catalyst, and the reaction was translated to continuous flow conditions. Glycerol carbonate was obtained accordingly in 82% selectivity at 80% glycerol conversion, using a reaction temperature of 120 °C and a moderate (16 min) residence time within the flow reactor, under neat conditions (entry 2). Monbaliu and coworkers reported a solvent-free procedure utilizing 1 mol% of Barton's base (2-*tert*-butyl-1,1,3,3-tetramethylguanidine).¹²⁴ Glycerol carbonate was obtained within only 2 min of residence at 135 °C, in 87% selectivity at 94% GL conversion (entry 5). Other organic superbases such as phosphazenes were evaluated and gave excellent results as well

under identical conditions (entry 4). Their elevated cost was however seen as a major drawback in view of an industrial application. In a follow-up paper, inexpensive ammonium and phosphonium salts were assessed as homogeneous catalysts.¹²⁵ The best results (conv. = 95%, selec. = 79%) were obtained at 180 °C with 3.5 mol% of tetrabutylammonium bromide (NBu₄Br, entry 3). An off-line liquid-liquid extraction procedure was developed for the purification of glycerol carbonate and the recycling of the catalyst. The methodology was extended to crude bio-based glycerol containing water, methanol, salts and organic matter. The conversion of glycerol was dramatically affected, and control experiments suggested that the competitive hydrolysis of glycerol carbonate was the main source for the drop in conversion. The procedure was eventually scaled-up in a commercial pilot-scale continuous flow reactor (Figure 26), and gave glycerol carbonate with a daily productivity of ~13.5 kg. Baxendale and colleagues reported a process with 3 wt% of tetraethylammonium pipercolinate as the catalyst.²³⁰ Ethanol was used as the solvent, and 30 min of residence at 140 °C was required to obtain glycerol carbonate with 90% conversion and 85% selectivity (entry 6).

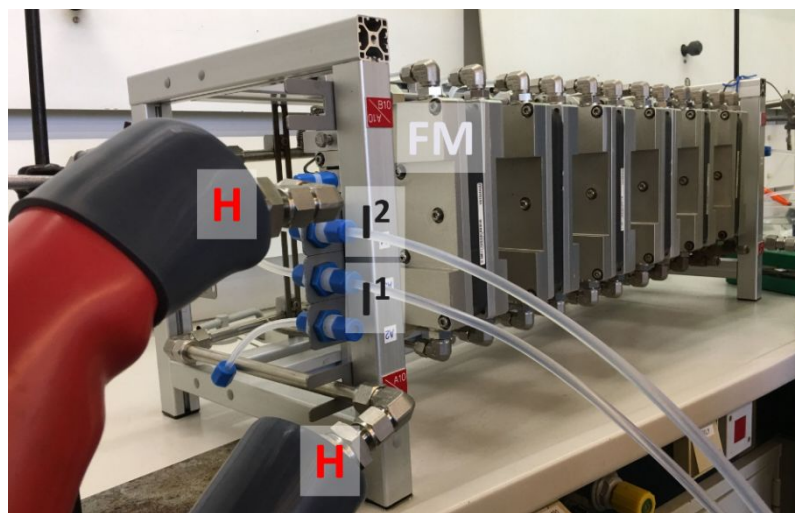


Figure 26. Photograph of the pilot-scale continuous flow reactor for the production of glycerol carbonate including 6 fluidic modules (FM) in Silicon Carbide with a total of 60 mL internal

volume (H = in and outlets for the thermofluid).¹²⁵ Reproduced with permission from ref 125.

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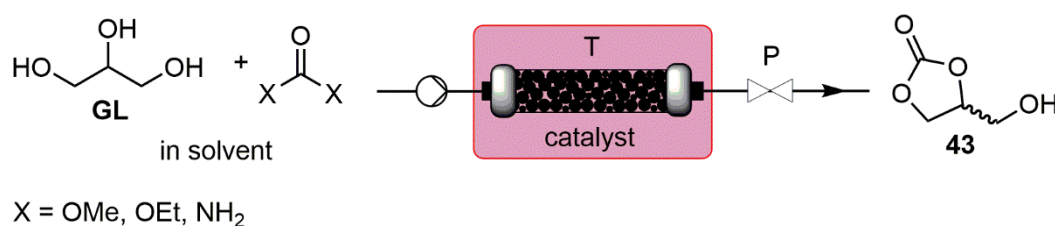


Figure 27. General flow procedure for the heterogeneous carbonation of glycerol.

Table 6. Catalysts and conditions of representative heterogeneous continuous flow processes for the carbonation of glycerol.

Entry	Carbonation reagent (equiv.)	Catalyst	Solvent	T (°C)	P (bar)	Space velocity	TOS (h)	Conv. (%)	Selec. (%)	Ref.
1	DEC (16.5 equiv.)	MgAl/Al ₂ O ₃	DMSO	130	- ^a	- ^b	1-9	>99-88	80-99	231
2	DMC (3 equiv.)	CaO-ZrO ₂	- ^b	90	- ^a	LHSV = 1.5 h ⁻¹	3-15	97	93	234
3	DMC (4 equiv.)	Ambersep 900 (OH)	MeOH	140	17	WHSV = 2.25 h ⁻¹	1-20	95-85	82	230
4	DMC (3 equiv.)	PS-P ₂ - <i>t</i> -Bu	- ^c	135	7	WHSV = 20.8 h ⁻¹	3-80	91-78	77-84	124
5	Urea (1 equiv.)	MgAl	GBL	150	10 ⁻²	LHSV = 12 h ⁻¹	1-100	60-40 ^d		232
6 ^e	Urea (1 equiv.)	Zn/MCM-41	H ₂ O	200	- ^a	LHSV = 0.34 h ⁻¹	2-97	50-45	>99	233

^aAtmospheric pressure. ^bUnclear. ^cNo solvent, glycerol and DMC were pumped as separate feeds. ^dYield. ^eN₂ was used as carrier gas.

Magnesium-aluminium hydrotalcites supported on alumina were studied in a fixed-bed flow reactor.²³¹ Diethyl carbonate was utilized as carbonating agent, and a homogeneous feed was prepared by mixing glycerol and DEC with DMSO. Using the best performing catalyst at a reaction temperature of 130 °C, glycerol conversion slightly decreased from quantitative to 88%, and the selectivity toward **43** increased from 80% to quantitative during a 9 h run, as a result of catalyst deactivation (Table 6, entry 1). Although glycerol carbonate yields were quite high, downstream separation of glycerol carbonate and DMSO, which both have high boiling

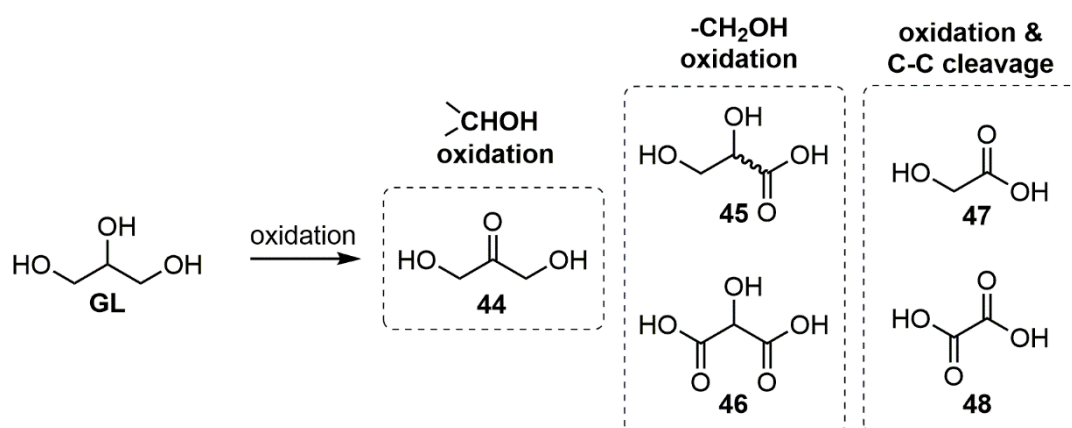
points and are water-soluble, negatively affected the competitiveness of the methodology. Additionally, a large excess (16.5 equiv.) of DEC was utilized in the study. A recent study reported the use of CaO-ZrO₂ as the catalyst and DMC as the carbonation reagent.²³⁴ Excellent conversion (97%) and selectivity (93%) were maintained for 15 h TOS without deactivation (entry 2). The process relied on a single feedstock solution of glycerol and DMC, and is described as solvent-free, which is surprising given the immiscibility of GL and DMC. The group of Pérez-Ramírez reported the carbonation of glycerol with urea over hydrotalcite-derived Mg-Al mixed oxides, with γ -butyrolactone (GBL) as solvent in the feed.²³² An internal pressure of 10 mbar was applied to continuously remove the 2 molar equivalents of NH₃ co-produced in the reaction. Extrudates of the catalyst were prepared as the poor mechanical stability of a crushed powder led to pressure increase within the reactor, and thus decreased the yield of **43**. At 150 °C, the yield of glycerol carbonate slightly decreased from 60% to 40% during a 100 h run, because of catalyst coking (entry 5). However, initial activity could be recovered by calcination. Again, the main drawback was the use of GBL as solvent, and the incomplete glycerol conversion, since the reactant, the product and the solvent are water-miscible and have high boiling points, which would ultimately increase purification costs. Rode and colleagues independently reported on Zn/MCM-41 as catalyst for the urea-mediated reaction.²³³ Similarly to Pérez-Ramírez's results,²³² good catalytic stability was demonstrated for 100 h of continuous operation, but low glycerol conversion values (50-45%) were obtained (entry 6). Baxendale and coworkers reported a procedure relying on Ambersep 900 hydroxide resin as heterogeneous organocatalyst with DMC as reagent.²³⁰ Four continuous runs of 5 h each, with intermediate solvent flushing of the catalytic bed, were conducted and the conversion of glycerol merely decreased from 95 to 85%. The reactor was operated at 140 °C and methanol was utilized as reaction solvent (entry 3). Monbaliu *et al.* reported a solvent-free process

utilizing a polymer-supported (PS) phosphazene, PS-P₂-*t*-Bu, and DMC as carbonation reagent.¹²⁴ The elevated cost of such organocatalyst was balanced by its excellent stability (80 h of continuous operation) at very high space velocity (WHSV = 20.8 h⁻¹): glycerol conversion merely decreased from 91 to 78% and the selectivity for glycerol carbonate remained in the steady 77-84% range (entry 4). In-line IR spectroscopy was notably implemented downstream the reactor to quantitatively monitor the concentration of glycerol carbonate over time, and thus the stability of the catalyst.

2.3.6. Oxidation

Glyceric, tartronic, glycolic and oxalic acids. The continuous flow aerobic oxidation of glycerol gave access to various compounds (Scheme 4), including dihydroxyacetone (**44**, resulting from the oxidation of the secondary alcohol of GL), glyceric (**45**) and tartronic (**46**) acids (formed by oxidation of the primary alcohols of glycerol), as well as glycolic (**47**) and oxalic (**48**) acids (resulting from both oxidation and C-C cleavage of GL).

Scheme 4. Main products observed in the continuous flow oxidation of glycerol.



Oxidation studies were conducted in fixed-bed flow reactors embedded with transition metal-containing catalysts, in the liquid-^{235–240} or gas-phase.²⁴¹ In liquid-phase processes, sodium

hydroxide in stoichiometric amount or excess was typically solubilized within the aqueous feedstock solution of glycerol, and pumped along with molecular oxygen (Figure 28). Catalysts were mostly based on metallic gold or bismuth. Representative catalysts and optimized conditions for liquid-phase oxidation processes are summarized in Table 7. Since the efficiency of catalysts is often reflected by their tendency to promote C-OH oxidation without triggering oxidative C-C bond cleavage, selectivity for compounds **44**, **45** and **46** only is reported.

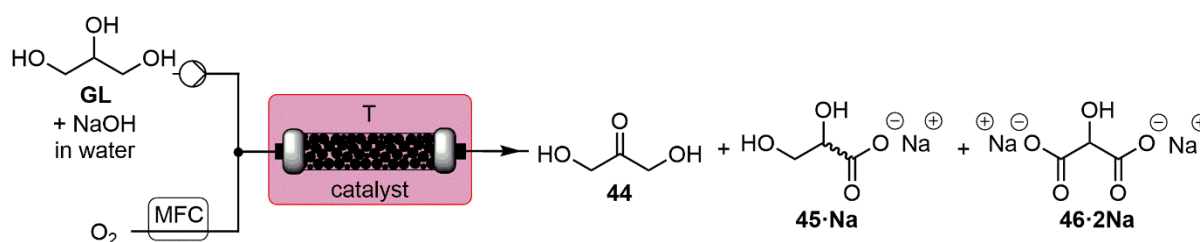


Figure 28. General flow process for the liquid-phase oxidation of glycerol.

Table 7. Catalysts and conditions of representative heterogeneous continuous flow processes for the oxidation of glycerol in the liquid phase.

Entry	Catalyst	NaOH (equiv)	T (°C)	Space velocity	TOS (h)	Conv. (%)	Selec. for 44 (%)	Selec. for 45 (%)	Selec. for 46 (%)	Ref.
1	Au/Al ₂ O ₃	4	70	WHSV = 0.33 h ⁻¹	1-30	60-80	5-10	30	40-45	240
2	Au/Dowex M-43	1	50	LHSV = 0.092 h ⁻¹	2-22	18-25	^a	37-42	20-25	236
3 ^b	Au/TiO ₂	1	60	WHSV = 33.2 h ⁻¹	^a	32	^a	37	15	235
4	Au-Pd/Amberlite IRA402BLCL	4	60	WHSV = 0.166 h ⁻¹	1-30	50-66	^a	55-60	25-30	238
5	Au-Pt/C	^c	60	LHSV = 0.046 h ⁻¹	1-80	29	^a	68	19	237
6	Bi-Au-Pt/C	^c	60	LHSV = 0.183 h ⁻¹	1-80	25-18	48-40	21-25	^a	237
7 ^b	Pt-Bi/C	^c	120	LHSV = 0.15 h ⁻¹	1-1000	90	88-40	^a	^a	239

^aTraces or unclear. ^bP = 10 bar. ^cBase-free conditions.

Prati *et al.* assessed gold nanoparticles supported on an anionic-exchange resin as catalyst, which was packed in a fixed-bed flow reactor.²³⁶ Moderate selectivities for glyceric (37-42%) and tartronic (20-25%) acids were obtained at low glycerol conversion (18-25%, Table 7, entry

2). In a follow-up paper, the group assessed the reaction under base-free conditions and over Au-Pt bimetallic catalysts supported on carbon.²³⁷ Most notably, a higher selectivity for glyceric acid (68%) at higher GL conversion (29%) was maintained for 80 h TOS (entry 5) . When the catalyst was modified with Bi, the main reaction product was switched to dihydroxyacetone (48-40% selectivity), still at low glycerol conversion (25%, entry 6). Zope and Davis investigated the reaction both in batch and flow reactors over Au/TiO₂.²³⁵ In flow, although moderate glycerol conversion (32%) and selectivity for **45** (37%) and **46** (15%) were obtained, experiments were carried out at a very high space velocity (WHSV = 33.2 h⁻¹, Table 7, entry 3). The difference between the batch and flow processes was clearly evidenced. Indeed, higher selectivities toward products resulting from double oxidation (**46** and **48**) were observed in the flow reactor (Table 8). In the flow process, an enhanced mass transfer between the gaseous/dissolved oxygen and the solid catalyst phase accounted for this observation. Mimura and coworkers investigated Au-Pd nanoparticles stabilized on an anionic-exchange resin as the catalyst.²³⁸ Steady results were maintained for about 70 h TOS. During the first 30 h, 50-66% glycerol conversion, along with 55-60% and 25-30% selectivity for glyceric and tartronic acids, respectively, were maintained (entry 4). In another report, the same group reported a high selectivity for tartronic acid (40-45%) over Au/Al₂O₃, maintained during a continuous run of 30 h (entry 1). Noteworthy, an induction period was observed, since GL conversion increased from 60 to 80% over the run. This induction period was rationalized by a progressive reduction of Au species into metallic Au triggered by glycerol.²⁴⁰

Table 8. Comparison between the batch and flow procedures reported in ref ²³⁵ for the aerobic oxidation of glycerol over Au/TiO₂.

Batch	Flow
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Conditions	60 °C, 10 bar of O ₂ , 170 min, 0.0125 mol% of Au 1 equiv. of NaOH	60 °C, 10 bar of O ₂ , 0.006 mol _{GL} min ⁻¹ g _{cat} ⁻¹ 1 equiv. of NaOH
GL conv. (%)	50	32
Selec. for 45 (%)	60	37
Selec. for 46 (%)	4.7	15
Selec. for 47 (%)	32	25
Selec. for 48 (%)	2.1	20

Dihydroxyacetone. The results obtained in the above-mentioned investigations are incompatible with the perspective of an economically-viable commercial application. An aqueous mixture of glycerol, glyceric acid and tartronic acid contaminated with other oxidation side-products would indeed be very challenging, and thus expensive, to purify. Additionally, most catalysts described rely on gold, further decreasing cost-efficiency.

Higher glycerol conversion and selectivity were reported for the related aerobic glycerol oxidation into dihydroxyacetone under continuous flow conditions. For instance, the liquid-phase preparation of **44** from glycerol over activated charcoal supported Pt-Bi catalysts was reported.²³⁹ At moderate temperature (120 °C) and pressure (10 bar), an aqueous glycerol solution was oxidized into dihydroxyacetone in a fixed-bed flow reactor co-fed with air. A conversion of 90% in glycerol was maintained for prolonged TOS (1000 h) but the selectivity toward **44** decreased from 88% to 40% (Table 7, entry 7). In one of the most advanced example of GL oxidation, the group of Pérez-Ramírez investigated the gas-phase oxidation of glycerol over various iron-containing zeolites in fixed-bed reactor (Figure 29).²⁴¹ Oxygen and N₂O were compared as oxidants, with the best results obtained with the former gaseous reactant. Neat glycerol was utilized as feed, reducing the environmental impact and the process cost. Using the best performing Fe-silicalite catalyst, 70% glycerol conversion and 80-90% dihydroxyacetone selectivity were obtained during a 24 h run. Most notably, the catalytic

system was not based on expensive noble metals, and a kilogram-scale preparation of the material was demonstrated with a method that was safe, cost-efficient and environmentally-friendly.²⁴²

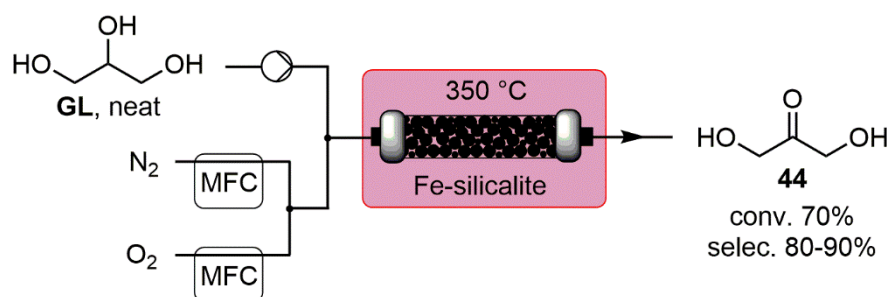


Figure 29. Gas-phase oxidation of glycerol into dihydroxyacetone.²⁴¹

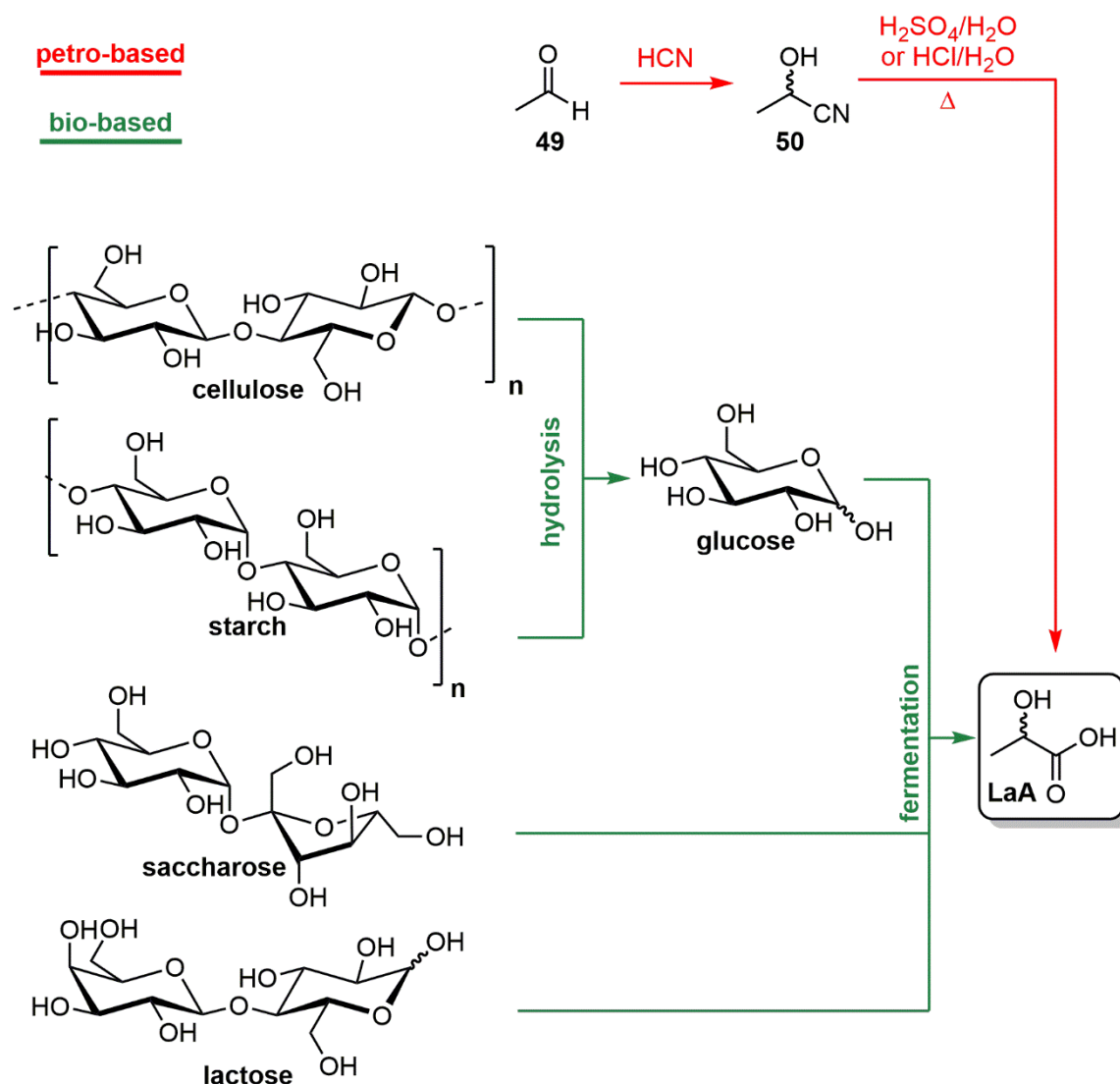
2.3.7. Oxidation-Dehydration into Pyruvaldehyde and Lactic Acid

Pyruvaldehyde. Pérez-Ramírez described the gas-phase oxidation-dehydration (oxidehydration) of glycerol into pyruvaldehyde (**18**) in a continuous flow reactor.²⁴³ Glycerol was co-fed with O₂/N₂ at 350 °C and atmospheric pressure, over an Ag/Al₂O₃ solid catalyst. Glycerol conversion slightly decreased from 82% to 72%, while the selectivity toward pyruvaldehyde remained at a steady 79% value during 24 h TOS. The high activity of the catalyst was related to its optimal redox and Lewis acidic properties. Most notably, pyruvaldehyde was then converted into lactic acid (LaA) and methyl lactate in another separated continuous flow reactor embedded with a Sn-zeolite catalyst. Accordingly, the authors emphasized the superiority of the glycerol-to-pyruvaldehyde methodology for the preparation of lactic acid and methyl lactate, in comparison to the glycerol-to-hydroxyacetone route.

Lactic acid. Lactic acid (LaA) can be produced according to chemical or fermentation processes.²⁴⁴ Chemical processes utilized at the industrial scale for the preparation of LaA rely on petro-based chemicals (Scheme 5), typically starting from the reaction of acetaldehyde (**49**)

1
2
3 and hydrogen cyanide. The intermediate lactonitrile (**50**) is then hydrolyzed in the presence of
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5 sulfuric acid or hydrochloric acid, hence forming racemic (D,L)-LaA. High purity LaA is
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7 obtained through distillation of the methyl or ethyl esters, followed with a final hydrolysis,
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9 which comes with overall high manufacturing costs and environmental footprint. The chemical
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11 process for the preparation of LaA became popular in the 60s but then faded progressively with
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13 the emergence of robust, commercial biotechnology processes. Among the producers of
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15 synthetic lactic acid, Musashino (Japan) is the only major company that still uses acetaldehyde
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17 and hydrogen cyanide as a starting materials for the production of racemic LaA. About 90% of
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19 the worldwide production of lactic acid relies nowadays on fermentation processes (Scheme 5).
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26 Scheme 5. Chemical and fermentation process for the preparation of lactic acid. Starch is
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28 represented here as amylopectin.
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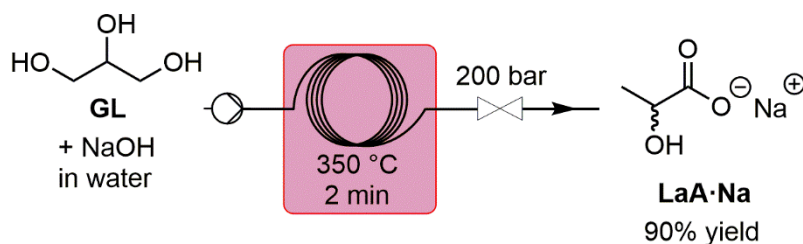
The fermentation processes start with carbohydrates originating from various biomass feedstock including starch crops, sugar crops, lignocellulose or whey as well as nutrients and various microorganisms such as *Lactobacillus*, *Bifidobacterium* and *Rhizopus*.^{245,246} The level of maturity for the production of LaA differs significantly depending on the nature of the starting biomass, and only the fermentation of hexose-rich carbohydrate feeds from sugar crops (*e.g.*, corn syrup or molasses) or starch crops (*e.g.*, rice or potato) have reached full commercial application, while other technologies are still at a Technology Readiness Level (TRL) of 3-7.²⁴⁷ The current fermentation processes co-generate large amounts of low value inorganic salts (typically calcium sulfate) and produces LaA in yields up to 90% in 2-4 days.¹¹⁶ As for the

chemical route, higher purity grades of LaA can be obtained through esterification and distillation.¹¹⁶ Recent developments led to the identification of new strains as well as genetically engineered yeasts that can produce lactic acid under neutral conditions, hence significantly reducing the formation of inorganic byproducts.²⁴⁴ The production of lactic acid from cellulosic biomass bears the most significant economic potential since it does not compete with the food industry, although its level of maturity is the lowest. Besides its low environmental footprint, one of the main strength of the industrial fermentation processes is that it enables the on-demand production of either enantiomers L-(+) or D-(-)-LaA depending on the nature of the strain.^{116,248} The fermentation process however still suffers from high separation and purifications costs.

Another emerging chemical route utilizes glycerol as alternative bio-based starting material.²⁴⁹ Chemical LaA production from GL could potentially be a more cost-effective alternative to the fermentation process. For instance, researchers studied the direct conversion of glycerol into lactate in the presence of strong bases,^{250–253} oxidants,²⁵⁴ or a combination of both,²⁵⁵ using continuous flow reactors. For instance, up to 61% yield in sodium lactate was obtained by Zhang *et al.*, upon heating a strongly basic (NaOH, 3.8 equiv.) aqueous solution of glycerol for 60 min residence time at 300 °C and using an internal pressure of 100 bar.²⁵⁰ In the study, the authors evidenced that reducing the reactor internal diameter improved the reaction performance as a consequence of enhanced heat and mass transfers. However, a detrimental effect of increasing the reactor surface-to-volume ratio was also noticed, as the Fe-containing reactor walls also catalyzed lactate decomposition. In a similar study, an aqueous solution of glycerol containing 4 equiv. of sodium hydroxide was superheated at 350 °C under 200 bar for 2 min of residence time, affording sodium lactate in 90% yield (Figure 30a).²⁵¹ The short residence time accounted for a reduced formation of side-products, despite extreme process conditions. Complementary experiments with NaOD/D₂O suggested a mechanism involving

acetol as intermediate (Scheme 6a). Milder process conditions were accessed by the group of Manfro with the utilization of CuO/MgO or Pt/ZnO heterogeneous catalysts within the reactor.^{252,253} In addition, both catalysts exhibited enhanced stability, as their performance was maintained for 30 h of continuous operation without deactivation. A steady 85-95% lactate yield was obtained during the whole run. The optimized conditions involved operating the reactor at 240 °C and 35 bar, a high WHSV (2 h⁻¹) and a glycerol/NaOH molar ratio of 1 using CuO/MgO as a catalyst. Changing the catalyst to Pt/ZnO led to a 62-74% yield. 1,2-PDO was identified as the main side-product, resulting from the hydrogenation of intermediate pyruvaldehyde (**18**) on the metallic sites of the catalyst. Upon utilization of a substoichiometric amount of NaOH, the glycerol aqueous phase reforming side-reaction became significant over the Pt-based catalyst.

(a)



(b)

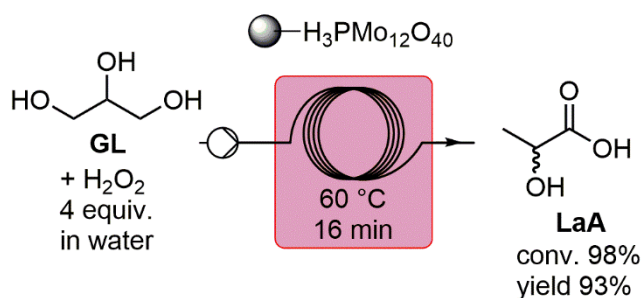


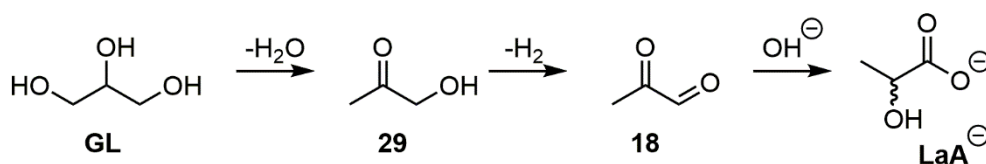
Figure 30. (a) Continuous flow conversion of glycerol into sodium lactate under alkaline superheated conditions²⁵¹ and (b) continuous flow conversion of glycerol into lactic acid under oxidative conditions.²⁵⁴

Wang *et al.* evaluated the reaction using H_2O_2 as reagent in the presence of a polyoxometalate catalyst anchored on the inner walls of a continuous flow reactor.²⁵⁴ The walls of a glass reactor were first functionalized with poly dimethyl diallyl ammonium chloride. Then, $\text{H}_3\text{PMo}_{12}\text{O}_{40}$ was pumped and anchored electrostatically on the polymer, resulting in a functionalized continuous flow reactor. Over-oxidation toward acetic acid, formic acid and CO_2 was observed at high H_2O_2 /glycerol ratio ($>4:1$) or temperature ($> 60\text{ }^\circ\text{C}$). Under optimized conditions, 93% yield in lactic acid (glycerol conv. = 98%) was obtained (Figure 30b). Most notably, the TOF under continuous flow conditions was 20000 h^{-1} , while it was only 200 h^{-1} under analog batch conditions. Up to 10 runs were conducted, and only minor catalyst deactivation was observed (conv. = 93%, yield = 86%). No catalyst oxidation or leaching was detected, and the minor deactivation was thus ascribed to the adsorption of organic matter. Glyceraldehyde (**51**) and dihydroxyacetone (**44**) were the main side-products, and the mechanism depicted in Scheme 6b was proposed.

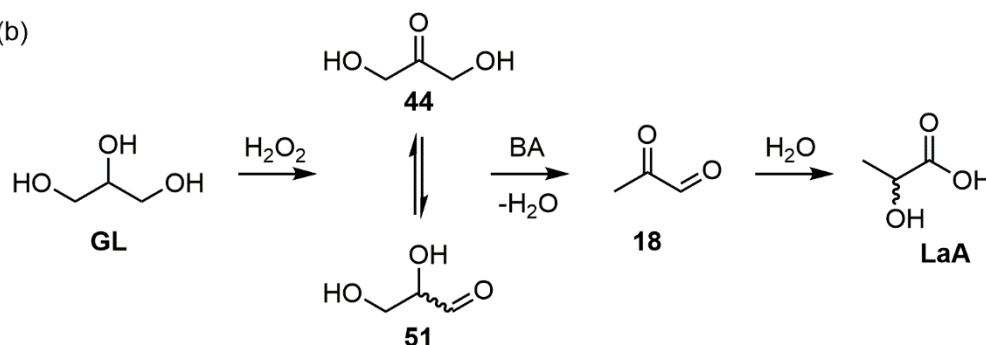
Mimura and colleagues recently reported a process involving both an oxidant and a strong base.²⁵⁵ NaOH was solubilized in an aqueous solution of GL, and the mixture reacted with a gaseous stream of O_2 within a fixed-bed reactor packed with a heterogeneous Au-Pt/ Al_2O_3 catalyst. Operation at $85\text{ }^\circ\text{C}$ and under atmospheric pressure yielded a stable 35-40% yield for lactate during 12.5 h TOS, and then a progressive deactivation of the catalyst occurred. A mechanism with glyceraldehyde as the first intermediate was proposed, since no conversion occurred in the absence of oxygen.

Scheme 6. Mechanisms proposed for the formation of lactic acid from glycerol under (a) alkaline conditions²⁵¹ and (b) oxidative conditions.²⁵⁴ BA = Brønsted acid.

(a)



(b)



2.3.8. Dehydration into Acetol and Acrolein

One of the main challenges in the transition from fossil to biomass resource as pool for the chemical industry, is that completely different catalytic technologies have to be designed. In the 20th century, catalysts were mostly designed to create new functionalities on poorly reactive hydrocarbon and hydrophobic compounds obtained from oil, coal and gas. In the current context, an opposite approach has to be considered, where highly reactive hydrophilic bio-based platform molecules have to be defunctionalized mainly through selective dehydration or deoxygenation processes. The following section is dedicated to the advances in such selective dehydration of glycerol under continuous flow conditions.

Acetol. Hydroxyacetone (29) is a valuable industrial target with various applications (see section 2.2.5). Researchers studied the elimination of a terminal hydroxyl group of glycerol for the preparation of 29, in continuous flow reactors packed with heterogeneous dehydration catalysts. In general, 5-30 wt% aqueous solutions of glycerol were injected in the presence of a carrier gas (Figure 31). Reactions were conducted in the gas-phase over catalysts that were designed to exhibit high water tolerance. In some examples, molecular hydrogen was co-fed

with glycerol. Co-feeding hydrogen promoted the dehydration reaction and inhibited the formation of coke, thus preventing catalyst deactivation.^{256,257} Silver-,²⁵⁶ aluminum-,²⁵⁸ cerium-,^{147,259–262} chromium-,²⁶³ copper-,^{139,257,264–267} lanthanum-,^{268,269} as well as cobalt- and ruthenium-based²⁷⁰ catalysts were reported as efficient heterogeneous catalysts for the reaction. The most relevant catalysts and optimized conditions for hydroxyacetone formation are summarized in Table 9.

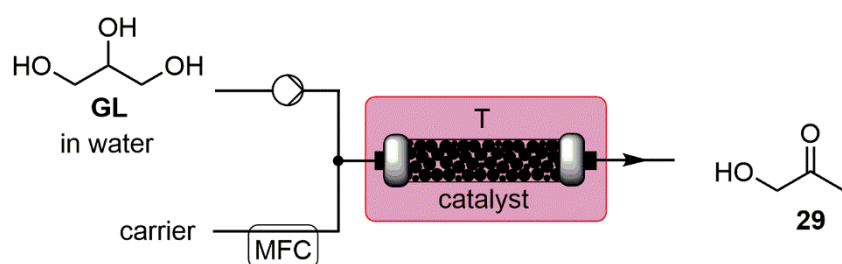


Figure 31. General gas-phase procedure for the dehydration of glycerol into acetol.

Table 9. Catalysts and optimized conditions for the dehydration of glycerol into hydroxyacetone.

Entry	Catalyst	T (°C)	Carrier gas	Space velocity	TOS (h)	Conv. (%)	Selec. (%)	Ref.
1	Ag/SiO ₂	240	H ₂	W/F = 169.5 g h mol ⁻¹	1-5	91	86	256
2	AlCuPO ₄	280	N ₂	W/F = 40 g h mol ⁻¹	3-22	98-85	34-60	258
3	CeO ₂	425	N ₂	- ^a	- ^a	50	26	147
4	Na-CeO ₂	350	- ^b	- ^a	2.5-25	85-25	60-63	259
5	CeO ₂ -MnO ₂ /SiO ₂	250	- ^b	- ^a	4-6	71	56	260
6	CeO ₂ -ZrO ₂	250	N ₂	GHSV = 38 h ⁻¹	2-10	75-95	30-40	261
7	CeO ₂ -ZrO ₂ + Co ₃ O ₄	250	N ₂	WHSV = 3.5 h ⁻¹	- ^a	82	60	262
8	CrO-Al ₂ O ₃ -PO ₄	280	- ^b	GHSV = 90 h ⁻¹	1-30	70-38	58-42	263
9	Cu/Al ₂ O ₃	250	N ₂	W/F = 84.7 g h mol ⁻¹	0.5-4.5	>99	65-90	139
10	CuO _x -Al ₂ O ₃ -PO ₄	280	He	GHSV = 75 h ⁻¹	7.5-32.5	82-96	50-55	264
11	Cu-Si oxides	250	H ₂	W/F = 3.33 g h mol ⁻¹	1-5	90-66	96	257
12	Cu/ZnO	270	H ₂	- ^a	1	76	86	265

13	Cu/ZnO/Al ₂ O ₃	240	H ₂	- ^a	1	>99	80	266
14	Cu-Zn/MgO	260	H ₂	WHSV = 0.122 h ⁻¹	12	93	75	267
15 ^c	La ₂ CuO ₄	260	N ₂	- ^a	0.2-20	98	81	268
16 ^c	La ₂ O ₃	400	N ₂	- ^a	2-10	99	36-30	269

^aUnclear. ^bNo carrier gas. ^cNeat glycerol feed.

Although moderate to high glycerol conversion and hydroxyacetone selectivity were obtained in most of the studies, rapid catalyst deactivation was often observed. As a result, interruption of the process and regeneration or replacement of the catalytic bed would have to be considered in view of an industrial application, decreasing cost-efficiency. Deactivation was related to carbonaceous deposition and blockage of the active sites of the catalyst. Acid sites promoted the formation of coke,^{257,270} while basic oxide such as La₂CuO₄ gave stable catalytic activity for prolonged time-on-stream.²⁶⁸ The best results were arguably obtained by Batiot-Dupeyrat *et al.* over La₂CuO₄ catalyst.²⁶⁸ In their report, neat glycerol was used as feed in the presence of nitrogen as carrier gas, and was dehydrated at moderate reaction temperature (260 °C). Under optimized conditions, stable glycerol conversion (98%) and acetol selectivity (81%) were maintained for 20 h TOS without any deactivation noticed (entry 15). Various species were identified as the catalytic active sites for the formation of acetol, depending on the catalyst studied. Researchers pointed out that the formation of **29** is favored on basic sites for Ce, Co, La and Ru oxide catalysts.^{260,261,269,270} Similarly, Auroux *et al.* showed that reducing the concentration and strength of acid sites promoted the formation of acetol on calcium phosphate systems.²⁷¹ Suprun and Papp pointed out that transition metal oxides supported on Al₂O₃-PO₄ with low acidities were more favorable for acetol formation.²⁶³ On the other hand, Chang *et al.* reported that a balance of acid and basic sites promoted the formation of **29** on Na-doped ceria.²⁵⁹ It was suggested that over copper catalysts supported on acidic oxides, glycerol dehydration proceeds on Cu⁰ sites.^{139,257} By contrast, for copper catalysts supported on basic La

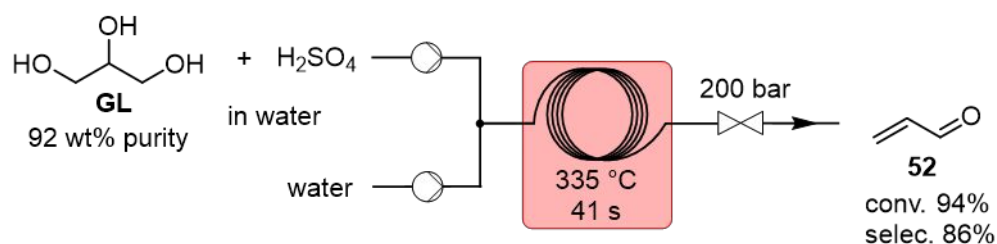
or Mg oxide, Cu⁰ was depicted as a poorly active species to catalyze the desired reaction, which rather occurred on Cu²⁺ and Cu⁺ sites.^{267,268}

Processes in sub- and supercritical water toward acrolein. Acrolein (**52**) is a very important bulk chemical at the global level. It serves as an intermediate for the production of methionine, acrylic acid, pyridines, 1,3-PDO and other raw chemicals, but is also directly used as a biocide.^{142–144} It is produced from the selective gas-phase aerobic oxidation of propene over BiMo-based catalysts at the industrial level.¹⁴⁴ Glycerol dehydration into acrolein is one of the most studied route for the valorization of this by-product of the biodiesel industry.^{272–275} Most studies operate under gas-phase continuous flow conditions, since the corresponding batch (liquid-phase) reaction is often associated with lower glycerol conversion.^{272–275}

The dehydration was studied under continuous flow conditions, in sub- and supercritical water and using homogenous catalysts such as zinc sulfate^{276,277} or sulfuric acid,^{278,279} as well as over a WO₃/TiO₂ heterogeneous catalyst.²⁸⁰ Vogel and coworkers reported that in the subcritical region of water (360 °C, 250 bar) and with 30 s of residence time, an aqueous solution of glycerol containing 470 ppm of ZnSO₄ gave acrolein with 75% selectivity at 50% glycerol conversion.^{276,277} Inomata *et al.* reported that the formation of acrolein reached a maximum in the supercritical region (400 °C, 345 bar) with a residence time of 10 s in the presence of H₂SO₄.²⁷⁸ Under such conditions, 92% glycerol conversion and 81% selectivity for **52** were obtained. The group of Ye studied the dehydration of purified and crude glycerol in the presence of H₂SO₄, and observed that acrolein yields were the highest in the subcritical region.²⁷⁹ Sulfuric acid was used to promote dehydration, but also to decrease the pH of crude glycerol before use, which enabled the removal of most of the fatty acid impurities present in the feedstock solution by straightforward centrifugation and decantation. Almost identical results were obtained both for refined and crude glycerol from the biodiesel industry. Crude glycerol reacted at 335 °C

under 200 bar for a residence time of 41 s, and excellent conversion (94%) and selectivity (86%) were obtained (Figure 32a). Akizuki and Oshima evaluated tungsten oxide supported on titania in a fixed-bed flow reactor, which was operated at 400 °C and 330 bar.²⁸⁰ Glycerol conversion and acrolein selectivity increased with the WO₃ loading, and about 50% acrolein yield was obtained on the best performing catalyst.

(a)



(b)

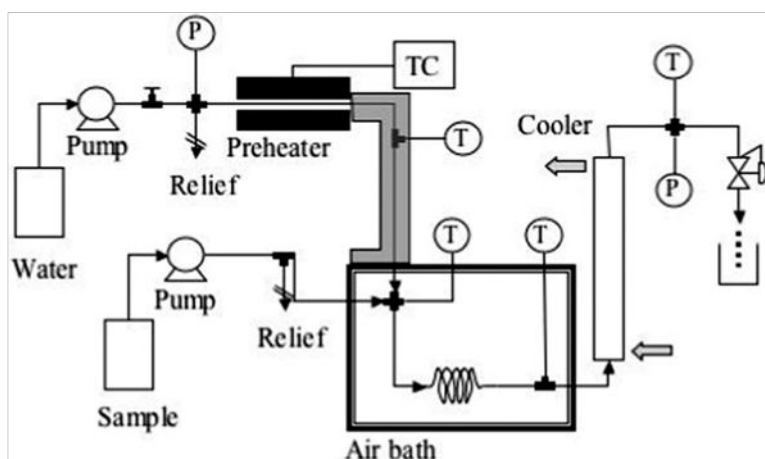


Figure 32. (a) Flow scheme for the continuous flow dehydration of crude glycerol into acrolein catalyzed by sulfuric acid.²⁷⁹ (b) Detailed continuous flow setup for the dehydration of glycerol into acrolein in hot compressed water.²⁷⁸ Reproduced with permission from ref 278. Copyright 2007 Elsevier.

Gas-phase processes toward acrolein – general considerations. The main advantage of the homogeneous process is that the setup can be run continuously for a virtually infinite period of time. However, high costs are associated with catalyst removal downstream the process.

Additionally, sub- and supercritical water processes require special equipment and maintenance, also leading to increased costs. Fluidic components must be robust enough to tolerate extreme temperatures and pressures, as well as corrosive media when sulfuric acid is utilized as the catalyst.^{278,279} Multiple pressure gauges, temperature probes and safety valves are often used to prevent any process failure, otherwise seriously threatening the safety of the operators (Figure 32b).

Out of such operational concerns, most of the studies on the dehydration of glycerol into **52** concerned the development of heterogeneous acidic catalysts. Such materials were evaluated under gas-phase continuous flow conditions. Conditions typically involved the dehydration of 5-40 wt% aqueous solutions of glycerol in the presence of a carrier gas (Figure 33, Tables 10, 11, 12 and 13). The catalysts were developed and optimized to exhibit high water tolerance. It was shown that in addition to decreasing the viscosity of the feed, the presence of large amounts of water was essential to promote the formation of acrolein in high selectivity and inhibit the formation of carbonaceous deposits on the catalyst.²⁸¹⁻²⁹⁰

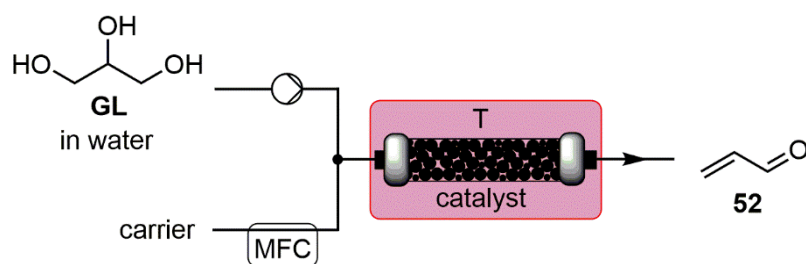


Figure 33. Typical flow setup for the dehydration of glycerol into acrolein.

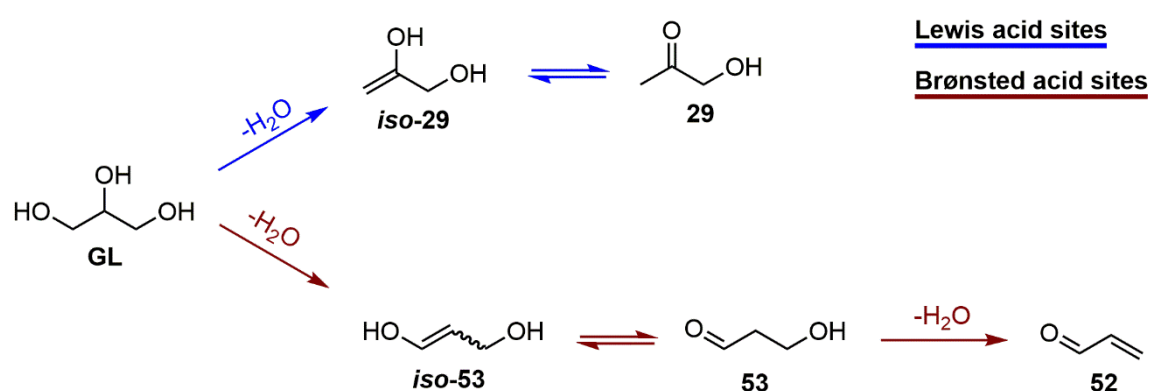
A plethora of catalysts were prepared and evaluated in gas-phase fixed-bed flow reactor, such as zeolites and molecular sieves,²⁸⁶⁻³¹⁴ heteropolyacids,^{284,285,309,315-340} niobium-based,^{282,309,341-352} vanadium-based,^{283,353-359} tungsten-based,^{263,264,309,318,347-349,351,352,360-372} and other transition metal-based^{258,281,309,373-380} as well as non-transition metal-based^{171,381-388} catalysts. It is well

accepted that glycerol dehydration into acrolein occurs on Brønsted acid sites, while Lewis acid sites promote the dehydration into acetol.^{171,282,285,288,291,293,294,302–304,309,312,318,321,323,325,331,332,334,336,337,339–342,346–348,351,352,356,360,367,370–372,375,378,379,382,385,386}

Exceptions were however observed by some authors. The group of Huang described a synergistic effect between Brønsted and Lewis acid sites of Al-modified H-ZSM-5 zeolites for glycerol dehydration into acrolein.³⁰⁵ Bautista and colleagues suggested that over transition metal-modified AlPO₄ catalysts, Brønsted acid sites catalyzed the dehydration of glycerol into hydroxyacetone, while a combination of basic and Lewis acid sites triggered the formation of acrolein.²⁵⁸ Similarly, Liu *et al.* described that among a series of HZSM-5 catalysts modified with nickel hydrogen phosphate, the highest yields were obtained over the catalysts possessing the highest ratio of Lewis over Brønsted acid sites.²⁹⁶ Other deviations were reported independently by Xu and Korneeva, who postulated that Brønsted acid sites were created *in situ* from water molecules interacting with Lewis acid sites on Ta₂O₅ and Mg-Al mixed oxides catalysts.^{380,387} Indeed, catalysts possessing a large amount of Lewis acid sites gave enhanced selectivity toward acrolein. Similarly, the group of Moreno-Tost pretreated zirconium-doped mesoporous silica under an He/water flow prior to reaction, which transformed Lewis acid sites of the catalyst into Brønsted acid ones.³⁷⁸ The efficiency of the methodology was evidenced as the pretreatment improved acrolein selectivity. The accepted mechanisms of acetol (**29**) and **52** formation involve the elimination of a secondary and primary alcohol of glycerol, respectively, followed by keto-enol tautomerization. Acetol is accordingly produced on Lewis acid sites, while 3-hydroxypropanal (**53**) is formed on Brønsted acid sites. **53** is then further dehydrated to give **52** (Scheme 7). In general, catalysts were therefore developed to exhibit high Brønsted acidity and low Lewis acidity. A completely different mechanism was proposed by Mijoin *et al.* over Fe-modified MFI zeolites.³¹³ Despite complete neutralization of the acid sites of their

catalysts after a few hours of operation, activity toward the reaction was somehow maintained. Therefore, the authors suggested a radical mechanism involving $\text{Fe}^{2+}/\text{Fe}^{3+}$ as the active sites. Additional experiments with hydroquinone as a radical scavenger supported the likeliness of such mechanism. The most advanced catalysts and optimized conditions for glycerol dehydration into acrolein, in terms of yield, productivity and stability, are reported in Tables 10, 11, 12 and 13.

Scheme 7. Competitive reaction pathways for the dehydration of glycerol.



Gas-phase processes toward acrolein catalyzed by zeolites/molecular sieves. Excellent activity and stability were obtained with nanosheet MFI zeolites by Fan *et al.*³¹² During 36 h of continuous operation at 320 °C, glycerol conversion decreased from quantitative to 83%, while the selectivity for acrolein maintained a stable 84-88% value (Table 10, entry 3). The presence of short micropores and of a large volume of mesopores within the material accounted for these enhanced results, since the diffusion of molecules within the catalyst was efficient. Iron-modified MFI zeolite stands as one of the most efficient catalyst reported so far in the literature. In a 2018 report from Mijoin *et al.*, the material gave initially quantitative glycerol conversion and 95% selectivity for acrolein at 320 °C and with air as the carrier gas.³¹³ It then underwent some deactivation during the next 8 h of continuous operation, until conversion and selectivity stabilized at 80% and 82%, respectively. These values were maintained until TOS = 24 h.

Following this run, the material was regenerated by air calcination and could be reutilized for another 24 h run that gave results identical to the first one. Most importantly, these results were obtained at very high space velocity ($\text{WHSV} = 8.8 \text{ h}^{-1}$) and with a concentrated glycerol aqueous solution (40 wt%). In a follow-up paper, the same group showed that the method of preparation for the catalyst significantly impacted the results.³¹⁴ With the best material, glycerol conversion merely decreased from 97% to 90% during a 24 h run, with a high acrolein selectivity (87%, entry 4). Ma *et al.* studied MCM-41 mesoporous molecular sieves that were impregnated with phosphoric acid.²⁸⁸ H_3PO_4 enhanced Brønsted acidity of the catalyst, and thus acrolein formation, but at too high concentration, it also altered the pore framework. Under optimized conditions, the conversion of glycerol was maintained at 92-94% and the selectivity toward acrolein at 84-82% for 12 h TOS, and then these values dropped to 76% and 57%, respectively, after 24 h TOS (entry 6). Hierarchical meso- and microporous ZSM-5 was prepared and its catalytic activity was compared to that of commercial microporous ZSM-5.²⁹⁵ The hierarchical framework was highly favorable for the stability of the catalyst, as coke formation was slower and as the catalyst exhibited a higher tolerance to carbonaceous deposits. Under optimized conditions, 82% acrolein selectivity and quantitative glycerol conversion were maintained for up to 50 h TOS (entry 10). By contrast, the micropores of the commercial ZSM-5 were rapidly coked and glycerol conversion decreased from quantitative to 50% during the first 8 h of the run. Liu and coworkers submitted HZSM-5 to an alkaline treatment to decrease the Si/Al ratio and to create mesoporosity.²⁹⁶ Then, the material was modified with a transition metal hydrogen phosphate (CuHPO_4 , $\text{Mo}_{0.33}\text{HPO}_4$, ZnHPO_4 , NiHPO_4 or MnHPO_4) to tune the acidity of the system. The best results (quantitative conversion, 85% selectivity) were obtained over $\text{MnHPO}_4/\text{HZSM-5}$ (entry 11), which possessed the highest ratio of strong acid sites over the total amount of acid sites. The group of Mallinson evaluated various zeolites such as HZSM-5,

HY, Mordenite and HZSM-22 in the presence of molecular hydrogen.²⁹⁸ The best results were obtained over HZSM-22, with quantitative glycerol conversion and 86% acrolein selectivity that were maintained for 20 h TOS without any catalyst deactivation (entry 14).

Table 10. Zeolite/molecular sieve catalysts and optimized conditions for the gas-phase dehydration of glycerol into acrolein.

Entry	Catalyst	T (°C)	Carrier gas	Space velocity	TOS (h)	Conv. (%)	Selec. (%)	Ref.
1	H-ferrierite	300	air	- ^a	2-34	79-60	69-55	310
2	ITQ-2	320	air	- ^a	1-10	99-41	99-61	311
3	MFI	320	- ^b	WHSV = 2.1 h ⁻¹	1-36	>99-83	84-88	312
4	Fe-MFI	320	air	WHSV = 8.8 h ⁻¹	0.5-24	97-90	87	313,314
5	Pd/LaY	275	H ₂	GHSV = 5933 h ⁻¹	0.3-3	91	78	291
6	H ₃ PO ₄ /MCM-41	320	N ₂	- ^a	2-12	94-92	84-82	288
7	H-ZSM-5	275	N ₂	WHSV = 0.75 h ⁻¹	1-5	95-85	80-70	292,293
8	HZSM-5	320	- ^b	GHSV = 719 h ⁻¹	2-24	>99-61	60-67	294
9	HZSM-5	350	He	W/F = 177 g h mol ⁻¹	5-7	>99	81	289
10	ZSM-5	320	- ^b	WHSV = 2.4 h ⁻¹	1-50	>99	82	295
11	MnHPO ₄ /HZSM-5	300	N ₂	- ^a	2-5	>99	85	296
12	H-ZSM-11	320	N ₂	GHSV = 873 h ⁻¹	0.5-8	>99-82	66-78	297
13	H-ZSM-11/SS	300	N ₂	WHSV = 0.75 h ⁻¹	2-8	96-25	60-35	290
14	HZSM-22	400	H ₂	WHSV = 1 h ⁻¹	5-20	>99	86	298

^aUnclear. ^bNo carrier gas.

Gas-phase processes toward acrolein catalyzed by heteropoly acids. Ding *et al.* evaluated phosphotungstic acids, H₃PW₁₂O₄₀ and H₆P₂W₁₈O₆₂, supported on MCM-41 molecular sieves.³³⁶ A high conversion of glycerol (94-84%) but a moderate selectivity for acrolein (61-56%) were obtained during a 5 h continuous run under optimized conditions (Table 11, entry 3). Serious leaching of the heteropoly acid was evidenced. In an attempt to improve the performance of their best catalyst, aminosiloxane-functionalized MCM-41 supports were

utilized instead.³³⁷ The strong interaction between the amino moieties and the heteropoly acid inhibited leaching and better results were obtained (glycerol conversion: 92-89%, acrolein selectivity 83-81%, entry 4). The group of Wang studied Cs-modified phosphotungstate, $\text{Cs}_{2.5}\text{H}_{0.5}\text{PW}_{12}\text{O}_{40}$ (CsPW) supported onto Nb_2O_5 .³³⁸ The best catalyst exhibited high stability, *i.e.* glycerol conversion decreased from 96% to 81%, and acrolein selectivity from 80 to 75%, during a 120 h run (entry 5). Chary and coworkers reported 92-89% acrolein selectivity at quantitative glycerol conversion over phosphotungstic acid, $\text{H}_3\text{PW}_{12}\text{O}_{40}$ (HPW), supported on niobia.³⁴⁰ However, these values were maintained for 10 h TOS, and then rapidly decreased at longer reaction time (entry 7). Wang and colleagues also supported HPW, in this case on Cs-modified SBA-15, and these catalytic systems exhibited excellent performance and stability.³¹⁶ Under optimized conditions, quantitative glycerol conversion and 86% acrolein selectivity were maintained for 150 h TOS (entry 9). The group of Ding and Shao evaluated the reaction in the presence of MCM-41 molecular sieves modified with phosphotungstic acid.²⁸⁵ HPW/Zr-MCM-41 was also modified with transition metals, and the best results were obtained with palladium. Indeed, Pd doping increased the number of Brønsted acid sites, and thus promoted the formation of acrolein. The catalysts also exhibited enhanced stability: after 50 h TOS, glycerol conversion slightly decreased from 97% to 87%, while acrolein selectivity decreased marginally from 85 to 80% (entry 15). The group of Martin prepared and evaluated phosphomolybdic, phosphotungstic and silicotungstic acids supported on silica, alumina and aluminosilicate.³²² Tungsten-based heteropolyacid catalysts gave the best results, and in particular silicotungstic acid, $\text{H}_4\text{SiW}_{12}\text{O}_{40}$ (HSiW) supported on alumina. During a 175 h run, glycerol conversion marginally decreased from quantitative to 75%, and acrolein selectivity from about 80% to 70% (entry 16). Hutchings and coworkers doped silicotungstic acid with cesium, and supported this material onto alumina.³²⁴ The resulting supported catalyst exhibited ground-breaking

performance, *i.e.* quantitative glycerol conversion and 85-90% acrolein selectivity were maintained for 90 h TOS (entry 18). At longer reaction time, marked catalyst deactivation was however noticed. In another report, the same group grafted ceria and zirconia on an alumina support, which was loaded with silicotungstic acid.³²⁹ HSiW supported on the zirconia-alumina support gave excellent results, *i.e.* quantitative glycerol conversion was achieved after a short period of activation, along with a steady 85% acrolein selectivity. These values were maintained for 10 h TOS without deactivation (entry 23). Katryniok *et al.* supported HSiW on ZrO₂-grafted SBA-15, and during a 25 h run, glycerol conversion slightly decreased from 96% to 78% while acrolein selectivity increased from 74% to 88% (entry 24).³³⁰

Table 11. Heteropoly acid catalysts and optimized conditions for the gas-phase dehydration of glycerol into acrolein.

Entry	Catalyst	T (°C)	Carrier gas	Space velocity	TOS (h)	Conv. (%)	Selec. (%)	Ref.
1	Pd/CsPW	275	H ₂	WHSV = 2.8 h ⁻¹	1-6	>99-75	82-96	334
2	Pd-HPW/C	260	N ₂	- ^a	1-8	>99-87	68-75	335
3	HPW/MCM-41	320	N ₂	- ^a	1-5	94-84	61-56	336
4	HPW/NH ₂ -MCM-41	320	N ₂	- ^a	1-5	92-89	83-81	337
5	CsPW/Nb ₂ O ₅	300	O ₂ + N ₂	GHSV = 97.4 h ⁻¹	1-120	96-81	80-75	338
6	CsPW/Nb ₂ O ₅	320	O ₂ + N ₂	WHSV = 0.24 h ⁻¹	9-10	94	77	339
7	HPW/Nb ₂ O ₅	325	N ₂	GHSV = 420 h ⁻¹	1-10	>99	92-89	340
8	HPW/SiO ₂	330	- ^b	GHSV = 80 h ⁻¹	5-36	62	70	315
9	HPW/Cs-SBA-15	300	O ₂ + N ₂	WHSV = 0.72 h ⁻¹	1-150	>99	86	316
10	HPW/W-SBA-15	225	N ₂	- ^a	8-10	>99	74	317
11	HPW/TiO ₂	280	N ₂	GHSV = 277 h ⁻¹	1.5	>99	74	318
12	HPW/ZrO ₂	315	- ^b	GHSV = 400 h ⁻¹	2-10	>99-75	70	319,320
13	HPW/WO ₃ -ZrO ₂	280	N ₂	GHSV = 277 h ⁻¹	1.5	>99	73	318
14	CsPW/Zr-MCM-41	315	- ^b	GHSV = 4 h ⁻¹	2-50	>99-82	73-69	321
15	Pd-HPW/Zr-MCM-41	320	N ₂	WHSV = 0.35 h ⁻¹	1-50	97-87	85-80	285
16	HSiW/Al ₂ O ₃	275	N ₂	W/F = 150 g h mol ⁻¹	25-175	>99-75	80-70	322

17	HSiW/Al ₂ O ₃	300	N ₂	WHSV = 0.6 h ⁻¹	1-7	>99-90	66-75	323
18	Cs-HSiW/Al ₂ O ₃	300	N ₂	GHSV = 6000 h ⁻¹	1-90	>99	85-90	324
19	Li-HSiW/aluminosilicate	300	N ₂	W/F = 150 g h mol ⁻¹	2	>99	73	325
20	HSiW/C	330	He	LHSV = 3.8 h ⁻¹	5	93	75	326
21	HSiW/SiO ₂	275	He	- ^a	1-5	98	86	327
22	HSiW-TiO ₂	280	- ^b	- ^a	1	>99	80	328
23	HSiW/ZrO ₂ -Al ₂ O ₃	300	N ₂	GHSV = 12000 h ⁻¹	1.5-10	90-quant.	85	329
24	HSiW/ZrO ₂ -SBA-15	275	N ₂	GHSV = 220 h ⁻¹	5-25	96-78	74-88	330

^aUnclear. ^bNo carrier gas.

Gas-phase processes toward acrolein catalyzed by transition metal oxides. A decade ago, Deleplanque and colleagues prepared and evaluated various mixed oxide catalysts and excellent results were obtained over a well-crystallized iron phosphate prepared by hydrothermal synthesis.³⁷⁴ Acrolein selectivity marginally decreased from 95% to 89%, and glycerol conversion from quantitative to 95% during a 20 h run. However, glycerol conversion further diminished at longer TOS (Table 12, entry 1). This advanced example probably discloses one of the highest acrolein yield reported so far in the literature. The group of Chary evaluated niobiumoxophosphate catalysts for the reaction, and excellent results were obtained with catalysts possessing high densities of medium strength Brønsted acid sites.²⁸² Under optimized conditions, glycerol conversion slightly decreased from quantitative to 95%, while acrolein selectivity remained at steady 84-86% values during a 9 h run (entry 2). Yi and coworkers studied mesoporous siliconiobium phosphate catalyst for the reaction.³⁴⁵ Quantitative glycerol conversion and 74% acrolein selectivity were maintained for about 60 h TOS, and then deactivation was noticed at longer reaction time. The enhanced stability was a result of the nearly pure Brønsted acidic character, the presence of large mesopores and the weaker acidity of the catalyst (entry 3). Millet and colleagues prepared and evaluated a highly stable ZrNbO catalyst by impregnation of a hydrated zirconia with an acidic aqueous solution of ammonium

oxalate-niobate (followed by calcination).³⁴⁶ During a 150 h run, glycerol conversion marginally decreased from quantitative to 85%, while acrolein selectivity maintained a steady 70-75% value (entry 4). The high catalytic stability was ascribed to neutralization of the non-selective Lewis acid sites that tend to initiate coke formation. Loridant *et al.* prepared tungstated zirconia from various methods, and it was demonstrated that catalysts possessing a high proportion of large mesopores (> 10 nm) versus small mesopores (< 5 nm) were dramatically more stable over time.³⁶³ Over the best catalyst, glycerol conversion slightly decreased from quantitative to 94%, while acrolein selectivity maintained a constant 70% value for 122 h TOS (entry 18). Millet *et al.* demonstrated the positive impact of doping WO_x/ZrO_2 with SiO_2 on the selectivity for acrolein and on the stability of the catalyst.³⁶⁴ 65-78% acrolein selectivity was maintained and glycerol conversion evolved from quantitative to 77% after 145 h TOS. Silica-doping created large mesoporosity and decreased the basicity of the support, which was favorable for acrolein formation and inhibited coke deposition (entry 20). Chary and colleagues investigated tungsten oxide supported on porous zirconium phosphate.³⁶⁷ It was found that the acidity and the density of Brønsted acid sites increased with tungsten oxide loading. Elevated acrolein yields were maintained for extended reaction times in the presence of oxygen in the reaction stream: glycerol conversion slightly decreased from quantitative to 95% and acrolein selectivity decreased from 82% to 78% during a 100 h run (entry 25). The group of Hou prepared and evaluated various zirconium phosphate catalysts for the reaction.³⁷⁶ It was demonstrated that a large specific surface area and the presence of medium strength acid sites were favorable for glycerol dehydration into acrolein. Under optimized conditions, a slight decrease in glycerol conversion (from quantitative to 94%) was observed, but acrolein selectivity maintained a steady 82% value for 24 h TOS (entry 26).

Table 12. Transition metal oxide catalysts and optimized conditions for the gas-phase dehydration of glycerol into acrolein.

Entry	Catalyst	T (°C)	Carrier gas	Space velocity	TOS (h)	Conv. (%)	Selec. (%)	Ref.
1	FePO ₄	280	N ₂	GHSV = 600 h ⁻¹	5-20	>99-95	95-89	374
2	NbP	320	N ₂	WHSV = 2.6 h ⁻¹	2-9	>99-95	84-86	282
3	NbPSi	250	N ₂	GHSV = 12390 mL g ⁻¹ h ⁻¹	2-60	>99	74	345
4	ZrNbO	300	He + Ne	GHSV = 1930 h ⁻¹	20-150	>99-85	70-75	346
5	NiSO ₄ /SiO ₂	340	air	GHSV = 873 h ⁻¹	2-10	>99-92	72	375
6	AlCoPO ₄	280	N ₂	W/F = 40 g h mol ⁻¹	3-22	>99-96	54-31	258
7	AlVPO ₄	280	N ₂	W/F = 40 g h mol ⁻¹	3	98	62	353
8	VPO	300	O ₂ + N ₂	WHSV = 10.2 h ⁻¹	10	>99	66	354,355
9	VPO	320	O ₂ + N ₂	LHSV = 4 h ⁻¹	2	>99	70	283
10	VPO/ZrP	300	air + N ₂	WHSV = 2.6 h ⁻¹	5-30	>99-85	65-50	356
11	WO _x /H ₃ PO ₄ -montmorillonite	320	N ₂	- ^a	3-10	90-65	85-77	372
12	WNbO	295	O ₂ + He	W/F = 81 g h mol ⁻¹	- ^a	>99	84	347
13	H ₃ PO ₄ -WNb	285	O ₂ + N ₂	W/F = 4.17 x 10 ⁻⁵ g h mL ⁻¹	1	>99	82	348
14	WO ₃ -SiO ₂	300	O ₂ + He	W/F = 110 g h mol ⁻¹	0.5-8	>99	80-85	360
15	WO _x /TiO ₂	305	- ^b	WHSV = 2.54 h ⁻¹	4-20	99	74-80	351
16	WO ₃ /TiO ₂	280	O ₂	WHSV = 0.92 h ⁻¹	1-96	>99-48	73	361
17	WTiO	310	O ₂ + N ₂	Contact time = 0.15 s	- ^a	>99	76	362
18	W/ZrO ₂	300	N ₂	GHSV = 2900 h ⁻¹	2-122	>99-94	70	363
19	WO _x /ZrO ₂	305	O ₂ + Ar	WHSV = 0.94 h ⁻¹	4-20	>99	78	352
20	WO _x -SiO ₂ /ZrO ₂	300	He + Ne	GHSV = 1930 h ⁻¹	5-145	>99-77	65-78	364
21	WO ₃ -ZrO ₂	280	N ₂	GHSV = 277 h ⁻¹	1.5	>99	72	318
22	WO ₃ /ZrO ₂	280	O ₂	- ^a	8	98	72	365
23	WO ₃ /ZrO ₂	315	O ₂ + N ₂	GHSV = 400 h ⁻¹	1-30	>99-93	66-68	366
24	Nb ₂ O ₅ -WO ₃ /ZrO ₂	290	N ₂	GHSV = 1117 h ⁻¹	4-24	99-81	69-72	349
25	WO _x /ZrP	300	air + N ₂	WHSV = 2.6 h ⁻¹	5-100	>99-95	82-78	367
26	ZrP	315	N ₂	- ^a	10-24	>99-94	82	376

^aUnclear. ^bNo carrier gas.

Gas-phase processes toward acrolein catalyzed by miscellaneous materials. Liu *et al.* studied rare earth pyrophosphates as catalysts for the dehydration of glycerol.³⁸¹ Among La, Ce, Nd, Sm, Eu, Gd, Tb, Ho, Er, Tm, Yb and Lu pyrophosphates, the best results were obtained with Nd₄(P₂O₇)₃, and its preparation was optimized. Over the best catalyst, the conversion of glycerol decreased from 98 to 96%, while the selectivity toward acrolein increased from 80 to 83% during an 8 h run (Table 13, entry 2). The group of Yi grafted propanesulfonic acid moieties on marigold-like silica possessing open macropores, and demonstrated the long-term performance of the catalyst.³⁸² With this system, quantitative glycerol conversion and 73% acrolein selectivity were maintained for 50 h without any deactivation (entry 3). The hierarchical structure of the catalyst was beneficial for stability, as pore plugging by coke deposition was reduced. Also, quick re-protonation of the Brønsted acid sites of the catalyst after the first dehydration of GL into 3-hydroxypropanal (**53**) was supported with DFT calculation. This swift regeneration behavior enabled the subsequent selective dehydration of **53** into acrolein (**52**), thus enhancing **52** yield and catalyst stability. Indeed, coke was formed from the non-selective conversion of reactive **53**. Similarly, Querini and coworkers grafted propanesulfonic acid on SBA-15 support, and evaluated the system for the reaction.³⁸³ Although high selectivity and (initial) conversion were observed at elevated space velocity, the catalytic system rapidly deactivated because of coke deposition and thermal degradation of the propanesulfonic acid moieties (entry 4). This type of catalyst is thus not compatible with an oxidative thermal treatment for regeneration (see below).

Table 13. Miscellaneous catalysts and optimized conditions for the gas-phase dehydration of glycerol into acrolein.

Entry	Catalyst	T (°C)	Carrier gas	Space velocity	TOS (h)	Conv. (%)	Selec. (%)	Ref.
1 ^a	H ₂ SO ₄ - Montmorillonite	200	H ₂	WHSV = 1.02 h ⁻¹	- ^a	70	84	171

2	Nd ₄ (P ₂ O ₇) ₃	320	- ^b	GHSV = 227 h ⁻¹	2-8	98-96	80-83	381
3 ^c	SiO ₂ -SO ₃ H	250	N ₂	W/F = 250 g h mol ⁻¹	1-50	>99	73	382
4 ^c	SBA-15-SO ₃ H	300	N ₂	WHSV = 3.5 h ⁻¹	0.5-10	85-45	85-75	383

^aUnclear. ^bNo carrier gas.

Gas-phase processes toward acrolein: catalyst deactivation. In most cases, catalyst deactivation by coke deposition was observed, and this remains one of the main technical obstacle in view of an industrial application toward bio-based acrolein from glycerol. Various methodologies were studied to inhibit coke formation or to maintain catalytic activity in the presence of carbonaceous deposits. Among them, O₂ co-feeding within the reactor, acidity and porosity tuning by catalyst modification, and utilization of supercritical CO₂ as reaction medium were applied, with moderate to good success. Such methodologies are detailed below.

The group of Li evidenced that co-feeding a carrier gas, such as nitrogen, within a flow reactor packed with zeolites was beneficial both for acrolein selectivity and catalyst stability.²⁹⁷ This indeed led to a better diffusion of compounds inside and outside the catalyst channels and reduced the formation of coke. Similarly, Millet and coworkers noticed an improved ZrNbO catalyst stability upon increasing the inert gas flow rate.³⁴⁶ It was postulated that the lower contact time between the catalyst and coke precursors inhibited carbonaceous deposition. Several groups clearly evidenced improved conversion, selectivity and catalytic stability when air or oxygen was used as carrier gas, as coke and precursors thereof were partially oxidized and removed from the active sites of the catalyst.^{284,310,311,313,316,333,339,351,352,354–356,359–361,366,367,375} In their contribution, Xu and coworkers compared H₂ and O₂ as reactive carrier gases to improve the stability of a WO₃/ZrO₂ catalyst.³⁶⁶ Although no stability improvement was observed in the presence of hydrogen, oxygen co-feeding clearly inhibited coke formation and catalyst deactivation, at the expense of a small decrease in acrolein selectivity. Deleplanque *et al.* observed a decrease in the formation of coke and acetol over iron phosphate upon co-

feeding oxygen in the reactor.³⁷⁴ However, acrolein yield also decreased because of the formation of oxidation products such as CO_x and acetic acid. Transition metal-containing catalysts with oxidative properties also demonstrated enhanced stability due to continuous coke elimination.^{263,264} Mijoin and coworkers reported that the chemical nature of the carbonaceous deposits strongly depended on the carrier gas utilized (nitrogen or air) over Fe-modified MFI zeolite as the catalyst.³¹³ Similarly, Contreras and colleagues compared the stability of a La-exchanged zeolite Y catalyst that was modified with a reducing element (Pd), using either N₂ or H₂ as carrier gas.²⁹¹ The results clearly evidenced that after 3 h of continuous operation, the catalyst did not deactivate in the presence of H₂, but did deactivate in the presence of N₂. It was proposed that coke and precursors were continuously hydrogenated and removed from the catalyst, preventing deactivation.

Strong acid sites in high concentration tend to promote carbonaceous deposits.^{258,282,304,306,307,309,310,316,321,322,336–339,341–343,345,353,370,372,374,386} Additionally, medium-strength acid sites were reported to be in general more selective for acrolein formation than strong ones.^{282,316,321,330,338–340,342,346,353,356,365,367,381} Therefore, several authors tuned the acidity of catalysts to inhibit coke formation and improve acrolein selectivity. For instance, Wang and coworkers showed that supporting Cs-modified phosphotungstate on Nb₂O₅ converted strong acid sites into medium-strength acid sites, which was favorable for acrolein formation and inhibited coke deposition.³³⁸ The same group also doped SBA-15 support with Cs, and then loaded the material with phosphotungstic acid.³¹⁶ It was demonstrated that Cs doping converted strong acid sites into medium-strength acid sites, which were more selective for acrolein formation and less prone to coke deposition. In another report, a MCM-41 support for H₆P₂W₁₈O₆₂ was functionalized with aminosiloxanes.³³⁷ As a result, the total acidity of the catalyst decreased, so did the tendency of coke to accumulate. Moreover, the total amount of

Lewis acid sites decreased while the total amount of Brønsted acid sites increased. Overall, the catalyst was more stable and more selective for acrolein than the parent unfunctionalized catalyst. Grafting Lewis acidic zirconia on silicotungstic acid supported on SBA-15 or alumina catalysts improved acrolein selectivity and inhibited coke formation.^{329,330} Ding *et al.* studied $\text{Cs}_{2.5}\text{H}_{0.5}\text{PW}_{12}\text{O}_{40}$ (CsPW) supported on Zr-MCM-41.³²¹ Preparation of the catalyst by supercritical impregnation instead of conventional wet impregnation not only reduced the concentration of strong acid sites in favor of medium/weak ones, but also increased the proportion of Brønsted acid sites over Lewis acid sites. Overall, a lower tendency for the formation of coke and a higher selectivity for acrolein were obtained.

Catalysts possessing large pore size are in general less prone to deactivation by coke deposition.^{384,389} For instance, coke formation was slower on hierarchical zeolites, presenting both meso- and microporosity, in comparison to the fully microporous counterpart.^{292,293,295,302,306,307} It was demonstrated that large, open and interconnected mesopores were beneficial for catalyst stability. Indeed, diffusion was enhanced within the network of mesopores, and thus coke promoters were less prone to accumulate within the pores of the catalyst. Additionally, the catalytic activity was more tolerant to carbonaceous deposits, as coke accumulated within the intracrystal mesopores, while micropores were preserved from coking. Thus, the active sites were not completely blocked, by opposition to those located within the micropores of the non-hierarchical zeolites. Similarly, Fan *et al.* reported that nanosheet MFI zeolites were more resistant toward deactivation than conventional HZSM-5 zeolites.³¹² Indeed, shorter micropores and a larger amount of mesopores led to a better diffusivity of molecules within the catalyst, resulting in efficient disposal of coke precursors. Additionally, larger amounts of coke could accumulate within the mesopores before deactivation of the catalyst. Bautista and colleagues compared the efficiency of transition-metal

modified mesoporous AlPO_4 catalysts to that of microporous HY and HZSM-5 zeolites.²⁵⁸ Despite similar levels of coking, phosphate catalysts were dramatically more stable over time. It was emphasized that the pores of microporous zeolites were rapidly blocked by coke, preventing access to the active sites. In the case of mesoporous phosphates, coke accumulated within the pores without plugging them, and thus slowing the deactivation process. Similarly, the group of Yi reported that hierarchical acidic aluminosilicate and aluminosilicophosphate nanospheres were more resistant to deactivation by coke deposition than microporous HZSM-5.³⁰⁴ Indeed, although their small mesopores were blocked by coke deposition, the large mesopores were partially preserved, and maintained the catalytic activity of these hierarchical materials to some extent. By contrast, the micropores of HZSM-5 were completely coked as TOS evolved, which rapidly led to catalyst deactivation. The same group reported a similar behavior for hierarchical meso-/macroporous silica functionalized with propanesulfonic acid moieties.³⁸² Indeed, the large pores were highly resistant toward complete blockage by coke, and the catalyst exhibited high stability for prolonged reaction times. They also prepared a mesoporous siliconiobium phosphate catalyst, and the presence of large mesopores stabilized the catalyst toward deactivation by pore blockage.³⁴⁵ Similarly, Dalil and colleagues reported that among a variety of TiO_2 supports for phosphotungstic acid, the supports displaying the largest pore size were more selective for acrolein formation and subjected to coke deposition to a lesser extent.³³² Suprun *et al.* immobilized phosphotungstic acid within a hierarchical silica matrix, and comparison with the monomodal counterpart evidenced an improved catalytic stability in the case of the hierarchical pore network.³¹⁵ This observation was ascribed to the enhanced mass transfer, which enabled efficient acrolein diffusion out of the pore system, and therefore inhibition of its condensation into carbonaceous deposits. The group of Sato evidenced that silicotungstic acid supported on silica gave better results with large-pore silica

(10 nm) than with small-pore silica (3-6 nm), the latter being deactivated to a greater extent by coke deposition due to poor mass transfer.³²⁷ The group of Loridant reported that among a variety of tungstated zirconia, the catalysts that possessed a high proportion of large mesopores (> 10 nm) in comparison to small mesopores (< 5 nm) were more stable over time, as large pores were able to accumulate more coke before clogging and deactivation.³⁶³ Xu and colleagues evidenced that the presence of micropores in binary metal oxide catalysts was detrimental to acrolein selectivity, because of a reduced diffusion ability.²⁸¹ Lu *et al.* described a procedure in rupture, which consisted in directly growing microporous ZSM-11 zeolite on a stainless steel (SS) microfiber.²⁹⁰ By comparison to the classical ZSM-11, the new catalyst gave enhanced stability and selectivity for acrolein since its microfibrinous structure improved the diffusion/mass transfer of compounds, thereby inhibiting side-reactions and coke formation.

An opposite trend was however described by Li and coworkers, where zeolites performance was enhanced upon decreasing the channel diameter of the catalyst.²⁹⁷ Indeed, when the average channel diameter was reduced from 0.74 nm to 0.54 nm, which is slightly larger than the molecular diameter of glycerol, the resulting steric hindrance of the active sites inhibited polycondensation and coke deposition. As a result, the stability of the catalyst was improved as well as the selectivity for acrolein. It was also evidenced that straight channels were favorable, enhancing diffusion within the catalyst. Similarly, Lin *et al.* partially exchanged the protons of zeolite β with sodium cations, resulting both in a decrease of the channel diameter (< 0.6 nm) and in an increase in the tortuosity of the channels (since the atomic radius of Na is larger than that of H).³⁰³ As a result, the unimolecular dehydration of 3-hydroxypropanal (estimated molecular diameter = 0.35 nm) into acrolein (Scheme 7) was favored over bimolecular side-reactions. These empirical results were complemented with a DFT study, supporting the trends observed.

Ye and colleagues investigated the reaction over commercial HZSM-5, and noticed a dramatic decrease of coking when supercritical CO₂ was used as the reaction medium.³⁰⁸ The yield in acrolein indeed slowly decreased from 60% to 45% during a 500 h run (Figure 34). When carbon dioxide was utilized at atmospheric pressure, rapid deactivation was observed, as the yield of **52** rapidly dropped from 60% to 30% after only 60-70 h TOS. The stabilizing effect of supercritical CO₂ on the activity of the catalyst was ascribed to the higher solubility and diffusivity of acrolein and other coke precursors in this medium. Coke precursors were efficiently removed from the catalytic bed, decreasing the overall amount of carbonaceous deposits and thus improving the lifetime of the catalyst.

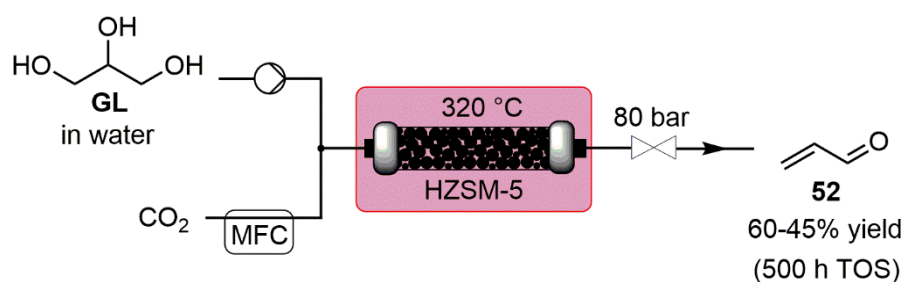


Figure 34. Glycerol dehydration into acrolein in supercritical-CO₂ flow reactor packed with HZSM-5.³⁰⁸

In many cases, it was also possible to fully regenerate the catalytic activity after reaction, by burning coke deposited on the spent catalyst using a thermal treatment under air or oxygen atmosphere.^{285,290,295,297,311–313,316,321,322,330,331,337,338,342,344–346,349,352,359,366,385,388} As pointed out by Katryniok *et al.*, this regeneration technology would represent an efficient method to continuously perform glycerol dehydration into acrolein.³³⁰ It would be particularly suitable if a given catalyst is stable over prolonged TOS after post-reaction oxidative thermal treatment. In this scenario, an ideal system would alternate catalytic beds between reaction under a glycerol feed and regeneration under an oxidizing feed. On the other hand, if a given catalyst

does not require an activation period, and is deactivated over prolonged TOS and/or after post-reaction thermal treatment, the utilization of fluidized-bed flow reactors would rather be advised.³³⁰

To sum up this section, intensive research has been devoted to the optimization of the dehydration of glycerol into acrolein. Efficient catalysts and continuous flow systems have recently emerged, but the main challenge limiting a potential industrially viable implementation is the deactivation of catalysts by coke deposition. However, as the price of crude propene is expected to increase, the glycerol route could become competitive in the future.

2.3.9. Dehydration/Oxidation into Acrylic Acid

Acrylic acid (**20**) is currently produced from propene through oxidation at the industrial level. In terms of volume, it is a very important bulk chemical, mainly used for the production of acrylate polymers.¹⁴³ Acrylic acid can be obtained by the dehydration and oxidation (oxidehydration) of glycerol, which stands as a sustainable alternative to the petro-based process.³⁹⁰ The consecutive two-step process involving the dehydration of glycerol into acrolein (**52**), followed by the aerobic oxidation of **52** into acrylic acid was studied in fixed-bed flow reactors, over single bifunctional catalysts (Figure 35),^{307,314,348,374,391–410} or in telescoped continuous systems comprising two different beds, packed with a dehydration and an oxidation catalyst (Figure 36).^{289,352,395,411,412} For bifunctional catalysts, vanadium or iron were the most common elements used as redox active sites to mediate the oxidation of acrolein into acrylic acid. The oxidehydration reaction was in most cases evaluated by co-feeding an aqueous glycerol solution with (diluted) oxygen. Therefore, catalysts were developed to exhibit stability both under hydrolytic and oxidative conditions. The most representative bifunctional catalysts and optimized conditions are reported in Table 14. Similarly, the most representative

dehydration and oxidation catalysts evaluated in two-bed systems, as well as the corresponding optimized conditions, are reported in Table 15.

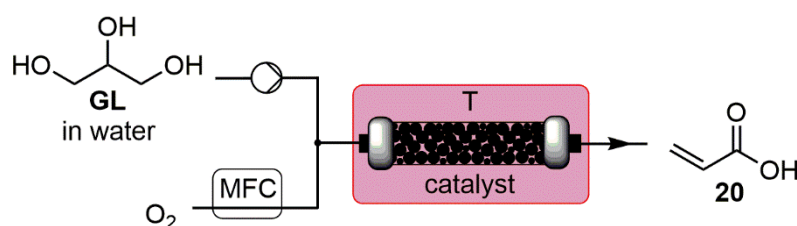


Figure 35. General flow scheme for the one-pot dehydration/oxidation of glycerol into acrylic acid.

Table 14. Bifunctional catalysts and optimized conditions for glycerol oxidehydration into acrylic acid.

Entry	Catalyst	T (°C)	Space velocity	TOS (h)	Conv. (%)	Selec. (%)	Ref.
1 ^{a,b}	Fe-BEA	275	GHSV = 9146 h ⁻¹	8	>99	23	406
2 ^a	Fe-MFI	320	GHSV = 2770 h ⁻¹	0.5-8 h	96-58	24-47	314
3	H ₃ Fe/MCM-22	320	WHSV = 8.6 h ⁻¹	2-10	97-93	26-61	407
4 ^b	V/BEA	275	- ^c	- ^c	75	25	409
5 ^a	V/H-MCM-22	320	WHSV = 8.6 h ⁻¹	3-10	93-76	15-21	410
6 ^a	Cs(VO) _{0.2} (PMo) _{0.25} (PW) _{0.75}	340	WHSV = 0.5 h ⁻¹	2-56	60-38 ^d		392
7	MoV	320	- ^c	4-6	>99	30-32	393
8 ^a	MoV/ZSM-5	320	WHSV = 5 h ⁻¹	1-8	>99	18-13	394
9 ^a	MoVW	250	contact time = 0.16 s	10-110	>99	31	395
10 ^a	WMoV	290	contact time = 0.4 s	1.5-69	>99	51-42	396
11 ^a	WVNb	265	contact time = 0.15 s	15-37	>99	48-51	397
12 ^a	H ₃ PO ₄ -WVNb	285	W/F = 1.67 x 10 ⁻⁴ g h mL ⁻¹	1-5	>99	59	348
13 ^a	MoVTeNb	280	GHSV = 2800 h ⁻¹	5	>99	28	374
14	WV	266	W/F = 145 g h mol ⁻¹	- ^c	>99	33	398
15 ^a	WV	300	- ^c	1	26 ^d		399
16 ^a	WV	318	W/F = 1.42 x 10 ⁻⁴ g h mL ⁻¹	2	>99	26	400

17	VSi	320	- ^c	1	94	85	401
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^aDiluted O₂ was used as carrier gas. ^bNeat glycerol was used in the feed. ^cUnclear. ^dYield.

Mascarenhas and colleagues reported on MCM-22 zeolites modified with Fe as catalysts.⁴⁰⁷ The best yields were obtained over the catalyst possessing the lowest iron content. Indeed, increasing the Fe loading decreased the total amount of acid sites and altered the textural properties since zeolite pores were obstructed by iron oxide species. Good performance was obtained at 320 °C, as a mere decrease in conversion (97-93%) but a sharp increase in selectivity (26-61%) were obtained over a 10 h run (Table 14, entry 3). Cesium salts of heteropoly acids substituted with vanadium were prepared and evaluated by Li and Zhang.³⁹² Cs(VO)_xPMo displayed high oxidation abilities, leading to substrates overoxidation into CO_x species. On the other hand, the acidic character of Cs(VO)_xPW promoted the formation of acrolein. A physical mixture of these catalysts was thus considered, and their synergy was demonstrated, with elevated yields of acrylic acid that decreased from 60% to 38% during a 56 h run (entry 6). The ionic nature of the catalytic material was beneficial for catalyst stability toward deactivation by coke deposition, and the deactivated catalyst could be regenerated under a post-reaction thermal oxidative treatment. In a series of papers, Martins *et al.* studied the catalytic activity of bulk and zeolite-supported molybdenum-vanadium oxides.^{393,394,403} MoV₂O₈ was described as the most active phase for the redox reaction. Acidic ZSM-5 zeolite was latter utilized as support for the MoV oxides to trigger the selective dehydration of glycerol into acrolein prior to oxidation toward acrylic acid, but also to improve the dispersion and the stability of the redox active phase (entries 7,8). Yi and coworkers designed MoVW oxides using both computational and mechanistic investigations.³⁹⁵ It was demonstrated that tungsten incorporation enhanced both acid and redox properties, thus promoting acrylic acid formation. The resulting catalyst exhibited excellent stability, with about 31% acrylic acid selectivity at quantitative glycerol

conversion that were maintained for 110 h TOS without any deactivation (entry 9). Similarly, López Nieto *et al.* prepared and evaluated WMoV oxides with a hexagonal tungsten bronze structure.³⁹⁶ Mo modulated the strong oxidizing properties of V, favoring the formation of acrylic acid, while W promoted Brønsted acidity, and thus acrolein formation. Quantitative glycerol conversion was maintained, and acrylic acid selectivity slightly decreased from 51% to 42% during a 69 h run, demonstrating the excellent stability of the catalyst (entry 10). The same group also investigated WVNb oxides with a similar hexagonal tungsten bronze structure, and excellent results were obtained as well.³⁹⁷ Quantitative glycerol conversion, along with a slightly increasing 48-51% acrylic acid selectivity were obtained when TOS evolved from 15 to 37 h (entry 11). Ueda and colleagues treated WVNb oxides with phosphoric acid.³⁴⁸ It was demonstrated that the acidic treatment promoted both Brønsted acidity, thus favoring acrolein formation, but also modulated the strong oxidizing properties of V, inhibiting over-oxidation into CO_x species. Quantitative glycerol conversion and 59% acrylic acid selectivity were obtained during a 5 h run without any catalyst deactivation (entry 12). The group of Nery assessed vanadosilicates as catalysts for the reaction.⁴⁰¹ Excellent performance was obtained with the best catalyst after 1 h TOS, *i.e.* 85% acrylic acid selectivity at 94% glycerol conversion, but deactivation occurred at longer reaction time (entry 17).

The bifunctional catalysts required both dehydration acidic sites and redox sites, to convert glycerol into acrolein and to promote acrolein oxidation into acrylic acid, respectively. The most common redox centers were vanadium oxide species.^{307,348,374,391–404,409,410} With these V-containing catalysts, some reports evidenced that the mechanism was of Mars-van Krevelen type, and involved V⁵⁺ reduction into V⁴⁺ during the acrolein oxidation process, followed by reoxidation to the initial oxidation state by molecular oxygen present in the reactant feed.^{307,391,393,394,397,398,401,403,410} Consequently, catalyst deactivation was related in some cases

to a decrease of the V^{5+}/V^{4+} ratio, as observed by comparison of the spent catalyst with the fresh one. A deviation was however reported by Soriano *et al.* on WV mixed oxides with hexagonal tungsten bronze structures, where deactivation was associated to the total oxidation of V^{4+} into V^{5+} .⁴⁰⁰ These oxidized centers were highly active but unselective toward acrylic acid, leading to major CO_x formation. A similar Mars-van Krevelen mechanism involving Fe^{3+} and Fe^{2+} species was proposed for iron-based catalysts.^{406–408} In most reports, CO_x species were identified as the main side-products, and resulted from the over-oxidation of species involved in the reaction, especially at high temperature, contact time, and oxygen concentration.^{314,348,374,392–400,402–405,407}

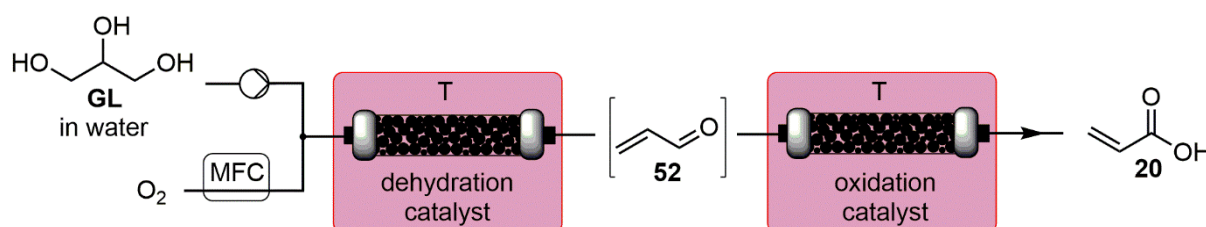


Figure 36. General flow scheme for the sequential dehydration of glycerol into acrolein, and subsequent oxidation of the latter intermediate into acrylic acid.

Table 15. Dehydration and oxidation catalysts, as well as corresponding optimized conditions for sequential glycerol oxidehydration into acrylic acid.

Entry	Dehydration catalyst	Oxidation catalyst	T (°C)	Space velocity	TOS (h)	Conv. (%)	Selec. (%)	Ref.
1 ^a	HSiW/Al ₂ O ₃	MoV	300	- ^b	2	>99	46	411
2 ^a	HZSM-5	VMo/silicic acid	300	1 st bed: W/F = 88 g h mol ⁻¹ 2 nd bed: W/F = 177 g h mol ⁻¹	2-7	40 ^c		289
3 ^a	CsPW/Nb ₂ O ₅	VMo/SiC	300	WHSV = 0.24 h ⁻¹	15-70	75-70 ^c		412
4 ^a	HZSM-5	MoVW	250	1 st bed: W/F = 20.8 g h mol ⁻¹	2	>99	47	395

				2 nd bed: W/F = 125 g h mol ⁻¹				
				1 st bed: W/F = 100 g h mol ⁻¹				
5 ^a	WO _x /ZrO ₂	WVMO	305	2 nd bed: W/F = 125 g h mol ⁻¹	3	>99	44	352

^aDiluted O₂ was used as carrier gas. ^bUnclear. ^cYield.

Wang and colleagues evaluated bifunctional Mo₃VO_x/H₄SiW₁₂O₄ supported on alumina in a single-bed system, and a low acrylic acid selectivity of about 12% was obtained.⁴¹¹ To address this issue, separation of the silicotungstic acid dehydration catalyst from the MoV oxidation catalyst was considered, and the selectivity toward acrolein was dramatically improved up to 46%, at quantitative glycerol conversion (Table 15, entry 1). Similarly, Witsuthammakul and Sooknoi compared a physical mixture of HZSM-5 and V-Mo oxides supported on silicic acid, and a two-bed system loaded with the separate catalysts.²⁸⁹ The latter configuration gave better results, as a 10% higher acrylic acid yield was obtained (entry 2). It was demonstrated that complete glycerol conversion in the first bed was necessary to avoid glycerol oxidation in the second bed and therefore maximize acrylic acid yield. The group of Wang reported a moderate acrylic acid yield (about 25%) using a physical mixture of a dehydration catalyst, CsPW/Nb₂O₅, and an oxidation catalyst, VMo/SiC.⁴¹² To avoid competitive dehydration and oxidation of glycerol, separation of these materials in a two-bed system was considered, resulting in a dramatic yield improvement. The yield of acrylic acid marginally decreased from 75 to 70% during 70 h TOS (entry 3). Moreover, post-reaction oxidative *in situ* thermal treatment enabled coke removal and complete regeneration of the catalytic activity. Although the bifunctional MoVW catalyst developed by Yi and coworkers gave promising results in the single catalytic bed (Table 14, entry 9), a telescoped dehydration/oxidation process was also considered, to avoid direct oxidation of glycerol.³⁹⁵ Using HZSM-5 zeolite as dehydration catalyst in the first bed, acrylic acid selectivity increased from 31 to 47% by comparison to the single-bed process

(entry 4). However, stability over time was not investigated, and it is likely that deactivation of the zeolite material would occur, as discussed previously in section 2.3.8. The group of Andersson observed a dramatic acrylic acid yield improvement from 0.5% to 44%, when their continuous flow setup was changed from a single-bed system containing a physical mixture of catalysts to a two-bed system with segregated catalysts.³⁵² In their report, tungsten oxide supported on zirconia was used as dehydration catalyst, and a commercial WVMo oxide was assessed as oxidation catalyst (entry 5).

To summarize, the two-bed system appears more effective than the single-bed flow process to attain high acrylic acid yields, mainly because competition between glycerol dehydration and oxidation occurs on bifunctional or physically mixed catalysts. However, the operation and maintenance of a two-bed continuous system would be more expensive. The main advantage of the glycerol-to-acrylic acid route in comparison to the dehydration of glycerol into acrolein is that the oxidizing medium partially inhibits coke formation, since coke precursors are continuously oxidized and removed from the surface of the catalyst.^{307,391,394} As a result, a higher catalytic stability is typically obtained. Additionally, acrolein is a harmful chemical, and direct oxidation into acrylic acid alleviates the need for isolation and storage. Further catalyst optimization is however still required to make the bio-based process competitive to the petro-based route.

2.3.10. Dehydration/Ammoxidation into Acrylonitrile

Similarly to the dehydration/oxidation of glycerol into acrylic acid, a few research programs have been devoted to the dehydration/ammoxidation (ammoxidehydration) of glycerol into acrylonitrile (**54**). Like acrolein and acrylic acid, acrylonitrile is currently produced at the industrial level from petro-based propene, which is reacted with oxygen and ammonia.

Acrylonitrile is mainly used in the resin industry to prepare acrylic fibers, acrylonitrile-butadiene-styrene (ABS) polymers, as well as acrylamide and adiponitrile.⁴¹³ The glycerol route stands as an attractive sustainable alternative to the fossil resource based process, but experts pointed out that the process is currently not economically viable.⁴¹⁴ Two studies have described glycerol ammoxidation into acrylonitrile, in a single-bed packed with a bifunctional catalyst⁴¹⁵ and in a two-bed continuous system with separate dehydration and ammoxidation catalysts.⁴¹⁶ In the single-bed process, neat glycerol was co-fed along with a blend of helium/oxygen/ammonia over a mixed VSbNb oxide phase supported on alumina.⁴¹⁵ The reaction was carried out at 400 °C under atmospheric pressure, converting 83% of glycerol with a 58% selectivity toward acrylonitrile. Initially, a SbV oxide catalyst was considered, yet only a slight improvement of the conversion and selectivity were observed upon addition of Nb to the catalytic system. These results were acquired after 30 min TOS, and deactivation was observed when reaction time was increased to 2 h. Paul and coworkers evaluated a two-bed continuous flow setup, comprising of a first WO₃/TiO₂ dehydration catalyst, and a subsequent ammoxidation catalyst, SbFe oxide.⁴¹⁶ Glycerol was co-fed along with oxygen to inhibit coke formation on the first dehydration bed, and ammonia was injected between the first and second bed (Figure 37). Acetic acid was injected after the second bed to quench the polymerization that could be initiated by ammonia. A rather promising overall yield (36%) was obtained, but it decreased to 25% after 26 h TOS, highlighting a mild deactivation of the dehydration catalyst.

