

An Innovative Approach to the On-Purpose Synthesis of 1,3-Butadiene

Ein Innovativer Ansatz zur Gezielten Herstellung von
1,3-Butadien

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Per aspera ad astra

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Abstract

In this work, a new concept for the on-purpose synthesis of butadiene was studied. Starting from acetaldehyde, derived from (bio-)ethanol as C₂ building block, a reaction cascade involving 3-hydroxy-2-butanone (acetoin) and 2,3-butanediol as intermediates was explored. The proposed route includes three main steps: *N*-heterocyclic carbene (NHC) catalysed self-addition of acetaldehyde to form acetoin, hydrogenation of acetoin to 2,3-butanediol, and subsequent dehydration to produce 1,3-butadiene.

For the NHC-catalysed acetaldehyde upgrading, thiazolium-based NHC precursors, combined with mild bases demonstrated excellent catalytic performance in both neat and solvated conditions. A key feature of the reaction was the exceptionally high selectivity towards acetoin, as well as its tolerance to ethanol as a solvent. The latter attribute is of particular significance, as it mitigates the requirements of a potential ethanol dehydrogenation reaction step with respect to acetaldehyde yield. Despite their high catalytic efficiency, homogeneous NHC precursors suffered from poor recyclability. To address this limitation, an immobilised NHC catalyst was developed and analysed. In this regard, solid-state NMR was performed to confirm the successful grafting of the catalytically active species onto a support material.

Though highly selective in the acetaldehyde self-addition, the heterogeneous catalyst exhibited activity loss under continuous-flow conditions. Careful evaluation elucidated that this decay could be attributed to leaching of the grafted species. To improve the catalyst stability, an ion exchange with a non-nucleophilic counterion was conducted which significantly enhanced longevity. This modified heterogenised catalyst enabled continuous-flow operation for up to 60 hours while maintaining high acetoin selectivity (> 94%).

Hydrogenation of the acetoin-containing product mixture from the continuous-flow acetaldehyde self-addition reaction was performed using a commercial 5 wt% Ru/C catalyst in batch mode, achieving near-quantitative conversion. Subsequent distillation enabled the isolation of 2,3-butanediol with approximately 95% purity, demonstrating the feasibility of separating the product from the reaction mixture, which is crucial for further downstream processing of the prepared 2,3-butanediol.

Finally, the gas-phase double dehydration of 2,3-butanediol *via* 3-butene-2-ol as essential reaction intermediate was investigated. A hydrothermally synthesised, Sc₂O₃ catalyst (HT-800-Sc₂O₃) exhibited high 3-butene-2-ol selectivity (> 90%) and stability over 10 hours of time-on-stream. When using a zeolite (ZSM-5)-catalysed second dehydration step in the same flow-reactor, a near-quantitative 2,3-butanediol conversion and an excellent selectivity (80%) towards 1,3-butadiene were achieved. The developed double dehydration process achieved a productivity nearly four times the industrial production barrier that is discussed in literature.

By employing the best performing processes and catalytic systems investigated in this work, a proof-of-concept for the proposed synthesis route was established, achieving an overall process efficiency of 17% for 1,3-butadiene production based on the mass of acetaldehyde fed into the beginning of the process.

Kurzdarstellung

In dieser Arbeit wurde eine neue Syntheseroute zur gezielten Herstellung von 1,3-Butadien untersucht. Der Prozess beginnt mit Acetaldehyd, das aus (bio-)Ethanol als C₂-Baustein gewonnen werden kann, und folgt einer Reaktionskaskade über die Zwischenprodukte 3-Hydroxy-2-butanon (Acetoin) und 2,3-Butandiol. Der vorgeschlagene Syntheseweg umfasst drei Hauptschritte: die *N*-heterocyclische-Carben (NHC) katalysierte Selbstaddition von Acetaldehyd zu Acetoin, die Hydrierung von Acetoin zu 2,3-Butandiol und die anschließende Dehydratisierung zu 1,3-Butadien.