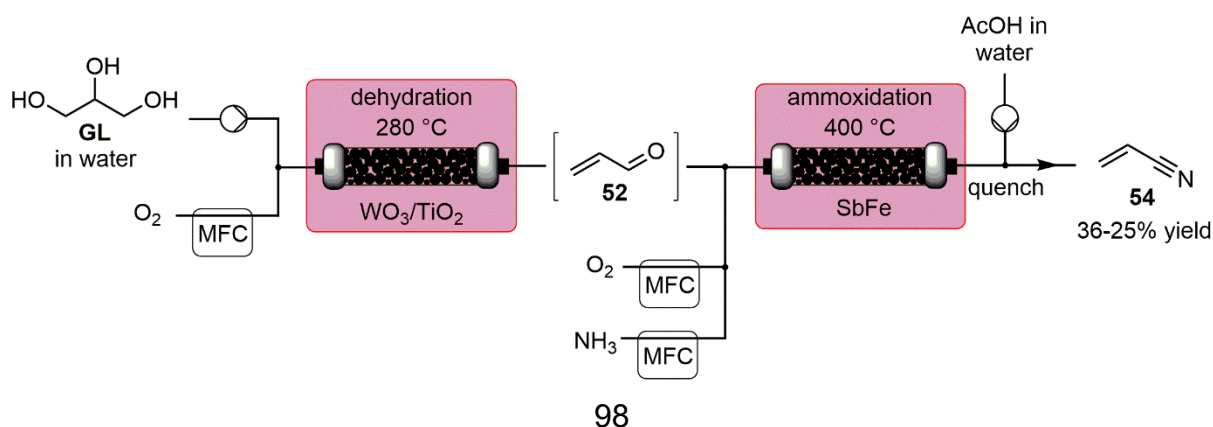


Figure 37. Tandem continuous flow process for the ammoxidation of glycerol into acrylonitrile.⁴¹⁶

2.3.11. Deoxygenation into Allyl Alcohol

Allyl alcohol (**19**) is an important industrial building block (see section 2.2.6). It was obtained from bio-based glycerol using heterogeneous catalysts loaded in fixed-bed reactors. Various catalysts based on bare oxides of transition metal,^{263,417–420} or on zeolite-supported^{421,422} as well as metal oxide-supported^{373,423,424} transition metals were studied. Most processes relied on aqueous glycerol solutions, and were conducted in the gas-phase, using either H₂ as reductant and carrier gas, or N₂ as inert carrier gas (Figure 38). Catalysts reported and the corresponding optimized conditions are summarized in Table 16. Allyl alcohol yields obtained were low (<35%), and would need to be improved for further commercial development.

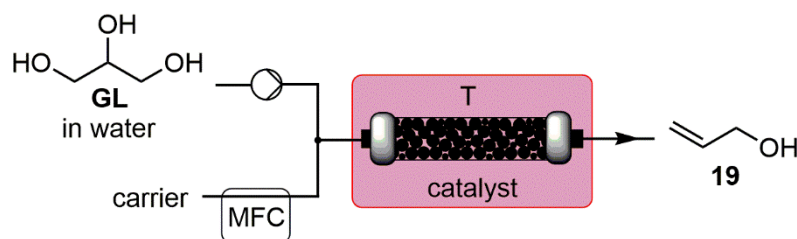


Figure 38. Representative flow scheme for the gas-phase deoxygenation of glycerol into allyl alcohol.

Table 16. Heterogeneous catalysts and optimized conditions for the conversion of glycerol into allyl alcohol.

Entry	Catalyst	Carrier gas	T (°C)	Space velocity	TOS (h)	Conv. (%)	Selec. (%)	Ref.
1 ^a	Ag/ZSM-5	H ₂ + N ₂	400	WHSV = 0.008 h ⁻¹	3-100	85-65	19-10	421
2	CuMo/Al ₂ O ₃	H ₂	250	W/F = 3.78 g h mol ⁻¹	0.5-5	98-60	15	373
3	Fe ₂ O ₃	N ₂	320	GHSV = 96.4 h ⁻¹	1-24	>99-95	23-20	417

4 ^b	Fe/Al ₂ O ₃	N ₂	340	GHSV = 1190 h ⁻¹	0.5-3	12-20 ^c	423
5	Rb-Fe/Al ₂ O ₃	N ₂	340	WHSV = 3.33 h ⁻¹	3	90 13	424
6 ^d	K/ZrO ₂ -FeO _x	N ₂	350	WHSV = 0.2 h ⁻¹	2-12	34-28 ^c	418
7 ^d	K/Al ₂ O ₃ -ZrO ₂ -FeO _x	N ₂	350	WHSV = 0.2 h ⁻¹	2-6	33-29 ^c	419
8	Rb/Fe/ZSM-5	N ₂	340	GHSV = 1240 h ⁻¹	3-6	10-12 ^c	422
6	V ₂ O ₅ -Al ₂ O ₃ -PO ₄	- ^e	280	GHSV = 90 h ⁻¹	1-30	>99 18-16	263

^aP = 40 bar. ^bFormic acid was utilized as sacrificial reductant. ^cYield. ^dCrude glycerol was utilized as starting material. ^eNo carrier gas.

In a pioneering report, the group of Schüth synthesized allyl alcohol under continuous flow conditions starting from aqueous glycerol that was processed at 320 °C under atmospheric pressure in the presence of nitrogen as carrier gas and with a Fe₂O₃ catalyst.⁴¹⁷ Empirical investigation on the reaction mechanism suggested that the dehydration into acrolein occurred first, followed by a hydrogen transfer reaction to yield **19**. During a 24 h run, the conversion of glycerol slightly decreased from quantitative to 95%, and the selectivity toward allyl alcohol evolved from 23% to 20% (Table 16, entry 3). Tago and coworkers evaluated the reaction over various catalysts based on ZrO₂-FeO_x.^{418–420} In their studies, crude glycerol (37 wt% purity) obtained from the biodiesel industry, containing fatty acids, methanol and potassium was diluted with water before being processed. Under optimized conditions, the mixed Zr-Fe catalyst was stabilized with Al₂O₃ and doped with K to reduce acidity, and could maintain a modest yield of allyl alcohol (25-33%) for 6 h time-on-stream at 350 °C under atmospheric pressure in the presence of nitrogen as carrier gas (entry 7). In a similar approach, Stockenhuber and colleagues assessed Fe/Al₂O₃ catalysts for the dehydration of glycerol into allyl alcohol in a fixed-bed reactor.⁴²⁴ Modification of the catalyst with alkali metals (Li, Na, K, Cs or Rb) not only inhibited the formation of acrolein, but it also enhanced the yield of **19** (entry 5). Indeed, alkali metal promotion neutralized the acid sites of the catalyst (responsible for acrolein formation) and increased the amount of basic sites (selective for the formation of allyl alcohol).

The decrease in acidity also resulted in an increase in the stability of the catalysts. Based on the selectivity obtained on such catalysts, the mechanism proposed involved the dehydration of glycerol into prop-2-ene-1,2-diol (*iso-29*), followed by its reduction into allyl alcohol (**19**). Alternatively, the same group developed iron supported on ZSM-5 zeolite as a potential catalyst.⁴²² As previously reported, treating the material with rubidium decreased its acidity and improved both its stability and performance toward the formation of allyl alcohol (entry 8). The zeolitic support was thought to promote dehydration reactions, while Fe²⁺ species catalyzed hydrogen transfer and deoxygenation reactions. In another report, they evaluated the influence of a sacrificial reductant such as ammonia, oxalic acid or formic acid, on the reaction.⁴²³ Their procedure relied on iron supported on alumina as catalyst, and the highest allyl alcohol yield (12-20%) was obtained with formic acid (entry 4). Addition of oxalic or formic acid to the glycerol feed not only increased the yield of allyl alcohol, it also increased the rate of formation of CO₂ and decreased the yield of hydroxyacetone, indicative that the mechanism proceeds through subsequent dehydration and reduction reactions. Pérez-Ramírez and colleagues prepared and evaluated Ag supported on hierarchical ZSM-5 for the upgrading of GL to **19**.⁴²¹ The ratio Brønsted acidity/Lewis acidity and the mesoporosity of ZSM-5 was enhanced by basic and acidic treatment of the support, which enhanced acrolein formation and catalyst stability. Deposition of metallic silver promoted the hydrogen-mediated reduction of acrolein into **19**, and also enhanced catalyst resistance toward coke deposition. Thus, glycerol conversion slightly decreased from 85% to 65%, and allyl alcohol selectivity evolved from 19% to 10% during a 100 h run on the bifunctional Ag/ZSM-5 material at 400 °C and 40 bar H₂ pressure (entry 1).

An alternative homogeneous continuous flow approach was described by Monbaliu, and relied on deoxydehydration reagents rather than heterogeneous catalysts (Figure 39).⁷⁷ Formic acid,

triethyl orthoformate (**55**), or a combination of both, were used as homogeneous deoxygenation reagents. The combination of formic acid and **55** also significantly reduced the viscosity of the glycerol feed solution, hence facilitating processability under continuous flow conditions. Short residence times (1-6 min), moderate pressure (17 bar) and elevated temperatures (250-300 °C) enabled the synthesis of allyl alcohol (**19**) and allyl formate (**56**), in high combined yields (85-97%), with a very high selectivity toward **19**. The use of triethyl orthoformate enabled the processing of glycerol containing various amounts of water, yet affording consistent results. In-line IR spectroscopy was notably implemented for real-time reaction monitoring through the vibration band of CO₂, a by-product of the reaction. The methodology was successfully extended to other bio-based polyols in a follow-up paper.⁴²⁵

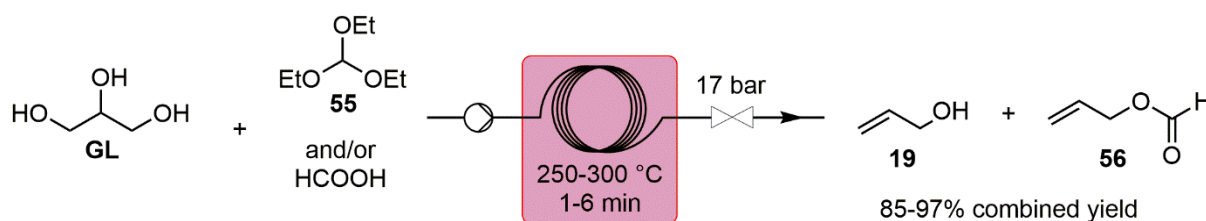


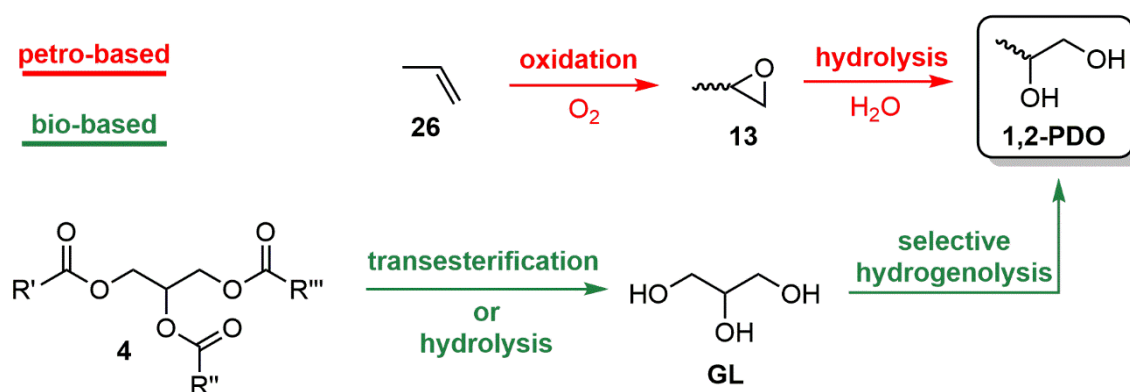
Figure 39. Continuous flow deoxydehydration of glycerol into allyl alcohol.⁷⁷

2.3.12. Hydrogenolysis into Propanediols, Propanols, Ethanol and Methanol

1,2- and 1,3-propanediols. 1,2-PDO can be produced either from petro-based chemicals or from bio-based chemicals.^{116,128,129} A typical petro-based process relies on the oxidation of propylene (**26**) to propylene oxide (**13**, Scheme 8), which is further reacted with an excess of water under moderate temperature and pressure to form 1,2-PDO. The reactor effluent is then distilled several times to recover high purity 1,2-PDO. Bio-based processes are also available such as hydrogenolysis of glycerol (GL), xylitol (XY) or lactic acid (LaA) and hydrocracking of sorbitol.^{116,129} With the increasing availability of glycerol as a side product of the biodiesel

industry, the most mature process technology by far relies on the selective conversion of bio-based glycerol toward 1,2-PDO by hydrogenolysis.^{116,129} A rhenium-based process is exploited by ADM since 2011 in a facility located in Decatur (US) with a capacity of 100,000 tons per year from glycerol.⁴²⁶ In 2015, Frye, Werpy and Zacher won the ACS Award For Affordable Green Chemistry for their contribution to the development of economically viable processes for the upgrading of renewable bio-based materials including glycerol and sorbitol toward 1,2-PDO. A similar process is now exploited by ADM. Oleon (Belgium) and BASF (Germany) jointly invested in a new production facility for producing bio-based 1,2-PDO from glycerol in Belgium in 2012 (20,000 tons per year).⁴²⁷ In 2019, Ayas Renewables (US) has announced the completion of the process engineering and the final selection stage for a site for the large-scale production (90,700 tons per year) to convert low value glycerol into 1,2-PDO under vapor-phase conditions.⁴²⁸ The announcement stated that Ayas Renewables' process enables extremely pure 1,2-PDO (99.0%) with minimal footprint and cost. Global Bio-Chem is a significant producer of 1,2-PDO in China. Developments toward fermentation-based processes are still at a low level of maturity and far from commercial scale.¹²⁸

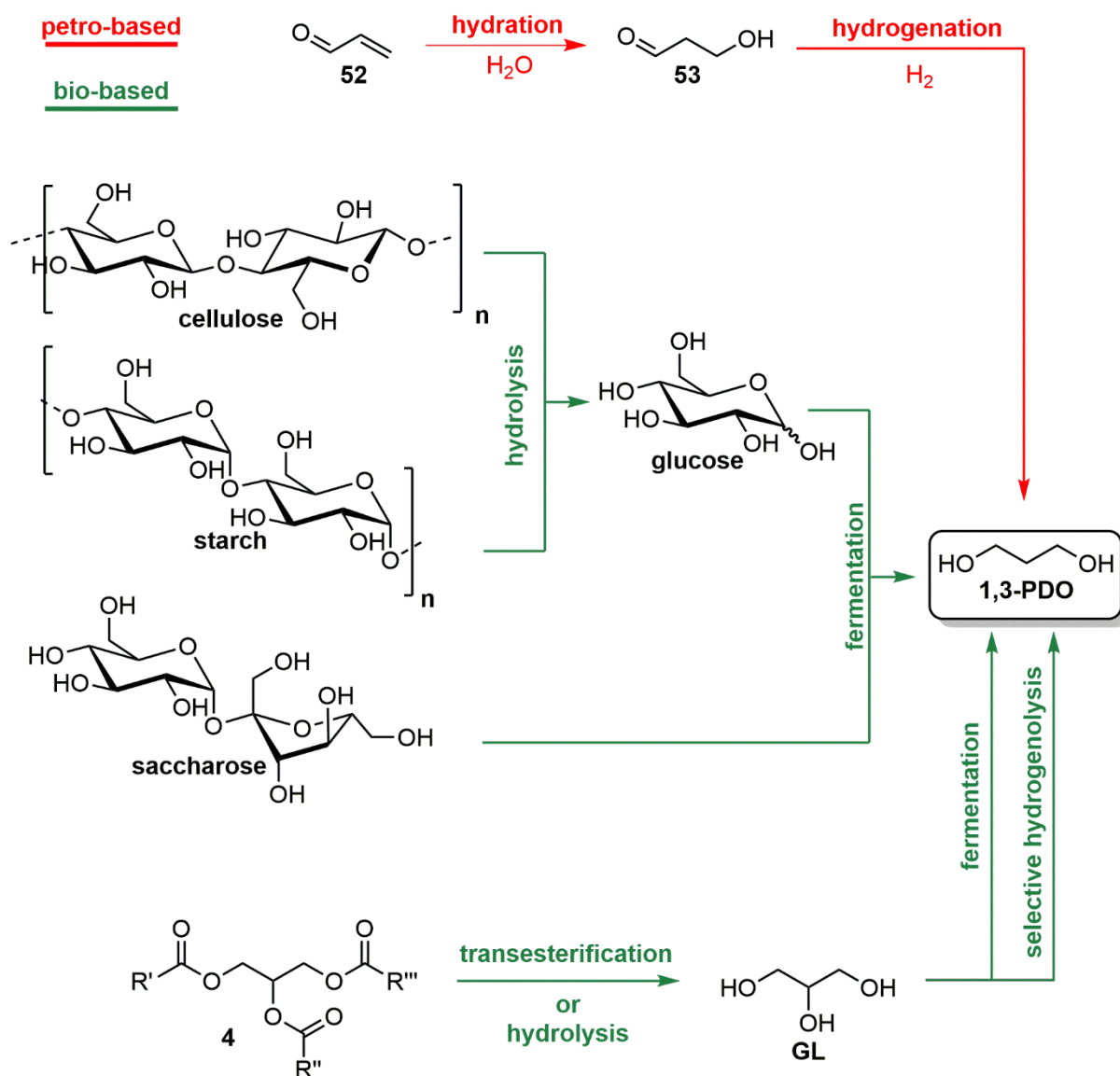
Scheme 8. Simplified representative chemical processes for the preparation of 1,2-propanediol from petro-based or bio-based feedstock.



1,3-PDO can be produced either from petro-based chemicals or from bio-based chemicals.^{128,129,429} A typical petro-based process includes a two-step sequence whereupon acrolein (**52**) is first hydrated to 3-hydroxypropanal (**53**), which is then reduced to 1,3-PDO. After distillation, the overall yield is typically low (45%). Another alternative petro-based process developed by Shell relies on the hydroformylation of ethylene oxide to yield 3-hydroxypropanal, which is then subjected to hydrogenation. Overall low performance and the use of toxic starting materials have encouraged the development of alternative bio-based processes.

A variety of bio-based processes were described for the preparation of 1,3-PDO, either using chemical strategies or fermentation processes (Scheme 9).^{128,129} For instance, bio-based glycerol can undergo a catalyzed hydrogenolysis reaction to give 1,3-PDO. Fermentation processes rely either on sugars from lignocellulosic feedstock or glycerol. The maturity of these processes is however still at rather low to medium TRL.⁴²⁹ The fermentation of glucose with genetically engineered *E. Coli* is the only full commercial application for the preparation of 1,3-PDO.⁴²⁹ DuPont Tate & Lyle Bio Products (US), a joint venture between DuPont and Tate & Lyle, is the leader (63,500 tons per year, with perspectives for further significant expansion) for the preparation of 1,3-PDO from corn-derived glucose.^{129,430,431} Significant developments are still needed to access commercial scale fermentation processes relying on lignocellulosic feedstock. Other players in the field of bio-based 1,3-PDO include Zhangjiagang Glory Biomaterial (China), Zouping Mingxing Chemical (China) and Metabolic Explorer (France).

Scheme 9. Simplified chemical processes and fermentation processes for the preparation of 1,3-propanediol from petro-based or bio-based feedstock.



Since GL is currently the most viable feedstock toward 1,2-PDO, the development of new catalysts and process conditions for this transformation is highly documented in the recent primary literature. The hydrogenolysis of GL toward 1,3-PDO is currently not commercially viable (as detailed above) since it comes with low selectivity. Yet, such process would be of high industrial relevance given the low price of GL - therefore motivating intense research in this field. Recent studies on the hydrogenolysis of GL into 1,2- and 1,3-PDO were both conducted under batch and continuous flow conditions.⁴³² Continuous flow setups consisted of packed-beds loaded with metal-containing solid catalysts and operated in the presence of

molecular hydrogen. Typical conditions relied on 10-50 wt% aqueous glycerol solutions that were co-fed with H₂ within the reactor under moderate to high counterpressure (Figure 40). Solid catalysts were thus specifically developed to exhibit high water tolerance.

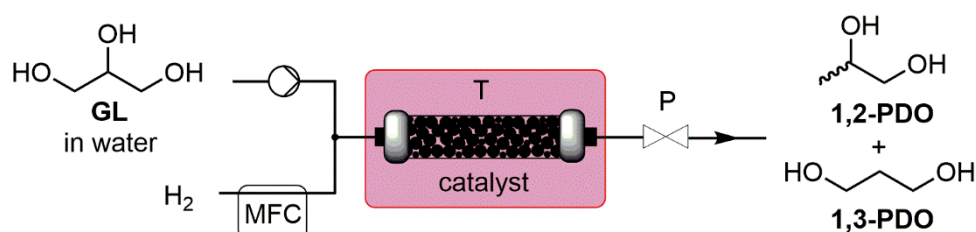
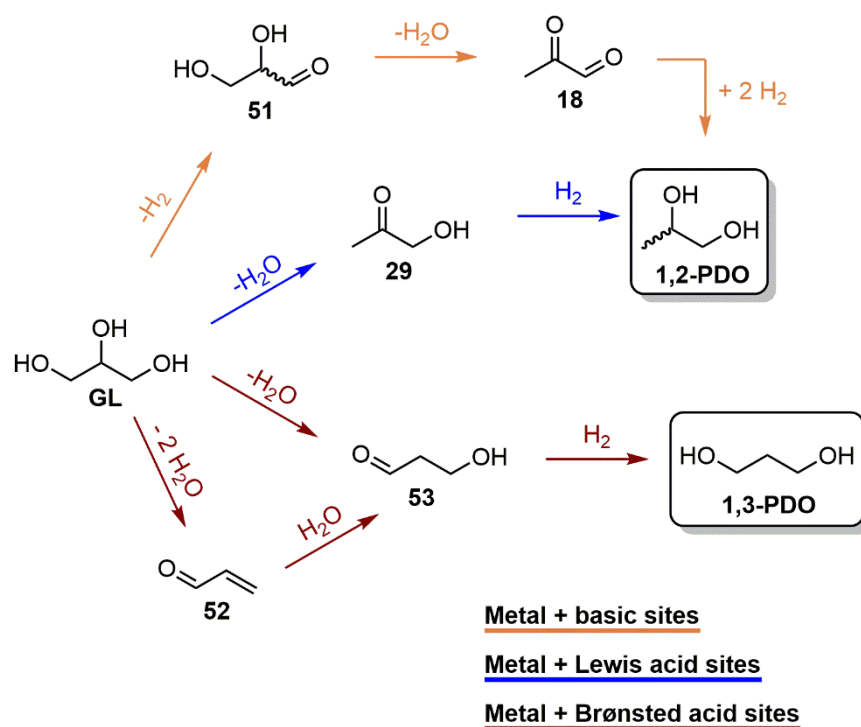


Figure 40. Continuous flow hydrogenolysis of glycerol into 1,2- and 1,3-propanediol.

The competitive reaction pathways leading to either 1,2- or 1,3-PDO that were proposed in the literature are depicted on Scheme 10. Different mechanisms are involved over basic or acidic catalysts. Over acidic sites, glycerol is first dehydrated either into acetol (**29**) or into 3-hydroxypropanal (**53**), depending on the nature of the acid site (Lewis/Brønsted, see section 2.3.8). Then, carbonyl reduction in the presence of molecular hydrogen, catalyzed by the metallic sites of the catalyst, transforms **29** and **53** into either 1,2- or 1,3-PDO, respectively.^{171,265–267,432–444} Some authors also suggested that glycerol undergoes a double dehydration into acrolein (**52**) that is then further rehydrated into 3-hydroxypropanal for the 1,3-PDO formation mechanism.^{171,445} Over basic sites, glycerol is dehydrogenated into glyceraldehyde (**51**) as the first step. Then, dehydration is triggered, and following a keto-enol tautomerism, pyruvaldehyde (**18**) is finally reduced over metallic sites by molecular hydrogen into 1,2-PDO.^{432,441} In general, 1,3-PDO formation is favored at lower temperature compared to 1,2-PDO formation.^{432,445} In most reports, the efficiency of the catalysts developed for the hydrogenolysis of glycerol into propanediols was related to the presence of widely-dispersed and small-sized metallic particles, resulting in a high availability of hydrogenation active sites.^{158,171,265,267,433,434,436,437,439–443,446–449} The presence of acid and/or basic sites of appropriate

strength and concentration was also key to the successful outcome of the reaction, since they provided active sites for dehydration reactions.^{171,265,267,433,434,436,437,439–441,448}

Scheme 10. Competitive pathways of glycerol catalytic hydrogenolysis.



The most relevant catalysts and optimized conditions for continuous flow hydrogenolysis of glycerol into 1,2-PDO are summarized in Table 17. Various supported monometallic^{265,440,441,446,450–453} and bimetallic^{158,267,442,443,454,455} catalysts based on copper were studied, as well as supported Ni,⁴⁴⁴ Ni-Ag,⁴⁴⁷ and Ru^{448,456,457} catalysts. The best results were obtained with copper catalysts (entries 1-13), which is interesting from economical and environmental viewpoints. Indeed, it was observed that copper, a mild metal center toward hydrogenation, favors C-O bonds cleavage over C-C bonds cleavage, resulting in general in high selectivity toward 1,2-PDO. Claus and coworkers have investigated the reaction both in batch (liquid-phase) and continuous flow (gas-phase, entry 3) reactors over copper catalysts.⁴⁵¹ Although process parameters were noticeably different, a slightly higher 1,2-PDO selectivity

was obtained in batch (98%) in comparison to flow (87%) under optimized conditions. However, a quantitative glycerol conversion was attained under flow conditions while batch conditions gave only 52%. The highest yield of 1,2-PDO (up to 98%) under continuous flow conditions was reported by Zhu *et al.* over Cu/SiO₂, and was maintained for a prolonged 300 h TOS.⁴⁴⁶ However, the procedure relied on a 10 wt% solution of glycerol in methanol that was processed at low WHSV (0.075 h⁻¹), and the hydrogen/glycerol molar ratio was set at 123, decreasing cost-efficiency (entry 4). In a follow-up paper, the same group reported excellent results as well with a Cu-Ce-SBA catalyst.¹⁵⁸ Quantitative glycerol conversion and excellent selectivity (97%) were maintained for 300 h of continuous operation. Most notably, the WHSV was increased twofold (0.15 h⁻¹) and a lower temperature (180 °C instead of 200 °C) was utilized. However, methanol was again utilized as the solvent and a high H₂/glycerol molar ratio (100) was utilized (entry 11). Good results as well were reported over a Ni-Cu bimetallic catalyst supported on alumina.^{442,443} 98% glycerol conversion and 89% selectivity for 1,2-propanediol were maintained for 42 h of continuous operation at 220 °C and 7.5 bar of H₂ counterpressure (entry 9). The most economically-viable continuous process was probably reported by Hwang and coworkers, which involved a highly concentrated aqueous glycerol feed (80 wt%), a relatively high WHSV (0.5 h⁻¹) and a small hydrogen/glycerol ratio (8).⁴⁵⁴ As a result, 91-92% selectivity toward 1,2-PDO was observed at quantitative glycerol conversion over a Ni-Cu/SiO₂ nanocomposite, and these values were maintained for 250 h TOS (entry 10). A high catalyst stability was reported as well by Pandey and Biswas, upon utilization of Cu-Zn/MgO.²⁶⁷ At 220 °C, and with only 7.2 bar of counterpressure, the conversion in glycerol merely decreased from 99 to 95% during a 84 h run, and the selectivity for 1,2-PDO was slightly more affected (89-75%, entry 13).

Table 17. Catalysts and optimized conditions for the hydrogenolysis of glycerol into 1,2-propanediol.

Entry	Catalyst	T (°C)	P (bar)	Space velocity	TOS (h)	Conv. (%)	Selec. (%)	Ref.
1	Cu/Al ₂ O ₃	180	- ^a	- ^b	1	>99	88	265
2	Cu/Al ₂ O ₃	250	40	WHSV = 2 h ⁻¹	1-6	>99-98	65-70	450
3	Cu/SiO ₂	255	15	- ^b	- ^b	>99	87	451
4 ^c	Cu/SiO ₂	200	50	WHSV = 0.075 h ⁻¹	10-300	>99	98	446
5	Cu/SBA-15	220	- ^a	WHSV = 1.03 h ⁻¹	1-10	90-80	84-75	452
6	Cu/SBA-15	250	40	LHSV = 0.8 h ⁻¹	6-20	96	92	453
7	Cu/H-mordenite	210	- ^a	WHSV = 1.02 h ⁻¹	3	78	54	440
8	Cu/Y-zeolite	210	2	WHSV = 1.04 h ⁻¹	3-20	92-20	83-40	441
9	Ni-Cu/Al ₂ O ₃	220	7.5	WHSV = 0.97 h ⁻¹	16-42	98	89	442,443
10	Ni-Cu-SiO ₂	220	30	WHSV = 0.5 h ⁻¹	30-250	>99	91-92	454
11 ^c	Cu-Ce-SBA	180	50	WHSV = 0.15 h ⁻¹	5-300	>99	97	158
12	Cu-ZnO/Al ₂ O ₃	220	40	LHSV = 4.6 h ⁻¹	- ^b	82	93	455
13	Cu-Zn/MgO	220	7.2	WHSV = 0.073 h ⁻¹	12-84	99-95	89-75	267
14	Ni/MgCr ₂ O ₄	250	20	- ^b	2	98	70	444
15	Ni-Ag/Al ₂ O ₃	200	- ^a	WHSV = 2.01 h ⁻¹	1-7	79-72	58	447
16	Ru/TiO ₂ -ZrO ₂	230	- ^a	WHSV = 2.09 h ⁻¹	1-7	52	35	448
17	Ru/MCM-41	230	- ^a	WHSV = 2.09 h ⁻¹	1-10	62	38	456

^aAtmospheric pressure. ^bUnclear. ^cMethanol was used as solvent in the glycerol feed.

An alternative approach was considered, where hydrogen was generated *in situ* from the glycerol aqueous phase reforming (APR) reaction, to be consumed in the hydrogenolysis reaction.^{435,450,458–460} The main advantage associated with this methodology was that it alleviated the use of molecular hydrogen. One equivalent of glycerol generates seven equivalents of H₂ in the APR reaction, but only 1 equivalent of H₂ is needed to reduce acetol (**29**) into 1,2-PDO (Scheme 10). Therefore, the optimal theoretical selectivity ratio for glycerol

dehydration into **29** over glycerol reforming is 7. A physical mixture of ZnO and NiMo was evaluated as catalyst for the reaction.⁴⁵⁸ When a mass ratio ZnO/NiMo of 2 was utilized, a hydrogenolysis/reforming selectivity ratio of 6.3 was attained, thus close to the optimal value. Increasing the surface area ratio between the nonpolar and the polar planes of the ZnO crystals led to a steady increase in turnover frequency (TOF) for 1,2-PDO production.⁴³⁵ Actually, CO₂ generated by the APR reaction was chemisorbed on the nonpolar planes, and increased the Lewis acidity of the co-catalyst. The increased acidity promoted glycerol dehydration into acetol, and thus accounted for an improved 1,2-PDO productivity. At 235 °C and under 31 bar of argon, aqueous glycerol was converted at 98% into 1,2-PDO with 51% selectivity over the best performing ZnO/NiMo packed catalyst. Bimetallic Cu-Ni supported on Al₂O₃ or ZSM-5 were also assessed as catalysts for the reaction.⁴⁵⁰ They both gave similar yields of about 25% in 1,2-PDO, when an aqueous solution of glycerol was co-fed along with nitrogen gas, and reacted over the catalytic bed at 250 °C under 40 bar of counterpressure. The beneficial synergistic effect of the bimetallic alloy was evidenced, as a physical mixture of the monometallic Ni- and Cu-based catalysts gave poor results. In an early report, Mane and Rode assessed Cu-Al oxide as heterogeneous catalyst, and quite surprisingly, a major increase in selectivity toward 1,2-propanediol was noticed upon utilization of crude glycerol instead of refined glycerol.⁴⁵⁹ In the latter case, the selectivity toward 1,2-PDO attained 20-23% at 95-85% glycerol conversion during a 400 h run. Acetol was the main side-product in the reactor effluent (55%). When crude glycerol from the biodiesel industry was processed under identical conditions, the selectivity toward 1,2-PDO increased to 81-75%, despite a lower glycerol conversion (66-71%); these values were maintained for up to 50 h TOS without catalyst deactivation (Figure 41). It was suggested that the presence of alkali in traces promoted the reduction of acetol into 1,2-PDO.

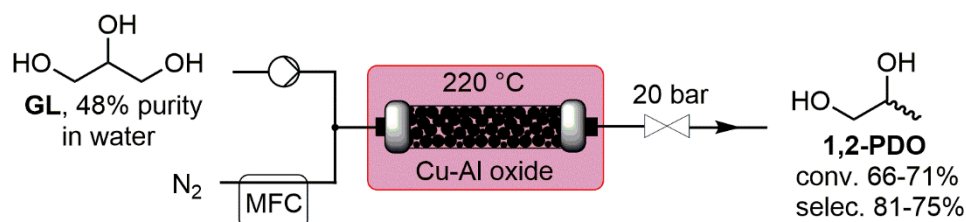


Figure 41. Glycerol hydrogenolysis into 1,2-PDO without external H_2 supply to the flow reactor.⁴⁵⁹

Similarly, glycerol hydrogenolysis into 1,3-PDO was studied in continuous flow reactors over supported monometallic^{171,433,434,436,437} and bimetallic^{438–440,445,449,461,462} platinum-based catalysts, as well as supported Cu-,²⁶⁶ Ir-Re,^{159,463} and Ru^{448,456,457} catalysts. The most relevant catalysts and optimized conditions for glycerol hydrogenolysis into 1,3-PDO are summarized in Table 18. Similar reaction setups were utilized as for glycerol hydrogenolysis into 1,2-propanediol (Figure 40), but in general, the selectivity was dramatically lower.

The highest initial yield of 1,3-PDO was obtained with Pt supported on sulfuric acid-treated Montmorillonite, although significant deactivation was observed.¹⁷¹ Indeed, the conversion of glycerol decreased from 94 to 80%, and the selectivity toward 1,3-PDO decreased from 62 to 50% during an 8 h run conducted at 200 °C (Table 18, entry 4). Another Pt catalyst supported on acidic zeolite, Pt/H-mordenite, gave excellent results as well.⁴³⁶ After 3 h TOS, the conversion of glycerol was 95% with 49% selectivity for 1,3-propanediol (entry 5). However, as the operation time further progressed, the catalyst deactivated. In a follow-up paper, the same group assessed a bimetallic Pt-Cu version of their catalyst, and the selectivity for 1,3-propanediol was slightly improved (entry 6).⁴⁴⁰ Similarly, the best performance was obtained after 3 h of continuous operation, and then deactivation occurred. Platinum-tungsten materials are the most common catalysts studied for the reaction (entries 7-13). It is well established that WO_x provides Brønsted acid sites for the dehydration of glycerol into 3-hydroxypropanal (**53**)

(see Scheme 10), while Pt is efficient for the reduction of the aldehyde toward 1,3-PDO. For instance, Pt-W was supported either on ZrO_2 (entry 8) or Al_2O_3 (entry 10).^{438,461} Relatively low temperatures were utilized (130 °C and 160 °C, respectively), resulting in high 1,3-PDO selectivity (46% and 66%, respectively) but relatively low glycerol conversion (70% and 64%, respectively). Similarly, very good results were obtained over a Pt/WO_x catalyst supported on ZrO_2 and modified with $\text{Li}_2\text{B}_4\text{O}_7$.⁴³⁷ At 150 °C and 40 bar of H_2 counterpressure, almost quantitative glycerol conversion and an elevated 48-50% selectivity for 1,3-PDO were maintained for 200 h of continuous operation (entry 9). Modification of the catalyst with $\text{Li}_2\text{B}_4\text{O}_7$ improved its hydrothermal stability, increased the amount of weak acid sites, and led to a higher dispersion of Pt particles. Additionally, introduction of lithium tetraborate somewhat inhibited sintering. Edake *et al.* studied the reaction over $\text{Pt}/\text{WO}_3/\text{Al}_2\text{O}_3$ in a fluidized-bed continuous flow reactor.⁴⁴⁵ Although the fluidized bed minimized concentration and temperature gradients within the flow reactor, a low 1,3-propanediol selectivity (14%) at quantitative glycerol conversion was obtained under optimized conditions (entry 12). Chary *et al.* studied the activity of $\text{Pt}-\text{WO}_3$ supported on SBA-15.⁴³⁹ Good conversion (86-84%) and selectivity (42-36%) were maintained for up to 7 h TOS at 210 °C under atmospheric pressure (entry 13).

From these results, it is noteworthy that expensive catalysts based on Pt, Ir-Re, or Ru are preferred for deoxygenation at the secondary alcohol of glycerol, while cost-efficient Cu-based catalysts gave excellent results for the conversion of GL into 1,2-PDO.

Table 18. Catalysts and optimized conditions for the hydrogenolysis of glycerol into 1,3-propanediol.

Entry	Catalyst	T (°C)	P (bar)	Space velocity	TOS (h)	Conv. (%)	Selec. (%)	Ref.
1	$\text{Cu}/\text{ZnO}/\text{TiO}_2$	280	- ^a	- ^b	1	>99	10	266

2	Ir-ReO _x /SiO ₂	130	80	WHSV = 0.5 h ⁻¹	36-500	61-32	31-41	159
3	Pt/AlPO ₄	260	- ^a	WHSV = 1.02, 2.09 h ⁻¹	2-5	>99	35-27	433,434
4	Pt/H ₂ SO ₄ -Montmorillonite	200	- ^a	WHSV = 1.02 h ⁻¹	1-8	94-80	62-50	171
5	Pt/H-mordenite	225	- ^a	WHSV = 1.02 h ⁻¹	3	95	49	436
6	Pt-Cu/H-mordenite	210	- ^a	WHSV = 1.02 h ⁻¹	3	90	51	440
7	Pt/WO _x	140	10	LHSV = 1 h ⁻¹	10-70	60-45	22-27	449
8	Pt/WO ₃ /ZrO ₂	130	40	- ^b	24	70	46	461
9	Pt-Li ₂ B ₄ O ₇ /WO _x /ZrO ₂	150	40	WHSV = 0.2 h ⁻¹	10-200	95-90	48-50	437
10	Pt-WO _x /Al ₂ O ₃	160	50	WHSV = 0.09 h ⁻¹	- ^b	64	66	438
11	Pt/WO _x /Al ₂ O ₃	180	50	WHSV = 1.13 h ⁻¹	12	80	35	462
12 ^c	Pt/WO ₃ /Al ₂ O ₃	260	- ^a	WHSV = 0.14 h ⁻¹	2	>99	14	445
13	Pt-WO ₃ /SBA-15	210	- ^a	WHSV = 1.02 h ⁻¹	3-7	86-84	42-36	439
14	Ru/TiO ₂ -ZrO ₂	230	- ^a	WHSV = 2.09 h ⁻¹	1-7	52	15	448
15	Ru/MCM-41	230	- ^a	WHSV = 2.09 h ⁻¹	1-10	62	20	456

^aAtmospheric pressure. ^bUnclear. ^cFluidized-bed flow reactor.

Catalyst deactivation as a function of TOS evolution, resulting in decreasing conversion and selectivity, was noticed for glycerol hydrogenolysis into both 1,2- and 1,3-propanediol (Tables 17 and 18). This deactivation resulted in most cases from the aggregation and growth of metal particles (*i.e.* sintering) within the catalysts; hence not only inhibiting their catalytic activity, but also preventing regeneration of the catalysts by a simple calcination procedure.^{159,267,436,437,439–441,446,453,454} Deposition of coke was also a parallel deactivation mechanism in most instances, covering and blocking the active sites of the catalysts.^{171,436,439–441,446,448,452,454,456} However, by comparison to those utilized for the dehydration reaction of glycerol into acrolein/acetol (see section 2.3.8), the catalysts utilized for the hydrogenolysis of glycerol into propanediols were generally more stable over time.

By comparison to the hydrogenolysis of glycerol into 1,3-PDO, higher yields were obtained for 1,2-PDO, over cheaper and more stable catalysts (see Tables 17 and 18). In view of the development of economically-viable commercial applications for the catalytic hydrogenolysis

of glycerol toward 1,3-propanediol, catalysts and process conditions have to be improved in the future.

Propanols. It is noteworthy that 1-propanol (1-PrOH) was also observed as a major product in some reports aiming at the continuous synthesis of 1,2- and 1,3-propanediol from glycerol. 1-Propanol is currently petro-based and comes with a broad range of applications (see section 2.2.7). For instance, after 36 h of continuous operation, Ding *et al.* reported 45% selectivity for 1-PrOH in their procedure relying on Ir-ReO_x/SiO₂ as the catalyst (Table 18, entry 2).¹⁵⁹ Wang *et al.* identified 1-propanol as the main product (55-60% selectivity) during the 70 h run performed over their Pt/WO_x catalyst (entry 7).⁴⁴⁹ Similarly, using their Pt/WO₃/ZrO₂ catalyst with the highest platinum loading, Chen and coworkers reported the formation of 1-PrOH in 56% yield (entry 8).⁴⁶¹ Edake *et al.* reported a 38% yield in 1-PrOH when the process temperature was raised to 300 °C using their Pt/WO_x/Al₂O₃ catalyst (entry 9).⁴⁴⁵ Chary and colleagues evaluated fixed-bed reactors embedded with zirconia-supported platinum/heteropoly acid bifunctional catalysts,⁴⁶⁴ as well as metal phosphate-supported platinum catalysts,⁴⁶⁵ for the direct hydrogenolysis of glycerol into 1- and 2-propanol. In the most advanced example, quantitative glycerol conversion, with 87% and 10% selectivity for 1- and 2-PrOH, respectively, were obtained over the Pt/TiPO₄ catalyst at 220 °C and under 1 bar of pressure in H₂.⁴⁶⁵ These results were maintained for 15 h TOS, and then worsened. Another approach was evaluated by Lin *et al.* to prepare 1-PrOH from glycerol, where a two stage continuous flow reactor was utilized.⁴⁶⁶ The first stage featured an H-β zeolite catalyst for the dehydration of glycerol into acrolein, and the second stage consisted of a fixed-bed of Ni/Al₂O₃ for the reduction of acrolein into 1-PrOH. Both beds were operated at 220 °C under a 20 bar internal pressure of H₂. Aqueous glycerol was quantitatively converted, with a 69% selectivity

toward 1-propanol. However, conversion and selectivity dropped by 30% and 20%, respectively, after 100 min TOS, as coke formed on the dehydration catalyst.

Ethanol. Recent research interests were devoted to the catalytic hydrogenolysis of glycerol into ethanol (EtOH). Hou and coworkers studied the reaction with external H₂ co-feeding,^{444,467} while Kostyniuk reported a H₂-free procedure.⁴⁶⁸ In the former case for instance, glycerol underwent hydrogenolysis toward ethanol over a Co/ZnO catalyst loaded in a fixed-bed reactor.⁴⁶⁷ Up to 99% glycerol conversion and 58% EtOH selectivity were obtained at 210 °C and under 20 bar of H₂ pressure. Experiments at various glycerol space velocities; and control experiments utilizing reaction intermediates as substrates, suggested that the reaction proceeds through two main parallel mechanisms. The first one involves the dehydration of glycerol into hydroxyacetone, its reduction into 1,2-propanediol, and then further C-O and C-C hydrogenolysis toward ethanol, propanols and methanol. The second pathway involves direct cracking of glycerol into ethylene glycol, and then further hydrogenolysis toward ethanol. The same group studied Ni supported on MgCr₂O₄ as catalyst for the reaction.⁴⁴⁴ The catalyst had a good stability and activity, as glycerol conversion merely decreased from quantitative to 92% after 17 h TOS. The selectivity (63%) for EtOH was similar to that obtained with Co/ZnO, but a slightly higher reaction temperature was required (250 °C) under 20 bar of H₂ pressure. In Kostyniuk's study, the catalyst consisted in a cesium-modified version of HZSM-5.⁴⁶⁸ Using a zeolitic support with a low SiO₂/Al₂O₃ ratio (30), hydroxyacetone was the main product and strong deactivation occurred. With a zeolitic support with a high SiO₂/Al₂O₃ ratio (1500), very high selectivity for EtOH (>99-92%) and milder deactivation were obtained: conversion decreased from quantitative to 40% during 52 h of operation (Figure 42). The absence of acid sites and the presence of basic sites accounted for this result. The mechanism proposed involved glycerol dehydration into acetol, Norrish type-I radical fragmentation into acetyl and

hydroxymethyl radicals. The acetyl and hydroxymethyl radicals were further reduced into EtOH and MeOH, respectively. Then, MeOH either (1) decomposed into methyl carbene or (2) reacted with methyl carbene to produce EtOH, accounting for the near quantitative selectivity of the reaction. It was suggested that water and/or glycerol acted as the H-sources required for the reaction to occur.

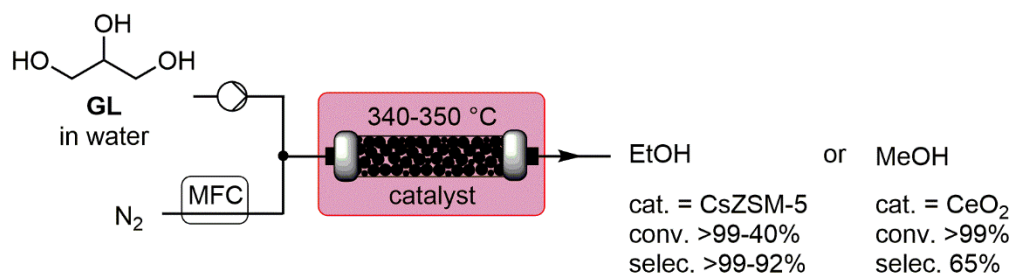


Figure 42. Gas-phase hydrogenolysis of glycerol into ethanol⁴⁶⁸ or methanol.⁴⁶⁹

Methanol. By analogy to the conversion of glycerol into ethanol reported by Kostyniuk,⁴⁶⁸ Hutchings and coworkers reported earlier a straightforward process for the direct conversion of glycerol into methanol, under H₂-free conditions and over Ce-based catalysts.⁴⁶⁹ The methodology is very appealing as it transforms a by-product formed during the synthesis of biodiesel into a reagent that is used for biodiesel production, thus potentially providing a process with a 100% atom economy for the conversion of triglycerides. In the report, quantitative glycerol conversion and 65% methanol selectivity were obtained by injecting a glycerol aqueous solution over a CeO₂ catalyst at 340 °C (Figure 42). Most importantly, crude glycerol obtained from the biodiesel industry gave similar results. Further investigation with various CeO₂ samples indicated that the selectivity observed in the reaction did not depend on the surface area, the crystallite size or the density of defects of the catalyst.⁴⁷⁰ In another follow-up paper, the same group further assessed the reaction over MgO as heterogeneous catalyst.⁴⁷¹ Under optimized conditions, an aqueous solution of glycerol was processed along with Ar as

carrier gas, at 400 °C and atmospheric pressure over the catalytic bed. Quantitative conversion and 35% selectivity for methanol were obtained. Acetol, ethylene glycol and acetaldehyde were the main side-products. Furthermore, the catalyst maintained its activity for 48 h of continuous operation despite accumulation of coke.

2.3.13. Hydrodeoxygenation into Propene

Propene (**26**) is a fundamental bulk chemical that serves for the production of common plastics and monomers, such as polypropylene, acrylonitrile and acrylic acid. Propene is currently exclusively produced from oil, gas and coal.⁴⁷² Glycerol is sometimes considered as a possible bio-based resource for drop-in propene. Research efforts were recently dedicated to the complete deoxygenation of glycerol to produce propene (**26**) in the presence^{473–476} or absence⁴⁷⁷ of hydrogen, under continuous flow conditions. In a pioneering report from 2014, Cao reported a concatenated continuous flow procedure involving two sequential fixed-bed reactors for the hydrogenolysis of glycerol into 1-propanol (**57**), followed by its dehydration into propene.⁴⁷³ A hydrogenolysis catalyst (Ir/ZrO₂) was loaded in the first bed operated at 250 °C, and a dehydration catalyst (HZSM-5 zeolite) was loaded in the second bed, also operated at 250 °C. Glycerol was pumped as an aqueous solution, along with hydrogen, in the system under 10 bar of counterpressure. Higher counterpressures triggered the reduction of propene into propane. The optimized system was operated continuously for 40 h, and no decrease in performance occurred (quantitative glycerol conversion, 85% selectivity for propene). Inspired by this study, Wu *et al.* reported on a similar process.^{474,475} In a representative example, MoO₃-modified Ni₂P supported on alumina was used as hydrogenolysis catalyst in the first bed, which was directly connected to the second bed - packed with ZSM-5 zeolite as dehydration catalyst. The whole system was operated at 250 °C and quantitatively converted glycerol, with a slightly higher (88%) selectivity toward propene than that reported by Cao. The authors demonstrated the

relevance of the methodology to process crude glycerol containing methanol: the temperature of the dehydration reactor was raised to 450 °C, and quantitative glycerol conversion with 72-69% propene selectivity were maintained for up to 550 h TOS (Figure 43). Mota and coworkers evaluated various activated carbon supported mono- and bimetallic catalysts in a single-stage flow reactor.⁴⁷⁶ The best results were obtained with a Fe/Mo catalyst, *i.e.* 90% yield in propene was maintained for 24 h TOS. In addition, a highly concentrated glycerol aqueous feed (90 vol%) was injected at elevated space velocity (WHSV = 5.4 h⁻¹), maximizing cost-efficiency. The proposed mechanism involved alternated dehydration/reduction reactions, with acetol, 1,2-propanediol, acetone and 2-propanol being the intermediates between glycerol and propene. Perez-Lopez described a H₂-free procedure for propene synthesis: glycerol was processed as an aqueous solution in the gas-phase over Fe-, Mo- and Nb-modified ZSM-5 catalysts.⁴⁷⁷ N₂ served as the carrier gas, and the best results were obtained over Fe/ZSM-5, possessing the strongest acid sites and the largest total acidity. The material gave quantitative glycerol conversion and 33% selectivity for propene at 450 °C. Acrolein (24%) and ethylene (19%) were the main side-products. It was speculated that a complex balance of parallel and successive reactions occurred, such as dehydration, dissociation, steam reforming, water gas shift and hydrogen transfer reactions, leading to a complex mixture of products.

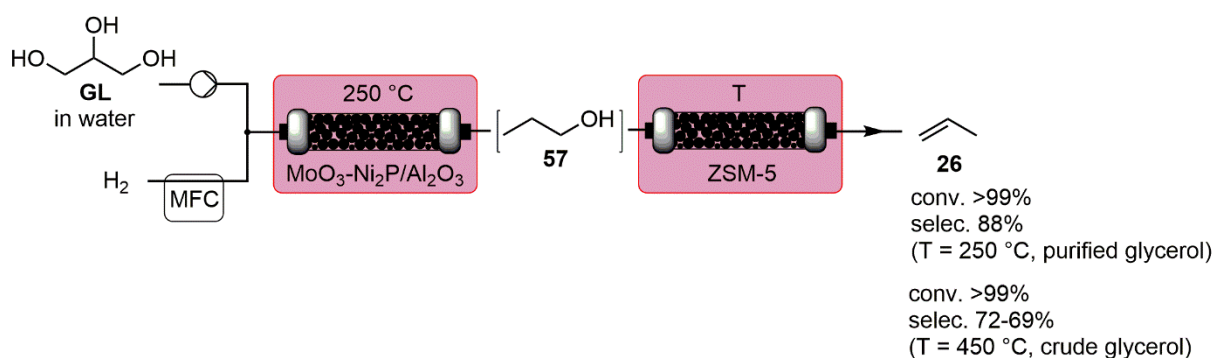


Figure 43. Two-stage continuous process for glycerol subsequent hydrogenolysis and dehydration into propene.^{474,475}

2.3.14. Aromatization into Carboaromatics

By analogy to the hydrodeoxygenation of glycerol into propene, the glycerol-to-aromatics (GTA) process is a bio-based alternative for the production of drop-in benzene, toluene and xylene (BTX), which are currently obtained from fossil resources at the industrial level.^{478–480} The GTA reaction was investigated in fixed-bed reactors at atmospheric pressure and pyrolysis temperatures (generally above 400 °C), over zeolites as heterogeneous catalysts.^{298,481–488} Low BTX yields were obtained in most instances, precluding any preparative value. In a pioneering work, neat glycerol was mixed with a stream of H₂ and heated over various acidic zeolites.²⁹⁸ HZSM-5 was reported as the best-performing catalyst among other systems, but higher (C_{8–10}) aromatics than BTX were formed and the catalyst rapidly deactivated. Huber and coworkers studied the conversion of aqueous solutions of various biomass-derived oxygenates into olefins and aromatics over ZSM-5 zeolite at 600°C, with He as the carrier gas.⁴⁸¹ It was found that when the H/C effective ratio of the polyol substrate increased, the yield for aromatics and olefins increased as well, while the amount of coke deposited on ZSM-5 decreased. For instance, glycerol (H/C_{eff} = 0.66) gave better results than sorbitol (H/C_{eff} = 0.33). In another report, various solvents were mixed with glycerol to improve the viscosity of the feed, and the effect of their nature and concentration on the reaction outcome was studied by Suh *et al.* under hydrogen-free conditions, with HZSM-5 as the catalyst.⁴⁸² With an aqueous glycerol solution, aromatic yields were low and catalyst deactivation occurred rapidly, while alcoholic solutions of glycerol improved yields and catalytic stability. Xiao and coworkers prepared hierarchical HZSM-5 by desilication of the parent catalyst under alkaline treatment.^{483,484} Mild treatments with bases such as sodium methoxide and sodium hydroxide created mesopores but also

preserved the microporosity within the catalyst framework. As a result, the desilicated samples gave enhanced performance in terms of BTX yields and catalytic stability. Another approach was assessed by the same group to enhance the HZSM-5 performance in the GTA reaction, where the catalyst was modified with metals such as Zn, Ni, Ag, Mo and Sn.^{485,486} The Sn-doped samples were the most promising, and could be further improved by introduction of a ZnO film by atomic layer deposition, which stabilized the SnO_x active sites. Overall, the ZnO/Sn-HZSM-5 catalyst was more stable and active for the formation of BTX, in comparison to the parent unmodified catalyst. A similar strategy was considered by Jongpatiwut *et al.*, who modified HZSM-5 zeolites with Zn species.⁴⁸⁷ The BTX yields increased with the metal loading. Neat glycerol was mixed with a stream of nitrogen as carrier gas, and injected in the flow reactor packed with Zn-doped HZSM-5. Under a 20 bar internal pressure, about 10%, 35% and 20% yields in benzene, toluene and xylenes, respectively, were obtained after 3 h TOS.

All of the above-mentioned studies relied on powdered or pelletized catalysts and refined glycerol, and therefore lacked of industrial relevance. To tackle these issues, Heeres and colleagues studied the conversion of crude glycerol (49 wt% purity) into BTX using a lab-scale fixed-bed reactor.⁴⁸⁸ The catalyst consisted of extrudates of ZSM-5/bentonite, and 200 g were loaded in a fixed-bed reactor. The catalytic bed was operated at atmospheric pressure, 536 °C and N₂ was utilized as carrier gas. The combined BTX yield was initially 14.6%, but severe deactivation was observed after only 4.7 h of operation. Coke deposition accounted for the main reversible deactivation mechanism through coverage of the acid sites and blockage of the pores of the catalyst.

2.3.15. Aromatization into *N*-Heterocycles

Pyridines. As for the above-mentioned BTX synthesis, the preparation of pyridines from glycerol represents a unique sustainable alternative for the preparation of these important industrial building blocks. Pyridine and methylpyridines (picolines) are indeed currently produced at an industrial level from the condensation of acrolein - generated from the reaction between acetaldehyde and formaldehyde - with ammonia.⁴⁸⁹ An analog methodology was considered by the group of Chao, where glycerol was dehydrated into acrolein and then reacted with ammonia either in a single or in a two-stage fixed-bed flow reactor, in the presence of zeolites as catalysts.⁴⁹⁰ Although Brønsted acid sites promoted the dehydration of glycerol into acrolein, they were poisoned by ammonia. Lewis acid sites were more favorable for the condensation of ammonia and acrolein. As a result, the single catalytic bed system gave moderate performance, and a two-stage flow reactor packed with separate catalysts was considered. The first catalytic bed was embedded with modified HZSM-22 zeolite that featured appropriate Brønsted acidity and mesoporosity for glycerol dehydration into acrolein. This flow reactor was telescoped to a second reactor packed with a ZnO-modified HZSM-5 catalyst, which exhibited enhanced Lewis acidity and mesoporosity for the condensation of acrolein and ammonia into pyridines. Under optimized conditions (temperature, flow rate, glycerol/ammonia ratio and glycerol feed concentration), 61-65% combined yield in pyridines was maintained for 9 h TOS in the two-bed system, but the yield then sharply dropped after longer operation time (Figure 44).

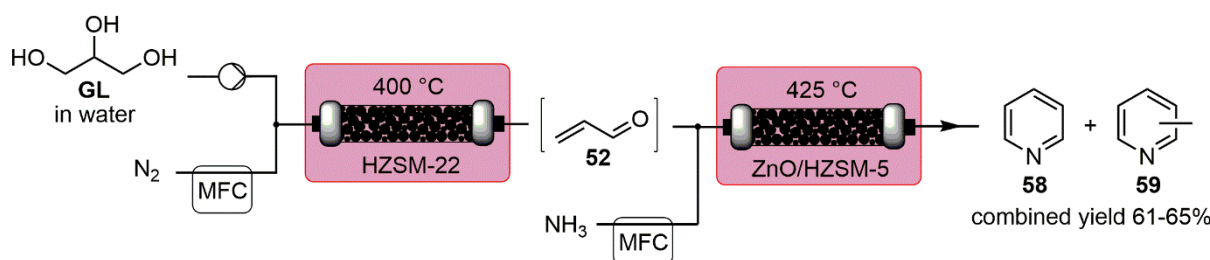
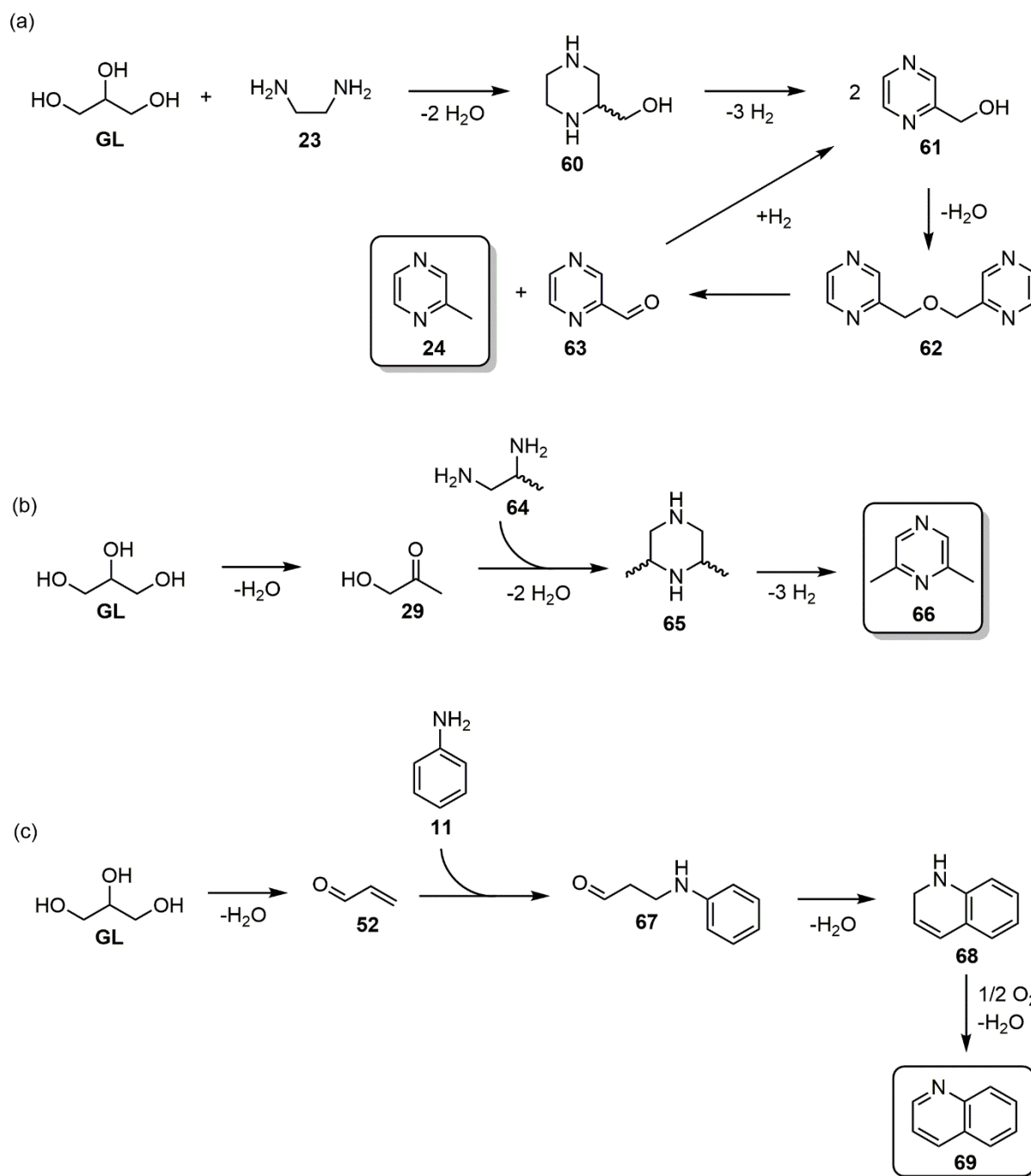


Figure 44. Preparation of pyridines in a two-stage continuous flow reactor.⁴⁹⁰

Pyrazines. 2-Methylpyrazine (**24**) and 2,6-dimethylpyrazine (**66**) were prepared from the reaction between glycerol and a vicinal diamine. To carry out such transformation, heterogeneous catalysts loaded in fixed-bed reactors were independently studied by the groups of Venugopal and Xu. The mechanism of 2-methylpyrazine formation from glycerol and ethylenediamine is believed to be analogous to that of the formation of **24** from 1,2-PDO and ethylenediamine (Scheme 1). The scheme proposed involves the direct condensation of glycerol and ethylene diamine into 2-(hydroxymethyl)piperazine (**60**), followed by the dehydrogenation of **60** into 2-(hydroxymethyl)pyrazine (**61**). The latter then undergoes self-condensation into bis(2-methylpyrazine)ether (**62**), and disproportionation of **62** into 2-methylpyrazine (**24**) and pyrazinaldehyde (**63**). Pyrazinaldehyde is then hydrogenated back into **61** (Scheme 11a).^{491–494} For the preparation of 2,6-dimethylpyrazine (**66**) from glycerol and 1,2-propanediamine (**64**), another mechanism was proposed: it involved the dehydration of GL into hydroxyacetone (**29**), followed by the condensation of **29** and **64**, and a final dehydrogenation of intermediate **65** into **66** (Scheme 11b).^{495–500}

Scheme 11. Proposed mechanisms for the conversion of glycerol into (a) 2-methylpyrazine, (b) 2,6-dimethylpyrazine and (c) quinoline.



24 was prepared from the gas-phase condensation of glycerol and ethylenediamine, over $\text{ZnO-ZnCr}_2\text{O}_4$ ^{491–493,501} and $\text{Mn-SiO}_2\text{-Al}_2\text{O}_3$ ⁴⁹⁴ catalysts, at high temperatures (375–400 °C) under atmospheric pressure. Although glycerol and ethylenediamine were typically injected in equimolar ratios, the conversion was always slightly superior for the diamine than for glycerol. Indeed, diamine self-condensation into pyrazine was noticed, especially with catalysts

possessing high concentration of strong acid sites.^{492,494} It was shown that catalysts possessing a combination of strong basic sites and weak acid sites were favorable for the formation of 2-methylpyrazine.^{492,493} In one of the most advanced example, **24** was prepared with 74% selectivity at 96% glycerol conversion, and these results were maintained for 48 h TOS without any catalyst deactivation (Figure 45).⁴⁹³ The reaction was also attempted with a glycerol feedstock that contained methanol and KOH to simulate a real sample of unrefined bio-based glycerol.⁴⁹² Under such conditions, a similar selectivity (65%) toward 2-methylpyrazine was observed, but ethylenediamine and glycerol conversions dropped to 48% and 64%, respectively.

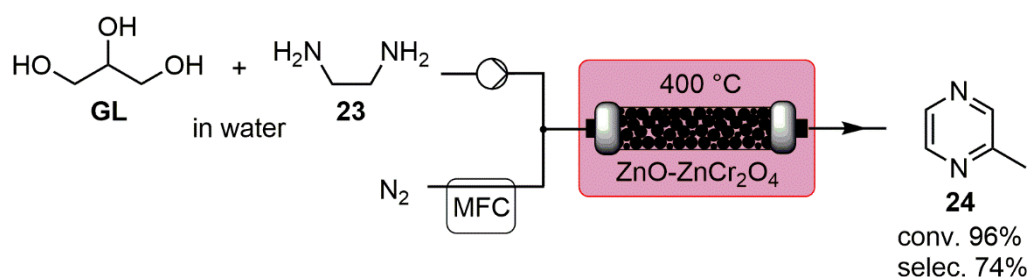


Figure 45. Preparation of 2-methylpyrazine from glycerol and ethylenediamine in a packed-bed continuous flow reactor.⁴⁹³

Similarly, **66** was obtained from the gas-phase reaction between glycerol and 1,2-propanediamine (**64**), over $CuO-CuCr_2O_4$,^{495,496} $CuCr_2O_4$,⁴⁹⁷ $Zn/CuCr_2O_4$,⁴⁹⁸ $Cu-TiO_2/Al_2O_3$,⁴⁹⁹ and $ZnO-ZnCr_2O_4$ catalysts,⁵⁰⁰ at high temperatures ($350-380\text{ }^{\circ}C$) under atmospheric pressure. It was evidenced that catalysts possessing a high metallic Cu surface area, along with a combination of moderate Lewis acid sites and strong basic sites, were favorable for 2,6-dimethylpyrazine formation. On the other hand, Brønsted acid sites did not influence the reaction.^{496-498,500} The highest prolonged yield for **66** was reported over $CuO-CuCr_2O_4$, where the conversion of GL evolved from 92% to 90%, while the selectivity toward 2,6-

dimethylpyrazine was maintained at a steady 91% during a 16 h run (Figure 46).⁴⁹⁵ Crude glycerol containing methanol and KOH could also be processed over a CuCr_2O_4 catalyst, although with a lower yield: 55% of glycerol was converted with 80% selectivity toward the formation of 2,6-dimethylpyrazine.⁴⁹⁷ A decreased yield was observed when crude glycerol was employed as starting material over $\text{ZnO-ZnCr}_2\text{O}_4$ and $\text{Zn/CuCr}_2\text{O}_4$ catalysts.^{498,500} Poisoning of the acid sites with KOH and NaCl accounted for this alteration in the yield of 2,6-dimethylpyrazine.

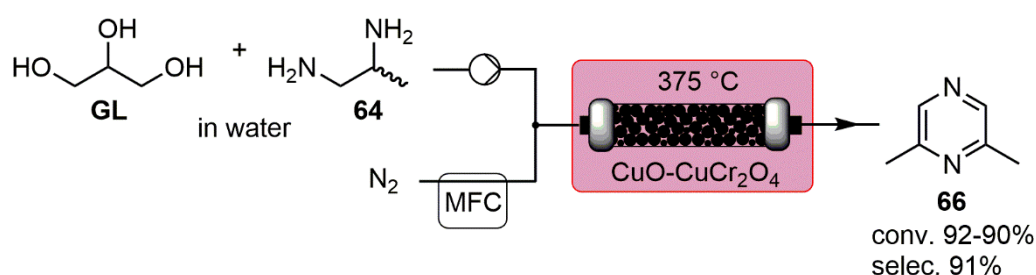


Figure 46. Preparation of 2,6-dimethylpyrazine from glycerol and 1,2-propanediamine in a packed-bed continuous flow reactor.⁴⁹⁵

Quinoline. In an early report, Reddy and Ganesh reported the continuous flow synthesis of quinoline (**69**) from aniline (**11**) and glycerol over $\text{CuO-ZnO/Al}_2\text{O}_3$.⁵⁰² In the proposed mechanism, glycerol first undergoes a dehydration into acrolein (**52**), and the reaction then proceeds through a Michael addition with aniline toward **67**, followed by cyclization/dehydration to form 1,2-dihydroquinoline (**68**). A final oxidative dehydrogenation leads to the target quinoline (**69**) (Scheme 11c). As an empirical evidence, the utilization of nitrogen as a carrier gas instead of oxygen dramatically reduced the formation of quinoline, preventing the oxidative dehydrogenation of 1,2-dihydroquinoline. Further insight on the reaction was provided by the group of Chao over Ni/mesoporous β -zeolites.⁵⁰³ They

demonstrated that Brønsted acid sites favored glycerol dehydration into acrolein (see section 2.3.8), while Lewis acid sites promoted quinoline formation. Coke deposition was the major deactivation mechanism, and the yield of quinoline dramatically decreased from 71% after 2 h TOS (Figure 47) to 15% after 6 h TOS, under optimized conditions. Nevertheless, the catalyst could be efficiently regenerated by calcination in the presence of air, for up to 3 reaction/regeneration cycles. The same group also assessed acid-treated $\text{ZnCl}_2/\text{Ni-USY}$ zeolites, but after 2 h TOS, a lower 40% yield in quinoline was obtained under the investigated conditions (410 °C, utilization of hydrogen as carrier gas).¹²⁷ Poliakoff and colleagues investigated the reaction with niobium phosphate as the heterogeneous catalyst. Glycerol and aniline were solubilized in water, and various conditions were screened (temperature, pressure, residence time and stoichiometry). Only 10% yield in quinoline could be obtained under optimized conditions. Further optimization evidenced that solketal (**30**, see section 2.3.3.) could be utilized as a substitute for glycerol, giving promising results.⁵⁰⁴

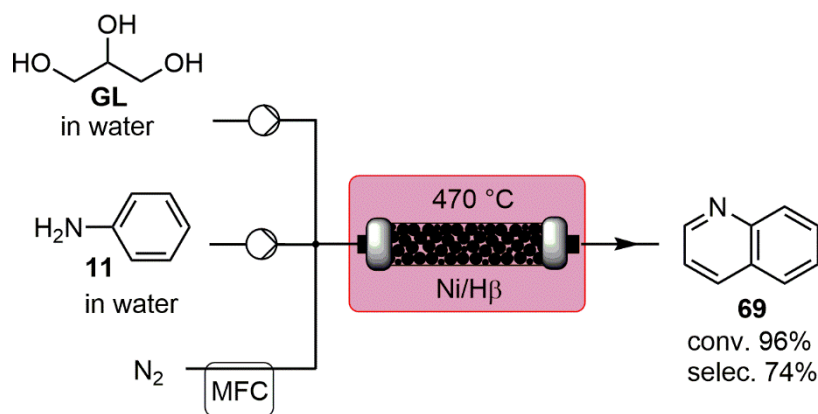


Figure 47. Quinoline synthesis from glycerol and aniline in a fixed-bed flow reactor.⁵⁰³

2.3.16. Miscellaneous

Epichlorohydrin. Epichlorohydrin (**27**) is a central building block of the polymer industry, mainly used in the manufacture of epoxy resins and elastomers. It used to be the starting

material for the production of glycerol (Scheme 2).¹⁸³ With the large surplus and the ever-decreasing price of glycerol, the reverse process, *i.e.*, the production of epichlorohydrin from glycerol using a two-step hydrochlorination/dechlorination sequence, sustained major research interests. The hydrochlorination step typically relies on gaseous HCl and a carboxylic acid catalyst, while the dechlorination step is conventionally triggered by an inorganic base. The reaction is already implemented at the industrial scale in batch reactors by Dow⁵⁰⁵ and Solvay.⁵⁰⁶ Continuous-flow processing is however of high relevance for the preparation of **27** from GL, since concatenation prevents manipulation of toxic chlorohydrin intermediates **71a,b** and **72a,b** (Figure 48). In this context, Monbaliu and coworkers reported a telescoped continuous flow procedure for the valorization of glycerol into high value-added oxiranes (glycidol and epichlorohydrin, Figure 48).¹⁷⁸ The first step consisted in the hydrochlorination of glycerol with aqueous HCl and pimelic acid (**70**) as the organocatalyst, and yielded 81% of mono-(**71a,b**) and dichlorohydrins (**72a,b**) in 20 min of reaction at 140 °C. By contrast, several hours and the utilization of gaseous HCl are required in batch to obtain similar results. Without isolation, the materials were then subjected to an intramolecular Williamson etherification step triggered by aqueous NaOH, affording a *ca.* 3:2 mixture of epichlorohydrin (**27**) and glycidol (**28**) in 74% combined yield (from GL). The epoxides could be quantitatively separated with a straightforward in-line liquid-liquid extraction relying on methyl *tert*-butyl ether (MTBE) as the extraction solvent and on a membrane-based separator. The resulting bio-based epichlorohydrin could be further utilized for the preparation of β -amino alcohol active pharmaceutical ingredients (APIs) under continuous flow conditions. The authors evaluated the scalability of the dechlorination step in a pilot-scale silicon carbide mesofluidic reactor (60 mL internal volume). The results evidenced that the mixing efficiency was critical.

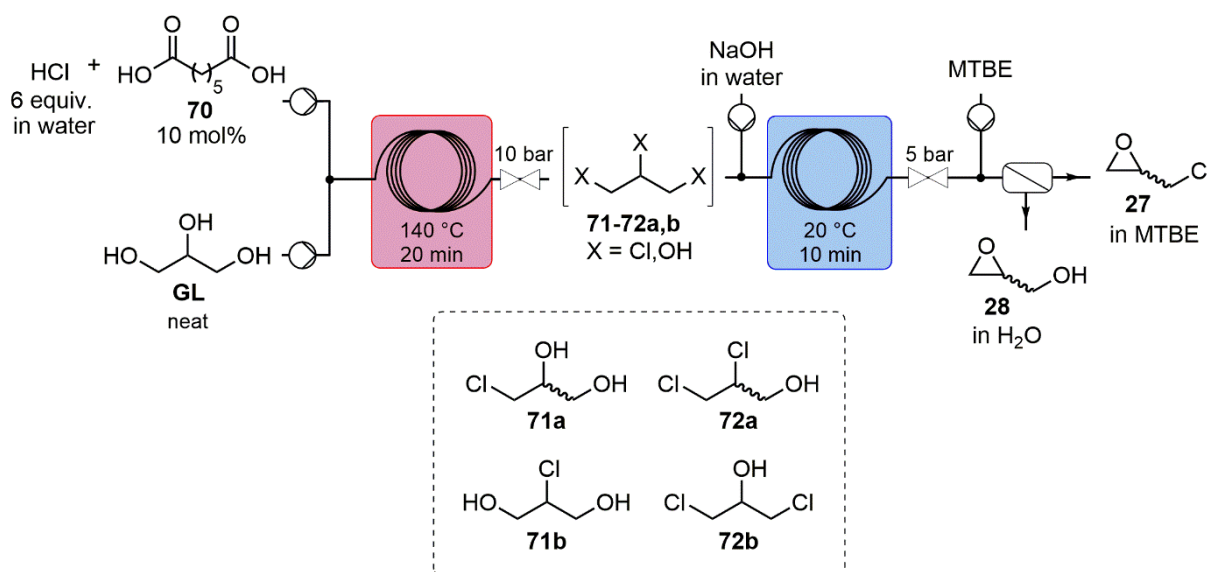


Figure 48. Hydrochlorination/dechlorination telescoped sequence for the upgrading of glycerol into epichlorohydrin and glycidol.¹⁷⁸

3-(Dimethylamino)propanal and (dimethylamino)acetone. The groups of Katryniok and Ding independently studied the reaction of glycerol with dimethylamine (Me₂NH), in the gas-phase, over heteropoly acid based catalysts packed in fixed-bed reactor (Figure 49).^{507,508} A different profile of products was obtained depending on the nature of the catalyst. Over Cs_{2.5}H_{0.5}PMo₁₂O₄₀ supported on silica, the product of the reaction was (dimethylamino)acetone (**73**), obtained in 70% selectivity at 47% glycerol conversion (conditions: 250 °C, 1.5 equiv. of Me₂NH).⁵⁰⁷ By contrast, H₆P₂W₁₈O₆₂/Zr-MCM-41 triggered the formation of 3-(dimethylamino)propanal (**74**) in 81% selectivity at 95% glycerol conversion (conditions: 300 °C, 2.5 equiv. of Me₂NH).⁵⁰⁸

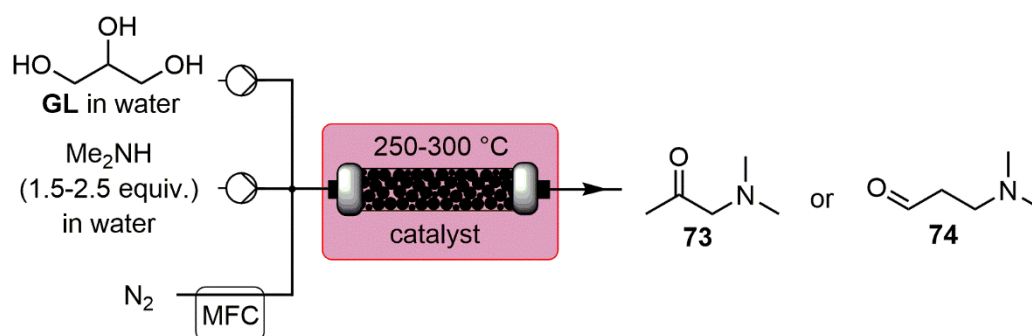


Figure 49. Continuous amination of glycerol over heteropolyacid-based catalysts.^{507,508}

Glycerol phosphates and nitrates. The group of Wever prepared glycerol-1-phosphate using a biocatalyzed reaction between glycerol and pyrophosphate in a packed-bed continuous flow reactor.⁵⁰⁹ An acid phosphatase was covalently immobilized within the reactor, and only mild deactivation was observed after 14 days of operation.

Zlotin *et al.* studied the nitration of alcohols under continuous flow conditions.¹¹² Dinitrogen pentoxide served as nitrating agent, and liquid 1,1,1,2-tetrafluoroethane (Freon R134a) as reaction medium. Freon R134a is an inert, non-flammable gas that has the potential to replace chlorinated solvents that are commonly utilized for nitration reactions with dinitrogen pentoxide. Most importantly, it is non-toxic and not classified as an ozone-depleting substance. Glycerol was included in the substrate scope and excellent conversion (99%) and selectivity for nitroglycerine (94%) were obtained in 4 s of reaction at 20 °C (Figure 50). The excess of nitrating agent was quenched downstream the reactor by aqueous NaOH, and a recycling loop for Freon R134a was included in the process. The continuous process for the manufacture of nitroglycerine (**75**) gave an eighty-fold higher space-time yield than the corresponding batch reaction (Table 1). Moreover, it was depicted as safer by comparison to a corresponding batch process, since (1) low amounts of nitroglycerine were present in the reactor, (2) the occurrence

of local heatspots was prevented and (3) the process could be swiftly terminated by switching off the feeding of reactants.

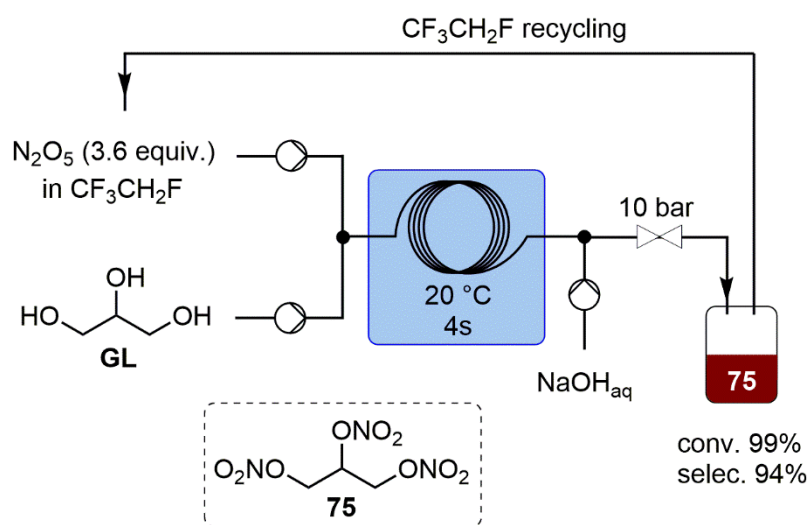


Figure 50. Zlotin's continuous process for the manufacture of nitroglycerin in liquid Freon R134a.¹¹²

2.4. 1,4-Butanediol

2.4.1. Presentation and Markets

1,4-Butanediol (1,4-BDO, CAS 110-63-4) is an important diol used in the manufacture of a variety of commodities.¹¹⁶ 1,4-BDO is a large volume chemical (2 million tons per year) that costs about \$2660 per ton. The global market for 1,4-BDO is estimated at \$5.7 billion. Europe and China are the biggest consumers of 1,4-BDO. 1,4-BDO can be produced either chemically from petro-based feedstock and bioresources or by fermentation processes (see section 4.2.2).¹¹⁶ About half of the production of 1,4-BDO worldwide is converted into tetrahydrofuran (THF, see section 2.4.4.), and about 35% feeds the polymer industry including polybutylene terephthalate (PBT), polyurethanes (PU) and biodegradable polybutylene succinate (PBS). The rest is mostly used for the preparation of γ -butyrolactone (see section 2.4.3.).^{116,117,510}

The main commercial routes, emerging continuous flow alternatives and major producers of 1,4-BDO are detailed in section 4.2.2.

2.4.2. Esterification into 1,4-Butanediol Diacetate

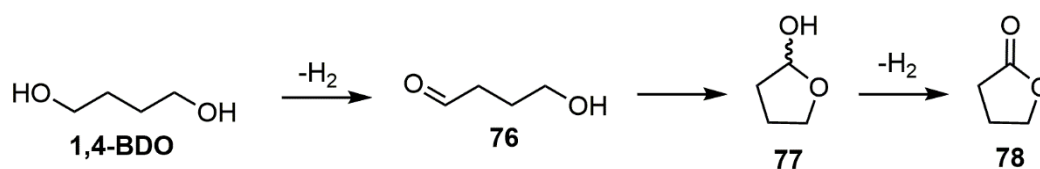
1,4-Butanediol was diacylated in a fixed-bed continuous reactor.⁵¹¹ In the report, acetic anhydride (Ac_2O) was used as esterifying agent, and silicotungstic acid supported on a silica monolith was assessed as heterogeneous catalyst. Quantitative yield was obtained under such conditions, and no performance decrease was observed upon increasing the diameter of the monolith from 3.2 to 6.4 mm.

2.4.3. Oxidation into γ -Butyrolactone and Succinaldehyde

γ -Butyrolactone. γ -Butyrolactone (**78**, GBL) is an important bulk chemical, mainly used as precursor for the preparation of pyrrolidones and as solvent. It is currently synthesized at a commercial scale from the catalytic dehydrogenation of 1,4-BDO or from the catalytic reduction of maleic anhydride.⁵¹² The dehydrogenation of 1,4-BDO in continuous flow reactors was studied on copper-based catalysts^{513–516} and on a Re cluster.⁵¹⁷ The group of Rao and Raju reported 95% conversion of 1,4-butanediol and 98% selectivity for γ -butyrolactone over bimetallic Co-Cu supported onto MgO.⁵¹³ 1,4-BDO was processed under solvent-free conditions using N_2 as the carrier gas, at 250 °C under atmospheric pressure. The catalytic stability was not assessed for more than 5 h TOS. Hwang and coworkers assessed conventional Cu/SiO₂ systems for the reaction, but copper sintering and oxidation led to premature catalyst deactivation.⁵¹⁴ Alternatively, they considered copper-silica nanocomposites with high Cu loading, and excellent results were obtained. The conversion of 1,4-BDO reached 99%, along with 99% GBL selectivity, and this excellent performance was maintained for 400 h TOS without any catalyst deactivation (Figure 51). Jadhav and colleagues evaluated copper

supported on ceria as catalyst.⁵¹⁵ Neat 1,4-BDO was processed at 240 °C under atmospheric pressure in the presence of N₂ as carrier gas. Although the selectivity for GBL remained at a steady 98% value, the conversion decreased from 93% to 70% during 7 h of continuous operation. Coking of the catalyst and Cu sintering accounted for the decrease in activity. The presence of both basic and metallic sites accounted for the enhanced performance of the catalyst, and a reaction mechanism was accordingly proposed (Scheme 12). A rhenium sulfide cluster was also reported to catalyze the reaction, but a poor yield (23%) and the high catalyst cost would preclude any commercial application.⁵¹⁷ Rao and coworkers reported that coupling the dehydrogenation of 1,4-BDO with the reduction of nitrobenzene over a single Cu/MgO catalytic bed improved the efficiency of both reactions.⁵¹⁶ Both a better catalytic stability and a better selectivity for GBL were obtained, by comparison to the independent reactions. Energy efficiency was also enhanced since the dehydrogenation reaction is endothermic while the hydrogenation reaction is exothermic. A solution of 1,4-BDO and nitrobenzene in a 3:2 molar ratio was pumped along with nitrogen as the carrier gas. The mixture reacted at 250 °C and atmospheric pressure over the catalytic bed. The conversion of 1,4-BDO decreased from 84% to 40% during 5 h of continuous operation. The selectivity for GBL merely decreased (92-82%) during the run.

Scheme 12. Proposed mechanisms for the catalytic dehydrogenation of 1,4-butanediol into γ -butyrolactone.⁵¹⁵



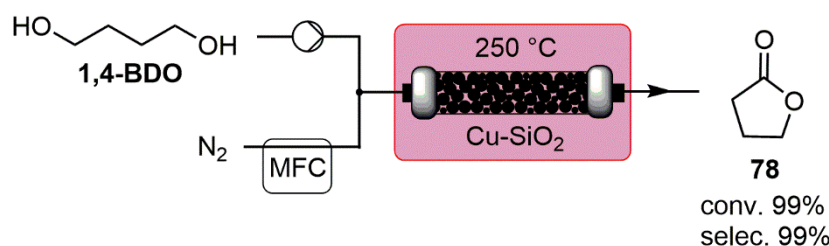


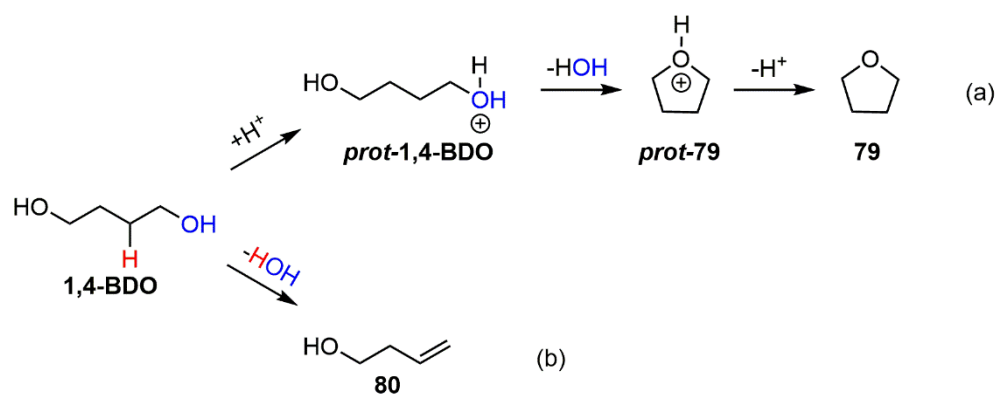
Figure 51. 1,4-Butanediol dehydrogenation into γ -butyrolactone in a fixed-bed of copper-silica nanocomposites.⁵¹⁴

Succinaldehyde. The group of Wirth studied alcohol oxidation reactions using a hypervalent iodine (III) reagent in the presence of TEMPO under microfluidic conditions.⁵¹⁸ 1,4-BDO was oxidized into succinaldehyde with 91% conversion. Over-oxidation into the corresponding carboxylic acid derivatives was not observed using such process.

2.4.4. Dehydration into Tetrahydrofuran and 3-Buten-1-ol

1,4-BDO can be dehydrated either into tetrahydrofuran (**79**, THF) or into 3-buten-1-ol (**80**). In supercritical water as the reaction medium, it was suggested that the dehydration into THF proceeds through a preliminary protonation of 1,4-BDO, leading to the corresponding oxonium derivative, followed by an intramolecular nucleophilic substitution, and a final deprotonation (Scheme 13a).⁵¹⁹ THF is widely used as monomer for the preparation of poly(tetramethylene oxide) and as a solvent. It is currently produced at an industrial level from 1,4-BDO using acid catalysts.⁵²⁰ The mechanism suggested for the dehydration of 1,4-butanediol into 3-buten-1-ol over heterogeneous catalysts involved the abstraction of a hydrogen in 2-position and the elimination of a terminal hydroxyl group (Scheme 13b).^{521–525}

Scheme 13. Competitive reaction pathways suggested for the catalytic dehydration of 1,4-butanediol into (a) THF⁵¹⁹ and (b) 3-buten-1-ol.^{521–525}



Tetrahydrofuran. The transformation of 1,4-butanediol into THF (**79**) was reported under continuous flow conditions, using sub- and supercritical water as reaction medium^{519,526} or in the gas-phase over solid catalysts (Figure 52).^{513,517,522,527–531} The most relevant acid catalysts and conditions utilized in the gas-phase processes are reported in Table 19. The reaction gave in general near to quantitative yield in THF over common acidic oxides such as alumina (entries 1-3), silica-alumina (entry 4), titania (entry 8) and zirconia (entry 9).

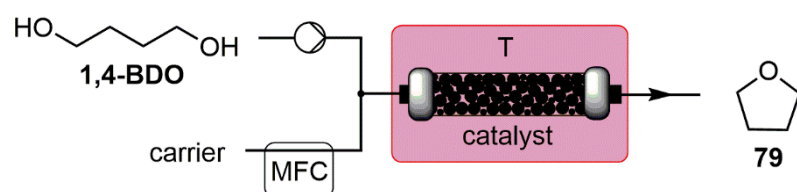


Figure 52. General flow scheme for the gas-phase dehydration of 1,4-butanediol into THF.

Table 19. Catalysts and optimized conditions for the gas-phase cyclodehydration of 1,4-butanediol into tetrahydrofuran.

Entry	Catalyst	T (°C)	Carrier gas	Space velocity W/F =	TOS (h)	Conv. (%)	Selec. (%)	Ref.
1	Al ₂ O ₃	275	He	0.113 g h cm ⁻³	1-5	>99	99	527
2	Al ₂ O ₃	325	N ₂	0.407 g h cm ⁻³	1-5	>99	97	528
3	Al ₂ O ₃	350	H ₂	WHSV = 3.34 h ⁻¹	1-5	>99	98	522

4	SiO ₂ -Al ₂ O ₃	425	He	W/F = 0.169 g h cm ⁻³	1-5	>99	93	527
5	Co-Cu/MgO	250	N ₂	LHSV = 2 h ⁻¹	1-5	98	98	513
6 ^a	[(Nb ₆ Cl ₁₂)Cl ₂ (H ₂ O) ₄].4H ₂ O/SiO ₂	350	He	- ^b	- ^b	>99	>99	529,530
7	Yb ₂ O ₃ /SiO ₂	325	N ₂	W/F = 0.407 g h cm ⁻³	1-5	>99	98	528
8	TiO ₂	350	H ₂	WHSV = 3.34 h ⁻¹	1-5	>99	98	522
9	ZrO ₂	325	N ₂	W/F = 0.407 g h cm ⁻³	1-5	>99	97	528
10	ZrO ₂	425	He	W/F = 0.169 g h cm ⁻³	1-5	>99	61	531

^aWater was used as the solvent. ^bUnclear.

3-Buten-1-ol. The gas-phase dehydration of 1,4-BDO into 3-buten-1-ol (**80**) was reported over various solid catalysts (Figure 53).^{146,147,521–525,527,528,531–534} Elaboration of more complex systems than in the case of THF production is required to selectively form 3-buten-1-ol. Indeed, a combination of both acid and basic sites favors the reaction, as the H of 1,4-BDO in the 2-position interacts with basic sites, while acidic sites of the catalyst bound the terminal OH of 1,4-BDO (Scheme 13).^{521–525} An alternative redox-based mechanism was proposed upon utilization of ceria as a catalyst.^{147,527,531} The most relevant catalytic systems and conditions for the gas-phase dehydration of 1,4-BDO into **80** are reported in Table 20.

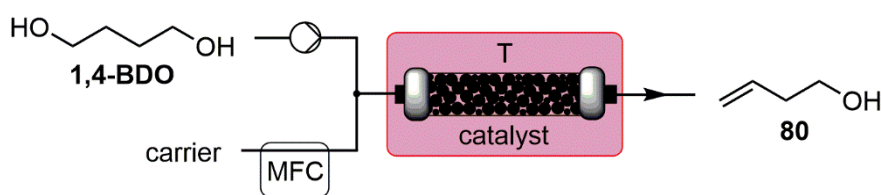


Figure 53. General flow scheme for the gas-phase dehydration of 1,4-BDO into 3-buten-1-ol.

Table 20. Catalysts and optimized conditions for the gas-phase dehydration of 1,4-butanediol into 3-buten-1-ol.

Entry	Catalyst	T (°C)	Carrier	Space velocity	TOS (h)	Conv. (%)	Selec. (%)	Ref.
1	CeO ₂	375	N ₂	LHSV = 1 mL g ⁻¹ h ⁻¹	- ^a	95	63	532
2	CeO ₂	400	He	W/F = 0.57 g h cm ⁻³	1-5	88	68	527
3	CeO ₂	425	N ₂	W/F = 0.075 g h cm ⁻³	- ^a	74	57	147
4	Er ₂ O ₃	350	N ₂	W/F = 2.78 x 10 ⁻³ g h cm ⁻³	1-5	71	81	533
5	MgYbO	350	N ₂	W/F = 0.93 g h cm ⁻³	2	90	79	525
6	Yb ₂ O ₃	375	N ₂	W/F = 0.046 g h cm ⁻³	1-5	34	88	521
7	ZrO ₂	350	He	W/F = 0.169 g h cm ⁻³	1-5	86	48	531
8	CaO/ZrO ₂	350	H ₂	WHSV = 1.67 h ⁻¹	2.5-24	95	89	522
9	Yb ₂ O ₃ /ZrO ₂	325	N ₂	W/F = 0.407 g h cm ⁻³	1-5	73	85	528

^aUnclear.

In one of the most advanced examples, 95% conversion of 1,4-BDO and 89% selectivity were maintained for 24 h TOS (Table 20, entry 8).⁵²² It was reported that addition of CaO to ZrO₂ promoted the reaction by creating new basic sites, while maintaining a similar level of acidity in comparison with unmodified ZrO₂.^{522–524} Additionally, the utilization of hydrogen as carrier gas improved the selectivity by inhibiting minor side-reactions such as the oxidation into γ -butyrolactone.⁵²² Elevated conversion (90%) and selectivity (79%) were reported as well over Mg-Yb mixed oxides (entry 5). Likewise, it was reported that the addition of Yb to magnesium oxide increased the number of acid sites on the catalyst, yet maintaining a high concentration of basic sites. Overall, this contribution of both acidic and basic sites accounted for the performance of the catalyst.⁵²⁵

2.4.5. Miscellaneous

1,4-Butanediol monophosphate. Faber and colleagues immobilized acid phosphatases on polymeric beads, which were utilized as packing material in a fixed-bed flow reactor.⁵³⁵ Using

such configuration, 1,4-BDO was monophosphorylated in the presence of pyrophosphate, to afford the corresponding phosphate ester in 41% yield on a multigram scale. Precise control of the reaction conditions minimized hydrolysis of the product.

2.5. Xylitol and Sorbitol

2.5.1. Presentation, Producers and Markets

(2*R*,3*R*,4*S*)-Pentane-1,2,3,4,5-pentol (xylitol, XY, CAS 87-99-0) and (2*S*,3*R*,4*R*,5*R*)-hexane-1,2,3,4,5,6-hexol (sorbitol, SO, CAS 50-70-4) are naturally occurring and important C-5 and C-6 polyols.⁵³⁶ XY has a global market volume of about 200,000 tons per year (\$624 million per year in 2015) with an average price of \$3900 per ton.¹¹⁶ By contrast, SO is accessible at a much lower price (\$650 per ton), yet it concerns a smaller market volume of 164,000 tons per year (\$107 million per year global market in 2015).¹¹⁶ Both XY and SO were included on the original 2004 list of most promising chemicals from biomass issued by the US Department of Energy.²⁶

XY is mainly used as a food additive and as excipient in personal care and pharmaceutical products. Roquette Frères (France) and DuPont (USA) are the leaders for the production for XY.^{116,536} Fortress Global Enterprises has recently purchased S2G Biochemicals and has announced their ambition to produce 2,000 tons per year of xylitol from wood pulp from 2020.⁵³⁷ China also counts a myriad of producers, including Futaste Pharmaceutical, Shandong Longlive Biotechnology and Zhejiang Huakang Enterprise, among others.

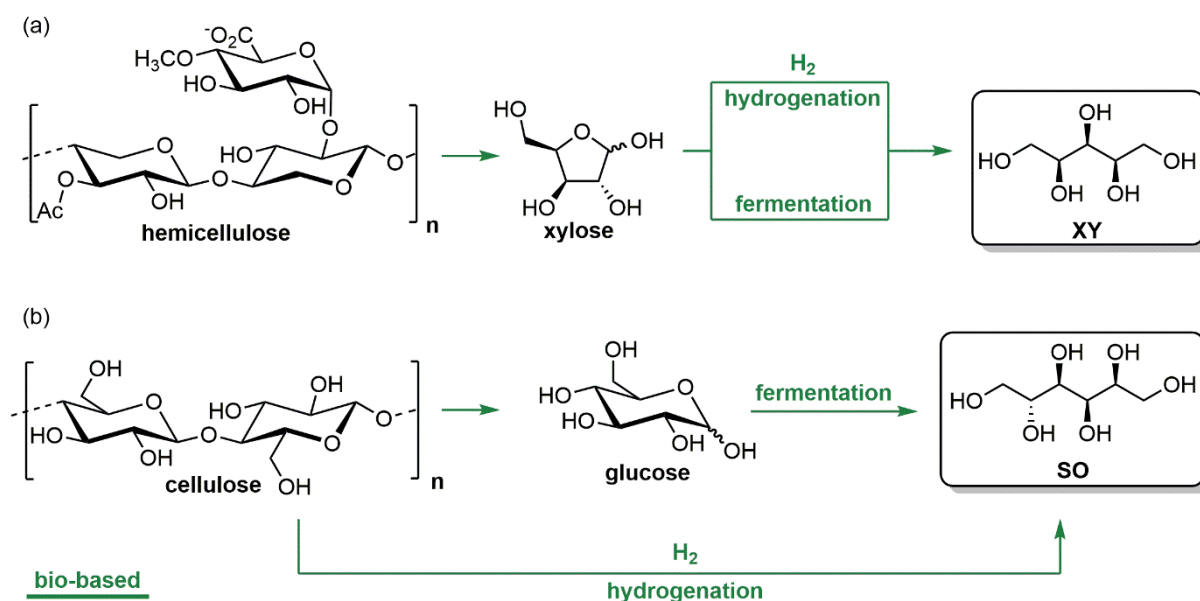
The world production of sorbitol is dominated by Roquette Frères (France) with several production sites across the globe. Other significant producers include for instance Cargill (USA), Shandong Tianli Pharmaceutical (China), STBC (Indonesia), ADM (USA) and Ingredion Incorporated (USA).^{116,536} SO is mainly used as a food additive and as excipient in

personal care and pharmaceutical products. A significant fraction of the global production of SO is transformed into ascorbic acid through fermentation, and SO is also the building block of isosorbide (see Section 2.5.3).^{536,538} Other applications are in development such as the preparation of fuels, EG and 1,2-PDO (see Section 2.5.4. and 2.5.5.).^{116,536}

2.5.2. Current Commercial Routes and Emerging Continuous Flow Alternatives

XY is typically obtained from xylose derived from hemicellulosic feedstock, either through hydrogenation or through fermentation (Scheme 14). Typical hydrogenation catalysts include Ni-, Ru- and Rh-based catalysts. Alternatively, xylan can be hydrolyzed to xylose, and the latter is then fermented into xylose with various strains.⁵³⁶ SO is typically obtained from glucose or fructose, either through hydrogenation or through fermentation (Scheme 14).^{116,536} A typical process includes the production of glucose from the fermentation of corn, cassava or wheat feedstock followed with its hydrogenation under medium to high pressure in the presence of Ru- or Ni-based catalysts.^{116,536} Other processes directly hydrogenate cellulose in the presence of Ru- or Pt-based catalysts to afford SO.^{116,536} Recent reports from the primary literature aimed at improving the preparation of XY and SO under continuous flow conditions, and are detailed below.

Scheme 14. Simplified (bio)chemical processes for the preparation of (a) xylitol and (b) sorbitol.



The hydrogenation of glucose was studied over supported Ni and Ru catalysts, under 80 bar of pressure in H_2 and at 80 °C.⁵³⁹ Excellent stability and activity were obtained particularly over the Ru/ Al_2O_3 system, with >99% glucose conversion and 99% selectivity toward sorbitol. A decrease in conversion below 98% was not observed before 1080 h TOS, and the main deactivation mechanism was evidenced to be poisoning by metal leaching from the reactor walls. Alternatively, Pérez-Ramírez and colleagues assessed alcohols as H-donors and hydrotalcite-derived CuNiAl oxide as heterogeneous catalysts (Figure 54).⁵⁴⁰ Under optimized conditions, SO and XY were obtained in 67% and 60% yield, respectively, using 1,4-BDO in the feed. γ -Butyrolactone was concomitantly produced through the diol lactonization, increasing the added value of the process. During a 48 h run, a minor decrease in yield (from 67 to 61%) was observed in the case of SO, highlighting a promising catalytic stability.

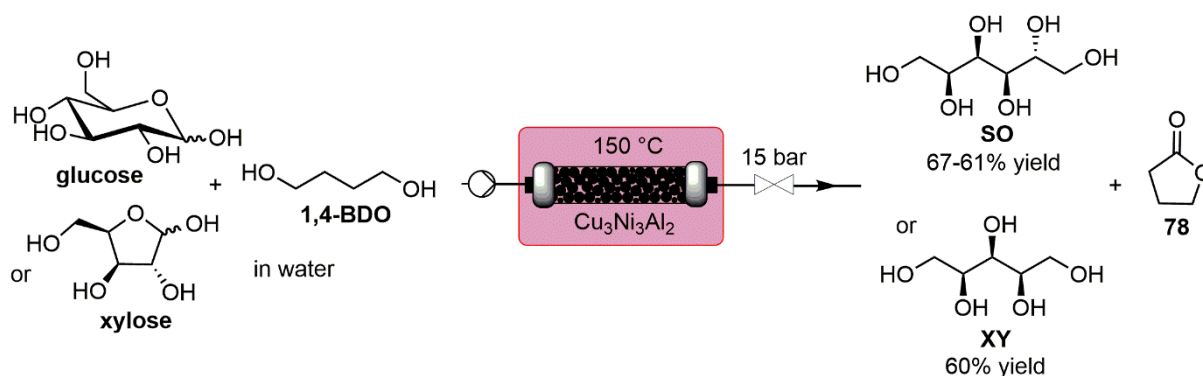


Figure 54. Continuous transfer hydrogenation for the production of sorbitol and xylitol from the corresponding sugars.⁵⁴⁰

2.5.3. Dehydration into Isosorbide

Isosorbide (**81**) is gaining increasing attention from the scientific community since it is a bio-based platform for the synthesis of various medicines, solvents, additives and polymers.⁵⁴¹ It is solely produced from the acid-catalyzed double dehydration of SO, and thus falls under the umbrella of dedicated bio-based chemicals.⁵⁴¹ The reaction was studied under continuous flow conditions by the group of Huang, over various solid acidic catalysts such as tin, zirconium or titanium phosphates,⁵⁴² sulfated metal oxides,⁵⁴³ supported phosphotungstic acids⁵⁴⁴ and H_3PO_4 -treated Ta_2O_5 .⁵⁴⁵ In most cases, 1,4-sorbitan, the monocyclic intermediate resulting from a single dehydration, was the major side-product in the reactor effluents. The highest yield was reported over sulfated copper oxide, with 68% selectivity toward **81** at quantitative SO conversion, and using a moderate temperature of $200\text{ }^\circ\text{C}$ by comparison to other reports (Figure 55).⁵⁴³

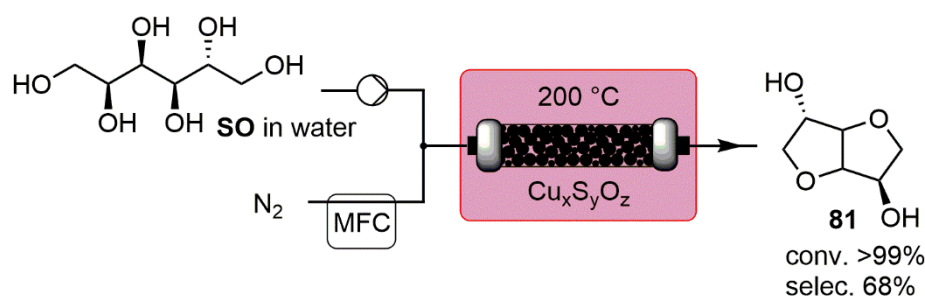


Figure 55. Double dehydration of sorbitol into isosorbide in fixed-bed flow reactor.⁵⁴³

2.5.4. Hydrogenolysis into *n*-Hexane, *n*-Pentane and Hexanols

Several reports were dedicated to the study of the hydrogenolysis of SO and XY, for the production of C5-C6 alkanes or alcohols, under continuous flow conditions. Complex mixtures of alkanes and oxygenates were obtained, and could potentially serve as fuels or fuel additives. The reaction sequence proceeds through subsequent dehydration and hydrogenolysis cycles, which are triggered on bifunctional catalysts possessing both acidic (dehydration) and metallic (reduction) sites. The catalysts were evaluated in the presence of molecular hydrogen co-feeding, although exploitation of the aqueous phase reforming (APR) reaction of the polyol substrate, for the *in situ* generation of H_2 , is also feasible. However, higher C5-C6 alkane yields were obtained upon implementation of the former option.⁵⁴⁶ Reported catalytic systems were based on Ir,⁵⁴⁷ Ni,⁵⁴⁸ Ni-Mo,⁵⁴⁹ Pd,^{546,547} Pd-Fe,⁵⁵⁰ Pd-Mo,⁵⁴⁹ Pt,^{546,547,551–558} Pt-Mo,⁵⁴⁹ Pt-Re,⁵⁵⁷ Rh-Mo,⁵⁴⁹ Ru,^{559,560} or Ru-Mo^{549,561–564} supported onto various materials. In regard of catalyst development, the most challenging aspect of the hydrogenolysis reaction is the design of catalytic systems that do not catalyze C-C bonds cleavage to avoid the detrimental formation of lower alkanes and oxygenates. SO or XY were typically pumped as aqueous solutions along with hydrogen within a fixed-bed reactor operated at high temperature and pressure (Figure 56). The most relevant catalysts and conditions reported in the literature are summarized in Table 21. Selectivity for hexane (82), pentane (83) and hexanol (84) are presented, since the formation

of these compounds is indicative of the efficiency of a catalyst (C-O cleavage favored over C-C cleavage).

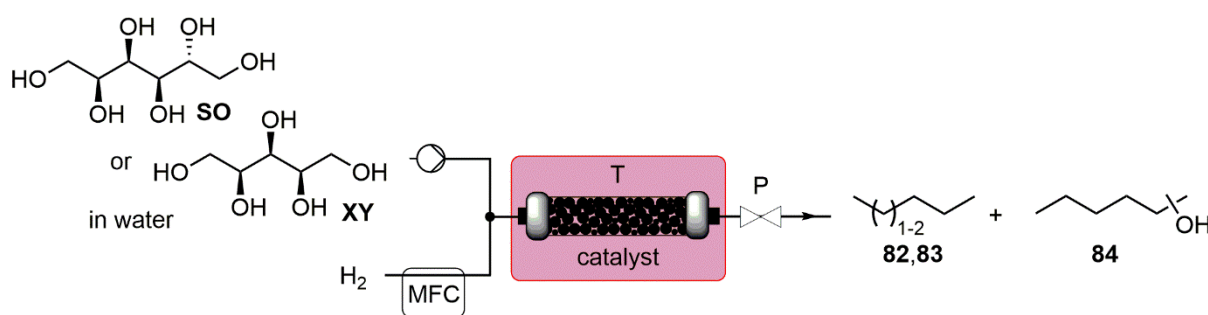


Figure 56. General flow scheme for the hydrogenolysis of sorbitol and xylitol.

Table 21. Catalysts and optimized conditions for the continuous hydrogenolysis of sorbitol and xylitol toward hexane, pentane and hexanols.

Entry	Substrate	Catalyst	T (°C)	P (bar)	Space velocity	TOS	Conv. (%)	Selec. for hexane (%)	Selec. for hexanols (%)	Selec. for pentane (%)	Ref.
1	Sorbitol	NiMo/C	280	40	LHSV = 0.24 h ⁻¹	- ^a	-	78 ^b	-	6 ^b	549
2	Sorbitol	PdMo/C	280	40	LHSV = 0.24 h ⁻¹	- ^a	-	47 ^b	-	26 ^b	549
3	Sorbitol	PtMo/C	280	40	LHSV = 0.24 h ⁻¹	- ^a	-	72 ^b	-	12 ^b	549
4	Sorbitol	RhMo/C	280	40	LHSV = 0.24 h ⁻¹	- ^a	-	56 ^b	-	25 ^b	549
5 ^c	Sorbitol	Ru/C	250	40	LHSV = 0.75 h ⁻¹	20 h	-	34 ^b	-	31 ^b	559
6	Sorbitol	RuMo/C	280	40	LHSV = 0.24 h ⁻¹	1-200 h	-	80 ^b	-	7.5 ^b	549
7	Sorbitol	RuMoP/CNT	300	40	LHSV = 3 h ⁻¹	1-7 days	91	4	20	0	563
8	Xylitol	Pt/Zr-P	245	62	WHSV = 0.36 h ⁻¹	60-84 h	>99	0	0	48	552

CNT = carbon nanotubes. ^aUnclear. ^bYield. ^cH₃PO₄ was added to the feedstock solution.

Cabiac and coworkers reported on a physical mixture of a dehydration (TiO₂-WO_x) and of a hydrogenation (Pt/ZrO₂) catalyst for the hydrogenolysis of SO.^{547,551,558} The same group assessed similar catalysts such as M/ZrO₂ + TiO₂-WO_x (with M = Ir or Pd),⁵⁴⁷ and Pt/SiO₂-Al₂O₃.^{555,556} Huber *et al.* studied Pt supported on zirconium phosphate for the hydrogenolysis

of both SO and XY, and reported good selectivity for the corresponding alkanes (sorbitol: 36% selectivity for hexane; xylitol: 48% selectivity for pentane, Table 21, entry 8) at quantitative polyol conversion.⁵⁵² The catalyst benefited from an outstanding stability (up to 200 h TOS), and no leaching could be detected in the reactor effluents. The same group also reported on Pt/SiO₂-Al₂O₃,⁵⁵⁴ Pt-ReO_x/C,⁵⁵⁷ and Pd₁Fe₃/Zr-P⁵⁵⁰ as catalysts for the hydrogenolysis of sorbitol. Wang and colleagues assessed a Ru-Mo catalyst supported on activated carbon, and a good combined yield of pentane (7.5%) and hexane (80%) was obtained under optimized conditions (280 °C, 40 bar H₂, entry 6).⁵⁴⁹ Most importantly, no deactivation could be evidenced after 200 h of continuous operation under optimized conditions. Transition metals other than Ru were assessed as well: Pt and Ni gave results similar to those of Ru (entries 1,3), while Pd and Rh gave higher yields of pentane (~25%, entries 2,4) in detriment of the yield in hexane, highlighting enhanced activity toward C-C cleavage. Similarly, Ma and coworkers described a ruthenium-molybdenum catalyst supported on carbon nanotubes as efficient for the reaction.⁵⁶¹ Excellent selectivity for hexane (40%) and pentane (22%) were obtained at quantitative sorbitol conversion. Most importantly, the catalyst remained stable for 7 days of continuous operation without deactivation. Activated carbon-supported,⁵⁶⁴ or phosphate-modified^{562,563} versions of their RuMo catalyst were studied in follow-up papers, and gave good results as well. The same group also considered an alternative approach, where a common Ru/C catalyst was utilized and H₃PO₄ was introduced as an additive in the sorbitol feedstock solution.⁵⁵⁹ It was proposed that phosphoric acid enhanced the catalyst acidity, thus promoting dehydration reactions; but also poisoned Ru metallic sites, therefore inhibiting C-C cleavage reactions. 34% yield in hexane and 31% yield in pentane were obtained after 20 h of continuous operation under optimized conditions (entry 5). The group also integrated the hydrogenation of glucose into sorbitol to the process (Figure 57).⁵⁶⁰ Since glucose is less stable than sorbitol, the process could not be

conducted in a single bed in one-pot and a sequential two-bed procedure was designed. Glucose was pumped along with phosphoric acid in a first Ru/C bed operated at moderate temperature (140 °C) to avoid degradation reactions and coke formation. Then, the effluent of the reactor, containing mainly sorbitol, entered the second Ru/C bed operated at 250 °C. Pentane and hexane were obtained in 19% and 25% yield, respectively.

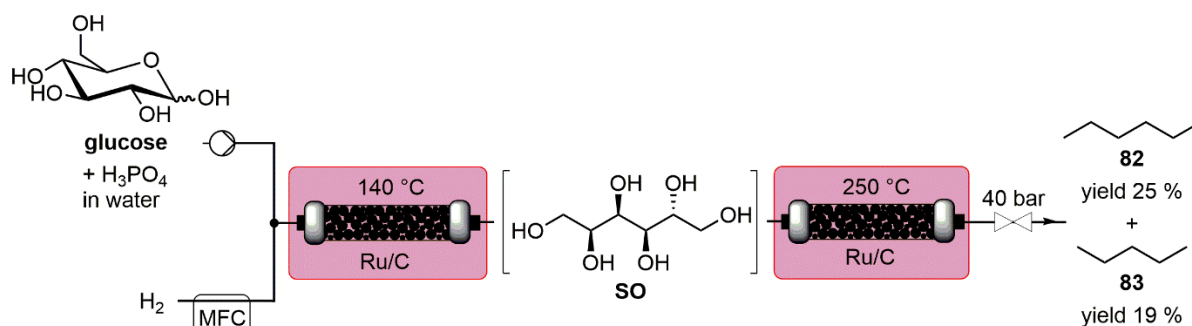


Figure 57. Sequential continuous flow process for the hydrogenation of glucose into sorbitol, and for the hydrogenolysis of sorbitol into alkanes.⁵⁶⁰

2.5.5. Hydrogenolysis into Ethylene Glycol and 1,2-Propanediol

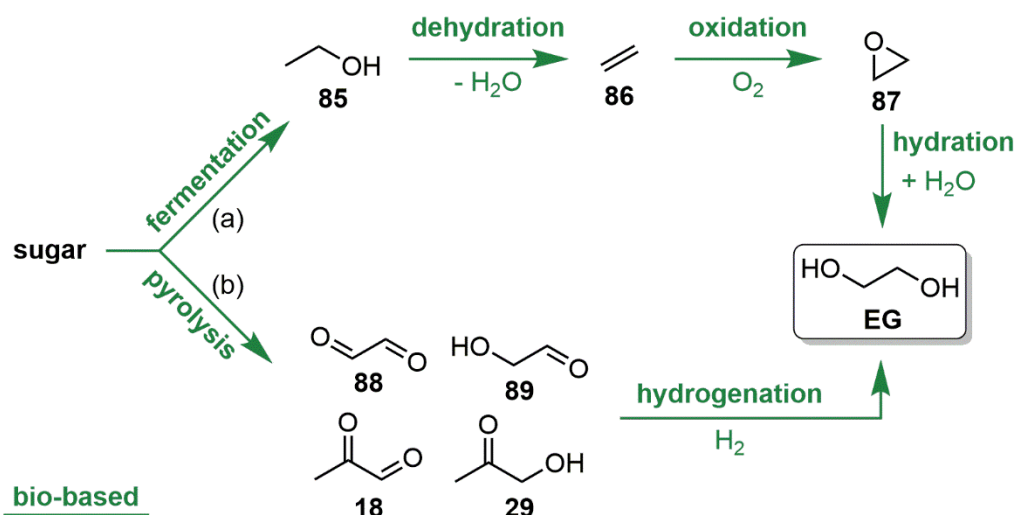
The industrial production of ethylene glycol (EG) started around World War I and historically relied on the hydration of ethylene oxide. Until the early 60s, other commercial routes were developed based on carbon monoxide, formaldehyde or directly ethylene. One of the most widely used process relies on the direct oxidation of petro-based ethylene into ethylene oxide and its subsequent thermal hydrolysis.^{118,129} An increasing effort toward bio-based ethylene is observed with the development of various chemical processes relying on bio-based feedstock. On the lab scale, EG can be obtained from the hydrogenolysis of glycerol or cellulose or from the fermentation of xylose.¹²⁹ Demonstration on pilot scale was achieved for the hydrogenolysis of glucose as well as for pyrolysis/hydrogenation of glucose.¹²⁹ Nowadays, the only bio-based process that reached the commercial scale relies on a multistep process starting from

bioethanol.¹²⁹ For instance, India Glycol Ltd (India) has been producing ethylene glycol since 2008 from bio-ethanol while Greencol Taiwan Corporation (GTC) operates since 2013 a bio-based EG facility with a capacity of 100,000 tons per year.

The landscape of EG producers is very diverse and the next paragraph only summarizes recent strategical developments. Two major chemical producers, the Brazilian Braskem and the Danish Haldor Topsoe signed a partnership in 2017 for the development of a demonstration plant in Denmark for the production of EG from sugar (Scheme 15).⁵⁶⁵ The startup of the demo unit was announced in early 2019. The demo unit named MOSAIK (MOnoSaccharide Industrial Cracker) performs the cracking of sugars toward intermediates than can be further transformed to EG, which is an appealing and economically viable alternative to the more conventionnal fermentation processes (Scheme 15). Topsoe's process relies on two steps, by contrast to the conventional ethanol route (5 steps). The commercial plant is scheduled in 2023.⁵⁶⁵ The Dutch company Avantium announced the startup of a 10 t per year demonstration facility in The Netherlands.^{566,567} The demonstration unit relies on Avantium's pioneering technology for the conversion of plant-based sugars into glycols in one step.⁵⁶⁸ In Asia, India Glycols limited (India, 175,000 tons per year) and Biochem Technology Group (China) are major leaders for the production of bio-based EG.^{569,570}

1,2-Propanediol is currently prepared at the industrial level from bio-based glycerol (see section 2.3.12).

Scheme 15. Simplified chemical processes for the preparation of ethylene glycol from (a) the fermentation of carbohydrates toward bioethanol and (b) the pyrolysis of carbohydrates followed with the hydrogenation of intermediate oxygenated compounds such as glyoxal, pyruvaldehyde, glycolaldehyde and acetol.



Emerging bio-based alternatives toward ethylene glycol and 1,2-propanediol utilize sorbitol and xylitol as the feedstocks. For instance, the group of Zhu converted sorbitol and xylitol into both 1,2-PDO and EG. The reaction was carried out in a fixed-bed flow reactor packed with a Cu-Ce-SBA catalyst, and hydrogen gas was co-fed.¹⁵⁸ In the case of SO, 99% conversion with 32% and 11% selectivity toward 1,2-PDO and EG, respectively, were obtained under optimized conditions. Upon utilization of XY as feedstock, slightly better results were obtained, with quantitative conversion, 42% selectivity for 1,2-PDO and 25% selectivity for EG. Similarly, Besson *et al.* assessed a Ru/C catalyst for the hydrogenolysis of xylitol into 1,2-PDO and EG.⁵⁷¹ Addition of NaOH to the feedstock solution increased the conversion of XY without affecting much the selectivity. The catalyst had an outstanding stability (mild deactivation after roughly 1200 h TOS).

3. Upgrading of Furans

3.1. Furfural

3.1.1. Presentation, Producers and Markets

Furan-2-carbaldehyde (furfural, FU, CAS 98-01-1) is a major chemical building block obtained from the dehydration of xylose-rich feedstocks (mostly hemicellulose) and is often considered

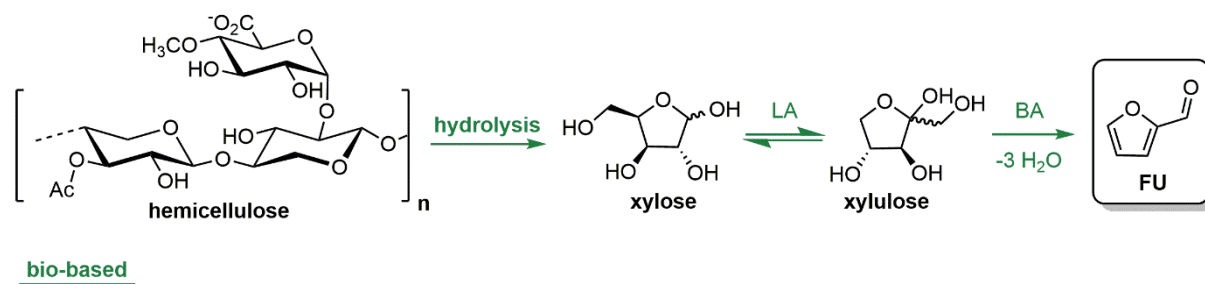
as one of the oldest bio-based chemicals.¹¹⁶ While FU was not formally part of the 2004 original list issued by the US Department of Energy, it was later included in the updated list (2010).⁴² FU was first isolated in 1821 (Döbereiner) and its first commercial production dates back to 1922 (Quaker Oats Company).¹¹⁶ FU's global market volume is expected to reach about 652,500 tons per year with an average price of \$1250-2100 per ton.^{116,117} The demand for FU is increasing steadily and China represents the largest market (*ca* 55% of the demand worldwide) through the applications of its main derivative, furfuryl alcohol.^{117,572} The EU is the second largest consumer (*ca* 15%) and its demand is expected to increase from about 50,000 tons per year (2015) to 200,000 tons per year in 2030. The main producers of FU are located in China (Tieling North Furfural Group and a myriad of other smaller companies), South Africa (Illovo Sugar Africa) and the Dominican Republic (Central Romana Corp). In Europe, major producers include Lenzing AG (Austria) and Tanin (Slovenia). While Central Romana remains the largest production facility worldwide (35,000 tons per year),⁵⁷³ Chempolis, Fortum and Numaligarh Revinery have announced the inception of a joint venture aiming at converting 300,000 tons per year of lignocellulosic biomass from bamboos in India. Operations are scheduled to begin in 2020.⁵⁷⁴

One of the most significant derivative of FU is furfuryl alcohol (85% of the global production), the largest production site of which is operated by TransFurans Chemicals (Belgium, 40,000 tons per year).^{117,573} FU can also be converted toward solvents such as 2-methyltetrahydrofuran, tetrahydrofuran and tetrahydrofurfuryl alcohol (7%) as well as other important chemicals (7%) including furan, methylfuran, cyclopentanone, 2,5-furandicarboxylic acid (FDCA), esters of levulinic acid and fuels.^{117,575,576}

3.1.2. Current Commercial Routes and Emerging Continuous Flow Alternatives

Current commercial routes. There is no commercial petro-based process toward FU and all current production routes rely on the dehydration of lignocellulosic biomass.⁵⁷⁷ Various process technologies are reported, including batch and continuous reactors. The preparation of FU begins with the hydrolysis of lignocellulose into xylose, followed by the dehydration of intermediate xylose.⁵⁷² It is suggested in the literature that the dehydration step involves first the isomerization of xylose into xylulose (typically catalyzed by Lewis acid sites), followed by the dehydration of xylulose into furfural (typically catalyzed by Brønsted acid sites, Scheme 16).^{578–581} There are two main types of commercial routes depending on the number of unitary process operations: (a) the one-step process, in which the hydrolysis and the dehydration occur simultaneously and (b) the two-step process, in which the hydrolysis and dehydration are separated.⁵⁷² Most commercial processes rely on sulfuric acid, although some commercial routes, such as the Supra Yield process, use phosphoric acid. FU is also obtained as a by-product during the production of ethanol from cellulose or from the paper industry.¹¹⁷

Scheme 16. General furfural formation pathway from hemicellulose. LA = Lewis acid, BA = Brønsted acid. Hemicellulose is illustrated here as xylan.



The further development of commercial routes toward FU is strongly encouraged by its non-competition with food resources and the wide diversity of chemicals obtained thereof.¹¹⁷ The current processes are however low yielding (~50%) and resource-consuming (large volumes of

sulfuric acid and energy), hence still feeding the need for the development of new processes.¹¹⁷ Several reports from the primary literature described the formation of furfural from sugars under continuous flow conditions, and these are detailed below. For instance, process conditions involving non-catalyzed thermal treatments in sub- and supercritical water,^{582–594} as well as acid-catalyzed reactions at moderate temperatures were reported.^{578–580,595–597}

Hydrothermal continuous flow processes. Studies describing the hydrothermal non-catalyzed conversion of hexoses reported very low yields for furfural. The investigations were however mostly dedicated to the elucidation of the different competitive reaction paths and various mechanisms involved in the degradation of sugars in hot compressed water. These studies did not aim at reaching high furfural yields, and some of the reports even lack of quantitative information for FU. Yet some authors managed to develop continuous flow systems of broader interest for process chemists, since they were compatible with the handling of slurries of cellulose under extreme temperature and pressure conditions.^{582,583,593,594}

Homogeneous and heterogeneous catalytic continuous flow processes. The continuous manufacturing of furfural requires the presence of water in the carbohydrate feedstock solution for solubility reasons. However, a higher selectivity for furfural is typically obtained upon utilization of an organic reaction medium. Additionally, heterogeneous catalysts are less prone to deactivation by leaching or by accumulation of organic matter on the active sites in the presence of an organic solvent.⁵⁷⁸ As a result, either (1) monophasic media comprising water and a polar organic solvent (typically γ -valerolactone or THF),^{579,580,595} or (2) biphasic systems consisting of water and a non-miscible solvent (typically *n*-BuOH, MIBK or toluene)^{578,596,597} were reported. The main asset of the biphasic medium is that furfural is continuously extracted in the organic phase as it forms in the aqueous phase. Side-reactions with water, with the carbohydrate substrate or with reaction intermediates occurring in the aqueous phase are thus

prevented.^{578,596,597} This methodology is also widely utilized for the analog continuous manufacturing of HMF from carbohydrates (see section 3.2.2).

For instance, Dumesic and coworkers studied the dehydration of xylose into furfural in a tubular continuous flow reactor, using superheated water/ γ -valerolactone as reaction medium and HCl as catalyst.⁵⁹⁵ Optimization of the reaction parameters revealed that the selectivity toward furfural did not critically rely on the temperature, the acid concentration or the acid nature. Most importantly, the selectivity toward furfural was also independent of the concentration in xylose. It was indeed demonstrated that high process temperatures inhibited the bimolecular condensation of xylose and furfural in the water/ γ -valerolactone reaction medium. It was therefore possible to process highly concentrated feedstock solutions (up to 10 wt% in xylose), yet giving furfural in about 90% conversion and 90% selectivity (process conditions: $T = 220$ °C, residence time = 96 s, 38 bar of counterpressure). Neira d'Angelo *et al.* described the use of H_2SO_4 as homogeneous catalyst for the continuous dehydration of xylose into furfural under biphasic conditions (toluene/water).⁵⁹⁶ Although increasing the temperature had a positive impact on the conversion of xylose, it also affected negatively the partition coefficient of furfural between toluene and water. The partition coefficient was indeed 4 at 20 °C, but only 1.4 at 190 °C. A conversion of 80% (based on xylose) and a selectivity of 70% toward furfural were obtained at 190 °C in less than 2.5 min of residence time. Process modelling suggested that utilizing other solvents with a higher extraction efficiency would further improve the selectivity toward furfural.

Gallo *et al.* also evaluated heterogeneous catalysts including niobia (Nb_2O_5) or niobia supported on silica (Nb_2O_5/SiO_2) for the continuous dehydration of xylose into furfural.⁵⁸⁰ Water or water/THF mixtures were studied as reaction media. The catalysts deactivated over operation time, but the authors demonstrated that Nb_2O_5/SiO_2 afforded longer steady-state operation in

comparison with the unsupported Nb oxide. Barbaro *et al.* developed a niobia-titania monolith and assessed the catalytic material for the continuous dehydration of xylose into furfural, using γ -valerolactone/water as reaction medium.⁵⁷⁹ The ratio between Lewis and Brønsted acid sites increased with the Nb content, so did the yield in furfural. 2,5-Anhydroxylulose, a reaction intermediate between xylulose and furfural, was detected in trace amounts in some reactor effluents. Up to 42% furfural yield was obtained at 140 °C and using a residence time of 141 s within the monolithic reactor. The stability of the catalyst was evaluated during a 29 h continuous run, and no deactivation or leaching could be evidenced. Pérez-Ramírez and coworkers prepared furfural from xylose or directly from hemicellulose in a continuous flow reactor.⁵⁷⁸ The setup involved a biphasic stream of water and an organic solvent, which was reacted through a packed-bed reactor (Figure 58). The packing material consisted of a physical mixture of two acid catalysts: (a) a Lewis acid catalyst based on a Ga-containing USY zeolite for triggering the isomerization of xylose into xylulose and (b) a Brønsted acid catalyst based on Amberlyst 36, for triggering the hydrolysis of hemicellulose and the dehydration of xylulose into furfural. Although some Ga leaching was evidenced, no performance loss was noticed during a 24 h run. Different organic solvents were assessed, and the performance increased following the order toluene < DCE < MIBK. Upon optimization, a yield of about 70% in furfural was obtained starting either from xylose or xylan. Xu *et al.* investigated the dehydration of xylose into furfural over a phosphoric acid-modified tantalum oxide catalyst in a biphasic water/organic solvent system.⁵⁹⁷ Batch optimization showed that better results were obtained with *n*-BuOH than with 2-BuOH, MIBK, isoamyl alcohol, MTBE or methyl isobutyl carbinol as organic solvents. Under optimized conditions, the batch process yielded 48% of furfural (160 °C, 3 h). Better results were obtained in flow, *i.e.* 59% yield in furfural (at 96% xylose

conversion) under operation at 180 °C and 20 bar of counterpressure. Most notably, stable results were obtained for 80 h TOS.

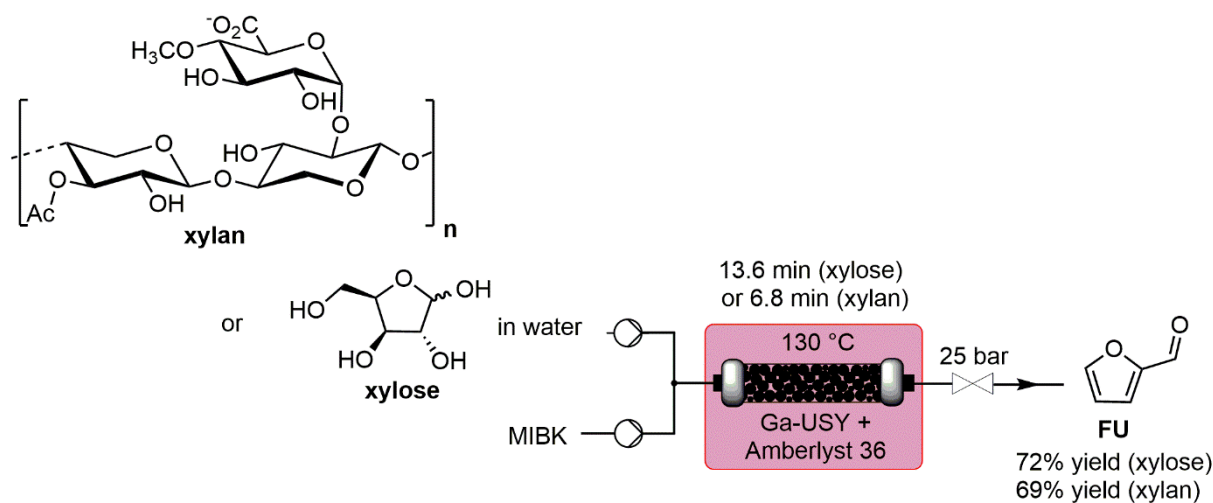


Figure 58. Continuous flow setup for the biphasic dehydration of sugars into furfural.⁵⁷⁸

3.1.3. Aldol and Related Condensation Reactions

α,β -Unsaturated ketones and aldehydes. Zhu *et al.* studied the aldol condensation of furfural with ketones under continuous flow conditions for producing C₈₋₁₆ alkane fuel precursors **91,92** (Figure 59).⁵⁹⁸ Various organic nitrogen-containing bases were screened in batch as homogeneous catalysts, and 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) gave the best results. Although no solvent was required for the reaction in batch, transposition under continuous flow conditions imposed a 1:1 methanol/water mixture as reaction medium. The flow conditions were more effective than the batch conditions, since the reaction time was significantly decreased from 2-24 h (batch) to 5-40 min (flow), yet affording the condensation products in 72-92% yield (Table 22). Additionally, the authors could decrease the excess of FU (from 2.5 to 2 equiv.) for the formation of the double condensation products **92** in flow. The catalyst was eliminated through off-line liquid-liquid extraction on the reactor effluents. The scope of the methodology was extended to single and double aldol condensation with acyclic symmetrical

and unsymmetrical ketones, as well as cyclic ketones (Table 22). Goulas and Gokhale studied the kinetics of the coupled dehydrogenation of butanol into butyraldehyde and its subsequent aldol condensation with furfural.⁵⁹⁹ The reaction was carried out in the gas phase using a fixed-bed reactor packed with Ni-MgO-Al₂O₃ as heterogeneous catalyst. The study demonstrated that both dehydrogenation and aldol condensation reactions were catalyzed by the basic sites of the catalyst.

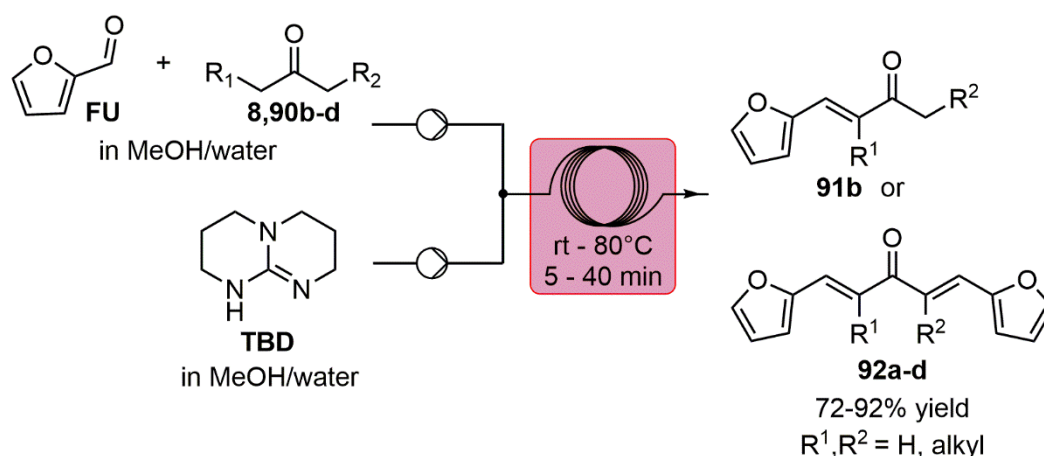
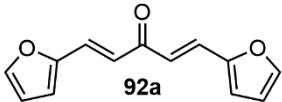
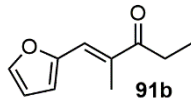
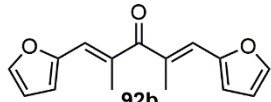
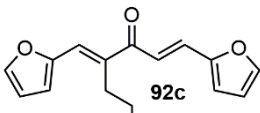
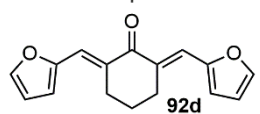


Figure 59. Continuous flow aldol condensation of furfural with ketones.⁵⁹⁸

Table 22. Comparison of representative results in batch and flow reported in ref ⁵⁹⁸ for the aldol condensation of furfural with various ketones.

Product	Temperature (°C)	Reactor	Reaction time (min)	Yield (%)
 92a	r.t.	batch	480	90
		flow	20	92
 91b	80	batch	240	92
		flow	20	91
 92b	80	batch	600	89
		flow	20	87
	80	batch	1400	80

 92c	flow	40	72
	batch	240	93
 92d	rt		
	flow	5	90

Other condensation products. Ha and coworkers studied the acid-catalyzed condensation of furfural with two equivalents of 2-methylfuran, yielding a C15 trimer with potential applications as a hydrocarbon fuel after further hydrodeoxygenation.⁶⁰⁰ The reaction took place in a fixed-bed continuous flow reactor packed with various catalysts based on supported phosphotungstic acid ($\text{H}_3\text{PW}_{12}\text{O}_{40}$). Silica-supported $\text{H}_3\text{PW}_{12}\text{O}_{40}$ improved the results by comparison to other supports, giving the C15 trimer in up to 43% yield.

3.1.4. Acetalization and Imination

2-(Furan-2-yl)-1,3-dioxolane. Uozumi and coworkers machined a microreactor setup featuring a polymeric catalytic membrane at the interface of two co-current laminar flow.⁶⁰¹ The membrane was prepared from the reaction of poly(4-styrenesulfonic acid) with poly(4-vinylpyridine). The system was able to drive an acetalization reaction to completion, as water and the acetal products were separated by the membrane within the microfluidic reactor, thus shifting the equilibrium toward the formation of the acetalization products (Figure 60). The methodology was successfully applied to a library of carbonyl derivatives including furfural, which was transformed into the corresponding 1,3-dioxolane **93** upon reaction with ethylene glycol. A short residence time (38 s) and a moderate process temperature (80 °C) enabled the synthesis of the target compound in high yield (86%).

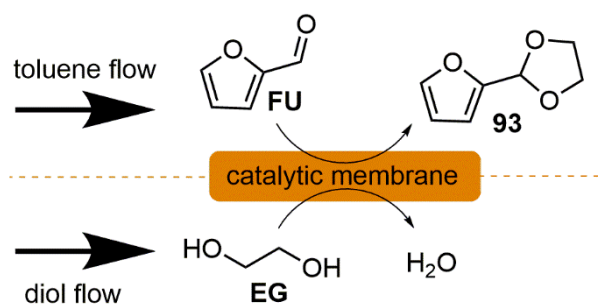


Figure 60. Schematic representation of Uozumi's catalytic membrane-based microreactor applied to the acetalization of ethylene glycol with furfural.⁶⁰¹

1-(Furan-2-yl)-*N*-propylmethanimine and **1-(furan-2-yl)-*N*-phenylmethanimine**. The continuous flow imination of aldehydes was also reported, and the methodology was notably applied to furfural that was coupled with either aniline or *n*-propylamine.⁶⁰² However, only moderate yields (45-46%) were reported due to the occurrence of polymerization side-reactions.

3.1.5. Amidation and Esterification

Furan-2-carboxamide. Wirth and colleagues developed a continuous flow process that enabled the conversion of aldehydes into amides using hydroxylamine hydrochloride and cesium carbonate under extreme process conditions (250 °C, 200 bar).⁶⁰³ Furfural was included in the substrate scope, and the corresponding amide **94** was prepared in 97% yield (Figure 61).

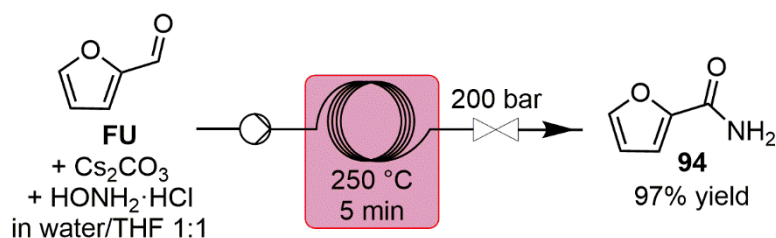


Figure 61. Continuous flow amidation of furfural.⁶⁰³

Furan-2-yl(pyrrolidin-1-yl)methanone and **butyl furan-2-carboxylate**. Massi *et al.*

described a procedure for the amidation and esterification of furfural under oxidative heterogeneous NHC-catalysis condition.⁶⁰⁴ The NHC was generated *in situ* from a polymer-supported triazolium salt precatalyst that reacted with DBU as homogeneous base. Although a combination of oxygen and iron(II) phthalocyanine could serve as oxidant system under batch conditions, tetra-*tert*-butyldiphenoquinone (**40**) was preferred under continuous flow conditions. The methodology was successfully exemplified with *n*-butanol or pyrrolidine as nucleophiles (Figure 62).

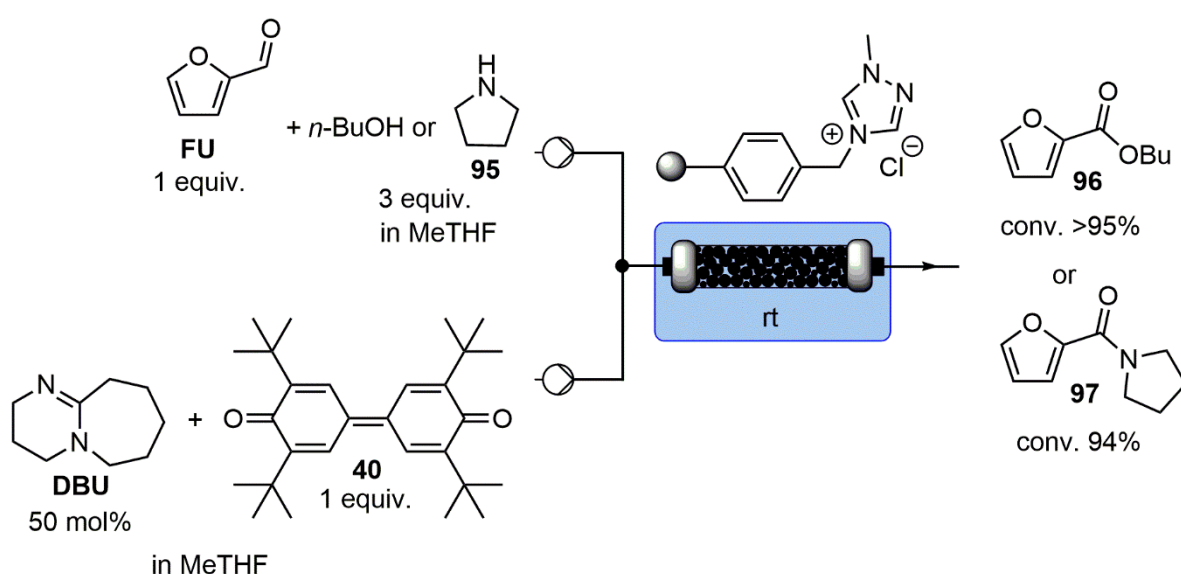


Figure 62. Oxidative esterification/amidation of furfural using heterogeneous NHC-catalysis.⁶⁰⁴

3.1.6. Oxidation into Maleic Anhydride

Maleic anhydride (**98**) is an important building block in the polymer industry, and is currently produced by the catalytic oxidation of benzene or C4-hydrocarbons.⁶⁰⁵ Various studies reported the direct oxidation of furfural into maleic anhydride under aerobic gas-phase continuous flow conditions, and using vanadium oxides as heterogeneous catalysts.^{606–609} In a preliminary report, Ojeda and coworkers reported $\text{VO}_x/\text{Al}_2\text{O}_3$ as an efficient heterogeneous catalyst for the

oxidation of furfural in the presence of O_2/He .⁶⁰⁶ The mechanism likely involved an oxidative decarboxylation of furfural into furan, followed by an oxidation toward furanone, and eventually its oxidation toward maleic anhydride. Stable operation for 12 h was reported under ambient pressure at 320 °C, providing up to 73% selectivity for maleic anhydride (quantitative conversion). In a follow-up paper, the authors further improved the robustness of the process.⁶⁰⁷ A longer catalytic stability was maintained at high temperature and high O_2 /furfural ratios. The rationalization of this observation relied on the inherent features of the Mars and van Krevelen mechanism. Upon reaction with furfural, the V(V) sites of the catalyst are reduced as furfural is oxidized, and then are oxidized back to the +V oxidation state by the stream of molecular oxygen. Accordingly, if mild oxidizing conditions are applied, the reoxidation toward the catalytically active +V state is inefficient, thus precluding further oxidation of furfural and triggering the formation of side-products. At excessive process temperatures (> 330 °C), however, furfural was decomposed mainly into carbon dioxide. A recent study confirmed that alumina stands as the best support for the vanadia active phase, by comparison with SiO_2 , TiO_2 and ZrO_2 supports.⁶⁰⁹ The performance of V_2O_5/Al_2O_3 was attributed to the higher dispersion of vanadium on the support. The most advanced results were reported by Zhang and colleagues.⁶⁰⁸ The authors utilized vanadium phosphorous oxide (VPO) as a heterogeneous catalytic material. A stable catalytic activity was maintained for 25 h of operation at 350 °C, with only a slight decrease in selectivity (from 95 to 90%) and an increase in conversion (from 92 to 99%) (Figure 63). Pure solid maleic anhydride was recovered by condensation downstream the reactor. Characterization of the catalyst after the prolonged run did not reveal any coking or structural modification.

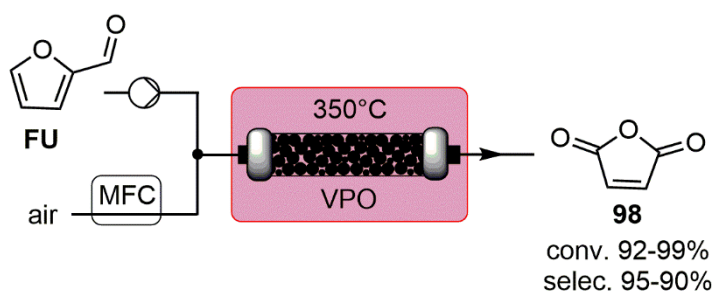
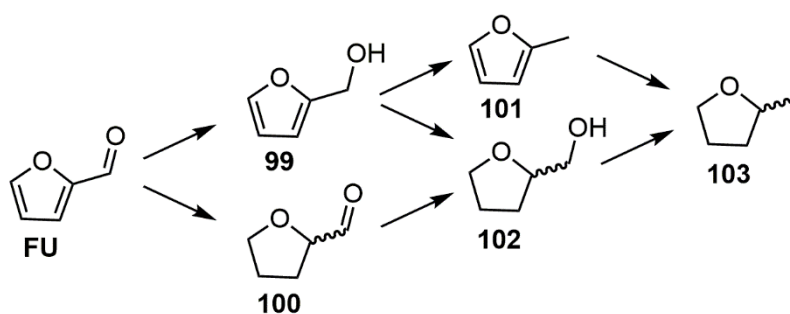


Figure 63. Gas-phase aerobic oxidation of furfural into maleic anhydride using vanadium phosphorous oxide (VPO) as a heterogeneous catalyst.⁶⁰⁸

3.1.7. Reduction into (tetrahydro)furfuryl alcohol and 2-Methyl(tetrahydro)furan

Furfuryl alcohol and ether derivatives. The main application of furfuryl alcohol (**99**) is rooted in the production of foundry sand binders, but it also has applications for the preparation of corrosion-resistant mortars and plastics, for wood protection, as well as in paint strippers.⁶¹⁰ Furfuryl alcohol is readily produced at the industrial level from the gas-phase reduction of furfural with hydrogen over Cu-based catalysts.⁶¹⁰ Nevertheless, numerous recent reports in the primary literature were still devoted to the development of new catalysts for the gas-phase reduction of furfural into furfuryl alcohol in the presence of hydrogen.^{611–647} The main challenge of this reaction is related to the activity of the catalyst, which has to be finely tuned to only reduce the aldehyde moiety of furfural. Catalytic sites endowed with an overly high reducing ability are also prone to further reduce furfuryl alcohol (**99**) into 2-methylfuran (**101**), tetrahydrofurfuryl alcohol (**102**) and 2-methyltetrahydrofuran (**103**) (Scheme 17), as well as many other undesired compounds resulting from ring-opening.

Scheme 17. Reaction pathways involved in the reduction of furfural. Products resulting from ring-opening are omitted for clarity.



Mild metal catalysts based on supported copper^{611–623,626,629,630,634,637,639,640,642–647} or cobalt⁶³⁸ are typically reported in the literature, while highly reactive hydrogenation catalysts such as supported Ni,^{624,625,636} Pd,^{631,632,641} Pt,^{627,633,635} and Ru⁶²⁸ are in general avoided. Several authors demonstrated that the performance of copper catalysts is generally enhanced if they are characterized by both (1) a strong interaction between metallic copper and the support^{612,616} and (2) the presence of small copper particles (resulting in a high metal dispersion and thus a high metal surface area).^{612,615–617,620,634,639,640} It was reported that both Cu⁺ and Cu⁰ are the active sites in such catalysts,⁶⁴² but others refuted this hypothesis and described metallic copper as the only active phase.⁶³⁰ Copper catalysts suffered from accumulation of organic matter on the active sites/coking as the main deactivation mechanism,^{612,613,615,617,618,621–623,630,639,640} but Cu sintering^{613,615,617,626} and oxidation^{612,613,623} were also reported to a lesser extent.

The most relevant catalysts and process conditions for the hydrogen-mediated gas-phase reduction are summarized in Table 23. Typical conditions involve mixing neat furfural and molecular hydrogen, and reacting the mixture in a heated (170–200 °C) catalytic bed under atmospheric pressure (Figure 64).

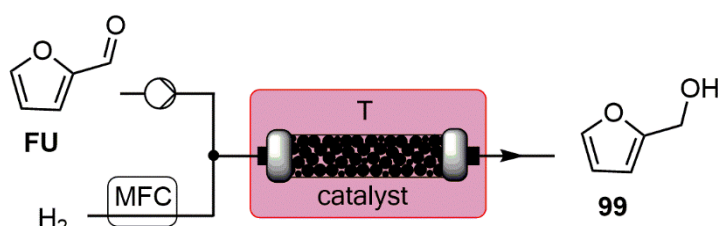


Figure 64. General flow scheme for the reduction of furfural with molecular hydrogen toward furfuryl alcohol.

Table 23. Catalysts and optimized conditions for the gas-phase H₂-mediated reduction of furfural toward furfuryl alcohol.

Entry	Catalyst	T (°C)	Space velocity	TOS (h)	Conv. (%)	Selec. (%)	Ref.
1 ^a	Co/SiO ₂	150	– ^b	1-3	>99	92	638
2	Co-Cu/SiO ₂	225	WHSV = 0.064 mol h ⁻¹ g ⁻¹	1-12	>99	85	611
3 ^c	Cu/bentonite	210	WHSV = 1.5 h ⁻¹	1-5	90-83	85-87	612
4 ^c	Cu/CeO ₂	190	WHSV = 1.5 h ⁻¹	1-5	89-83	45-82	623
5	Cu/MgO	180	GHSV = 0.05 mol h ⁻¹ g ⁻¹	1-5	98	98	634,642
6 ^d	Cu-MgO	180	WHSV = 1.7 h ⁻¹	1-10	95-70	94-96	643–645
7	Cu/SiO ₂	270	W/F = 41.3 g h mol ⁻¹	0.25	77	92	646,647
8 ^c	Cu/SBA-15	170	W/F = 65 g h mol ⁻¹	1-5	>99-54	90-97	613
9 ^e	Cu/TiO ₂ -SiO ₂	180	WHSV = 1.0 h ⁻¹	– ^b	97	96	614
10 ^c	Cu/ZnO	190	WHSV = 1.5 h ⁻¹	1-24	95-60	56-98	615
11	Cu-Ca/SiO ₂	130	LHSV = 0.33 h ⁻¹	5-80	>99	98	616
12 ^c	CuCe/(kerolite+Mg-smectite)	190	WHSV = 1.5 h ⁻¹	1-5	95-81	92-99	617
13 ^f	CuO-CeO ₂ /Al ₂ O ₃	175	W/F = 60 g h mol ⁻¹	1-6	65-78 ^g		618
14	Cu-Co/MgO	180	WHSV = 1.7 h ⁻¹	1-4	83-75	93-97	619
15	Cu-Cr/TiO ₂	180	WHSV = 1.7 h ⁻¹	1-4	85-70	95	620
16	CuCrO/TiO ₂	140	– ^b	0.5	90	88	621
17	CuFe/Al ₂ O ₃	175	LHSV = 1 h ⁻¹	4-24	94-90	98	626
18 ^h	CuFeAl	160	LHSV = 2 h ⁻¹	1-75	>99-90% ^g		639
19	Cu-La/MCM-41	140	GHSV = 0.087 mol h ⁻¹ g ⁻¹	1	98	>99	622
20	Ni-Co-Al	155	– ^b	1	98	72	624
21 ^c	Ni ₃ N/C/SiO ₂	170	WHSV = 6 h ⁻¹	1-5	96-86	46-57	636
22	Ni ₃ Sn ₂ -Al ₂ O ₃	280	WHSV = 0.5 h ⁻¹	1-10	74-50	50-65	625
23	Pt/TiO ₂ -V ₂ O ₅ /SiO ₂	150	LHSV = 2 h ⁻¹	0.5	87	91	627
24 ^{h,i}	Ru/C	90	W/F = 56 g h mol ⁻¹	0.3-4 h	>98-85	85	628

^aP = 60 bar, Solvent = EtOH. ^bUnclear. ^cSolvent = Cyclopentyl methyl ether. ^dN₂ was used as diluent for H₂. ^eP = 10 bar. ^fP =

5 bar. ^gYield. ^hP = 50 bar. ⁱsolvent = AcOEt.

De Oliveira Vigier *et al.* compared batch and flow reactors for the reduction of FU over Co/SiO₂.⁶³⁸ They reported that catalyst stability issues encountered in batch – related to coke accumulation - could be overcome with flow reactors. It was proposed that the lower contact time between the organics and the catalyst in flow prevented accumulation of furanic compounds on its surface, and thus coke formation. Despite a higher yield (>99%) in batch by comparison to flow (92%, Table 23, entry 1), the space time yield was almost 3-fold higher in flow (13.2 and 30.6 g L⁻¹ h⁻¹ in batch and flow under optimized conditions, respectively). Copper supported on ceria was assessed during a 5 h run and showed initially poor selectivity toward furfuryl alcohol (45%), as overhydrogenation toward 2-methylfuran occurred.⁶²³ However, the selectivity increased after a prolonged operation time (up to 82%), as a consequence of the deactivation of the active sites endowed with a strong reducing ability, due to coking and water-mediated oxidation (entry 4). A similar behavior was reported with Cu/ZnO, where a similar increase of the selectivity from 56 to 98% was noticed after a long operation time (24 h, entry 10).⁶¹⁵ Copper supported on magnesia (MgO) gave excellent results (98% conversion, 98% selectivity, entry 5).^{634,642} Hydrogenation of the furan ring was observed only at process temperatures higher than 180 °C, thus affecting the selectivity toward furfuryl alcohol. Similarly, Ghashghaee *et al.* evaluated Cu-MgO as a heterogeneous catalyst, and high selectivity (94-96%) and conversion (95-70%) were obtained during a 10 h run (entry 6).⁶⁴³ Mechanistic studies using computational chemistry indicated that the reduction of the carbonyl moiety most likely involved a homolytic mechanism with the addition of H radical to the sp² carbon of the aldehyde, followed with the transfer of another H radical toward the newly formed O-centered radical. The intermediate alkoxide radical was indeed depicted as more stable than the intermediate hydroxyalkyl radical counterpart (Figure 65a). Resasco and colleagues

1
2
3 assessed Cu supported on SiO₂, and complemented their empirical results with a computational
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5 study (entry 7).^{646,647} The results from this work contradicted somehow Ghashghaee's study
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7 (see above). Here, the DFT computations indicated that the first step of the reduction
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9 mechanism involved first a radical reaction at the sp² oxygen of the carbonyl moiety, followed
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11 with an additional radical addition on the newly created C-centered radical, as the intermediate
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13 hydroxylalkyl radical was stabilized by the aromatic furanyl ring. Repulsion between the copper
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15 surface and the furanyl ring was also evidenced, and accounted for the absence of di- or
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17 tetrahydrofuran products in the reactor effluents. It was proposed that furfural binds the copper
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19 active sites in a $\eta^1(\text{O})$ -aldehyde configuration (Figure 65b).
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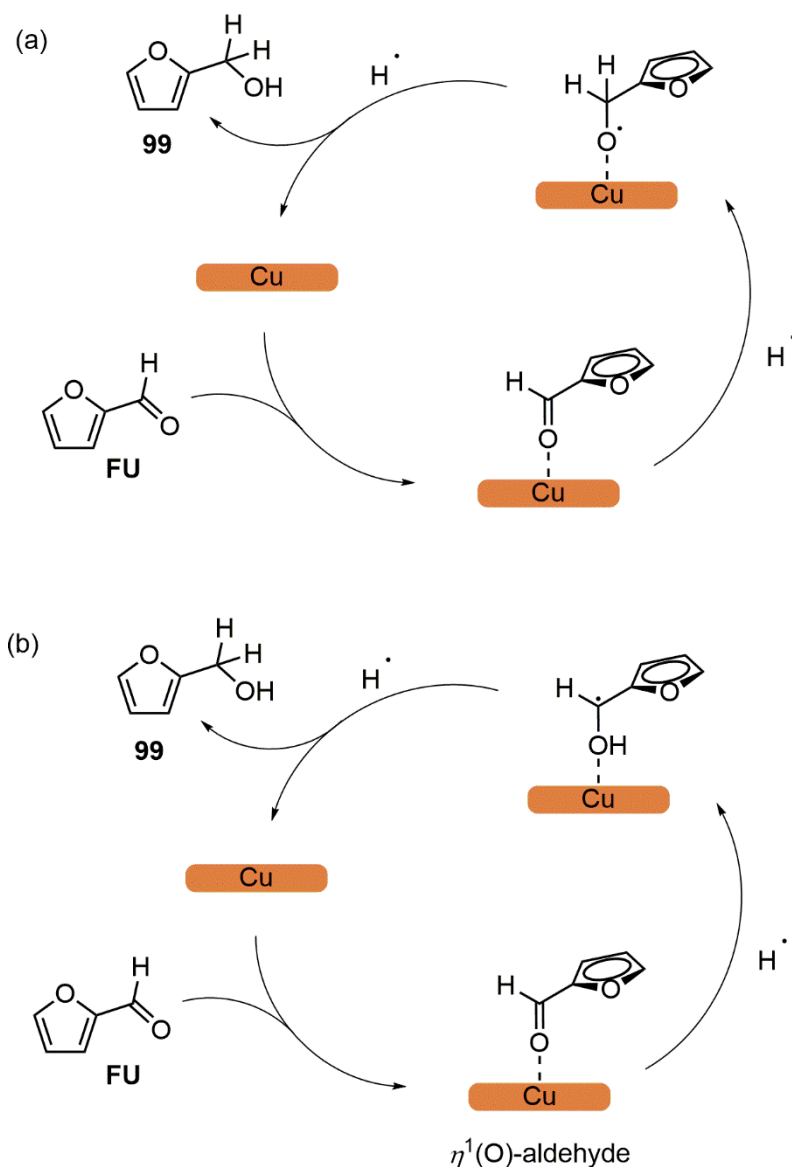


Figure 65. Proposed catalytic cycles for the reduction of furfural into furfuryl alcohol over Cu involving (a) an alkoxide radical intermediate⁶⁴³ or (b) a hydroxyalkyl radical intermediate.^{646,647}

The most advanced results were most likely reported fifteen years ago by Wu *et al.* over a Cu-Ca/SiO₂ catalyst.⁶¹⁶ The catalyst gave quantitative conversion and 98% selectivity for up to 80 h operation, without any deactivation and operating at a low process temperature (130 °C). Ca promotion enhanced the dispersion of copper, and strengthened the catalyst toward deactivation

by sintering (entry 11). A similar strategy was considered by Liu and coworkers, who doped a Cu/MCM-41 catalyst with La.⁶²² As a result, excellent conversion (98%) and selectivity (>99%) were obtained after 1 h of operation, probably because of the high electron-donating ability of La, which increased basicity and favored C=O hydrogenation (entry 19). However, after 8 h TOS, the catalyst lost 32% of its activity. The deactivation behavior was related to catalyst coking, resulting in the blockage of the zeolite channels and of the active sites. Raja and colleagues prepared and evaluated bimetallic FeCu supported on alumina as catalyst.⁶²⁶ Excellent conversion (94-90%) and selectivity (98%) were maintained for 24 h, by opposition to the pure monometallic Cu/Al₂O₃ counterpart that gave lower conversion (60-45%) and selectivity (90-75%), and underwent rapid deactivation (entry 17). A synergistic effect between Fe and Cu accounted for these enhanced results: Fe is strongly oxophilic, and therefore prone to interact with the sp² oxygen of the carbonyl moiety of the substrate, while Cu is highly performant for the activation of H₂. In addition, the incorporation of Fe inhibited Cu sintering for prolonged runs, thus providing longer operational stability than the monometallic catalyst. Similarly, excellent results were reported over a catalyst consisting of copper nanoparticles (2-5 nm) formed on the surface of Cu(FeAl)O_x spinel.^{639,640} >99-90% yield was maintained during a 75 h run at a rather mild temperature (160 °C, entry 18).⁶³⁹ However, the low temperature was balanced by 50 bar of H₂. CuO-CeO₂/Al₂O₃ gave 65-78% yield during a 6 h run (entry 13).⁶¹⁸ It was demonstrated that a 5 bar counterpressure was critical for improving the yield in furfuryl alcohol (**99**) and the stability of the catalyst. Dimerization of furfuryl alcohol into difurfuryl ether catalyzed by acidic sites was the main degradation pathway. Peter and coworkers assessed Ni_xSn_y nanoparticles dispersed onto alumina.⁶²⁵ The non-active Sn modulated the reactivity of Ni, which otherwise comes with an excessive reducing ability. Ni₃Sn₂-Al₂O₃ gave the best catalytic results (entry 22), while pure Ni gave quantitative conversion but only 8% selectivity

for **99**. Further insight on the reaction mechanism was obtained through DFT computations: the Ni surface has a high furfural adsorption energy (65 kJ/mol), while Ni_xSn_y phases all had an adsorption energy below 30 kJ/mol. This weaker adsorption allows shortening the residence time of the reactant at the vicinity of the catalyst surface thereby limiting over-reduction. Additionally, the angle between the furfural plane and the catalytic Ni_3Sn_2 surface (29.6°) allowed to minimize side-reactions resulting from ring saturation and opening. On the contrary, on a surface of pure Ni, the furfural plane was parallel to the catalytic surface, hence resulting in unselective transformations. Pt deposited on different inorganic supports (SiO_2 , TiO_2 , MgO , Al_2O_3) functionalized with one or two monolayers of transition metal oxides (V_2O_5 , ZrO_2 , TiO_2) were also assessed.⁶²⁷ Silica and titania gave the best results, while electron-deficient supports such as alumina led to strong interactions between furfural and the catalyst, thus triggering unselective reactions. On the other side, electron-rich supports such as MgO increased the repulsion between furfural and the catalyst, thus resulting in poor conversions. The performance of transition metal oxide monolayers followed the order: $\text{TiO}_2 > \text{ZrO}_2 > \text{V}_2\text{O}_5$, which is also the order of electronegativity difference between Pt and the metal from the oxide monolayer. Therefore, a strong polarization of the surface seemed to be beneficial to the catalytic performance. The best results were obtained with the two transition metal oxide monolayer based catalyst $\text{Pt/TiO}_2\text{-V}_2\text{O}_5/\text{SiO}_2$ (entry 23). Luque and coworkers assessed Ru/C in a commercial H-Cube Mini continuous flow reactor (ThalesNano), and a 85% selectivity for **99** was obtained at only 90 °C.⁶²⁸ After 20 min of operation, conversion was high (>98%) but it decreased to 85% after 4 h. Ru sintering was incriminated as the source of deactivation (entry 24).

Alcohols were also studied as alternative hydrogen-donors for the continuous reduction of furfural into furfuryl alcohol (Figure 66). Catalysts based on metallic copper,^{648–651} metallic

palladium,⁶⁵² basic oxides,⁶⁵³ and acidic zeolites^{654–656} were reported. The most relevant catalysts, alcohols and optimized conditions used in these studies are reported in Table 24. In some cases, a cascade process triggered by a single catalyst was developed, where alcohols served both as reducing agents and as coupling partners with furfuryl alcohol toward alkoxyethylfurans.^{654,655} These furfuryl-derived ethers have a bright forecast as fuel and fuel additives.

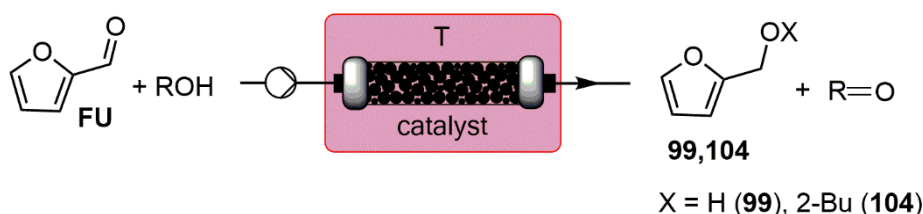


Figure 66. General flow scheme for the reduction of furfural into furfuryl alcohol and ethers thereof, using alcohols as H-sources.

Table 24. Catalysts, alcohols and optimized conditions for the molecular hydrogen-free reduction of furfural into furfuryl alcohol and ether derivatives.

Entry	Catalyst	Alcohol	T (°C)	Space velocity	Product	TOS (h)	Conv. (%)	Selec. (%)	Ref.
1	Cu-Cr-MgO	CyOH	200	- ^a	99	6	72	>99	648
2	Cu-MgO-Cr ₂ O ₃	CyOH	200	- ^a	99	6	88	>99	649
3 ^b	Cu/AlO _x	1,4-BDO	220	res. time = 0.65 min	99	- ^a	99 ^c		650
4 ^d	Cu/CaAlO	1,4-BDO	210	LHSV = 1.8 h ⁻¹	99	1-100	96	>99	651
5 ^d	MgO-C	<i>i</i> PrOH	180	- ^a	99	1-12	>99-95	98	653
6 ^e	Pd/Fe ₂ O ₃	<i>i</i> PrOH	180	res. time = 5 min	99	1	81	70	652
7 ^f	[2Sn,0.5Al]-β	2-BuOH	120	- ^a	104	1-80	- ^a	70-87	654,655

^aUnclear. ^bP = 16 bar. ^cYield. ^dN₂ was used as carrier gas. ^eP = 25 bar. ^fP = 10 bar.

Cu-MgO catalysts doped with various metals (Zn, Ni, Co, Fe, Cr and Pd) were assessed using

cyclohexanol as H-donor (thus leading to cyclohexanone as by-product).⁶⁴⁸ The best results were obtained with the Cr-doped material (72% conversion, >99% selectivity, Table 24, entry 1). Cr-doping induced the stabilization of Cu^+/Cu^0 species, improved the reducibility of copper oxide and led to a higher dispersion of copper on the MgO support, hence accounting for improved performance.^{648,649} Additionally, it was demonstrated that conducting furfural hydrogenation and cyclohexanol dehydrogenation in a single process enhanced both reactions. Indeed, furfural hydrogenation is exothermic, and cyclohexanol dehydrogenation is endothermic and equilibrium-limited. Higher conversions were obtained when both reactions were conducted simultaneously, by comparison to segregated processes. Hermans and colleagues assessed copper nanoparticles dispersed on AlO_x with 1,4-butanediol as H-donor.⁶⁵⁰ Quantitative yield was obtained within 0.65 min residence time in the catalytic bed operated at 220 °C. γ -Butyrolactone was generated through 1,4-BDO lactonization (entry 3). Li and coworkers assessed bifunctional base-metal catalysts such as copper supported on mixed Ca-Al oxides and also used 1,4-butanediol as hydrogen-donor.⁶⁵¹ The uptake of hydrogen through the reduction of furfural shifted the equilibrium toward the formation of γ -butyrolactone as well. The dehydrogenation of 1,4-BDO involved a synergistic interaction between strong Lewis basic sites with the hydroxyl protons and between defective copper nanoparticles with the vicinal C-H protons. The presence of Cu^+ species was also reported as beneficial for the reduction of the aldehyde of furfural. As a result, quantitative conversion and 96% furfural conversion were maintained for up to 100 h TOS (entry 4). Carbon-MgO was also assessed as a heterogeneous catalyst.⁶⁵³ Rice grains were used as the carbon source, thus maximizing the cost-efficiency for this catalytic system. The best catalyst contained 32 wt% MgO, and its high activity and selectivity was related to the high concentration of basic sites, but also to its low particle size. Very high conversion (>99-95%, based on furfural) and selectivity toward furfuryl

alcohol (98%) were maintained for 12 h of operation. In this example, isopropanol (*i*PrOH) served as H-donor, leading to the generation of acetone as by-product (entry 5). Hermans *et al.* evaluated Cu-, Ni- and Pd-loaded Fe₂O₃ catalysts in batch and continuous flow mode.⁶⁵² Cu- and Ni-based catalysts were highly selective toward furfuryl alcohol, while Pd/Fe₂O₃ produced furfuryl alcohol, 2-methylfuran, furan and a variety of tetrahydrofuran products. The enhanced hydrogenation/hydrogenolysis activity of the palladium catalyst was ascribed to the strong metal-support interaction. It was demonstrated that secondary alcohols, such as isopropanol, were better H-donors than primary alcohols. Under continuous flow operation, it was possible to finely tune the selectivity either for furfuryl alcohol or 2-methylfuran (see Table 26, entry 4), by altering the residence time (Table 24, entry 6). Sn- and Al-containing β -zeolite was assessed as bifunctional Lewis and Brønsted acidic catalyst by Hammond and coworkers, and gave excellent results for the cascade reduction/etherification into (2-butoxy)methylfuran (**104**).^{654,655} It was demonstrated that purely Lewis acidic catalysts triggered the cascade reaction, but their limited stability and activity reduced their competitiveness. By contrast, physical mixtures of Brønsted acidic and Lewis acidic catalysts gave good catalytic performance, but deactivated faster than a single bifunctional Lewis-Brønsted acid catalyst. For instance, the bifunctional Sn- and Al-containing β zeolite was described as a very promising catalyst, achieving 70-87% selectivity toward **104** (entry 7). After about 2300 turnovers, the main deactivation mechanism was identified as fouling of the micropores, and the catalyst could thus be fully regenerated by aerobic calcination at 550 °C. Therefore, the catalyst was able to maintain its selectivity toward **104** for about 3000 turnovers (107 h time-on-stream) with a single regeneration.

Recently, Noël reported an electrocatalytic continuous flow procedure for the reduction of furfural into furfuryl alcohol, using copper as working electrode and graphite as counter

electrode (Figure 67).¹¹³ The high surface-to-volume ratio of the electrodes and the short diffusion path within the reactor afforded better results in flow, by comparison to a batch setup. The flow procedure gave 90% yield within 10 min of reaction, at high faradaic efficiency (90%). By comparison, the batch setup yielded 31% of furfuryl alcohol after 5 h of reaction and at 60% faradaic efficiency, resulting overall in a space-time yield lower by 3 orders of magnitude (Table 1). The yield dropped slightly from 90 to 87% after 1 h of continuous operation, but the activity could be restored by intermediate flushing of the electrodes. Huber described an analog electrocatalytic continuous flow process, where Pd/C was used as cathode catalyst.⁶⁵⁷ High selectivity for furfuryl alcohol (70-99%) was obtained at low voltages, thus corresponding to a low furfural conversion (1-5%).

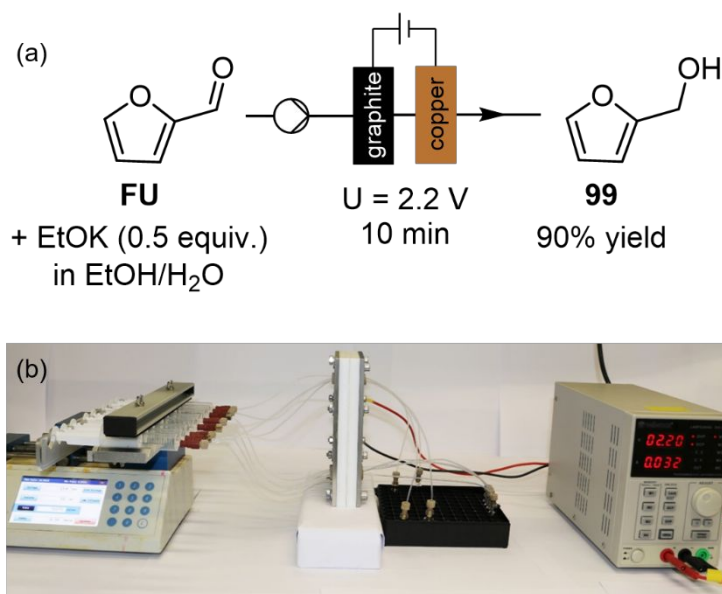


Figure 67. (a) Schematic representation of Noël's electrocatalytic continuous flow procedure for the reduction of furfural into furfuryl alcohol.¹¹³ (b) Photograph of the setup utilized. Reproduced with permission from ref 113. Copyright 2019 American Chemical Society.

2-Methylfuran. 2-Methylfuran (**101**) has received considerable attention as a potential biofuel. By comparison to bioethanol, it is not water-miscible and has a higher energy density (28.5 vs

21 MJ/L). The production of 2-methylfuran for fuel applications is however not yet commercially viable.^{658,659} The preparation of 2-methylfuran from furfural and hydrogen in fixed-bed reactors, using various metal-based heterogeneous catalysts, was extensively studied. A typical procedure involves neat furfural that is reacted with hydrogen in the gas-phase at atmospheric pressure over the catalytic bed (Figure 68). Advanced catalytic systems are required for the reaction to proceed in high selectivity: the catalyst has to selectively trigger C=O reduction and C-O cleavage over C=C reduction and C-C cleavage (Scheme 17). Active sites with a stronger reducing ability than those utilized for the reduction of furfural into furfuryl alcohol were described. For instance, catalytic materials based on Co,⁶⁶⁰ Cu,^{629,637,661} Mo₂C,^{662–664} Ni,^{665–667} Pd,^{628,631,668,669} Pt,^{670–672} or on alloys of various metals⁶⁷³ were reported to be selective for the reaction (Table 25). Similarly to catalysts reported for the reduction of FU toward furfuryl alcohol, accumulation of organic matter on the active sites/coking accounted for the main deactivation mechanism.^{661,663,664,667,672,673} Deactivation by change in the oxidation state or sintering of the metallic active phase were also reported in some instances.^{628,661} In general, the deactivation of the catalysts resulted in a decrease in the selectivity for 2-methylfuran, but led also to an increase in the selectivity for furfuryl alcohol.^{628,661,673} Such empirical observation is consistent with the reaction pathways described on Scheme 17. Furan was also commonly observed as a side-product of the reaction, especially on Pd or Ni catalyst (see also section 3.1.8).^{631,660,662,665–669,671–673}

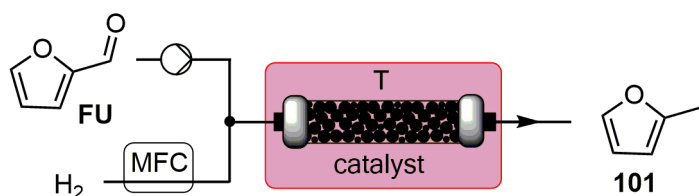


Figure 68. General flow scheme for the hydrogenolysis of furfural into 2-methylfuran using H₂

as the reductant.

Table 25. Representative catalysts and conditions for the gas-phase H₂-mediated reduction and hydrogenolysis of furfural into 2-methylfuran.

Entry	Catalyst	T (°C)	Space velocity	TOS (h)	Conv. (%)	Selec. (%)	Ref.
1	Co-Fe-Al	180	W/F = 10.9 g h mol ⁻¹	0.7	90	67	660
2	Cu-Al-Co	240	W/F = 3.4 g h mol ⁻¹	1-5	65-40 ^a		673
3 ^b	Cu/SiO ₂	210	W/F = 130 g h mol ⁻¹	1-24	>99-90	>99-48	661
4	Co/Mo ₂ C	250	W/F = 10 g s mL ⁻¹	1-17	97-35	92-50	662
5	Mo ₂ C	150	- ^c	2-5.5	68-10	81-65	663,664
6 ^d	Ni-Fe/C	180	W/F = 2 g min mL _{solution} ⁻¹	2	98	88	665
7	Ni-Fe/SiO ₂	250	W/F = 0.1 h	- ^c	96	41	666
8 ^b	Ni ₂ P/SiO ₂	190	W/F = 65 g h mol ⁻¹	1-5	>99-88	75-82	667
9 ^e	Pd/C	90	W/F = 56 g h mol ⁻¹	0.3-2	>99-80	75-18	628
10	Pd-Fe/SiO ₂	250	W/F = 0.1 h	- ^c	95	60	668
11 ^{b,f}	Pt/C	150	WHSV = 27 h ⁻¹	0.7-2.7	92-91	83-71	670
12 ^d	Pt/C	180	WF = 0.6 g min mL _{solution} ⁻¹	- ^c	41 ^a		671
13 ^g	Fe-Pt/SiO ₂	300	WHSV = 0.33 h ⁻¹	0.3-4 h	84-28	52-48	672

^aYield. ^bSolvent = cyclopentyl methyl ether. ^cUnclear. ^dP = 33 bar, solvent = *i*PrOH. ^eP = 50 bar, solvent = AcOEt. ^fP = 50 bar, WHSV is relative to the mass of metal in the catalyst. ^gDiluted H₂ was used as the carrier gas.

Jiao and coworkers described a self-supported nanoporous Cu-Al-Co alloy as catalyst.⁶⁷³ The addition of oxophilic elements, such as Al and Co, to Cu enabled higher hydrogenolysis activity by comparison to other purely Cu-based systems. However, the yield in 2-methylfuran dropped from 65 to 40 % after 5 hour of continuous operation (Table 25, entry 2). Maireles-Torres and coworkers evaluated copper supported on silica as a heterogeneous catalyst (entry 3).⁶⁶¹ Coke deposition accounted for the main deactivation mechanism at low copper loading, while sintering was additionally observed at high copper loading. With the best performing catalyst and during a 24 h run, the conversion slightly decreased from quantitative to 90%, but the

selectivity toward 2-methylfuran significantly dropped from quantitative to 48%. In a contribution from Chen and Bhan, DFT calculations, surface vibrational spectroscopy and temperature programmed desorption (TPD) identified molybdenum carbide as a promising precious metal-free heterogeneous catalyst, which was then experimentally evaluated in a fixed-bed flow reactor.⁶⁶³ The material exhibited enhanced selectivity toward C-O cleavage without triggering ring-opening or decarbonylation. Unfortunately, rapid deactivation occurred (entry 5). Yet, the procedure is interesting from an economic standpoint in the sense that a low process temperature was utilized (150 °C). Further experiments evidenced that, on such Mo₂C catalyst, (1) the hydrogenolysis reaction occurs on metal-like sites and (2) two distinct active sites are necessary for the reaction to occur.⁶⁶⁴ In a follow-up paper, molybdenum carbide was doped with cobalt to enhance the hydrogenolysis activity.⁶⁶² By comparison to the non-modified catalyst, DFT calculations and experiments evidenced both a higher stability and an enhanced formation of 2-methylfuran for the Co-doped material. The weaker binding of both furfural and oxygen to the catalytic material, resulting in an easier clearance of the catalytic surface, accounted for the enhancement of the catalytic performance. In addition, the incorporation of Co was shown to weaken the carbonyl bond of furfural upon surface binding, thus promoting its reduction toward 2-methylfuran. By comparison to neat Mo₂C, higher conversion (97-35%) and selectivity (92-50%) were obtained for a longer operation time (17 h, entry 4), but at a process temperature higher by 100 °C. Resasco and coworkers evaluated Ni-based catalysts supported on silica; the parent Ni/SiO₂ yielded mainly furan through a decarbonylation reaction (see section 3.1.8) and furfuryl alcohol through reduction (see above).⁶⁶⁶ By contrast, Ni-Fe/SiO₂ favored the reduction and hydrogenolysis of the C=O bond toward 2-methylfuran (41% selectivity at 96% conversion, entry 7). Additional DFT computations provided mechanistic insights that helped rationalizing these observations: interactions between aldehyde or alcohol

moieties and the surface of the catalyst were stronger in the presence of oxophilic Fe species, thus favoring the reduction and hydrogenolysis over the decarbonylation process. In a follow-up article, the same group assessed Pd and Pd-Fe catalysts supported on silica (entry 10), and similar experimental and theoretical conclusions were drawn.⁶⁶⁸ Querini *et al.* initially studied an inexpensive catalyst, Fe/SiO₂. It was selective for the formation of 2-methylfuran, but gave low conversion and poor stability since important coking occurred.⁶⁷² By contrast, Pt/SiO₂ gave complete conversion and high stability, but was unselective under the conditions attempted. Thus, decision was made to prepare and evaluate bimetallic Fe-Pt/SiO₂. Such catalyst had a better balance between activity, selectivity and stability (entry 13). Enhanced metal-support interactions, small iron particle size, and good hydrogen spillover accounted for these enhanced results. Control experiments suggested that coke was mainly formed from furfural, and introduction of Pt enabled swift furfural conversion before formation of coke, enhancing catalyst stability. A synergy between Pt and Fe was demonstrated since a physical mixture of monometallic counterparts gave poorer results. Material characterization evidenced the formation of a Pt-Fe alloy. Regeneration of the spent catalyst by calcination in air even improved conversion and selectivity by comparison to the fresh catalyst. Alternatively, Maireles-Torres and coworkers reported the use of nickel phosphide supported on silica.⁶⁶⁷ The presence of P decreased the metallic character of the Ni active sites, and thus weakened the interaction of the catalyst with the substrate, intermediates and products. Additionally, the presence of P-OH species increased the Brønsted acidity of the catalyst, and thus its activity for the hydrogenolysis of intermediate furfuryl alcohol into 2-methylfuran. Elevated conversion (>99-88%) and selectivity (75-82%) were maintained for 5 h TOS under optimized conditions (entry 8). Luque and colleagues reported a continuous procedure using an H-cube Mini reactor (ThalesNano) and a Pd/C catalyst. A low temperature (90 °C) but a high hydrogen pressure (50

bar) were utilized to generate initially 2-methylfuran in quantitative conversion and high selectivity (75%).⁶²⁸ The catalyst however deactivated after about 2 h of continuous operation, and furfuryl alcohol became the main reaction product (entry 9). Gorte reported that over a Pt/C catalyst, the H₂ pressure dramatically influenced the outcome of the reaction.⁶⁷¹ At 0.1-1 bar H₂ pressure, furan was the main reaction product through decarbonylation while at 33 bar H₂ pressure, furfuryl alcohol and 2-methylfuran became the main products, the latter being formed in up to 41% yield (entry 12).⁶⁶⁵ In a follow-up paper, similar observations were reported for Ni/C as for Pt/C. However, using a bimetallic Ni-Fe/C catalyst, the reaction remained selective for 2-methylfuran irrespective of the H₂ pressure utilized. Very high conversion (98%) and excellent selectivity (88%) were obtained under optimized conditions (entry 6).

Alcohols were also reported as alternative H-sources for the reduction of furfural into 2-methylfuran (Figure 69).^{652,674-677} Representative catalysts, alcohols and conditions are summarized in Table 26. Over metal oxide catalysts and using MeOH as the H-source, it was demonstrated that molecular hydrogen is generated *in situ* from the dehydrogenation of methanol, yielding formaldehyde as by-product.^{674,675,677}

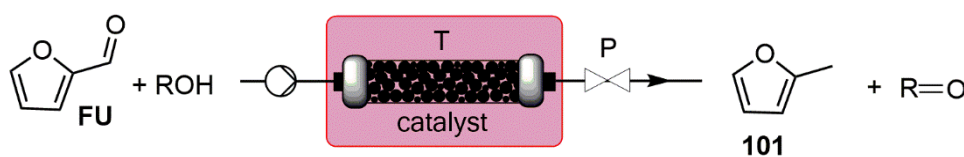


Figure 69. General flow scheme for the hydrogenolysis of furfural into 2-methylfuran triggered by alcohols as H-donors.

Table 26. Catalysts, alcohols and optimized conditions for the alcohols-mediated reduction and hydrogenolysis of furfural into 2-methylfuran.

Entry	Catalyst	Alcohol	T (°C)	P (bar)	Space velocity	TOS (h)	Conv. (%)	Selec. (%)	Ref.
1 ^a	FeVO ₄	MeOH	320	- ^b	contact time = 1.0 s	1-6	>99-80	75-80	674
2 ^a	MgFeO	MeOH	380	- ^b	contact time = 1.1 s	1-3	93-42	79-65	675
3	Ni-W/C	<i>i</i> PrOH	230	30	W/F = 5.5 g min mmol ⁻¹	1-9	90-22	65-99	676
4	Pd/Fe ₂ O ₃	<i>i</i> PrOH	180	25	res. time = 9 min	1	85	35	652

^aCarrier gas = N₂. ^bAtmospheric pressure.

In a report from the group of Cavani, methanol was used as H-source and affordable MgO-based catalysts were assessed.⁶⁷⁵ The reaction was studied in the gas-phase using a fixed-bed reactor, at temperatures ranging from 200 to 500 °C. Over pure MgO, furfuryl alcohol was the main product, but addition of iron within the MgO catalyst triggered the selective formation of 2-methylfuran. The catalytic bed of MgFeO suffered from serious deactivation after 3 h of continuous operation, and conversion of furfural dropped from 93 to 42% (Table 26, entry 2). Carbonaceous deposits accounted for the deactivation of the catalyst. In a follow-up paper, the nature of the active sites was investigated in more details.⁶⁷⁷ It was concluded that basic sites favor furfuryl alcohol formation. On the other hand, Lewis acid sites are necessary for 2-methylfuran formation, but they are not the key active sites, yet. The same group improved the methodology by means of a FeVO₄ catalyst.⁶⁷⁴ Upon optimization, the authors concluded that a preactivation of the catalyst with a stream of methanol (1 h) prior to the injection of furfural (in methanol) was required to avoid extensive deposition of carbonaceous deposits on the surface of the catalyst. The yield toward 2-methylfuran and the stability of the catalyst were significantly improved accordingly (entry 1). Furfuryl alcohol was observed as a very elusive reaction intermediate. 2-Vinylfuran and 2,5-dimethylfuran were also reported as main side-products. It was speculated that 2,5-dimethylfuran was formed through the hydroxymethylation of 2-methylfuran with formaldehyde, followed by subsequent hydrogenolysis of the corresponding alcohol intermediate. Additional experiments supported that 2-vinylfuran

formation involved furfural methyl hemiacetal, 2-furanyl methyl ketone and then its corresponding alcohol as reaction intermediates.

Tetrahydrofurfuryl alcohol and 2-methyltetrahydrofuran. Tetrahydrofurfuryl alcohol (**102**) and 2-methyltetrahydrofuran (**103**) are valuable alternative bio-based solvents that can be directly produced from the reduction of furfural,⁶⁷⁸ although requiring careful development of catalytic systems. This statement is particularly true for tetrahydrofurfuryl alcohol, as the catalysts and conditions utilized must ensure complete and selective saturation of the molecule, but without triggering C-C or C-O bonds cleavage (see Scheme 17). The most relevant catalysts and conditions for such transformation are summarized in Table 27. Neat furfural is typically reacted along with a hydrogen gas stream in a fixed-bed reactor in the gas-phase (Figure 70).^{679–681} It is noteworthy that tetrahydrofurfuryl alcohol is already manufactured at the industrial level from the reduction of furfural or furfuryl alcohol, typically over Ni-based catalysts.⁶¹⁰

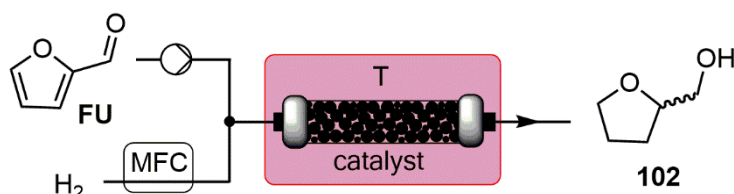


Figure 70. General flow scheme for the continuous reduction of furfural into tetrahydrofurfuryl alcohol.

Table 27. Process conditions and catalysts for the continuous reduction of furfural into tetrahydrofurfuryl alcohol.

Entry	Catalyst	T (°C)	Space velocity	TOS (h)	Conv. (%)	Selec. (%)	Ref.
1	Ni/SiO ₂	140	W/F = 0.884 g h mol ⁻¹	1-8.5	94-91 ^a		679
2 ^b	Pd/C	150	WHSV = 3.8 h ⁻¹	0.3-26	98	83-64	680

3^b Pd/Al-SBA-15 90 res. time = 35 s 0.3-2 91-10 >99-0 681

^aYield. ^bSolvent = AcOEt, P= 50 bar.

Tomishige *et al.* studied the continuous flow reduction of furfural into tetrahydrofurfuryl alcohol over Ni/SiO₂.⁶⁷⁹ It was found that the reduction of furfural into furfuryl alcohol was not structure-sensitive, as similar TOF values were obtained irrespective to Ni particle size. By contrast, the hydrogenation of the furan ring of furfuryl alcohol toward tetrahydrofurfuryl alcohol was highly structure-sensitive, as strong adsorption of furfural onto the catalyst inhibited the reaction by competitive adsorption with furfuryl alcohol. Small Ni particle sizes (< 4 nm) promoted this second step and the TOF was lower on catalysts possessing larger particle size. An excellent yield (94-91%) was maintained for 8.5 hour of continuous operation at 140 °C (Table 27, entry 1). Luque and coworkers studied the hydrogenation of furfural in a H-cube Pro commercial continuous flow reactor (ThalesNano).⁶⁸⁰ Several commercial and home-made Pd and Pt catalysts were assessed and compared. On the one hand, Pt catalysts have a strong affinity for C=O bonds, but also induce a strong repulsion between the metal d electrons and the furan ring π electrons. On the other hand, Pd catalysts combine a strong affinity for both the C=O bond and the furan ring. As a result, Pt-catalysts were selective toward furfuryl alcohol and Pd-catalysts selectively triggered the formation of tetrahydrofurfuryl alcohol. Upon optimization, almost quantitative conversion was maintained for 26 h of continuous operation over a Pd/C catalyst (150 °C, 50 bar of H₂), but selectivity slightly decreased from 83 to 64% (entry 2). This decrease in selectivity was accompanied by an increase in furfuryl alcohol formation.

Guan *et al.* reported a two-step continuous procedure toward tetrahydrofurfuryl alcohol.⁶⁸² Supported Pd and Ru catalysts were first studied separately, but gave low to moderate selectivity toward the target compound. Pd catalysts gave furfuryl alcohol (**99**) and

tetrahydrofurfural (**100**) as main side-products of the reaction. By contrast, Ru-based catalysts were efficient for the reduction of the carbonyl moiety of furfural. The authors thus designed a two-bed sequential process involving Pd/Al₂O₃ and Ru/ZrO₂: the Pd-based catalyst triggered the formation of tetrahydrofurfural and the Ru-based material reduced the carbonyl bond toward the formation of tetrahydrofurfuryl alcohol. Almost quantitative yield was maintained for 8 h of continuous operation at very low process temperature (50 °C) and moderate pressure (10 bar, Figure 71).

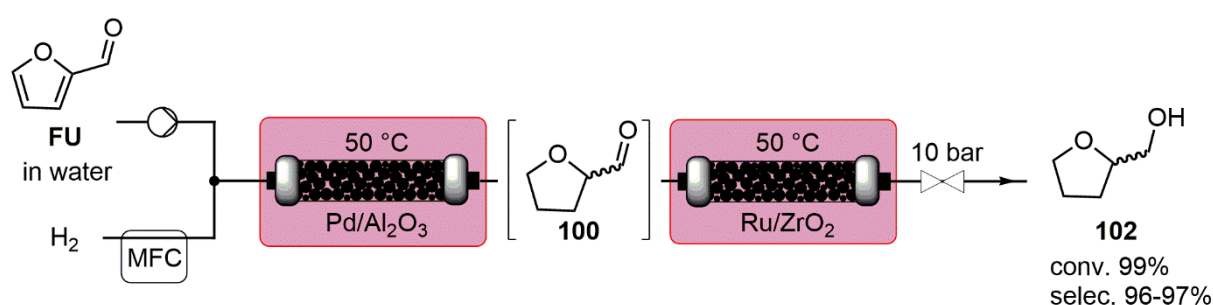


Figure 71. Guan's continuous procedure for the conversion of furfural into tetrahydrofurfuryl alcohol.⁶⁸²

In 2010, Poliakoff and colleagues reported a versatile continuous setup relying on supercritical CO₂ as the reaction medium and using two consecutive packed-bed reactors.⁶²⁹ Copper chromite and Pd/C were packed in the first and second reactors, respectively. The procedure was amenable to the hydrogenation of furfural into furfuryl alcohol (**99**), 2-methylfuran (**101**), tetrahydrofurfuryl alcohol (**102**) and 2-methyltetrahydrofuran (**103**), as well as its decarbonylation into furan (see section 3.1.8) depending on the conditions utilized (Figure 72). Upon hydrogenolysis of the C=O bond of FU, H₂O was formed as by-product and an in-line continuous extraction was implemented between the two beds to remove water from the medium. Real-time product switching was applied without any modification of the system

configuration, simply by adapting the H₂ dosing and the reaction temperature applied in each catalytic bed. Each target compound could be prepared in >80% yield and the catalysts did not suffer from deactivation over a 14 h run. In the most advanced demonstration of the system performance, each target compound was produced during a 700 min run, and 2-methyltetrahydrofuran could be produced at the beginning of the run and produced again at the end, without any loss in yield. A decade later, a very similar process was reported by Hu and coworkers.⁶³⁷ A first catalytic bed was packed with Cu/SiO₂ for reduction of the aldehyde bond of FU. A second bed was loaded with Ni/SiO₂ for saturation of the furan ring, and a separator was inserted between the two beds to remove water. The main difference with Poliakoff's procedure⁶²⁹ is the absence of supercritical CO₂. By variation of the operating conditions of the catalytic beds, furfuryl alcohol (99% yield), 2-methylfuran (92-95% yield), tetrahydrofurfuryl alcohol (75-78% yield) and 2-methyltetrahydrofuran (95-96% yield) could be selectively produced. Both beds were amenable to at least 100 h of continuous operation without deactivation.

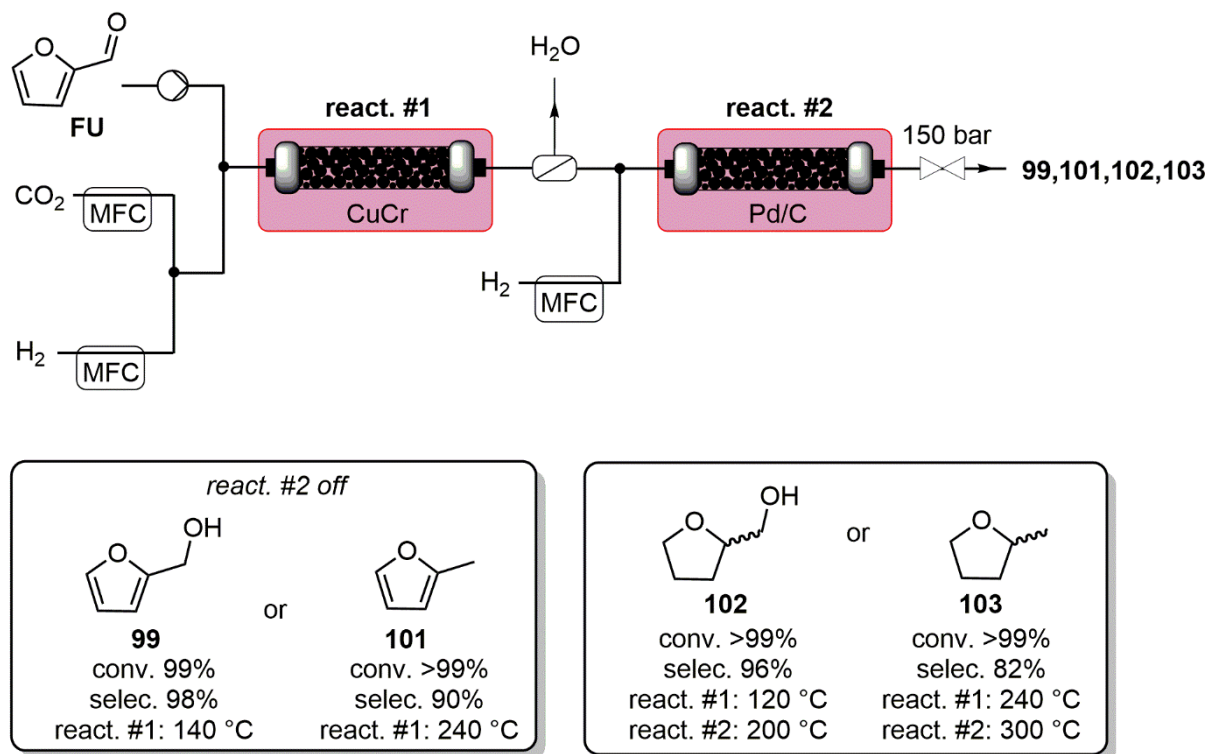


Figure 72. Poliakoff's continuous setup for the hydrogenation of furfural into various high-value added compounds.⁶²⁹

To sum-up, numerous reports studied the continuous reduction of furfural. The most value-added products include furfuryl alcohol, 2-methylfuran, tetrahydrofurfuryl alcohol and 2-methyltetrahydrofuran. This variety of products is one of the main challenge related to the reaction, as processes were often hampered by a low selectivity. Another future prospect is to address catalyst deactivation. Catalysts often suffered from extensive deactivation over operation time, mainly through the accumulation of carbonaceous deposits on the active sites, as furfural and reduced derivatives tend to oligomerize and degrade into humins and coke. Both molecular hydrogen and alcohols were assessed as reductants. The utilization of H_2 and precious metal catalysts is the gold standard, but recent literature aimed at the development of precious metal free procedures that utilized alcohols as the H-source. Another main side-product often encountered in the reduction of furfural is furan, and the latter reaction is surveyed

below.

3.1.8. Decarbonylation into Furan

Furan (**105**) is already produced at the industrial scale from the gas-phase decarbonylation of furfural (Figure 73) over Pd-based catalysts.⁶¹⁰ Hydrogen gas is optionally co-fed to increase the efficiency of the process. The main application of furan is as a chemical building block for the manufacture of specialty chemicals.⁶¹⁰ The development of catalysts and processes for the decarbonylation of furfural is still a vibrant research topic in the primary literature. It is already well established that Pd is a highly active metal center toward the decarbonylation of furfural, but more affordable Ni-based catalysts are reported as well.^{629,633,636,646,667,683–687} Representative conditions and catalysts are summarized in Table 28.

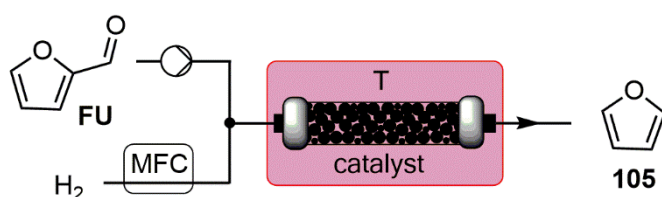


Figure 73. General flow scheme for the gas-phase decarbonylation of furfural into furan.

Table 28. Process conditions and catalysts for the continuous decarbonylation of furfural into furan.

Entry	Catalyst	T (°C)	Space velocity	TOS (h)	Conv. (%)	Selec. (%)	Ref.
1 ^a	Ni-MgO	190	W/F = 65 g h mol ⁻¹	1-24	96-65	92-85	683
2 ^a	Ni ₂ P/SiO ₂	210	W/F = 65 g h mol ⁻¹	1-5	>99	45-55	667
3 ^a	Ni ₃ N/C/SiO ₂	230	WHSV = 6 h ⁻¹	5	85	61	636
4 ^a	Ni/sepiolite	190	W/F = 32.6 g h mol ⁻¹	1-24	98-74	63-55	684
5	Pd-K ₂ CO ₃ /Al ₂ O ₃	260	WHSV = 0.77 h ⁻¹	- ^b	>99	>99	685
6 ^c	Pd/C	250	W/F = 10 g h mL ⁻¹	1	99	98	629

7	Pd/SiO ₂	250	W/F = 0.2 h	0.25	96	75	646,686
8 ^d	Pd/silicalite	200	- ^b	5-45	>99-70	96	687

^aSolvent = cyclopentyl methyl ether. ^bUnclear. ^cNo H₂, solvent = supercritical CO₂, P = 150 bar. ^dSolvent = *n*-BuOH.

Maireles-Torres and coworkers studied silica-supported nickel phosphide and nickel nitride-based catalysts for the reduction of furfural into furfuryl alcohol and 2-methylfuran (see section 3.1.7).^{636,667} Although the catalysts were selective for the reduction reactions at moderate temperatures (170-190 °C), significant decarbonylation occurred at higher temperatures (210-230 °C), resulting in the formation of furan in preparative amounts (Table 28, entries 2-3). In another report, they prepared Ni catalysts using sepiolite as support.⁶⁸⁴ The conversion of furfural decreased from 98 to 74%, and the selectivity to furan from 63 to 55% during a 24 h run conducted at moderate temperature (190 °C, entry 4). The most significant results were obtained on a Ni-MgO catalyst.⁶⁸³ The same group reported elevated selectivity toward furan (92-85%) that were maintained over a 24 h run at 190 °C. Deactivation was however reported, as furfural conversion decreased from 96 to 65% (entry 1). Zhu *et al.* reported that doping a Pd/Al₂O₃ catalyst with K promoted the decarbonylation reaction by suppression of the hydrogenation side-reaction, and the authors rationalized this observation *via* a change in furfural adsorption mode on the catalyst.⁶⁸⁵ Quantitative yield was obtained at 260 °C (entry 5). Resasco and colleagues studied the reaction over silica-supported catalysts.^{646,686} Excellent results were obtained using the Pd-based material, by comparison with supported Cu, Ni and Pd-Cu (entry 7). DFT computations further suggested that the formation of an acyl species, resulting from the strong interaction between the carbonyl C and the catalytic surface, favored the decarbonylation reaction (Figure 74). Wang and coworkers evaluated Pd nanoparticles supported on silicalite-1 zeolite as potential heterogeneous catalysts for the preparation of furan.⁶⁸⁷ It was reported that appropriate adjustment of the zeolite wettability, and thus of the catalyst hydrophilicity, enabled quantitative yield in furan at reaction temperatures of 250-

275 °C. The enhanced performance was related to an appropriate control of the diffusion within the catalyst pores, where furfural adsorption, but also furan desorption, were favored. The catalytic bed sustained a 583 g g_{Pd}⁻¹ day⁻¹ productivity. A prolonged run conducted at 200 °C evidenced mild deactivation after 45 h TOS, as conversion decreased from quantitative to 70% (entry 8). Catalyst coking accounted for the observed deactivation, but complete regeneration of the catalytic activity was possible by calcination at 550 °C for 4 h in oxygen, followed by another 40 h run, and again complete regeneration. Pd leaching or sintering was negligible.