Für die NHC-katalysierte Selbstaddition von Acetaldehyd zeigten thiazoliumbasierte NHC-Präkursoren in Kombination mit milden Basen eine exzellente katalytische Leistung unter sowohl lösungsmittelfreien als auch solvatisierten Bedingungen. Ein zentrales Merkmal der Reaktion war die außergewöhnlich hohe Selektivität zum Acetoin, sowie die Toleranz gegenüber Ethanol als Lösungsmittel. Letzteres könnte künftig besonders relevant sein, da es die Anforderungen an eine Ethanol-zu-Acetaldehyd Dehydrierung deutlich verringert. Trotz der hohen katalytischen Effizienz wiesen homogene NHC Präkursoren eine geringe Recyclingfähigkeit auf. Um diese Einschränkung zu überwinden, wurde ein immobilisierter NHC-Katalysator entwickelt und charakterisiert. Die erfolgreiche Verankerung der katalytisch aktiven Spezies auf einem Trägermaterial konnte mittels Festkörper-NMR nachgewiesen werden.

Der heterogene Katalysator zeigte jedoch unter kontinuierlichen Versuchsbedingungen im Rührkessel einen Aktivitätsverlust, der auf das Auslaugen der aktiven Spezies zurückgeführt werden konnte. Zur Verbesserung der Katalysatorstabilität wurde ein Ionenaustausch mit einem nicht-nukleophilen Gegenion durchgeführt, was die Langzeitstabilität erheblich erhöhte. Diese Modifikation ermöglichte einen kontinuierlichen Betrieb über bis zu 60 Stunden bei hoher Acetoin-Selektivität (> 94%).

Die vollständige Hydrierung der Produktmischung aus der kontinuierlich betriebenen Selbstadditionsreaktion wurde mit einem 5 wt% Ru/C-Katalysator durchgeführt. Die anschließende Destillation erlaubte die Isolierung von 2,3-Butandiol mit einer Reinheit von etwa 95%, wodurch die effiziente Abtrennung dieses Produkts aus dem Reaktionsstrom demonstriert wurde.

Abschließend wurde die zweistufige Dehydratisierung von 2,3-Butandiol in der Gasphase untersucht. Ein hydrothermal synthetisierter, Sc₂O₃-Katalysator zeigte eine hohe Selektivität hin zum essentiellen Intermediat 3-Buten-2-ol (> 90 %) sowie eine Stabilität von 10 Stunden. Kombiniert mit einer Zeolith-katalysierten (ZSM-5) Dehydratisierung im gleichen Rohrreaktor, konnte eine nahezu vollständige 2,3-Butandiol Umsetzung bei ausgezeichneter Selektivität hin zum 1,3-Butadien erzielt werden (80%). Der entwickelte zweistufige Dehydratisierungsprozess erzielte eine Produktivität, die fast das Vierfache der in der Literatur diskutierten industriellen Produktionsgrenze beträgt.

Durch die Kombination der in dieser Arbeit erforschten Prozessbedingungen und katalytischen Systeme, konnte ein Machbarkeitsnachweis für den vorgeschlagenen Syntheseweg erbracht werden. Die Gesamtprozesseffizienz für die 1,3-Butadien Produktion erreichte 17%, bezogen auf die zu Beginn des Prozesses eingesetzte Acetaldehyd Menge.