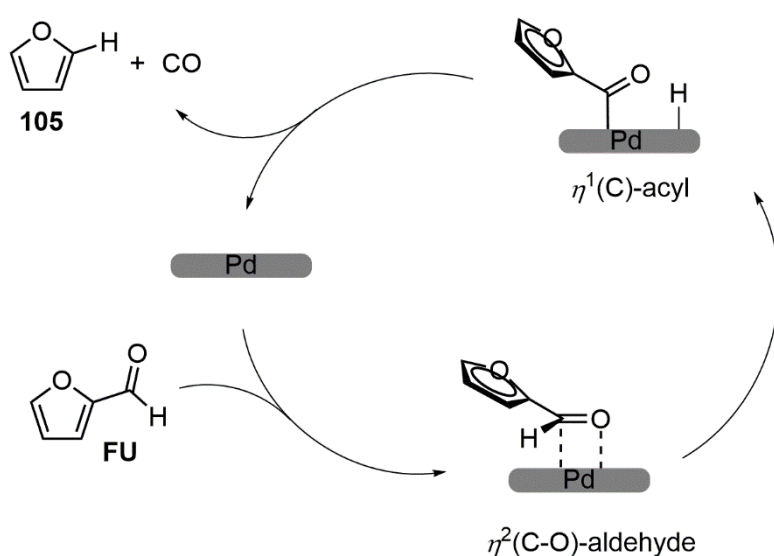


Figure 74. Proposed catalytic cycle for the decarbonylation of furfural over Pd.^{646,686}

3.1.9. Conversion into Benzene, Toluene and Xylenes

In a seminal report, aromatics that are typically petrosourced such as benzene (**106**), toluene (**107**) and xylenes (**108**) (BTX) were prepared from subsequent Diels-Alder (D-A) and dehydration reactions between ethylene or propene as dienophiles and furan, 2-methylfuran, furfural or furfuryl alcohol as bio-based dienes.⁶⁸⁸ The reactions were performed in a fixed-bed flow reactor packed with ZSM-5 as the heterogeneous catalyst (Figure 75). The concomitant injection of furfural and propene over the catalyst at 600 °C gave quantitative FU conversion

with an overall 43% selectivity toward aromatic compounds (including traces of styrene, indene, naphthalene and other heavier aromatics).

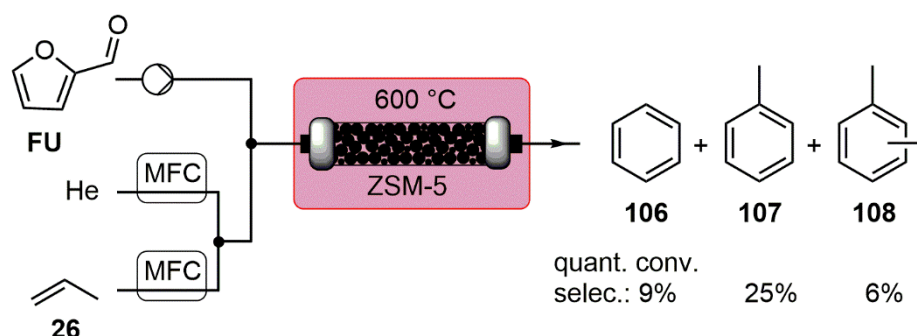


Figure 75. Gas-phase continuous process for the upgrading of furfural into carboaromatics.⁶⁸⁸

Other dienophile-free processes were described as well. Brown and coworkers reported the formation of benzene (9% yield), toluene (11% yield) and xylenes (3% yield), when furfural was fed in a carrier gas over a catalytic bed of HZSM-5 at 600 °C.⁶⁸⁹ Li *et al.* reported 12% yield for *para*-xylene upon reacting a methanolic feed of FU over a La/Ce/HZSM-5 catalyst at 450 °C.⁶⁹⁰

3.1.10. Conversion into Indoles

Indole (**109**) and methyloindoles (**110**) were prepared from furfural in gas-phase continuous flow reactors packed with HZSM-5. Furfural was mixed with a stream of ammonia before entering the catalytic bed, which was operated at 600-650 °C and atmospheric pressure.^{691,692} In a preliminary report, indoles were obtained in 21% combined yield.⁶⁹¹ Other zeolites than HZSM-5 were assessed, but gave lower yields. In a follow-up paper, the combined yield of indoles was improved to 33% by diluting NH₃ with N₂ (Figure 76).⁶⁹²

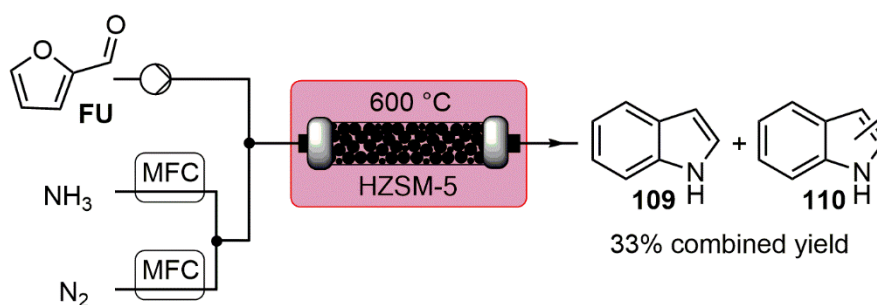


Figure 76. Continuous thermal conversion and ammonization of furfural toward indoles.⁶⁹²

3.1.11. Miscellaneous

Hydroxymethylation. The group of Nishimura reported on the direct hydroxymethylation of furfural into HMF with aqueous formaldehyde.^{114,693} The procedure is appealing since furfural is already produced on the industrial scale from non-edible biomass,⁵⁸¹ while HMF production still struggles to reach cost-efficiency on the large scale (Figure 6).¹⁶ The authors initially assessed the reaction in batch with various homogeneous and heterogeneous acid catalysts.¹¹⁴ Amberlyst 15 resin gave promising results, with up to 43% yield in HMF. HMF hydration into levulinic and formic acids was one of the main side-reaction (Scheme 18). The procedure was next translated under continuous flow conditions, and the yield remained modest (about 36%), but a 15-fold increase in the space-time yield was obtained (Table 1). However, the packed-bed reactor containing Amberlyst 15 was operated for 24 h without any decrease in performances (Figure 77, $\text{W/F} = 1667\text{ g h mol}^{-1}$). In a follow-up paper, the same group described the use of zeolite β as an alternative heterogeneous catalyst.⁶⁹³ The reaction was carried out under similar conditions ($90\text{ }^\circ\text{C}$, aqueous formaldehyde) although using higher flow rates with respect to the amount of catalyst ($\text{W/F} = 208\text{ g h mol}^{-1}$). As a result, the catalyst rapidly deactivated and conversion dropped from about 90% to 60% after 3.5 h of continuous operation. However, the decrease in conversion came with an increase in selectivity for HMF from about 20 to 40%.

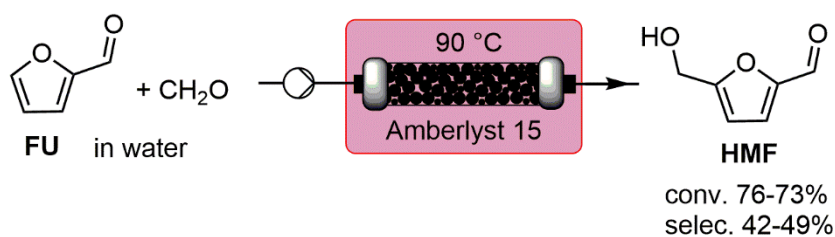


Figure 77. Continuous hydroxymethylation of furfural toward HMF using aqueous formaldehyde.¹¹⁴

3.2. 5-Hydroxymethylfurfural (HMF)

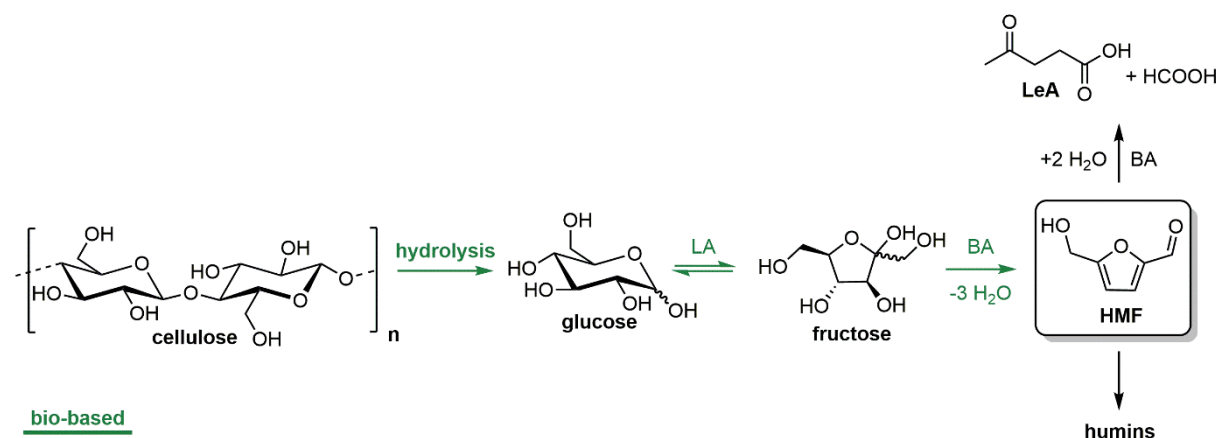
3.2.1. Presentation, Producers and Markets

5-(Hydroxymethyl)furan-2-carbaldehyde (5-hydroxymethylfurfural, HMF, CAS 67-47-0) has attracted considerable attention from the research community worldwide.^{16,694} As for FU, HMF was not formally contained within the 2004 original list issued by the US Department of Energy, yet it was included later in the 2010 updated list.⁴² The first reports on the preparation of HMF date back to the end of the 19th century.⁴² The instability of HMF makes its storage quite challenging, and it must be rapidly transformed into other chemicals, hence leading to a significant price (estimated at \$10,000 per ton) that fluctuates a lot as a function of its purity.^{694–696} To date, only one commercial process is operated by AVA Biochem (Switzerland) on a relatively moderate scale (*ca* 300 tons per year).^{697,698} Avantium reported a process (20–40 tons per year) for the preparation of HMF methyl ether, a derivative with a much longer storage life.^{699,700} The Avantium process feeds various collaborations with *e.g.* NatureWorks and Teijin Aramid for the preparation of new polymeric materials, with DAF Trucks for the development of furanic fuels and with BASF for the development of a production plant dedicated to 2,5-furandicarboxylic acid, one of HMF's most prominent derivatives.⁷⁰¹ HMF serves as an intermediate for the preparation of a variety of chemical such as furfuryl alcohol, 2,5-diiformyl and 2,5-dimethylfuran, caprolactam and levulinic acid.^{21,694,699}

3.2.2. Current Commercial Routes and Emerging Continuous Flow Alternatives

Current commercial routes. HMF is obtained from the dehydration of hexose-rich feedstock in the presence of an acid catalyst.²¹ Typically, cellulose is hydrolyzed into glucose, and the latter is further dehydrated into HMF. The selection of an appropriate solvent is cumbersome given the hydrophilicity of the starting carbohydrate feedstock and the low lipophilicity of HMF, hence precluding straightforward and efficient extraction.¹⁶ Commercial procedures typically rely on acidic zeolites.¹⁶ It is accepted in the literature that the catalyzed conversion of glucose into HMF proceeds first through glucose isomerization toward fructose (usually catalyzed by Lewis acid sites) followed by dehydration of fructose into HMF (usually catalyzed by Brønsted acid sites).^{581,702–704} The rehydration of HMF yields levulinic and formic acids (Scheme 18), and as such HMF is an intermediate in the commercial production of bio-based levulinic acid from 6-carbon sugars, such as in the Biofine Process.^{117,577}

Scheme 18. Simplified HMF formation and degradation pathways from cellulose. LA = Lewis acid, BA = Brønsted acid.



The development of advanced continuous flow procedures for the preparation of HMF stimulated intense research efforts in the primary literature. By analogy to FU, non-catalyzed

hydrothermal treatments and acid-catalyzed processing of sugar feedstocks were reported. Details on such processes are given below.

Hydrothermal continuous flow processes. As for the preparation of furfural, studies reporting the formation of HMF from the continuous flow treatment of sugars in sub- and supercritical water were not synthetically viable since very low yields were obtained, and HMF was often obtained along with a complex mixture of oxygenates.^{582–584,586–594,705–714} Yet, some authors developed continuous systems that are of broader interest for the upgrading of bio-based molecules, since they could handle aqueous slurries of water-insoluble cellulose and starch under extreme temperature and pressure conditions.^{582,583,593,594,709,710,713} In other cases, the insoluble biopolymers were typically packed in a stainless steel (SS) column followed by an optional residence time unit (reaction loop), and hot compressed water was passed through the system.^{586,587,705–708} It is noteworthy that these studies did not aim at reaching high yields in HMF. On the contrary, glucose was the main reaction target, and HMF was often considered a side-product since it was formed through the dehydration of glucose.

Homogeneous and heterogeneous catalytic continuous flow processes. Continuous procedures involving homogeneous (Table 29) and heterogeneous (Table 30) acid catalysts typically enabled dramatically higher yields for HMF by comparison to hydrothermal processes. A common strategy for maximizing the yield involves biphasic solvent mixtures (Figure 78).^{115,702,704,715–721} Sugars are dehydrated in a polar solvent (typically water), and once HMF is formed, it is continuously extracted in a less polar cosolvent (typically methyl isobutyl ketone, MIBK). This strategy prevents degradation reactions of HMF, such as the acid-catalyzed rehydration into levulinic and formic acids (Scheme 18), or the combination of oligomerization and degradation toward humins. Representative homogeneous catalysts include HCl^{115,704,715–718,722} H₃PO₄⁷⁰² and H₂SO₄⁷²³ (Table 29).

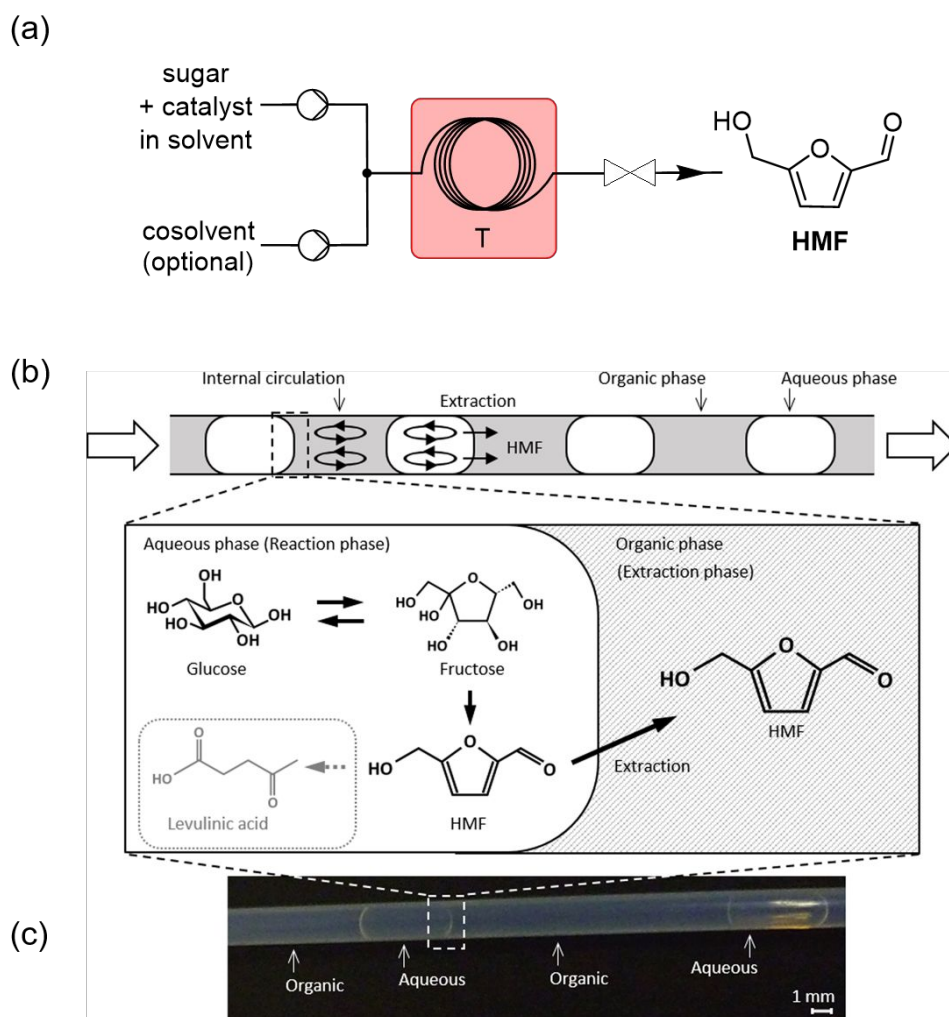


Figure 78. (a) General flow scheme for the conversion of sugars into HMF catalyzed by homogeneous acids. (b) Schematic representation of the reactive extraction of HMF in a biphasic medium.⁷⁰² (c) Photograph of a segmented flow utilized for the reactive extraction of HMF.⁷⁰² Reproduced with permission from ref 702. Copyright 2017 American Chemical Society.

Table 29. Homogeneous continuous flow procedures for the dehydration of sugars into HMF.

Entry	Substrate	Solvent	Cosolvent	Catalyst	T (°C)	P (bar)	Residence time (s)	Conv. (%)	Selec. (%)	Ref.
1	fructose	water/DMSO	-	HCl	180	40	- ^a	98	92	722
2	fructose	water	MIBK	HCl	150	20	37	91 ^b		715

3	fructose	water	MIBK	HCl	180	100	- ^a	97	91	716
4 ^c	fructose	water + NaCl	MIBK	HCl	180	30	240	99	93	115
5	fructose	water/MeOH	MIBK	HCl	140	8	900	74 ^b		717
6	fructose	water/DMSO	MIBK/ <i>s</i> -BuOH	HCl	185	17	60	97	85	718
7	fructose	water (phosphate buffer)	2- <i>sec</i> - butylphenol	H ₃ PO ₄	180	20	720	81 ^b		702
8	fructose	acetone	-	H ₂ SO ₄	180	200	180	>99	77	723
9	glucose	water/DMSO	-	HCl	200	40	- ^a	94	35	722
10	glucose	water + NaCl	MIBK	HCl + AlCl ₃	160	10	960	83	80	704
11	glucose	water (phosphate buffer)	2- <i>sec</i> - butylphenol	H ₃ PO ₄	180	20	2820	76 ^b		702

MIBK = methyl isobutyl ketone. ^aUnclear. ^bYield. ^cMembrane dispersion microreactor.

For instance, Du *et al.* reported on the use of a membrane dispersion microreactor for the dehydration of fructose into HMF in a biphasic water/MIBK system.¹¹⁵ Fructose was pumped as an aqueous solution containing also NaCl as an additive and HCl as a catalyst. The aqueous phase crossed the membrane (average pores size ~5 μm) where it divided into multiple small droplets before entering the organic phase. The biphasic aqueous droplets/organic stream next entered a tubular reactor operated at 180 °C under 30 bar where the dehydration reaction occurred (Figure 79). As fructose dehydrated into HMF within the aqueous droplets, it was instantaneously extracted in the organic phase, thus preventing degradation. The authors reported high yield (93%) within 4 min of reaction under such conditions (Table 29, entry 4), and the space-time yield was 3 orders of magnitude higher than in an analog batch setup (Table 1). In an early report, Vogel and colleagues reported a unique procedure involving supercritical acetone as monophasic reaction medium.⁷²³ Upon the addition of water as solubility improver and of sulfuric acid as a catalyst in the sugar feed, quantitative conversion (>99%) and a good selectivity (77%) were obtained under optimized conditions (entry 8). Heeres and colleagues

reported the combination of homogeneous Lewis and Brønsted acidic catalysts, AlCl_3 and HCl , for the isomerization/dehydration of glucose into HMF (Scheme 18).⁷⁰⁴ Good conversion (83%) and selectivity (80%) were obtained with a loading of only 4 mol% of each catalyst (entry 10). Higher reaction rates and HMF yields were obtained in flow in comparison to batch, mostly because of enhanced heat transfer (mass transport limitation in batch was ruled out). Moreover, higher space-time yields were obtained in flow ($0.351\text{--}1.01\text{ mol m}^{-3}\text{ min}^{-1}$) than in batch ($0.188\text{--}0.438\text{ mol m}^{-3}\text{ min}^{-1}$).

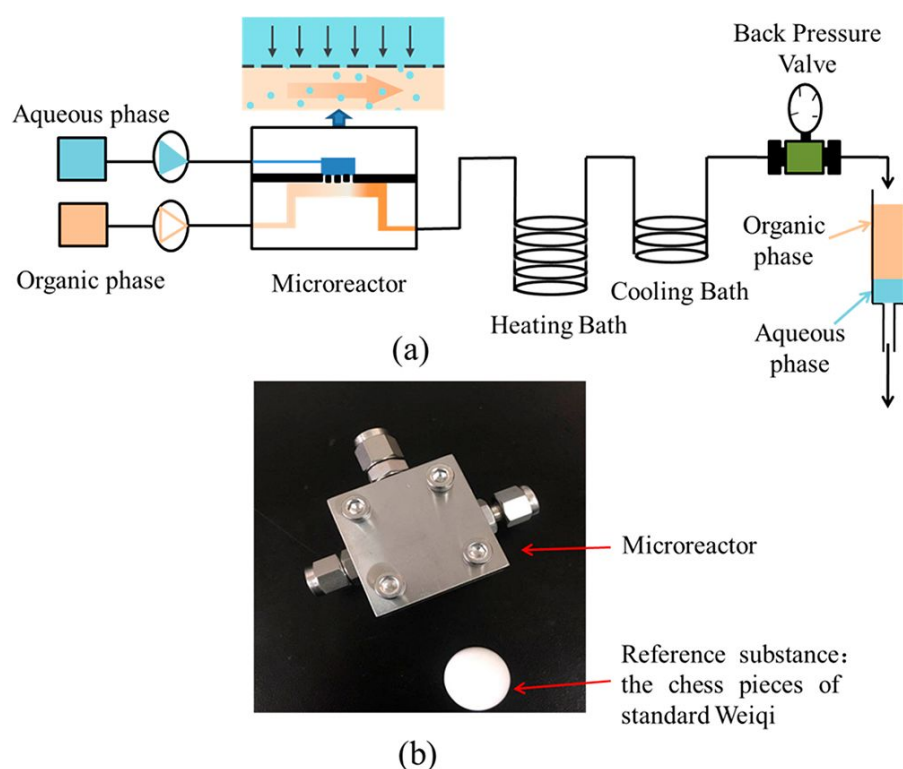


Figure 79. (a) Schematic representation of Du's continuous flow setup and (b) photograph of the membrane dispersion microreactor.¹¹⁵ Reproduced with permission from ref 115. Copyright 2018 American Chemical Society.

The use of homogeneous mineral acid catalysts such as HCl , H_3PO_4 and H_2SO_4 however requires dedicated reaction setups and neutralization steps on the industrial level, thus

negatively impacting cost-efficiency. As an illustration, leaching of the walls of a stainless steel reactor was notably described by Muranaka upon utilization of H_3PO_4 as catalyst (Table 29, entry 11).⁷⁰² Up to 6200 ppm of Fe, 710 ppm of Mn and other metals in traces were detected in the aqueous effluents of the reactor. Therefore, researchers alternatively studied continuous flow processes involving packed-bed reactors loaded with solid heterogeneous acid catalysts (Figure 80). Catalysts described included resins,^{721,724–732} metal oxides,^{719,720,733–735} or metal oxides functionalized with organic sulfonic acid moieties.^{736,737} Although processes catalyzed by homogeneous mineral acids almost exclusively relied on biphasic solvent conditions (Table 29), the literature describing the use of heterogeneous catalysts mostly relies on homogeneous reaction media. The sugar substrate typically requires polar solvents in the feedstock solution for solubility reasons, but water tends to promote a side-reaction toward levulinic acid (Scheme 18). With acidic resins as the catalyst, comparison between water and DMSO as the solvents showed that the utilization of polar aprotic solvents reduces coking of the catalyst since it increases its acidity (and thus the selectivity for HMF), but also prevents adsorption of dehydration products onto the catalyst surface.⁷³² Polar organic solvents such as DMSO, THF, acetone or alcohols were commonly utilized for the dehydration of sugars into HMF, and were sometimes diluted with water (Table 30). Although excellent yields were reported with DMSO (entries 3,4,7,9), its utilization negatively affects downstream processing since it has a high b.p. (189 °C) and HMF is thermally unstable.

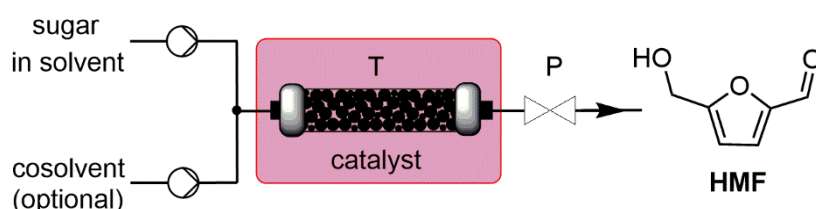


Figure 80. General flow scheme for the dehydration of sugars into HMF catalyzed by heterogeneous catalysts.

Table 30. Heterogeneous continuous flow procedures for the dehydration of sugars into HMF.

Entry	Substrate	Catalyst	Solvent	Cosolvent	T (°C)	P (bar)	Space velocity	TOS (h)	Conv. (%)	Selec. (%)	Ref.
1	pre-treated cellulose	P-TiO ₂	water	MIBK/NMP	220	60	LHSV = 18.9 h ⁻¹	0.66-6	53-46 ^a		720
2	fructose	Amberlyst 15	TEAB/water	-	100	- ^a	- ^b	- ^b	90 ^c		724
3	fructose	Amberlyst 15	dioxane/DMSO	-	110	- ^a	res. time = 3 min	0.5-72	98-97	94-93	725
4	fructose	Amberlyst 15	iPrOH/DMSO	-	110	5	WHSV = 0.34 h ⁻¹	0.5-40	95 ^c		726,727
5	fructose	Amberlyst 70	water/acetone	-	160	350	res. time = 38 s	5-90	85-45	55-63	728
6	fructose	DIAION RCP160 M	water/NMP	MIBK	120	7	res. time = 30 min	- ^b	92	>99	721
7	fructose	Dowex DR-2030	DMSO	-	110	- ^a	WHSV = 1.3 h ⁻¹	1.25-14.75	98-91	84	729
8	fructose	Lewatit K2420	HFIP/water	-	95	20	WHSV = 0.1 h ⁻¹	6-209	99-95	80-74	730
9	fructose	Purolite SGC650 H	DMSO	-	110	- ^a	res. time = 14 min	0.7	92 ^c		731
10	fructose	HO ₃ S-Al ₂ O ₃ -SH	THF/water	-	90	- ^a	W/F = 0.5 g min mL ⁻¹	0.05	95	73	736
11	fructose	NbOPO ₄	water	-	100	2-6	W/F = 55 g min mL ⁻¹	25	65	32	733
12	fructose	Nb ₂ O ₅ -SiO ₂	water	-	100	3	W/F = 21 g min mL ⁻¹	5-95	21-30	10	734

13	fructose	SBA-15-SO ₃ H	THF/water	-	130	14	- ^b	10-55	95-50	57-70	⁷³⁷
14	glucose	TiO ₂	water	MIBK	180	34	contact time = 2 min	2		29 ^c	⁷¹⁹

MIBK = methyl isobutyl ketone. NEt₄Br = tetraethylammonium bromide. HFIP = hexafluoroisopropanol. ^aAtmospheric pressure. ^bUnclear. ^cYield.

Beltramini described an alternative process relying on cellulose, a non-edible and widely available biopolymer that is insoluble in water, as the sugar substrate.⁷²⁰ The authors reported that phosphated TiO₂ efficiently catalyzed the dehydration of fructose, glucose, sucrose, cellobiose and starch. The presence of NMP as a co-solvent was beneficial to the reaction, as it inhibited the deposition of humins on the surface of the catalyst. A moderate yield was obtained with cellulose as substrate, but could be improved by a depolymerization pre-treatment with an acid, followed by ball-milling, prior to use in the reaction. Pre-treated cellulose could be efficiently processed in a continuous flow reactor using a biphasic water and MIBK/NMP system (Table 30, entry 1). Aellig and Hermans reported a flow process that maintained excellent conversion (98-97%) and selectivity toward HMF (94-93%) for an extended operation time (72 h) over an Amberlyst 15 heterogeneous organocatalyst (entry 3).⁷²⁵ A mixture of dioxane and DMSO was utilized as the reaction medium. Variation of the catalyst particles size and of the flow rate demonstrated that the reaction is mass transfer limited. By comparison to an analog batch process, the continuous flow procedure gave a 75-fold increase in space-time yield. Indeed, a maximum yield of 75% was obtained in batch and required 2 h of reaction at 100 °C (versus 92% yield in flow with only 3 min of contact time at 110 °C). Pastre and coworkers reported a procedure relying also on Amberlyst 15 as catalyst, but utilizing *i*PrOH/DMSO as reaction medium.^{726,727} Similar observations were made: optimization with a design of experiments (DoE) both in batch and flow evidenced that a better yield could be obtained in flow (95%) by comparison to batch (71%), along with a 14-fold higher space-time

yield. Excellent stability (40 h of continuous operation without deactivation) was demonstrated (entry 4). Alfonso *et al.* reported an alternative continuous flow procedure relying on an organic salt as reaction medium.⁷²⁴ Indeed, the m.p. of HMF is 30-34 °C, making its purification by crystallization cumbersome. Thus, the authors used a mixture of tetraethylammonium bromide (NEt₄Br) and water (w/w 75:25) as solvent for the fructose feed that was passed through a fixed bed of Amberlyst 15. Elimination of NEt₄Br was then performed by precipitation using EtOH/AcOEt and filtration. Almost pure HMF (97% purity) was recovered in high yield (90%) after evaporation of the solvents, which could be reused for further operations (entry 2). The most advanced example was most likely reported by Prübe *et al.* upon utilization of hexafluoroisopropanol (HFIP)/water as reaction medium and Lewatit K2420 acidic resin as catalyst.⁷³⁰ High selectivity toward HMF (80-74%) and almost quantitative conversion (99-95%) were maintained for an outstanding time (almost 9 days) of continuous operation (entry 8). Moreover, the low b.p. of HFIP (58 °C) enabled straightforward separation from HMF. Other commercially available acidic resins such as Amberlyst 70, DIAION RCP160M, Dowex DR2030 and Purolite SGC650H were reported, affording good performance as well (entries 5-7,9).^{721,728,729,731} Carniti studied the dehydration of aqueous fructose solutions over niobium oxide-based catalysts.^{733,734} Moderate conversions and low yields were obtained (entries 11-12). The catalysts were studied over prolonged operation times (up to 220 h TOS), and deactivation was observed with Nb₂O₅ and NbOPO₄ due to coke/humins deposition. By contrast, Nb-Si mixed oxide had an excellent stability over time: the conversion even increased from 21 to 30% during a 95 h run (entry 12). Dumesic *et al.* studied mesoporous ordered silicas, on which propylsulfonic acid moieties were grafted, as fructose dehydration catalysts.⁷³⁷ Among them, one inorganic SBA-15 type mesoporous silica, and two ethane-bridged SBA-15 type mesoporous organosilica materials were evaluated, and compared with a non-ordered

mesoporous silica. Poor selectivity for HMF and low stability were obtained on the non-ordered material. The organosilica materials displayed an increased stability under hydrothermal conditions compared to inorganic silica, because of the hydrophobic environment. Hydrolytic cleavage of the acid sites accounted for catalyst deactivation in each case. However, higher yields were obtained over the inorganic ordered SBA-15 silica: the conversion of fructose decreased from 95 to 50% over 55 h of continuous operation, but the selectivity toward HMF increased from 57 to 70% (entry 13). In a similar approach, Rivera de la Rosa prepared an alumina-based catalyst grafted with organic thiol and sulfonic acid functional groups.⁷³⁶ Thiols catalyzed the isomerization of fructose into its furanose form, while sulfonic acids triggered the dehydration reaction. The catalytic material gave elevated conversion (95%) and selectivity (73%) at 90 °C, upon processing fructose in a THF/water medium (entry 10). The catalyst was also assessed for a 24 h run at 70 °C and remained stable despite a 15% loss in sulfur content (leaching). Conversion (36-37%) and selectivity (60-63%) were lower by comparison to the run conducted at 90 °C. McNeff and coworkers studied the continuous flow dehydration of fructose, glucose, starch and cellulose into HMF using liquid-liquid biphasic conditions.⁷¹⁹ Porous zirconia and titania were assessed as catalysts, and the best results were obtained with TiO₂. Various cosolvents were assessed such as neat *n*-butanol; or MIBK diluted with alcohols, such as 2-butanol or 4-methyl-2-pentanol. With such solvents, poor yields were obtained due to their relative solubilities in water or due to poisoning of the active sites of the catalyst. HCl was also studied as a potential homogeneous co-catalyst, but despite promising results, it damaged the stainless steel (SS) walls of the reactor, preventing further attempts. In a series of more advanced trials, a heated cartridge packed with cellulose was positioned upstream the catalytic bed and used as substrate. Cellulose was solubilized in the water/MIBK mixture and was then subsequently hydrolyzed/dehydrated in the catalytic bed (Figure 81). After flowing the biphasic

solvent mixture for 60 min through the system and maintaining a temperature of 270 °C, up to 87% of cellulose was consumed, with 34% HMF yield.

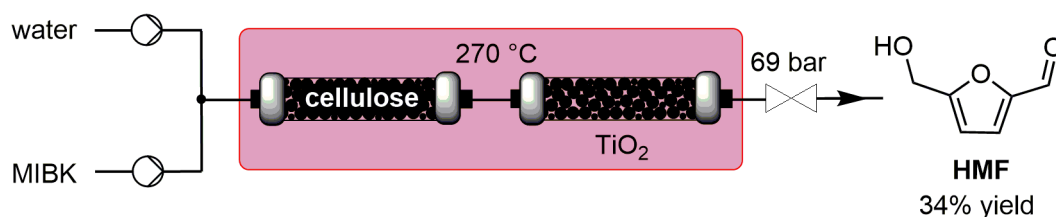


Figure 81. McNeff's process for the conversion of cellulose into HMF.⁷¹⁹

A process in rupture was recently described by Visan and Lammertink.⁷³⁵ The authors built a homemade catalytic microreactor from scratch, relying on ZrO₂ or TiO₂ as the active materials. The system was evaluated for the dehydration of fructose. The reactor was built from silicon using photolithography and deep reactive ion etching, followed by anodic bonding of a glass cover, and the channels were coated with layers of ZrO₂ or H₃PO₄-treated TiO₂ (Figure 82). The outlet of the reactor was connected to an in-line UV detector, for real-time monitoring of the HMF concentration. Despite low activities (~1.5% and ~4.5% HMF yields over ZrO₂ and TiO₂, respectively), the microreactor platform enabled rapid screening of catalysts and accurate measurement of kinetics since mass transport limitations were ruled out.

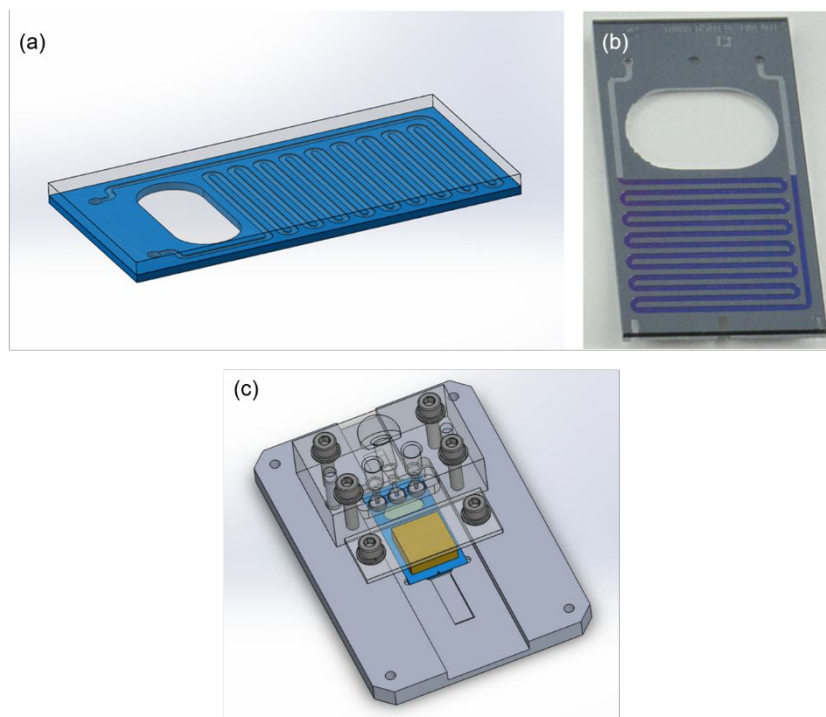


Figure 82. Homemade catalytic microreactor for the dehydration of fructose into HMF.⁷³⁵ (a) Schematic representation of the catalytic chip, (b) actual chip with ZrO₂-functionalized channels (in purple), and (c) schematic representation of the thermoregulating chipholder. Reproduced with permission from ref 735. Copyright 2020 Springer. [CC LICENSE] [<http://creativecommons.org/licenses/by/4.0/>].

3.2.3. Amidation and Esterification

(5-(Hydroxymethyl)furan-2-yl)(pyrrolidin-1-yl)methanone and **methyl 5-(hydroxymethyl)furan-2-carboxylate**. Massi and coworkers studied the oxidation of HMF into 5-hydroxymethyl-2-furancarboxylic acid using heterogeneous NHC-catalysis under batch conditions.⁶⁰⁴ The procedure was extended to the oxidative (thio)esterification and amidation of HMF, and then translated to flow conditions. The NHC was generated in situ from a polymer-supported triazolium salt precatalyst that reacted with DBU as homogeneous base, and tetra-

tert-butylidiphenoquinone (**40**) served as the stoichiometric oxidant. The methodology was successfully exemplified with methanol or pyrrolidine (**95**) as nucleophiles (Figure 83).

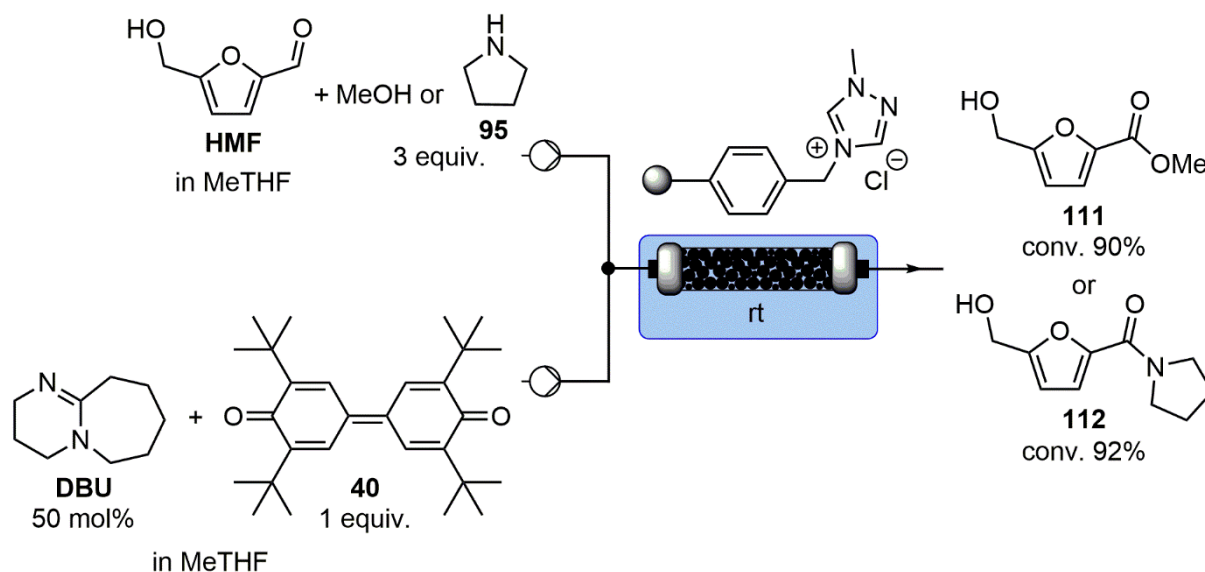


Figure 83. Oxidative esterification/amidation of HMF using heterogeneous NHC-catalysis.⁶⁰⁴

3.2.4. Etherification

Gorte and colleagues studied the etherification of HMF with *i*PrOH in a continuous flow reactor.⁷³⁸ Oxides such as Al₂O₃, ZrO₂, TiO₂, Al₂O₃/SBA-15, ZrO₂/SBA-15 and TiO₂/SBA-15 as well as zeolites including H-BEA and Sn-BEA were evaluated as catalysts for the reaction. It was found that catalysts with strong Brønsted acid sites, such as H-BEA zeolite and Al₂O₃/SBA-15, were selective for the condensation of *i*PrOH and of the alcohol moiety of HMF toward the corresponding ether **113**. On the other hand, catalysts with Lewis acid sites, such as γ -Al₂O₃, TiO₂ and ZrO₂, or weak Brønsted acid sites, such as ZrO₂/SBA-15 and TiO₂/SBA-15, favored transfer hydrogenation from the alcohol to HMF, resulting in 2,5-bis(hydroxymethyl)furan formation, but also further etherification into the corresponding mono or bis(isopropyl) ethers (see section 3.2.6). Up to 97% selectivity for 5-isopropoxymethylfurfural (**113**) at 65% HMF conversion was obtained over an H-BEA

catalytic bed operated at 180 °C and 69 bar (Figure 84a). Alternatively, the use of Amberlyst 15 as a heterogeneous organocatalyst for the synthesis of the propargyl ether of HMF was also reported.⁷³⁹ Up to ten 20-min runs were possible with the same catalytic bed, without any deactivation noticed. In a typical run, HMF and propargyl alcohol were solubilized in ethyl acetate, and pumped over the catalytic bed operated at 70 °C. The target ether was obtained in 78% yield, and could be further processed in batch for the synthesis of a library of phenols. In an early report, Vogel reported a continuous flow procedure in sub-/supercritical methanol for the one-pot dehydration of fructose into HMF, and subsequent etherification into 5-methoxymethylfurfural.⁷⁴⁰ A fructose feedstock solution in methanol containing H₂SO₄ in catalytic amounts was thermolyzed for 2 s at 240 °C under 200 bar. Methoxymethylfurfural (**114**) was accordingly obtained with 79% selectivity at quantitative fructose conversion (Figure 84b).

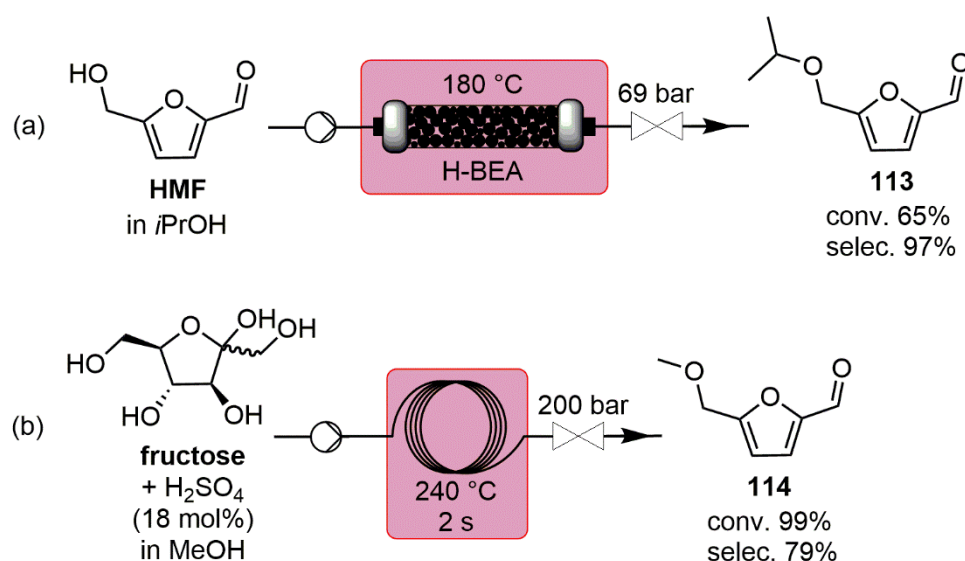


Figure 84. Continuous flow procedures for the etherification of HMF with (a) isopropanol⁷³⁸ and (b) methanol.⁷⁴⁰

3.2.5. Oxidation

Diformylfuran. Wirth described a homogeneous procedure relying on TEMPO and an hypervalent iodine reagent, $\text{PhI}(\text{OAc})_2$, for the oxidation of HMF into 2,5-diformylfuran (**115**).⁵¹⁸ The target compound was obtained in 61% yield after 4.5 min of residence at 35 °C. Dichloromethane was however utilized as the reaction solvent. Hermans and colleagues reported a continuous process relying on SiO_2 -supported TEMPO as heterogeneous catalyst.⁷⁴¹ O_2 and HNO_3 served as oxidant and co-oxidant, respectively. Excellent results were obtained (97% conversion, 98% selectivity) using mild conditions (55 °C, 5 bar, 2 min of contact time). The main drawback of the process was again the use of a chlorinated solvent (dichloroethane) as reaction medium. Lilga *et al.* reported an alternative procedure using air as the oxidant and water/acetic acid as the solvent (Figure 85).⁷⁴² Process conditions involved pumping a HMF solution in a water/acetic acid 3:2 mixture along with air, and the biphasic mixture was reacted in a fixed-bed reactor packed with a Pt/ZrO_2 catalyst and operated at 100 °C and 10 bar. Diformylfuran was formed with 67-70% selectivity and 80-85% conversion.

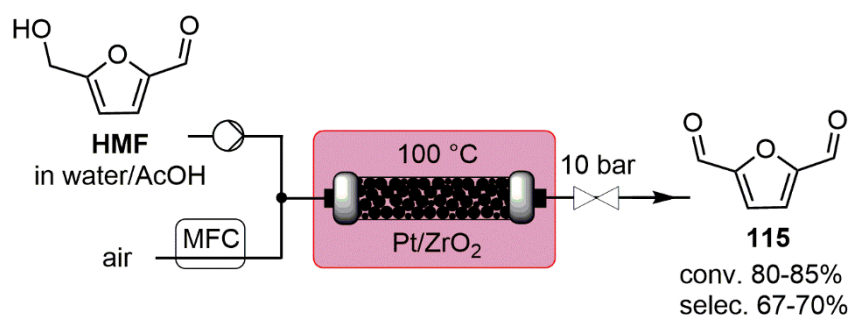


Figure 85. Aerobic oxidation of HMF into diformylfuran.⁷⁴²

Furandicarboxylic acid (FDCA). 2,5-Furandicarboxylic acid (**116**) has received considerable attention as a bio-based monomer for the manufacture of polyesters. It is considered an alternative to petro-based terephthalic acid, widely used in the manufacture of polyethylene terephthalate (PET). If polymerized with bio-based ethylene glycol, polyethylene furanoate

(PEF) would be a 100% renewable alternative to PET. PEF also possesses enhanced barrier properties by comparison to PET, making it particularly appealing for the manufacture of beverage-containing bottles.⁷⁴³ In 2010, Lilga described a continuous process for the oxidation of a 3 wt% solution of HMF into FDCA, involving air as the oxidant, water as the solvent and a platinum heterogeneous catalyst (Figure 86).⁷⁴² A stoichiometric base was added in the feed to prevent FDCA precipitation, since the target compound has a low solubility in water. The reaction was thus conducted in the presence of Na_2CO_3 at 100 °C and 10 bar. The water-soluble sodium salt of FDCA (**116·2Na**) was obtained in almost quantitative yield. Almost a decade later, Barbaro and colleagues described a related procedure under base-free conditions.⁷⁴⁴ HMF was pumped as an aqueous solution and reacted with molecular oxygen in a fixed-bed reactor embedded with a catalysts consisting of Pt supported on a Dowex-Na resin. A low substrate concentration (0.025 M) was utilized to maintain FDCA in solution even at high conversion, thus negatively impacting the space-time yield of the procedure. Process conditions involved 5 bar of counterpressure and a reaction temperature of 120 °C, yielding FDCA in 99%. The catalyst did not deactivate and did not leach Pt during 43 h TOS. FDCA was obtained in 99% purity after water evaporation. Dumesic also reported a base-free continuous flow procedure.⁷⁴⁵ γ -Valerolactone/water 1:1 was utilized as the reaction solvent and enabled efficient continuous processing of HMF at concentration up to 1 wt%. The reaction took place in a fixed-bed reactor over a Pt/C catalyst, at 100 °C and 40 bar of O_2 . The authors reported a high yield in FDCA (94%) that was maintained for more than 60 h of continuous operation, without any catalyst deactivation noticed. Recently, Len *et al.* reported a continuous process for the synthesis of FDCA relying on a microwave-heated fixed-bed reactor.⁷⁴⁶ An aqueous solution of HMF and Na_2CO_3 reacted with a solution of H_2O_2 over a Ru/C catalyst operated at ~ 95°C. During 30 min of operation, the yield decreased from 47 to 42%. 5-Formyl-2-furancarboxylic acid was

the main side-product (38-40%). Deactivation of the catalyst occurred through structural damages (coking of micro- and mesopores), and through Ru leaching, precluding any commercial viability of the process.

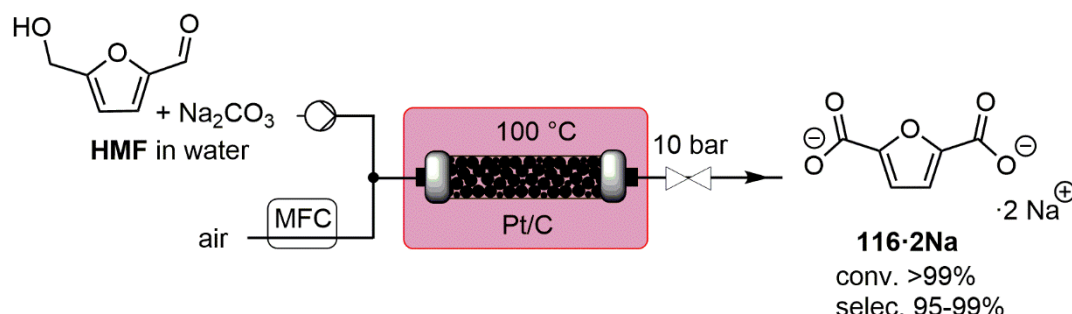


Figure 86. Continuous aerobic oxidation of HMF into FDCA.⁷⁴²

5-Hydroxy-5-(hydroxymethyl)-furan-2(5H)-one. Kappe *et al.* reported a continuous process for the oxidation of HMF with singlet oxygen.⁷⁴⁷ The latter reactive oxygen species was generated using catalytic amounts of rose Bengal as an organic photosensitizer under irradiation with visible light. Solvent optimization revealed that an *i*PrOH/water mixture was the most suitable system to avoid acetalization of the aldehyde of HMF, which was typically encountered with methanol as the solvent. Under optimized conditions, 98% yield in 5-hydroxy-5-(hydroxymethyl)-furan-2(5H)-one (**117**) was obtained. **117** was then isomerized in batch toward 5-hydroxy-4-keto-pentenoic acid oligomers (Figure 87), highlighting the potential of this photo-oxygenated building block for the preparation of bio-based polyesters.

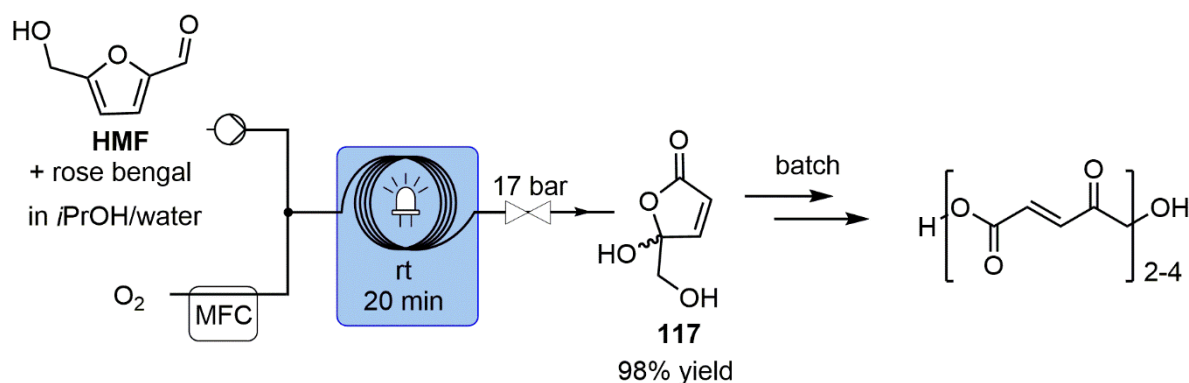


Figure 87. Kappe's continuous photocatalytic procedure for the singlet-oxygen oxidation of HMF.⁷⁴⁷

3.2.6. Reduction into 2,5-bis(Hydroxymethyl)furan, 2,5-Dimethylfuran and 1,6-Hexanediol

2,5-bis(Hydroxymethyl)furan and ether derivatives. By analogy to FDCA being an alternative to petro-based terephthalic acid (see section 3.2.5), 2,5-bis(hydroxymethyl)furan (**118**) is a potential bio-based alternative to benzenedimethanol, a common monomer for the manufacture of polyesters.⁷⁴⁸ Like the reduction of furfural into furfuryl alcohol (section 3.1.7.), the H₂-mediated reduction of HMF into **118** was mostly studied over catalysts endowed with a mild reducing ability in order to preserve the furan ring from saturation. Copper-^{749–751} and cobalt-based⁷⁵² catalysts were noteworthy reported. The group of Heeres reported the continuous reduction of HMF toward 2,5-bis(hydroxymethyl)furan over a Cu-Mg-Al mixed oxide catalysts.⁷⁴⁹ A solution of HMF in ethanol was co-fed with H₂ and reacted in a fixed-bed reactor (100 °C, 50 bar). During a 10 h run, the conversion merely decreased from quantitative to 85%, and the selectivity varied in the 70-91% range (Figure 88). Wang and coworkers reported an analog procedure, relying on a K-doped Cu/Al₂O₃ catalyst.⁷⁵⁰ Process conditions involved pumping a solution of HMF in ethanol along with molecular hydrogen, and reaction in a fixed-bed reactor packed with the copper-based catalyst. Operation at 120 °C and 20 bar

afforded very high yield (99%), but the stability of the catalyst over time was not studied. Excellent results were reported by Hellgardt over Raney copper as catalyst.⁷⁵¹ Aqueous HMF was processed in an H-cube reactor (ThalesNano) and reacted with H₂ at 90 °C and 90 bar. Steady conversion (94%) and selectivity (85-98%) were maintained for 24 h TOS. A very high yield (90%) was also reported over cobalt nanoparticles with a thin carbon shell as the catalyst.⁷⁵² The procedure involved a methanolic feed of HMF that reacted with H₂ in a fixed-bed reactor at 10 bar and 90 °C. No deactivation occurred during 60 h of operation.

Alternative reductants to H₂ were studied, such as alcohols. For instance, Hermans *et al.* described the reduction of HMF in *i*PrOH, which was used as solvent and reductant.⁶⁵² It was reported that secondary alcohols were better reductants than primary alcohols. The solution was pumped in a fixed-bed reactor packed with Pd/Al₂O₃ and operated at 150 °C under 25 bar, yielding 2,5-bis(hydroxymethyl)furan in 70% selectivity at 50% conversion. In another report, the same group described a process involving 1,4-butanediol as reductant and a Cu/AlO_x catalyst derived from a Cu-Al hydrotalcite precursor.⁶⁵⁰ 1,4-BDO underwent an oxidative ring-forming reaction into high value-added butyrolactone, and a higher yield in 2,5-bis(hydroxymethyl)furan was obtained (93%), but the conditions were more demanding (220 °C, 16 bar) and 1,4-dioxane was used as a co-solvent.

A coupled transfer hydrogenation and etherification of HMF was also described. In this route, a single catalyst triggered the reduction of HMF using alcohols as H-donors, and next the etherification of 2,5-bis(hydroxymethyl)furan using also these alcohols as coupling partners. Román-Leshkov and coworkers studied such procedure: in a typical run, a solution of HMF in ethanol or 2-butanol was pumped and reacted through a heated and pressurized catalytic bed of Hf- or Sn-beta zeolites (Figure 89).⁷⁵³ The results corroborated those reported by Hermans (see above) in the sense that EtOH was less reactive than 2-butanol as hydrogen donor. Sn-beta was

more stable and selective toward etherification, but Hf-beta was more efficient to promote the reduction of HMF. Similarly, Gorte *et al.* studied the etherification of HMF over various catalysts, and reported that Sn-BEA zeolites, possessing a high Lewis acidity, triggered both reduction and etherification.⁷³⁸ Process conditions involved a catalytic bed of Sn-BEA zeolites heated at 180 °C and a counterpressure of 69 bar. Injection of an isopropanol solution of HMF afforded 2,5-bis(isopropoxymethyl)furan in 69% conversion and 86% selectivity.

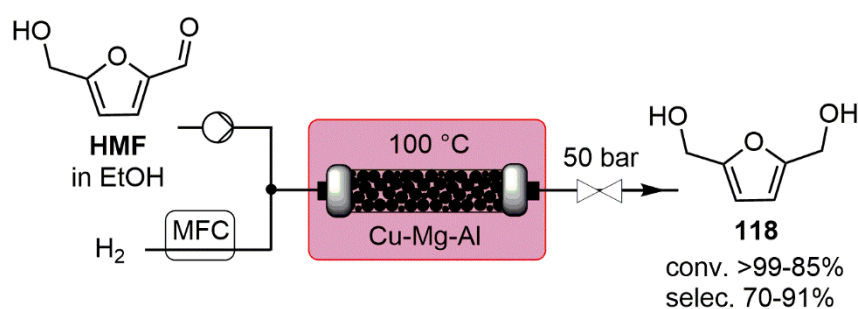


Figure 88. H_2 -mediated continuous reduction of HMF into 2,5-bis(hydroxymethyl)furan.⁷⁴⁹

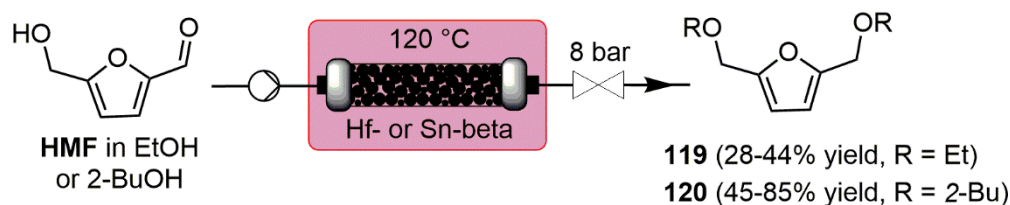
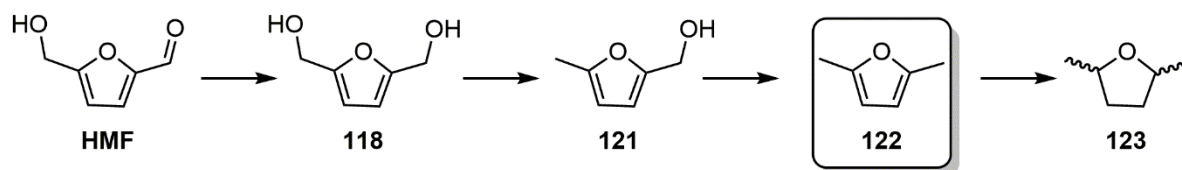


Figure 89. Coupled transfer hydrogenation and etherification of HMF toward 2,5-bis(alkoxymethyl)furan under continuous flow conditions.⁷⁵³

2,5-Dimethylfuran. By analogy to 2-methylfuran (see section 3.1.7), 2,5-dimethylfuran (**122**) has been extensively studied as potential biofuel, since it is not miscible with water and has a high energy density (29.3 MJ/L). As for 2-methylfuran, its production is however currently not viable for a fuel application.^{658,659} Typical continuous procedures for the synthesis of 2,5-dimethylfuran involved H_2 as reductant and a fixed-bed reactor embedded with a supported metal catalyst. HMF was most commonly pumped as a solution in an alcohol, and reacted with

H₂ in the liquid phase as high counterpressures were applied (Figure 90). Various active metallic centers were studied, such as supported monometallic Co,⁷⁵⁴ Cu,⁷⁵⁵ Ir,⁷⁵⁴ Ni,⁷⁵⁴ Pd,⁷⁵⁴ Pt,⁷⁵⁶ Ru,^{754,757} or bimetallic CuRu,^{758,759} NiCu,⁷⁶⁰ PtCo,⁷⁶¹ PtNi⁷⁶² or PtZn.⁷⁶² As for the reduction of furfural into 2-methylfuran, careful catalyst design and conditions optimization are required, since the HMF scaffold offers a palette of reducible and cleavable bonds, often leading to unselective transformations (Scheme 19). Representative conditions and catalysts for the H₂-mediated hydrogenolysis of HMF are summarized in Table 31. By analogy to the reduction of furfural into 2-methylfuran (see section 3.1.7), catalyst deactivation was often related to the deposition of humins/coke on the active sites.^{754,759–761} Gorte and colleagues extensively studied the reaction over carbon-supported catalysts (see below). They suggested that over such catalysts, the reaction leading from HMF to 2,5-dimethylfuran is sequential, where reduction of the aldehyde C=O bond occurs in the first place, followed by cleavage of C-O bonds. 2,5-Dimethylfuran can then further be reduced into the corresponding tetrahydrofuran **123** and ring-opening products in consecutive side-reactions (Scheme 19). As the reaction was conducted in alcohols as solvents, ethers of HMF and of reduced derivatives were commonly observed as reaction intermediates^{754,756,761,762}

Scheme 19. Sequential reaction pathway for the reduction of HMF over metal-based heterogeneous catalysts. Depending on the nature of the alcohol solvent, ether derivatives of HMF, **118** and **121** were often involved in the pathway. Products resulting from ring-opening are omitted for clarity.



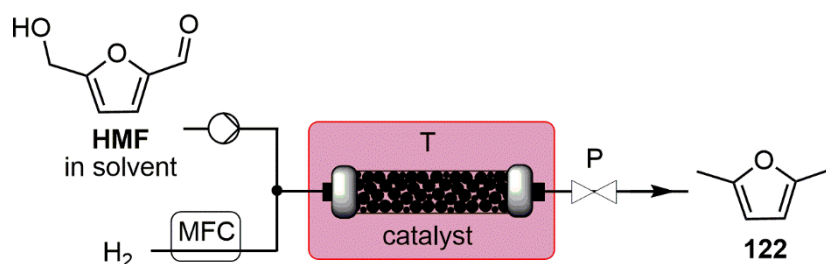


Figure 90. General flow scheme for the continuous hydrogenolysis of HMF into 2,5-dimethylfuran using H₂ as the reductant.

Table 31. Representative catalysts and conditions for the liquid-phase, hydrogen-mediated, continuous hydrogenolysis of HMF into 2,5-dimethylfuran.

Entry	Solvent	Catalyst	T (°C)	P (bar)	Space velocity	TOS (h)	Conv. (%)	Selec. (%)	Ref.
1	<i>n</i> -PrOH	Co/C	180	33	W/F = 0.067 g h mL ⁻¹	1	>99	55	⁷⁵⁴
2	<i>n</i> -BuOH	Cu/ZrO ₂	200	15	WHSV = 0.06 h ⁻¹	2-4	>99	61-45	⁷⁵⁵
3	<i>n</i> -BuOH	CuRu/C	220	17	WHSV = 0.15 h ⁻¹	0.25-0.5	>99	72	⁷⁵⁸
4	<i>n</i> -BuOH	CuRu/ZrO ₂	200	15	WHSV = 0.15 h ⁻¹	4.5-10.5	46-18 ^a		⁷⁵⁹
5	<i>n</i> -PrOH	Ir/C	180	33	W/F = 8.3 x 10 ⁻³ g h mL ⁻¹	1	85	60	⁷⁵⁴
6	<i>n</i> -PrOH	Ni/C	180	33	W/F = 0.033 g h mL ⁻¹	1	91	60	⁷⁵⁴
7	<i>n</i> -PrOH	NiCu ₃ /C	180	33	W/F = 0.036 g h mL ⁻¹	1	98 ^a		⁷⁶⁰
8	<i>n</i> -PrOH	Pd/C	180	33	W/F = 8.3 x 10 ⁻³ g h mL ⁻¹	1	60	55	⁷⁵⁴
9	EtOH	Pt/C	180	33	W/F = 0.83 h	^{-b}	95	72	⁷⁵⁶
10	<i>n</i> -PrOH	Pt ₃ Co ₂ /C	160	33	W/F = 0.017 g h mL ⁻¹	1-14	98 ^a		⁷⁶¹

11	<i>n</i> -PrOH	Pt ₃ Ni/C	200	33	W/F = 0.017 g h mL ⁻¹	1-5	98 ^a	762	
12	<i>n</i> -PrOH	Pt ₂ Zn/C	200	33	W/F = 0.017 g h mL ⁻¹	1	98 ^a	762	
13	<i>n</i> -PrOH	Ru/C	180	33	W/F = 0.067 g h mL ⁻¹	1	>99	38	754
14	<i>n</i> -BuOH	Ru-Sn/ZnO	240	- ^c	WHSV = 0.2 h ⁻¹	5-280	>99	99-98	757

^aYield. ^bUnclear. ^cAtmospheric pressure.

The 2007 report of Dumesic pioneered this research area.⁷⁵⁸ It is particularly relevant since crude HMF was utilized. The latter was sourced from the HCl-catalyzed dehydration of fructose in a biphasic *n*-butanol/water system. A straightforward purification procedure involving phase separation, concentration and filtration eventually afforded the crude starting material. A carbon-supported copper-ruthenium catalyst was utilized for the hydrogenolysis of HMF, and assessed both under batch and flow conditions. By comparison to the batch procedure, the continuous process benefited from a decreased formation of side-products, affording 72% selectivity at quantitative conversion (Table 31, entry 3). Operating under gas-phase continuous flow conditions stabilized the catalyst, since non-volatile NaCl contaminating crude HMF tended to deactivate CuRu/C in the batch process. Deactivation of the catalyst was observed only upon utilization of highly concentrated HMF solutions. Moreover, operating under continuous flow conditions enabled straightforward regeneration of the deactivated catalyst, by flowing H₂ through the fixed-bed reactor at the reaction temperature. Requies and coworkers alternatively assessed ZrO₂ as support for a Ru-doped copper catalyst.⁷⁵⁹ Process conditions were similar to Dumesic's report, but the yield was moderate with purified HMF in this case (up to 46%, entry 4). Upon utilization of crude HMF sourced from the dehydration of glucose, the yield in 2,5-dimethylfuran dropped to 16%. Similar results were obtained by Iriondo *et al.* with a Cu/ZrO₂ catalyst.⁷⁵⁵ Both purified and crude HMF were evaluated as potential starting

material. Up to 61% yield was obtained with purified HMF (entry 2), while it never exceeded 15% with crude HMF. Authors incriminated putative impurities in the crude HMF feedstock to account for this performance drop. Gorte and colleagues studied the reaction over a Pt/C heterogeneous catalyst.⁷⁵⁶ Preliminary investigation in a batch reactor revealed that short contact times with the catalyst and a fast heating were necessary, as it was observed that 2,5-dimethylfuran is an intermediate of a sequence of reduction reactions under such conditions (Scheme 19). Thus, operation in flow gave dramatically higher selectivity by comparison to batch since it enabled efficient control of the contact time, in conjunction with a fast heating of the solution. Additionally, it was shown that the use of a flow reactor led to an improved contact between the liquid, the hydrogen and the catalyst phases. In the flow reactor and under optimized conditions, 95% conversion and 72% selectivity were obtained (180 °C, 33 bar H₂, entry 9). Later on, the same group studied Co, Ir, Ni, Pd and Ru catalysts supported on carbon (entries 1,5,6,8,13).⁷⁵⁴ The iridium catalyst had a similar activity to that of the reference Pt/C catalyst, *i.e.* it was the most active of the series toward the reduction of HMF, as a high conversion (85%) was obtained at low W/F (8.3×10^{-3} g h mL⁻¹). The activity toward HMF reduction then followed the order Ni ~ Pd > Co ~ Ru. All catalysts gave moderate selectivity toward 2,5-dimethylfuran (38-60% under optimized conditions). Catalyst deactivation was moderate for the Ir, Pd and Pt catalysts, but severe for the Co, Ru and Ni ones. In another report, the same group reported that Cu/C was almost inactive toward the formation of 2,5-dimethylfuran, and Zn/C was not active at all for the reduction of HMF.⁷⁶² By contrast, alloying these metals with Pt enabled the continuous preparation of 2,5-dimethylfuran in up to 98% yield at 200 °C, 33 bar of H₂ and using propanol as the solvent (entries 11-12). Similarly, a Pt₃Co₂/C afforded 98% yield for 14 h of continuous operation without any deactivation (entry 10).⁷⁶¹ DFT computations provided insight on the activity and selectivity obtained over such catalytic

system: the catalyst consisted in a Pt-rich core coated by a Co oxide monolayer, the latter interacting weakly with the furan ring. As a result, ring saturation and opening reactions were inhibited. Later on, the same group reported on a Pt-free catalyst, NiCu₃/C.⁷⁶⁰ Assessment of the material under continuous flow conditions gave an excellent initial 98% yield under optimized conditions (180 °C, 33 bar), but a moderate stability as conversion decreased by 10% after 4 h of operation (entry 7). In one of the most advanced example, Hwang *et al.* reported a Ru-Sn catalyst supported on zinc oxide, which provided almost quantitative yield in 2,5-dimethylfuran for 280 h of continuous operation (entry 14).⁷⁵⁷ By contrast to other reports, the reaction took place at atmospheric pressure. Most importantly, these results were obtained with a solution of crude HMF in *n*-butanol, sourced from the batch dehydration of fructose catalyzed by Amberlyst 15.

As for the synthesis of 2,5-bis(hydroxymethyl)furan (**118**), alcohols were also studied as alternative reductants to H₂ (Figure 91).^{650,652,763,764} Typical catalysts, alcohols and process conditions are exemplified in Table 32.

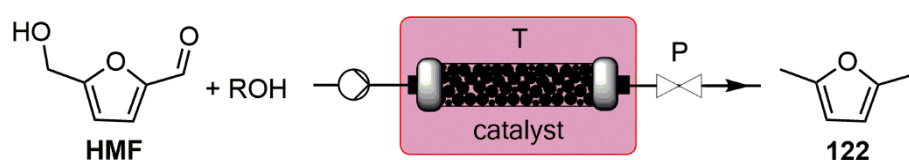


Figure 91. General flow scheme for the hydrogenolysis of HMF into 2,5-dimethylfuran using alcohols as H-source.

Table 32. Catalysts, alcohols and optimized conditions for the H₂-free reduction and hydrogenolysis of HMF into 2,5-dimethylfuran.

Entry	Catalyst	Alcohol	T (°C)	P (bar)	Space velocity	TOS (h)	Conv. (%)	Selec. (%)	Ref.
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1 ^a	Cu/AlO _x	1,4-butanediol	220	16	res. time = 29 min	- ^b	72 ^c	650	
2	Cu-Pd/rGO	<i>i</i> PrOH	180	15	WHSV = 5.73 h ⁻¹	3.5-8 h	93-67	97	763
3 ^{a,d}	Ni-Cu	cyclohexanol	240	- ^e	LHSV = 1 h ⁻¹	1-160	99	99	764
4	Pd/Fe ₂ O ₃	<i>i</i> PrOH	180	25	res. time = 24 min	1	72 ^c	652	

rGO = reduced graphene oxide. ^aCosolvent = 1,4-dioxane. ^bUnclear. ^cYield. ^dCarrier gas = N₂. ^eAtmospheric pressure.

Luque *et al.* reported on reduced graphene oxide (rGO)-supported metal catalysts.⁷⁶³ Monometallic Cu/rGO was moderately active and selective, and rapidly deactivated since copper particles underwent leaching and sintering. By contrast, bimetallic Cu-Pd gave up to 99% yield of 2,5-dimethylfuran (DMF) without any noticeable decrease in activity during 2 h TOS. These results suggested a synergistic interaction between copper and palladium. The catalyst was assessed for 8 h of continuous operation under optimized conditions, and underwent moderate deactivation and the conversion decreased from 93 to 67% (Table 32, entry 2). The deactivation was ascribed mainly to leaching of Cu, and to moderate sintering. No change in the oxidation state of Pt or Cu could be evidenced. In an advanced example, Li and coworkers reported a gas-phase hydrogenation-dehydrogenation coupled process for the production of phenol and 2,5-dimethylfuran from cyclohexanol and HMF.⁷⁶⁴ Bimetallic Ni-Cu alloy nanocatalysts were assessed for the reaction. The triple dehydrogenation of cyclohexanol into phenol produced the hydrogen required for the hydrogenation of HMF into 2,5-dimethylfuran. It was demonstrated that the utilization of HMF as hydrogen acceptor drives the dehydrogenation of cyclohexanol toward phenol, as significant amounts of 2-cyclohexen-1-one and cyclohexanone were formed in the absence of HMF. Almost quantitative yield in DMF was obtained at 240 °C (entry 3). The stability of the catalyst was assessed in a 160 h run, and no decrease in activity was noticed despite a slight metal leaching (0.4 wt% loss over the whole run). The synergistic effect of both metals in the nanostructured alloy was evidenced as

monometallic or physical mixture counterparts gave poor results. Finally, the substrate scope was extended to 9 phenol derivatives, and excellent results were obtained as well.

Braun described a two-stage, telescoped continuous flow process for the conversion of fructose into 2,5-dimethylfuran and ethyl levulinate (Figure 92).⁷⁶⁵ Formic acid was added in a tenfold molar excess within the feedstock solution, to improve the solubility of fructose in ethanol. The sugar was first dehydrated into HMF in a column packed with Amberlyst 15 as a solid acidic dehydration catalyst. HMF then underwent series of parallel reactions over Amberlyst 15, such as etherification into 5-(ethoxymethyl)furfural (**124**), esterification into the corresponding formate **125**, or hydration into the corresponding ring-opening products: levulinic and formic acids (Scheme 18). Levulinic acid underwent direct esterification into ethyl levulinate (**126**). As a result, **124**, **125** and **126** were the main products obtained from the first dehydration reactor. In the second step, the mixture entered an H-Cube reactor (ThalesNano) equipped with a cartridge packed with Ni nanoparticles supported on tungsten carbide. Ethyl levulinate did not react in the hydrogenation reactor, but HMF derivatives were hydrogenolyzed into 2,5-dimethylfuran in this second step. The setup was continuously operated for 7 h, with a minor decrease in ethyl levulinate formation noticed. This was ascribed to sulfonic acid leaching and coke deposition on the Amberlyst catalyst. At the end of the process, 2,5-dimethylfuran (b.p. 95 °C) and ethyl levulinate (b.p. 205 °C) were separated by straightforward off-line vacuum distillation.

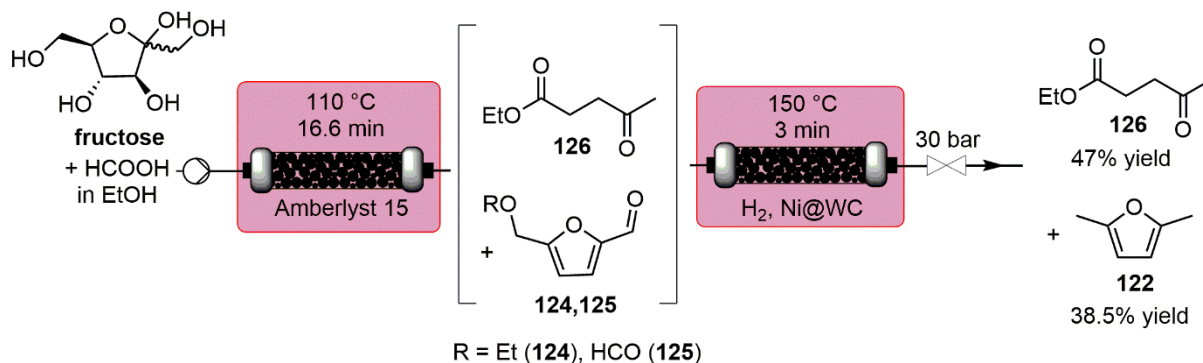


Figure 92. Braun's concatenated procedure for the conversion of fructose into 2,5-dimethylfuran.⁷⁶⁵

1,6-Hexanediol. By analogy to 2,5-bis(hydroxymethyl)furan, 1,6-hexanediol derived from renewable resources has a bright forecast for the manufacture of polyesters and polycarbonates.⁷⁶⁶ Zhang and coworkers reported a two-stage concatenated continuous flow process for the reduction of HMF into 1,6-hexanediol using molecular hydrogen as reductant (Figure 93).⁷⁶⁷ Two fixed-bed reactors embedded respectively with Pd/SiO₂ and Ir-ReO_x/SiO₂ catalysts were utilized. The later configuration improved the results by comparison to a single Pd-Ir-ReO_x/SiO₂ catalyst. It was found that the Pd-based catalyst was highly active and selective for saturation of the furan ring and of the C=O bond of HMF, affording mainly 2,5-bis(hydroxymethyl)tetrahydrofuran (**127**), while the Ir-ReO_x catalyst favored the hydrogenolysis of the tetrahydrofuran ring into 1,6-hexanediol (**128**). It was noted that conversion increased by a fivefold factor, and selectivity for 1,6-hexanediol was also enhanced, when the Ir-ReO_x/SiO₂-catalyzed hydrogenolysis of 2,5-bis(hydroxymethyl)tetrahydrofuran was translated from batch to continuous flow conditions. The reaction solvent also had a dramatic importance, and the best results were obtained with THF/water 60:40. Water created Brønsted acidic sites on the surface of the Ir-ReO_x/SiO₂ catalyst, favoring the formation of 1,6-hexanediol, while THF played a key role in the adsorption of reactants on the surface of the

catalyst. High hydrogen pressure within the reactor inhibited over-hydrogenolysis to hexane, as hydrogen was more prone to cover the active sites, and thus remove 1,6-hexanediol swiftly from the catalyst surface. Catalyst deactivation during a 24 h run was ascribed to Re leaching, and yield decreased from 58 to 40%.

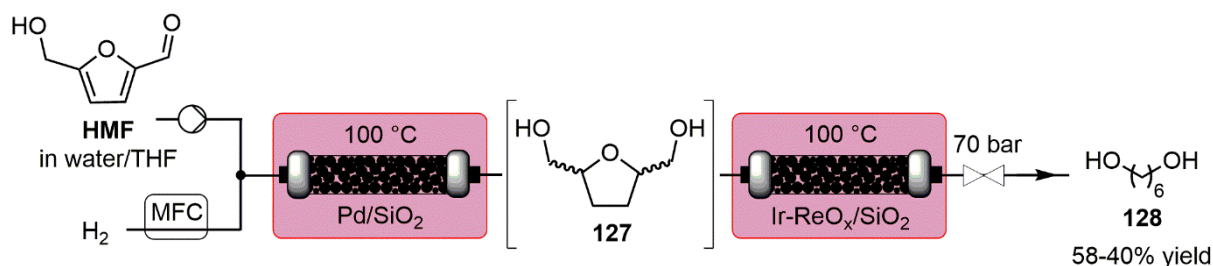


Figure 93. Two-stage continuous process for the reduction/hydrogenolysis of HMF into 1,6-hexanediol.⁷⁶⁷

3.2.7. Conversion into Benzene, Toluene and Xylenes

Carboaromatics that are typically sourced from crude oil, such as benzene, toluene and xylene (BTX), could also be prepared from the pyrolysis of HMF. For instance, zeolites including β -zeolite, HZSM-5, Ga/HZSM and In/HZSM, were assessed for the catalytic pyrolysis of HMF into aromatics, and the best results were obtained with HZSM-5.⁷⁶⁸ A high HMF conversion (96%) but a moderate selectivity for the individual aromatics (2-21%) were obtained upon pyrolysis in a nitrogen atmosphere at 600 °C (Figure 94). Later on, another group reported yields of 6%, 8% and 3% in benzene, toluene and xylene, respectively, using similar process conditions (600 °C) and HZSM-5 as catalyst.⁶⁸⁹

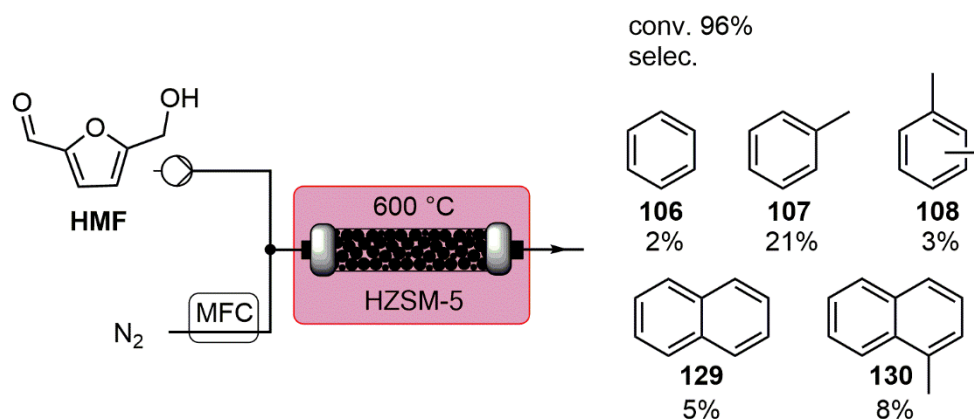


Figure 94. Gas-phase pyrolysis of HMF into carboaromatics over HZSM-5 zeolite.⁷⁶⁸

3.2.8. Miscellaneous

Wirth reported a concatenated process for the oxidation of HMF into diformylfuran (**115**), and its direct conversion into 2,5-furandicarboxamide using hydroxylamine as reagent.⁶⁰³ Furfural was oxidized in the first reactor into diformylfuran (**115**) using TEMPO and a hypervalent iodine reagent, in 4.5 min at 60 °C. Without isolation, the material was then treated with hydroxylamine hydrochloride and cesium carbonate, and thermolyzed for 5 min at 250 °C and 200 bar in a THF/water medium. 2,5-Furandicarboxamide was formed in 61% yield overall.

In 2015, Kim and coworkers reported a modular continuous platform for the telescoped preparation of HMF from fructose, and its direct upgrading into various target chemicals (Figure 95).⁷⁶⁹ In the first reactor, fructose was dehydrated into HMF, by a sulfonic acid catalyst immobilized on the reactor walls, giving the target compound in almost quantitative yield. The second telescoped flow reactor implemented magnetic-based catalysts, which were immobilized on the walls of the tubular reactor by external magnet rings. This second microreactor efficiently performed several transformations, using two- (liquid-solid) or three-phase (gas-liquid-solid) reactions. In binary phase transformations, HMF could be decarbonylated into furfuryl alcohol (**99**) in high yield (94%) using Pd/Fe₃O₄/SiO₂ as a catalyst

at 150 °C for a 12 min reaction time. Alternatively, the combination of ethanol as a co-reagent and Fe₃O₄ loaded on reduced graphene oxide (rGO) as a catalyst gave 5-ethoxymethylfurfural (**124**) in 99% yield. Mild temperature (70 °C) and short residence time (6 min) were used, and no deactivation of the catalyst was observed during 2 days of continuous operation. For ternary phase reactions, a tube-in-tube reactor with magnetically immobilized catalysts was used as the second microreactor. The first example was the aerobic oxidation of HMF into diformylfuran (**115**) using magnetic salen-manganese core-shell as catalyst. At 150 °C and applying a 60 min residence time, diformylfuran was obtained in 82% yield and the catalytic activity remained stable for 24 h. A final demonstrator showcased the reduction of HMF into 2,5-dimethylfuran (**122**) using Ru/Cu/Fe₃O₄/N-rGO as catalyst and hydrogen gas as reductant. Dimethylfuran was obtained in 90% yield, using 20 min residence time at 150 °C. Again, stability of the catalyst was demonstrated for 2 days of continuous operation.

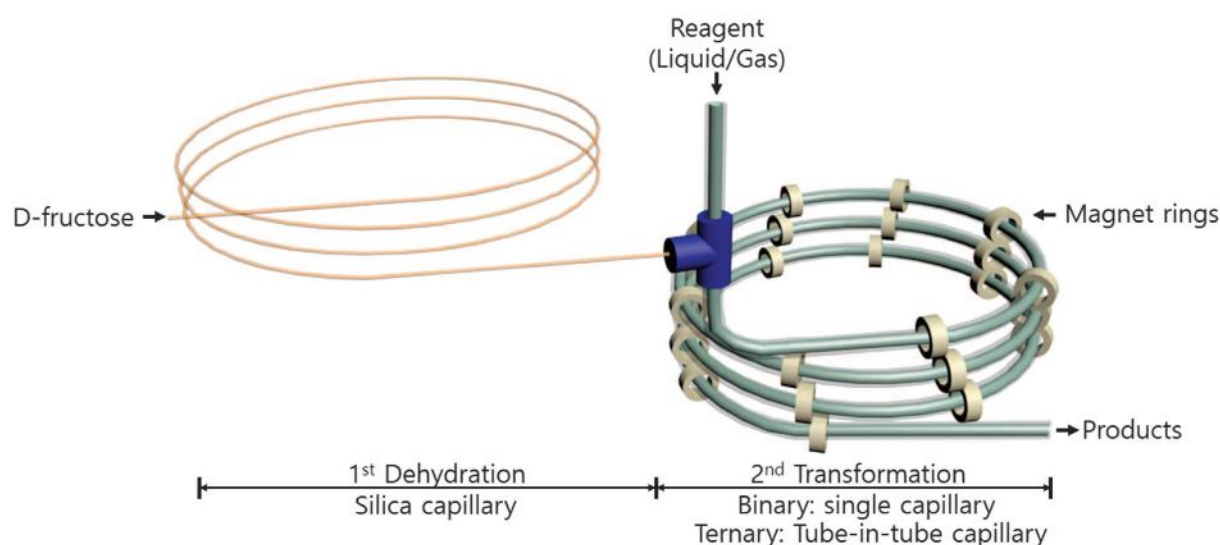


Figure 95. Schematic representation of the modular platform developed by Kim *et al.* for the continuous preparation and upgrading of HMF to various target chemicals.⁷⁶⁹ Reproduced with permission from ref 769. Copyright 2015 Springer Nature. [CC LICENSE] [<http://creativecommons.org/licenses/by/4.0/>].

4. Upgrading of Carboxylic acids

4.1. Lactic Acid and Derivatives

4.1.1. Presentation, Producers and Markets

2-Hydroxypropionic acid (lactic acid, LaA) is a widely available and naturally occurring α -hydroxycarboxylic acid discovered in 1780 by Scheele.⁷⁷⁰ LaA is the simplest α -hydroxycarboxylic acid featuring a stereogenic center, hence it exists as two enantiomers. (L-(+) and D-(-)-LaA.²⁴⁴ Enantiopure (L-(+)-LaA, CAS 79-33-4; D-(-)-LA, CAS 10326-41-7) or racemic LaA ((D,L)-(±)-LA CAS 50-21-5) are currently produced on the industrial scale with a market volume of 120,000 tons per year (\$2.22 billion market value) at \$1300-2300 per ton.¹¹⁶ The first industrial production of LaA dates back to 1881 (USA), and the two last decades have witnessed considerable expansion of its industrial preparation.⁷⁷¹ Lactic acid is mainly manufactured in the USA, Europe, China and Japan. Cargill (USA), Henan Jindan Lactic Acid Technology (China), Corbion (The Netherlands), Galactic (Belgium) and Jungbunzlauer (Switzerland) are among the world's biggest producers relying on fermentation processes.

Almost $\frac{3}{4}$ of the global production of LaA is used for the food, pharmaceutical and cosmetic industries, mostly as is or after esterification.²⁴⁸ The rest of the production feeds the biopolymer industry, where polylactic acid (PLA) bears significant potential for the production of sustainable, biocompatible and biodegradable polymers (see section 4.1.4).⁷⁷² The increasing demand for PLA will sustain a continued growth for lactic acid production.¹¹⁶ For instance, the Total-Corbion joint venture PLA announced in 2018 the start-up of a 75,000 tons per year PLA factory in Thailand, and NatureWorks (USA, a Cargill-PTT Global Chemical joint venture) has an overall production capacity of 150,000 metric tons.⁷⁷³ Besides the direct use of LaA and its esters, it can also be transformed to other industrially relevant building blocks such as acrylic acid, pyruvic acid and 1,2-propanediol.

The main commercial routes and emerging continuous flow alternatives toward LaA are detailed in section 2.3.7.

4.1.2. Condensation into 2,3-Pentadione

Lactic acid can undergo a condensation reaction to give 2,3-pentanedione (**131**), which has the potential to be valorized as a flavoring agent or as a photoinitiator.⁷⁷⁴ Sodium nitrate modified silicas were assessed as catalysts in a study dedicated to the conversion of lactic acid into mixtures of valuable chemicals, including acrylic acid and 2,3-pentanedione.⁷⁷⁵ The authors observed that the controlled presence of sodium nitrate could increase the selectivity for the target diketone up to 26%. Later on, Li *et al.* suggested the use of cesium-doped hydroxyapatite in a fixed-bed quartz tubular reactor to obtain 2,3-pentanedione from a 20 wt% solution of lactic acid.⁷⁷⁶ The main side-products of the reaction were acetaldehyde, propanoic acid and acrylic acid. Under optimized conditions, a selectivity of 73% for 2,3-pentanedione was obtained at 86% conversion using $\text{Cs}_2\text{Ca}_{1.662}\text{P}_{0.958}$ at 300 °C (Figure 96). Amongst the different parameters influencing the outcome of the reaction, the concentration of both acidic and basic sites was key, since they were both involved in the activity of the catalyst. Additionally, an over-acidic nature favored the formation of large amounts of side-products, such as acrylic acid (**20**) or acetaldehyde (**49**).

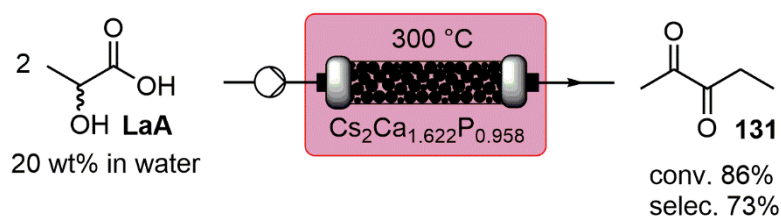


Figure 96. Conversion of lactic acid into 2,3-pentanedione using a cesium-doped hydroxyapatite catalyst.⁷⁷⁶

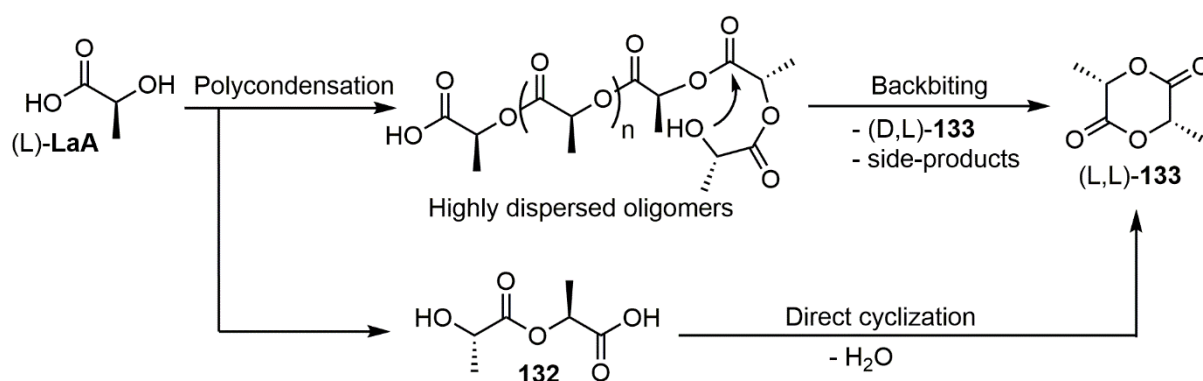
Cesium-doped dibarium diphosphate was also reported as catalyst for the conversion of a 20 wt% aqueous solution of lactic acid.⁷⁷⁷ This report also pointed out the critical nature of the ratio of acid sites over basic sites. Optimized conditions were obtained with a catalyst prepared from $\text{CsNO}_3/2.5\text{Ba}_2\text{P}_2\text{O}_7$ calcined at 600 °C and upon operation of the catalytic bed at 300 °C. Under such conditions, a conversion of 91% and a selectivity of 60% were obtained for a LHSV of 3.0 h⁻¹, and these values decreased merely to 89% and 58%, respectively, when the LHSV was increased to 4.3 h⁻¹. As TOS evolved from 1 to 9 h, the conversion and selectivity reached 92% and 61%, respectively (at LHSV = 4.3 h⁻¹). A porous solid catalyst composed of potassium lactate and titanium (IV) pyrophosphate (TiPO) was loaded with KNO_3 and evaluated in a fixed-bed reactor for the same reaction.⁷⁷⁸ The KNO_3/TiPO ratio was critical – the potassium salt increased the surface basicity – and values around 4 or 5 appeared optimal to get good yields in 2,3-pentanedione. Lower loading in KNO_3 led to lower selectivity notably through the formation of acetaldehyde. With a LHSV of 2.6 h⁻¹ and upon operating the reactor at 270 °C, a conversion of 87% and a selectivity of 80% in 2,3-pentanedione were obtained. Noteworthy, this type of catalyst exhibited a good stability for a TOS of 116 h with a stable selectivity (~73%).

4.1.3. Dimerization into Lactide and Esterification into *n*-Butyl Lactate

Lactide. The main application for lactic acid is as a building-block of polylactic acid (commonly abbreviated PLA), which is a biodegradable thermoplastic used in many consumer goods such as cold drink cups, window envelop films and plastic bags.⁷⁷² High molecular weight PLA is obtained at the industrial scale through the ring-opening polymerization (ROP) of lactide (**133**), a cyclic diester composed of two molecules of lactic acid.⁷⁷⁹

In 2015, an innovative synthesis of lactide was proposed by Sels and colleagues using 12-membered ring-shaped H-zeolites and a continuous removal of water in a batch process.⁷⁸⁰ The shape-selective zeolite favored a pathway consisting in the direct cyclization of lactic acid into its dimer **133**, instead of the traditional two-step pathway involving polycondensation and cyclization of end-chains (Scheme 20). This one-step process increased the selectivity by comparison to the traditional reaction that is associated with racemization and with the formation of side-products during the back-biting of the oligomeric intermediates.

Scheme 20. Reaction pathways for the synthesis of (L,L)-lactide from lactic acid.⁷⁸⁰



Building on this work, Chang *et al.* performed the reaction in the gas-phase using a composite $\text{SnO}_2/\text{SiO}_2$ nanocatalyst.⁷⁸¹ Using a packed-bed reactor, an enantiopure (L,L)-lactide could be obtained from an aqueous solution of lactic acid in very high yields (up to 94%) within an extremely short residence time (40 ms). The catalyst maintained an outstanding stability of 2500 h TOS. Others also reported on a gas-phase continuous process for the production of lactide using the same catalyst, but including a purification of (L,L)-lactide from crude lactide by crystallization in ethanol at 10 °C.⁷⁸²

Noteworthy, lactide could also been obtained in a water-free reaction starting from methyl lactate instead of lactic acid.⁷⁸³ The use of the methyl ester **136** enabled processing in a solvent-free procedure therefore preventing water-triggered side-reactions. Selectivity up to 90% could

be obtained with Ti(IV) oxide supported on SiO₂ (Figure 97). In a follow-up study, the structure-activity relationship (SAR) of the Ti-Si catalysts was assessed, and it was shown that the productivity in lactide greatly benefited from a high dispersion of the titanium sites on the catalyst surface.⁷⁸⁴

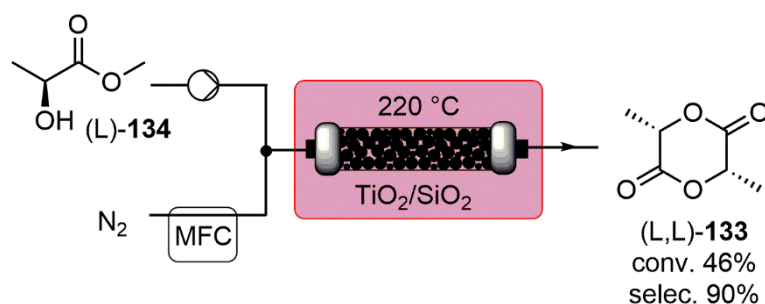


Figure 97. Gas-phase condensation of (L)-methyl lactate into (L,L)-lactide.⁷⁸³

***n*-Butyl lactate.** A specific microreactor consisting in acid-functionalized monolithic silica has been used for the Fischer esterification of lactic acid with *n*-butanol.⁷⁸⁵ In such systems, the chemicals flow through the pores of a well-defined inert material functionalized by catalytic active sites, preventing the heterogeneity (e.g., hot spots, stagnant zones) that is often encountered in traditional packed bed reactors.⁷⁸⁶ Using an arenesulfonic acid functionalized silica, 99% conversion was obtained using a 12-fold excess of *n*-butanol at 140 °C for a flow rate of 0.15 mL min⁻¹.⁷⁸⁵

4.1.4. Polymerization into Polylactic Acid (PLA)

Polylactic acid can be obtained from the direct condensation of lactic acid (Scheme 20), but it generally leads to polymers of low molecular weights, while more interesting high molecular weight polymers are typically obtained *via* the ring-opening polymerization (ROP) of lactide (**133**).⁷⁷² The use of microfluidic devices is appealing for polymerization reactions – as long as high viscosity, gelation or solidification are avoided – since they enable extremely well

controlled parameters for such reactions. The high repeatability in terms of both mass and heat transfers ensures a good reproducibility concerning the properties of the polymers synthesized in flow. The absence of hot spots and the precise control of the local stoichiometry of reactants generally lead to a good control of the chemical properties of the polymers, such as the molecular weight, and therefore to accurate and reproducible physical properties of the final material. Taking advantage of these unique features, microreactors have been used for the ROP of *N*-carboxyanhydrides in 2005, providing polymers with a narrower molecular weight distribution by comparison to corresponding batch processes.⁷⁸⁷ This concept was extended to the ROP of (L)-lactide using a chip reactor (1 μ L volume) fitted in a Chemtrix Lab system.⁷⁸⁸ The use of a flow setup alleviated the need for a glove box as the design of the system prevented the introduction of water. A good polydispersity index of the polymer ($PDI < 1.3$) was obtained using different alcohols as initiators and 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) as a homogeneous catalyst (Figure 98). Noteworthy, this very potent catalyst is known to promote the ring opening polymerization of cyclic esters but also to trigger side-reactions by catalyzing the transesterification of the polyester backbone.^{789,790} Such a phenomenon leads to an increase of the polydispersity of polymer and it is therefore necessary to rapidly quench the reaction using, for example, benzoic acid (**138**). The use of flow chemistry enabled a very efficient and controlled quench therefore leading to a low polydispersity (below 1.3), for an extremely short residence time (ranging from 2 to 5 seconds). Under identical conditions (20 °C, 0.5 mol% of catalyst, quench with **138** after 3 s), a much higher conversion was obtained in flow (91%) than in batch (49%). The continuous flow procedure tolerated a wide range of alcohols to cap the end-chains by comparison to corresponding batch systems. For instance, the very short reaction time and immediate quench enabled the use of base-labile tetrazine initiator (**136**) without degradation reactions observed. Such end-chain groups can subsequently be modified using

either click chemistry or inverse Diels-Alder reaction.⁷⁸⁸

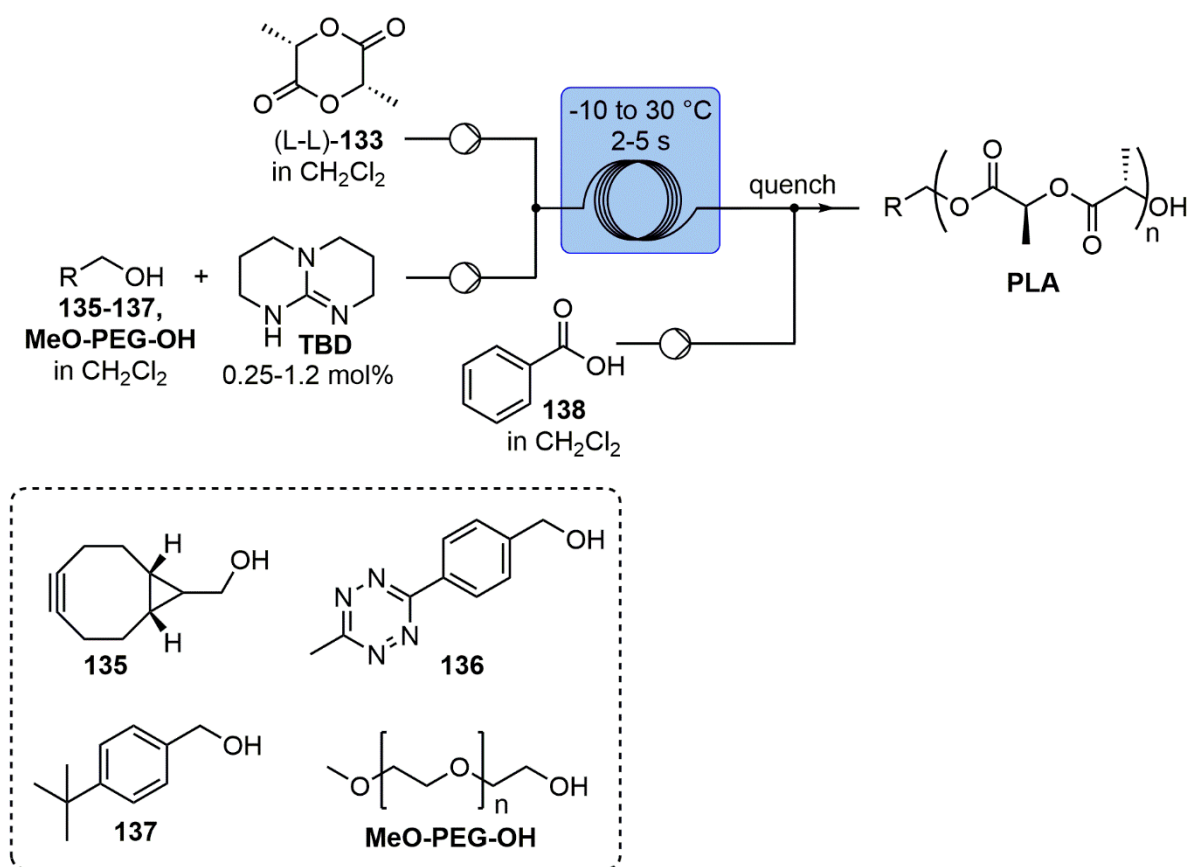


Figure 98. Continuous synthesis of PLA from L-lactide using 1,5,7-triazabicyclo[4.4.0]dec-5-ene as the catalyst.⁷⁸⁸

More recently, microfluidic devices have been used for the copolymerization of (L,L)-lactide with a lactone (ϵ -caprolactone, **139**) and/or a cyclic carbonate (trimethylene carbonate, **141**) using either homogeneous TBD or immobilized Novozyme 435 as the catalyst, and benzyl alcohol (**140**) as the initiator.⁷⁹¹ At first, the independent ROPs of each monomer were studied both in batch and flow reactors, and promising results were obtained in flow: PLA was notably obtained with a better PDI (Table 33). Then, the authors took advantage of the possibility to telescope multiple reactors to generate block copolymers. The synthesis of PLA was coupled with the biocatalyzed ROP of ϵ -caprolactone and trimethylene carbonate using grafted Novozyme 435. An example of experimental setup leading to a triblock copolymer of

polycaprolactone (PCL), polytrimethylene carbonate (PTMC) and polylactic acid (PLA) is depicted in Figure 99.