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List of Abbreviations

2B1OL	2-butene-1-ol
3B1OL	3-butene-1-ol
3B2OL	3-butene-2-ol
APT	Attached proton transfer
BD	1,3-butadiene
BDO	butanediol
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BPR	Back-pressure-regulator
CP	Cross polarisation
DD	Dipolar Dephasing
DFT	Density functional theory
DRIFTS	Diffuse reflectance infrared Fourier transform spectroscopy
ee	Enantiomeric excess
eq	Equivalents
ESI	Electrospray ionisation
EtOH	Ethanol
f-Amphox	ferrocene aminophosphoxazoline
FID	Flame Ionisation Detector
GC	Gas Chromatography
h	Hour
HAZOP	Hazard and Operability
HT	Hydrothermal
IBA	<i>iso</i> -butyraldehyde / 2-methylpropanal
IM-NHC	Immobilised <i>N</i> -heterocyclic carbene
INEPT	Insensitive nuclei enhanced polarization transfer
<i>i</i> PrOH	<i>iso</i> -Propanol
LOPA	Layer of Protection Analysis
MAK	<i>Maximale Arbeitsplatz-Konzentration</i>
MAS	Magic angle spinning
MCF	Meso cellular foam
MEK	Methyl ethyl ketone (butanone)
MeOH	Methanol
MFC	Mass-flow-controller
min	Minutes
MPV	<i>Meerwein-Ponndorf-Verley</i>
MS	Mass spectrometry
MVK	Methyl vinyl ketone / 3-buten-2-on
NHC	<i>N</i> -heterocyclic carbene
NMR	Nuclear Magnetic Resonance
ODH	Oxidative dehydrogenation
OTf	Trifluoromethanesulfonate
P&ID	Process and Instrumentation Diagram
r.t.	Room temperature
REO	Rare-earth oxide
SBR	Styrene butadiene rubber
SEM	Scanning electron microscopy
TDI	Turn-over-frequency determining intermediate
TDS	Turn-over-frequency determining transition state
THF	Tetrahydrofuran

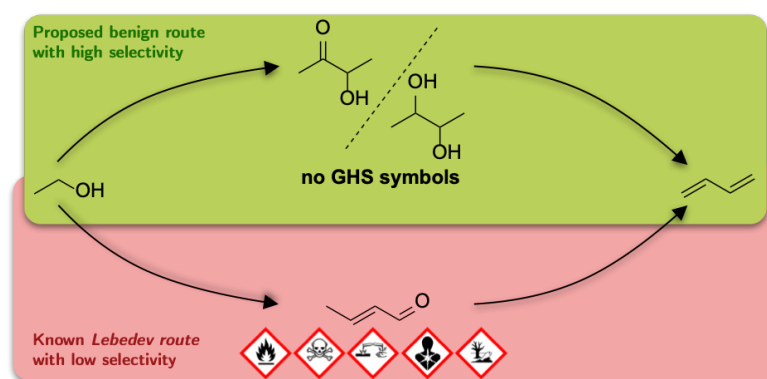
TON	Turn-over-number
TOS	Time on stream
TPD	Temperature programmed desorption
TsDPEN	<i>N</i> -tosyl-1,2-Diphenyl-1,2-ethylenediamine
TTON	Total turn-over-number
UCC	Union Carbide and Carbon Chemicals Corporation
WHSV	Weight hourly space velocity
XRD	X-ray diffraction
ZSM-5	Zeolite Socony Mobil-5

1 Introduction

1,3-Butadiene is an extremely important building block used in a wide range of chemical processes, including the manufacture of synthetic rubbers and adiponitrile.^[1-3] Currently, around 95% of the world's production volume of 1,3-butadiene is obtained as a by-product from the steam-cracking of naphtha to produce ethylene.^[1, 3-4] The fossil-based resources used and the energy intensive production method, make butadiene a very unsustainable building block.^[5] Besides this, due to the recent shift towards the use of lighter feedstocks for ethylene production, less butadiene is yielded as by-product from the same amount of ethylene. Consequently, butadiene production *via* steam cracking of naphtha is suspected to decline in the near future.^[3]

Therefore, it is highly desired to find an alternative way to produce 1,3-butadiene from bio-based raw materials to ensure a steady butadiene supply and part from the petrochemical production method to a more sustainable one. As this is the ultimate goal of the current developments in the chemical industry, in a more general context, ethanol is often considered as more sustainable bio-based feedstock for fuels and chemicals. More specifically, it is already known since the mid-20th century that ethanol can be converted to butadiene using heterogeneous catalysts.^[5-9]

However, the established *Lebedev* and *Ostromislensky* processes suffer from low selectivity towards butadiene, which is partly due to the complexity of the reaction network.^[3, 6, 9-12] To circumvent the problems associated with the one-step *Lebedev* or two-step *Ostromislensky* process, this work will focus on an alternative pathway to convert ethanol into butadiene. In the sequence, consisting of several stepwise reactions, 3-hydroxy-2-butanone and 2,3-butanediol will be the main intermediates, whereas in the *Lebedev* and *Ostromislensky* processes, crotonaldehyde is a major intermediate. Using a keen combination of homogeneously and heterogeneously catalysed reactions, a novel pathway with presumed high selectivity and productivity towards butadiene will be studied (Scheme 1).