Table 33. Comparison between the preliminary batch and flow ROP of (L,L)-lactide reported in ref.⁷⁹¹

	Batch process	Flow process
Conditions	25 °C, 15 s, 0.5 mol% of TBD, 0.1 equiv. of 140	25 °C, 10 s, 0.5 mol% of TBD, 0.1 equiv. of 140
Conv. (%)	96	95
M _n (g/mol)	1690	1670
PDI	1.18	1.05

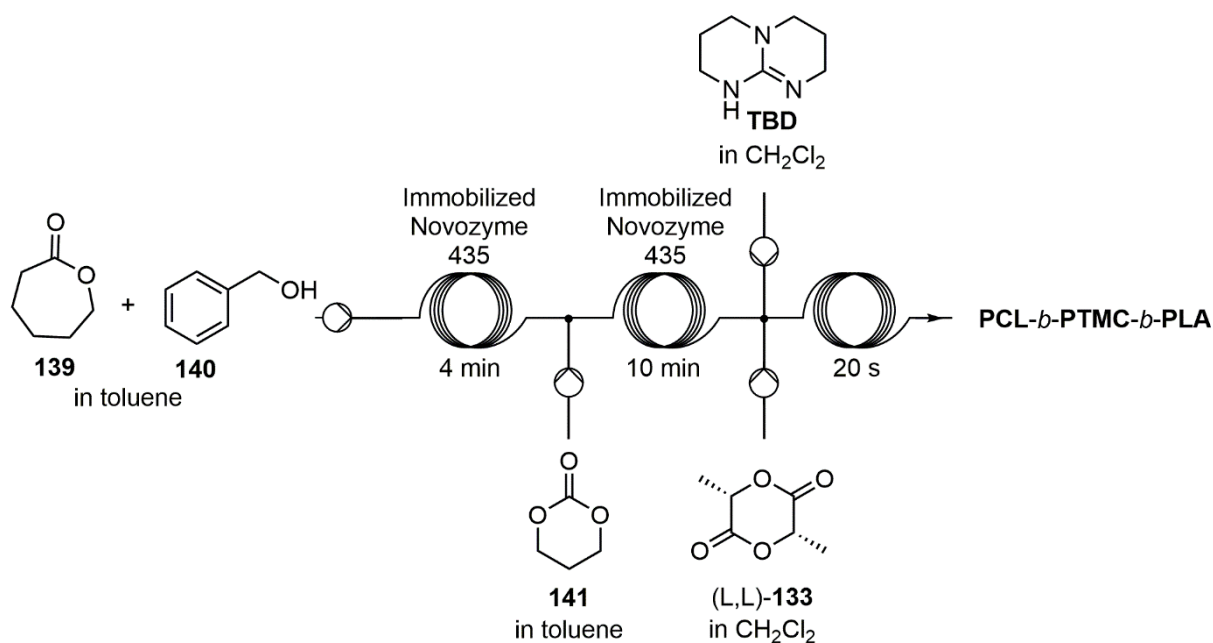


Figure 99. Synthesis of copolymers of polylactic acid, polycaprolactone and polytrimethylene carbonate in flow.⁷⁹¹

4.1.5. Oxidation into Pyruvic Acid and its Esters

Hermans and colleagues described a catalytic system for the oxidation of alcohols, and lactic acid was included in the substrate scope. Pyruvic acid (**142**) was accordingly prepared using a

mixture of nitric acid and silica-supported TEMPO.⁷⁴¹ A highly selective conversion into pyruvic acid was obtained (98% conversion, 98% selectivity) using 5 bar of O₂ and 5% of nitric acid as co-oxidant within less than 15 seconds (Figure 100). The use of a microreactor enabled a gain in safety since low amounts of the HNO₃/O₂ oxidant system were present at a given time in the system, by comparison to a corresponding batch process. In addition, only small amounts of HNO₃ were used as the efficient heat/mass transfer enabled very fast reaction rates. No decarboxylation side-reaction was observed. 1,2-Dichloroethane (DCE) was however utilized as the reaction solvent, negatively impacting the sustainability of the process.

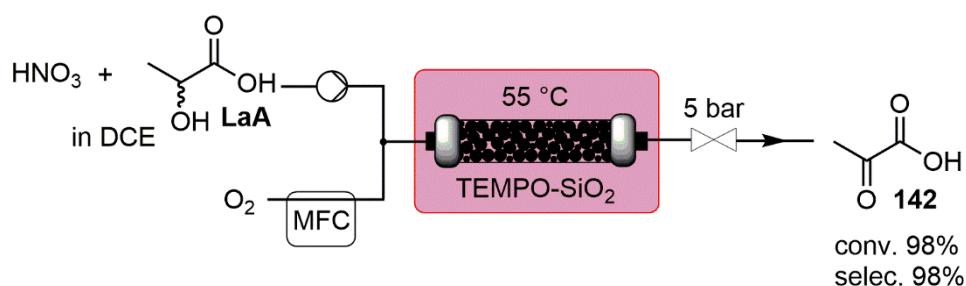


Figure 100. Oxidation of lactic acid into pyruvic acid using silica-supported TEMPO as the catalyst.⁷⁴¹

The oxidative dehydrogenation of lactic acid into pyruvic acid has also been studied using MoO₃-TiO₂ catalyst in a fixed-bed reactor.⁷⁹² The optimal results were obtained with a binary oxide obtained by dispersing Mo onto titanium oxide, in which highly dispersed tetrahedral molybdenum oxide species predominates over oligomeric oxide species. Up to 60% yield in pyruvic acid could be obtained at a relatively low flow rate (0.05 mL min⁻¹ of 20 wt% aqueous lactic acid). The mixture was vaporized at 190 °C and diluted in air before reacting over a catalyst with 2 wt% loading. Based on XPS measurements, a mechanism was suggested: lactic acid was adsorbed onto the basic site of the titanium surface, and was subsequently oxidized over the vicinal Mo=O moiety of a tetrahedral Mo site. Then, the adsorbed pyruvate species

1
2
3 were hydrolyzed and water was desorbed prior to the regeneration of Mo via O₂-mediated
4
5 oxidation.
6
7

8 Alkyl lactates can also be converted into alkyl pyruvates through oxidation. These α -keto esters
9
10 find applications as food additives and as building blocks for the synthesis of pharmaceuticals
11
12 and agrochemicals.⁷⁹³ Yasukawa *et al.* described the catalytic oxidation of lactate into pyruvate
13
14 using different types of vanadium-based catalysts in a heterogeneous liquid/gas system using
15
16 O₂ as oxidant.⁷⁹⁴ As VOCl₃ was the most efficient catalyst, the same group published a follow-
17
18 up paper on that matter.⁷⁹⁵ By using two T-shape micromixers (id of 0.5 or 1 mm), a gas-liquid
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20 slug flow was generated between the acetonitrile solution of ethyl lactate/VOCl₃ and molecular
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22 oxygen. The mass transfer between the gas and the liquid was key for the efficiency of the
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24 reaction. The efficient mixing related to the use of a slug flow gave a twelve-fold increase in
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26 the yield of ethyl pyruvate (per unit of time and at 323 K) by comparison to a corresponding
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28 batch process (Figure 101b). Under optimized conditions, a yield of about 60% was obtained
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30 in less than 4 min of residence time (Figure 101a).
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Figure 101. (a) Oxidation of ethyl lactate in ethyl pyruvate using VOCl_3 as the catalyst.⁷⁹⁵ (b) Yield of ethyl pyruvate as a function of the reaction time for the batch and flow aerobic oxidation of ethyl lactate catalyzed by VOCl_3 . Reproduced with permission from ref 795. Copyright 2011 Elsevier.

4.1.6. Dehydration into Acrylic Acid

Acrylic acid (**20**) is an important commodity for the polymer industry. It is generally produced from the oxidation of petro-based propylene,¹⁴³ but its production from bio-based feedstocks has raised interest, especially *via* the dehydration of lactic acid or the dehydration and oxidation of glycerol (see section 2.3.9.). The former reaction is generally performed in the gas-phase using aqueous solutions of lactic acid at temperature ranging from 280 °C to 460 °C. Several reviews detail the conversion of lactic acid into acrylic acid comprehensively.^{793,796–798}

The dehydration of lactic acid into acrylic acid is a rather complex reaction as it can compete with different side-reactions such as decarboxylation/decarbonylation (toward acetaldehyde, **49**), reduction (toward propionic acid, **145**), condensation (toward 2,3-pentanedione, **131**), or esterification, overall leading to low selectivity in many instances. Such a problem was observed by Aida *et al.* during the thermal treatment of lactic acid in supercritical water using a tube flow reactor, since relatively large amounts of side-products (mainly acetaldehyde) were observed.⁷⁹⁹ By working at high temperature (450 °C) and pressure (1000 bar), they managed to get a relatively high selectivity (44%) for a very short residence time but the overall yield remained low (13%) due to poor conversion. As detailed in section 4.1.8, the formation of acetaldehyde appears to be triggered by the presence of acidic sites and it is therefore not surprising that the authors obtained a significant amount of acetaldehyde under catalyst-free conditions, since the concentration of H⁺ is higher in supercritical water by comparison to ambient water.⁸⁰⁰

Alternatively, various studies proposed the use of different families of catalysts to accelerate selectively the formation of acrylic acid. Inspired by the pioneering work of Holmen,⁸⁰¹ most of the studies were performed in the gas-phase using fixed-bed reactors loaded with heterogeneous catalysts. In a patent, Holmen disclosed that traditional acid catalysts for dehydration reactions such as WO₃, MoO₃ or NiMoO₂ led to poor yields, while 68% yield could be obtained with a mixture of calcium and potassium sulfates at 400 °C.

Concerning micro/mesofluidic reactors, recent studies mainly focused on three families of heterogeneous catalysts: sulfates, phosphates and zeolites. The most relevant catalysts and optimized conditions are summarized in Table 34. Only the conditions leading to the highest yield are described for each publication.

Tang and colleagues studied various metal sulfates to catalyze the dehydration of lactic acid

(20 wt% in water) in a fixed-bed reactor.⁸⁰² Different metals were tested (Al, Ni, Zn, Mg, Ba, Ca and Na) and the best results were obtained using Mg^{2+} , Ca^{2+} or Ba^{2+} salts. Optimized conditions are shown in Figure 102, where BaSO_4 was preferred to CaSO_4 due to its higher hydrothermal stability (Table 34, entry 21). By studying the acidity strength of the different catalysts using the Hammett indicator method, it was observed that the acid strength of MgSO_4 , BaSO_4 and CaSO_4 were lower than those of their Al^{3+} , Zn^{2+} and Ni^{2+} counterparts, preventing the formation of acetaldehyde and therefore increasing the selectivity of the process. On the other hand, the acid strength of Na_2SO_4 was too low and a poor conversion was observed. The authors suggested to use a catalyst with a Hammett acidity function between +3.3 and +4.8 to maintain a good selectivity in acrylic acid. Later on, the same group studied the influence of crystal defects on the catalysis by thoroughly controlling the conditions of BaSO_4 preparation regarding reagents, pH and calcination temperature.⁸⁰³ The presence of surface defects modified the acidic properties of the catalyst, therefore altering its efficiency. Optimal results were obtained for BaSO_4 precipitated by aqueous ammonia at pH 5 and without using a calcination treatment: a selectivity of 81% and quantitative conversion were obtained at 400 °C for a WHSV of 2.8 h^{-1} (entry 22). Selectivity was very high (78%) even at high WHSV (16.8 h^{-1}), but conversion decreased to 71%. In terms of stability, both a decrease in conversion (from quantitative to 85%) and in selectivity (from 81% to ~75%) were observed after 28 h of TOS, but the catalyst could be reactivated by calcination at 500 °C.

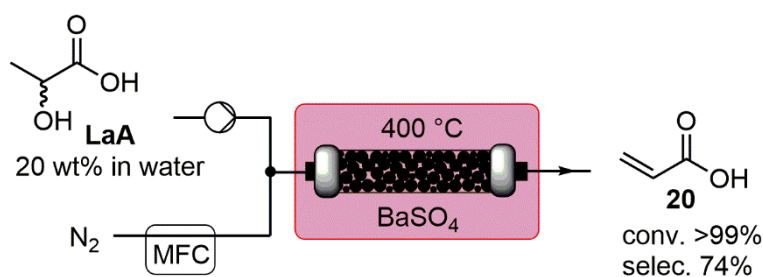


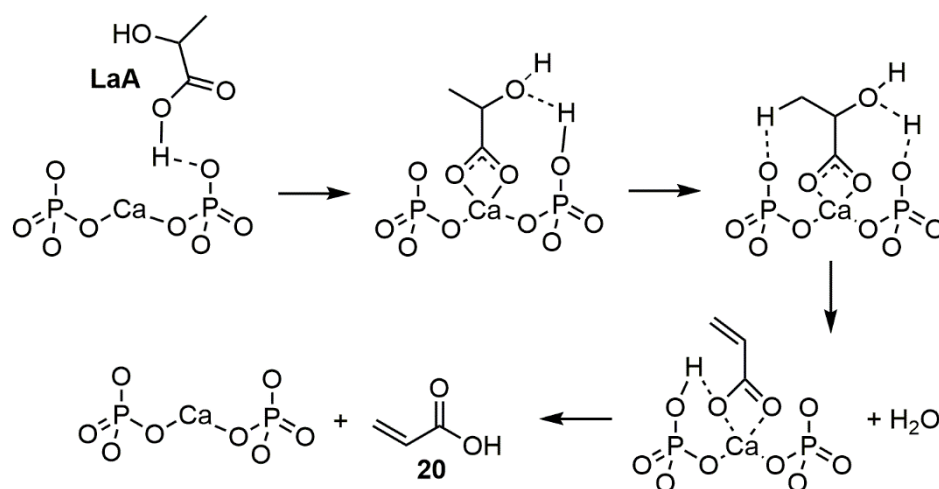
Figure 102. Representative flow scheme for the dehydration of lactic acid into acrylic acid in the gas-phase. Barium(II) sulfate is used as the catalyst in the present example (see also Table 30, entry 21).⁸⁰²

Tang *et al.* studied the reaction using a mesofluidic packed-bed reactor with different strontium sulfate, phosphate and diphosphate catalysts.⁸⁰⁴ Strontium diphosphate exhibited the highest activity due to the presence of acid sites of moderate strength in high concentration on its surface, especially when impregnated with a small amount of phosphoric acid. A 71% selectivity and quantitative conversion were obtained for a WHSV of 2.54 h⁻¹ (entry 19). Noteworthy, the use of lower WHSV led to lower selectivity, since longer residence times favored the formation of acetaldehyde. The selectivity dropped significantly down to 59% after 6 h on stream, while the conversion remained constant. The same group evaluated barium phosphates for the reaction, and dibarium pyrophosphate gave 76% selectivity and a quantitative conversion (entry 18).⁸⁰⁵ The stability of the catalyst was evaluated, and selectivity evolved from about 70% after 16 h before decreasing to about 55% after 18 h, while conversion remained constant. Cerium phosphates of various composition were also used for the dehydration of lactic acid using a fixed-bed reactor.⁸⁰⁶ A 2.5 ratio of Ce/P was optimal to moderate the acidity of cerium and inhibit decarboxylation/decarbonylation toward acetaldehyde. The highest yield (64%) was obtained for a WHSV of 1.74 h⁻¹ at 380 °C (entry 20). Conversion and selectivity dropped to 93% and 50%, respectively, upon increasing the WHSV to 6.95 h⁻¹. Regarding the stability of the catalyst, conversion remained almost constant up to 15 h on stream before decreasing, due to carbonation of the catalyst.

Hydroxyapatites – a naturally occurring family of calcium phosphate with the formula Ca₁₀(PO₄)₆(OH)₂ – are extremely versatile catalyst, which properties can be tuned by either modifying the Ca/P ratio,⁸⁰⁷ by substituting one of its components,⁷⁹⁷ or by modifying the

conditions of its synthesis such as pH or calcination temperature.⁸⁰⁸ Xu and coworkers suggested a mechanism for the formation of acrylic acid over hydroxyapatites, involving both acidic and basic sites (Scheme 21).⁸⁰⁸ Based on this mechanism, the Ca/P ratio appeared critical and the authors found that a ratio of 1.62 was optimal for the dehydration. In addition, they noticed that the calcination temperature impacted the catalytic performance, which was related to a modification of the catalyst surface acidity. On the other hand, basicity was not affected by the calcination temperature. For a calcination temperature of 360 °C, 62% yield in acrylic acid was obtained at WHSV = 1.4 h⁻¹ (entry 16). The activity of the catalyst rapidly decreased after 2 h of continuous operation due to the deposition of carbonaceous species on its surface, but it could be reactivated by treatment with air at the reaction temperature.

Scheme 21. Mechanism proposed for the hydroxyapatite-assisted dehydration of lactic acid into acrylic acid.⁸⁰⁸



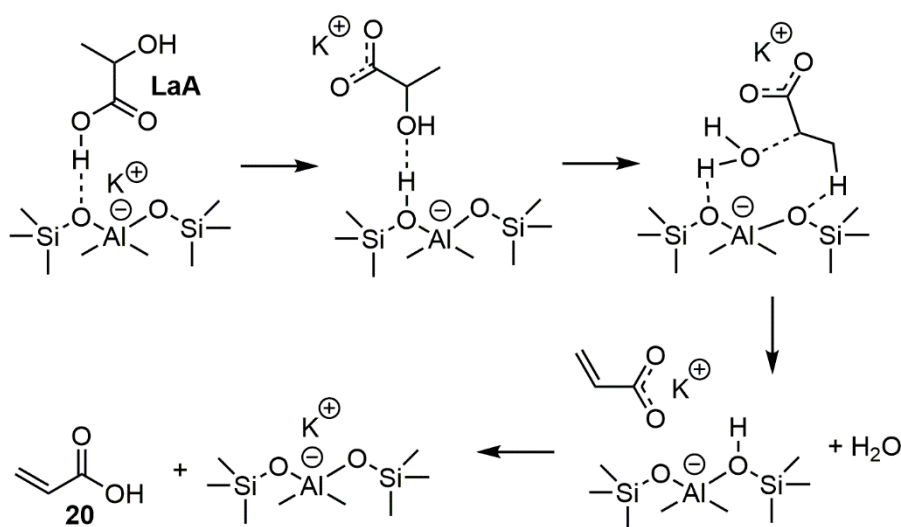
Similarly, Onda and coworkers reported on calcium phosphate as catalyst for the reaction, and studied the impact of the Ca/P ratio as well as the effect of the partial substitution of Ca by Na.⁸⁰⁹ The best results (78% yield, entry 15) were obtained with a Ca/P ratio of 1.55 and a (Ca+Na)/P ratio of 1.65. The authors rationalized the improvement in yield associated with this

composition by a good balance between acidity and basicity. In a follow-up report, the same group reported that modification of the hydroxyapatites, either by changing the metal or by substituting the phosphate, could modify the selectivity of the reaction since the acidic/basic properties of the catalyst were modified in this instance as well (entry 17).⁸¹⁰

Zeolites have been tested as catalyst for dehydration of lactic acid in the gas-phase. For mesofluidic systems, a larger part of the attention was focused on Na-Y, a faujasite-type zeolite. Using Na-Y zeolite in a mesofluidic packed-bed system, 56% yield in acrylic could be obtained for a Si/Al molar ratio of 2.5 after 165 min on stream at 325 °C (entry 1).⁸¹¹ A significant decrease both in terms of conversion and selectivity was observed for TOS above 165 min, and was ascribed to coking. Various studies employing fixed-bed reactors detailed the use of modified Na-Y *via* cation-ion exchange with alkali metals such as sodium⁸¹² and potassium,^{813,814} with alkaline earth metals such as Mg, Ca, Sr and Ba^{815,816} or lanthanides (La, Ce, Sm and Eu).^{815,817} Amongst the different metals used, potassium appears to lead to the most interesting results as a selectivity of 68% and a conversion of 98% were obtained at 325 °C and TOS = 2 h (entry 5).⁸¹⁴ Based on NH₃-TPD, the authors rationalized the efficiency of KI as promoter (by comparison to other potassium salts) by a decrease of the strength of the acid sites of the zeolites. They suggested an elimination mechanism, in which a cyclic intermediate was formed *via* interaction between K⁺ and the hydroxyl of lactic acid, as well as between the oxygen of the aluminosilicate and the methyl group of lactic acid. Later on, another mechanism was proposed involving the formation of potassium lactate (Scheme 22),⁸¹⁸ since this compound was detected by FTIR spectroscopy.⁸¹⁹ Rapid catalyst deactivation was observed in most instances, even if modification of the catalyst can improve its stability. For example, the selectivity decreased from 60 to 36% after 22 h TOS with potassium-doped NA-Y, while it dropped below 15% after only 5 h with the unmodified counterpart.⁸¹³ In a report from Pérez-

Ramírez, stability of zeolitic catalysts was shown to be greatly improved by dealumination followed by an alkaline treatment (entry 11).⁸²⁰ Indeed, selectivity merely decreased from about 25% after 380 h on stream with the modified zeolite, while the unmodified counterpart lost more than 80% of selectivity (at WHSV = 6 h⁻¹).

Scheme 22. Mechanism proposed for the dehydration of lactic acid using potassium-doped zeolites as catalyst.⁸¹⁸



Other classes of zeolites, such as β -zeolites, have been tested for the dehydration of lactic acid, although to a lesser extent than Na-Y. Partial substitution of sodium with other alkali cations (Li, K, Rb, Cs) impacted the efficiency of the catalyst also in this case. For instance, an alkali-modified β zeolite $K_{0.94}Na_{0.06}\text{-}\beta$ gave 64% selectivity for acrylic acid at a WHSV of 2.1 h⁻¹ after a TOS of 8 h (entry 8), while only 27% selectivity was obtained with the unmodified Na- β .⁸¹⁸ As described for other catalysts, a fine tuning of the acidity/basicity of the surface appeared to be critical. Rubidium- and cesium-doped β -zeolites were optimized for this reaction and the best results were obtained with $Rb_{0.95}Na_{0.05}\text{-}\beta$. The catalyst gave a selectivity of 70% and a conversion of 91% using a WHSV of 2.1 h⁻¹ and after a time on steam of 9-10 h (entry 13).⁸²¹ In this study, the deactivation of the catalysts was relatively low over 10 h of continuous operation. The group of Xu also reported that the activity of zeolite catalysts could be tuned by

modifying the $\text{SiO}_2/\text{Al}_2\text{O}_3$ ratio, since this parameter influences surface acidity and basicity. The group investigated such a parameter for potassium modified β -zeolites and observed that after 2 h on stream, a very high yield of 80% was obtained at 360 °C ($\text{WHSV} = 3.9 \text{ h}^{-1}$) for a $\text{SiO}_2/\text{Al}_2\text{O}_3$ ratio of 22, while 33% yield was obtained at $\text{SiO}_2/\text{Al}_2\text{O}_3$ ratio of 111 under identical operating conditions.⁸²² In addition, the former sample appeared much more stable than the ones with a higher $\text{SiO}_2/\text{Al}_2\text{O}_3$ ratio, as it gave yields around 60% after 32 h on stream. The authors suspected that the stronger basicity of the surface of zeolites with a higher ratio is responsible for its faster deactivation. Other types of zeolites were tested such as ZSM-5, and the $\text{SiO}_2/\text{Al}_2\text{O}_3$ ratio appeared to be critical as well. Similar conversion and selectivity (96% and 81%, respectively at $\text{WHSV} = 2.1 \text{ h}^{-1}$) were obtained using $\text{K}_{0.97}\text{Na}_{0.03}\text{ZSM-5}$ with a $\text{SiO}_2/\text{Al}_2\text{O}_3$ ratio of 27. Noteworthy, the $\text{K}_{0.97}\text{Na}_{0.03}\text{ZSM-5}$ sample was very stable since conversion and selectivity reached 80% and 70%, respectively, after 80 h on stream (entry 14). The zeolitic catalyst could be regenerated by flowing air at 450 °C through the sample. $\text{K}_{0.97}\text{Na}_{0.03}\text{ZSM-5}$ is currently one of the best catalyst reported in the primary literature for the dehydration of lactic acid so far, in terms of yield and stability.

Supported catalysts such as NaNO_3 -modified mesoporous silica SBA-15⁷⁷⁵ (entry 23) or potassium lactate supported on silica-alumina⁸²³ (entry 24) were also studied in fixed-bed reactors. In the latter case, despite a relatively low selectivity, the supported catalyst appeared to be remarkably stable as both selectivity and conversion dropped by only a few percents after 90 h on stream. This stable behavior supported the hypothesis that potassium lactate is smoothly regenerated during the reaction. The efficiency of this catalyst also supports the mechanism proposed by Xu and coworkers for the zeolite-catalyzed dehydration of lactic acid,⁸¹⁸ in which potassium lactate was a key intermediate.

Table 34. Catalysts and optimized conditions for the dehydration of lactic acid into acrylic acid.

Entry	Catalyst	Type	T (°C)	Space velocity	TOS (h)	Conv. (%)	Selec. (%)	Ref.
1	NaY	Zeolite	325	^a	2.75	94	60	811
2	2%La/ NaY	Zeolite	350	LHSV = 3 h ⁻¹	^a	>99	56	817
3	2.8%K/NaY	Zeolite	325	LHSV = 3 h ⁻¹	6	99	50	813
4	La-Ba/NaY	Zeolite	325	LHSV = 3 h ⁻¹	^a	>99	42	815
5	KI/NaY	Zeolite	325	^a	2	98	68	814
6	14%Na ₂ HPO ₄ /NaY	Zeolite	340	LHSV = 2.7 h ⁻¹	^a	85	69	812
7	2%Ba/NaY	Zeolite	325	LHSV = 3 h ⁻¹	^a	>99	45	816
8	K _{0.94} Na _{0.06} -β	Zeolite	360	WHSV = 2.1 h ⁻¹	2-4	95	64	818
9	K-ZSM-5	Zeolite	365	LHSV = 2 h ⁻¹	4	98	77	824
10	Na-ZSM-5	Zeolite	325	LHSV = 3 h ⁻¹	4.75	96	53	825
11	NaY-DA-0.15	Zeolite	350	^a	6	>99	75	820
12	NaOH/Na ₂ HPO ₄ modified ZSM-5	Zeolite	350	LHSV = 4 h ⁻¹	9	97	78	826
13	Cs _{0.81} Na _{0.19} -β	Zeolite	360	WHSV = 2.1 h ⁻¹	9-10	91	70	821
14	K _{0.97} Na _{0.03} ZSM-5	Zeolite	360	WHSV = 2.1 h ⁻¹	9-10	93	80	822
15	Ca-HAP Ca/P=1.55	Phosphate	350	^a	6	90	87	809
16	Ca-HAP Ca/P=1.62	Phosphate	360	WHSV = 1.4 h ⁻¹	6-8	84	74	808
17	Sr-HAP Sr/P=1.66	Phosphate	350	^a	6	72	63	810
18	Ba ₂ P ₂ O ₇	Phosphate	400	LHSV = 2.7 h ⁻¹	7.5	>99	76	805
19	Sr ₂ P ₂ O ₇ , 0.1% H ₃ PO ₄	Phosphate	400	WHSV = 2.54 h ⁻¹	4	>99	71	804
20	CePO ₄ (Ce/P=2.5)	Phosphate	380	WHSV = 1.74 h ⁻¹	16	>99	64	806
21	BaSO ₄	Sulfate	400	WHSV = 0.4 h ⁻¹	~1	>99	74	802
22	BaSO ₄ treated w/NH ₃	Sulfate	400	WHSV = 2.8 h ⁻¹	2-4	>99	81	803
23	23%NaNO ₃ /SBA-15	Supported catalyst	360	LHSV = 6 h ⁻¹	^a	91	42	775
24	K-Lactate/SiO ₂ Al ₂ O ₃	Supported catalyst	350	WHSV = 1.8 h ⁻¹	5	78	45	823

^aUnclear

4.1.7. Reduction into Propanoic Acid

Tang and coworkers studied the reduction of lactic acid into propanoic (propionic) acid (**145**) using different Fe_xO_y catalysts under an N₂ atmosphere and Fe₃O₄ was identified as the active species.⁸²⁷ Different parameters such as temperature, LHSV and stability were studied. The optimized conditions obtained for a LHSV of 2.6 h⁻¹ with a TOS of 3-4 h are described in Figure

103.

Interestingly, increasing the LHSV from 1.3 to 39.5 h⁻¹ led to a minor decrease in conversion from 98% to 88%, without affecting selectivity. The conversion of lactic acid decreased from 96% to 69% after a 100 h TOS (at LHSV = 26.3 h⁻¹), and the catalyst could be regenerated by calcination. In a follow-up paper, the same group used a fixed-bed reactor packed with Fe₃O₄ to reduce a 20 wt% aqueous solution of lactic acid into propanoic acid with a selectivity of about 59% and a conversion of 96% at 390 °C. The efficiency of the catalytic system remained constant for up to 9 h TOS.⁸²⁸ Mo(IV) oxide was also evaluated as heterogeneous catalyst by the same group, and good conversion (97%) and selectivity (63%) were obtained at 390 °C.⁸²⁹ A good stability of the catalyst was observed even after 45 h on stream. The authors performed control experiments with acrylic acid as the substrate, and poor yields in propanoic acid were obtained (14-15% depending on the conditions). These results suggested that the reaction proceeds through a direct hydrogenolysis rather than a dehydration into acrylic acid followed by a hydrogenation reaction. It was suggested that MoO₂ reduced lactic acid into propionic acid, forming MoO₃ which was subsequently reduced into MoO₂ by H₂ formed *in situ*, closing the catalytic cycle.

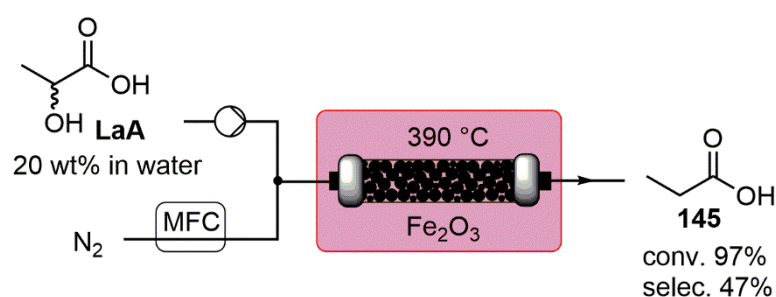


Figure 103. Reduction of lactic acid into propanoic acid through hydrogenolysis in the gas-phase.⁸²⁷

4.1.8. Decarbonylation/Decarboxylation into Acetaldehyde

Lactic acid can be converted into acetaldehyde (**49**) *via* decarboxylation or decarbonylation reactions. Supported heteropoly acids (HPAs) enabled a very efficient and selective decarbonylation process in the gas-phase.⁸³⁰ Four different catalysts were evaluated in a gas-phase fixed-bed reactor fed with aqueous lactic acid (20 wt%) and operated at 275 °C. Better results in terms of conversion and yield were obtained for the more acidic tungsten-based HPAs compared to molybdenum-based ones, which had a less acidic profile. Moreover, molybdenum-containing HPAs are known for their higher redox features which led to the formation of propanoic acid besides acetaldehyde. The authors also studied the impact of the silica support while using tungsten-based HPAs. A commercially available silica CARiACT® and a SBA-15 support were chosen for their significant differences in terms of specific surface (272 and 541 m² g⁻¹ respectively). With H₄SiW₁₂O₄₀ (HSiW) as the active phase, the CARiACT® support led to 91% conversion and 81% yield, while the SBA-15 support led to lower conversion (85%) but higher yield (83%, Figure 104). No catalyst deactivation was noticed after 5 h of continuous operation. Later on, Tang and coworkers tested different solid catalysts for the same reaction using a fixed-bed reactor operated at 380 °C.⁸³¹ Aluminum sulfate exhibited the best catalytic properties by comparison to other solid catalysts with higher concentration of acidic sites, such as heteropoly acids (H₄SiW₁₂O₄₀ and H₃PMo₁₂O₄₀). Heteropoly acids led to coking through C-C cleavage, therefore leading to a fast deactivation *via* carbon deposition. Other metal sulfates, such as Ba(II), Ni(II) or Fe(III), provided also quantitative conversion but with a much lower selectivity ranging from 19% for BaSO₄ to 54% for NiSO₄. Noteworthy, a significant decrease in both conversion and selectivity was observed after 10 h TOS, probably due to the formation of PLA on the catalyst. The latter could be regenerated by calcination at 380 °C in air. The same group reported on magnesium aluminium oxides in a fixed-bed reactor for the decarbonylation of a 20 wt% solution of lactic acid in the gas-phase.⁸³² Among different Mg/Al

oxides, $\text{Mg}_{0.388}\text{Al}_{2.408}\text{O}_4$ exhibited the best catalytic activity leading to quantitative conversion and a selectivity of 93% in acetaldehyde upon operation at 380 °C. During 400 h TOS, the selectivity remained constant, while the conversion marginally decreased to 75%. The same authors used magnesium aluminate spinel obtained from the co-precipitation of $\text{Mg}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ and $\text{Al}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ (ratio Mg/Al = 0.5) as catalyst for the same reaction.⁸³³ The ratio of magnesium over aluminium, determining the acidity and alkalinity features of the catalyst, was important since it was observed that an increase of the Mg/Al ratio led to a poorer selectivity for acetaldehyde. Under optimal conditions (380 °C, LHSV = 2.63 h⁻¹), quantitative conversion was obtained with a selectivity of 87.5% for acetaldehyde. The same group evaluated mesoporous carbon, activated charcoal and carbon nanotubes as catalysts for the conversion of lactic acid into acetaldehyde.⁸³⁴ Unmodified activated charcoal and carbon nanotubes were compared to their nitric acid treated counterparts. Mesoporous carbon was obtained from a mixture of H_3PO_4 (85%), Al(III) nitrate and citric acid that was subsequently heated, carbonized and treated. The acid properties of the different materials were determined using NH_3 -TPD and the mesoporous carbon catalyst exhibited larger amounts of weak and medium acid sites. This material provided the best catalytic activity, as medium acidic sites are known to favor the formation of acetaldehyde.⁸³¹ Temperature affected significantly the reaction since an increase from 300 °C to 380 °C led to an improvement of the conversion and a decrease of the selectivity. Under optimized conditions (350 °C), quantitative conversion was obtained with a selectivity of 92%. In addition, a significant decrease of the conversion was observed as operation time evolved. It decreased from 97% after 10 h TOS at 380 °C, to 70% after 20 h, and then plateaued at longer TOS. In another report, they described the conversion of lactic acid (20 wt% in water) into acetaldehyde using a mesoporous aluminium phosphate as a catalyst.⁸³⁵ The methodology for the preparation of the catalyst appeared to be critical, and

the best results were obtained when phosphoric acid and an aqueous solution of aluminium(III) nitrate were used as precursors. A quantitative conversion of lactic acid could be obtained at 325 °C with a selectivity of 92%. The major side-products detected in the effluents of the reactor were acetic acid, acrylic acid and 2,3-pentanedione.

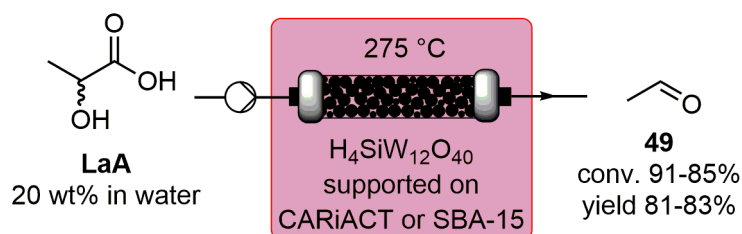


Figure 104. Decarbonylation of lactic acid using a supported heteropoly acid as catalyst.⁸³⁰

4.1.9. Miscellaneous

Lactamide/acrylonitrile. Recently, Traa and coworkers described the synthesis of acrylonitrile (54) from lactic acid in a two-step reaction involving the conversion of lactic acid in lactamide (146), followed by its subsequent dehydration into acrylonitrile using acetic anhydride as the dehydrating agent.⁸³⁶ The amidation of lactic acid was performed in the gas-phase and the best results were obtained using NH_4 -exchanged ZSM-5 zeolite as the catalyst. An NH_3/N_2 mixture was utilized as reactive carrier gas, and 92% selectivity for lactamide was obtained at 33% conversion, resulting overall in a space-time-yield of $188 \text{ g l}^{-1} \text{ h}^{-1}$ (Figure 105).

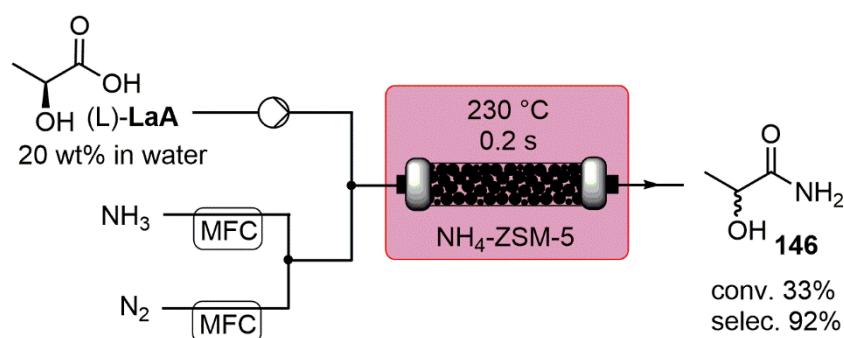


Figure 105. Synthesis of lactamide from lactic acid using NH_4 -modified zeolite.⁸³⁶

Higher ketones. Serrano-Ruiz and Dumesic proposed the use of lactic acid as a bio-based feedstock to reach valuable products, such as C₄-C₇ ketones, using a Pt(0.1%)/Nb₂O₅ catalyst loaded in a fixed-bed reactor and operating under a flow of H₂.^{837,838} Comparing this dual catalyst to platinum supported on an inert support (Vulcan[®]), the authors observed not only a better conversion in lactic acid, but also an increased formation of C₄-C₇ products. They subsequently proposed a complex mechanism in which both platinum and niobium oxide were responsible for the catalytic activity.⁸³⁸

4.2. Succinic Acid

4.2.1. Presentation, Producers, Current Commercial Routes and Markets

1,4-Butanedioic acid (succinic acid, SA, CAS 110-15-6) is a widely available and naturally occurring dicarboxylic acid that is encountered as an important metabolic intermediate. It was first isolated by Agricola in 1550 through the distillation of amber. SA was featured on the original 2004 list of most promising chemical from biomass issued by the US Department of Energy.²⁶ SA is currently produced on the industrial scale with an estimated market volume of 50,000 tons per year (\$ 131.73 million market value) at \$2500 or \$2860 per ton for petro- and bio-based SA, respectively.¹¹⁶ Besides being a versatile chemical, an increased demand for green and renewable chemicals is expected to sustain a steadily increase for the production of SA. The production should reach 94,000 metric tons by 2025 according to the Nova-Institute.⁸³⁹ Other sources foresee a significant market growth of 25-30% yearly with a demand of 500,000 tons or more by 2020.⁸⁴⁰ Such seemingly favorable context led to the inception of ambitious industrial programs in 2010-2015,⁸⁴¹ while the emergence of competitive non-renewable processes based on shale gas from 2015 jeopardized some of the pioneering bio-based SA plants.^{841,842}

SA can be produced according to chemical or fermentation processes.^{843,844} The world production of SA still uses fossil resources and mainly relies on the hydrogenation of maleic acid, maleic anhydride or fumaric acid with various catalysts such as Ni- or Cu-based catalysts (Scheme 23).⁸⁴⁵ The most common conditions on commercial scale involved liquid phase hydrogenation at moderate pressure (5-40 bar) and temperatures (120-180 °C) using either batch or continuous flow setups.⁸⁴⁶ Raw SA requires purification through distillation, often passing through the formation of succinic anhydride upon heating. High purity crystalline SA is then recovered after dissolution of the anhydride in hot water.⁸⁴⁶ SA is also co-generated as a side-product of the commercial production of adipic acid from cyclohexanol–cyclohexanone.⁸⁴⁵ SA can also be produced from the oxidation of 1,4-butanediol, from the carbonylation of ethane or ethylene glycol.⁸⁴⁷ Major players for the petro-based manufacturing of SA include DSM (The Netherlands), Gadiv Petrochemical Industries (Israel); Mitsubishi Chemical Corp. and Kawasaki Kasei Chemicals (Japan), Anqing Hexing Chemical and Anhui Sunsing Chemicals (China).¹¹⁶

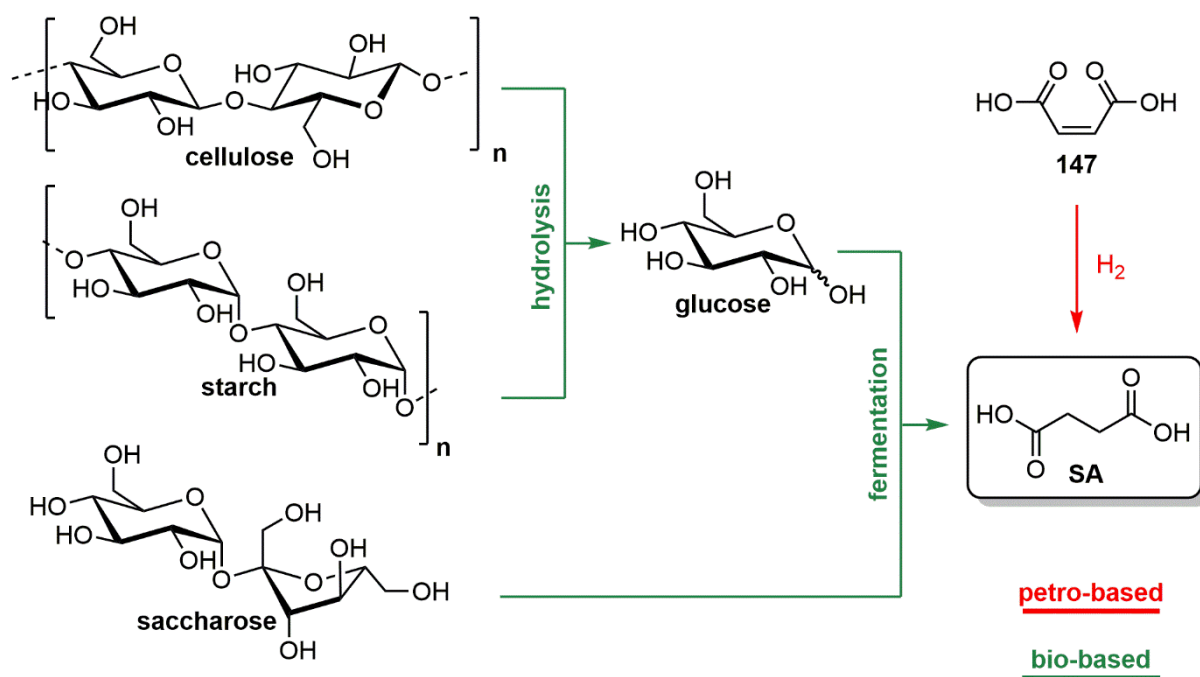
The development of fermentation processes toward SA has attracted considerable attention from 2010 and is still feeding significant research efforts (Scheme 23).^{848–852} The fermentation processes typically rely on the use of either bacteria strains from rumen or engineered microorganisms such as *E. coli* or *S. cerevisiae*. Such strategies were successfully implemented at pilot and demonstration scales, with the more mature technology (TRL 8) relying on the fermentation of sugars from sugar and starch crops.⁸⁴⁴ Other technologies aiming at the production of SA from glycerol or lignocellulosic material are currently at much lower TRLs (3-5), and full commercial development is not expected before a decade.⁸⁴⁴ The theoretical yield for SA from glucose is however very appealing (1.12 kg kg⁻¹).^{853,854} Glucose, glycerol, sucrose, maltose, lactose, and fructose have been used as carbon sources for SA production, although

glucose remains the most common and successfully implemented bio-based resource for SA.^{853,854} Among the world's biggest producers, BioAmber (Canada), Myriant (USA), Succinity (Spain) and Reverdia (Italy) dominated the market until 2016 with an overall production capacity of about 65,000 tons per year.^{855,856} Since 2019, Roquette operates alone the bio-based SA plant in Italy (10,000 tons per year).^{856,857} While not providing information concerning its production, Shandong Landian Biological Technology (China) is also a major player in the field.

As for the fermentation processes toward LaA (see section 2.3.7), the fermentation processes toward SA cogenerates large amounts of low value-added inorganic salts, hence resulting in high production costs and an overall high environmental footprint. Current research efforts are focused on improving the yield of SA at low pH as well as on increasing the efficiency of the separation and purification steps.^{844,858} Actually, the fermentation processes still suffer from high separation and purifications costs: the separation is complex since SA is typically produced simultaneously with other carboxylic acids.⁸⁴⁴

Industrial applications for SA are wide and range from niche applications such as personal care and food additives, to large-volume applications such as biopolymers.⁸⁵³ SA is also a precursor of a range of industrially relevant C-4 building blocks such as 1,4-butanediol (see section 4.2.2.), tetrahydrofuran, γ -butyrolactone, 1,4-butanediamine, 2-pyrrolidone, succinic anhydride, maleic anhydride, maleic acid, and other higher homologs compounds such as *N*-methylpyrrolidone and adipic acid.^{847,859}

Scheme 23. Most common chemical and fermentation processes for the preparation of succinic acid. See below for the preparation of maleic acid (**147**) from butane (Scheme 25). Starch is represented here as amylopectin.



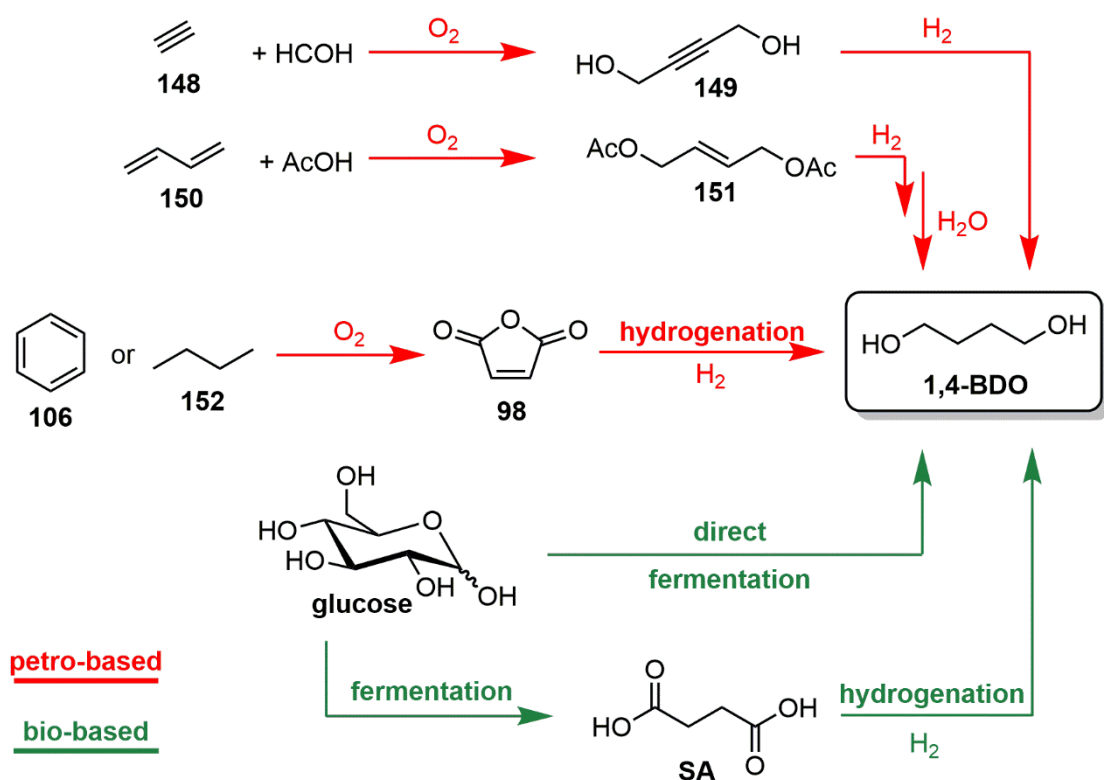
4.2.2. Reduction into 1,4-Butanediol

The most common petro-based process for the commercial production of 1,4-BDO is the Reppe process (BASF, Germany) that accounts for more than 40% of the petro-based 1,4-BDO. It relies on acetylene (**148**) and formaldehyde as primary feedstock (Scheme 24).^{117,510} The reaction first produces 1,4-butyndiol (**149**) through the condensation of 2 equivalents of formaldehyde with **148**; further reduction of the alkyne **149** by continuous hydrogenation over a Ni-based catalyst yields 1,4-BDO.^{116,510} Another commercial process is operated by Mitsubishi (Japan) since 1979. It relies on the reaction of butadiene (**150**) and acetic acid that gives 1,4-diacetoxy-2-butene (**151**) (Scheme 24). 1,4-Diacetoxy-2-butene is next subjected to hydrogenation and the corresponding 1,4-diacetoxybutane is eventually hydrolyzed to 1,4-BDO.^{116,510} Other technologies relying on maleic anhydride (from benzene or butane), as well as propylene or propylene oxide, were also developed (Scheme 24). The price of 1,4-BDO fluctuates with the price of the primary petro-based starting materials. Major producers of petro-

based 1,4-BDO include Darien Chemical Corporation (Taiwan), BASF (Germany), LyondellBasell (USA), Ashland (USA) and Xinjiang (China).¹¹⁷

The commercial production of 1,4-BDO also relies on fermentation processes.^{116,117,510,860} Two main fermentation processes are exploited: a one-step fermentation of glucose to 1,4-BDO or a two-step process with glucose fermentation toward succinic acid (SA) and its subsequent hydrogenation toward 1,4-BDO (Scheme 24).^{116,510} Novamont (Italy) operates since 2016 a fermentation process for the direct production of 1,4-BDO from glucose (30,000 tons per year). DSM (The Netherlands) and Genomatica (USA) have announced joint ambition for the commercial production of 1,4-BDO from glucose.⁸⁶¹ Bio Amber and Myriant exploit technologies based on the conversion of SA into 1,4-BDO.^{117,862} The forecast for bio-based 1,4-BDO is excellent, especially with the increasing availability of bio-based succinic acid to sustain the fermentation process toward 1,4-BDO, although the actual fermentation processes rely exclusively on corn-syrup and thus compete with the food industry.¹¹⁷

Scheme 24. Simplified chemical processes for the preparation of 1,4-BDO from petro-based or bio-based feedstock.



The reduction of SA to 1,4-BDO was studied by Vardon and colleagues under continuous flow conditions.⁸⁶³ The method relied on the development of a bimetallic Ru-Sn catalyst supported on granular activated carbon that was compatible with aqueous conditions and that remained active for prolonged time-on-stream. The authors reported that the addition of Sn to Ru significantly increased the catalyst affinity for H_2 . The flow reactor (a stainless steel tube) was coated with an inert layer of silica to reduce the leaching of Ni from stainless steel to the bimetallic Ru-Sn catalyst and maintain stable performance. With a WHSV of 0.06 h^{-1} , complete conversion of succinic acid was noticed and the product composition contained essentially 1,4-BDO (71%) and THF (15%), with traces of GBL (3%) and butanol (2%). Typical process conditions implied reacting an aqueous solution of succinic acid (5 wt%; flow rate ranging from $0.10\text{--}0.25 \text{ mL min}^{-1}$) and H_2 (flow rate of 200 sccm) under 124 bar of pressure. The catalyst bed was operated at $165\text{--}195^\circ\text{C}$ (Figure 106).

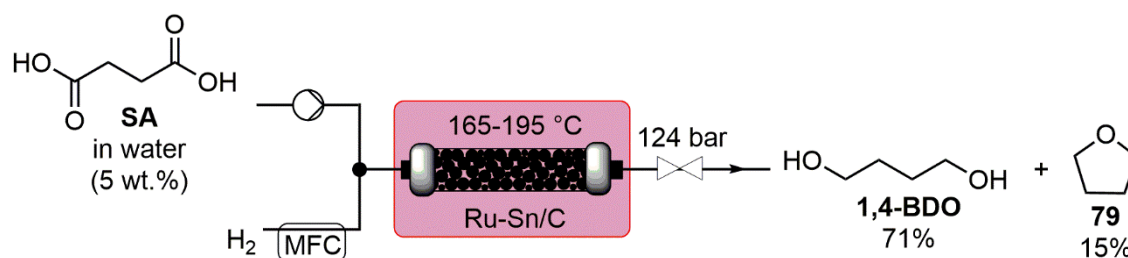


Figure 106. Reduction of SA in water using a bimetallic Ru-Sn catalyst supported on granular activated carbon.⁸⁶³

4.3. Fumaric Acid

4.3.1. Presentation, Producers, Current Commercial Routes and Markets

trans-Butenedioic acid (fumaric acid, FA, CAS 110-17-8) is an important metabolic intermediate in Krebs' cycle and the reductive carboxylation pathway that was first isolated from herbaceous annual *F. officinalis*.⁸⁶⁴ It was included on the original 2004 list of most promising chemicals from biomass issued by the US Department of Energy.²⁶ FA is currently produced on the industrial scale with an estimated market volume of 240,000 tons at \$1280-1700 per ton, with a 350,000 tons per year forecast by 2020.^{864,865} FA was produced in the first half of the 20th century using a fermentation-based process relying on glucose-rich feedstocks and fungus *Rhizopus arrhizus* by Pfizer, National Distillers and Chemical Corporation as well as DuPont.^{864,866} Following the rapid development of economically viable petrochemical routes, the fermentation process was progressively abandoned. The most common chemical process relies on the hydrolysis of maleic anhydride (**98**) and isomerization of the resulting maleic acid (**147**); this commercial route only absorbs a few percent (3-5%) of the global production of maleic acid.⁶⁰⁵ **147** was originally prepared on the commercial scale from the oxidation of benzene (**106**) and that process remained predominant until the 1980's.⁶⁰⁵ Butane (**152**) is nowadays considered as an economical and environmentally acceptable feedstock.^{605,867} Butane

(152) is transformed under aerobic conditions in the presence of vanadyl pyrophosphate, using various types of reactor technologies (Scheme 25).^{868,869} Maleic anhydride (98) is preferably purified and then hydrolyzed and isomerized. The isomerization of maleic acid (147) is performed on the commercial scale under thermal conditions (typically 150 °C) in the presence of different types of catalysts, including mineral acids, peroxy compounds and thiourea or derivatives.^{605,865,867} Crystallization of FA from an aqueous solution provides high purity material.^{605,867} China largely dominates the production of FA.⁸⁶⁵ The era of petrochemical production of FA is still staffing for the many years to come with the construction of new industrial facilities. For instance, the Indian producer Thirumalai Chemicals has plans to build a 30,000 tons per year facility on US soil for the production of food grade maleic and fumaric acid. Bartek Ingredients (Canada) has also recently upgraded its production capacity with a new 22,000 tons per year reactor. Huntsman Corporation is one of the world leaders for the production of FA. In Asia, Changzhou Yabang Chemical Co. Ltd. (China), Changmao Biochemical Engineering Company Limited (China), Nippon Shokubai (Japan) and Yongsan Chemicals (Korea) are significant producers for FA.

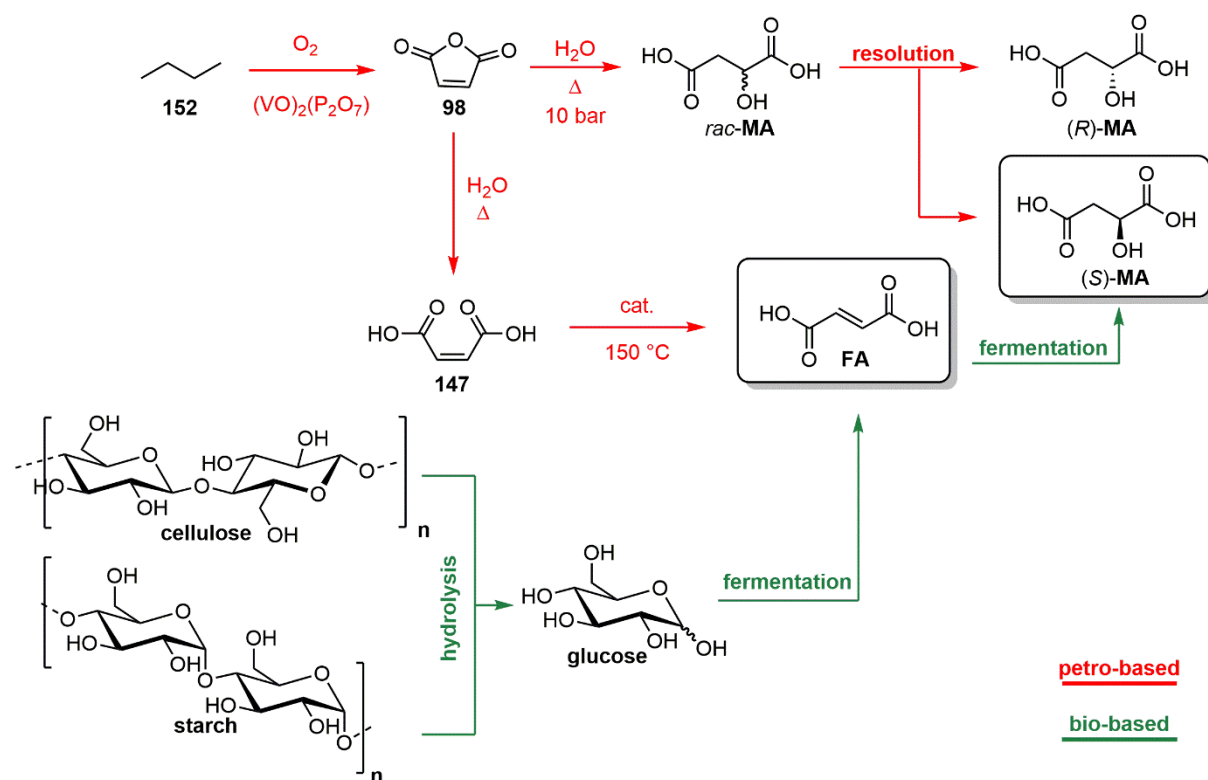
Despite the hegemony of the petrochemical process toward FA, the development of new technologies and engineered strains for bacteria fermentation-based processes is still a very vivid research topic in the primary literature.^{245,870–872} The fermentation processes typically rely on various strains from *Rhizopus* fed on glucose (Scheme 25).²⁴⁵ Fructose can also be considered as an alternative feedstock, although it is poorly metabolized in *Rhizopus*. Other microorganisms such as *Mucor*, *Cunninghamella*, and *Circinella* have been considered as potential tools for the fermentation processes.^{245,865} Developments toward the use of starch crops rather than sugar crops have been reported as well.⁸⁶⁵ As for other fermentation processes toward carboxylic acid, pH management is critical to maintain high productivity, hence co-

generating large amounts of low value inorganic salts.²⁴⁵ From the data available in the literature, it appears that the most advanced fermentation processes are still at intermediate TRL, with only a few examples of significant steps toward full scale commercial production.^{865,873,874}

Myriant (now GC Innovation America) has expanded its portfolio toward fermentation technologies for the commercial production of FA.^{864,875}

A significant portion (*ca.* 30%) of the production of fumaric acid is absorbed in the food industry where FA is used as an acidulant, preservative and flavoring agent.⁸⁶⁴ The second largest application (*ca.* 20%) concerns the paper industry, followed with the polymer/resin industry (polyester resins *ca.* 20% and alkyd resins *ca.* 10%).⁸⁶⁴ FA and some of its derivatives have also found direct medical applications such as for the treatment of psoriasis (Fumaderm®), Skiladerm®) and sclerosis (Tecfidera®).⁸⁶⁴

Scheme 25. Most common chemical and fermentation processes for the preparation of fumaric and malic acids. Starch is represented here as amylopectin.



4.3.2. Esterification into Dimethyl Fumarate

De Souza and colleagues reported a continuous flow process for the preparation of dimethyl fumarate, an API for treating psoriasis and multiple sclerosis.⁸⁷⁶ The process relied on the Fischer esterification of fumaric acid with methanol, catalyzed by sulfuric acid. 98% yield was obtained in flow under optimized conditions, corresponding to 10.2 kg day⁻¹ productivity. Optimized conditions in batch involved 2 h of reaction at 55 °C, while only 12 min of reaction at 120 °C were necessary in flow since the system could be operated under pressure.

4.3.3. Enzymatic Hydration to Malic Acid

Malic acid (MA) can be produced according to chemical or fermentation processes. The most common chemical processes rely on the hydration of either maleic anhydride, maleic acid or fumaric acid. In a typical process, maleic acid is hydrated at 180 °C (10 bar), and high purity MA is recovered after recrystallization (Scheme 25). One of the most significant producers of MA acid is Fuso (Japan),⁸⁷⁷ which uses maleic anhydride as starting material. Changmao Biochemical Engineering Company Limited (China), Yongsan Chemicals (Korea) and Thirumalai Chemicals (India) are significant producers of MA and FA. In Europe, Polynt (Italy) emerges has a leading producer of MA with a 22,000 tons per year capacity announced in 2016.⁸⁷⁸ In North America, Bartek (Canada) is the world's largest producer of malic acid.^{879,880} The Indian Thirumalai Chemicals has also very strong ambitions in the US.⁸⁸¹ Isegen (South Africa) is the sole producer of malic acid in Africa.

The fermentation process gained significant attention over the last decade.⁸⁸² The most common and economic fermentation process relies on the enzymatic conversion of FA mediated by fumarase hydratase or using *Saccharomyces cerevisiae* cells containing the overexpressed gene

for fumarate hydratase.^{853,882,883} Such process produces enantiopure L-(-)-MA (Scheme 25). Novozymes reported in 2012 the successful metabolic engineering of fungus *Aspergillus oryzae* that enables an optimized production of malic acid from glucose.^{882,884} The Industrial Biotechnology Group of Fraunhofer IGB (Germany) develops industrial fermentation processes for the preparation of MA from biogenic raw materials. Industrial Microbes has reported a fermentation process to manufacture malic acid from CO₂ and natural gas.⁸⁸⁵ Other attempts for its production starting from other resources such as glycerol have been reported as well.⁸⁸⁶

In a series of two papers, Žnidaršič-Plazl reported functionalized microfluidic reactors for the enzymatic hydration of FA into (L)-MA.^{887,888} In a first report,⁸⁸⁷ glass microfluidic chips (332 of 664 mm length, 220 μm width, and 100 μm height) from Micronit Microfluidics were functionalized with porcine fumarase. The enzyme was covalently bound to the inner wall of the microfluidic chips using a standard glass functionalization protocol (activation with NaOH, then HNO₃ followed with a treatment with APTES and next 5% glutaraldehyde). The functionalized microreactors were next fed with FA (5 to 500 mM) in phosphate buffer (0.1 M, pH 7) and operated at 30 °C. A residence time of 15 min was required to reach 80% conversion at the maximum concentration of FA (500 mM), while shorter residence times down to 2 min gave a similar conversion with the lowest concentration of FA (5 mM). In a follow-up study,⁸⁸⁸ the authors described the functionalization of PFA tubing using a similar procedure. The authors used whole cells from the *S. cerevisiae* strain for the transformation of FA. Once the cells were covalently anchored on the inner wall of the PFA tubing, infusion with cetrimonium bromide was applied to increase cell permeability. The cell-functionalized PFA flow reactor was next fed with FA (1 to 20 mM) in phosphate buffer (0.1 M, pH 7) and operated at 30 °C. Conversion of *ca* 80% was obtained with a residence time of 20 min with 2 mM FA. Stability trials over 4 consecutive days indicated that less than 5% of the cells originally anchored on the reactor wall

detached, although the volumetric productivity significantly decreased (50% of the initial value after 34 h of continuous operation) most likely through fumarase deactivation.

4.3.4. Upgrading to Butyrolactones

Monbaliu and coworkers reported the upgrading of FA toward a small library of value-added butyrolactones **154** compounds through the addition of radicals derived from alcohols under photosensitized irradiation at 365 nm (Figure 107).⁸⁸⁹ The conditions were first optimized in microfluidic glass chips (92 μ L internal volume). The preliminary conditions involved a solution of FA in isopropanol in the presence of benzophenone (**153**) as a photosensitizer. The conditions were next transposed to a mesofluidic lab scale photoreactor (2.5 mL internal volume), which was integrated with a downstream in-line low field NMR for real-time process analysis.

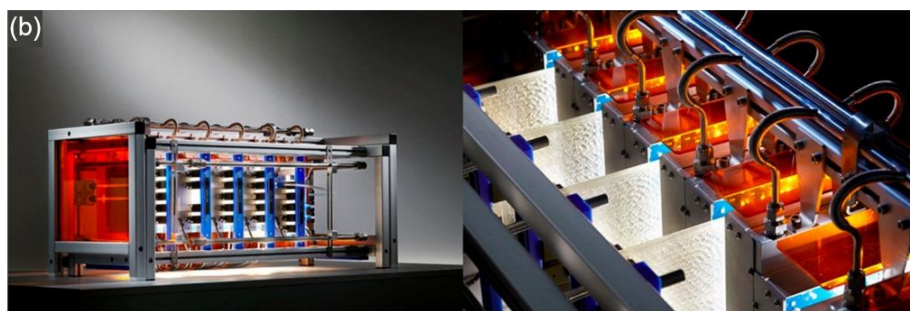
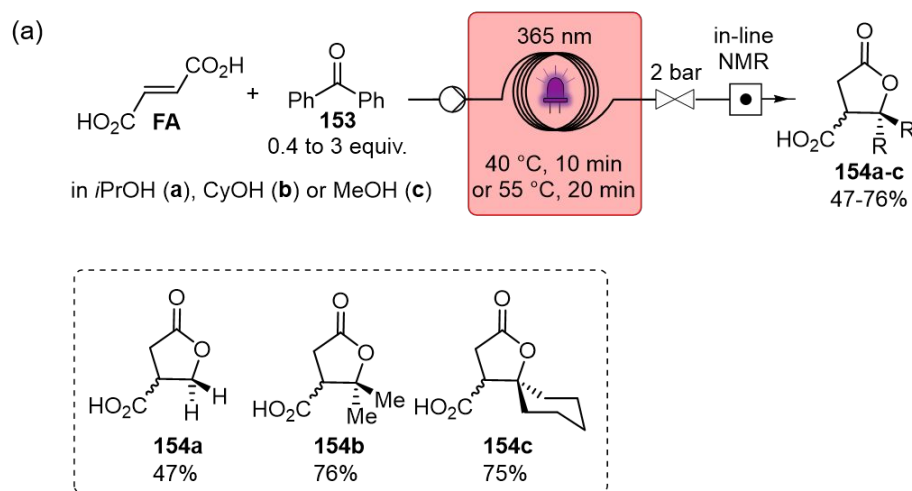


Figure 107. (a) General flow chart for the upgrading of fumaric acid into valued-added butyrolactones.⁸⁸⁹ (b) Photograph of the commercial pilot scale photoreactor used for the assessment of scalability for the upgrading of FA into butyrolactones (40 mL internal volume).

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FA underwent a Michael-type radical addition upon UV irradiation at 365 nm, followed with lactonization to form various butyrolactones, the backbone of which depended on the alcohol used as solvent. Methanol, isopropanol and cyclohexanol were successfully utilized as both reaction medium and reagent for the upgrading of FA (0.2 M in the corresponding alcohols). Butyrolactones **154a-c**, including a spiro derivative, were prepared in moderate to good isolated yields (47-76% isolated yields). Upon optimization, the upgrading of FA in isopropanol was transposed to larger scales and implemented in a commercial pilot scale mesofluidic photoreactor (40 mL internal volume), leading to an unprecedented productivity of 83 g per day of the corresponding butyrolactone **154a** (60% conversion, 10 min residence time).

4.4. Malic Acid

4.4.1. Presentation and Markets

2-Hydroxybutanedioic acid (malic acid, MA) is a saturated dicarboxylic acid bearing a hydroxyl group and a stereogenic center. It exists as two enantiomers (L-(-)-MA and D-(+)-MA), although only L-MA is naturally occurring as an important metabolite in Krebs' and glyoxalate cycles.^{853,890} MA was isolated for the first time from apple juice by Scheele in 1785.⁸⁹⁰ Enantiopure (L-(-)-MA, CAS 97-67-6; D-(+)-MA, CAS 636-61-3) or racemic MA ((D,L)-(±)-MA CAS 6915-15-7) are currently produced on the industrial scale. Synthetic MA is produced as a racemate ((D,L)-(±)-FA), while fermentation processes starting from FA lead to L-(-)-MA. Both enantiomers can be separated through the resolution of (D,L)-(±)-MA. MA was featured on the original 2004 list of most promising chemicals from biomass issued by the

US Department of Energy.²⁶ MA has a global market of 60,000 tons per year (\$1700-2500 per ton) with an overall estimated market value of \$186 million.^{885,891} The market forecast for MA is estimated at 200,000 tons per year.^{853,892} The most important current market for MA is the food industry where MA is used as acidulant and flavor enhancer. It also has applications in the pharmaceutical and polymer industries. MA bears a significant industrial forecast since it can be converted as other bio-based C₄-diacids into 1,4-butanediol, and potentially access a market of about US\$2.5 billion.⁸⁹³

The main commercial routes, emerging continuous flow alternatives and major producers of MA are detailed in section 4.3.3.

4.4.2. Esterification into Dimethyl Malate

Fukuyama *et al.* developed a simple yet robust flow protocol for the Fischer esterification of a library of carboxylic acids, including MA.⁸⁹⁴ The procedure relied on a stainless steel column packed with a modified sulfonic acid supported on silica. The packed-bed reactor was operated under super-heated conditions (110 °C) under 5 bar of counterpressure. Methanol was used both as reaction solvent and coreactant for the esterification of malic acid (1 M). Dimethyl malate (**155**) was obtained in 96% yield within 3 min of residence time using a packed-bed loaded with 340 mg of sulfonic acid modified silica (Figure 108).

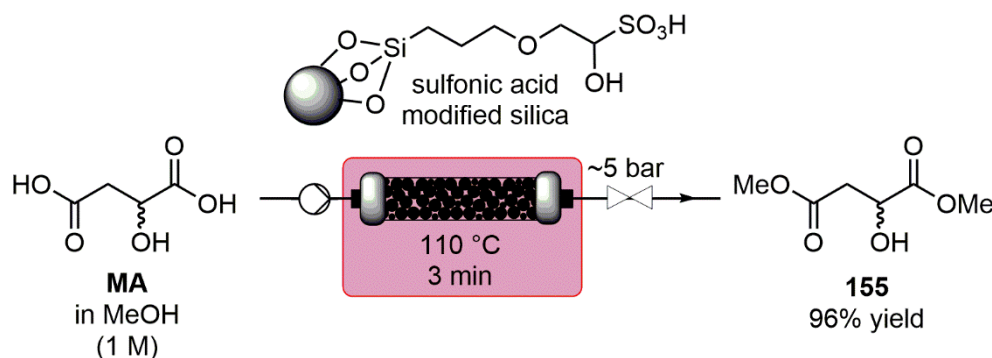


Figure 108. Fischer esterification of malic acid with methanol in a fixed-bed flow reactor.⁸⁹⁴

4.5. Itaconic Acid

4.5.1. Presentation, Producers, Current Commercial Routes and Markets

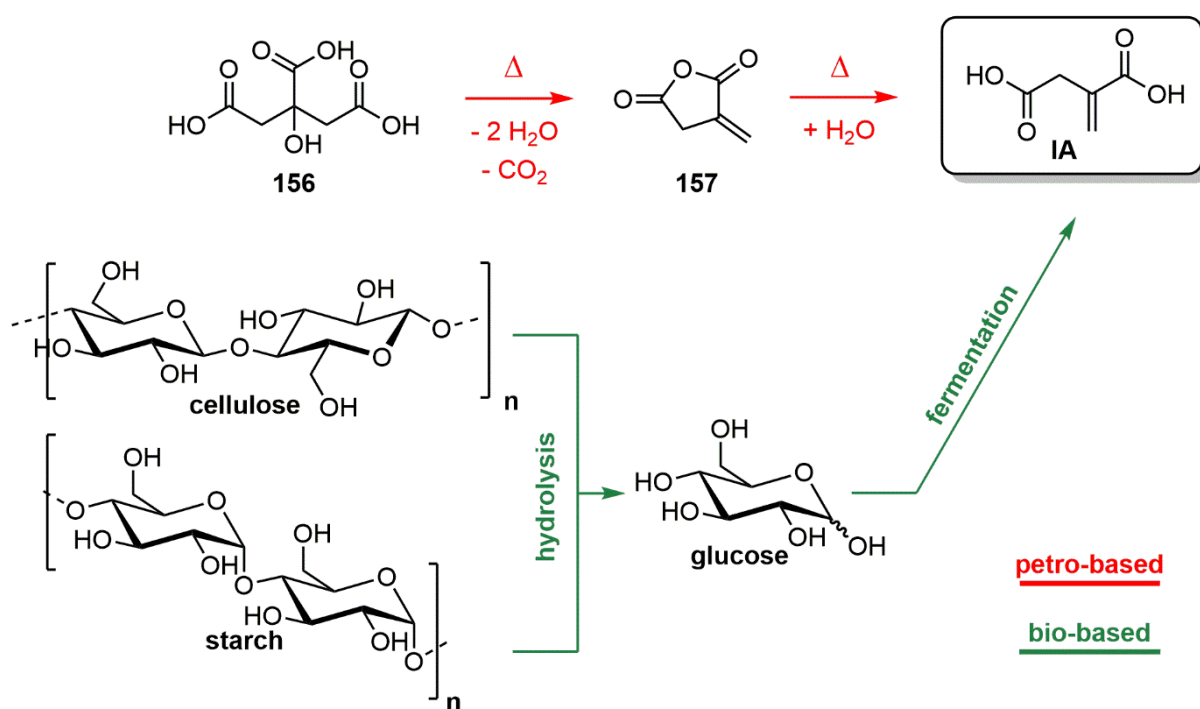
2-Methylidenebutanedioic acid (itaconic acid, IA, CAS 97-65-4) is a naturally occurring and important unsaturated organic dicarboxylic acid platform. The biosynthesis of IA involves the decarboxylation of *cis*-aconitate from Krebs' cycle.⁸⁹¹ It was discovered in 1837 by Baup from the pyrolysis of citric acid.⁸⁹⁵ It was included on the original 2004 list of most promising chemical from biomass issued by the US Department of Energy.²⁶ IA is produced on the industrial scale with still a relatively modest market volume of 40,000 tons per year (\$79 million market value) at \$1900 per ton in 2015.¹¹⁶ Unless significant process advances leading to a decrease in production costs, the projections for the market size of IA will not exceed 197,000 tons per year (\$315 million market value) by 2020.⁸⁹⁶

IA can be produced according to chemical or fermentation-based processes. The chemical processes rely on various starting materials including citric acid (**156**) (Scheme 26), isoprene and mesityl oxide, though none of these reactions are economically viable and utilized on the commercial scale.^{845,895}

The first industrial trace of a fermentation process toward IA dates back to 1945 (Pfizer).⁸⁴⁵ IA is mainly produced on the commercial scale from the fermentation of sugar-based feedstocks with *Aspergillus* strains (Scheme 26). Low to moderate yields are typically obtained, unless glucose is utilized as primary carbon source.^{24,116,897,898} Recent works emphasized the potential use of lignocellulosic-derived feedstocks.^{871,898} Large producers of IA such as Rhodia (France) and Cargill (USA) interrupted their production over the last decade. China is nowadays the largest producer of IA. The main producers in China include Qingdao Kehai Biochemistry, Jinan Huaming Biochemistry, Alpha Chemika and Zhejiang Guoguang Biochemistry.^{116,891,899} IA is used primarily as a specialty monomer; it can be used as a copolymer with acrylic acid and/or with styrene and butadiene.⁹⁰⁰ The main hurdle for the generalized adoption of IA for

the preparation of bio-based polymer is its high production costs. The escalation of the commercial war between President Trump's and President Jinping's administrations has therefore a significant impact on the potential use of IA in the USA, regardless of its end use.⁹⁰¹ Itaconix (UK) has received AkzoNobel's support to further expand the development of bio-based itaconic acid polymers.^{902–904} This partnership was further extended in 2019, with applications for bio-based itaconic polymers to the markets of detergents and personal care.^{905–}⁹⁰⁷ IA can also be transformed into other important chemicals such as 4-methyl- γ -butyrolactone, 3-methyltetrahydrofuran, 3-methylpyrrolidine and various pyrrolidones.⁸⁹⁸

Scheme 26. Simplified chemical and fermentation processes for the preparation of itaconic acid.



4.5.2. Reduction into 2-Methylsuccinic Acid

In a series of papers, Szöllősi and coworkers studied the enantioselective reduction of itaconic acid into 2-methylsuccinic acid (**154**).^{908,909} The authors developed an enantioselective protocol relying on cinchonidine (**152**) and benzylamine (**153**). The protocol was adapted to continuous

flow conditions with a H-Cube reactor from ThalesNano using a cinchona alkaloid-modified Al_2O_3 -supported Pd catalyst. Reaction conditions involved a 2 MPa pressure of hydrogen at *ca.* 10 °C and a flow rate of 1 mL min⁻¹ for the feed solution of IA. The authors used a feed concentration of 50 mM IA in methanol, and reported full conversion, yet with a modest 40% ee in the presence of 5 mol% of cinchonidine and 2 equiv. of benzylamine (Figure 103).

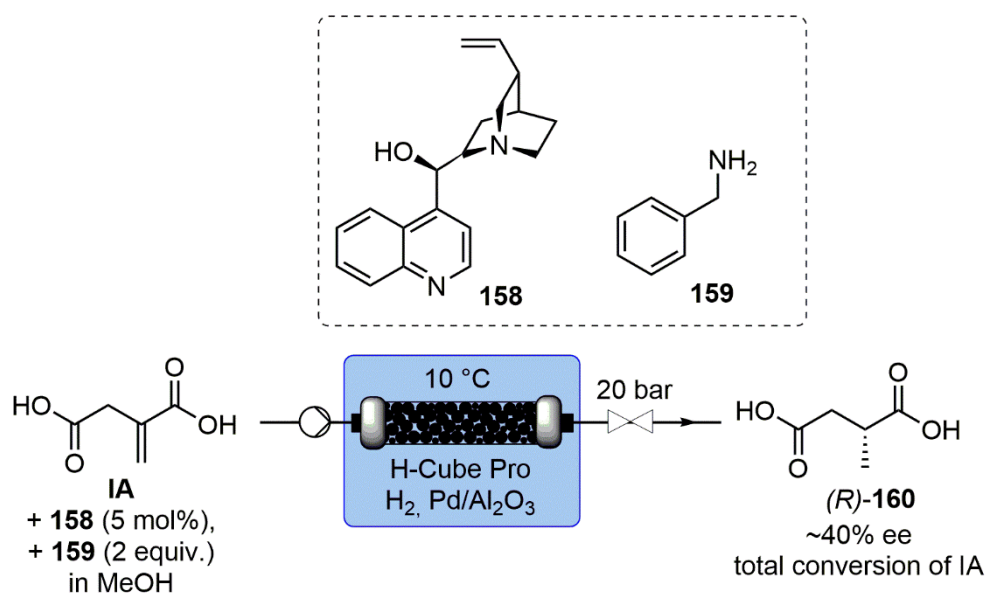


Figure 109. Reduction of IA toward 2-methylsuccinic acid under enantioselective continuous flow hydrogenation.^{908,909}

4.5.3. Upgrading to Butyrolactones

Building upon the development of a continuous flow photochemical process for the upgrading of FA (see section 4.3.4), Monbaliu and coworkers applied a similar strategy for the transformation of IA toward a small library of value-added butyrolactone compounds **156a,b** (Figure 110).⁸⁸⁹ The conditions implied reacting a feed solution of IA (0.2 M) in either isopropanol or cyclohexanol in the presence of benzophenone as a photosensitizer under 365 nm irradiation in a commercial 2.5 mL internal volume flow reactor. Complete conversion was obtained within 10 min of irradiation time, with isolated yields of 52% and 72% for the addition

products with isopropanol and cyclohexanol, respectively (Figure 110a). By contrast to the process with FA, the reaction with MeOH failed. The addition products formed through a two-step process, starting with the addition of either isopropanol or cyclohexanol-derived radicals followed with a 5-exo-trig lactonization of linear intermediate **155** (Figure 110b).

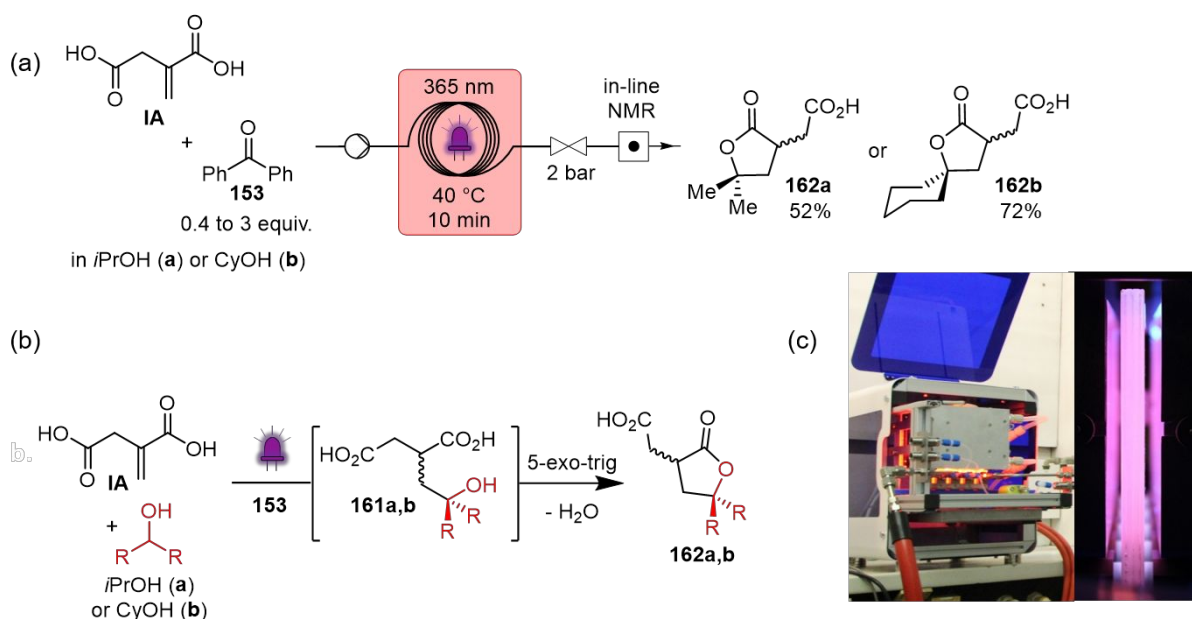


Figure 110. (a) General flow chart for the upgrading of itaconic acid into valued-added butyrolactones. (b) Details of the two-step reaction process: addition of a secondary alcohol-derived radical upon irradiation at 365 nm and 5-exo-trig lactonization. c. Photograph of the commercial lab scale photoreactor used for the upgrading of IA into butyrolactones (2.5 mL internal volume). Adapted with permission from ref 889. Copyright 2017 American Chemical Society.

4.6. Levulinic Acid

4.6.1. Presentation, Producers, Current Commercial Routes and Markets

4-Oxopentanoic acid (levulinic acid, LeA, CAS 123-76-2) is one of the simplest and most important oxocarboxylic acids. It was synthesized for the first time in 1840 by Mulder by

heating fructose in the presence of hydrochloric acid.^{576,882,910} LeA was featured as a promising chemical from biomass on the original 2004 publication from the US Department of Energy.²⁶ It has gained modest commercial importance since the 60's. LeA is considered as the end product of the thermal acid-catalyzed hydrolysis of lignocellulosic feedstock.^{26,882,911} Reliable metrics on current LeA's market size and value are difficult to obtain. LeA is produced on the industrial scale with at a high price of *ca.* \$ 2500-3000 per ton (2016) and serves mostly specialty markets.⁹¹² China dominates the production of LeA with a global capacity of 5,000 tons per year. The maturity of the processes toward LeA is expected to increase within the next few years along with a significant decrease of production costs. The current market for LeA is estimated at 6,000 tons per year (\$10 million), yet the forecast for 2029 is huge especially for biofuels derived from LeA with a potential market value of over \$1,000 billion.²⁶

Though LeA can also be produced from petro-based chemicals such as maleic acid,⁹¹³ it is mainly produced through the acid-catalyzed dehydration of either 5- (e.g. xylose, arabinose) or 6-carbon lignocellulosic carbohydrates according to multistep processes.^{576,882,910,913,914} When starting from 5-carbon carbohydrates, the reaction proceeds through the formation of furfural that requires subsequent reductions toward furfuryl alcohol (**99**) and eventually LeA,⁹¹⁵ while when starting from 6-carbon carbohydrates, the reaction proceeds most likely through the intermediate formation of HMF (see Scheme 18).⁹¹⁵ Isolation of high purity LeA is cumbersome and typically proceeds through distillation.⁵⁷⁶ The Biofine process uses diluted sulfuric acid as a catalyst for the fractioning of lignocellulosic feedstock to give levulinic acid and furfural, as well as formic acid.⁵⁷⁷ DSM has developed an economically attractive process for processing wood into LeA and furfural with a claimed carbon neutrality.⁹¹² DSM's process relies on wood and is an interesting alternative to the most common methods that rely on corn cobs or bagasse (300,000 tons per year). GFBiochemicals (Italy) is another major producer of LeA;⁹¹⁶

1
2
3 GFBiochemicals has acquired Segetis in 2016 (a US leader for the production of LeA),⁹¹⁷ and
4
5 operates a 10,000 tons per year facility (2017-2018).^{918–921}
6

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8 The Dutch company Avantium operates a process for the production of levulinic acid methyl
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10 ester starting from plant carbohydrates.⁹¹³ In 2017, Avantium announced a co-investment with
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12 AkzoNobel for the construction of a pilot plant for the Zambezi process that uses concentrated
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14 hydrochloric acid at low temperatures to fractionate cellulose, hemicellulose and lignin in wood
15
16 feedstock. Still in 2017, Bio-on (Italy) and Eridania Sadam Group (Italy) launched the
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18 production of LeA (5,000 tons per year) using by-products of the sugar industry.^{918,922,923} In
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20 China, major producers include for instance Hefei, Langfang Triple Well Chemicals and Apple
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22 Flavor & Fragrance Group or Simagchem.
23
24

25
26 The potential market for levulinic acid is huge: it is a building block for commercial
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28 applications toward pharmaceuticals, plasticizers, fragrances and cosmetics.⁹²⁴ LeA can also
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30 serve as a substitute for bisphenol-A (through diphenolic acid). Besides, LeA can also be
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32 upgraded into a variety of higher value-added industrial building blocks such as levulinic acid
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34 esters and levulinic acid derived ketals, 5-aminolevulinic acid, valeric acid and derived esters,
35
36 γ -valerolactone (GVL), angelica lactones, succinic acid, maleic anhydride, 2-
37
38 methyltetrahydrofuran, as well as transport fuels.^{21,576,913,915,924,925}
39
40

41
42 Intense research efforts were dedicated to the hydrogenation of levulinic acid into gamma-
43
44 valerolactone (GVL) which can be used as a solvent, a food additive, a fuel, or as a key building
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46 block for organic synthesis.^{926–928}
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49 50 4.6.2. Esterification into Alkyl Levulinates

51
52 Alkyl levulinates are either produced by the direct alcoholysis of various carbohydrates, or
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54 sourced from the esterification of LeA with various alcohols. Alkyl levulinates have potential
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56 applications in the transport fuel sector (e.g. as blend components in diesel formulations), as
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59

green solvents, in the production of fine chemicals, as plasticizers and as precursors in flavoring and fragrance industries.^{929–931} It can be noted that a dense body of literature is also available on the upgrading of alkyl levulinates under continuous flow conditions, targeting mainly GVL and using various reducing agents.^{932–935} Alkyl levulinates have a lower boiling point as compared to LeA, which makes them easier to handle in the gas phase and to separate as compared to LeA. In this section, we cover the continuous flow mode conversion of LeA to alkyl levulinates.

Vaccaro and colleagues explored the esterification of levulinic acid toward alkyl levulinates using various sulfonated cation exchange resins.⁹³⁶ Various alcohols were tested as reactants to yield a library of structurally diverse alkyl levulinates. Among the various acidic catalysts tested in batch, the perfluorosulfonic polymer Aquivision® PFSA (Aquivion mP98) showed the most promising results partially due to its non-porous structure that inhibits water adsorption. The process was translated into a continuous flow reactor, allowing quantitative conversion and a productivity of 4.8 g h⁻¹ at 90 °C. Kong *et al.* reported the use of the cerium salt of phosphotungstic acid (CePW) supported on silica gel pellets for the continuous flow esterification of levulinic acid toward ethyl levulinate.⁹³⁷ 99% of conversion and quantitative selectivity were obtained upon utilizing a 1:10 molar ratio of levulinic acid/EtOH and 30 wt% of CePW as the catalyst at 160 °C (Figure 111). Catalyst characterization showed that Ce ions were mainly present in Ce³⁺ states. A high CePW loading was needed to develop mainly weak acid sites, which seemed to inhibit the formation of angelica lactones, and therefore increased the selectivity. The CePW-based catalyst retained its catalytic activity nearly unchanged for 50 h. Other phosphotungstic acid metal salts based on Cs and La did not improve the catalytic effectiveness.

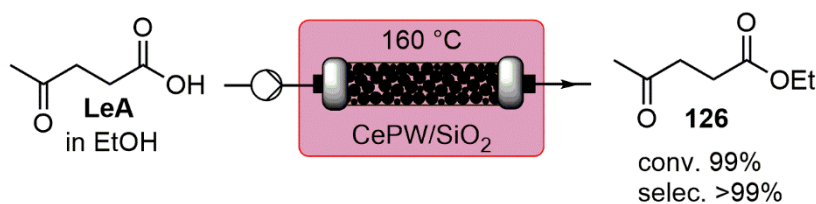


Figure 111. Continuous flow process for the synthesis of ethyl levulinate from LeA and ethanol, using a cerium salt of phosphotungstic acid as the catalyst.⁹³⁷

The reaction can also be carried out in the presence of a homogeneous catalyst such as *p*-toluenesulfonic acid or sulfuric acid.⁹³⁸ Quantitative conversion could be obtained by reacting LeA with ethanol at 120 °C under moderate pressure (17 bar), with 2.5 mol.% of catalyst and a residence time of 5 min. Interestingly, upon translation to a pressurized (200 bar) stainless steel reactor and using a higher reaction temperature (270 °C), the authors demonstrated a catalyst-free process for the esterification of LeA. Using an ethanol/LeA ratio of 3, conversion as high as 85% could be obtained, corresponding to 8.3 g of levulinic acid processed per hour.

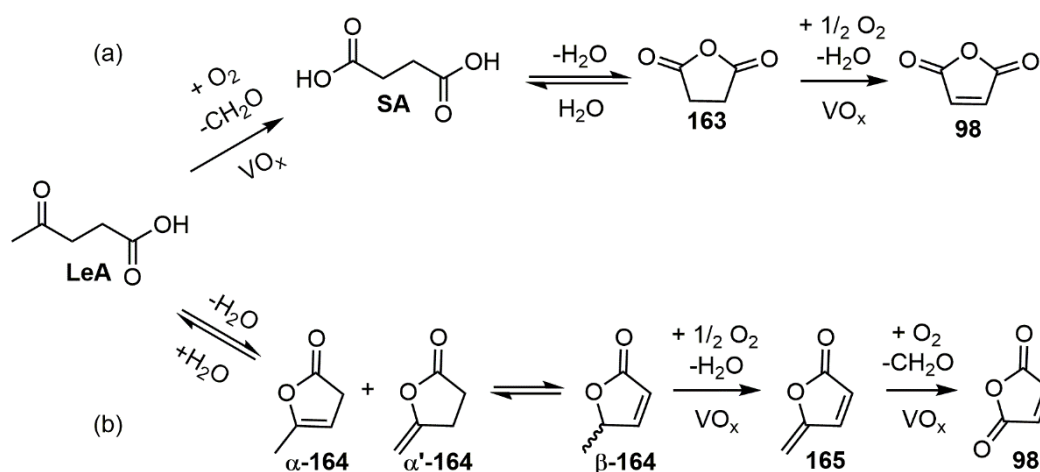
Enzymes, in particular lipases, can also catalyze such reactions, and flow processes can be implemented upon immobilization of the enzyme on a suitable support.^{51,939} The esterification of *n*-butanol with levulinic acid was investigated by Bhavsar and Yadav using immobilized lipases as catalysts in a packed bed borosilicate glass tubular microreactor.⁹⁴⁰ In comparison with a batch process, superior performance was highlighted. After a systematic optimization of the process, the reaction was most efficiently carried out at 60 °C and with Novozym 435 as the catalyst, 3 equiv. of *n*-butanol and MTBE as the solvent. Up to 85% conversion could be achieved, using a contact time of 2 min, and this level of activity was rather stable for 25 h of continuous operation. By contrast, operation in batch under similar conditions required 105 min of reaction to reach a conversion of 78%.

4.6.3. Oxidation into Maleic Anhydride

Maleic anhydride (**98**) is industrially produced from the aerobic oxidation of petro-sourced hydrocarbons (butane or benzene), and used for the production of a range of bulk chemicals (including butanediol, THF, γ -butyrolactone, etc.), surfactants and polymers (see section 3.1.6). Recently, LeA has been proposed as a possible bio-based alternative source of maleic anhydride.^{941,942} Over supported vanadate, the conversion of LeA to maleic anhydride was achieved in a gas-phase flow stainless steel reactor. In the seminal paper, the reaction was proposed to proceed through an oxidative cleavage of the $\text{CH}_3\text{-C(O)}$ bond of LeA, leading to equimolar quantities of formaldehyde and succinic acid. The latter would then reversibly form its anhydride **163** by dehydration. Succinic anhydride (**163**) would then undergo a final oxidative dehydrogenation to form maleic anhydride (**98**) (Scheme 27a). In parallel, the by-product – formaldehyde – is lost through deep oxidation in the form of CO and CO_2 .⁹⁴¹ The reaction was studied in more details in a follow-up study, and the mechanism was revised. Control experiments indicated that it would rather involve at first a dehydration of levulinic acid into α - and α' -angelica lactones (**164**). These species would then isomerize into the β -isomer of angelica lactone, which would then undergo an oxidative dehydrogenation into protoanemonin (**165**, a toxin notably found in plants). Eventually, oxidative scission of the alkene would form maleic anhydride and formaldehyde (Scheme 27b). The oxidative dehydrogenation of β -angelica lactone was depicted as fast enough to limit the oxidative scission of α -angelica lactone, rationalizing the selectivity obtained for the oxidative scission of levulinic acid, *i.e.* a favored scission on the methyl side of the ketone.⁹⁴² Over $\text{VO}_x/\gamma\text{-Al}_2\text{O}_3$, at 320 °C and with a contact time of 4-16 min, quantitative conversion of LeA was achieved with a selectivity for maleic anhydride in the 50-60% range. A first order dependence of maleic anhydride selectivity on O_2 pressure was also demonstrated. The selectivity of the process was

increased by (i) tuning down the acidic properties and (ii) decreasing the reducibility of the support (to lessen the oxidative capacity of the supported VO_x phase and avoid over-oxidation reactions). Consistently, VO_x/SiO_2 and VO_x/TiO_2 were significantly more active than $\text{VO}_x/\gamma\text{-Al}_2\text{O}_3$ and V_2O_5 . The best result (quantitative LA conversion and 71% selectivity toward maleic anhydride) was obtained at 300 °C with VO_x/SiO_2 using a contact time of 3.9 min.⁹⁴¹

Scheme 27. Mechanisms (a) originally proposed and (b) revised for the formation of maleic anhydride from levulinic acid.^{941,942}



4.6.4. Dehydration-Reduction into γ -Valerolactone (GVL)

γ -Valerolactone (GVL, **167**) is a potential gasoline blending agent and is also considered a green solvent.⁹⁴³ As a platform molecule, GVL has been proposed as an important precursor for renewable bulk chemicals (such as methylpentenoates and adipic acid), for fine chemicals and for fuels (*i.e.* “valeric biofuels”).^{944,945} Another promising option for the valorization of GVL is its further conversion into pentanoic acid, which can be subsequently converted into 1-butene (through a decarboxylation reactions) or upgraded to 5-nonanone to target applications in the polymer industry or in the paints, resins and fuels sectors.

The conversion of LeA into GVL is triggered either by hydrogenation and cyclization in the presence of a metal-based catalyst under H₂ pressure, or by a hydrogen transfer reaction (also followed by cyclization) with an organic reducing agent – e.g., a secondary alcohol or formic acid – in the presence of an acidic catalyst.

Processes relying on a metal-based catalyst and on H₂ as the reductant. Table 35 collects the reported syntheses of GVL from LeA under continuous flow conditions and using hydrogen gas as the reducing agent in combination with a redox heterogeneous catalyst (Figure 112). The reaction mechanism to GVL can proceed following two pathways (Scheme 28), depending on the order in which dehydration and hydrogenation occur.⁹⁴⁶ Producing GVL from LeA requires both hydrogenation and dehydration active sites. It was suggested that the contribution of each route is temperature-, solvent- and catalyst-depend, among other parameters.⁹⁴⁷ Pathway 1 is initiated by hydrogenation of the LeA ketone group to form 4-hydroxypentanoic acid (**166**). Then, **166** undergoes acid-catalyzed, intramolecular esterification to form the target lactone, GVL. In Pathway 2, angelica lactones (**164**) form via endothermic dehydration of LeA. It should be noted that the targeted production of angelica lactones via LeA lactonization can be catalyzed by acid solid catalysts (e.g., aluminosilicate) and performed in the vapor phase in flow mode.⁹⁴⁸ In the presence of an appropriate hydrogenation catalyst, and under a reducing atmosphere, angelica lactones are rapidly reduced, forming GVL.