Scheme 1: Proposed benign route to 1,3-butadiene *via* the acetoin/2,3-butanediol stage (top) as well as the known heterogeneously catalysed *Lebedev/Ostromislensky* process to convert ethanol to 1,3-butadiene *via* crotonaldehyde (bottom).^[3, 6, 9-12]

2 Theoretical Background

Before elaborating on the particular reactions and molecular transformations studied in this work to deliver a proof of concept for a novel ethanol-to-butadiene route, it is first necessary to provide an overview of the current chemical value chain and the role of butadiene. Additionally, this chapter will provide a concise overview of the state-of-the-art as well as historical industrial processes starting from naphtha or ethanol as feedstock. Furthermore, the utilisation of bio-based C₄ alcohols as feedstock will be briefly reviewed, as well as the on-purpose synthesis thereof.

2.1 About the use and Importance of Butadiene in the Chemical Value Chain

1,3-Butadiene (BD) is mainly used as monomer in the production of various elastomers and synthetic rubbers. Though BD is also used as reagent in organic chemistry, *e.g.* in Diels-Alder reactions, synthetic elastomers like styrene butadiene rubber (SBR) and polybutadiene rubber (PBR), represent the largest share of the downstream use of BD.^[3, 11] BD derived elastomers and rubbers find widespread application in the sealant and textile industry. Downstream products of BD are mainly used in the automotive industry which consumes about 70% of the world's production capacity.^[1, 13-15] A medium-sized car contains about 23 kg of BD-based polymers, including tires.^[3] Hence, BD is of extreme importance to the automotive industry and the global consumption of BD heavily depends on it.^[3, 10, 16] The production of butadiene was estimated to be around 16 million tons in 2018 and increased to 20 million tons in 2023, with a current average growth rate estimated at 2-4% per year.^[17-18] Below in Figure 1, a schematic overview is given about the downstream use of BD.

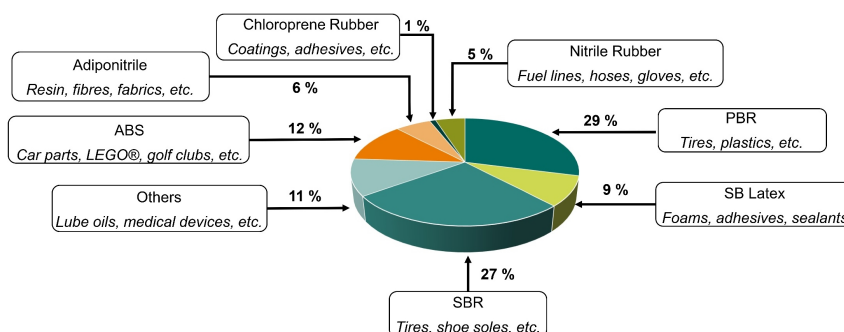


Figure 1: Schematic overview of the uses of BD in the year 2015, as adapted from^[1, 3, 19].

The global BD market is currently valued at approximately 40 billion euros, with projections indicating a gradual increase in the coming years.^[20-21] This forecasted growth is largely driven by Asian countries and their rising demand for vehicle ownership.^[20-21] Considering this growing demand for car tires, BD production must keep pace with the automotive industry. This could become an issue considering the state-of-the-art production of BD *via* steam-cracking of naphtha. Whereas BD used to have close ties with ethylene production, the most important monomer in the world, these ties have substantially loosened due to changes in the ethylene production process. Therefore, the so-called on-purpose catalytic synthesis of BD is gaining interest.^[22-24] Before elaborating on the current fossil-based BD production process, its attendant problems, and the necessity for sustainable alternatives, a brief overview will be given of catalysis, a key-technology in the on-purpose synthesis of BD.