Scheme 28. Pathways leading to γ -valerolactone during hydrogenation of levulinic acid. BA = Brønsted acid.⁹⁴⁶

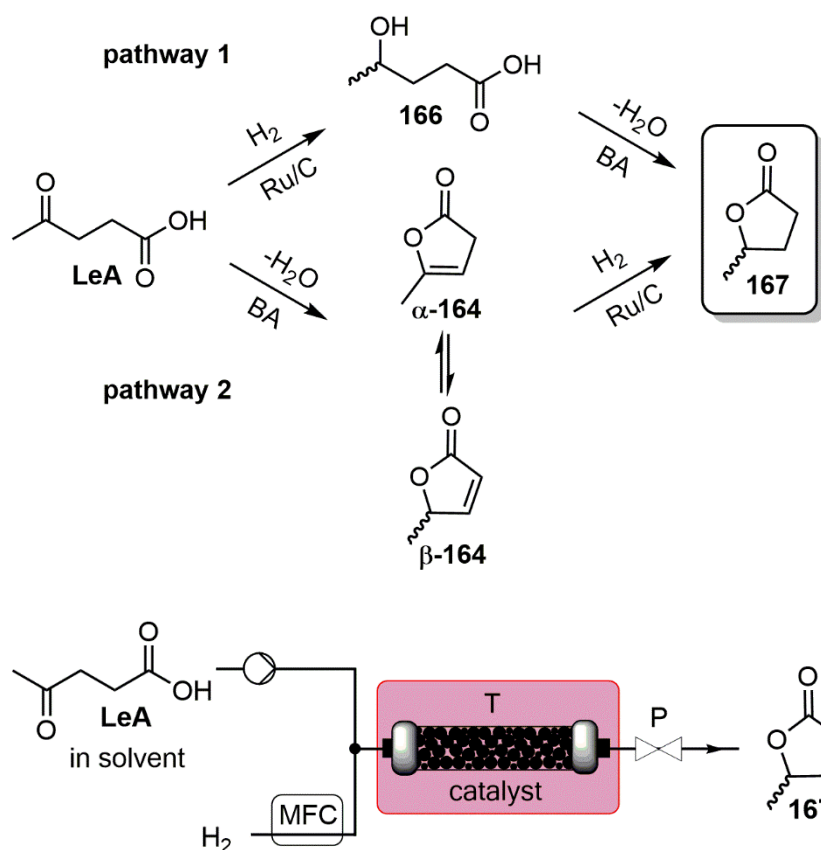


Figure 112. General flow scheme for the conversion of levulinic acid into γ -valerolactone.

Table 35. Representative conditions and catalysts for the continuous synthesis of GVL from LA using molecular hydrogen as the reducing agent.

Entry	Catalyst	T (°C)	P (bar)	Solvent	Space velocity	TOS (h)	Conv. (%)	Selec. (%)	Ref.
1	Ru-HHDMA.TiSi ₂ O ₆	130	20	water	W/F = 0.006 g h cm ⁻³	15	- ^a	>95	949
2	Ru@DOWEX	70	5	water	W/F = 4.5 g h mol ⁻¹	10	95	99	950
3	Mo ₂ C/CNT	200	30	water	LHSV = 3 h ⁻¹	6	99	90	951
4	Ru/C + Amberlyst-15	50	41	water	WHSV = 5 h ⁻¹	- ^a	92	88	946
5	Ru/C	140	10	water	W/F = 0.0023 g h cm ⁻³	- ^a	97	- ^a	952
6	Ru-Sn/C	180	35	2-sec-butylphenol	WHSV = 1.2 h ⁻¹	300	- ^a	>99	953

7	Ru/C	265	1	1,4-dioxane	WHSV = 0.512 h ⁻¹	50	>99	98	954
8	Ru/C	150	35	water	WHSV = 4.8 h ⁻¹	- ^a	>99	96	955
9	Ni/SiO ₂	250	1	- ^b	WHSV = 3.3 h ⁻¹	5	>99	89	932
10	Cu/Al ₂ O ₃	250	1	- ^b	WHSV = 3.3 h ⁻¹	5	98	97	932
11	Co/SiO ₂	250	1	- ^b	WHSV = 3.3 h ⁻¹	5	69	59	932
12	CuNi/SiO ₂	250	1	- ^b	WHSV = 6.6 h ⁻¹	8	99	98	956
13	Ni/SiO ₂	270	1	water	GHSV = 19.5 cm ³ s ⁻¹ g _{cat} ⁻¹	6	16	91	957
14	NiRu/γAl ₂ O ₃	90	50	AcOEt	W/F = 0.006 g h cm ⁻³	0.3	<35	99	958
15	Ru/C	90	45	water	WHSV = 30 h ⁻¹	8	98	83	959
16	Cu/Al ₂ O ₃	265	1	water	WHSV = 0.169 h ⁻¹	36	98	87	960
17	Ru/SiO ₂	200	100	scCO ₂ ^c	W/F = 0.046 g h cm ⁻³	- ^a	99	99	961
18	Ru-Fe/SBA-15	250	75	- ^b	LHSV = 1.5 h ⁻¹	- ^a	87	83	962
19	Ru/Al ₂ O ₃ -TiO ₂	80	40	water	WHSV = 1.8 h ⁻¹	120	>99	97	963
20	Ru-HRO/H-β	50	10	- ^b	W/F = 0.044 g h cm ⁻³	40	>99	99	964

AcOEt = ethyl acetate. CNT = carbon nanotubes. ^aUnclear. ^bNo solvent, levulinic acid was vaporized in H₂. ^cSupercritical CO₂, LA is fed as a mixture with water, CO₂ is fed with H₂.

Pérez-Ramírez and coworkers compared a state-of-the-art Ru/C catalyst (5 wt% Ru) to a catalyst prepared from Ru nanoparticles modified with a water-soluble ligand (hydroxyethyl-dimethyl ammonium dihydrogen phosphate) supported on a titanium silicate, with only 0.24 wt% Ru.⁹⁴⁹ The reaction was carried out in a flooded-bed reactor in which gaseous H₂ was fed co-currently with and aqueous solution of LeA. The presented catalyst was about 4 times more active (per mol of Ru) than the reference and showed no sign of deactivation after 15 h on stream (Table 35, entry 1). Barbaro *et al.* studied the liquid phase continuous flow reduction of

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2
3 levulinic acid into γ -valerolactone over a sulfonated resin (DOWEX) embedded with Ru
4 nanoparticles (0.87 wt%) as bifunctional heterogeneous catalyst.⁹⁵⁰ 99% selectivity to GVL was
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6 obtained at almost quantitative conversion, under moderate pressure and temperature, and using
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8 an aqueous feedstock solution of LeA and a co-feed of H₂ (entry 2). No catalyst leaching was
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10 observed, and the material maintained its activity during four runs of 8 h. The high stability of
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12 the catalyst was related to the utilization of mild conditions, preventing Ru sintering, coke
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14 deposition, and degradation of the resin. When the size of the catalyst beads was reduced from
15
16 276 to 84 μm , conversion higher by 10% were obtained, highlighting possible internal mass
17
18 transfer limitations. This latter finding is interesting because it points to intraparticle mass
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20 transfer limitations (*i.e.* intrinsic kinetics are similar or faster than mass transfer rates in the
21
22 catalyst particles). With this in mind, and knowing that typical particle sizes for packed-bed
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24 reactors in commercial applications are usually in the millimeter range to avoid excessive
25
26 pressure drops, Heeres *et al.* have reported a study on Ru-based catalysts with particle sizes in
27
28 the millimeter range in a continuous packed-bed reactor.⁹⁵⁹ Effects of intraparticle hydrogen
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30 and LeA mass transfer on catalyst performance were assessed by performing experiments with
31
32 Ru-based catalyst particles in the millimeter range. For such catalyst particles, intraparticle
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34 mass transfer limitations of both H₂ and LeA were proven to occur to a significant extent,
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36 thereby creating a bias in the results of experimental studies and limiting the conclusions that
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38 can be drawn in terms of intrinsic activity and stability. Under realistic working conditions
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40 (LeA inlet feed of 1.2 mol L⁻¹ in water, WHSV = 30 h⁻¹, 90 °C, 45 bar H₂ pressure) and with a
41
42 Ru(0.5)/C catalyst having an average particle diameter of 1.88 mm, the highest productivity
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44 was 770 g_{LA} g_{Ru}⁻¹ h⁻¹ (entry 15). The catalyst was stable for 6 h TOS. Good conversion (83%)
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46 was achieved in flow mode by Mika *et al.* using a Ru/C catalyst operated at 100 °C and 100 bar
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48 of H₂.⁹⁵² The authors showed that the conversion could be further boosted (97%) by increasing
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the temperature to 140 °C and running the reaction at 10 bar only (entry 5). Interestingly, the addition of a butyl-bis-(*m*-sulfonated-phenyl)phosphine ligand ($\text{Bu-P}(\text{C}_6\text{H}_4\text{-}m\text{-SO}_3\text{Na})_2$) in the LA feed led to a significant increase in the conversion as well (98.5% at 100 °C and 100 bar). It was not possible to interpret the origin of the activity boost, as several explanation could be put forward (modification of the solid catalyst or dissolution of Ru species catalyzing homogeneous reactions). Using a Ru(5%)/C catalyst and moderate conditions (150 °C, 35 bar of H_2), it was possible to reach almost quantitative conversion of LeA to GVL, even with a highly concentrated (50 wt%) feed of aqueous LeA (entry 8).⁹⁵⁵ To study the stability of the catalyst, it was needed to increase the space velocity (up to $\text{WHSV} = 32 \text{ h}^{-1}$) to decrease the conversion below 100%; a slow deactivation was observed with time-on-stream (conversion decreased from 90% to 68% after 106 h) but the catalyst activity could be partially recovered via a thermal treatment under flowing hydrogen at 400 °C. Carbon-supported Ru-Sn bimetallic catalysts were studied for the hydrogenation of LeA to GVL using 2-*sec*-butylphenol as the reaction solvent.⁹⁵³ Ru/C catalyst was initially more active for the hydrogenation reaction to GVL, but underwent deactivation versus time-on-stream. Also, this catalyst was also active for the hydrogenation of the phenolic solvent. In contrast, the catalyst containing a 1:1 ratio of Ru and Sn had a lower activity for LeA to GVL but displayed stable activity versus time on stream and gave quantitative selectivity for hydrogenation of LeA versus the solvent (entry 6). Further increasing the amount of Sn resulted in the formation of an additional phase ($\beta\text{-Sn}$) that was not active for hydrogenation, leached into the solvent, and sintered under the reaction conditions utilized. The same authors demonstrated the deconstruction of cellulose into levulinic acid, using a biphasic solvent system under batch conditions.⁹⁶⁵ The biphasic batch process was coupled with a continuous flow process for the production of GVL (Figure 113). In this advanced example, GVL was both the organic solvent and the final product. At 155 °C,

cellulose was deconstructed in the biphasic reactor and both formic and levulinic acids were extracted by GVL. The organic phase was then fed to a fixed-bed flow reactor loaded with the RuSn-based catalyst where LeA was converted to GVL. This approach is appealing since it alleviates the need to separate the final product from the solvent.

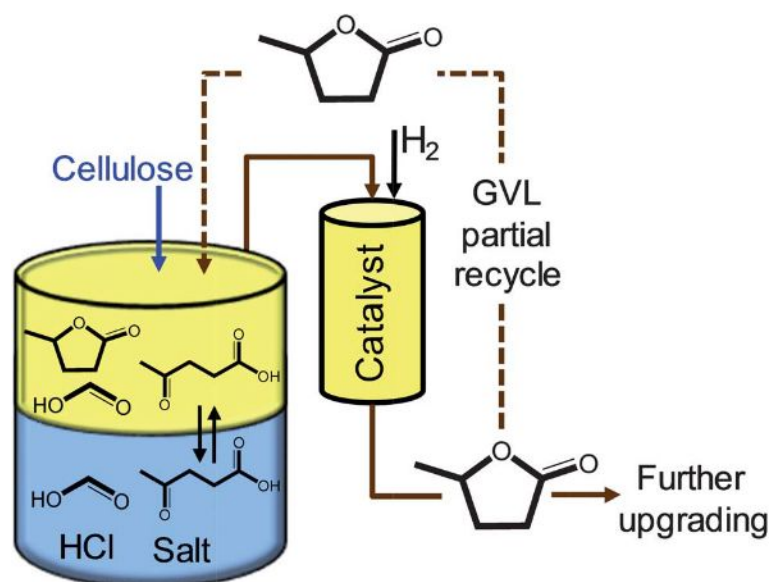


Figure 113. Schematic view of the system proposed by Dumesic *et al.* for the direct conversion of cellulose to LeA and GVL.⁹⁶⁵ Deconstruction of cellulose is carried out in a biphasic GVL-mineral acid system and the organic phase is fed to a flow mode reactor where the conversion of LeA to GVL takes place. Adapted with permission from ref 965. Copyright 2012 the Royal Society of Chemistry.

Bond and coworkers studied the kinetics and reaction pathways involved in the synthesis of GVL in a fixed-bed reactor loaded with a Ru/C catalyst.⁹⁴⁶ Interestingly, they showed that at relatively low temperature, the ring closure of **166** is the rate-limiting step (pathway 1 in Scheme 28). Therefore, high yields could be obtained at temperatures as low as 50 °C by using stacked beds of Ru/C followed by Amberlyst 15 resin to favor this acid-catalyzed dehydration reaction (entry 4). Screening the ability of Ru/C, Pd/C and Pt/C catalysts to trigger the

hydrogenation of LeA to GVL, Chang and colleagues have clearly evidenced the superiority of the Ru-based catalyst.⁹⁵⁴ 1 g of catalyst gave quantitative conversion at 265 °C and 1 atm of H₂, using a 10 wt% LeA solution in 1,4-dioxane and a WHSV of 0.512 h⁻¹, regardless of the catalyst utilized. By contrast, the selectivity to GVL was highly dependent on the nature of the active metal. The Ru-based catalyst gave almost quantitative selectivity to GVL (entry 7). On the other hand, significant amounts of angelica lactones were produced with the Pd-based catalyst, and it was even the main reaction product (69% selectivity) when the Pt-based catalyst was used.

Moving away from expensive and noble metals, transition metal-based catalysts can be used as well, for example Ni-based catalysts.^{966–968} The continuous flow reduction of levulinic acid into γ -valerolactone was reported to occur effectively over molybdenum carbide nanoparticles supported on carbon nanotubes (CNT).⁹⁵¹ The catalyst gave excellent conversion and selectivity, and was stable for up to 24 h time-on-stream (entry 3). By comparison, when molybdenum carbide was supported on activated carbon, the catalyst was prone to rapid deactivation, highlighting a strong influence of the support nature. Comparison with Ru supported on activated carbon evidenced that higher TOF and selectivity were obtained on the Mo₂C/CNT catalyst.

The reaction can also advantageously be carried out in the vapor phase,⁹⁶⁹ and a wide range of catalyst formulations have been tested in continuous flow mode (Table 35). Using a 5 wt% Cu/Al₂O₃ catalyst, Chary *et al.* reported a conversion of 98% and a selectivity to GVL of 87% at 265 °C (entry 16).⁹⁶⁰ Sato and colleagues have tested Co, Cu and Ni-based catalysts supported on either silica or alumina in the vapor phase hydrogenation of LeA to GVL (entries 9–11).⁹³² Al₂O₃ was a better support for Cu, but SiO₂ support gave better results for Co and Ni. Venugopal and coworkers also studied the influence of the support for the Ni-catalyzed hydrogenation of

LA to GVL.⁹⁵⁷ Compared to γ -Al₂O₃ and ZrO₂, SiO₂ led to higher LeA conversion and GVL selectivity (entry 13). Also, the catalyst was stable for 15 h TOS.

Since Ni tends to be highly active for the conversion of LeA, while Cu tends to show high selectivity for GVL, Hutchings and coworkers investigated Ni-Cu bimetallic catalysts with the idea to benefit from the respective advantages of the two metals.⁹⁵⁶ Under ambient pressure of H₂, silica-supported bimetallic catalysts were compared to the corresponding monometallic counterparts and a clear synergy was evidenced. In terms of stability, the Cu-rich catalysts appeared to undergo a relatively fast deactivation, while the Ni-rich catalysts were relatively stable. The catalyst having a loading of 6 wt% Cu and 14 wt% Ni gave the best performance, reaching a productivity of 6.48 kg_{GVL} kg_{cat}⁻¹ h⁻¹ at 250 °C, with a WHSV of 6.6 h⁻¹ (entry 12). A further improvement of catalyst performance (activity and stability) was achieved by developing a preparation route (aided by citric acid) which improved the dispersion of Cu and Ni.⁹⁷⁰ Using a similar approach, Luque and coworkers proposed a bimetallic NiRu/ γ -Al₂O₃ catalyst (0.6 wt% Ni and 1.9 wt% Ru) which performed better than the monometallic counterparts (entry 14).⁹⁵⁸ A 2% Ru/1.07% FeSBA-15 catalyst afforded a LeA conversion of 87% and a selectivity to GVL of 83% under a H₂ pressure of 7.5 bar, at 250 °C (entry 18).⁹⁶² The authors reported that the selectivity switched to 2-methyltetrahydrofuran (see section 4.6.6) when the H₂ pressure was increased to 30 bar.

The reaction can also be carried out in flow mode under supercritical CO₂ conditions, as demonstrated by Poliakoff *et al.* in an early report.⁹⁶¹ A LeA-water feed (75 wt% LeA) was introduced together with pressurized CO₂ in mixture with H₂ over a Ru/SiO₂ catalyst, which gave full conversion and almost full selectivity (entry 17). Interestingly, water appeared to be a suitable solvent for the synthesis of GVL despite the fact that one equivalent of H₂O is generated

by the reaction. The advantage of this process is the possibility to combine it with an easy separation which yielded GVL in high purity (0.4 wt% H₂O), since it is not water-miscible.

A series of mixed oxide materials (Al₂O₃–TiO₂, Al₂O₃–MoO₃ and Al₂O₃–Co₃O₄) were synthesized by co-precipitation, and tested as supports for Ru.⁹⁶³ The hydrogenation of LA to GVL was carried out in a fixed-bed reactor that was fed with a 5 wt% aqueous solution of LA and with H₂ (40 bar). The promotion of alumina by TiO₂ (which is proposed to be preferentially located at the surface) weakened the acidic properties of the catalyst and this led to improved performance. The best catalyst was Ru/Al₂O₃–TiO₂ (entry 19), achieving a GVL yield of ~97% under mild conditions (WHSV = 1.8 h⁻¹ at 80 °C). Importantly, this catalyst was shown to be much more stable (120 h) than the catalyst prepared from a pure alumina support and much more active than the catalyst prepared from a pure titania support (Figure 114). The poor stability of the alumina-based catalyst was ascribed to the leaching of both Al and Ru in the collected liquid (such leaching was not observed with the Ti-containing catalysts).

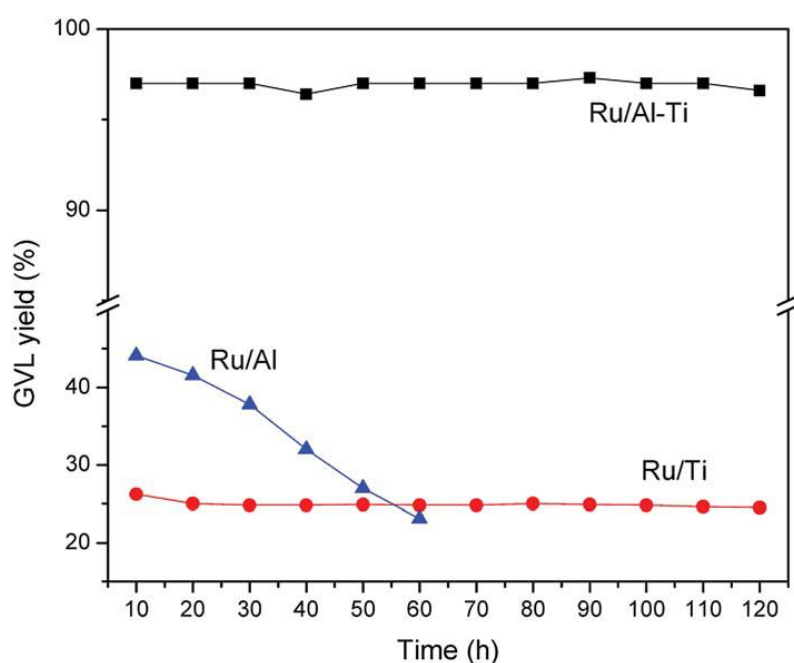


Figure 114. Stability of Ru-based catalysts prepared from different supports (Al_2O_3 , TiO_2 , or a mixed oxide Al_2O_3 - TiO_2). Conditions: $\text{WHSV} = 1.8 \text{ h}^{-1}$, $T = 80 \text{ }^\circ\text{C}$, $P_{\text{H}_2} = 40 \text{ bar}$ (flow = 40 mL min^{-1}).⁹⁶³ Reproduced with permission from ref 963. Copyright 2018 The Royal Society of Chemistry. [CC LICENSE] [<https://creativecommons.org/licenses/by-nc/3.0/>].

The continuous liquid phase hydrogenation of LeA to GVL was achieved using a catalyst prepared from hydrous ruthenium oxide supported on an H- β zeolite (3.2 wt% of Ru) in aqueous medium using molecular H_2 as reductant.⁹⁶⁴ Metallic Ru was formed *in situ* during the reaction. Under optimized reaction conditions (4 g of catalyst, 1.5 mL min^{-1} of aqueous LeA (5 wt%) feed, $100 \text{ }^\circ\text{C}$, 10 bar H_2 and 2 mL min^{-1} flow of H_2), the catalyst gave complete conversion of LeA with 99% to quantitative yield of GVL for 40 h TOS (entry 20).

Processes relying on alcohols as reductants. Although Group VIII metals, and especially ruthenium, are recognized as very effective to catalyze the reduction of LeA into GVL using molecular hydrogen, it is nowadays considered that the use of precious metal catalysts is detrimental to the overall process economics for the production of bulk chemicals.⁹⁷¹ An attractive alternative to the H_2 -mediated reaction, is the reduction of LeA by catalytic transfer hydrogenation using alcohols as hydrogen donors via the so-called Meerwein-Ponndorf-Verley (MPV) mechanism.^{972–974} The MPV reaction is chemo-selective for the reduction of carbonyl groups under mild reaction conditions and in the presence of other functional groups. Additionally, it can be triggered by non-precious metal heterogeneous catalysts. Importantly, the hydrogen donor (usually a secondary alcohol) is oxidized (to the ketone) and can be either sold as a commodity chemical or recycled after hydrogenation.

Wang *et al.* studied the continuous flow reduction of levulinic acid into γ -valerolactone using Zr- β zeolite as heterogeneous catalyst, using *i*PrOH both as the solvent and the reducing agent.⁹⁷⁵ Nearly quantitative yield was achieved when running the reaction at $250 \text{ }^\circ\text{C}$, with a

WHSV of 0.64 h^{-1} , and this level of activity could be maintained for 87 h on stream (Figure 115). At longer operation time, however, the conversion dropped dramatically and increasing amounts of isopropyl levulinate were formed. Yet, regeneration by air calcination at 500°C was possible, and enabled recycling of the material for two other reaction/regeneration cycles. The high performance of the zeolite was attributed to the presence of Lewis acidic sites of moderate strength.

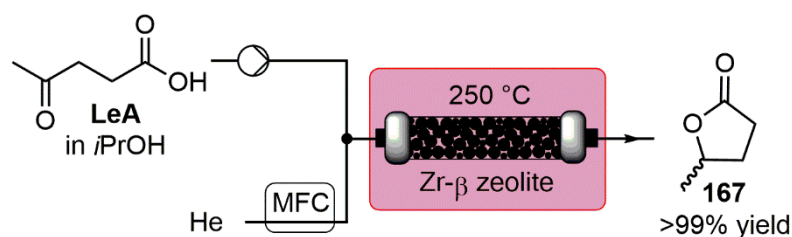


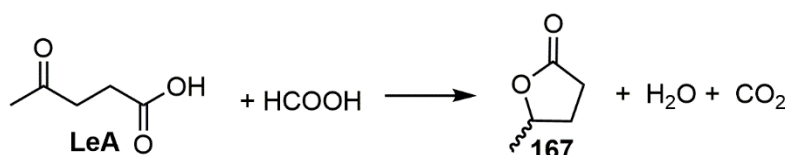
Figure 115. Continuous flow process for the conversion of LeA to GVL using Zr-β as the catalyst and isopropyl alcohol both as the solvent and the reducing agent.⁹⁷⁵

Kamaraju *et al.* have reported on the performance of SBA-15-supported ZrO_2 -based catalysts for the conversion of LeA to GVL, using isopropanol as the H-donor.⁹⁷⁴ The reaction was carried out in the vapor phase, at atmospheric pressure, in a fixed-bed reactor. A catalyst prepared by wet impregnation with 25 wt% of ZrO_2 gave quantitative conversion and 93% selectivity, when operated at 250°C with a feed of 1 : 7 (LeA : isopropanol molar ratio) and a LHSV of $2 \text{ mL g}_{\text{cat}}^{-1} \text{ h}^{-1}$. The good performance of this catalyst was attributed to a favorable combination of acidic and textural properties. However, a slight decrease in GVL selectivity was observed after 7 h TOS, evolving down to ~80% after 20 h of operation. This was attributed to the accumulation of carbonaceous species over the catalyst surface.

Processes relying on formic acid as the reductant. Considering that LeA is typically produced from the acidic hydrolysis of biomass in a mixture with formic acid,⁹⁷⁶ a relevant

strategy for its reduction consists in using formic acid as the reducing agent instead of H_2 .⁹⁷⁷ It appears convenient to use formic acid as reducing agent in a transfer hydrogenation (Scheme 29). In this way, the by-product of the first reaction is used as a hydrogen source for the second. This process can be run in the vapor phase, under continuous flow conditions. Solid catalysts based on noble or transition metals have been reported as suitable catalysts for this reaction. For example, a Cu/SiO_2 prepared by simple impregnation was shown to exhibit the appropriate Cu dispersion to give good conversion and selectivity toward GVL.⁹⁷⁸

Scheme 29. Synthesis of GVL from LA with formic acid as the hydrogen donor.



Varkolu *et al.* have used Ni/SiO_2 prepared *via* different methods (impregnation, co-precipitation, deposition-precipitation, and citric acid assisted impregnation-combustion). They found that the catalyst prepared by a citric acid assisted method and treated in inert gas flow before reaction was the most efficient, owing to a good Ni dispersion and optimal textural properties.⁹⁷⁹ The catalysts were assessed in a fixed-bed reactor that was loaded with 1 g of catalyst and fed with a 1 mL h^{-1} mixture of LeA and formic acid (1:5 molar ratio). Nitrogen was utilized as the carrier gas. At $250\text{ }^{\circ}\text{C}$, a LeA conversion of $\sim 98\%$ was achieved, with GVL selectivity of $\sim 92\%$. However, a marked decrease in activity was noticed with TOS, probably due to the accumulation of coke on the catalyst surface. A catalyst based on silver and palladium nanoparticles deposited by impregnation over a graphitic carbon nitride support ($AgPd@g-C_3N_4$) was used for the continuous flow synthesis of GVL from LeA, using formic acid as the hydrogen source.⁹⁸⁰ This particular support was selected for its ability to hold metal nanoparticles firmly, avoiding the metal leaching in the recycling process. Using a 1/16" SS

coil reactor of 5.03 mL internal volume, a quantitative yield of GVL could be obtained at 70 °C with a residence time of 50 min, in water and methanol. A Ni-promoted Cu/SiO₂ catalyst gave stable (200 h) and selective conversion of LeA to GVL using formic acid as the reducing agent.⁹⁸¹ A tubular flow reactor was filled with 1 g of catalyst and fed with a vaporized mixture of LeA and formic acid dissolved in 1,4-dioxane (10 wt%, molar ratio LeA:formic acid = 1:1) using nitrogen as a carrier gas. Using a catalyst with 80 wt% loading (Cu:Ni weight ratio of 3:1), at 285 °C and under atmospheric pressure, the LeA conversion reached 99% and the selectivity for GVL was 96% (the remaining 4% was unconverted angelica lactones). The authors argued that the addition of Ni to Cu-based catalysts enhanced the thermal stability by offering a stronger resistance against sintering. The transfer hydrogenation from formic acid to LeA can also be performed under hydrothermal conditions, using simple sulfates as homogeneous catalysts.⁹⁸² Aqueous solutions of these ions can be close to neutral at ambient conditions but become more and more basic with increasing temperature. In fact, the pH modification that is observed at higher temperature is directly induced by the presence of the salt. Sulfate salts were defined as “switchable” bases by the authors. The reaction was tested with Na₂SO₄ (0.125 M), in a microfluidic reactor operated at 200 bar with a flow of 0.1 M of LeA and 0.15 M of formic acid in water. At 300 °C (reaction time = 14.7 min), a mere ~12% yield of GVL was obtained. The production of levulinic acid from cellulose is commonly carried out using aqueous sulfuric acid as the hydrolysis catalyst.⁹⁸³ Typically, LeA must be separated from the mineral acid both for recycling concerns and to prevent poisoning of the subsequent (catalytic) steps. However, the purification of low concentration aqueous solutions of LeA is costly. Thus, it is appealing to optimize the catalytic formulations used for the reduction of LeA to GVL so they can operate in the presence of sulfuric acid. With this in mind, Dumesic *et al.* have tested Ru/C and RuRe/C catalysts in acidic conditions.⁹⁸⁴ A rapid

deactivation of the Ru/C catalyst was highlighted along with the formation of a levulinic acid-sulfuric acid anhydride. When a bimetallic 15 wt% RuRe(3:4)/C catalyst was used instead, a stable level of activity (production rate of $0.034 \text{ mmol min}^{-1} \text{ g}_{\text{cat}}^{-1}$) was maintained with or without sulfuric acid, and the selectivity of the process remained higher than 95%. Along the same line, the hydrogenation of LeA to GVL can be advantageously carried out in alkyl phenol solvents, thereby allowing to couple the reaction with a subsequent liquid-liquid extraction and solvent recycling step.⁹⁸⁵ In this case, the key is to avoid the hydrogenation of the solvent that is encountered with the classical Ru/C catalysts. This was achieved by promoting the catalyst with Sn, allowing to selectively catalyze the conversion of LeA to GVL.

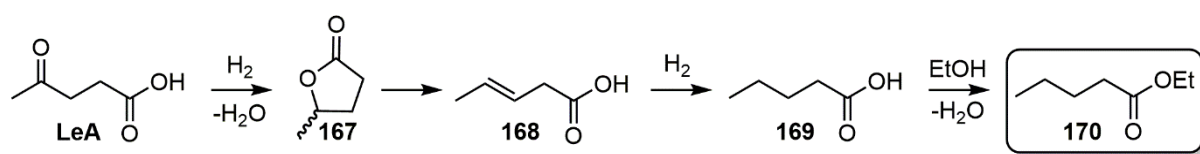
4.6.5. Reduction into Pentanoic Acid (Valeric Acid) and Esters Thereof, and into 1,4-Pentanediol

Pentanoic acid and derived esters. Pentanoic acid (**169**) is an interesting target for the valorization of LeA. LeA is usually converted in two separate steps, first to GVL (see section 4.6.4) which is then converted to pentanoic acid (Scheme 30). However, the single step conversion of LeA to pentanoic acid or its esters is also achievable and has been carried out in continuous flow mode. Pentanoic acid can be converted to 1-butene through a decarboxylation or to 5-nonanone via a ketonization,⁹⁵⁵ hence opening a wide range of applications for the paint and coating, resin and fuel industries. The esters of pentanoic (valeric) acid find applications in the perfume and food industries. Valeric esters have been recognized as a new class of cellulose-derived fuels, called “valeric biofuels”, since they have promising potential for blending with gasoline and diesel components.^{986,987}

A HZSM-5 supported Ni catalyst - prepared by simple impregnation - has been used for the continuous flow cascade conversion of LeA into ethyl valerate (**170**) (Scheme 30).⁹⁸⁸ The reaction was carried out in a stainless steel fixed-bed reactor, in the 220-260 °C temperature

range and under 30 bar of H_2 . Using a feed of 16.7 wt% LeA in ethanol, and a GHSV of 2.96 h^{-1} , quantitative conversion and a high combined yield of ethyl valerate + valeric acid (90-95%) could be obtained for about 20 h of continuous operation. Importantly, the authors discovered that a K-doped formulation was able to maintain this level for up to 80 h TOS. This effect was attributed to the mitigation of acidity by K-promotion, which allowed to decrease the tendency of the catalyst to accumulate coke and especially heavy coke species.

Scheme 30. Reaction mechanism for the conversion of LA to pentanoic acid and its esters (represented hereafter as the ethyl ester).⁹⁸⁸



The conversion of LeA to pentanoic acid was recently demonstrated under continuous flow conditions, using a W-modified Ni/H-ZSM-5 catalyst.⁹⁸⁹ When the reaction was carried out with an aqueous solution of LeA (10 wt%) at 270 °C, under 1 bar of H_2 and with a GHSV of 9.74 $mL\ s^{-1}\ g_{cat}^{-1}$, a specific productivity of pentanoic acid of 1.24 $\mu mol\ s^{-1}\ g_{cat}^{-1}$ was achieved (conversion = 40%; selectivity = 65%, with GVL as the main by-product). The catalyst was stable over 10 h TOS. A key feature of this catalyst (as compared to other formulations based on SiO_2 or Al_2O_3 supports which showed poorer performance) is the high content in Brønsted acid sites, which are thought to favor the further conversion of the intermediate (GVL).⁹⁹⁰

Pd-based catalysts can also catalyze the reaction, and Mariscal *et al.* have screened the effect of different acidic supports on their catalytic behavior in the conversion of LeA to valeric acid and valeric ester.⁹⁹¹ The reaction proceeds via the GVL intermediate and the ring opening – catalyzed by acid centers – is the rate determining step (Scheme 30). Supports with weak acidity (amorphous silica-alumina) were not able to catalyze the ring opening and were therefore

poorly active in the targeted reaction. Supports with strong acidity (such as BEA zeolite) were poorly selective. The best performance was achieved by a 2 wt% Pd supported on a ZSM-5 zeolite and prepared by a simple impregnation technique. The moderate acidity of the support was also shown to promote a high Pd dispersion. In a fixed-bed reactor operated at 250 °C and 30 bar of H₂ fed with a 10 wt% ethanolic solution of LeA (WHSV = 2 h⁻¹), the yield of valeric acid and ethyl valerate was maintained at ~40% for about 90 h. It should be noted however that the formation of carbonaceous deposits was observed.

1,4-Pentanediol. While most of the research concerning the hydrogenation of levulinic acid aims at the formation of γ -valerolactone, the direct production of 1,4-pentanediol (**171**) is interesting for the production of polyesters and for the synthesis of many other chemicals and fuels.^{992,993} The direct hydrogenation of levulinic acid toward 1,4-pentanediol was conducted in flow and under relatively mild temperature (70 °C) using a Ru/activated carbon catalyst modified with Mo oxide.⁹⁹³ Such bifunctional formulations was needed because the reaction requires the activation and dissociation of H₂ (on the noble metal) and the activation of the carbonyl bond (on the acidic oxide).

The conversion of LeA to 1,4-pentanediol was also achieved using a continuous flow reactor and Mo-modified Rh/SiO₂ heterogeneous catalyst (Figure 116).⁹⁹⁴ Quantitative conversion (>99%) and good selectivity (70%) were achieved for a Mo/Rh atomic ratio of 0.13 at 80 °C. Other noble metals (Ir, Pt, Ru, Pd) were also combined with Mo but no further improvement was notified in terms of selectivity and/or yield. Moreover, γ -valerolactone could be converted to 1,4-pentanediol as efficiently as levulinic acid using Rh-MoO_x/SiO₂, which suggested that γ -valerolactone was a major reaction intermediate. Concerning the stability of the catalyst, no evident change of activity and/or selectivity was notified after 30 h of continuous operation.

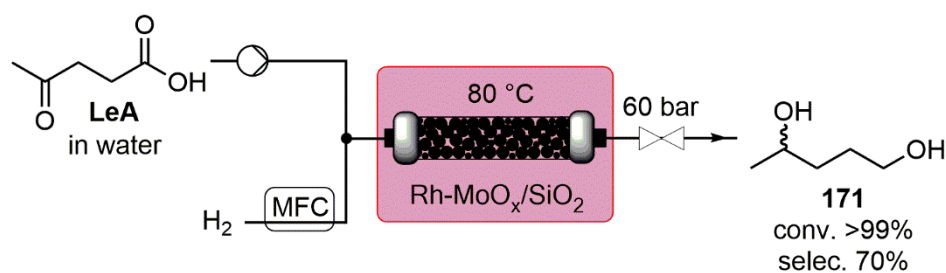


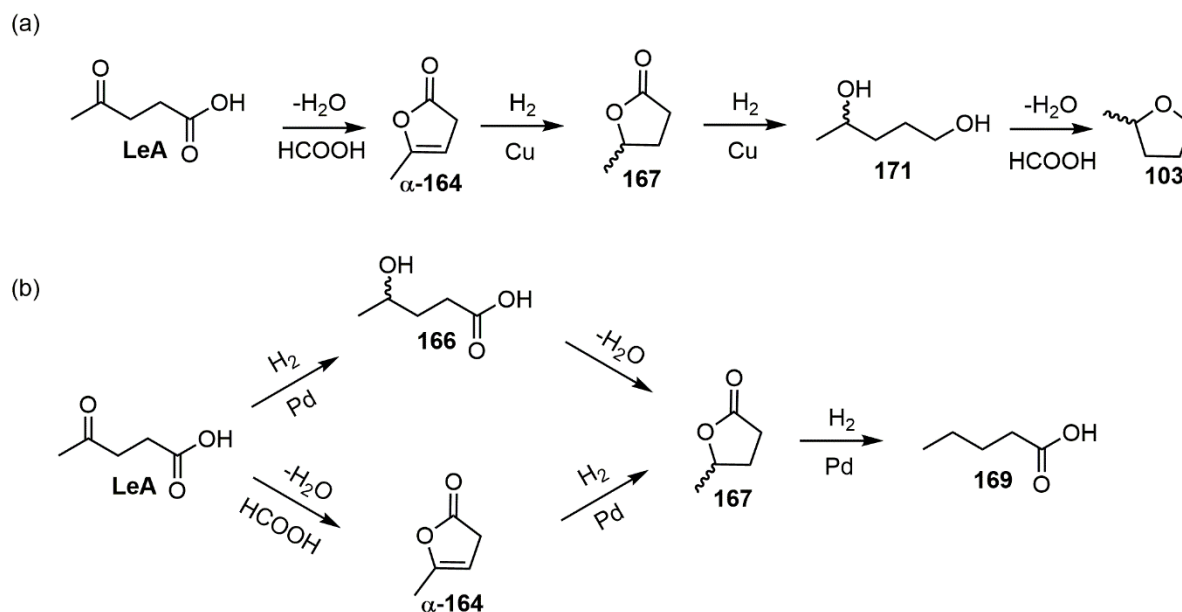
Figure 116. Continuous flow process for the conversion of LeA to 1,4-pentanediol over a Mo-modified Rh/SiO₂ catalyst.⁹⁹⁴

4.6.6. Upgrading into 2-Methyltetrahydrofuran and Other Liquid Fuels

2-Methyltetrahydrofuran. LeA can be directly converted to 2-methyltetrahydrofuran (**103**), with potential applications as biofuel (or green solvent).⁹⁹⁵ The reaction proceeds through the formation of GVL which further undergoes a hydrogenation step to **103**. This reaction could be carried out under continuous flow and solvent-free conditions in the presence of pressurized H₂, and using a Co/SiO₂ catalyst.⁹⁹⁶ Using formic acid as the reducing agent and Cu- or Pd-based heterogeneous catalysts, Luque *et al.* showed that the conversion of LeA to **103** could be achieved in the liquid phase at 150 °C with a simple commercial flow system (X-Cube, Thalesnano).⁹⁹⁷ Initially, the catalyst made of 0.5 wt% Cu supported on silica nanotubes gave 79% conversion and 60% selectivity to **103**, but then deactivated rapidly, as it was prone to leaching under acidic conditions. Using a 13 wt% CuO/Al₂O₃ catalyst, more stable performance was obtained with a conversion around 50% and a stable selectivity of about 80%. Yet, this high loading commercial catalyst also showed signs of Cu leaching. The Pd/C catalyst gave similar conversion levels and was initially less selective (28%) but remained much more stable. By comparing the selectivity of different catalysts, the authors suggested different pathways to explain the great variability of the products obtained. Over Cu catalysts, it was suggested that LeA underwent dehydration into angelica lactones, followed by reduction into GVL,

hydrogenation of GVL into 1,4-pentanediol and a final dehydration toward **103** (Scheme 31a). Over the Pd catalyst, pentanoic acid was the main product and the suggested mechanism proceeded through GVL that was further reduced into pentanoic acid (Scheme 31b).

Scheme 31. Mechanisms proposed for the formation of (a) 2-methyltetrahydrofuran and (b) pentanoic acid from LeA over Cu- and Pd-based catalysts, respectively.⁹⁹⁷



A silica-supported copper-based catalyst was also investigated for the continuous flow conversion of LeA to 2-methyltetrahydrofuran.⁹⁹⁸ It was shown that the copper loading in Cu/SiO₂ catalysts had a marked effect on the selectivity of the process. Low copper loading (< 50 wt%) favored the selective hydrocyclization of LeA to GVL; but at high copper loading (50 to 80 wt%), further hydrogenation to 2-methyltetrahydrofuran (and 1-pentanol) was favored (Figure 117). Interestingly, Ni-doping (metal loading of 80 wt%; atomic Cu/Ni ratio = 9) resulted in a further increase in **103** selectivity. Complete conversion was reported with a stable selectivity for 2-methyltetrahydrofuran of 89% for 320 h TOS (265 °C, 25 bar of H₂, WHSV = 0.513 h⁻¹) and with no leaching of the catalyst observed.

Using a 2% Ru/1.07% FeSBA-15 catalyst, Yuan *et al.* showed that – keeping the temperature constant at 250 °C – the selectivity of the hydrogenation of LeA could be tuned by playing on the H₂ pressure applied.⁹⁶² While at relatively low H₂ pressure (7.5 bar) the catalyst was selective for GVL (83 %, see above), at higher pressure (30 bar) the conversion increased slightly and the production of **103** was favored (72% selectivity).

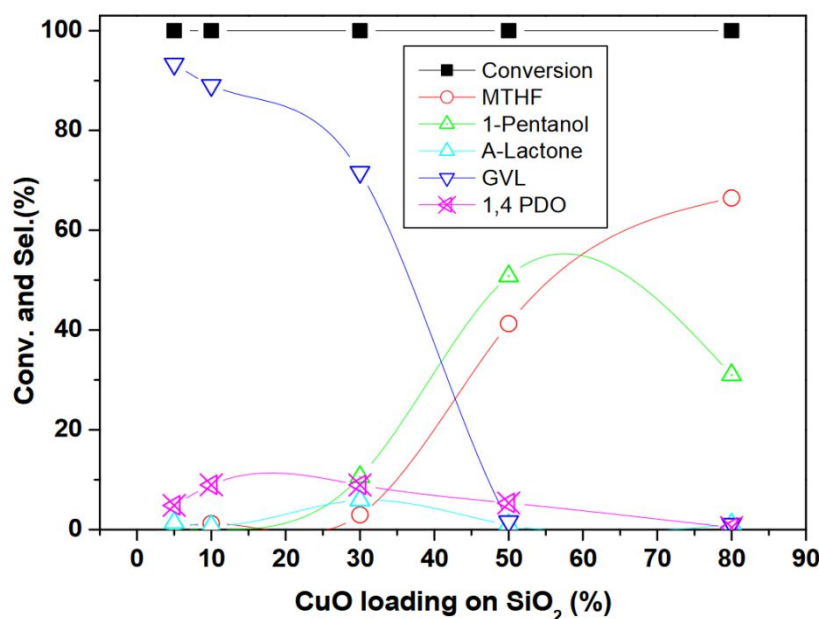


Figure 117. Effect of the copper loading on the activity of Cu/SiO₂ catalysts.⁹⁹⁸ Reproduced with permission from ref 998. Copyright 2011 Wiley.

Alkanes and other valuable chemicals. While platform molecules originating from lignocellulose-derived sugars typically range between C₂ and C₆, liquid fuels have a carbon chain length that is in the range of C₄-C₁₂ for gasoline, C₁₂-C₂₅ for diesel, and C₉-C₁₆ for aviation fuels. Producing such grades from lignocellulose sugars via lignocellulosic-derived platform molecules therefore requires some carbon chain length increasing reactions.⁹⁹⁹

Ketonization is a possible way to valorize LeA, both removing oxygen atoms and increasing the number of carbons. The process yields open-chain hydrocarbons of high interest in the fuel industry. In a recent study by Lilga *et al.*,¹⁰⁰⁰ an aqueous solution of LeA or GVL was vaporized,

together with formic acid or EG, in a N₂ feed and passed through a fixed bed containing a commercial ketonization catalyst (Ce- and La-doped zirconia), at a reaction temperature ranging between 330 and 400 °C, and at atmospheric pressure. Under such conditions, a biphasic system was formed, where the organic phase contained a complex mixture of deoxygenated and oligomerized hydrocarbons (alkanes, olefins, aromatics, plus low concentrations of ketones, ethers, carboxylates and lactones).

An integrated process was proposed in 2011, which combines (i) the sulfuric acid-catalyzed hydrolysis of cellulose to an equal molar mixture of LeA and formic acid (in batch), (ii) the conversion of the aqueous stream of LeA and formic acid to GVL (and CO₂) on a RuRe/C hydrogenation catalyst in flow mode, (iii) the purification of GVL by extraction with butyl acetate and distillation, and (iv) the upgrading of GVL to alkene oligomers.⁹⁸⁴ In this last step,¹⁰⁰¹ GVL was first decarboxylated to form a mixture of butene isomers over a silica-alumina catalyst at 375 °C and 36 bar. The butenes were then oligomerized over an acidic catalyst (e.g. Amberlyst resin) at 170 °C and 36 bar.

4.6.7. Miscellaneous

4-Oxo-pentanitrile. Kappe and Cantillo described a catalyst-free continuous process for the conversion of carboxylic acids into the corresponding nitriles.¹⁰⁰² Acetonitrile was used both as the solvent and the reagent for a direct acid-nitrile exchange reaction. Process conditions (350 °C, 65 bar, 25 min) were beyond the supercritical point of acetonitrile (T_c = 275 °C, P_c = 48 bar). The substrate scope notably included levulinic acid, and the corresponding product, 4-oxo-pentanitrile was isolated in 85% yield.

N-substituted pyrrolidinones. Zhang and coworkers reported a catalyst-free continuous flow process for the reductive amination of levulinic acid into N-substituted pyrrolidinones.¹⁰⁰³

Formic acid was utilized as liquid reductant instead of gaseous molecular hydrogen. Optimization of the reaction parameters with model *n*-butylamine showed that the best results were obtained at a temperature of 140 °C, and using a residence time of 10 min and 2 equiv. of both formic acid and amine. A single feedstock solution containing levulinic acid, formic acid and the amine was prepared in DMSO or MeCN, and pumped within the microreactor. The reaction was extended to a broad range of aliphatic and aromatic amines that gave the desired products in good to excellent yields (17 examples, 53-89%). Luque and coworkers employed Ru/TiO₂ catalysts for the continuous flow synthesis of *N*-heterocycles from LeA.¹⁰⁰⁴ An original aspect of this study was linked to the preparation of the catalyst itself, using orange peel residues as a sacrificial template for the solvent-free sol-gel synthesis of the TiO₂ support. The latter material was based on anatase crystallites and displayed a specific surface area of 20 m² g⁻¹. It was then impregnated with Ru chloride and reduced with hydrazine to yield the final catalyst. At 90 °C and with a 2 min residence time (0.3 M solution of LeA in acetonitrile, 50 bar H₂ pressure), the catalyst with a Ru loading of 3 wt% reached 76% LeA conversion. Initially, the reaction yielded mainly 1-ethyl-5-methylpyrrolidin-2-one (**172**) and after about 1 h, the selectivity switched to 1-ethyl-2-(ethylideneamino)-5-methylpyrrolidin-2-ol (**173**) (Figure 118). Actually, ethylamine was formed *in situ* by hydrogenation of acetonitrile, and reacted with levulinic acid to obtain the *N*-heterocyclic compounds. The catalyst proposed in this contribution was shown to be more active than more conventional catalysts (Ru/TiO₂ catalyst based the commercial P25 titania support from Degussa, or a commercial Ru/C catalyst).

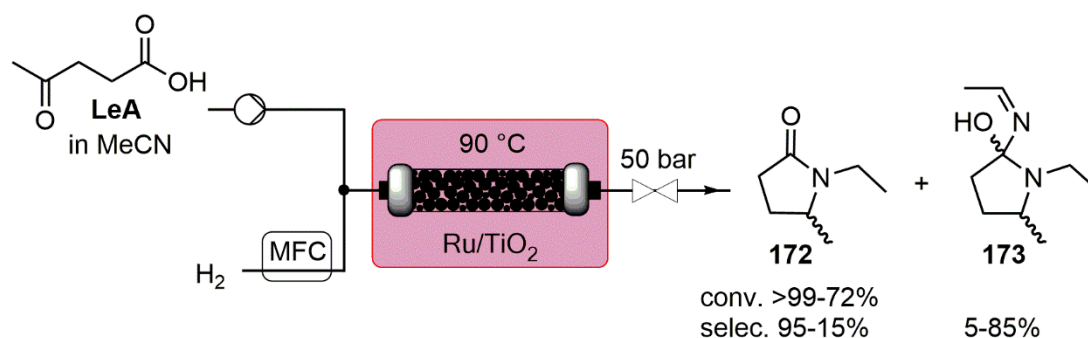


Figure 118. Continuous flow procedure for the conversion of levulinic acid into N-heterocycles, using a Ru/TiO₂ catalyst and MeCN both as the solvent and the nitrogen source.¹⁰⁰⁴

In an advanced example, Kim and colleagues described a multistep continuous flow procedure for the generation, purification and utilization of isocyanides (**175**).¹⁰⁰⁵ The utilization of continuous flow conditions was particularly relevant since isocyanides have a very pungent smell, and a concatenated process would therefore alleviate isolation, handling and storage prior to other steps. Isocyanides were generated from the corresponding *N*-substituted formamides **174** using a POCl₃-mediated dehydration. The organic stream was then washed with an aqueous solution, and the biphasic mixture underwent phase separation through a membrane-based separator. The purified organic stream of isocyanide was then utilized in various applications, including an Ugi 3-component reaction involving levulinic acid. The procedure yielded functionalized pyrrolidinones **176** in excellent 77-88% yields (Figure 119).

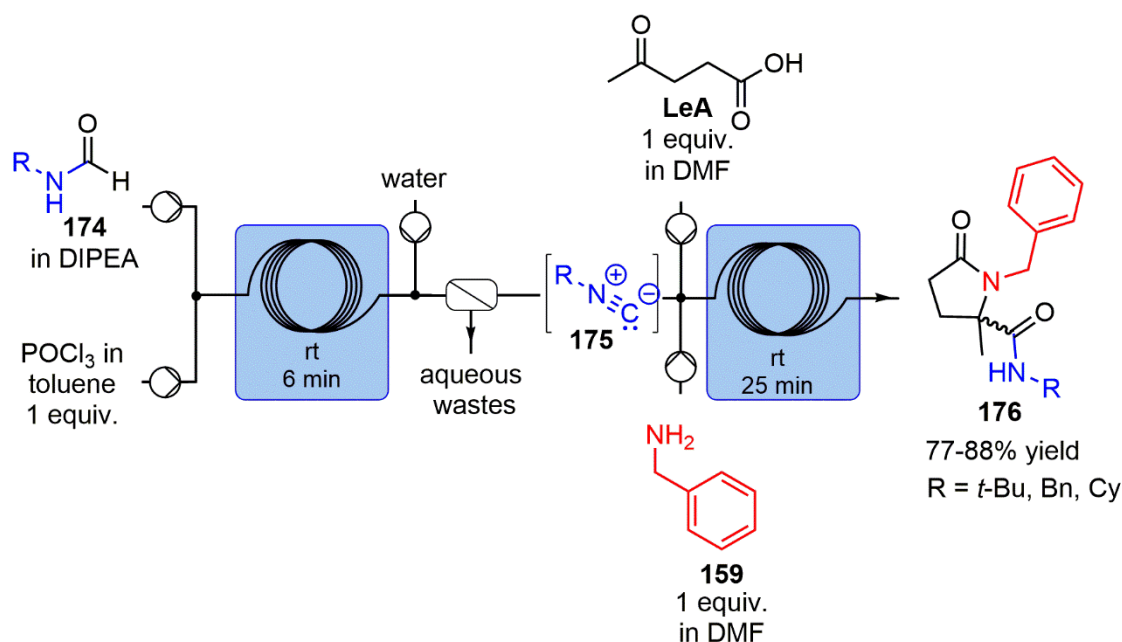


Figure 119. Continuous flow process for the conversion of levulinic acid into *N*-substituted pyrrolidinones using an Ugi 3-component reaction. *t*-Bu = *tert*-butyl, Bn = benzyl, Cy = cyclohexyl.¹⁰⁰⁵

5. Perspectives on Further Developments

Compared to other areas of research (such as the pharmaceutical sector) where flow chemistry became an enabling tool for R&D and process chemists, the continuous flow upgrading of bio-based chemical platforms can still be considered as a developing area of research, despite an increasing number of reports over the last decade. Not that opportunities are lacking, but the current effort of organic chemists and process chemists is rather oriented on revisiting the immense diversity of strategies for the preparation of high valued-added compounds that are distinctive features of organic chemistry at the interface with pharmaceutical sciences. As explained in the Introduction (see section 1.1), the inherent concepts of bio-based chemical strategies are very different than the conventional comfort zone of most organic, catalysis and process chemists that have been educated through a petro-based mindset. In the latter, the

chemist must use its creativity to construct molecular diversity from a wide range of structurally simple petro-based chemical platforms with a high C/O ratio. Commercially exploitable bio-based platforms are less diverse than petro-based ones and have typically a higher structural complexity with a much lower C/O ratio; building added-value molecules thereof is therefore a very different game that requires different approaches.

The general assets of flow chemistry that are briefly discussed in section 1.2 are very supportive to the development of novel chemical processes that can be tailored to meet the specific requirements for the upgrading of bio-based chemical platforms. There is still plenty of opportunities and perspectives to further improve these processes with flow chemistry and related technologies and hence to compete with established petro-based routes (Figure 120). The development of viable alternative chemical processes exploiting sustainable resources should consider all the aspects from upstream extraction from biomass to downstream transformation into value-added chemicals.

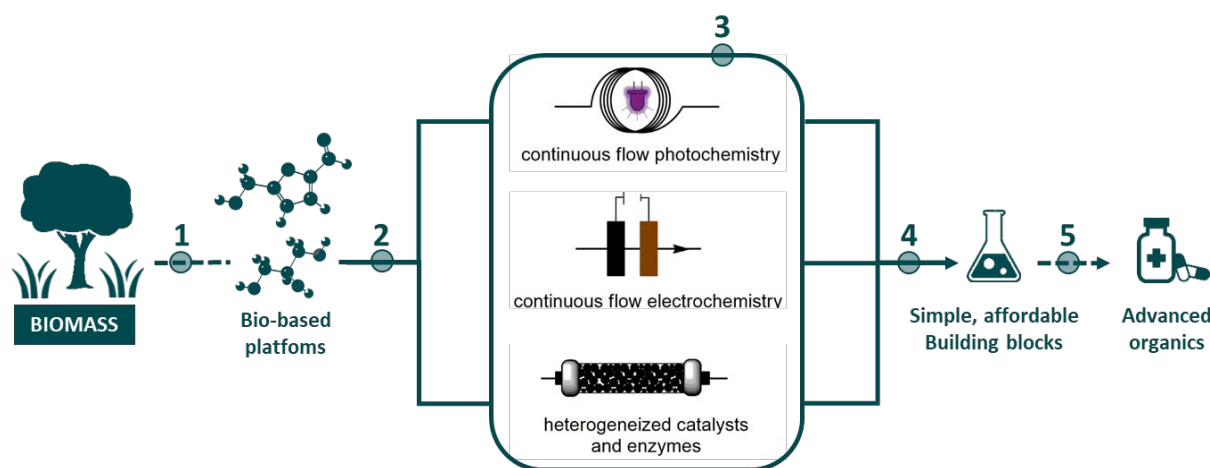


Figure 120. Perspectives for the development of continuous flow processes targeting the upgrading of bio-based platform molecules: Perspective 1: Sourcing from biomass; Perspective 2: New process process windows and emerging process technologies; Perspective 3:

Automation, feedback control and Artificial Intelligence; Perspective 4: In-line purification; Perspective 5: Advanced multistep concatenation.

Although out of the scope of this review, one of the most critical point (Perspective 1, Figure 120) relates to the direct sourcing of bio-based platform molecules from biomass. The conversion of biomass and the extraction of platform molecules typically relies on time-, energy- and resource-consuming protocols^{23,1006–1013} that are often overlooked for the overall assessment of the global footprint of the process.¹⁰¹⁴ The reader is redirected to specialized resources for further reading on the development of innovative processes for the sourcing of bio-based platform molecules from biomass.^{1011,1012,1014,1015} The implementation of continuous flow processes for the sourcing of bio-based platforms molecules directly from raw solid biomass would be very challenging, although significant advances for the processing of solids and slurries under flow have been reported over the last decade.^{57,1016–1022}

Perspectives 2-5 relate directly to the core topic of this review. While flow chemistry enables to explore new process process windows with unique process experiences and reaction conditions, the emergence of new flow process technologies for preparative applications (Perspective 2, Figure 120) such as photochemical and electrochemical reactors further expand the horizon.^{86,87,90,1023–1025} Besides, since catalysis science has always been an essential key to unlock progress in chemistry, it is expected that further developments in continuous flow upgrading of biomass will also largely rely on the design of innovative catalysts and their use in flow setups. Apart from intrinsic catalytic performance, the latter catalysts must fulfil two specific requirements: (i) ability to work in flow conditions and (ii) ability to work in a polar environment. Homogeneous catalysts and free enzymes can be used in continuous flow reactors, but this comes with a price: the need to recover or eliminate the soluble catalyst from the product streams. For flow processes, important advance is expected in the field of heterogeneous

1
2
3 catalysis and heterogeneous biocatalysis, where the solid catalyst can either be packed in the
4 reactor or transported with the flow and then easily separated.

5
6
7 The science of catalyst preparation is evolving at a fast pace, and while new catalysts
8 specifically designed for biomass upgrading are often developed through batch studies, some
9 could very well find their way into continuous flow applications.¹⁰²⁶ An important focus is on
10 catalysts that are resistant in hydrothermal conditions. The surface of inorganic heterogeneous
11 catalysts can be functionalized to become more hydrophobic, and this can be exploited to
12 develop more stable catalysts for example in the continuous mode dehydration of bio-
13 alcohols.^{1027,1028} Other hybrid material including metal-organic frameworks¹⁰²⁹ (MOF) and
14 covalent organic frameworks¹⁰³⁰ (COF) are being developed specifically for biomass upgrading
15 applications, and can be applied in flow mode.^{933,1031} Since many biomass upgrading reactions
16 rely on hydrogenation reactions, metal-based catalysts are essential as well.²⁵ In this field,
17 important developments can be expected from the progress made in colloidal methods for the
18 preparation of catalysts with monodisperse metal nanoparticles, or featuring well-controlled bi-
19 (or multi)metallic particles with peculiar reactivity. Again, stability in reaction conditions will
20 be key.

21
22 It is important to keep in mind that many of the high-performance catalysts that may be obtained
23 in the form of fine powders will need further shaping so that they can be used in continuous
24 flow reactors, especially if it is in the liquid phase. Shaping larger objects is needed to operate
25 fixed-bed reactors with reasonable pressure drop. A telling example is that of microporous
26 catalysts, such as zeolite, where intra-particle diffusion is hampered and where researchers
27 solve this issue by reducing the elementary particles size. Thus, zeolite nano-crystals are often
28 much more active than the corresponding large crystals because they have larger external
29 surface-to-volume ratio. Nevertheless, nano-catalysts cannot be used as such in continuous flow

mode because they either plug the reactors, or are difficult to recover by simple filtration or settling. Thus, while many developments are observed in the field of biomass upgrading with efficient “nano-catalysts” – including zeolites,¹⁰³² MOFs,¹⁰³³ clays,¹⁰³⁴ *etc.* – we point out that the shaping of larger microparticles that can be handled easily is an important aspect of catalyst development that will pave the way to a transfer in continuous flow mode processes. In that sense, the design of hierarchically porous materials^{1035–1038} is currently booming and represents a promising land of exploration. Also of particular interest is the preparation of structured monoliths able to host various catalytically active species, including highly dispersed metal sites for acido-basic or redox catalysis,¹⁰³⁹ metal nanoparticles,¹⁰⁴⁰ grafted organometallic complexes,¹⁰⁴¹ enzymes,¹⁰⁴² or even whole cells.¹⁰⁴³ These structures can be specifically designed for continuous flow chemistry, offering large active surface area, good mechanical resistance, and an open porosity.⁵⁴

The recent literature on flow mode biocatalysis essentially focuses on the synthesis pharmaceutical ingredients or other high value compounds.¹⁰⁴⁴ Yet, we argue that some decisive steps are currently being made, that will open up the field to the upgrading of biomass. On the one hand, the power of protein engineering has been largely demonstrated,¹⁰⁴⁵ and it could be exploited to design enzymes that better withstand immobilization, shear stress, temperature, pressure, etc. On the other hand, mastering the preparation of solid biocatalysts and reactors will help designing new flow-mode biocatalytic processes. Indeed, in flow-mode biocatalysis, enzyme immobilization is essential, as it must be designed to allow the anchoring of the enzyme on the solid support, in a way that it does not leach in the reaction medium but also that it resists denaturation. A variety of methods can be envisaged for the immobilization of enzymes on carriers or directly at the surface of structured reactors.^{1046,1047} Apart from the most classical immobilization techniques (physical adsorption, covalent anchoring, affinity immobilization,

entrapment),¹⁰⁴⁸ progress can be expected from elegant strategies such as layer-by-layer constructions using protein-polyelectrolyte complexes.¹⁰⁴⁹ Indeed, the latter could allow immobilizing large amounts of enzyme, irrespectively of their surface charge, on various types of solid supports, and preserving activity.

The field of hybrid chemo-bio catalysis is also emerging. Hybrid catalysis refers to the combined use of a biocatalyst and a chemo-catalyst, and it is often envisaged for cascade chemical reactions.^{1050,1051} The idea is to leverage on the qualities of each catalytic partners – for example the robustness of a heterogeneous catalyst and the (enantio)selectivity of an enzyme – to run intensified multistep reactions. In the context of continuous flow chemistry, both catalytic partners are located on the same solid support.^{1052,1053} With such bi-(or multi)functional solid catalysts in hand, it can be envisaged to run intricate cascade reactions in flow mode, including those concerning biomass upgrading.

A challenge in the field of flow biocatalysis concerns the use of cofactor-dependent enzymes, for which inventive solutions must be found to avoid wasting these sometimes costly compounds in the reactor effluent. The exogenous addition of cofactor complicates the work-up because it must be separated from the final products, increasing the process costs. Interestingly, it has been proposed to co-immobilize the enzyme and the cofactor on the same solid support specifically designed to allow the cofactor “come and go” in the cofactor binding sites, without being washed away with the flow.¹⁰⁵⁴ This example¹⁰⁵⁴ deals with transaminase and pyridoxal 5'-phosphate (PLP) co-factor, but could be inspirational for biomass upgrading, for example for biomass upgrading reactions that can be catalyzed by oxidoreductases.¹⁰⁵⁵

The design of novel synthetic routes for the upgrading of bio-based chemical platforms toward value-added chemicals is a multifacet and challenging task that relies on the creativity of expert organic, catalysis and process chemists. Such design of novel routes requires a cutting-edge

expertise in the field, a considerable amount of literature survey for identifying the most suitable route and then resource-consuming lab work, including a laborious trial-and-error screening to optimize and validate the process experimentally. Similar challenges are typically bottlenecking all areas related to the preparation of organic compounds. The idea of a computer program that would output a sequence of reactions and a list of commercially available building blocks from an input complex organic target dates back to the early 70's.^{1056,1057} Early works in this area relied on expert-coded rules, therefore not only suffering from human bias, but also relying on non-exhaustive collections of reaction rules.^{1058,1059} Developments on self-optimizing continuous-flow reactor setups equipped with analytical tools for real-time reaction monitoring coupled with automated feedback optimization of chemical reactions,¹⁰⁶⁰ as well as on continuous-flow platforms coupled with Artificial Intelligence (AI),⁸⁰ have been recently reported (Perspective 3, Automation, feedback control and Artificial Intelligence, Figure 120). AI can be trained with collections of preliminary experiments, rather than on human-coded synthetic rules. The integration of AI with automation for the assembly of fluidic elements with advanced synthesis and purification capabilities, in-line analysis tools for continuous monitoring of reactions, and algorithms for self-optimization of complex multistep reaction sequences and purification procedures is foreseen as a major step forward in the development of continuous flow processes.^{81,1061} Yet already engaged for the preparation of pharmaceuticals and other high value-added compounds, it is expected that the combination of AI and advanced automation will open up new possibilities for the upgrading of bio-based platforms through unique process conditions. To enable self-optimization of a broad range of reactions, as well as of purification procedures, such perspective also relies on the integration of various analytical tools.^{62,81,1062} These include for instance in-line infrared (IR) spectrometers, in-line Raman spectrometers, in-line nuclear magnetic resonance (NMR) spectrometers, on-line high

performance liquid chromatographs (HPLC), on-line gas chromatographs (GC) and on-line mass spectrometers (MS). Additional potential improvements concern the integration of new algorithms taking into account both the cost, the availability and the potential toxicity of any reaction partner (reagents, solvents, catalysts) as well as green metrics such as the E-factor.

From the fast developments that were observed for flow chemistry in pharmaceutical and related sciences, flow chemistry really came of ages when in-line purification and analysis protocols were adopted, thereby enabling the concatenation of multistep processes and the further exploration of pristine chemical spaces.^{45,64,65,98,1063–1069} It is therefore expected that the generalized implementation of advanced in-line purification technologies for the continuous flow upgrading of bio-based chemical platforms will be a major step toward maturity and generalized adoption. The development of efficient, reliable and scalable tools for both upstream⁷⁰⁴ (biomass to platforms) and downstream¹⁷⁸ (platforms to added value molecules) in-line purifications amenable for the specifications of bio-based chemicals can be foreseen as an important research field for the next decade (Perspective 4, In-line purification, Figure 120). Other technologies such as in-line distillation^{1070,1071} and pervaporation^{1072–1076} present great potential of development. However, they have not been applied yet to the separation in continuous flow of bio-based components. A significant research effort will also have to be spent on filling the gap between the laboratory and the industrial scales. Only membrane-based liquid-liquid separation have been fully transposed to pilot-scales, yet in the context of high valued-added chemicals.¹⁰⁷⁷

Some efforts for the integration of the up- and downstream in-line purification methods have been reported in the literature, and this section aims at illustrating the most significant advances of such upstream purification strategies.

In order to ensure fast development of new chemical processes under continuous flow conditions, an effective in-line purification system of intermediates and products will always be a plus when integrated within the production process. Indeed, downstream product separation often bottlenecks the development of fully integrated continuous processes.¹⁰⁷⁸ This is particularly true for the upgrading of unstable bio-based platform chemicals such as HMF that must be quickly extracted from the reaction medium and processed to avoid decomposition and to maintain high purity (see section 3.2.2). Continuous flow liquid-liquid extraction using micro- and mesofluidic devices has been by far the main technique documented for the separation and purification of bio-based molecules. As indicated above, other technologies are also potentially of interest, such as in-line distillation^{1070,1071} or pervaporation.¹⁰⁷⁹ Nevertheless, in-line liquid-liquid separation extraction is the only separation technique that was successfully applied for the separation of a range of compounds that fit the scope of this review. In addition, in-line liquid-liquid or liquid-gas separation relies on various technologies including (automated) settling tanks,^{98,1080–1083} evaporators^{178,1084} and membrane-based technologies.^{65,98,1077,1085}

Liquid-liquid extraction is one of the most important, applied and mature unit operations in the (bio)chemical industry. The separation method is based on the different solubility of compounds between two immiscible fluids. First, the two immiscible fluids are intimately mixed to create a large interface and to enhance the mass transfer. Then, a phase separation based on a difference in density^{98,1080–1083} (in macroscopic setups such as settling tanks) or based on the differential wettability of a porous membrane^{65,98,1077,1085} is performed to finally recover the extracted component. The recognized disadvantages of conventional liquid-liquid extractors, such as their low efficiency, large size, long mixing time and high energy

consumption, have promoted the development of microchannel devices to perform liquid-liquid separations.^{1086,1087}

Liquid-liquid extraction has been widely applied as a standard procedure for sample pretreatment before analysis, in which a stationary organic phase is contacted with an aqueous moving sample.^{1088,1089} The application of liquid-liquid microextraction for continuous purification has flourished during the last four decades in the field of flow analysis, starting with the works by Bergamin *et al.* (1978) and of Karlberg and Thelander (1978).^{1090,1091} Although the objective in flow analysis applications is quite different, *i.e.* the pre-concentration and/or separation of multiple analytes (*e.g.*, by isolating the analyte from matrix interfering species or by concentrating the analyte from a large sample volume) for further analysis,¹⁰⁹² the accumulated know-how is directly applicable to bio-based chemicals upgrading in flow chemistry. Extensive analyses focused on mass transfer performance, droplet formation and two-phase microfluidics can be found in the literature.^{1093–1095}

Similar concepts are increasingly utilized to achieve continuous liquid-liquid micro-extraction processes allowing the application of new and greener approaches toward bio-based molecules. Liquid-liquid extraction under continuous flow features unique advantages, including short diffusion lengths, high surface-to-volume ratio, short mixing times, flexibility, moderate operating parameters, small dimensions, and the possibility of numbering up.^{1078,1086} Three types of flow regimes are typically described in the literature when dealing with extraction between two immiscible liquid phases in narrow channels: (1) parallel flow characterized by the side-by-side contacting flows of immiscible fluids; (2) slug flow (also referred to as segmented or Taylor flow) characterized by alternating and well defined slugs of immiscible fluids; and (3) dispersed flow, closely fitting the definition of emulsion and that typically relies on dispersion membrane microfluidic devices. In parallel flow, mass transfer is limited mainly

by molecular diffusion given the well-structured and undisturbed nature of fluids lamellae in microchannels, and an easy separation between the two immiscible liquids is often guaranteed.¹⁰⁹⁶ Slug flow devices are characterized by a high interfacial area and enhanced mass transfer by the internal circulation inside each slugs.^{1078,1097} In a membrane dispersion device, the droplets are formed through the microporous membrane, and they are mixed with the other phase. The membrane allows a fine control of the droplet size and high interfacial areas are achieved, improving the extraction efficiency.¹⁰⁹⁸ These three configurations can be used either for the separation of a target compound only or for a combination of reaction and separation. In the first approach, the main advantage is that one phase can be removed out of the system by using an in-line phase separator, achieving a fast mass transfer between phases and a rapid purification.^{1077,1099} In some instances, the second approach presents the additional advantage of enhancing reaction yields since products can be separated from reactants and/or from by-products while the reaction is taking place, which is of great interest when reactions are thermodynamically limited by the position of the equilibrium at the process temperature (*e.g.*, esterification and transesterification reactions). Nevertheless, for both kinds of systems, a continuous phase separation is necessary to ensure a successful continuous extraction process, for example, using membranes, flow splitters, capillary separators, centrifugal separators, or a combination of these components.¹⁰⁸⁶

Parallel flow liquid-liquid extraction in microfluidic devices is mostly applied to analysis and sample preparation since the volumes involved are typically very small and the diffusive mass transfer is too slow for high-throughput applications.¹⁰⁷⁸ The laminar flow nature and undisturbed side by-side flow configuration in microchannels lead to limitations of mass transfer mainly by molecular diffusion, although higher flow rates and/or smaller microchannels have been proved to increase the mass transfer rate.¹⁰⁹⁶ Nevertheless, the parallel

flow involves the main advantage of allowing an easy separation between the two immiscible liquids at the microchannel outlet, which can be more challenging for slug flow and dispersed flow regimes.

In order to apply parallel flow efficiently, multiple stages are commonly placed forming a cascade of separation units, with cross-current or counter-current configurations. Multistage extraction enables excellent separation, especially for systems with small partition coefficients or low selectivity. In the cross-current configuration, the solvent fed in each stage is fresh, and the extract (solvent stream enriched with the target component) does not enter another stage but is combined with the effluents obtained from other extraction stages. Regarding the counter-current configuration, the extract leaving one stage enters the next one, keeping a maximum driving force for separation and, thus, giving the highest extraction efficiency.¹¹⁰⁰ As example, a liquid-liquid microflow extraction in a counter-current configuration was proposed by Jensen and coworkers for the separation of three mixtures: acetone between toluene and water; acetic acid between water and ethyl acetate; and, tetrahydrofuran (THF) and ethyl acetate from methanol, ethanol, isopropanol, *tert*-butanol and trace water.¹¹⁰¹ Figure 121 is a schematic representation of the liquid-liquid microfluidic extraction. Results proved a very high extraction efficiency (about 100%) and showed a potential technique to generate also equilibrium data for the development of extraction processes.

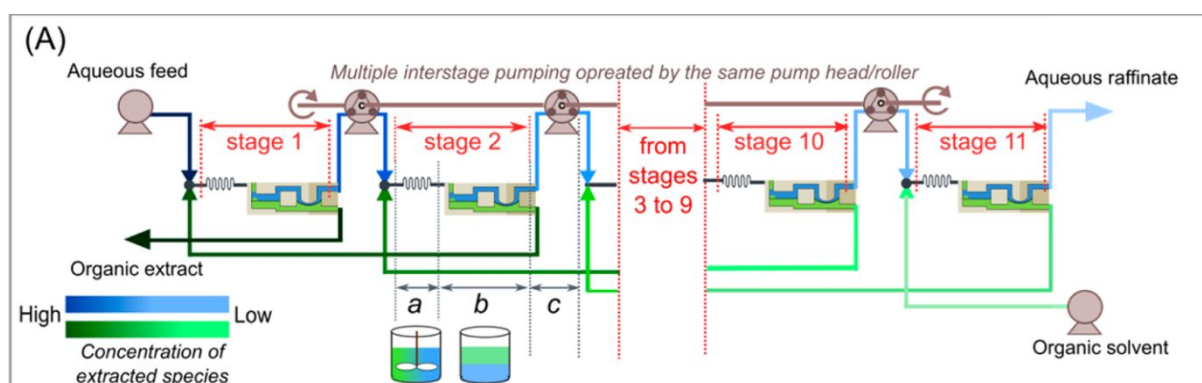


Figure 121. Schematic diagram of the 11-stage countercurrent liquid-liquid extraction developed by Jensen and colleagues.¹¹⁰¹ Reproduced with permission from ref 1101. Copyright 2017 American Chemical Society.

The mixing of immiscible fluids in a submillimetric channel leads to a slug flow regime with an enhanced mass transfer between the two immiscible phases. Such system is often utilized for liquid-liquid extractions, but can also be deployed for enhancing gas-liquid reactions.^{58,100,1102–1104} T- or Y-junction mixing elements are common for installing such segmented regimes. Subsequent separation is envisaged by simple decantation,^{98,1080–1083} flow splitters that separate the two phases efficiently,¹⁰⁹⁷ or membrane-based separators.^{65,98,1077,1085,1105,1106} The potential of such liquid-liquid microextractor/reactors is based on the superior performance and greater efficiency observed in terms of mass transfer coefficients in comparison with conventional contactors.¹⁰⁹⁷ The application of this technology has been extended to perform extractions.^{1097,1107–1109} or reactive extraction.^{1110–1114} In the field of purification of bio-based molecules, an illustration for such segmented flow-based extraction systems was applied to the liquid-liquid extraction of several non-reactive systems.¹⁰⁹⁷ In addition, biphasic chemical reactions have been also performed in such devices.¹¹¹²

Dispersed flow in a microextractor can be achieved by a microporous membrane (membrane dispersion microreactor), which produces a large amount of droplets that are mixed with the other phase. In this case, the interfacial areas are increased and mass-transfer distances between liquid-liquid phases are decreased, which greatly improves the extraction efficiency.^{1098,1115–1117} Figure 79 illustrates an example of a membrane dispersion microreactor for the production of HMF (see also section 3.2.2).¹¹⁵

Moving away from the synthesis of HMF using microfluidic reactive extraction, which has been thoroughly reviewed in section 3.2.2, other examples integrating reaction and separation in the

production of bio-based molecules can be found in the literature, such as the separation of lactic acid from an aqueous phase using liquid–liquid reactive extraction,¹¹¹⁸ the synthesis of GVL combined with the extraction of levulinic acid,⁹⁶⁵ or the synthesis of 5-chloromethylfurfural.¹¹¹⁹ Last but not least, the development of concatenated strategies relying on the integration of multiple continuous flow steps within the same reactor network (Perspective 5: advanced multistep concatenation, Figure 120) is another mature approach that was originally developed in the context of the manufacturing of fine pharmaceuticals that is still underexploited for the upgrading of bio-based chemical platforms.^{66,69,178} Advanced multistep concatenation is typically seen as the ultimate goal for flow chemistry applications, especially when unstable intermediates are at stakes, a remarkable impact on the overall footprint of the corresponding processes.^{66,69}

6. Conclusion

The development and the implementation of new process technologies from R&D labs to production facilities is seen as an opportunity to support the transition from an exclusively petro-based to an alternative bio-based chemical industry. Compared to other sister research areas that have generalized the adoption of flow technologies such as the pharmaceutical area, the continuous flow upgrading of bio-based platform chemicals is still considered a developing area of research. Research efforts are definitively stepping up the pace as emphasized in this review. Several doors had to be opened through the breaking of some chemical and technological obstacles, and such advances relying on multidisciplinary approaches combining the development of new chemical strategies, the engineering of new catalysts and of advanced process technologies to meet the inherent specifications of bio-based chemicals. Owing to its inherent assets in terms of unique process experience, scalability and reduced environmental footprint, flow chemistry arguably stimulates lots of hope for the future advancement of bio-

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3 based chemistry. Not only continuous flow reactors enable to explore pristine chemical space,
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5 but they also help to provide process solutions with a lower environmental footprint and fast
6
7 lab-to-market transition. The perspectives for the development of “traceless” and scalable
8
9 photochemical and electrochemical processes will definitively open new perspectives in the
10
11 near future.
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14 In most examples, even if the commercial exploitation of bio-based platform chemicals aims at
15
16 feeding existing facilities and processes with chemical building blocks that are structurally
17
18 identical to the petro-based standards (see the definitions of “drop-in” and “smart drop-in”
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20 platform chemicals in section 1.1), the underlying chemistry challenges our petro-based
21
22 mindsets and stimulates the emergence of new concepts and strategies. For other bio-based
23
24 platform chemicals (see the definition of “dedicated” bio-based platforms in section 1.1), the
25
26 challenges are much greater, as are the potential opportunities associated with the development
27
28 of unique bio-based commodity and specialty chemicals, as well as the corresponding markets.
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30 Bio-based platform chemicals are characterized by a much lower C/O ratio than petro-based
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32 platforms chemicals, and the successful development of chemical strategies for their upgrading
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34 toward bio-based alternatives of petro-based standards or to value-added chemicals mostly
35
36 relies on the engineering of new catalysts for selective dehydration or deoxygenation reactions
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38 without altering the C-C backbone. In some instances, however, the C-C backbone can be
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40 affected, thus emphasizing the great diversity of catalysts that is required for the development
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42 of such research area. With their typical high OH content, bio-based chemical platforms are
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44 often either processed as aqueous solutions or in the gas phase at high temperature and pressure,
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46 which also imposes specific stability criteria for the catalysts. Such challenging process
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48 conditions are very different from what is currently exploited on a commercial scale in the
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50 petro-based industry, and will stimulate high-end research for the next decade. Another
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challenge to be met relates to the high process temperatures that are typical for the upgrading of bio-based chemicals: many of the processes described in this review that rely on heterogeneous catalysts are still limited to rather short production campaigns due to extensive coking and deactivation of the catalyst. Flow technology enables the implementation of regeneration sequences, although it is still considered as a major hurdle for full scale commercial applications.

Besides chemical challenges, the development of appropriate and reliable process technologies including in-line analytics, in-line purification, advanced automation and AI-supported chemical development will be very supportive for the further expansion of commercially viable bio-based strategies.

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ACKNOWLEDGEMENT

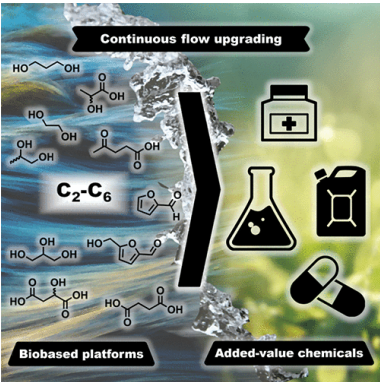
This work was supported by the European Regional Development Fund (ERDF) and Wallonia within the framework of the program “Wallonie-2020.EU” (INTENSE4CHEM, project no. 699993-152208).

ABBREVIATIONS

ABS, acrylonitrile-butadiene-styrene; AcOEt, ethyl acetate; AcOH, acetic acid; Ac₂O, acetic anhydride; AI, artificial intelligence; APIs, active pharmaceutical ingredients; APR, aqueous phase reforming; APTES, (3-aminopropyl)triethoxysilane; BA, Brønsted acid; 1,4-BDO, 1,4-butanediol; b.p., boiling point; BTX, benzene-toluene-xylene; 1-BuOH, 1-butanol; *t*-BuOH, *tert*-butanol; CDI, carbonyldiimidazole; CNT, carbon nanotubes; COF, covalent organic frameworks; CsPW, Cs_{2.5}H_{0.5}PW₁₂O₄₀; CyOH, cyclohexanol; D-A, Diels-Alder; DABCO, 1,4-diazabicyclo[2.2.2]octane; DBU, 1,8-Diazabicyclo[5.4.0]undec-7-ene; DCE, 1,2-dichloroethane; DEC, diethyl carbonate; DFT, density functional theory; DMC, dimethyl carbonate; DMF, dimethylformamide; DMSO, dimethylsulfoxide; DoE, design of experiments; EtOH, ethanol; EG, ethylene glycol; FA, fumaric acid; FDCA, furandicarboxylic acid; FTIR, fourier transform infrared; FU, furfural; GBL, γ -butyrolactone; GC, gas chromatography; GHSV, gas hourly space velocity; GL, glycerol; GTA, glycerol-to-aromatics; GVL, γ -valerolactone; HFIP, hexafluoroisopropanol; HMF, 5-hydroxymethylfurfural; HPAs, heteropoly acids; HPLC, high performance liquid chromatography; HPW, H₃PW₁₂O₄₀ or H₆P₂W₁₈O₆₂; HSiW, H₄SiW₁₂O₄₀; IR, infrared; IA, itaconic acid; IUPAC, international union of pure and applied chemistry; LA, Lewis acid; LaA, lactic acid; LeA, levulinic acid; LHSV, liquid hourly space velocity; MA, malic acid; Me₂NH, dimethylamine; MIBK, methyl isobutyl ketone; M_n, number average molar mass; m.p., melting point; MOF, metal-organic frameworks; MPV, Meerwein-Ponndorf-Verley; MS, mass spectrometry; MTBE, methyl *tert*-butyl ether;

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3 NBu₄Br, tetrabutylammonium bromide; NEt₄Br, tetraethylammonium bromide; NHC, N-
4 heterocyclic carbenes; NMR, nuclear magnetic resonance; PBS, polybutylene succinate; PBT,
5 polybutylene terephthalate; PCL, polycaprolactone; PDI, polydispersity index; 1,2-PDO, 1,2-
6 propanediol; 1,3-PDO, 1,3-propanediol; PEF, polyethylene furanoate; PEG, polyethylene
7 glycol; PET, polyethylene terephthalate; PLA, polylactic acid; 1-PrOH, 1-propanol; *i*PrOH,
8 isopropanol; PS, polymer-supported; PTMC, polytrimethylene carbonate; PU, polyurethane;
9 rGO, reduced graphene oxide; ROP, ring-opening polymerization; SA, succinic acid; SAR,
10 structure-activity relationship; SBP, 2-*sec*-butylphenol; SO, sorbitol; SS, stainless steel; STBE,
11 solketal *tert*-butyl ether; TBD, 1,5,7-triazabicyclo[4.4.0]dec-5-ene; TEMPO, (2,2,6,6-
12 tetramethylpiperidin-1-yl)oxyl; THF, tetrahydrofuran; TOF, turnover frequency; TOS, time-
13 on-stream; TPD, temperature programmed desorption; TRL, technology readiness level; US
14 DoE, US Department of Energy; UV, ultraviolet; VPO, vanadium phosphorous oxide; W/F,
15 weight/flow; WHSV, weight hourly space velocity; XPS, X-ray photoelectron spectroscopy;
16 XY, xylitol.
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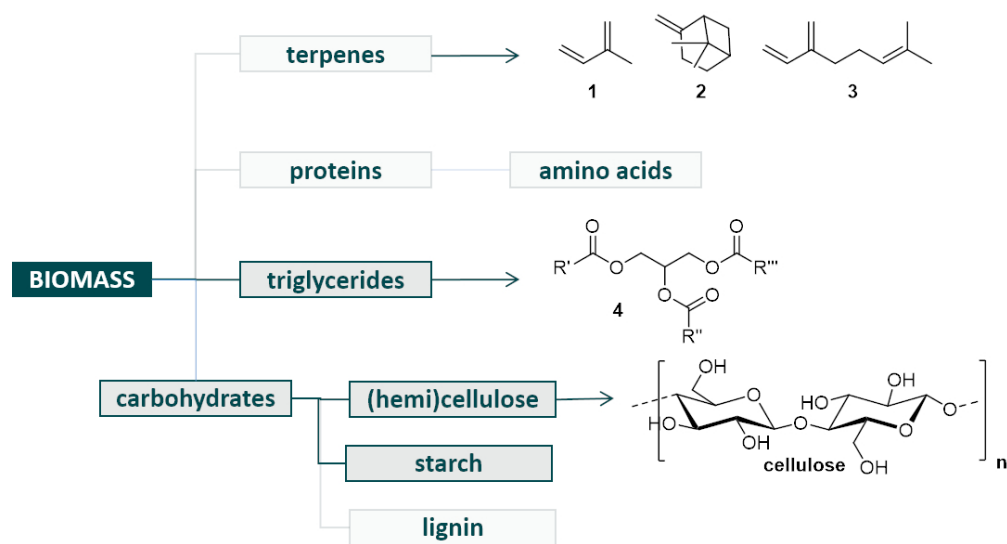


Figure 1

182x100mm (150 x 150 DPI)

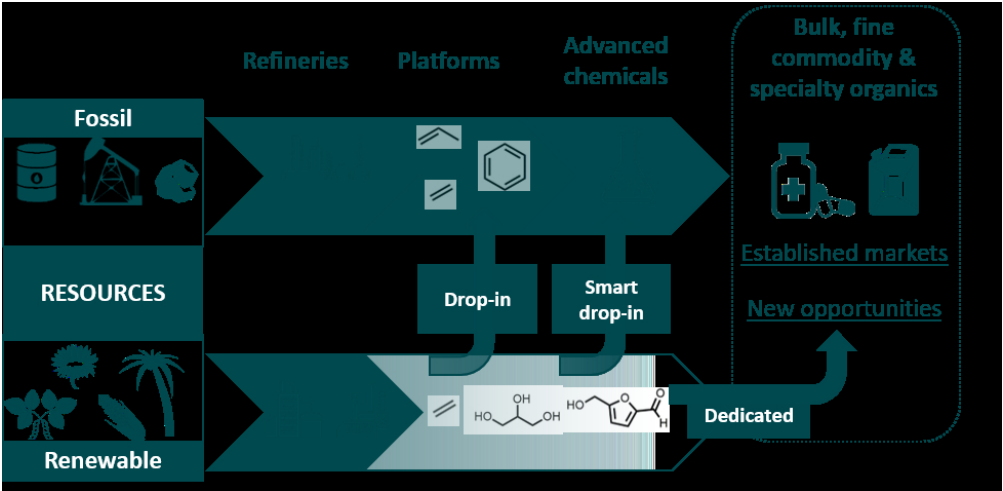


Fig2

165x80mm (150 x 150 DPI)

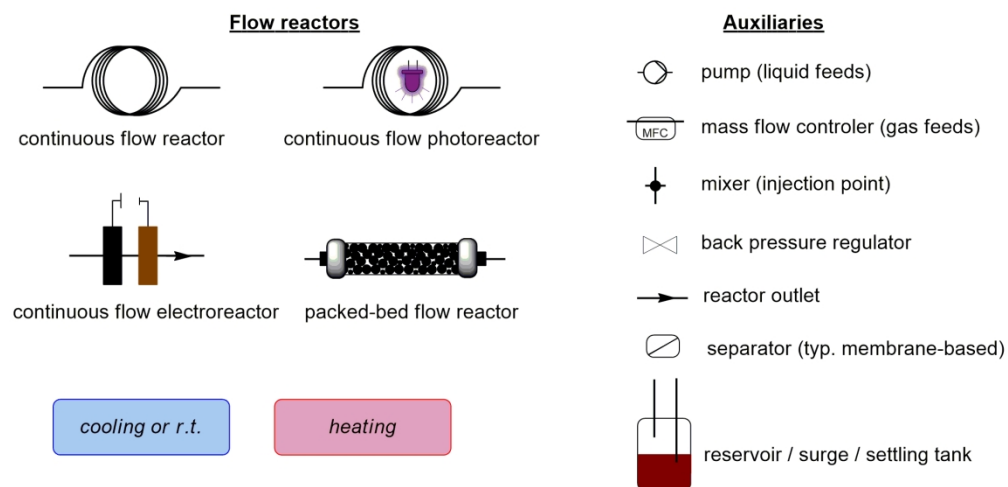


Figure 3

176x86mm (300 x 300 DPI)

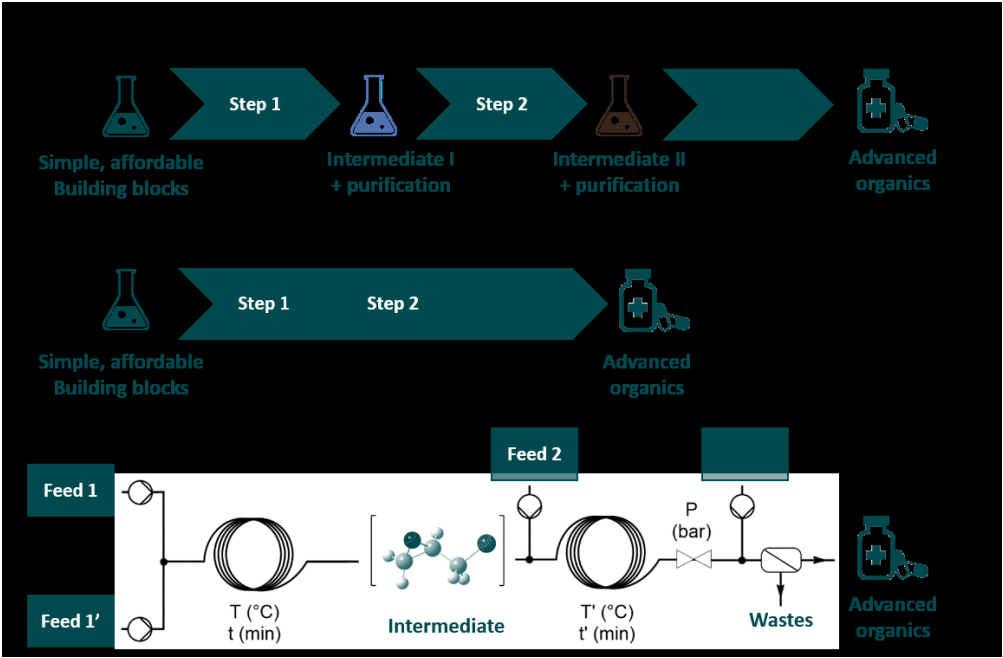


Figure 4

195x128mm (150 x 150 DPI)

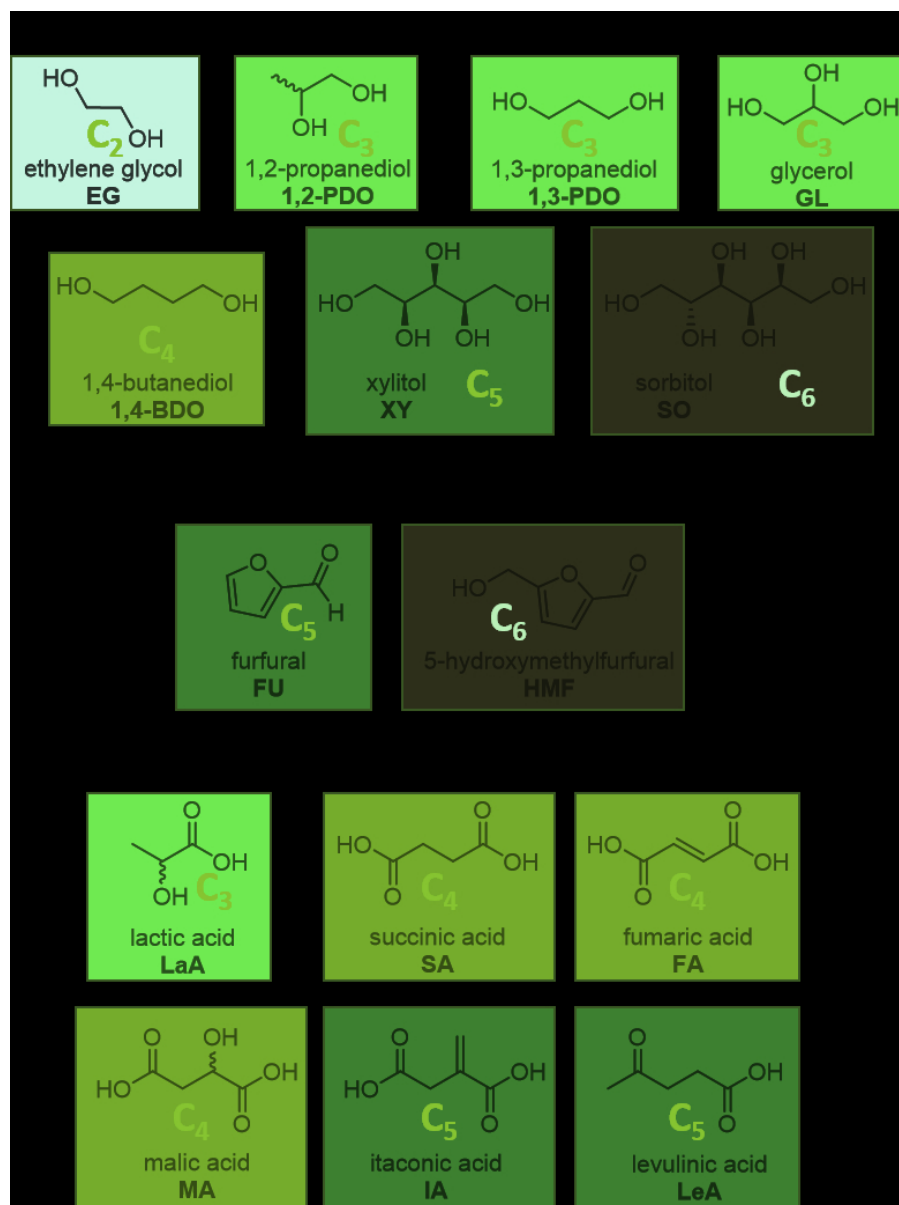


Figure 5

132x175mm (150 x 150 DPI)

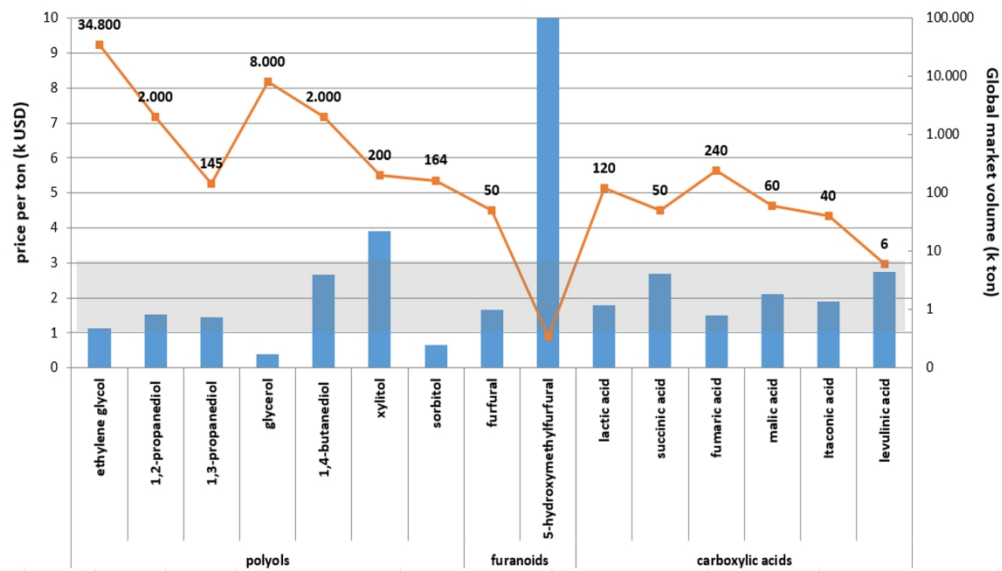


Figure 6

358x188mm (136 x 146 DPI)

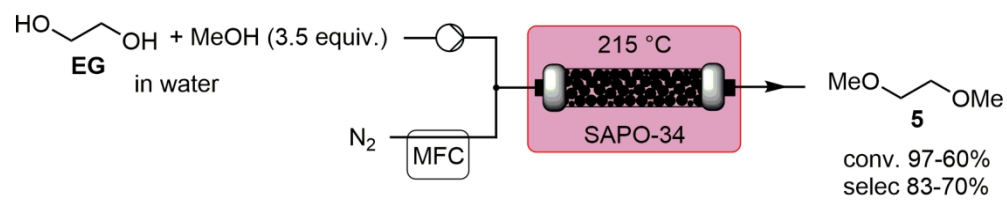


Figure 7

146x29mm (300 x 300 DPI)

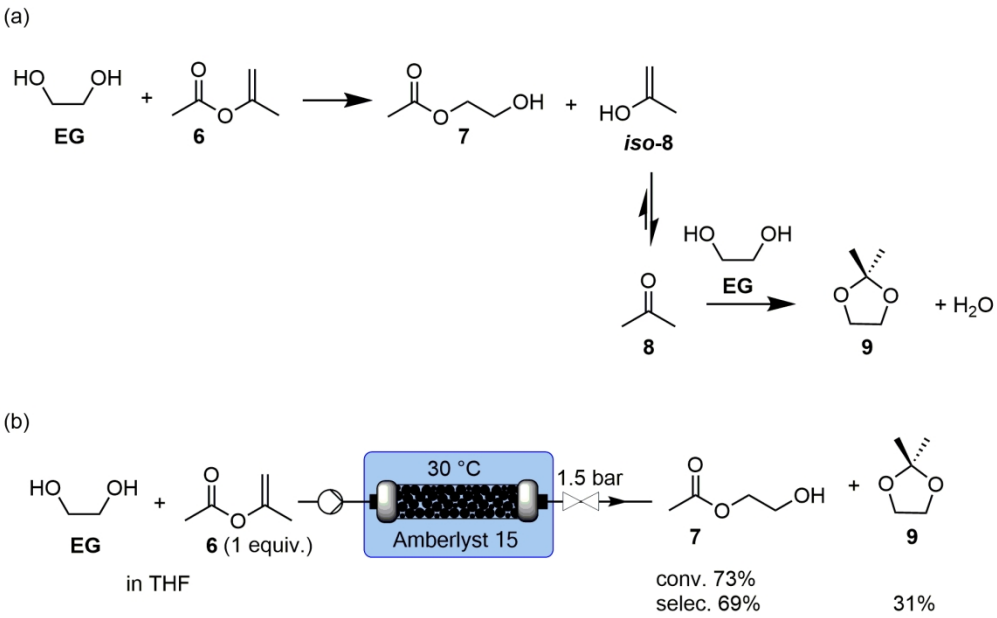


Figure 8

164x102mm (300 x 300 DPI)

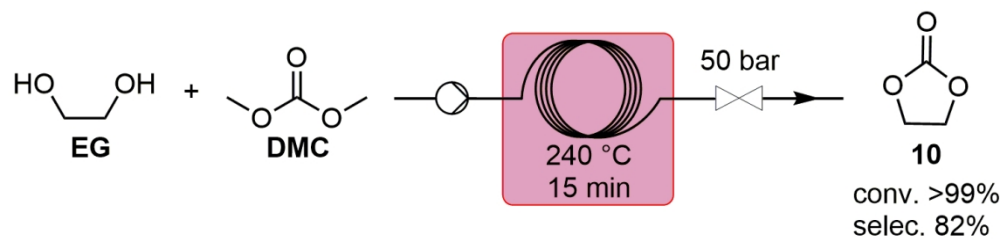


Figure 9

125x30mm (300 x 300 DPI)

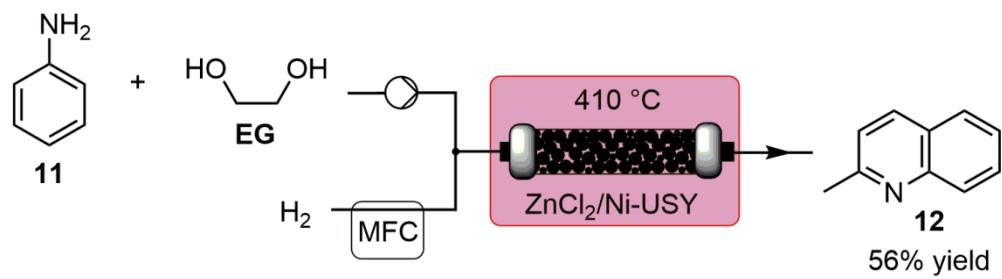


Figure 10

125x34mm (300 x 300 DPI)

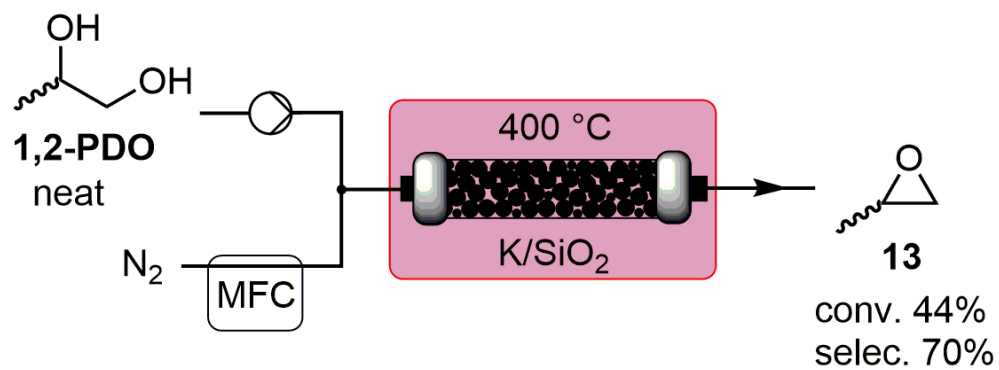


Figure 11

95x40mm (300 x 300 DPI)

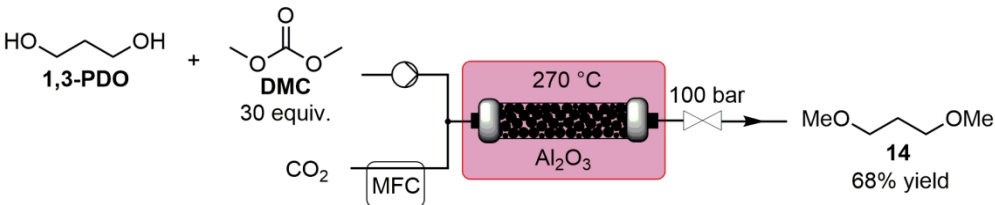


Figure 12

156x33mm (300 x 300 DPI)

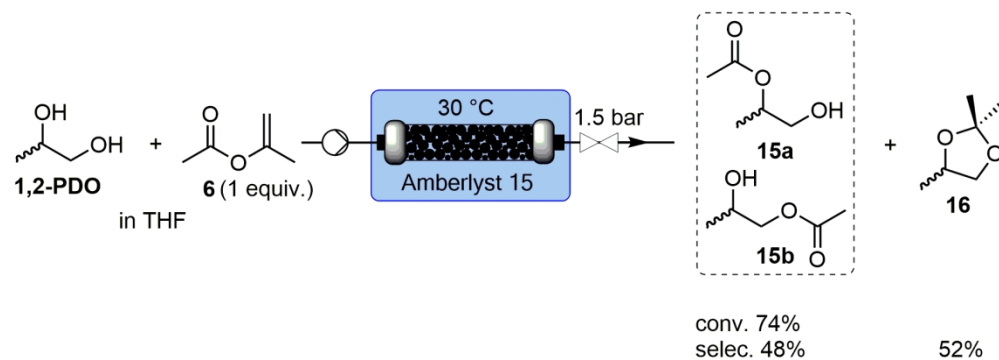


Figure 13

156x56mm (300 x 300 DPI)

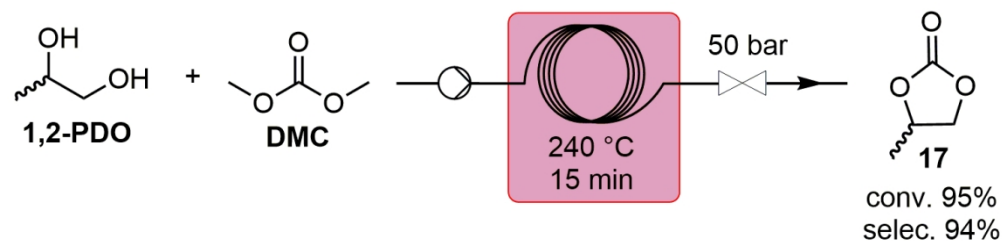


Figure 14

125x31mm (300 x 300 DPI)

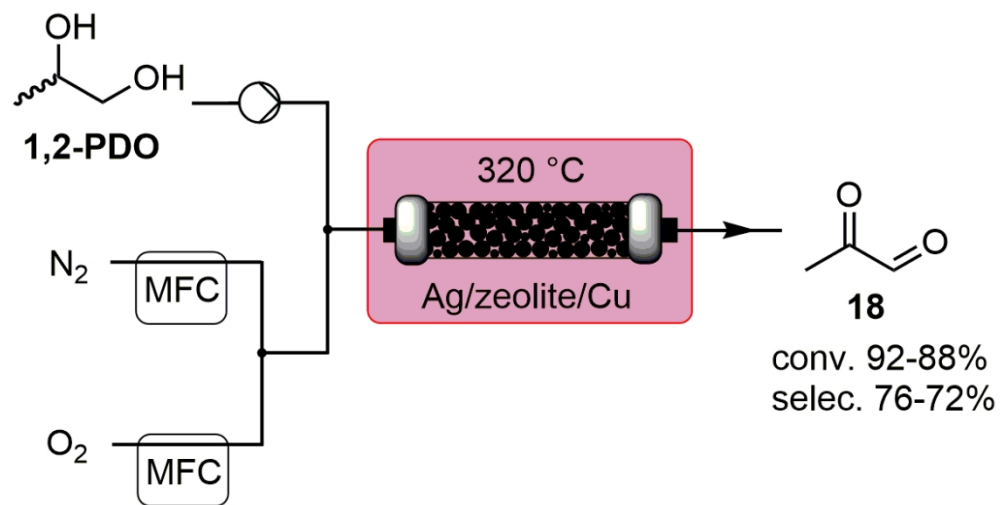


Figure 15

99x51mm (300 x 300 DPI)

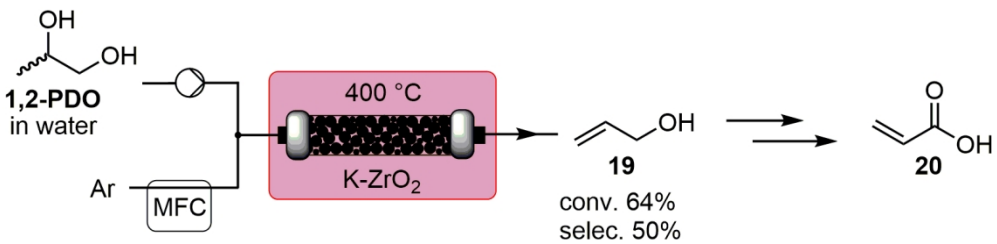


Figure 16

141x35mm (300 x 300 DPI)

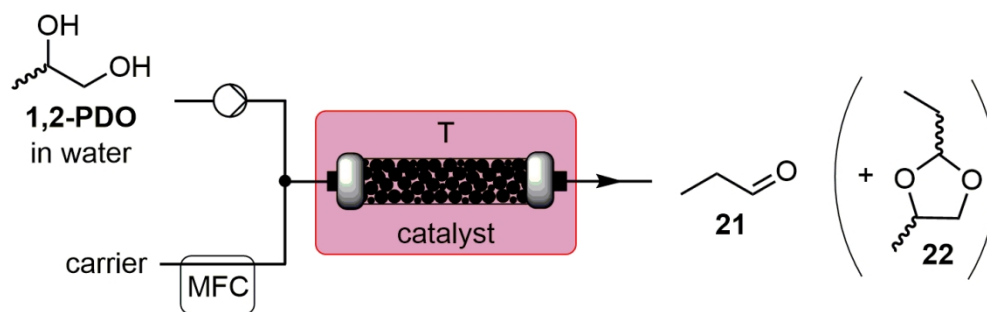


Figure 17

122x38mm (300 x 300 DPI)

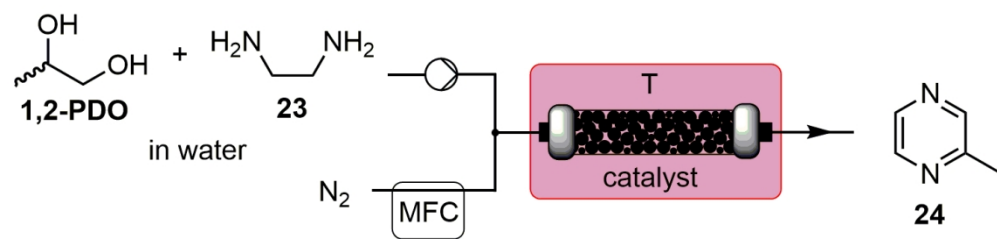


Figure 18

125x30mm (300 x 300 DPI)

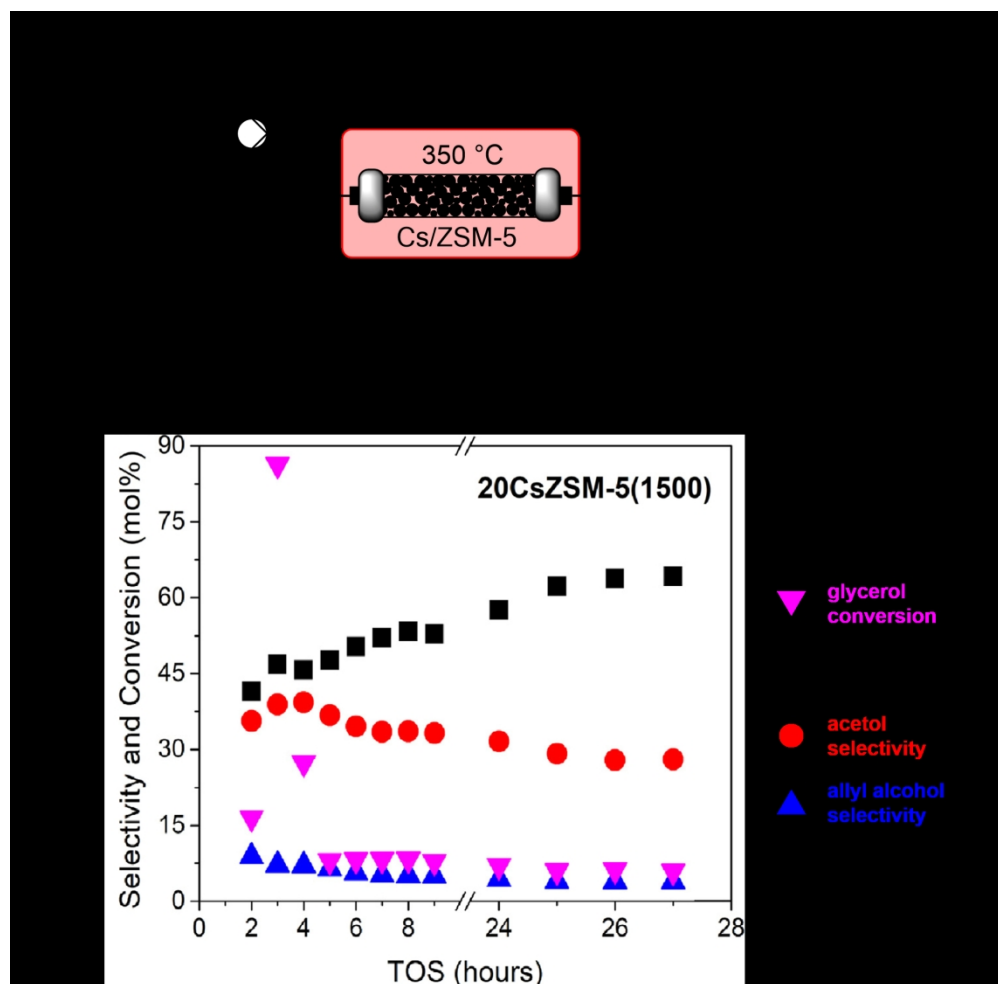


Figure 19

344x336mm (150 x 150 DPI)

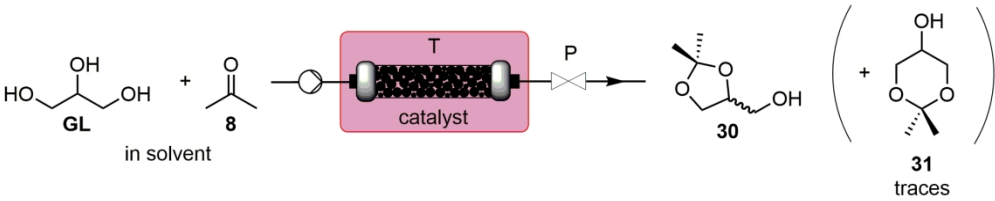


Figure 20

172x35mm (300 x 300 DPI)

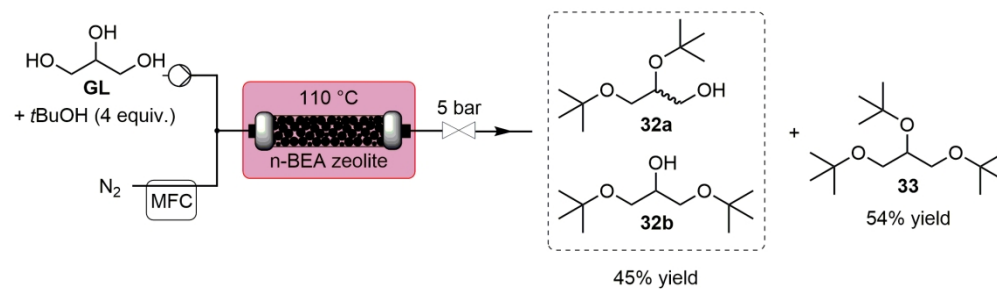


Figure 21

180x51mm (300 x 300 DPI)

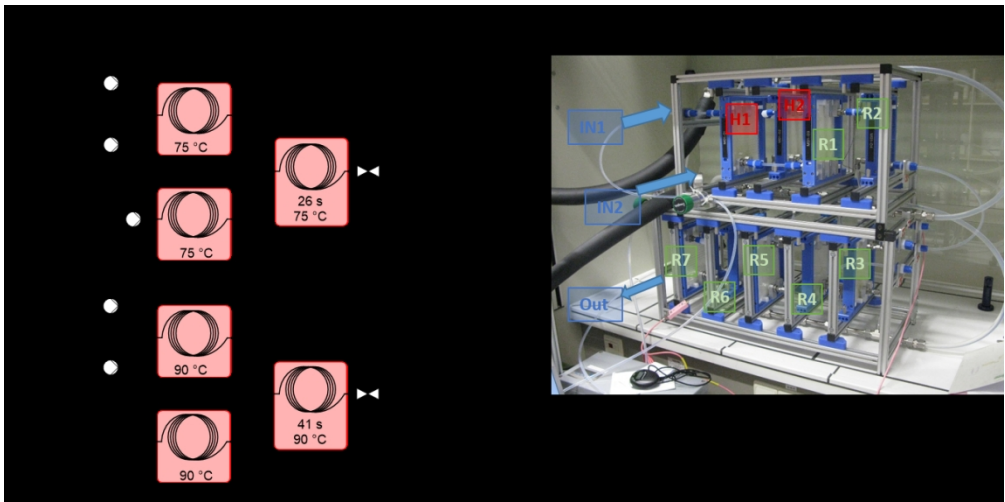


Figure 22

228x113mm (150 x 150 DPI)

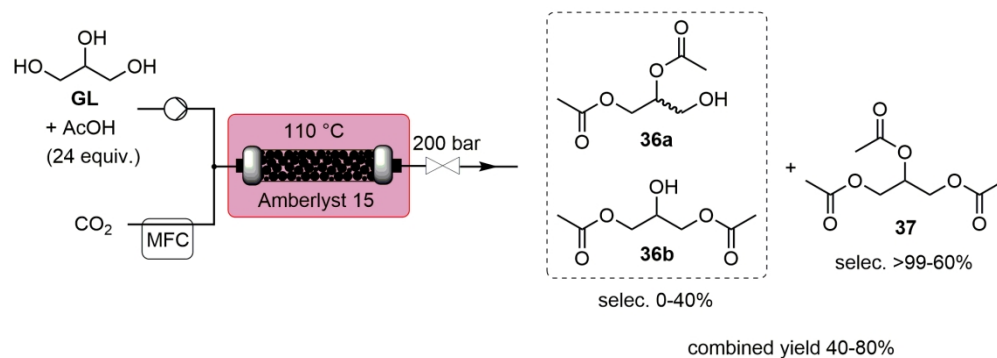


Figure 23

177x63mm (300 x 300 DPI)

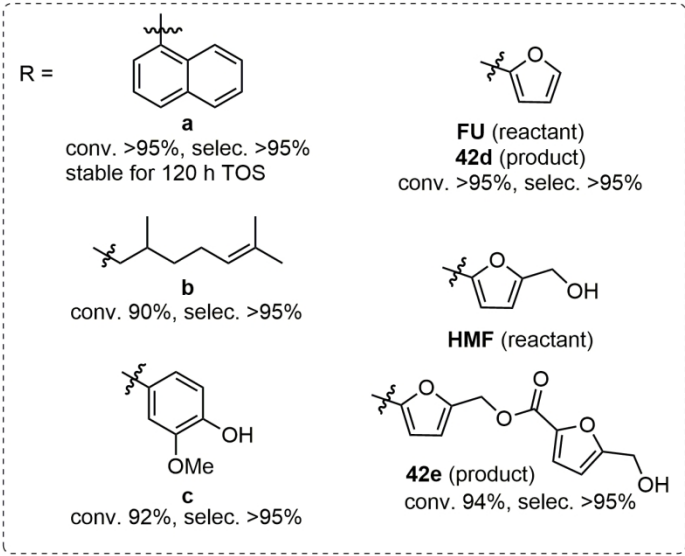
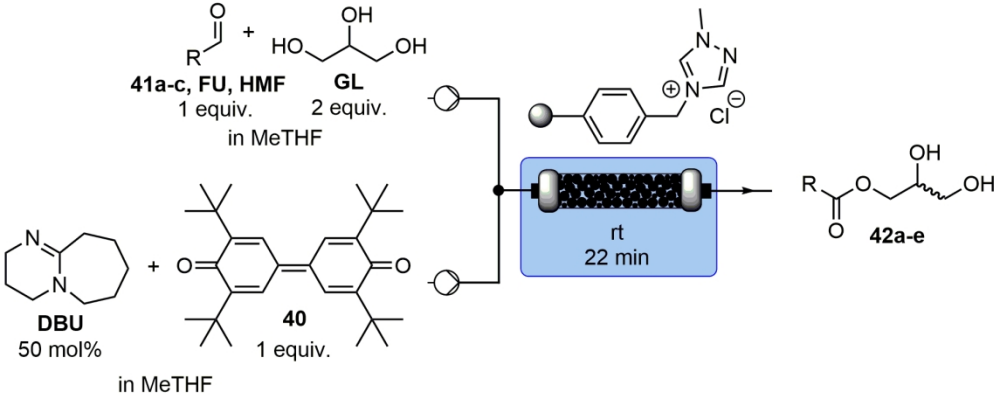


Figure 24

162x162mm (300 x 300 DPI)

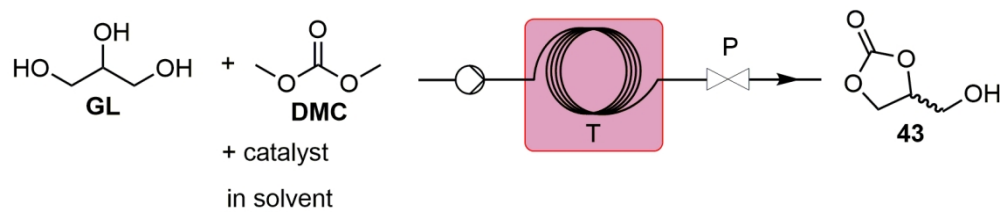


Figure 25

140x30mm (300 x 300 DPI)

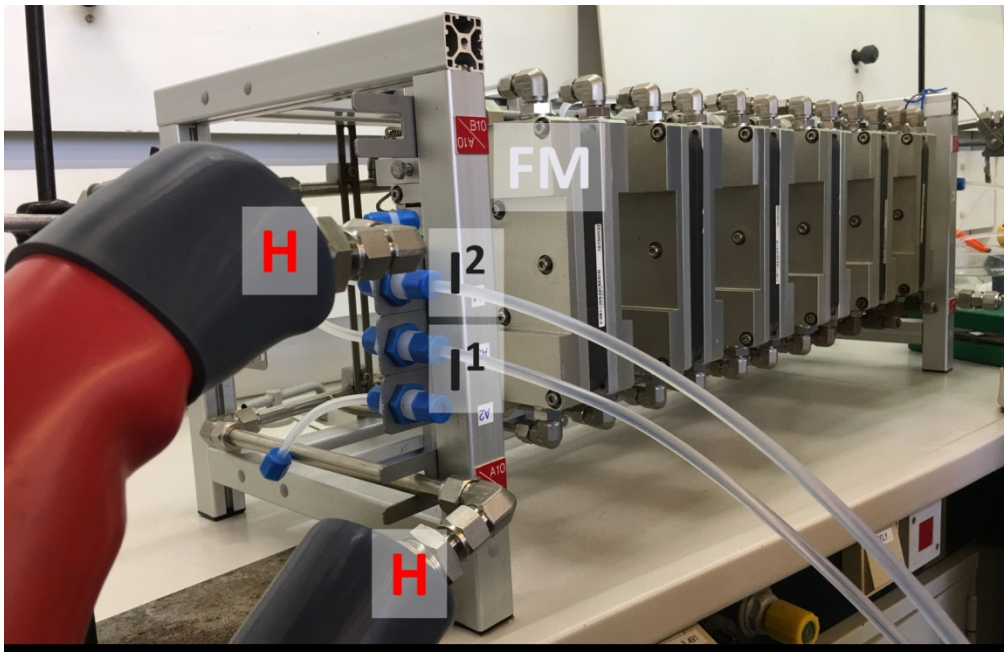


Figure 26

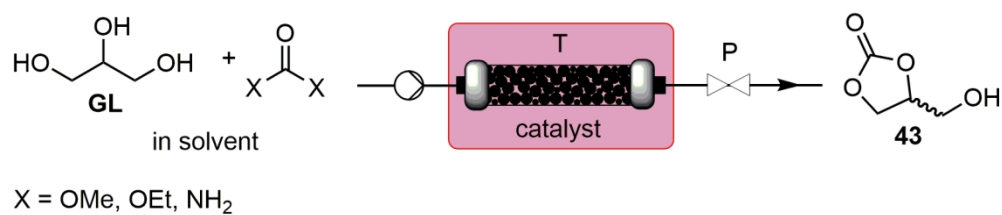


Figure 27

139x29mm (300 x 300 DPI)

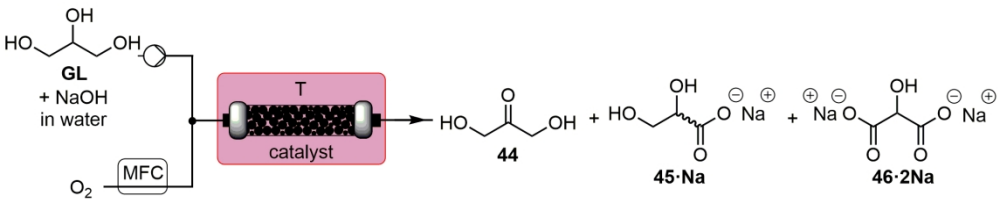


Figure 28

185x37mm (300 x 300 DPI)

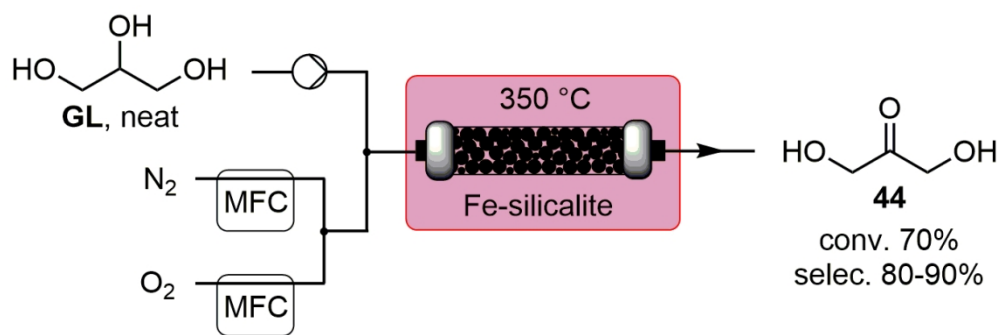
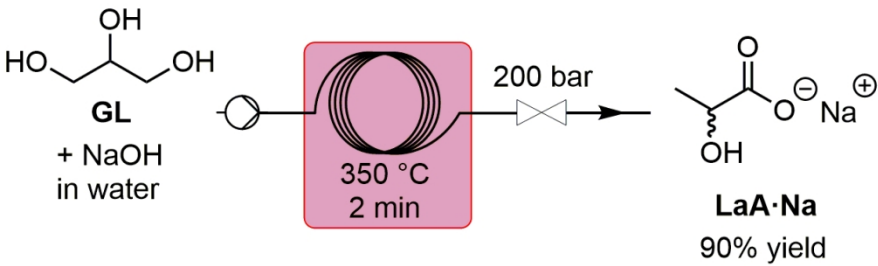


Figure 29

117x39mm (300 x 300 DPI)

(a)



(b)

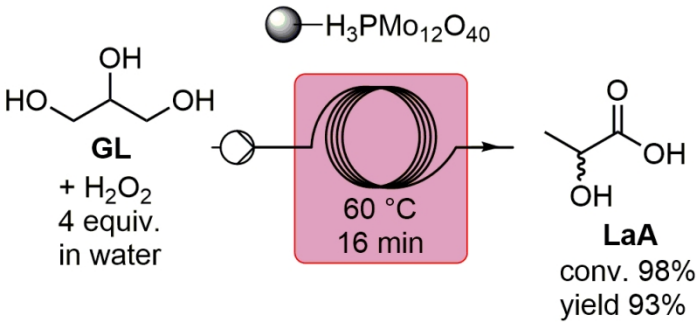


Figure 30

120x80mm (300 x 300 DPI)

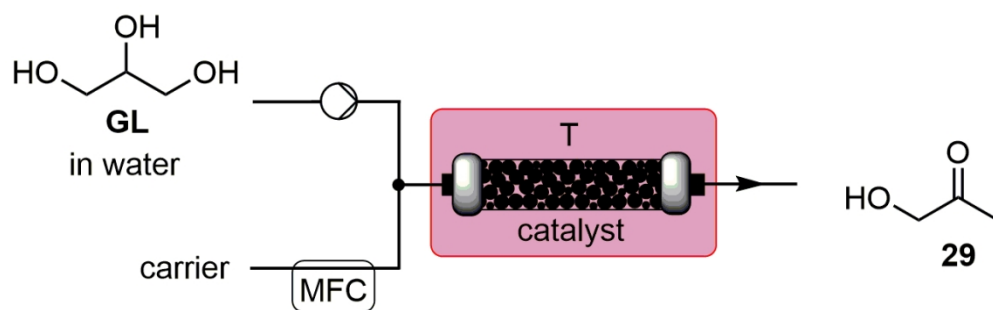


Figure 31

111x35mm (300 x 300 DPI)

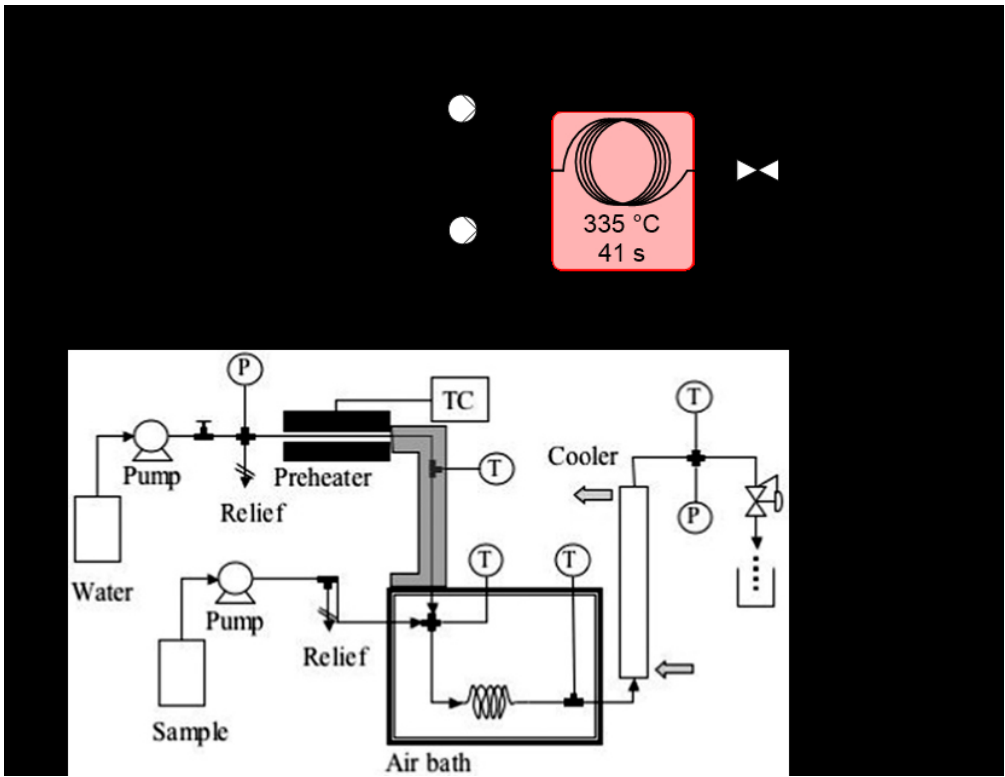


Figure 32

140x107mm (150 x 150 DPI)

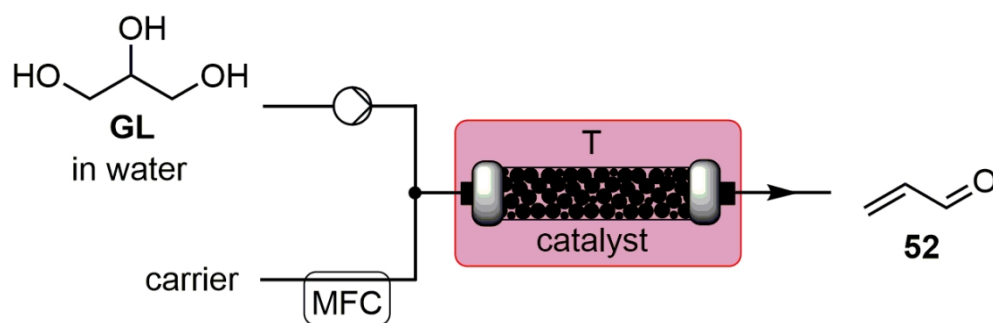


Figure 33

106x35mm (300 x 300 DPI)

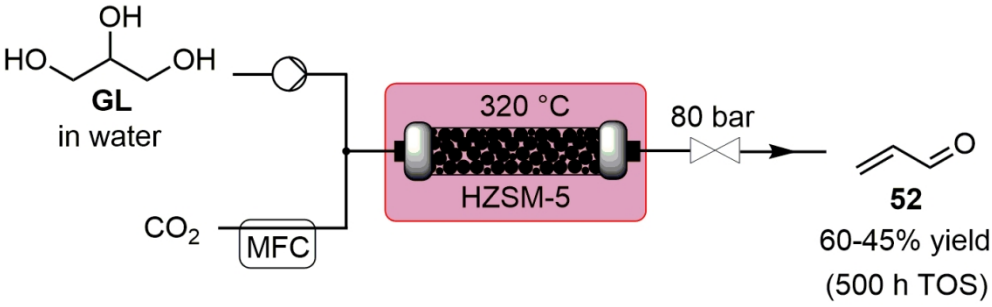


Figure 33

119x37mm (300 x 300 DPI)

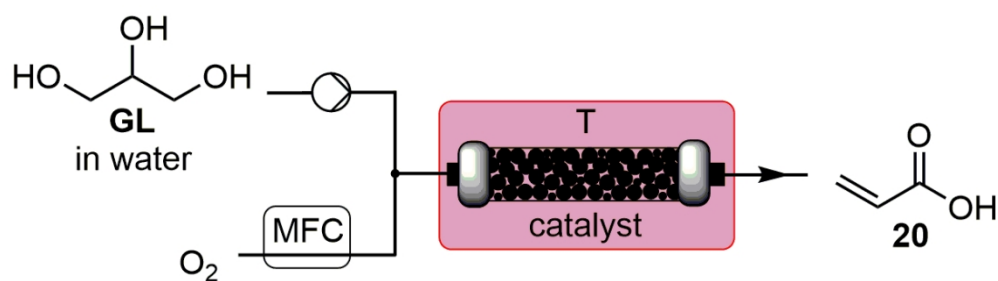


Figure 35

105x29mm (300 x 300 DPI)

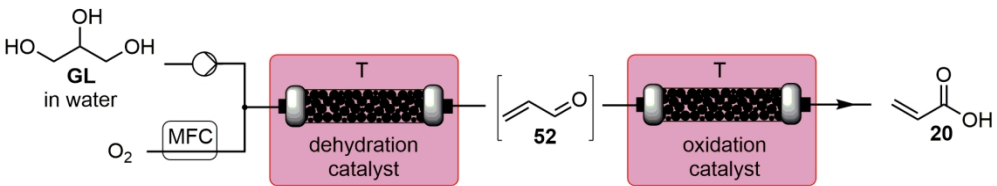


Figure 36

167x31mm (300 x 300 DPI)

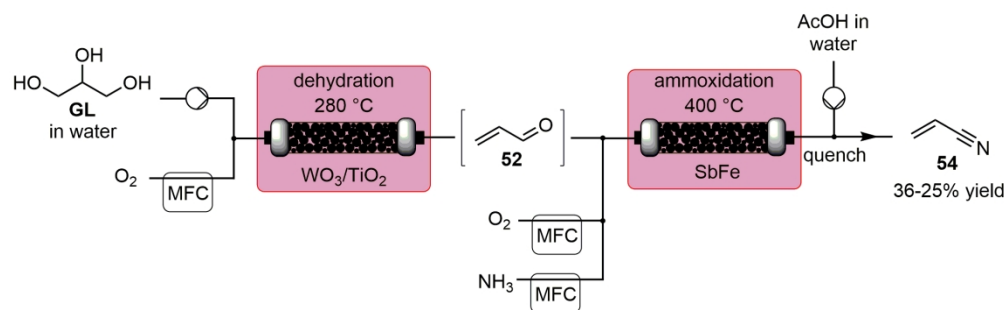


Figure 37

183x56mm (300 x 300 DPI)

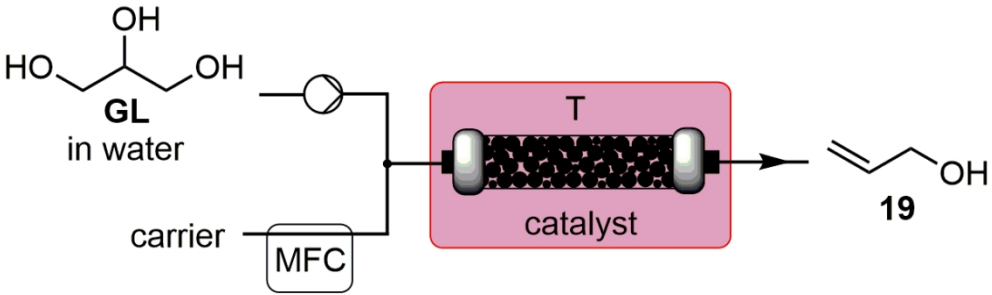


Figure 38

105x32mm (300 x 300 DPI)

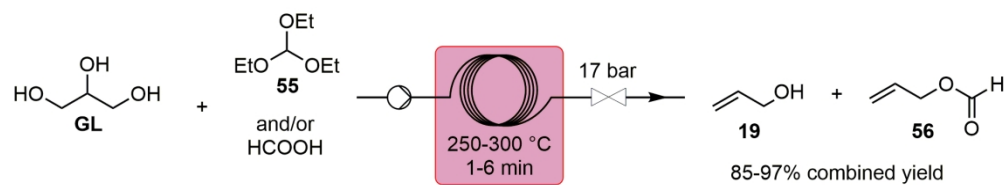


Figure 39

171x31mm (300 x 300 DPI)

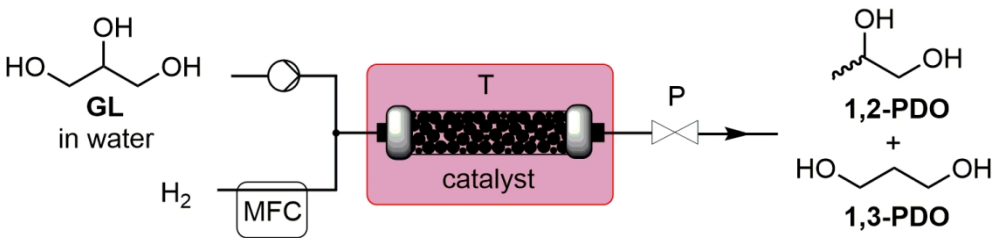


Figure 40

128x31mm (300 x 300 DPI)

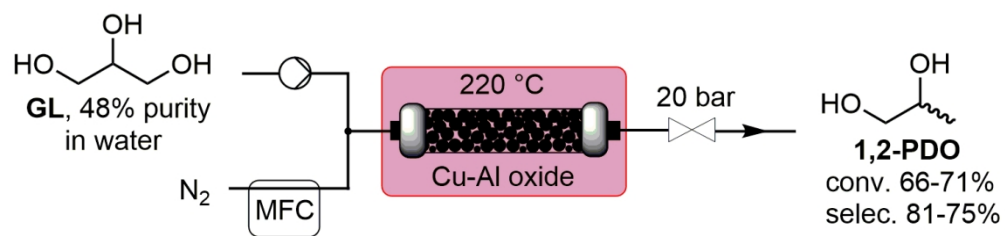


Figure 41

127x30mm (300 x 300 DPI)

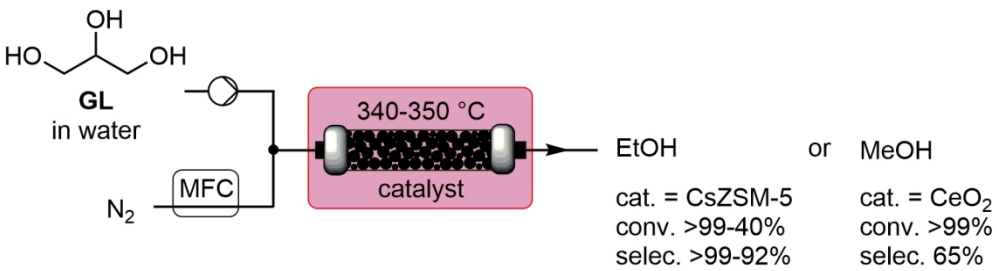


Figure 42

138x38mm (300 x 300 DPI)

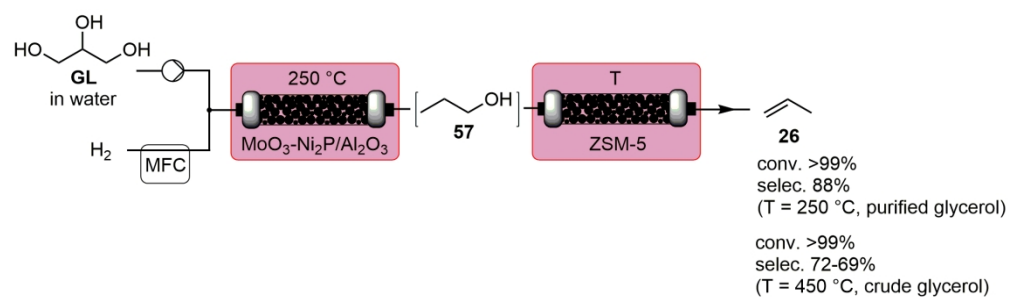


Figure 43

185x54mm (300 x 300 DPI)

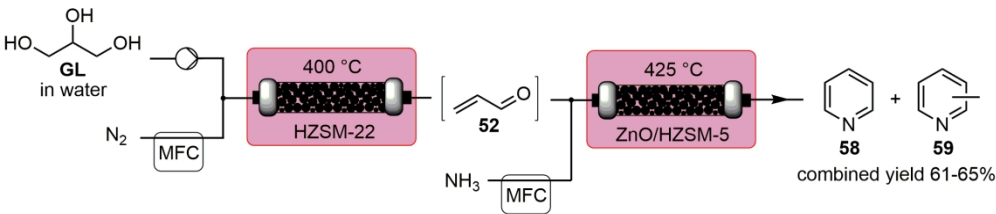


Figure 44

184x40mm (300 x 300 DPI)

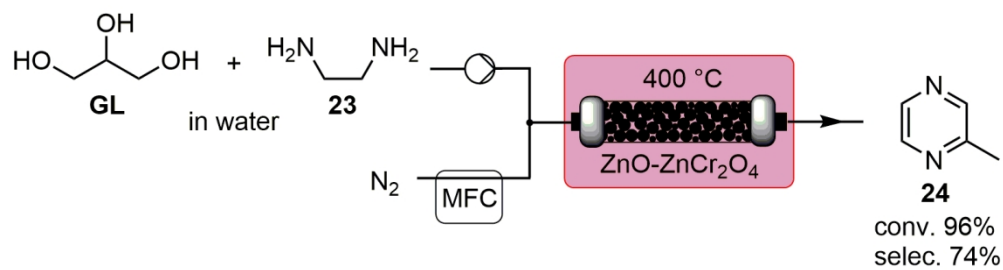


Figure 45

135x38mm (300 x 300 DPI)

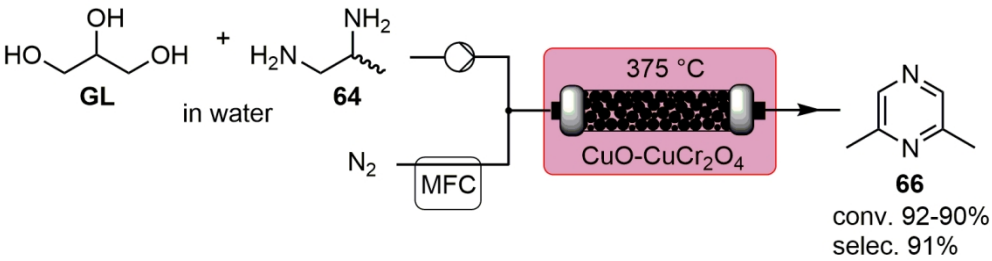


Figure 46

136x36mm (300 x 300 DPI)

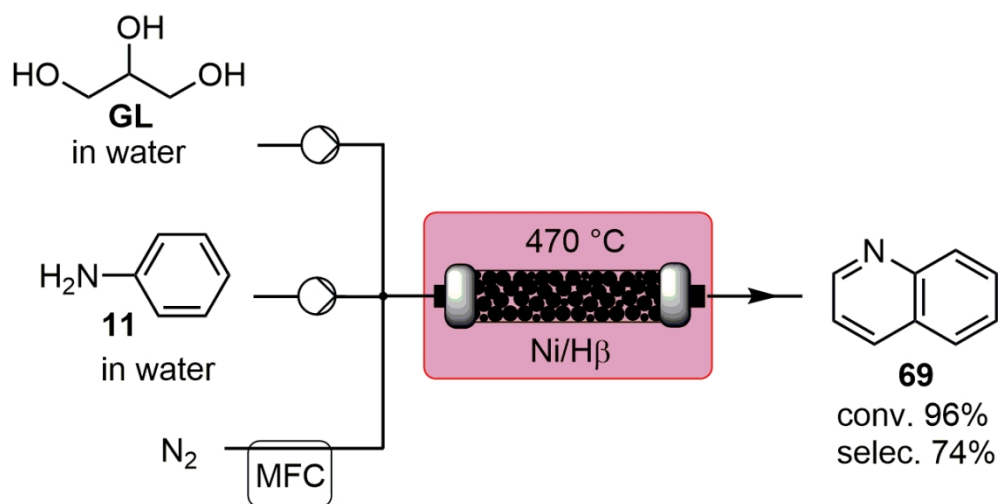
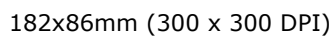


Figure 47

108x55mm (300 x 300 DPI)



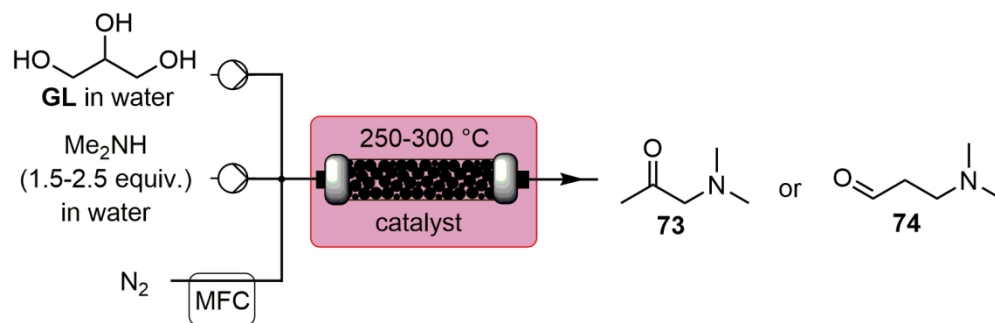


Figure 49

137x44mm (300 x 300 DPI)

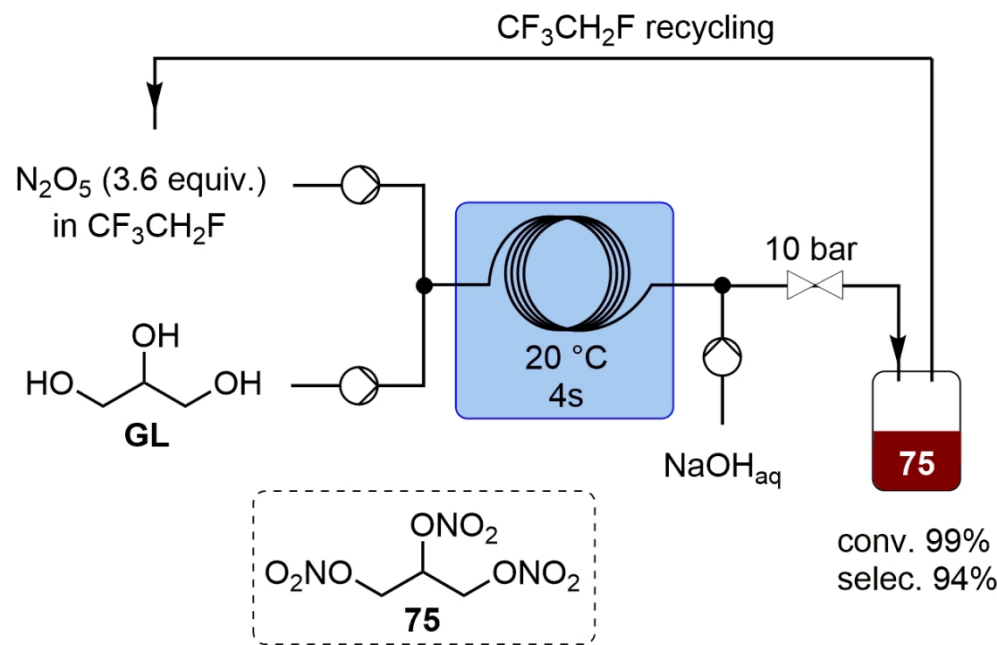


Figure 50

106x69mm (300 x 300 DPI)

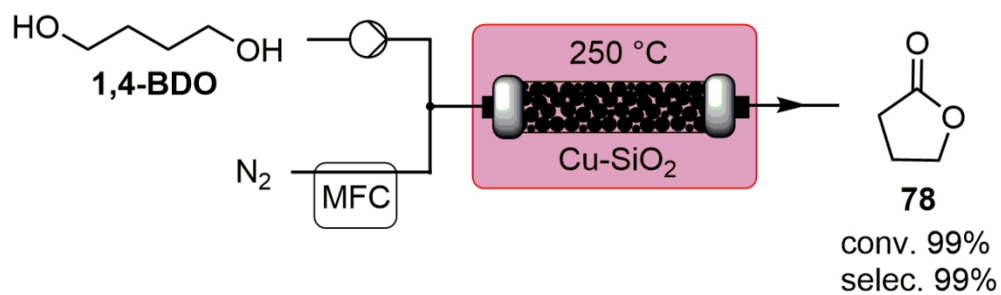


Figure 51

109x33mm (300 x 300 DPI)

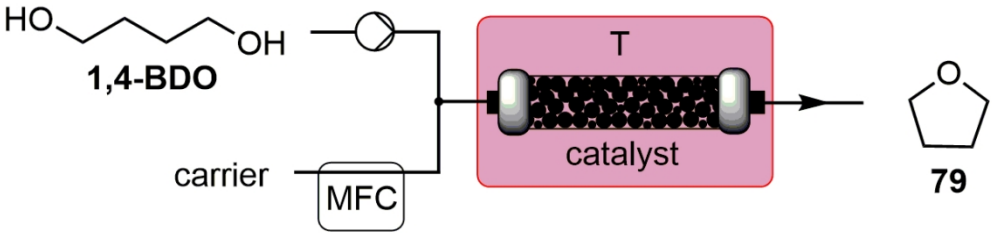


Figure 52

105x25mm (300 x 300 DPI)

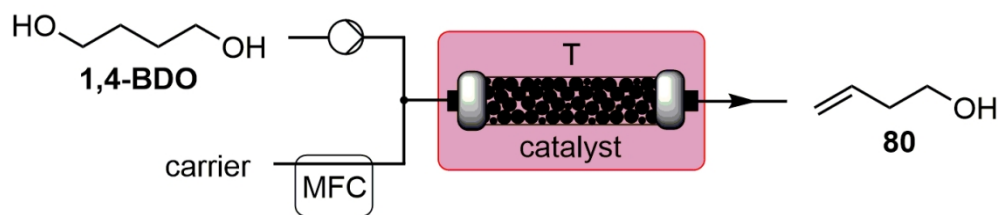


Figure 53

116x25mm (300 x 300 DPI)

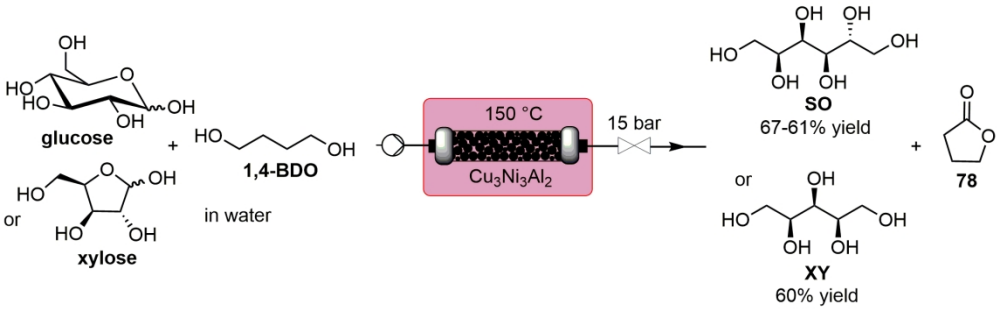


Figure 54

184x57mm (300 x 300 DPI)

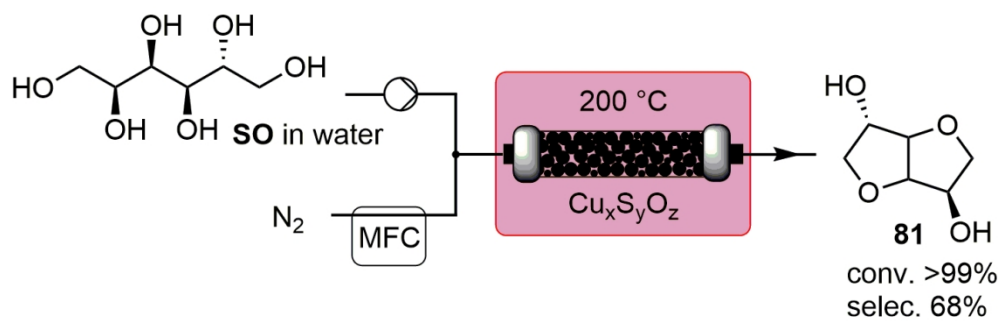


Figure 55

122x39mm (300 x 300 DPI)

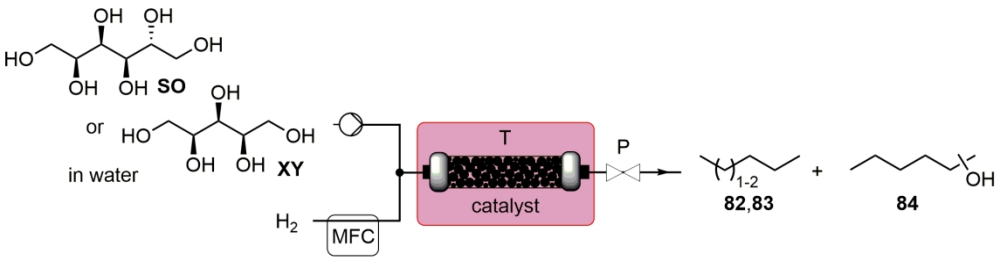


Figure 56

176x45mm (300 x 300 DPI)

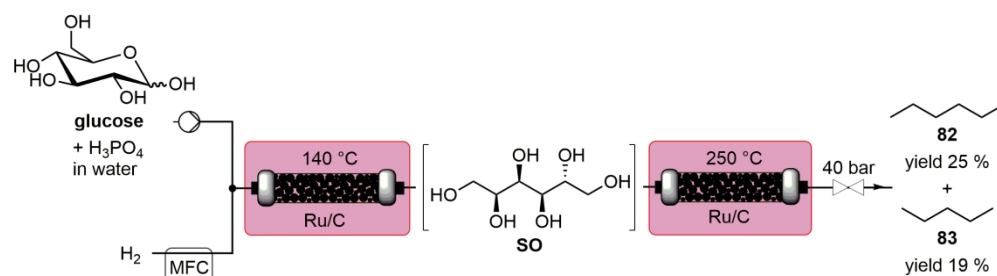


Figure 57

191x53mm (300 x 300 DPI)

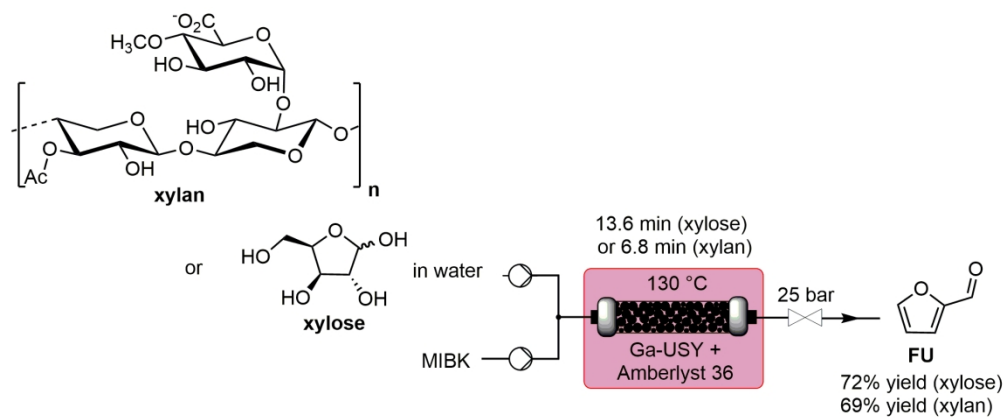


Figure 58

176x73mm (300 x 300 DPI)

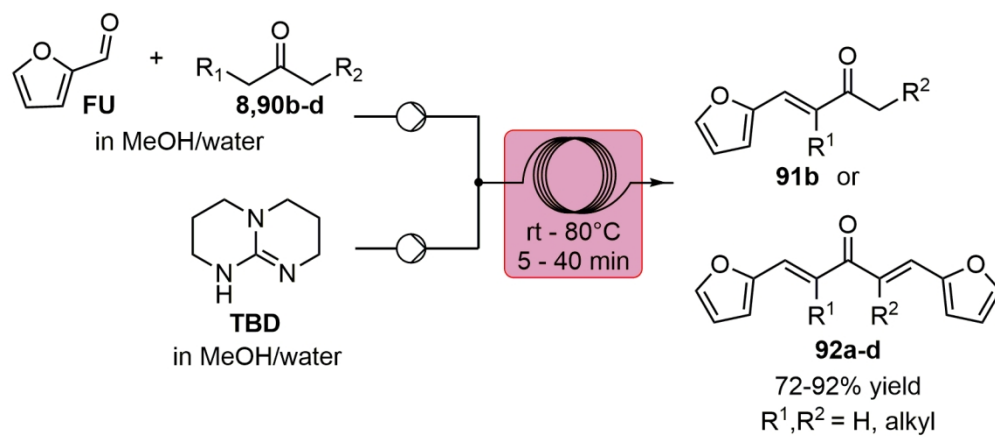


Figure 59

139x60mm (300 x 300 DPI)

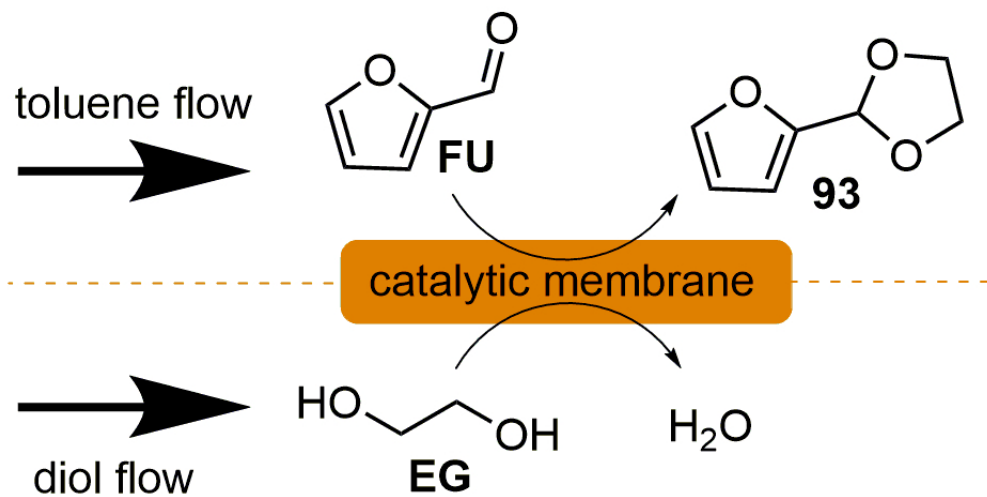


Figure 60

79x40mm (300 x 300 DPI)

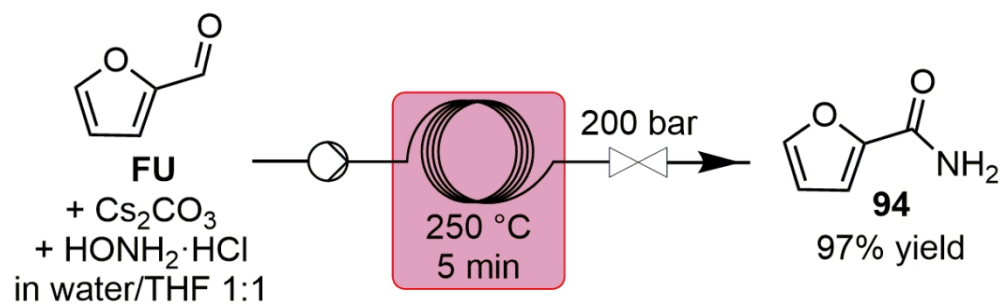


Figure 61

102x32mm (300 x 300 DPI)

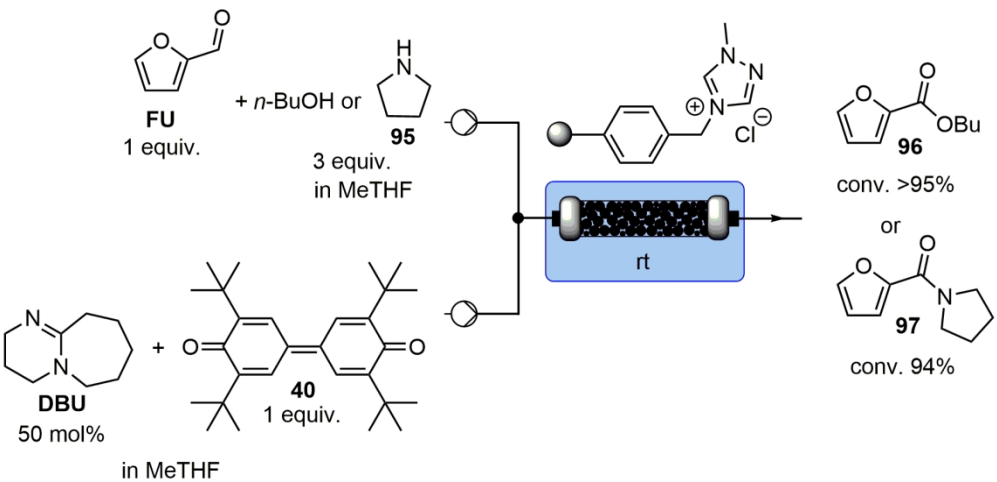


Figure 62

156x76mm (300 x 300 DPI)

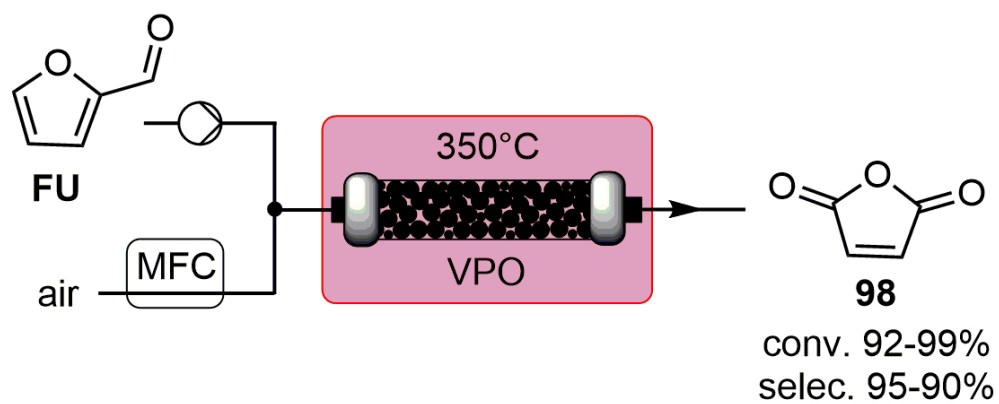


Figure 63

94x39mm (300 x 300 DPI)

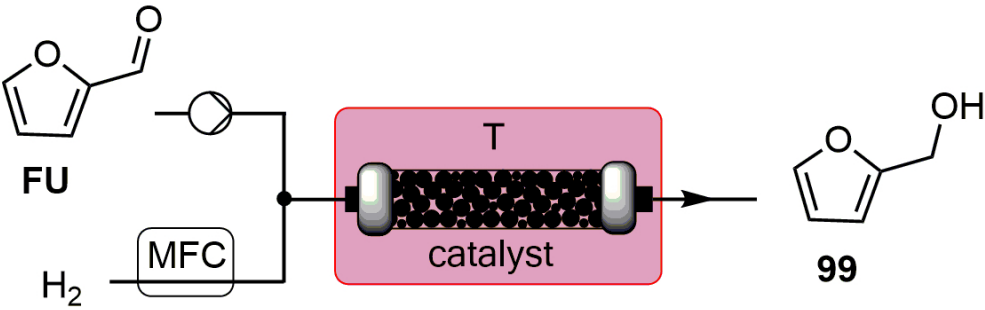
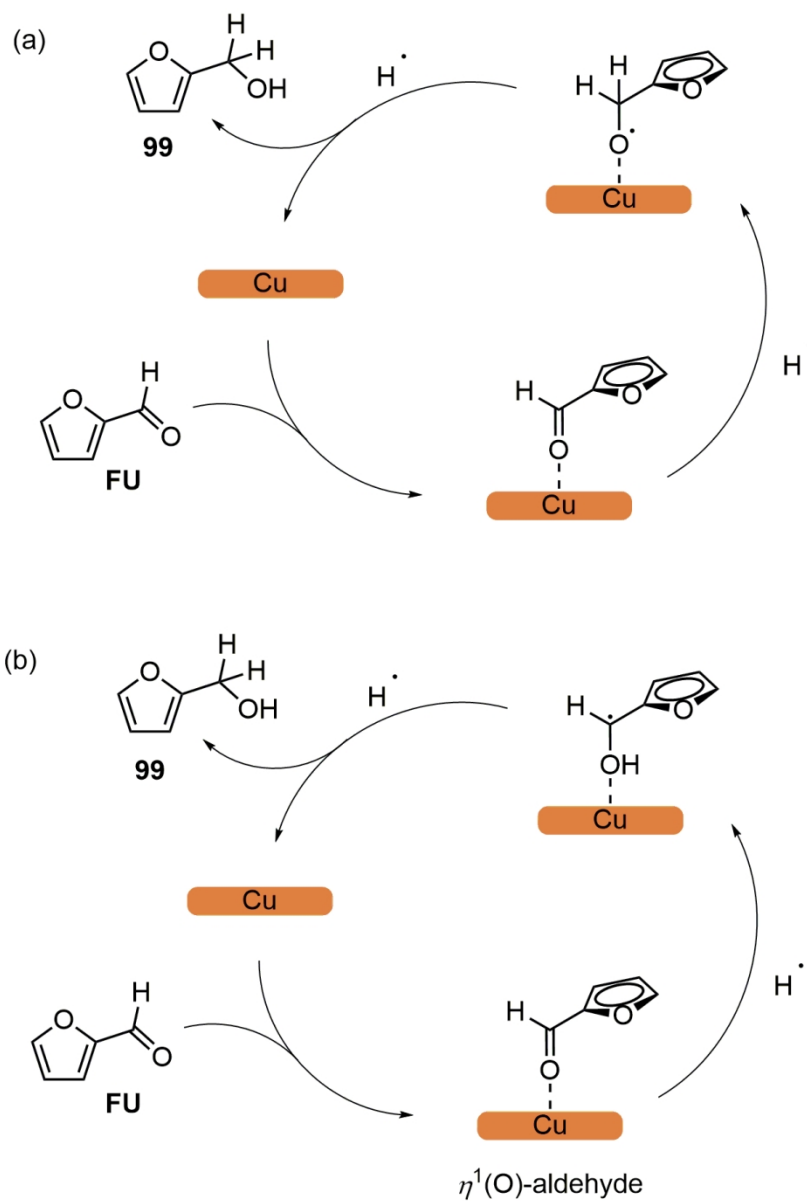


Figure 64

95x30mm (300 x 300 DPI)



105x154mm (300 x 300 DPI)

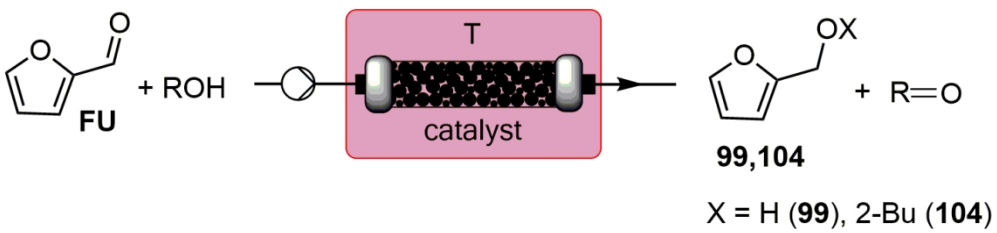


Figure 66

122x28mm (300 x 300 DPI)

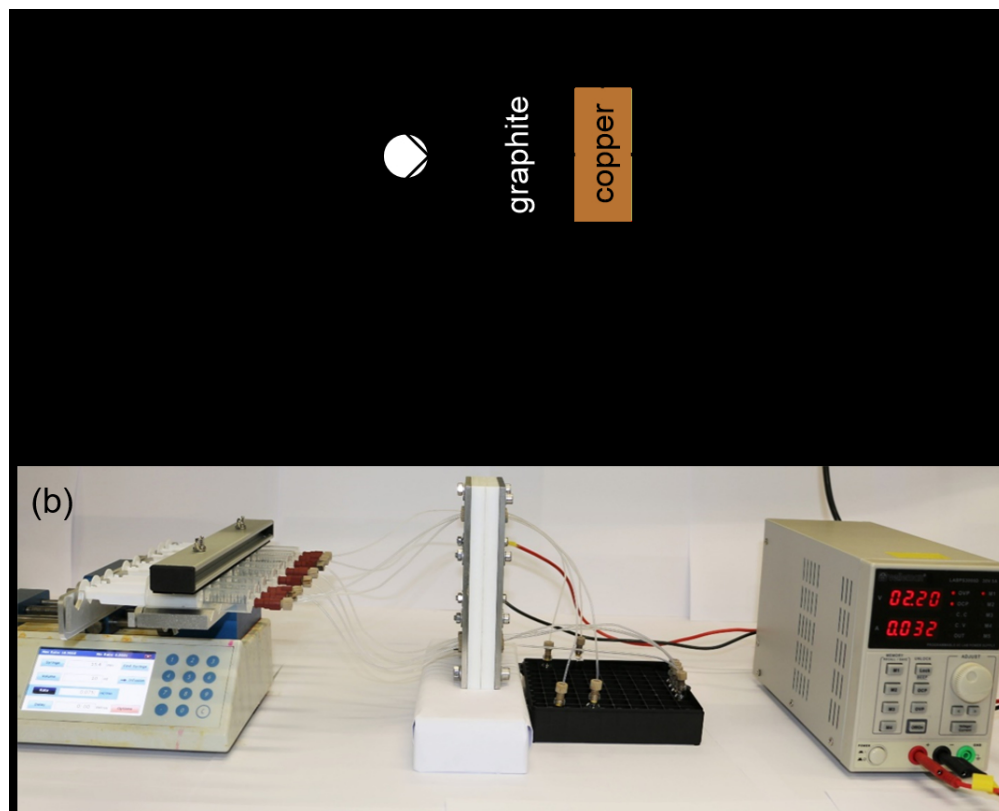


Figure 67

181x146mm (150 x 150 DPI)

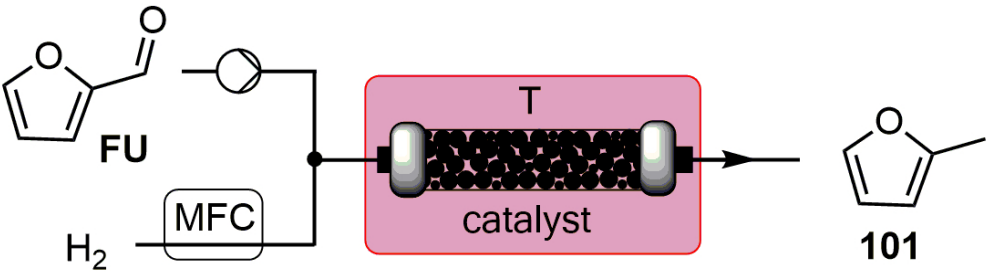


Figure 68

92x26mm (300 x 300 DPI)

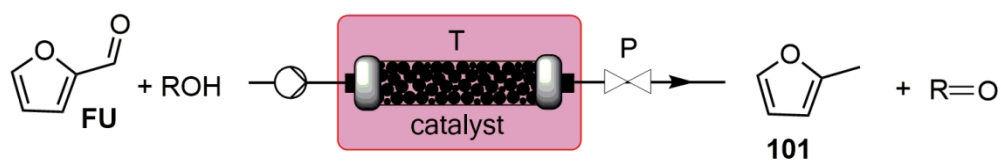


Figure 69

127x21mm (300 x 300 DPI)

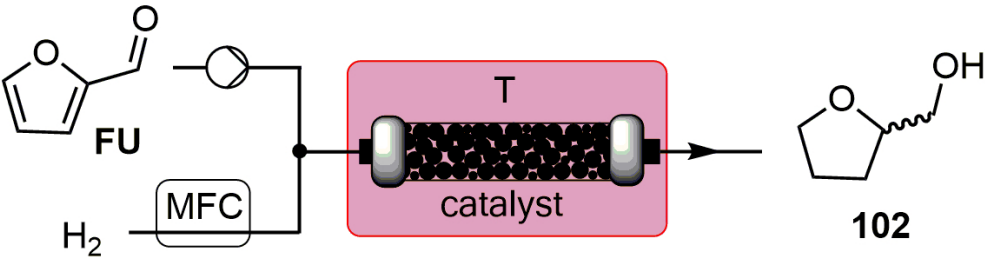


Figure 70

97x26mm (300 x 300 DPI)

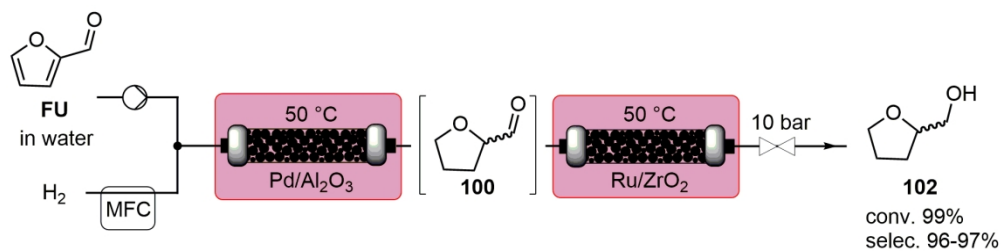


Figure 71

166x42mm (300 x 300 DPI)

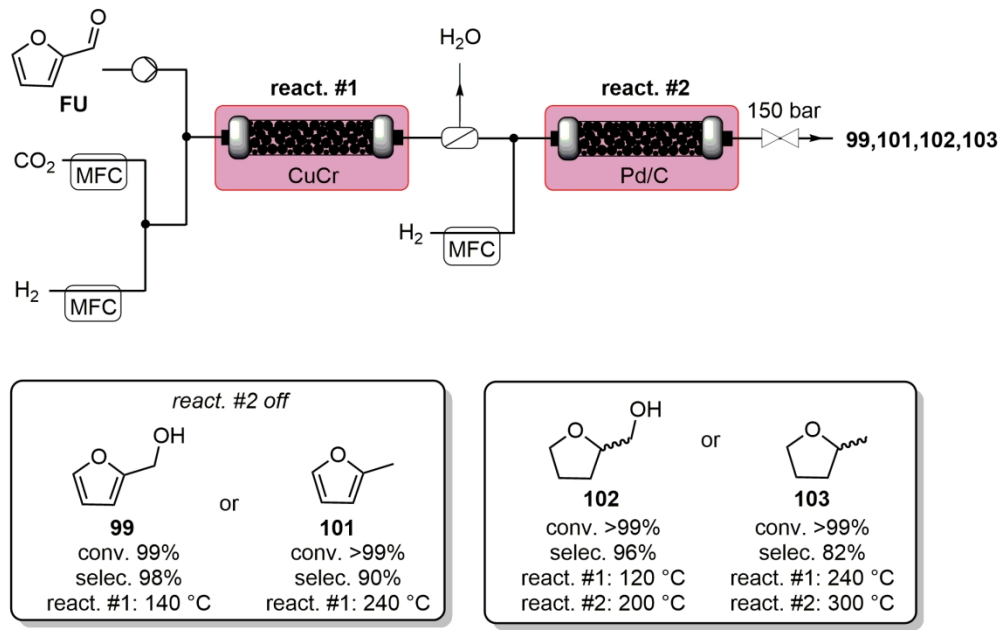


Figure 72

160x102mm (300 x 300 DPI)

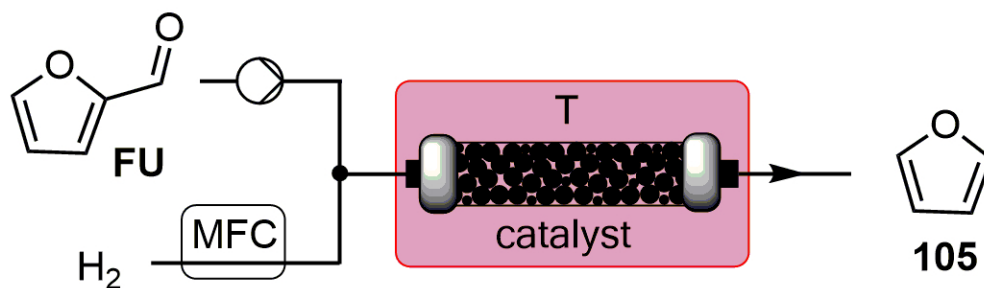


Figure 73

88x26mm (300 x 300 DPI)

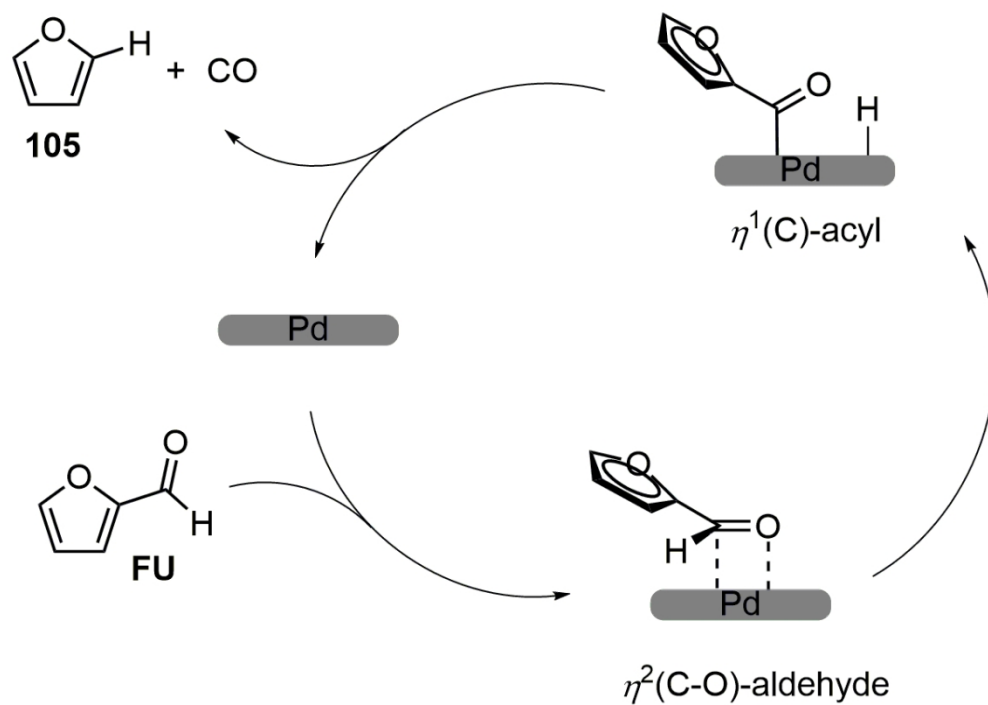


Figure 74

103x72mm (300 x 300 DPI)

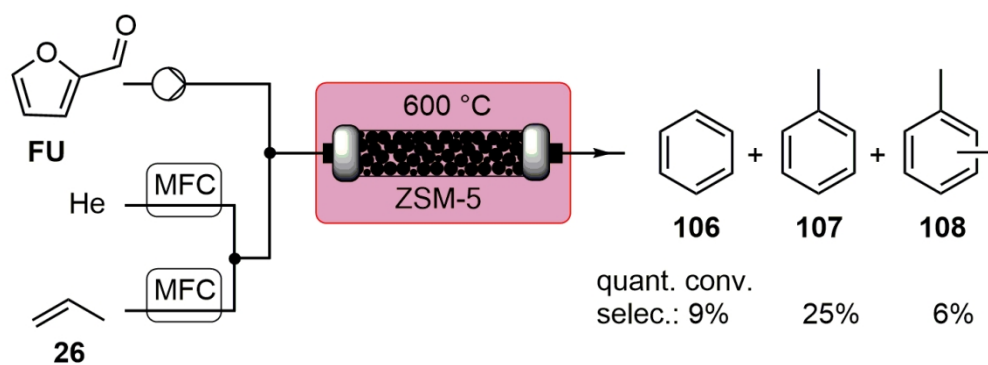


Figure 75

122x45mm (300 x 300 DPI)

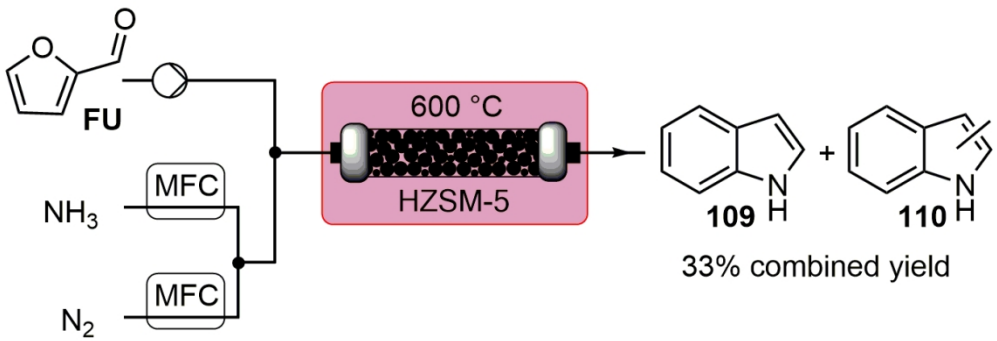


Figure 76

117x40mm (300 x 300 DPI)

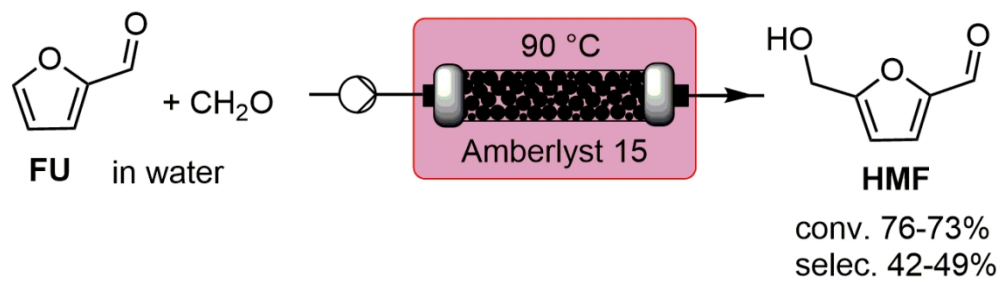


Figure 77

110x31mm (300 x 300 DPI)

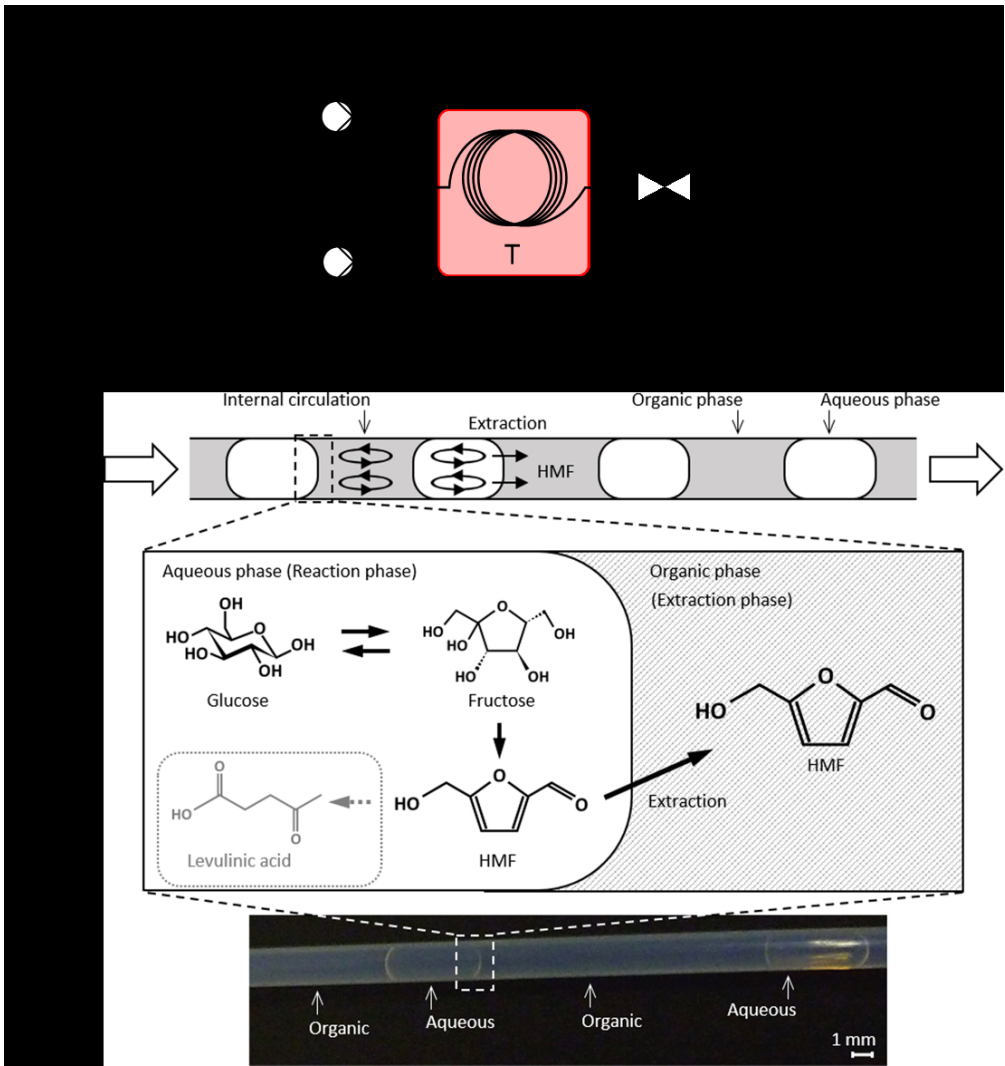


Figure 78

187x198mm (150 x 150 DPI)

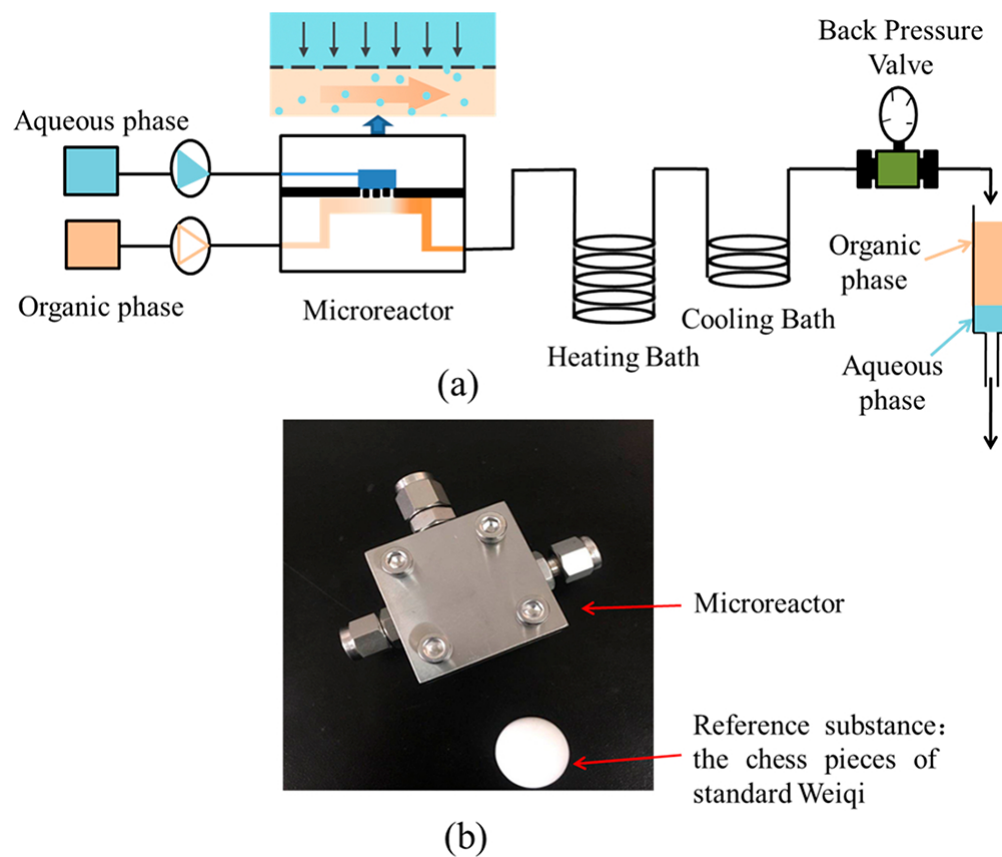


Figure 79

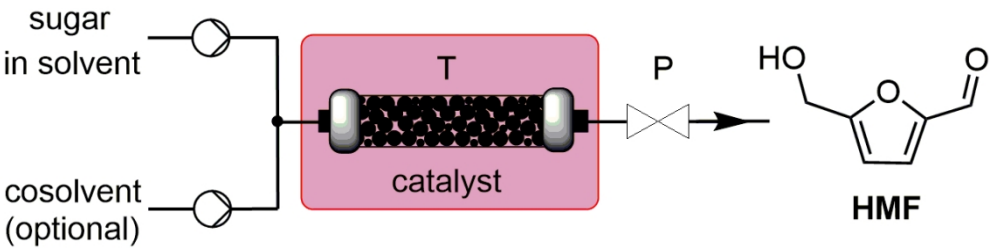


Figure 80

108x28mm (300 x 300 DPI)

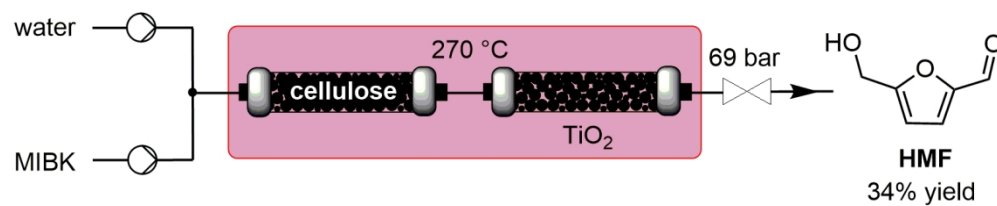


Figure 81

140x29mm (300 x 300 DPI)

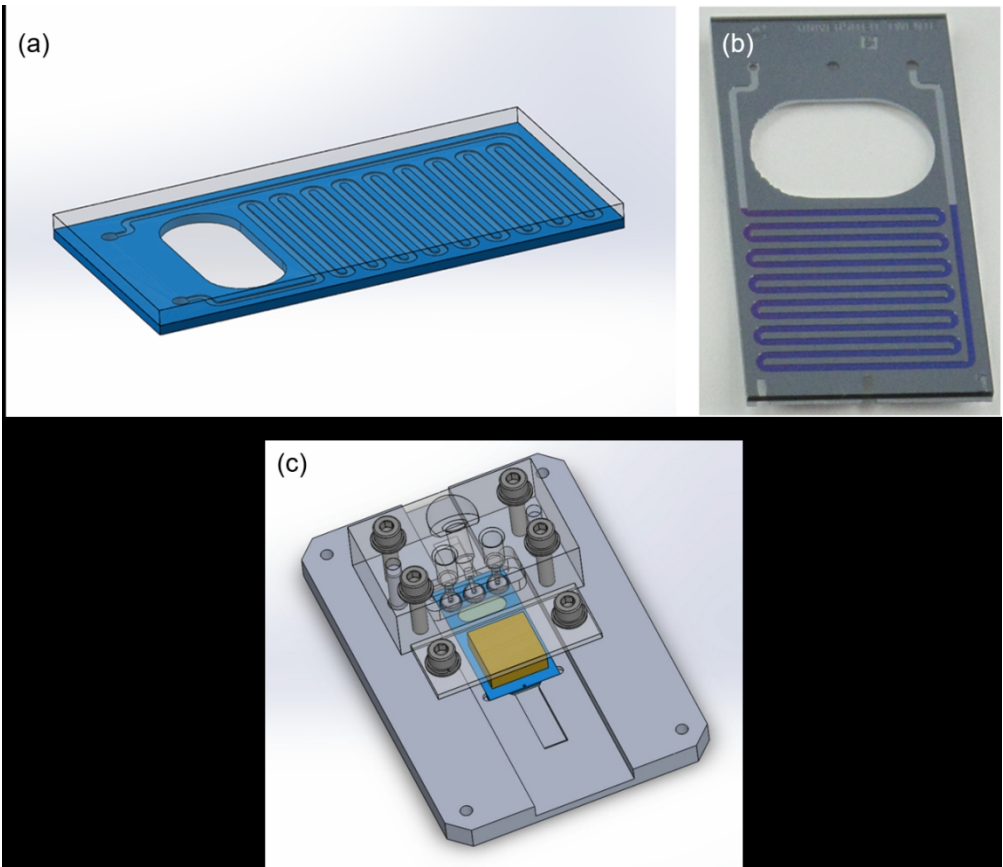


Figure 82

215x185mm (150 x 150 DPI)

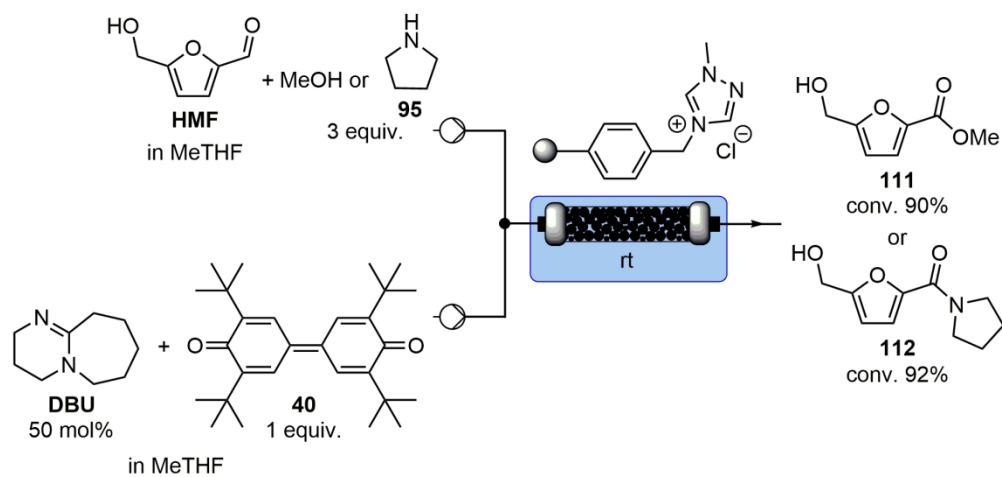


Figure 83

160x76mm (300 x 300 DPI)

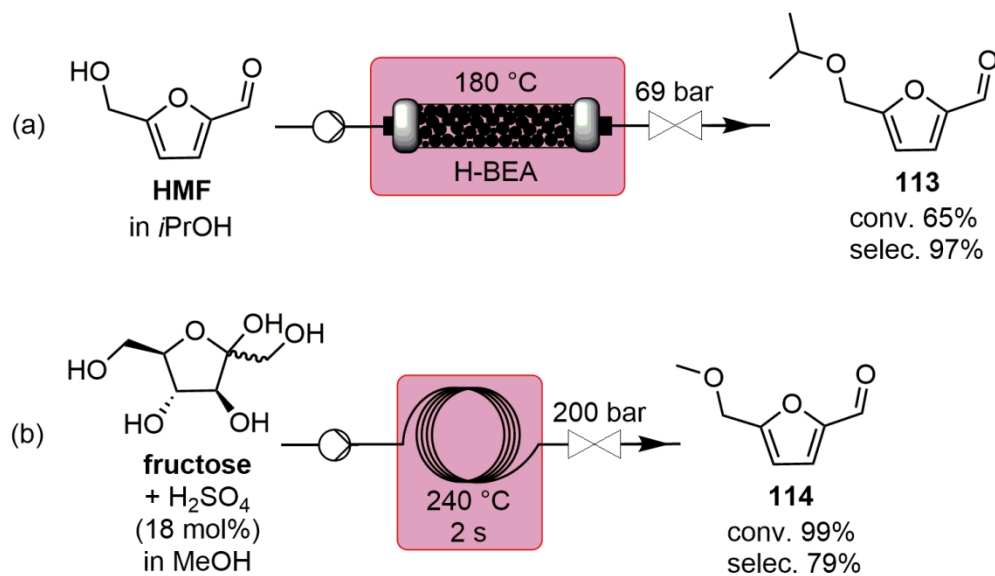


Figure 84

128x74mm (300 x 300 DPI)

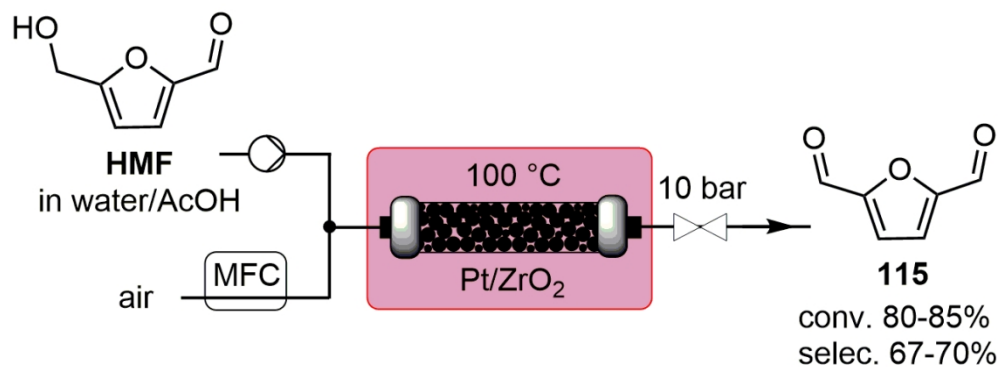


Figure 85

112x42mm (300 x 300 DPI)

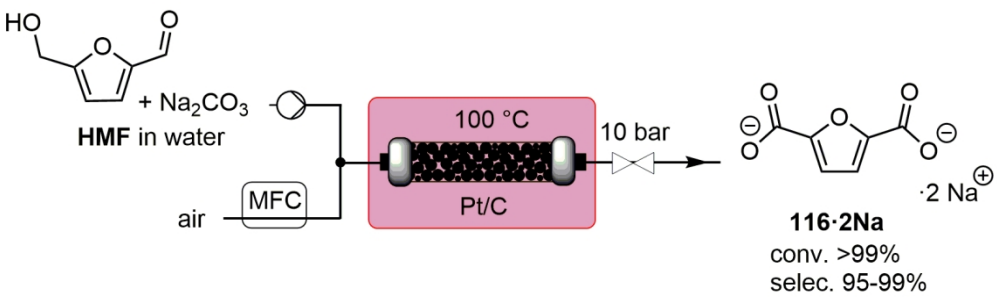


Figure 86

142x42mm (300 x 300 DPI)

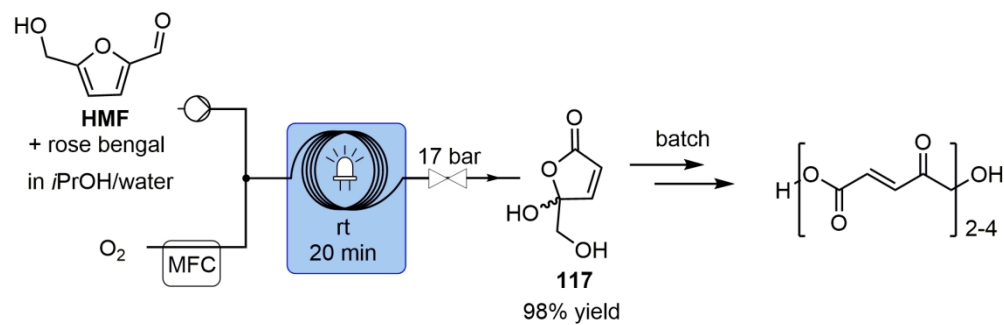


Figure 87

157x51mm (300 x 300 DPI)