2.2 Catalysis

The definition of a catalyst, as proposed by Wilhelm Ostwald, is a substance that alters the rate of a chemical reaction without being consumed.^[25] The transition state theory provides an explanation of the phenomenon of catalysis.^[26] It is acknowledged, that reactants must overcome an energy barrier, or activation energy (E_A), in order for the products to form. In catalytic reactions, the catalyst binds to the reactant to form an active complex. The complex formed has a lower activation energy compared to the uncatalyzed reaction, which consequently enhances the rate of the chemical reaction. A catalyst does not influence the thermodynamic and chemical equilibrium of the reaction. Both forward and reverse reaction benefit from catalysis. A catalyst merely serves to enhance the rate of the chemical reaction by providing an alternative reaction pathway.^[19, 27]

A catalytic pathway is often visualised as a cycle, where a multitude of different transition states and intermediates are formed on the reaction coordinates between educts and products.^[28] The rate at which a reaction proceeds, is governed by the amount of turn-overs of the catalytic cycle. This turn-over-frequency (TOF), is a very important measure for catalytic reactions, though it is no universal measure of catalytic activity. The TOF describes the average activity of a catalyst under a given set of reaction conditions.^[29] Within the catalytic cycle, it is acknowledged, that there is no such thing as a rate-determining step, but rather two rate-determining states that govern the chemical reaction. These states are referred to as TOF determining intermediate (TDI) and TOF determining transition state (TDTS). The so-called energetic span of the reaction (δE), is defined as the difference in *Gibbs* energy of the TDTS and TDI and serves as apparent activation energy of the catalytic reaction.^[19, 28-29] The TOF is directly related to the energetic span, as shown in **Figure 2**.

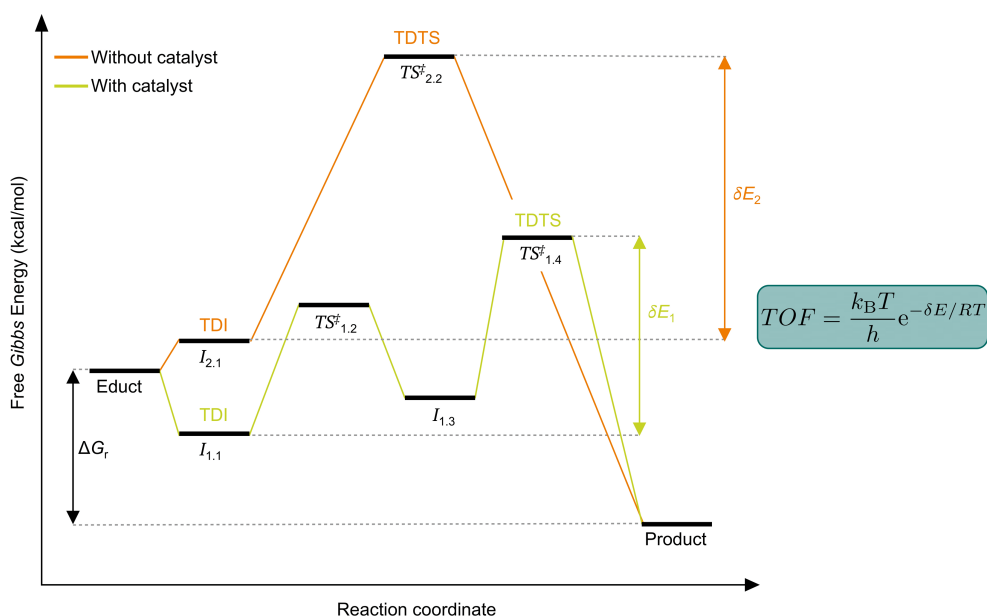


Figure 2: Schematic representation of an uncatalyzed (orange) and catalysed reaction (green) according to the energy span model. Presence of a catalyst enables a different reaction pathway and proceeds through different intermediates (I_n) and transition states ($TS_n^{\ddagger}$). The energy span, or apparent activation energy of the catalysed reaction δE_1 is smaller compared to the energy span of the uncatalyzed reaction (δE_2).^[19, 28-29] Usually, for uncatalyzed reactions, $\delta E_2 \gg \delta E_1$ not represented to scale in the above figure. Reactions are uncatalyzed if δE is so large that TOF values $< 10^{-16} \text{ h}^{-1}$ result.^[28-29]