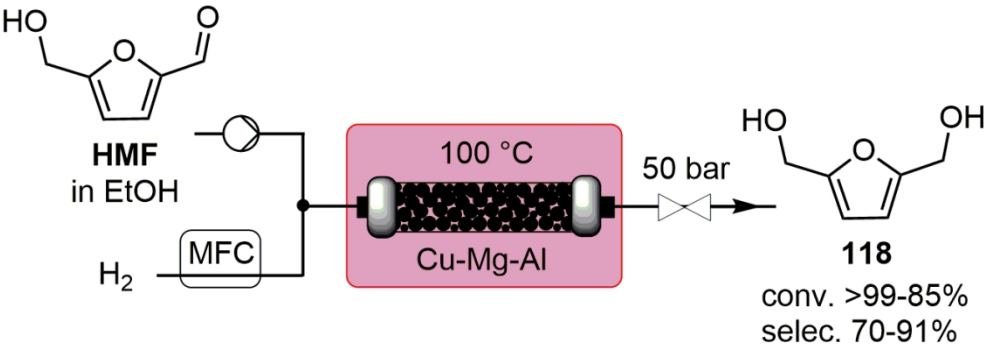


Figure 88

113x40mm (300 x 300 DPI)

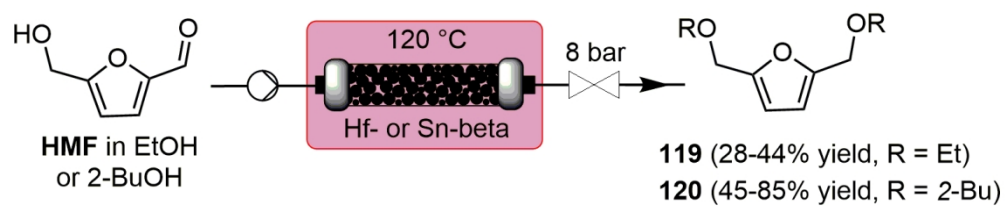


Figure 89

133x27mm (300 x 300 DPI)

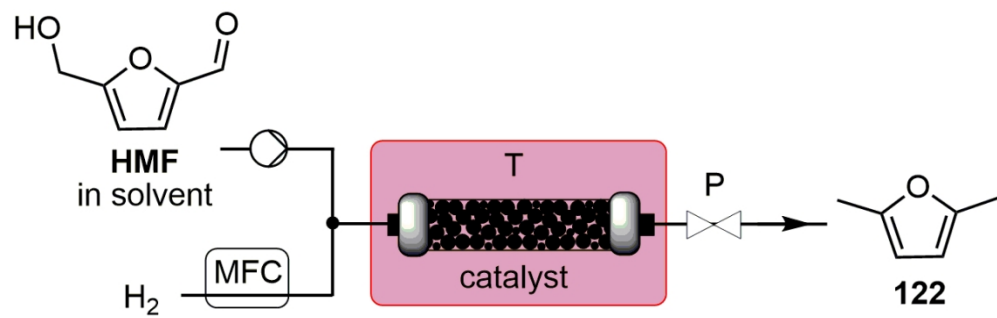


Figure 90

109x35mm (300 x 300 DPI)

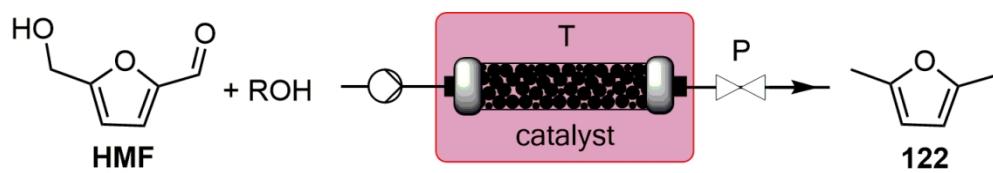


Figure 91

120x21mm (300 x 300 DPI)

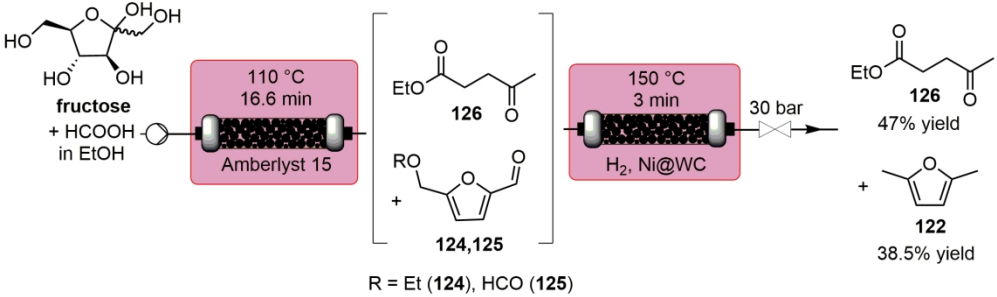


Figure 92

186x56mm (300 x 300 DPI)

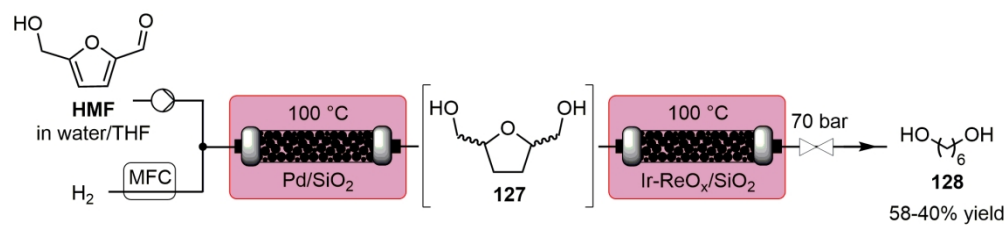


Figure 93

176x39mm (300 x 300 DPI)

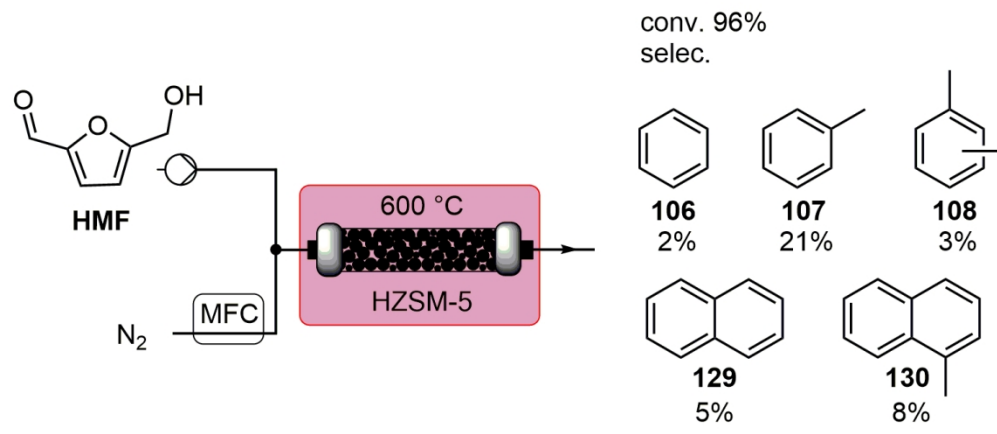


Figure 94

129x56mm (300 x 300 DPI)

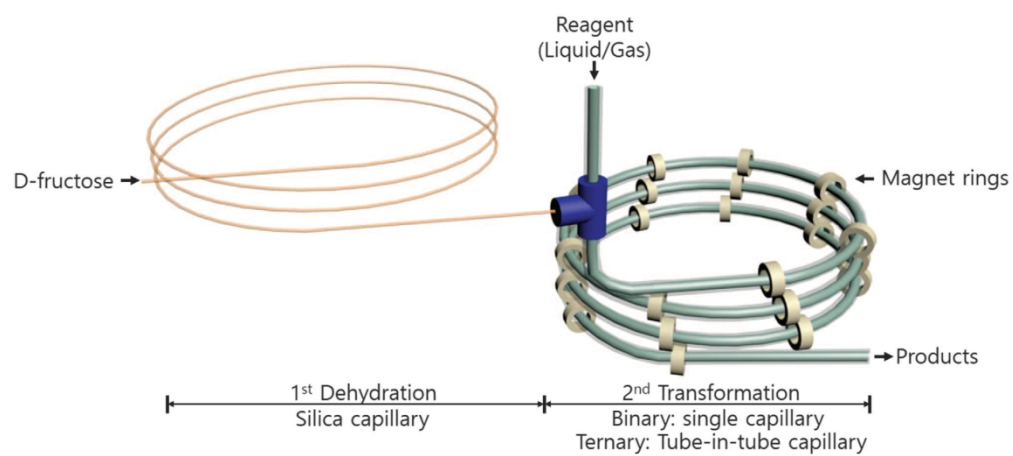


Figure 95

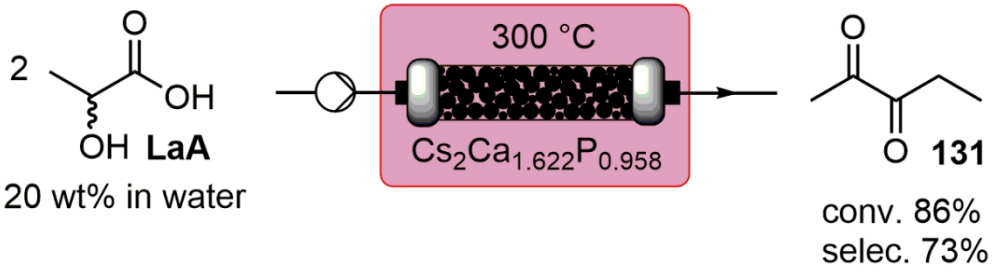


Figure 96

102x29mm (300 x 300 DPI)

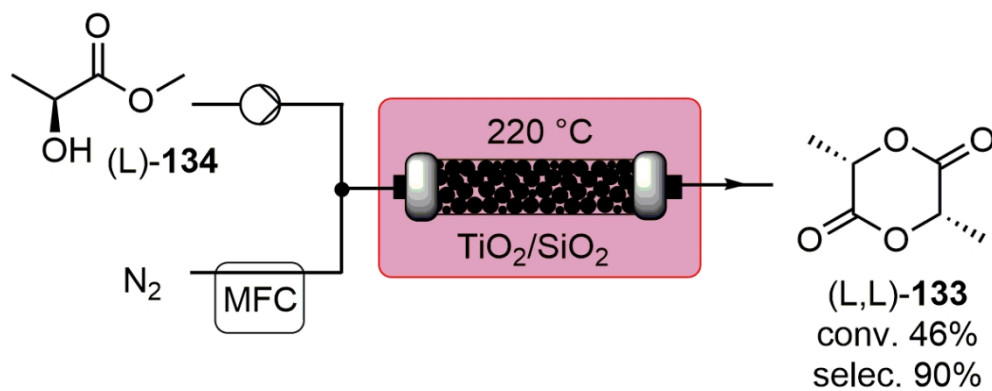


Figure 97

101x40mm (300 x 300 DPI)

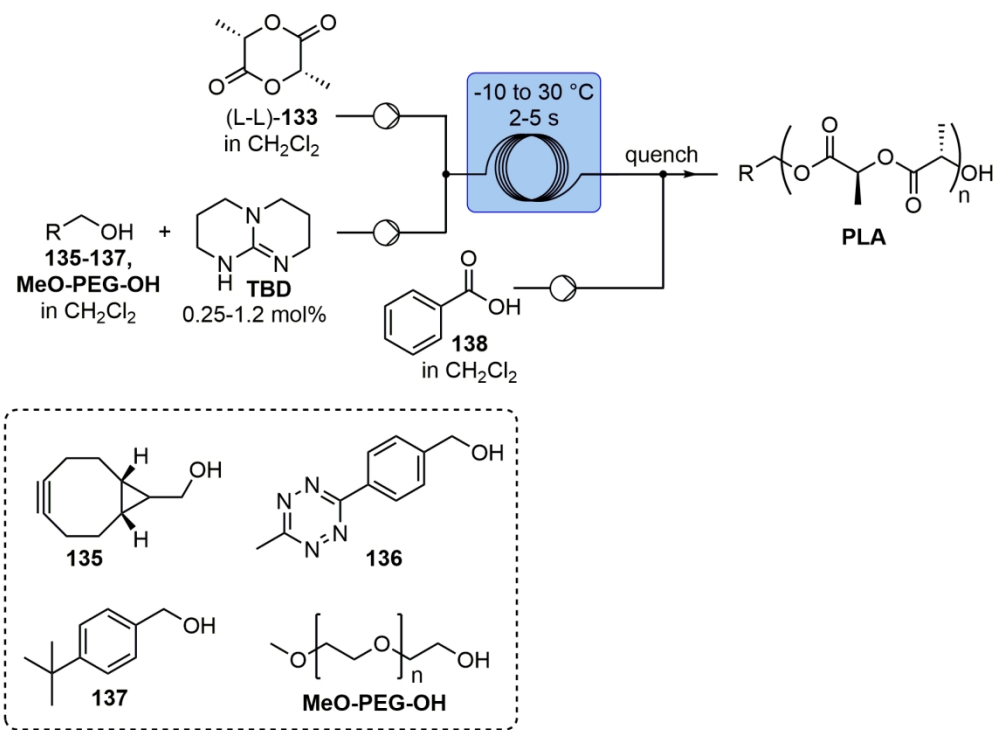


Figure 98

157x114mm (300 x 300 DPI)

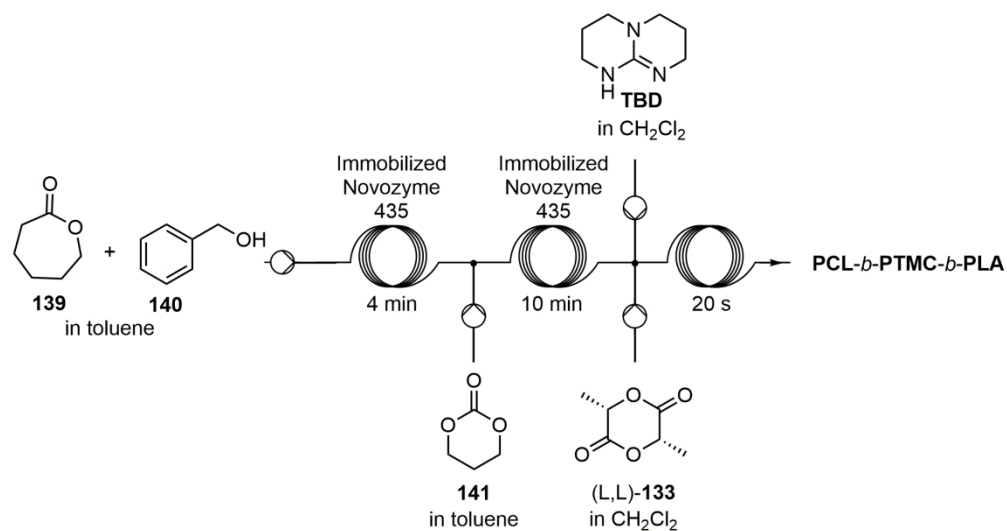


Figure 99

170x89mm (300 x 300 DPI)

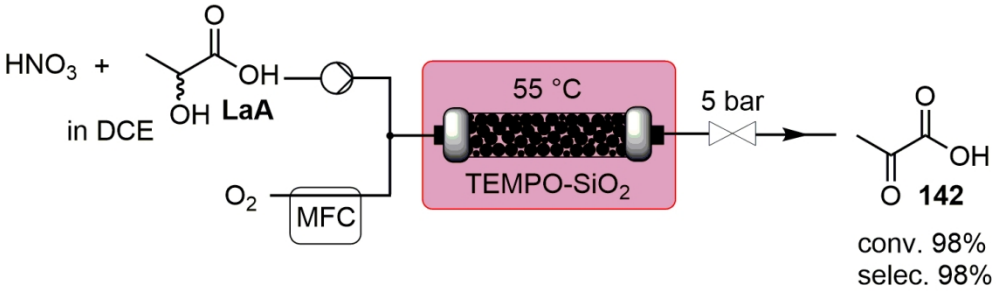


Figure 100

127x40mm (300 x 300 DPI)

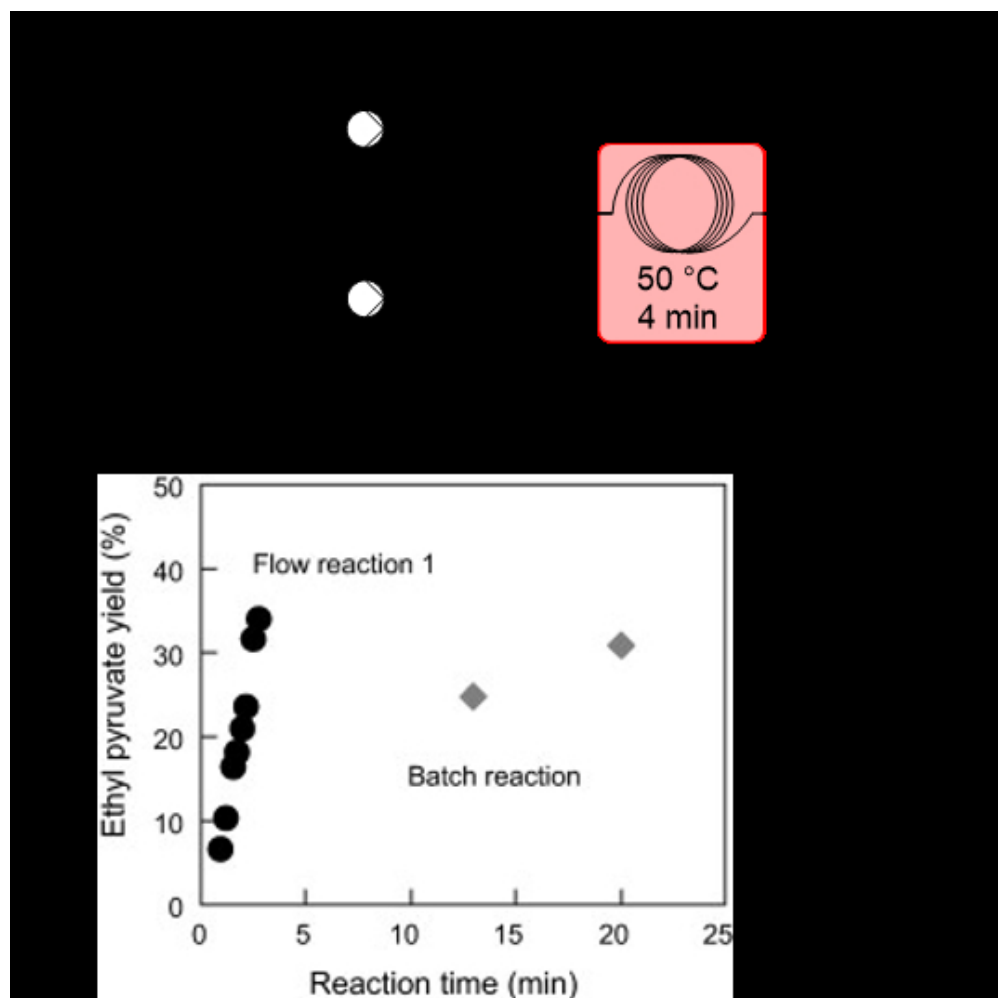


Figure 101

91x90mm (150 x 150 DPI)

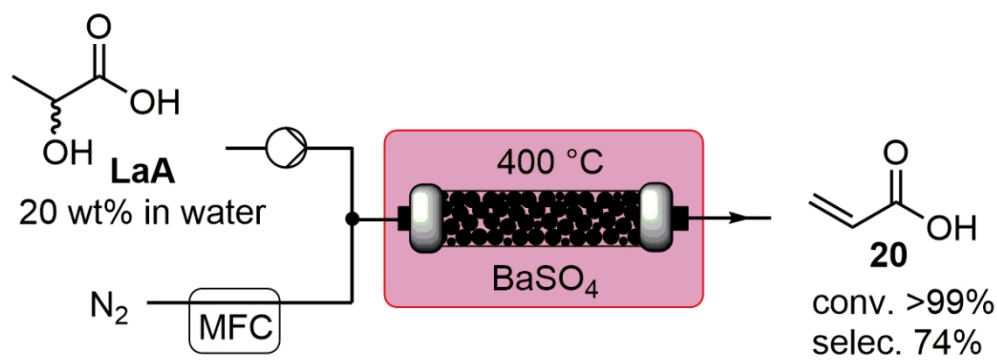


Figure 102

100x37mm (300 x 300 DPI)

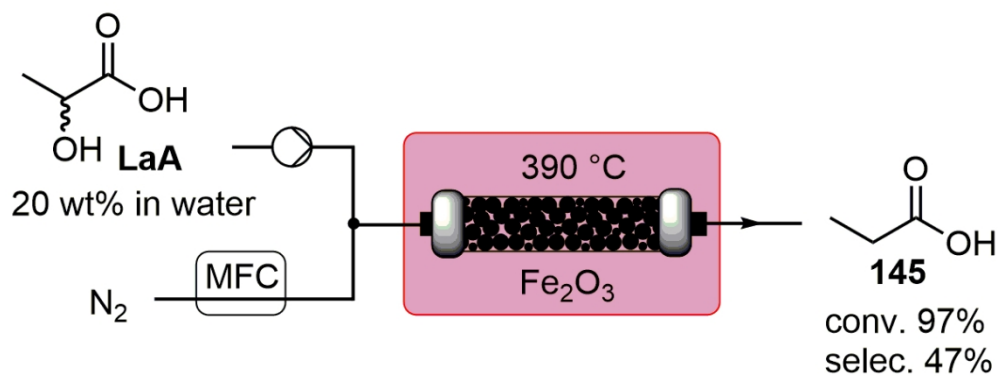


Figure 103

102x39mm (300 x 300 DPI)

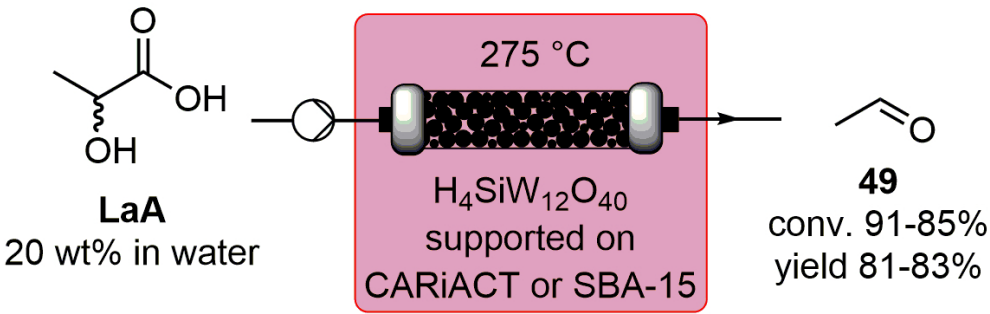


Figure 104

97x31mm (300 x 300 DPI)

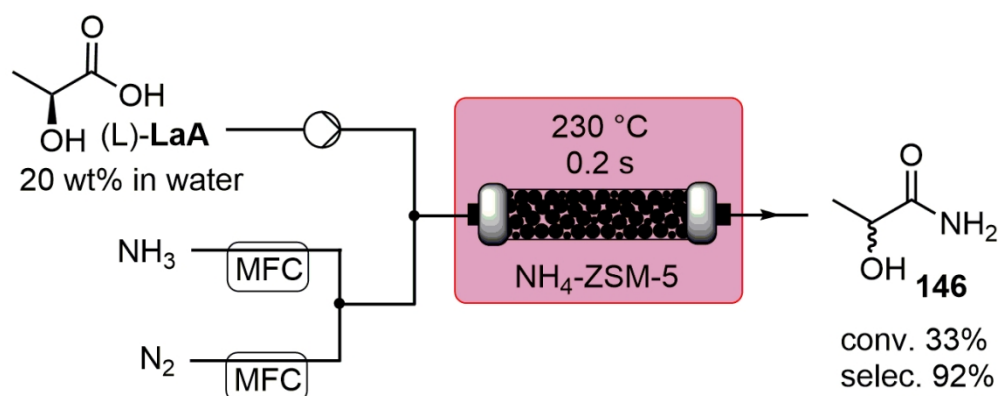


Figure 105

111x45mm (300 x 300 DPI)

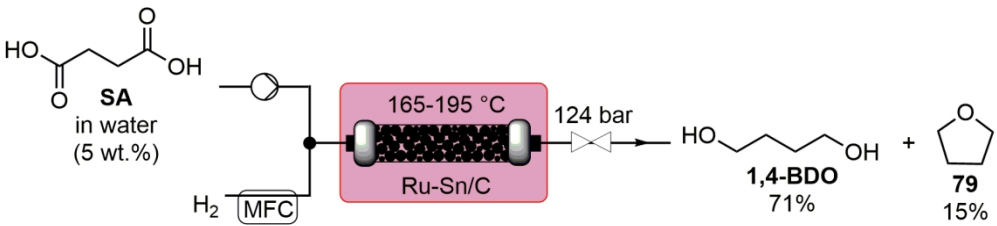


Figure 106

150x34mm (300 x 300 DPI)

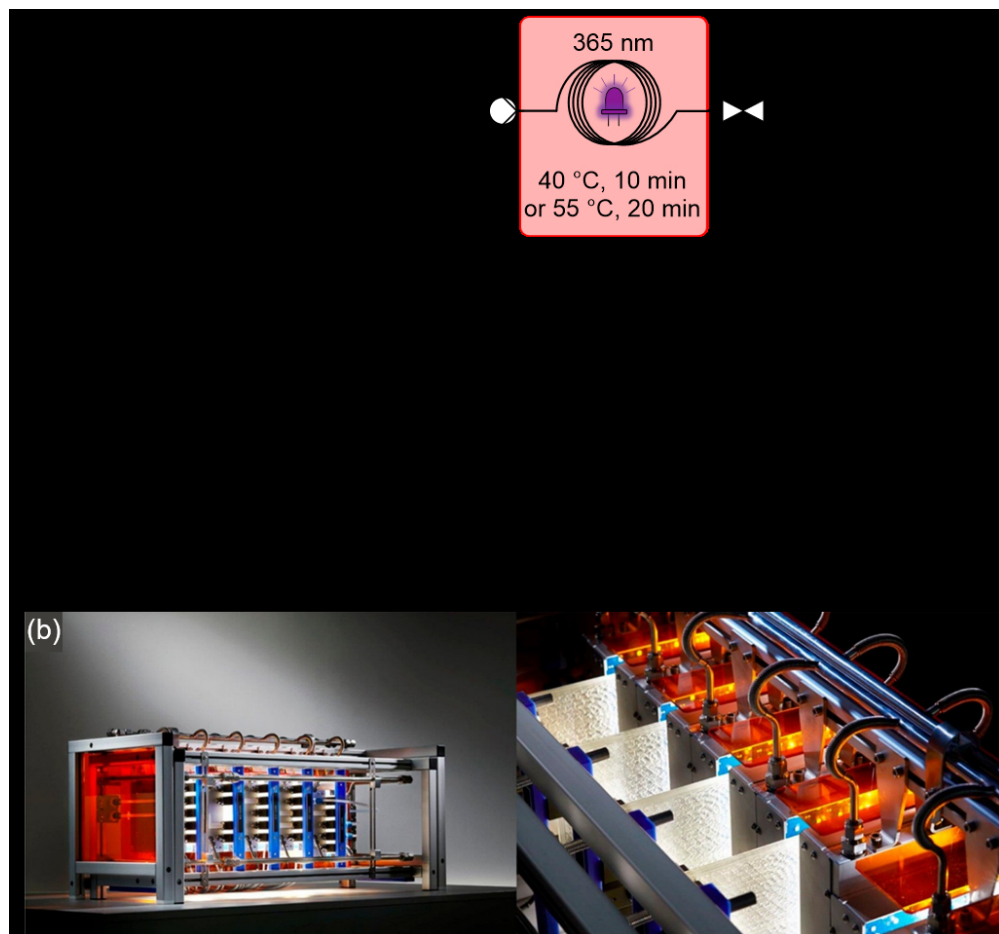


Figure 107

173x161mm (150 x 150 DPI)

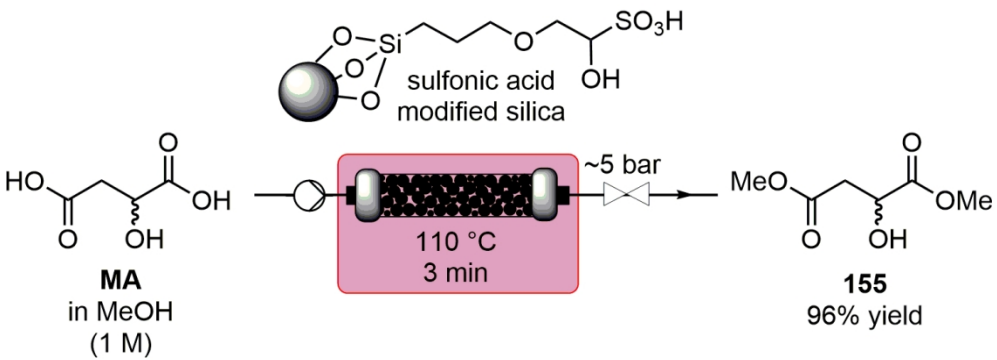


Figure 108

131x47mm (300 x 300 DPI)

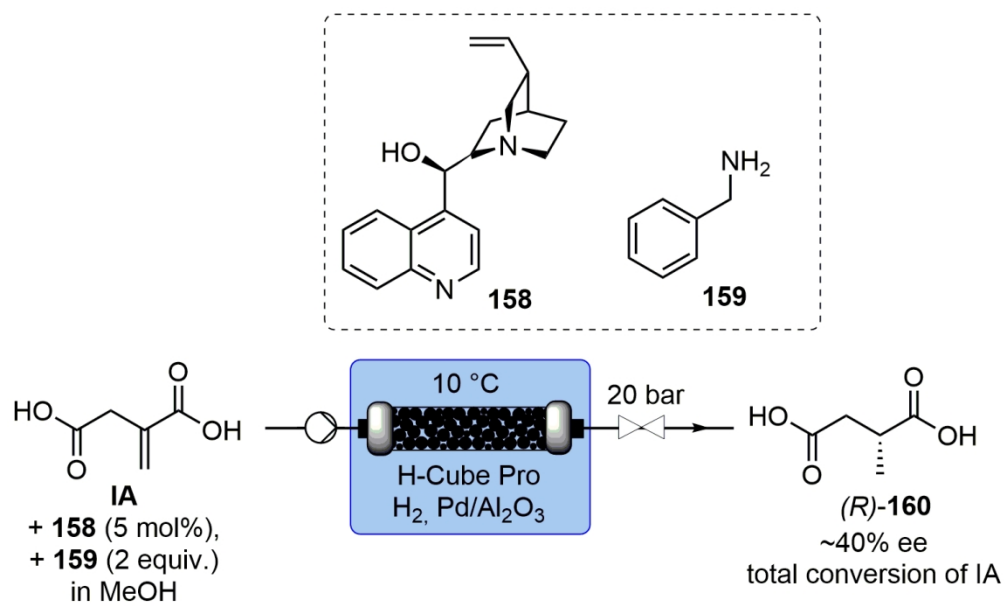


Figure 109

129x78mm (300 x 300 DPI)

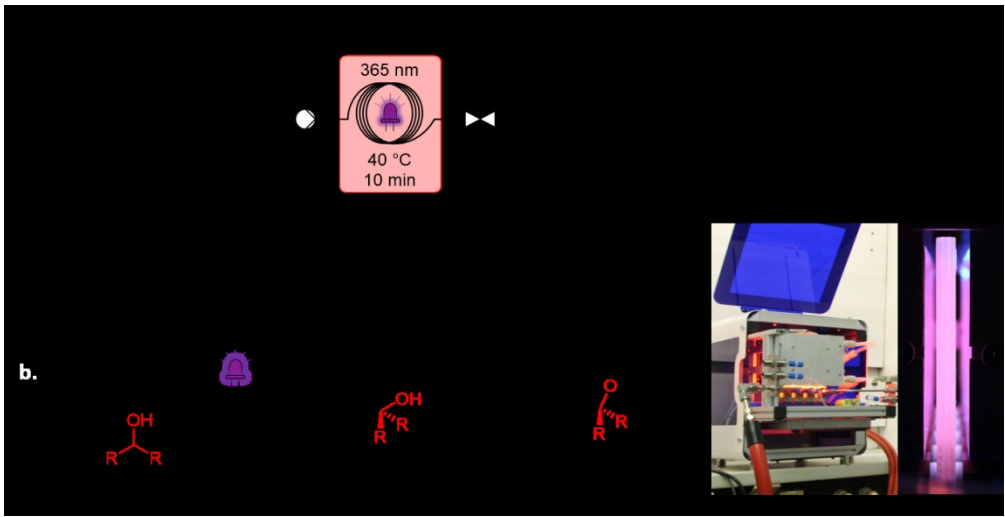


Figure 110

234x119mm (150 x 150 DPI)

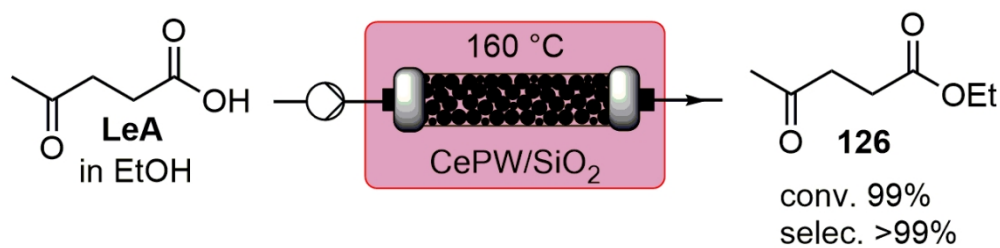


Figure 111

107x27mm (300 x 300 DPI)

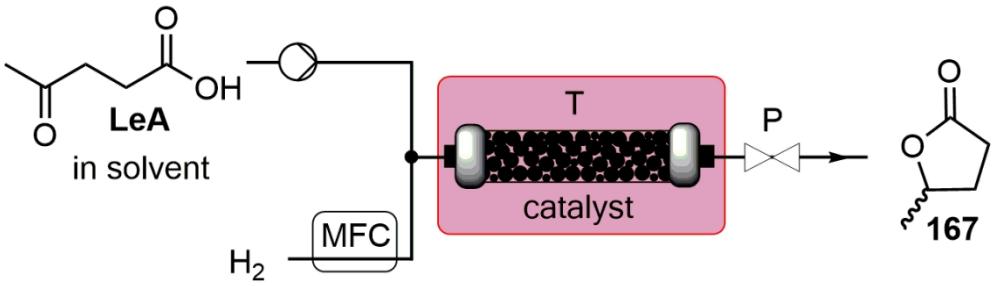


Figure 112

108x31mm (300 x 300 DPI)

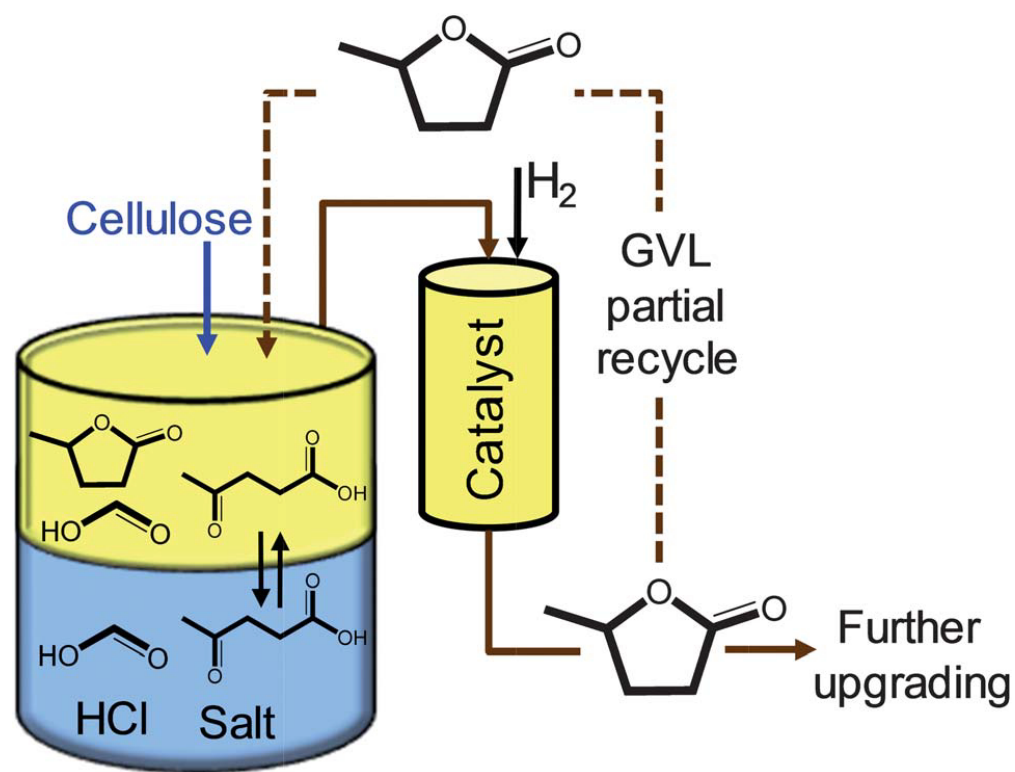


Figure 113

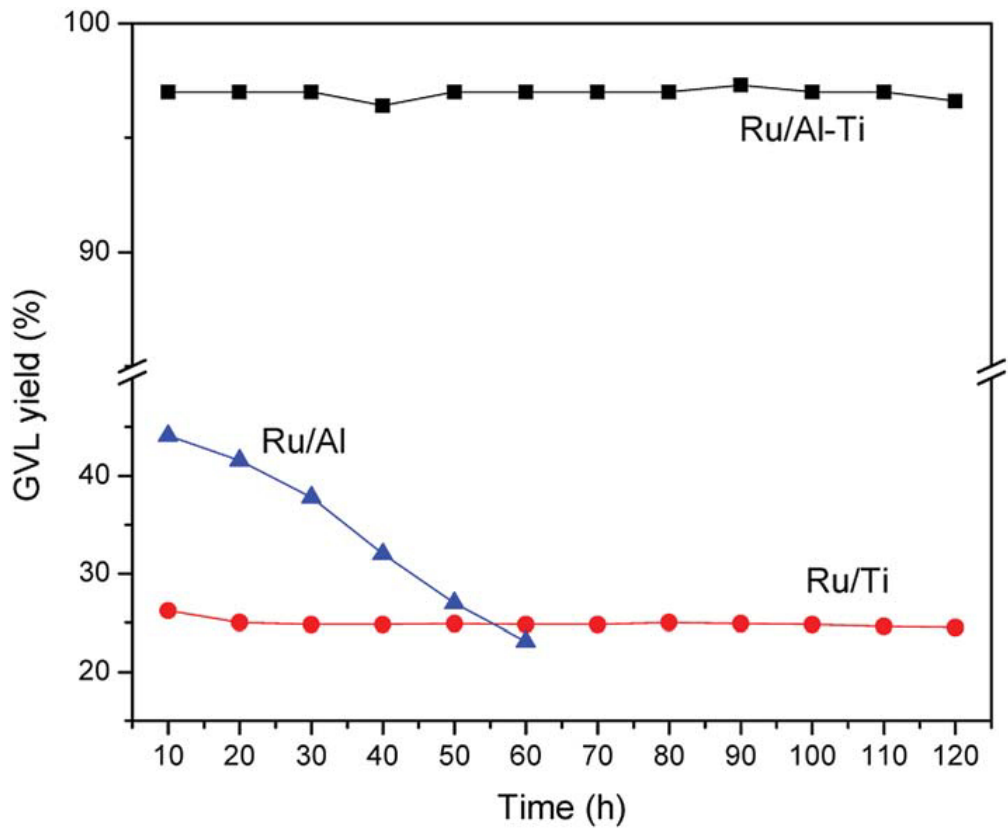


Figure 114

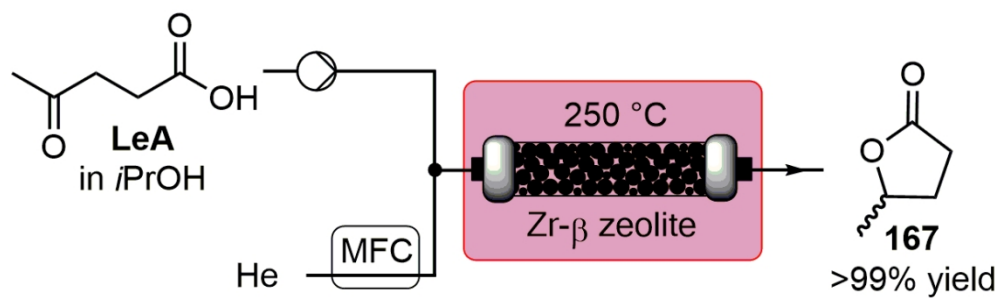


Figure 115

104x31mm (300 x 300 DPI)

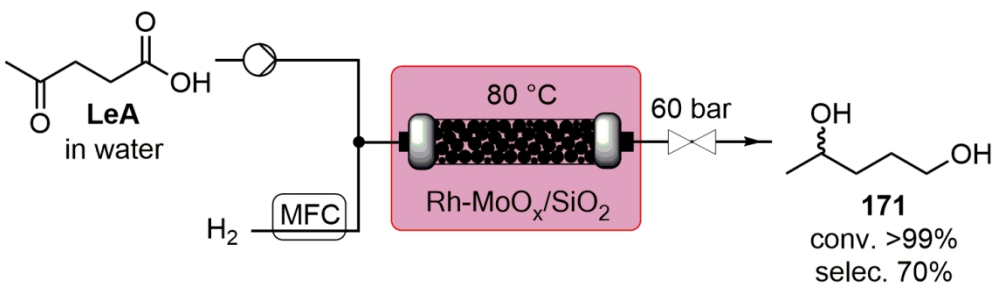


Figure 116

124x36mm (300 x 300 DPI)

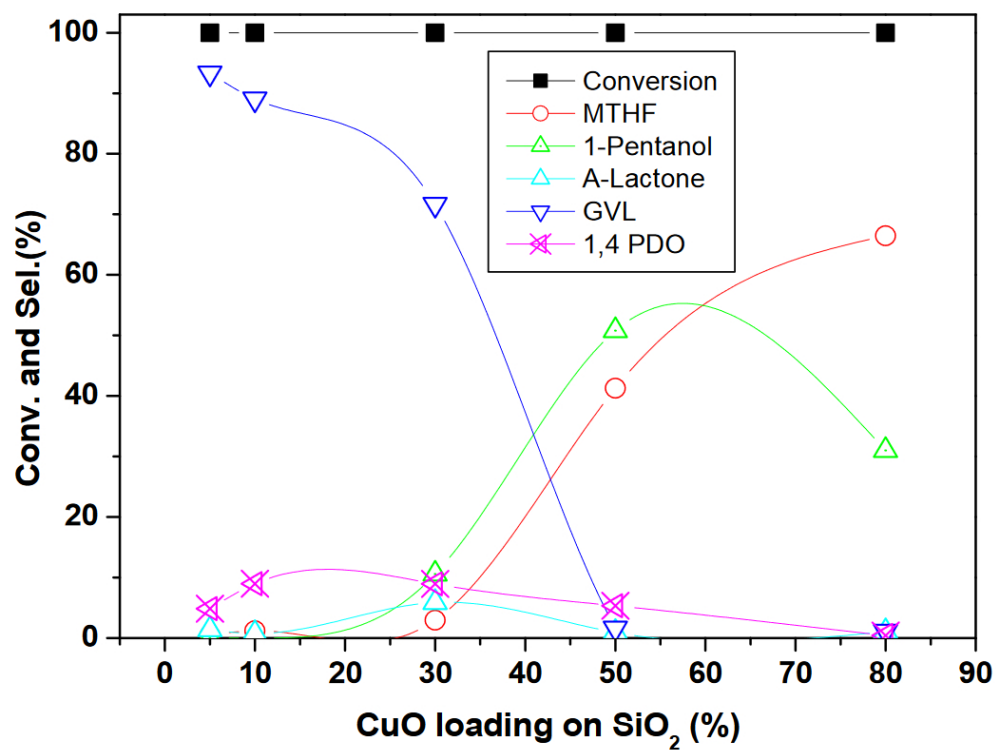


Figure 117

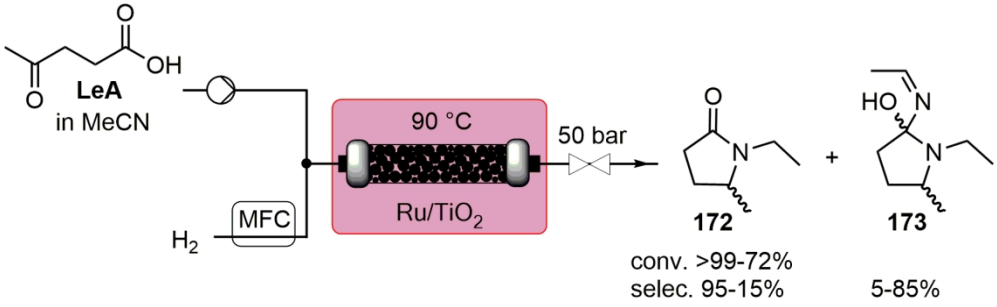


Figure 118

145x45mm (300 x 300 DPI)

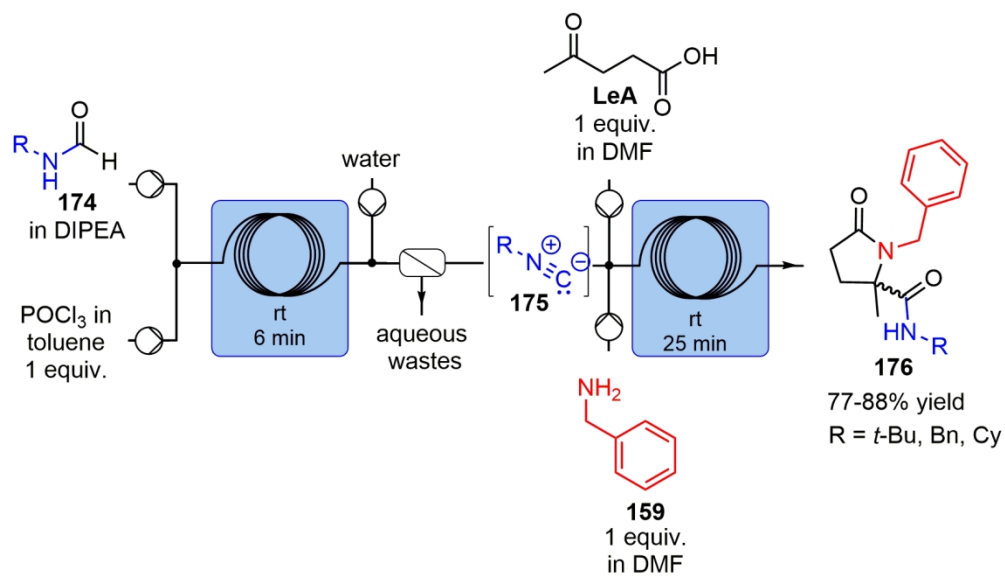


Figure 119

148x85mm (300 x 300 DPI)

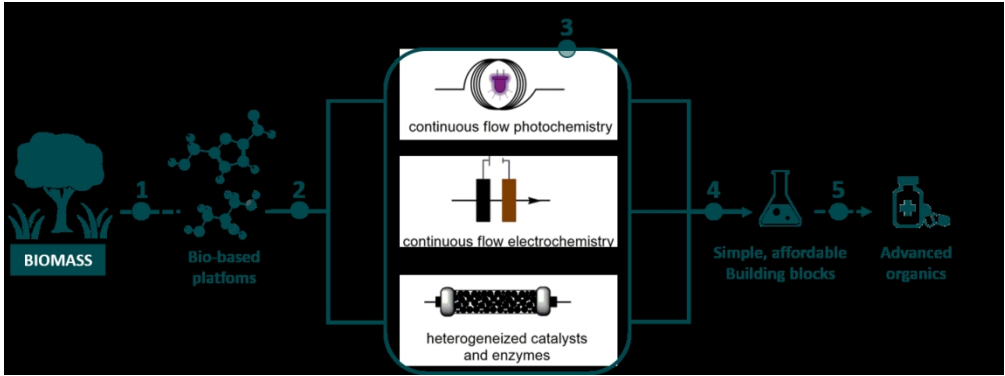


Figure 120

241x90mm (150 x 150 DPI)

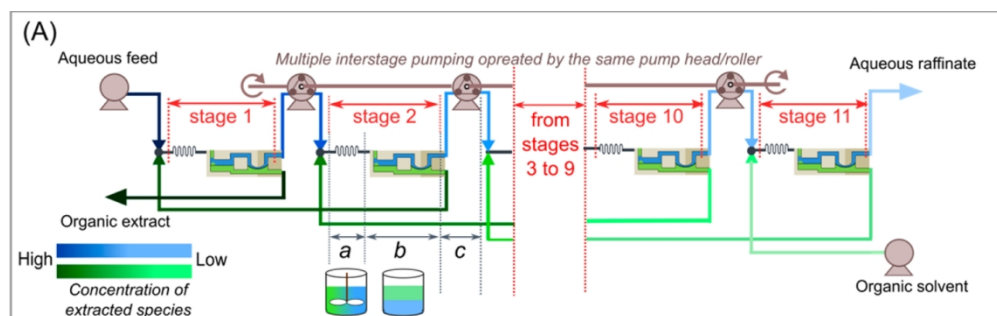
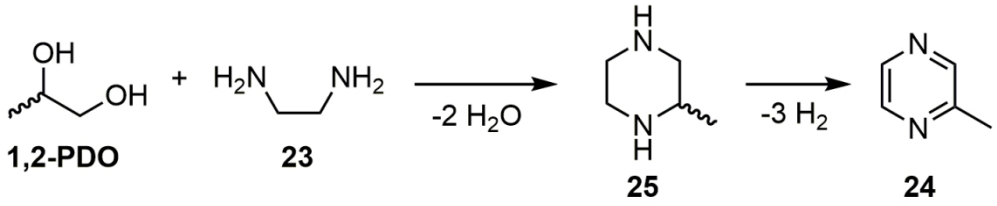
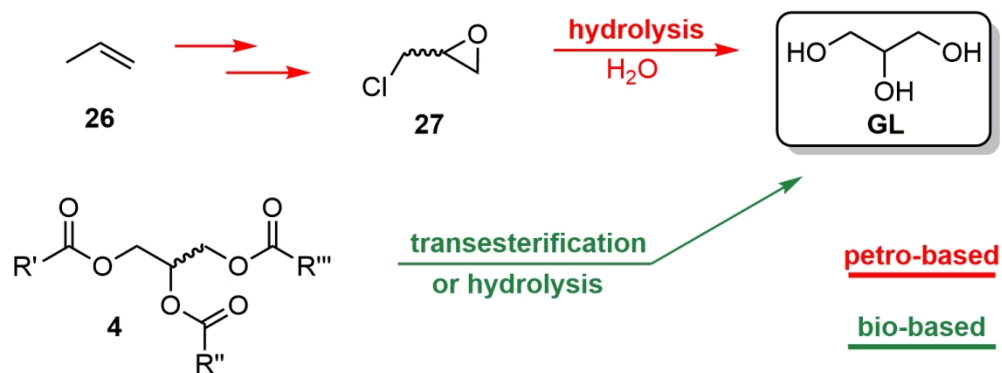


Figure 121



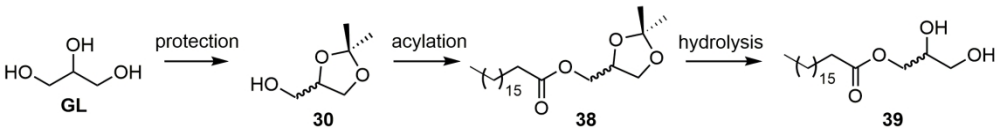
Scheme 1

120x25mm (300 x 300 DPI)



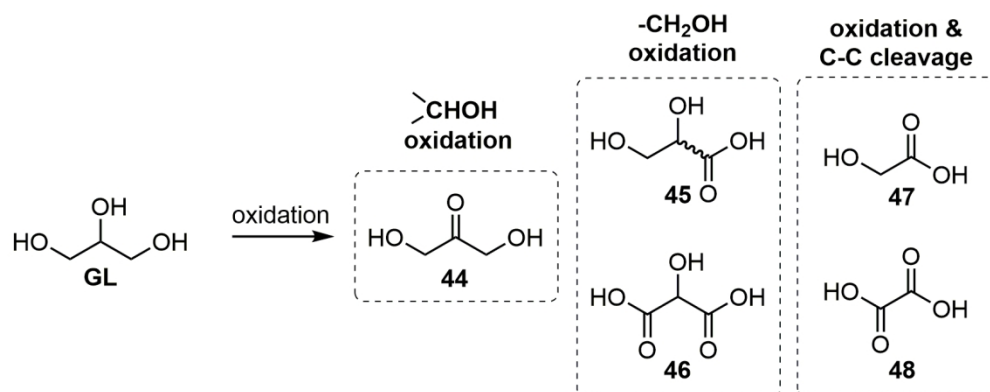
Scheme 2

129x48mm (300 x 300 DPI)



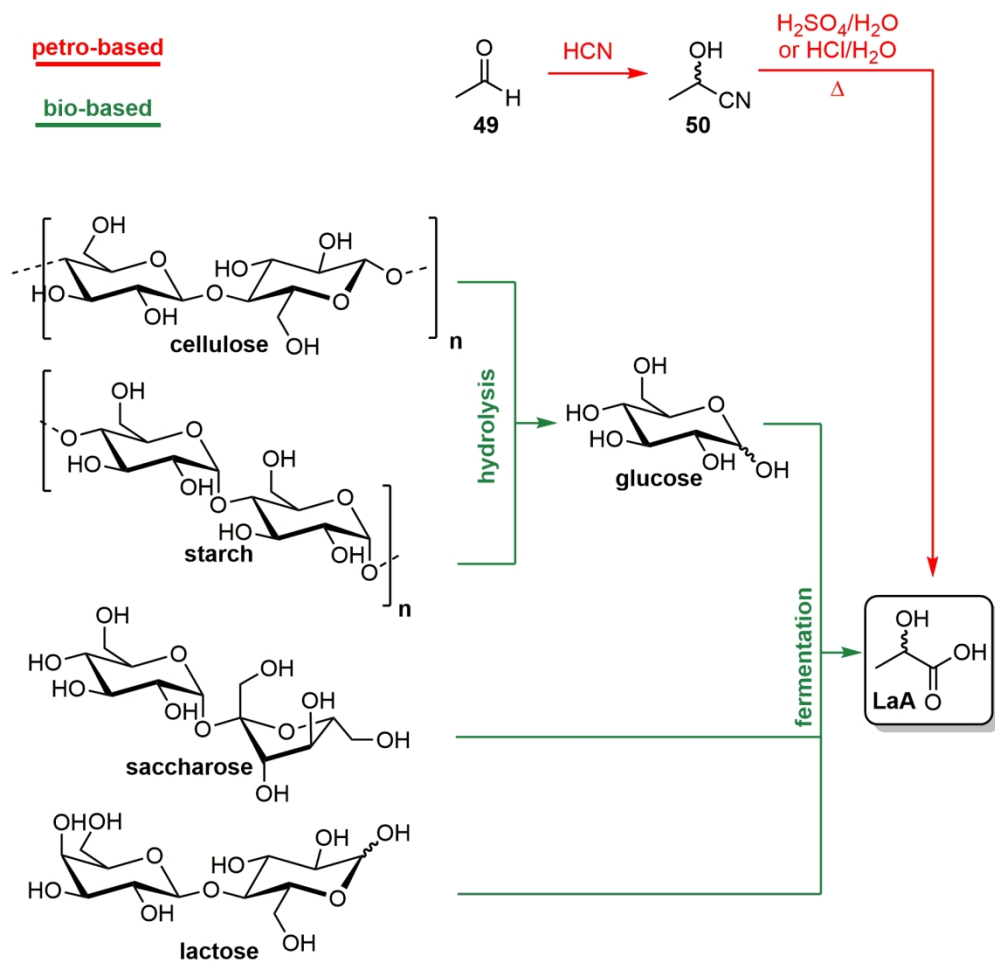
Scheme 3

183x24mm (300 x 300 DPI)



Scheme 4

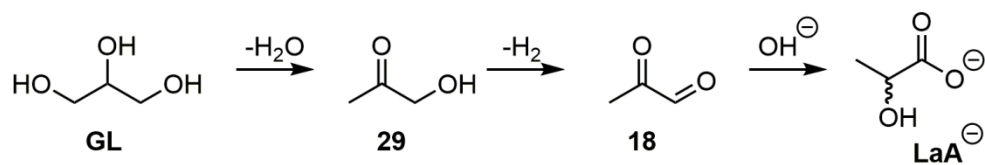
144x57mm (300 x 300 DPI)



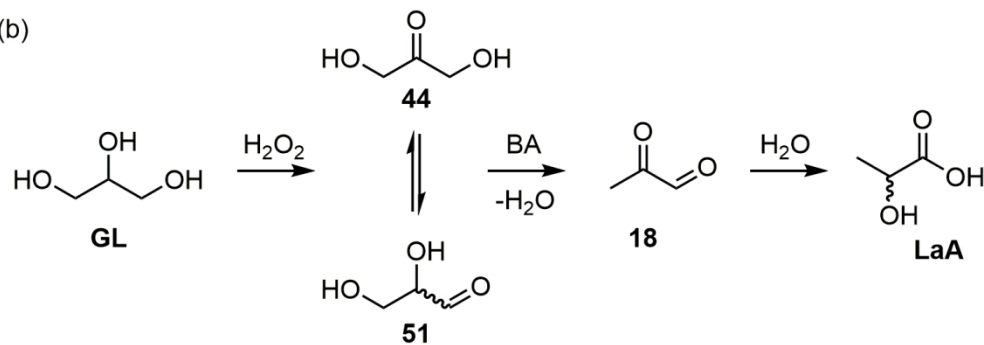
Scheme 5

152x146mm (300 x 300 DPI)

(a)

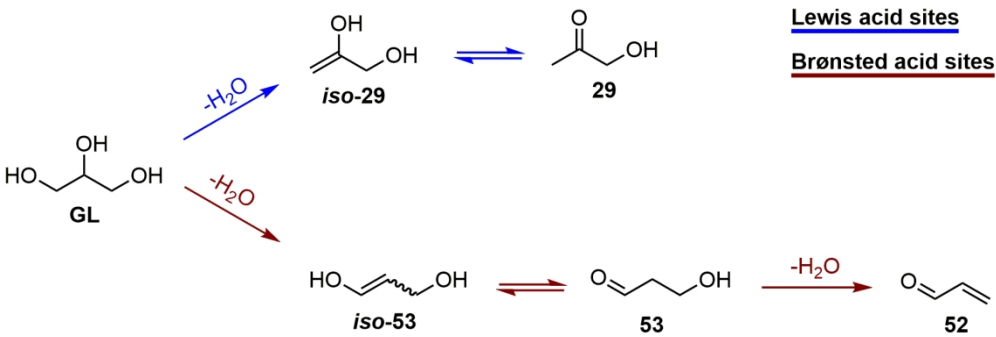


(b)



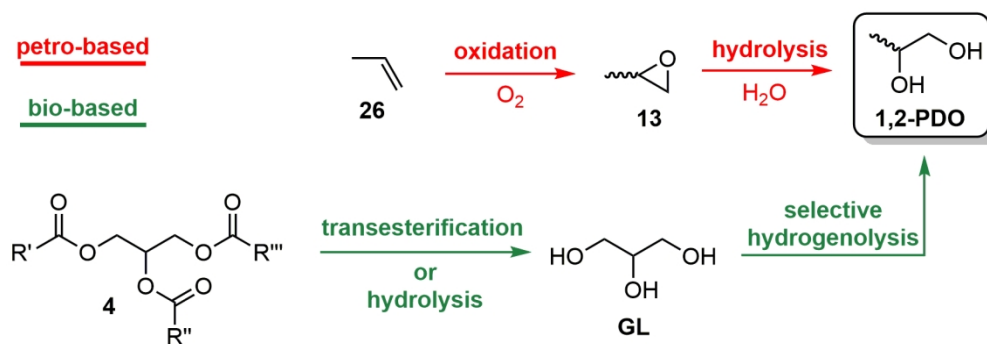
Scheme 6

133x81mm (300 x 300 DPI)



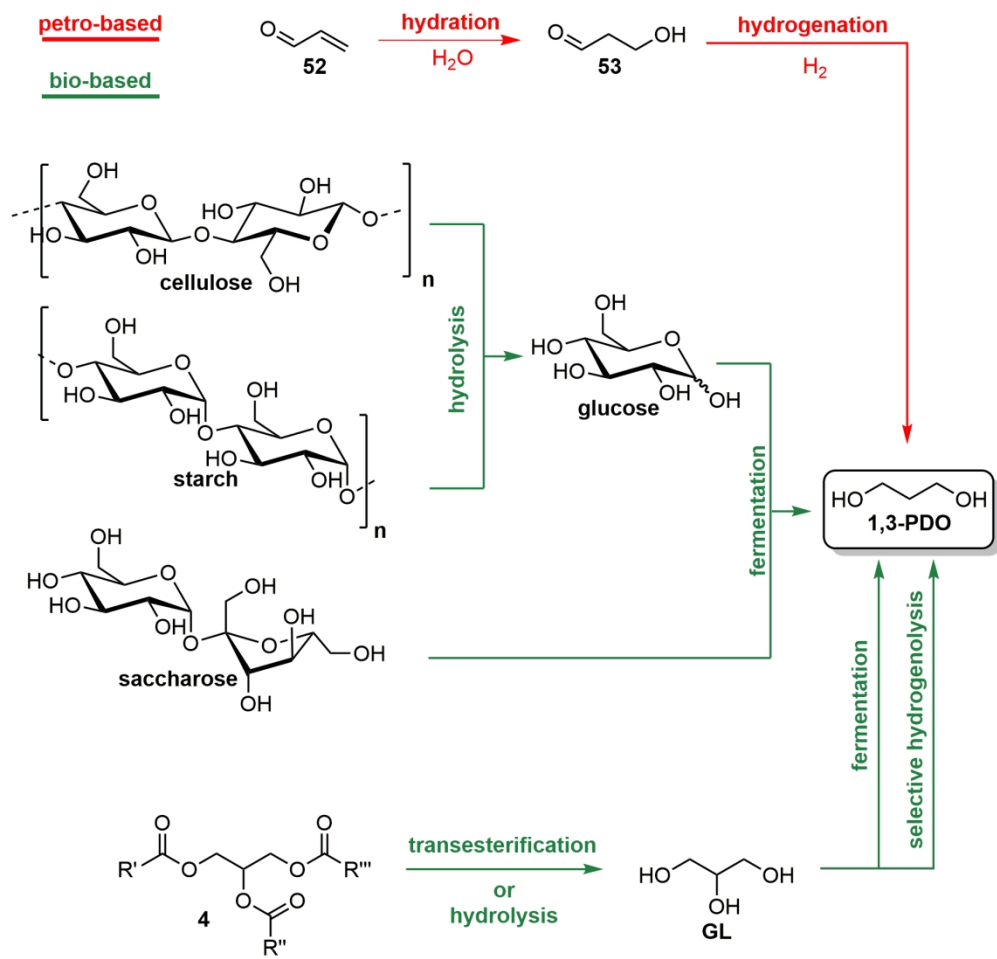
Scheme 7

159x54mm (300 x 300 DPI)



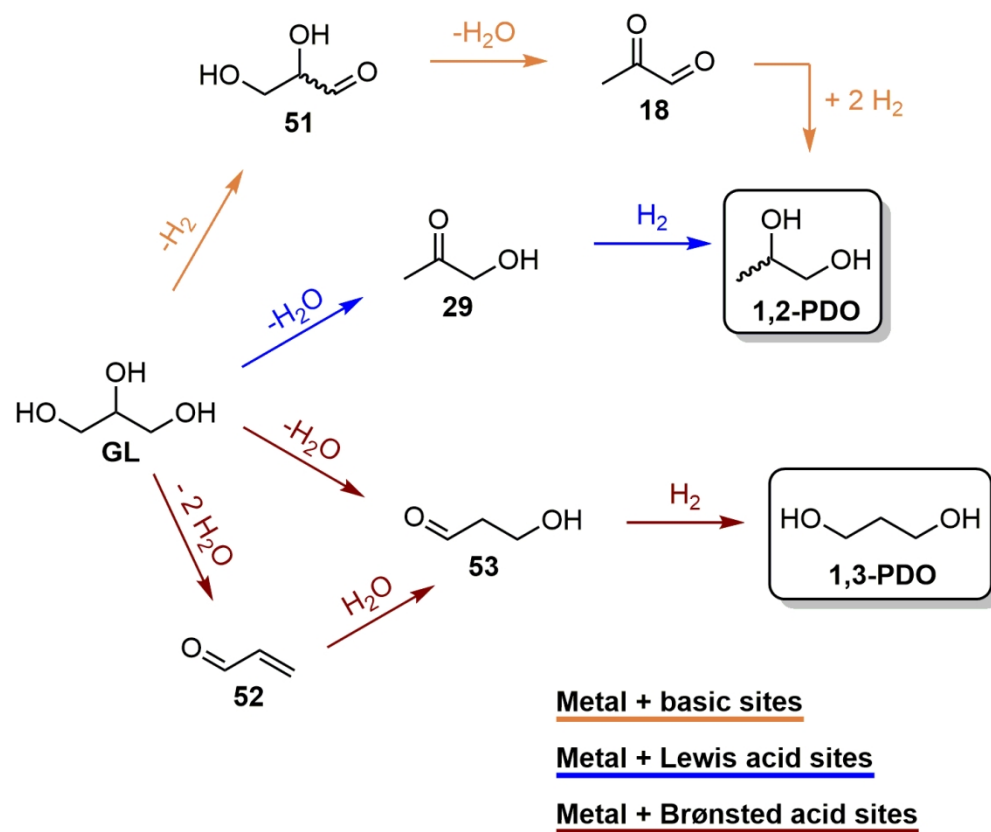
Scheme 8

151x51mm (300 x 300 DPI)



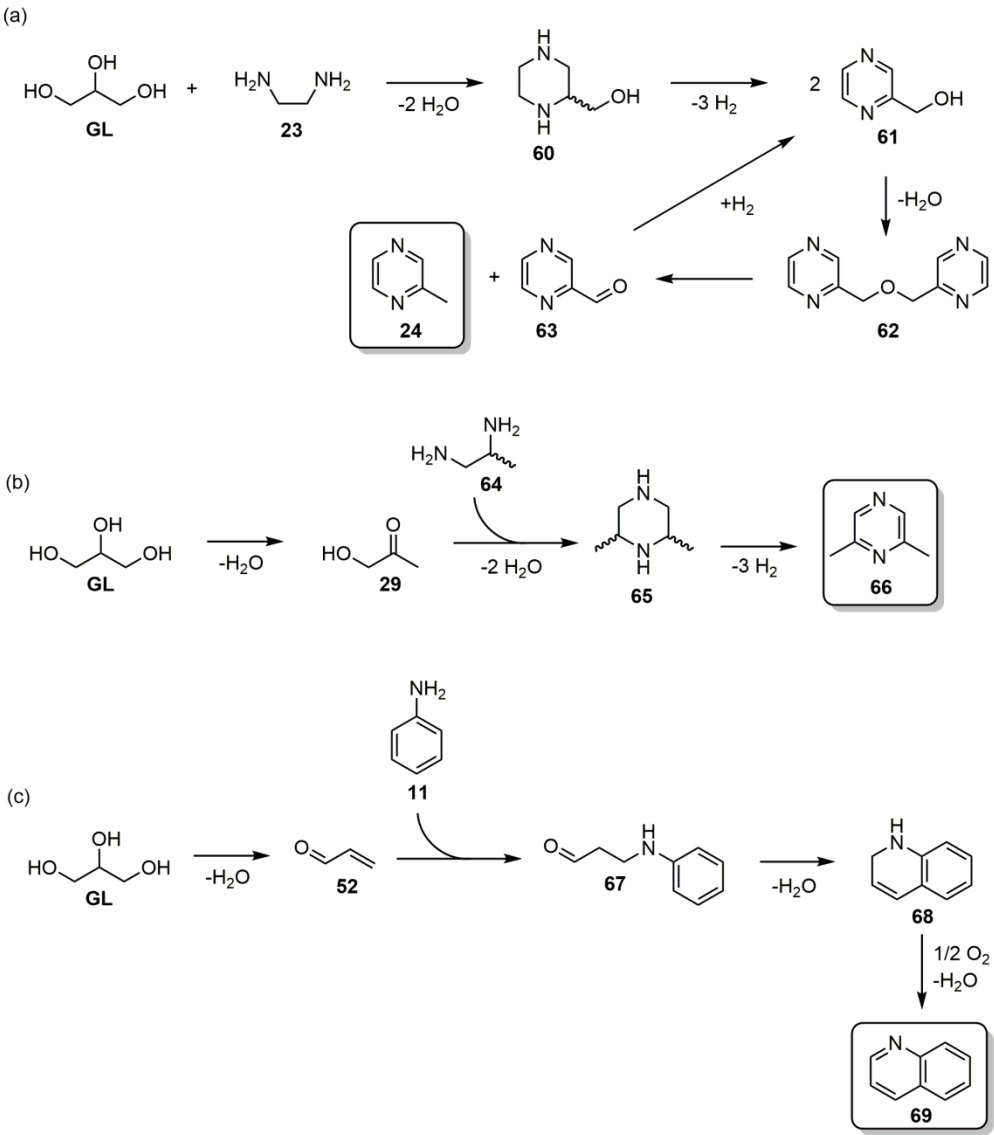
Scheme 9

162x154mm (300 x 300 DPI)



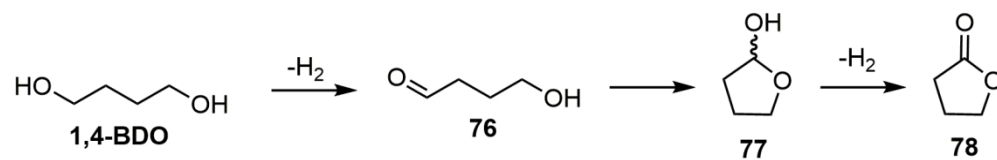
Scheme 10

126x105mm (300 x 300 DPI)



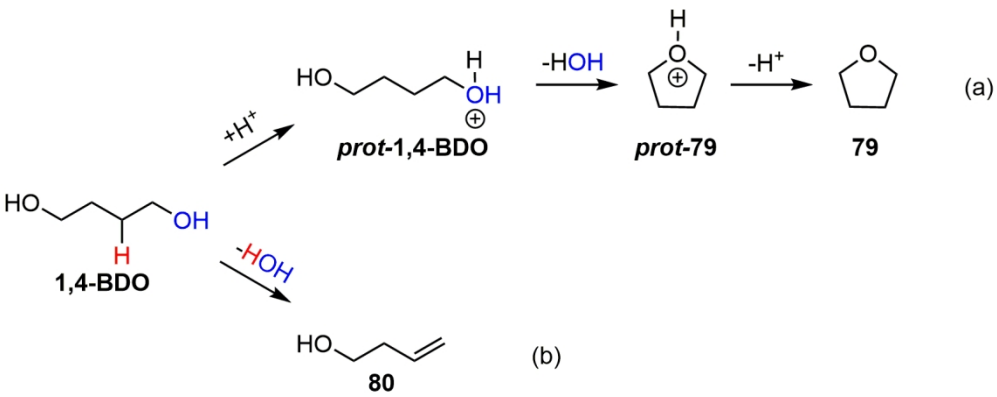
Scheme 11

177x201mm (300 x 300 DPI)



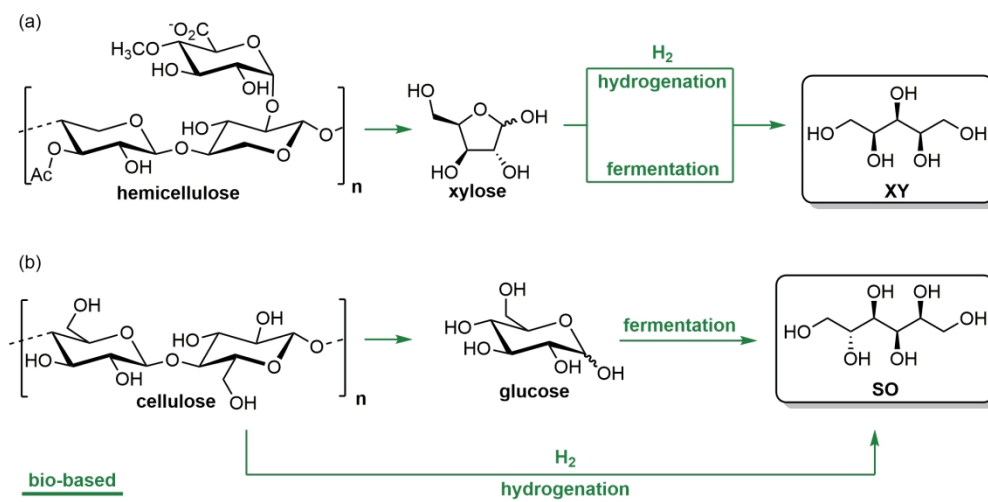
Scheme 12

138x23mm (300 x 300 DPI)



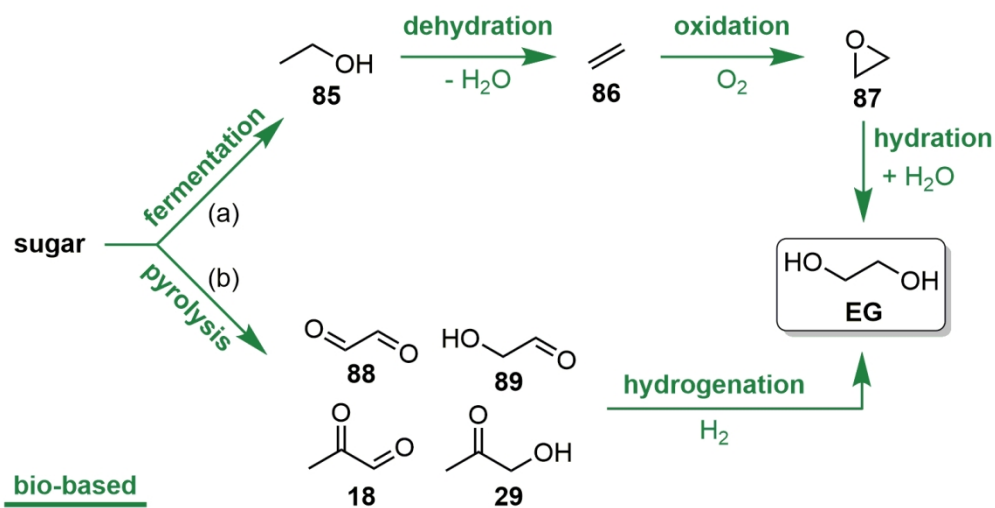
Scheme 13

144x58mm (300 x 300 DPI)



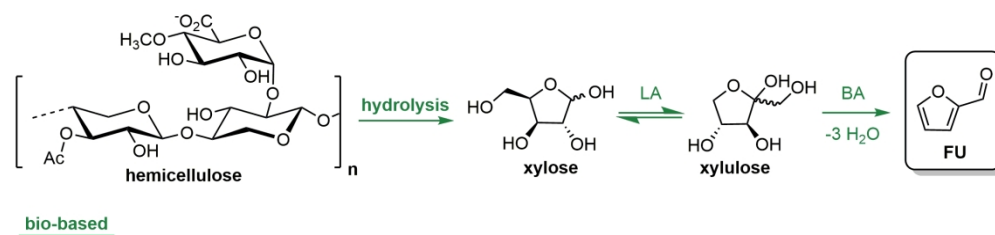
Scheme 14

189x93mm (300 x 300 DPI)



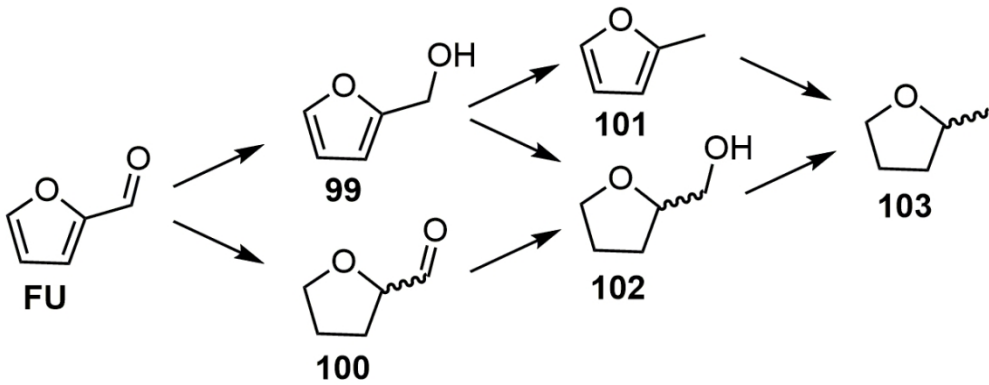
Scheme 15

134x68mm (300 x 300 DPI)



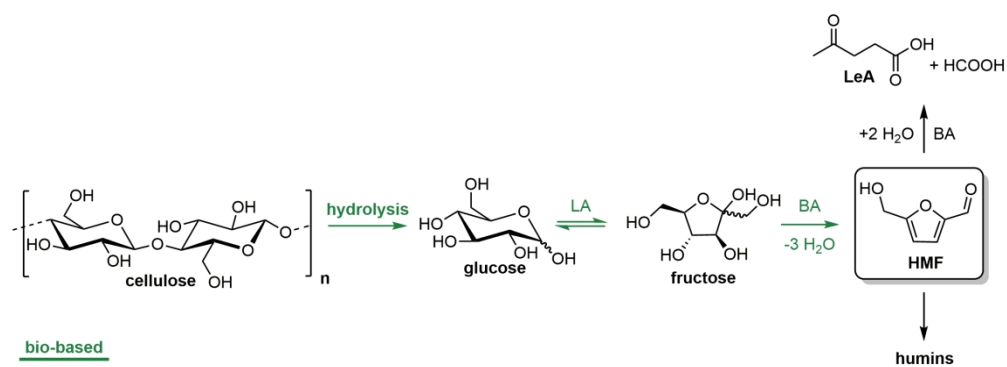
Scheme 16

199x46mm (300 x 300 DPI)



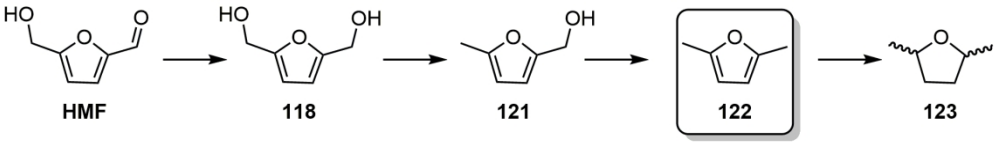
Scheme 17

105x41mm (300 x 300 DPI)



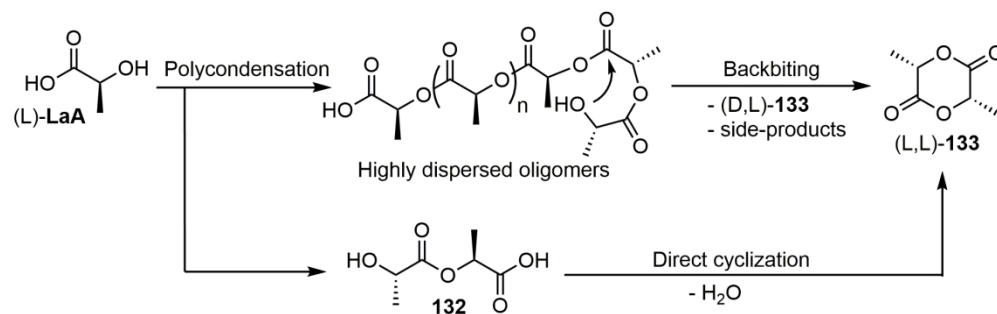
Scheme 18

213x77mm (300 x 300 DPI)



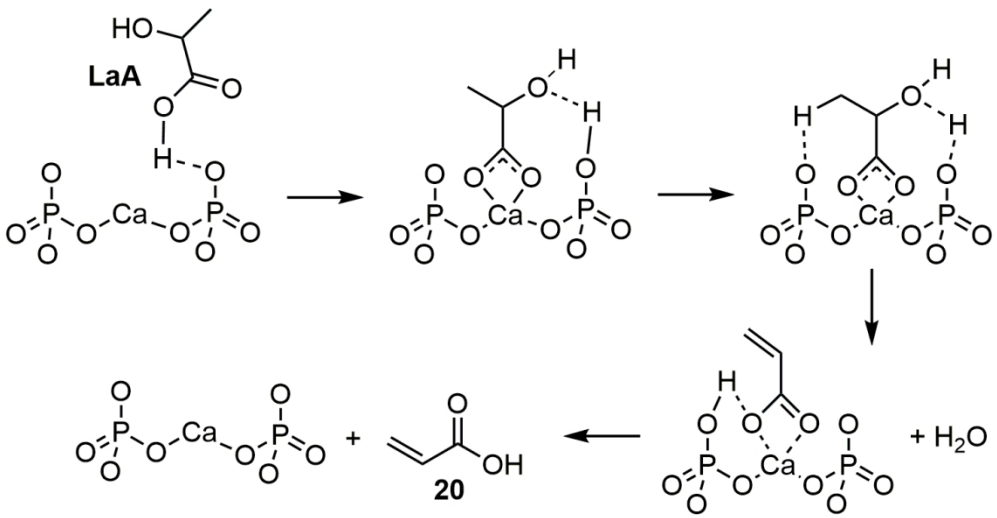
Scheme 19

170x25mm (300 x 300 DPI)



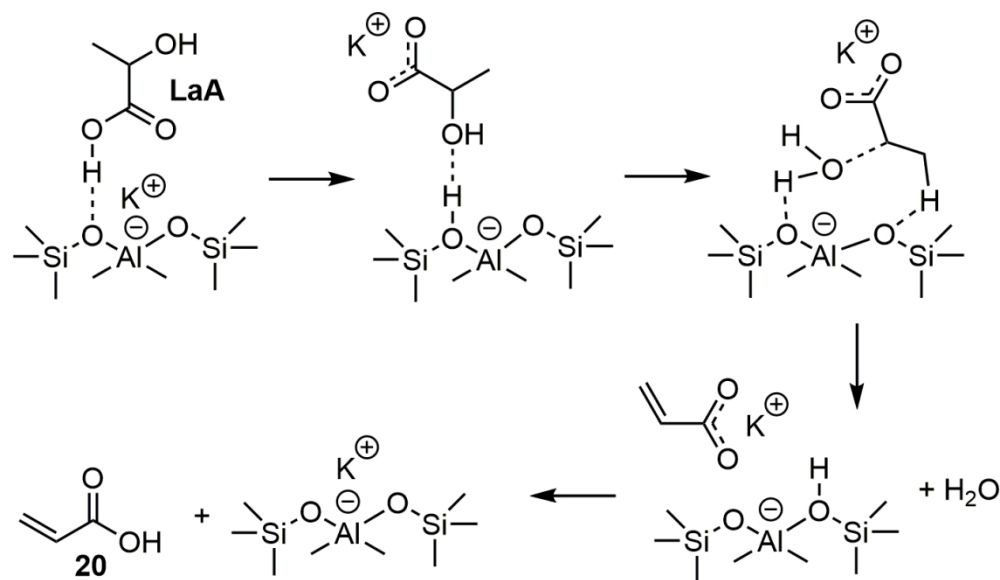
Scheme 20

167x53mm (300 x 300 DPI)



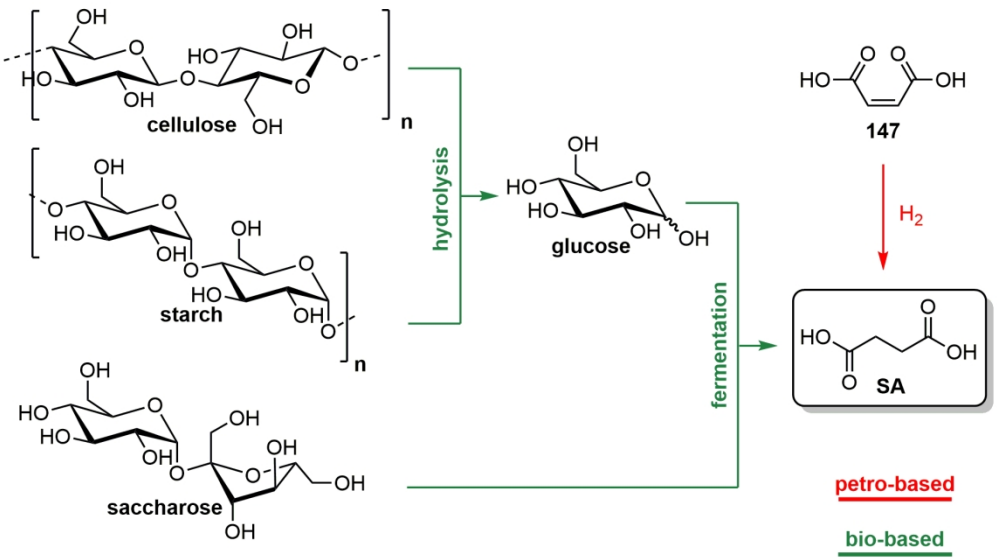
Scheme 21

124x64mm (300 x 300 DPI)



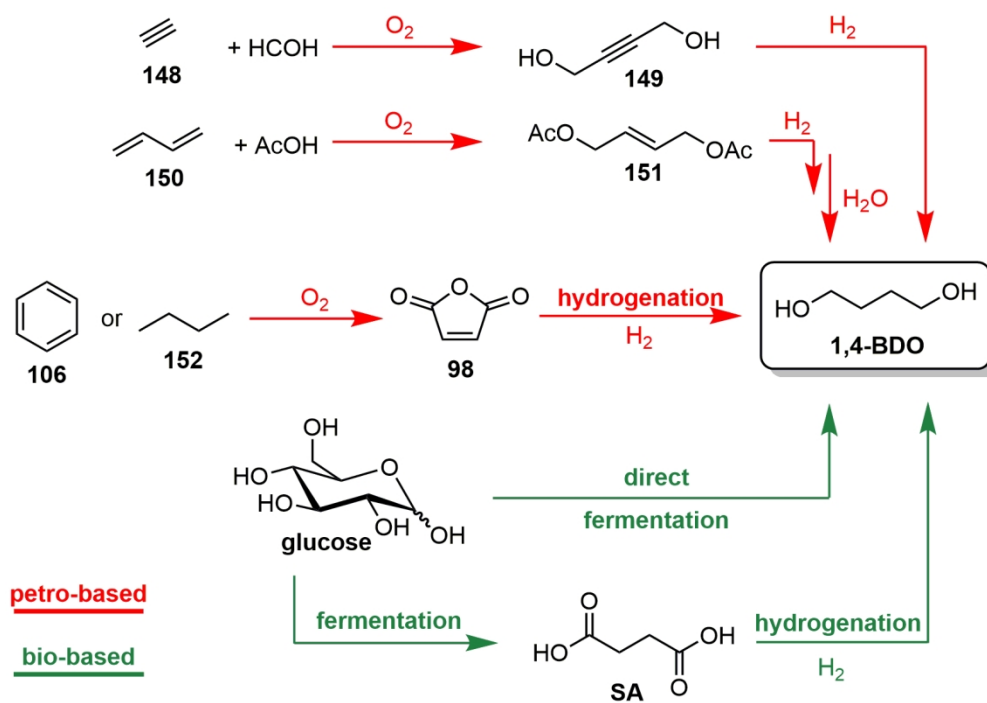
Scheme 22

119x69mm (300 x 300 DPI)



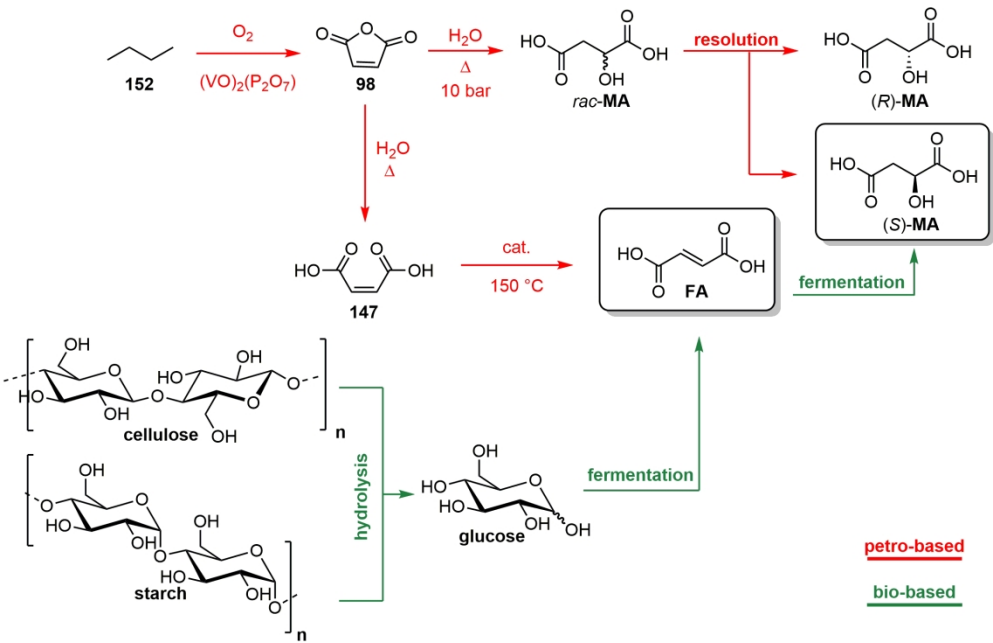
Scheme 23

167x93mm (300 x 300 DPI)



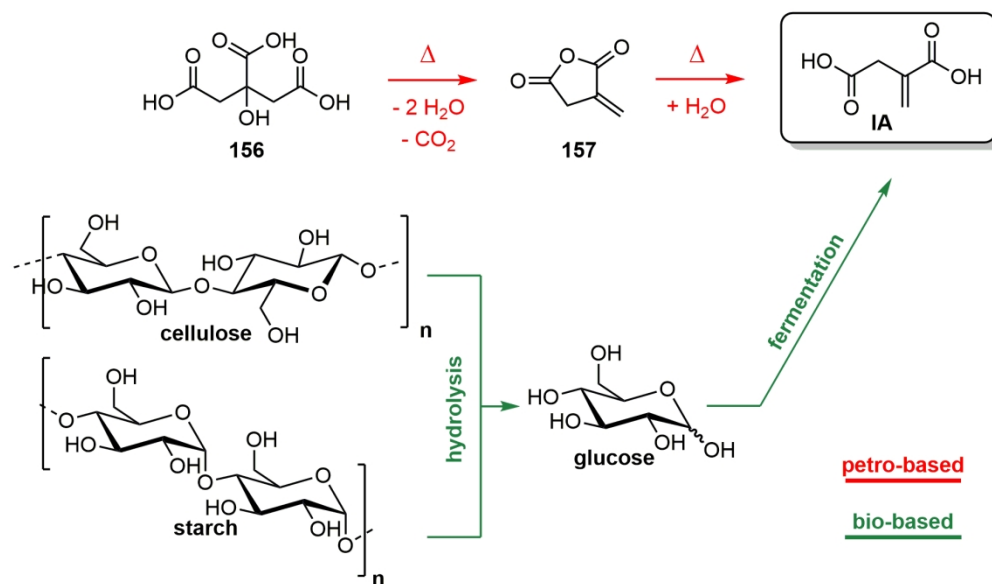
Scheme 24

146x103mm (300 x 300 DPI)



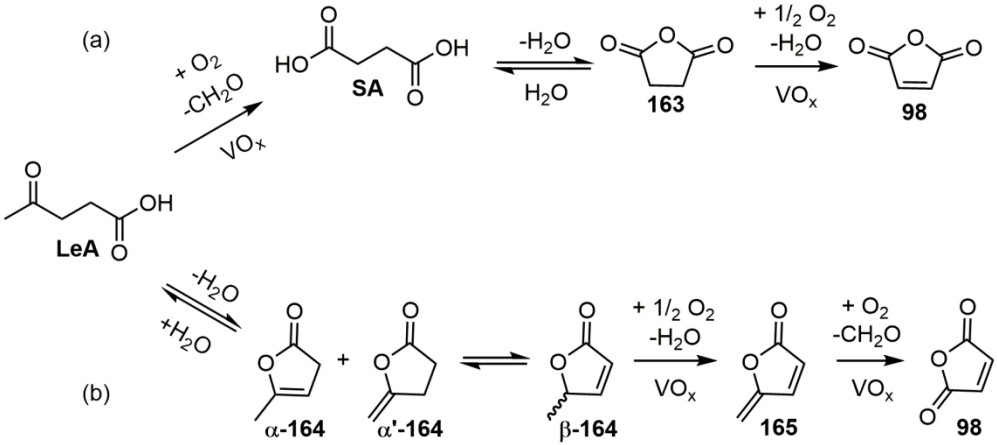
Scheme 25

200x130mm (300 x 300 DPI)



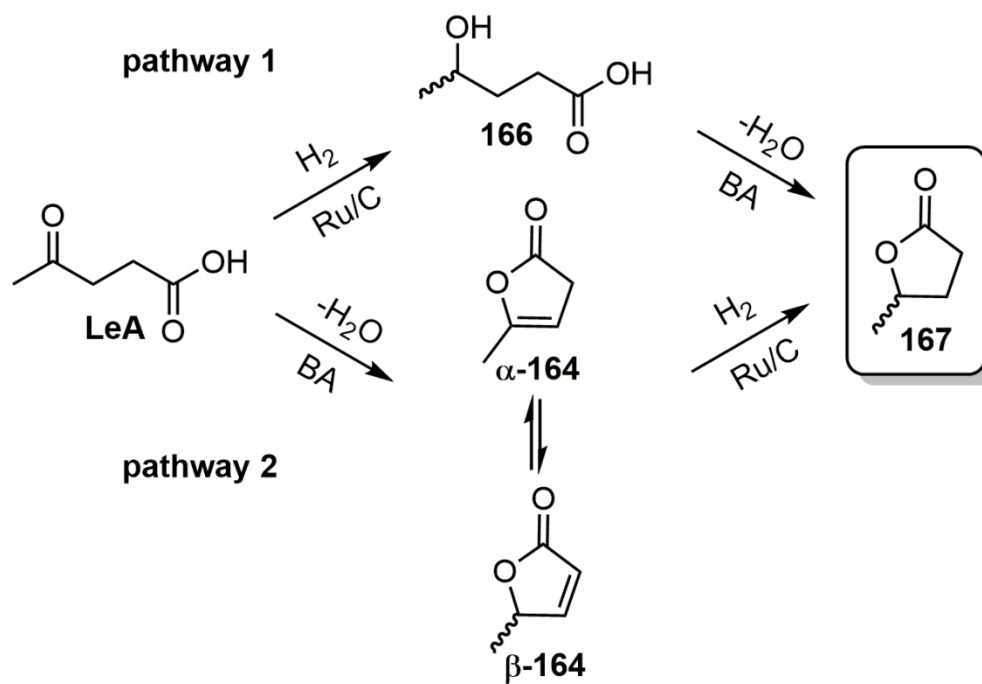
Scheme 26

164x96mm (300 x 300 DPI)



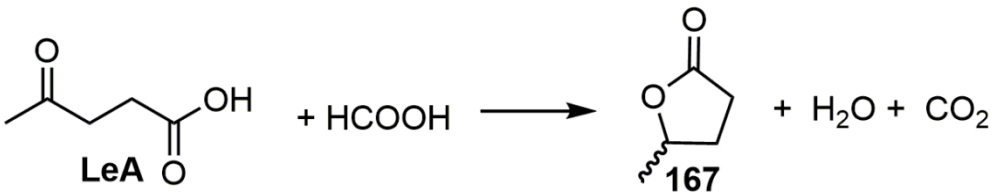
Scheme 27

152x68mm (300 x 300 DPI)



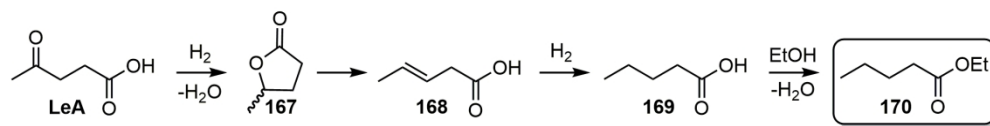
Scheme 28

109x75mm (300 x 300 DPI)



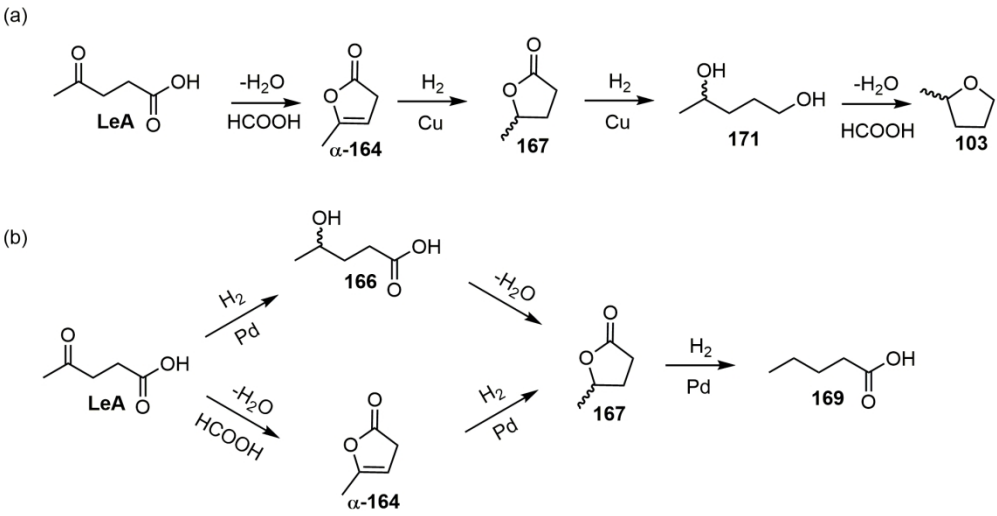
Scheme 29

104x21mm (300 x 300 DPI)



Scheme 30

180x23mm (300 x 300 DPI)



Scheme 31

176x90mm (300 x 300 DPI)

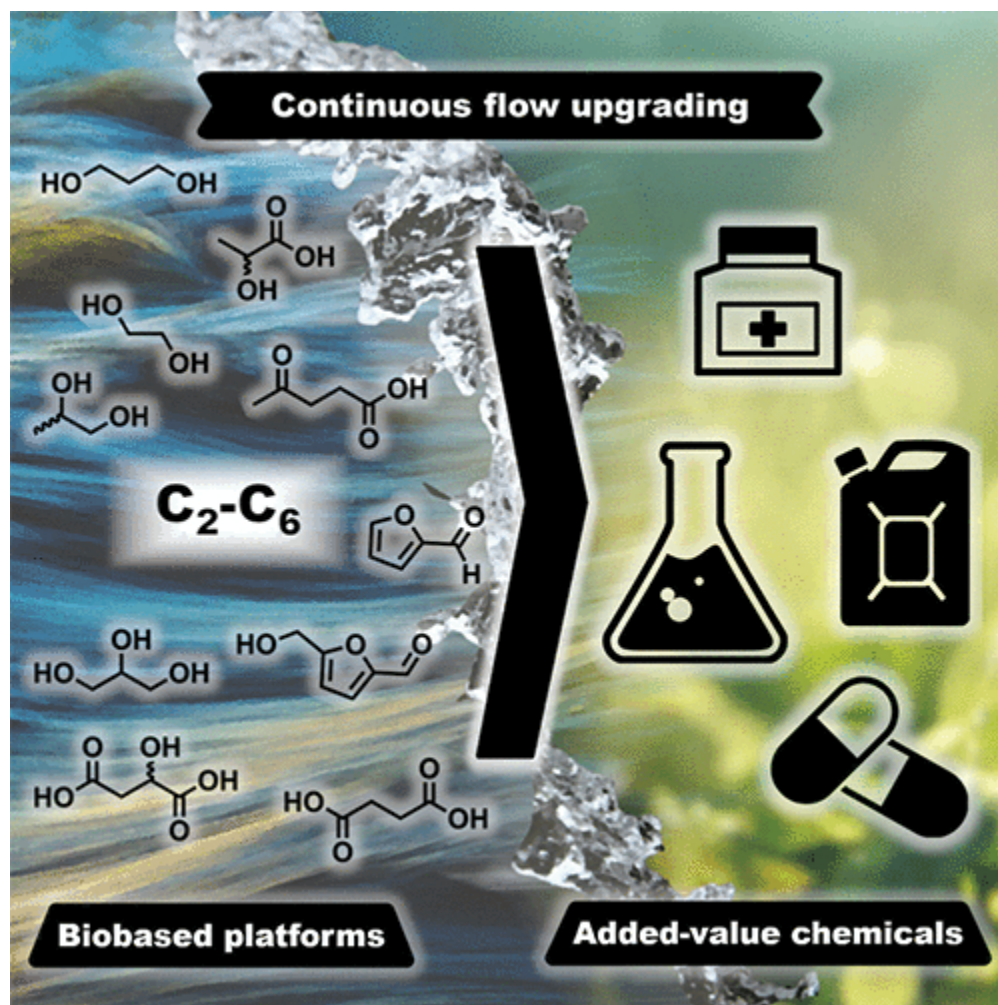


Table of Content - Graphical abstract

42x42mm (300 x 300 DPI)