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Catalysis can be grouped into three main categories: homogeneous, heterogeneous and bio catalysis.^[30] Catalysts are of high importance in industrial chemistry, as it is estimated that in around 90% of chemical processes catalysts are employed. Catalysis can be divided into three main categories: homogeneous, heterogeneous and bio-catalysis. While homogeneous and heterogeneous catalysts are commonly used in the manufacturing of bulk chemicals, bio catalysis has become an important aspect in the pharmaceutical industry where tailor-made enzymes are used to catalyse complex molecular transformations.^[30-31]

In the majority of homogeneously catalysed industrial catalysed processes, a transition or noble metal is combined with one or more ligands to form a stable metal complex, which is then solvated in the reaction medium. Each metal atom within the complex is considered to possess catalytic activity. Ligands are an indispensable component of homogeneous catalysis. They are responsible for dictating the electronic and steric properties in the proximity of the metal centre, influencing the catalytic activity of the complex to great extent. Ligands form a coordinative bond with the metal centre. The activity and selectivity of a homogeneous catalyst can be influenced by selecting an appropriate combination of (noble) metal and ligands. This enables to fine-tune the activity and selectivity of the catalyst in the molecular transformation. In homogeneous catalysis, the catalyst and reactants are dissolved in the same phase. After the reaction, separation of the catalyst from the remaining educts/products often represents a challenge in homogeneous catalysis. A variety of techniques are employed for the separation of catalysts from product streams, including distillation, precipitation and extraction. However, these methods can have negative effects on the catalyst lifetime, especially when the catalyst is prone to decompose at high temperatures or when the solubility of the catalyst is unknown.^[32] Moreover, the concentration of homogeneous catalysts is typically low to minimise the cost of precious metal. These low catalyst concentrations hamper effective recovery as well. Despite this, given the potential toxic impact of the transition metal complexes involved, it is desirable to completely remove the catalyst from the product stream.^[33]

In heterogeneous catalysis, solid materials are used as catalyst. The reactants and catalysts are in different phases, as opposed to homogeneous catalysis. In heterogeneous catalysis, the reactants and products are in a liquid or gas phase and pass over the solid catalyst. After the reaction, the catalyst can be readily recovered by filtration or retained in fixed-bed reactors.^[30] The chemical reaction is catalysed by surface atoms onto which substrates adsorb. Upon adsorption, the substrate gets activated, weakening the chemical bonds within the substrate allowing the consecutive reaction steps to proceed with lower activation energy.^[30] Heterogeneous catalyst either consist of transition or noble metal nanoparticles immobilised onto a solid inert support to ensure high dispersion, or fully consist of catalytically active material where the whole surface of the catalyst is catalytically active, e.g. zeolites.^[30] The ratio of catalytically active surface atoms to the bulk atoms of the catalytically active material is known as the dispersion. The dispersion of the catalyst plays an important role in ensuring optimum catalytic performance, achieving the desired selectivity and minimising the total amount of costly material used. Fine-tuning the dispersion to achieve the desired catalytic properties can be achieved by careful selection of the catalyst support or preparation method for example. Though easily separable after the reaction, heterogeneous catalysts frequently

encounter mass transport and diffusional limitations of educts and products into and out of the catalyst pores.

Every so often, there is the desire to unify the benefits of both homogeneous and heterogeneous catalysis, *i.e.* having an a molecularly defined complex, achieving high selectivity, together with the ease-of-separability of the catalyst after the reaction. In general, this is a long-held dream within the catalytic community.^[34] In order to bridge the gap between both worlds, several strategies can be adapted. For example, a homogeneous catalyst can be ‘immobilised’ and recycled by carrying out the reaction in a biphasic medium. The catalyst resides in a different liquid phase during and/or after the reaction. In those cases, reaction often takes place at the liquid-liquid interface. However, usual heterogenous mass transport limitations can apply that can however be overcome by keen reaction engineering and process intensification.^[35-36] Also, there is the possibility to covalently link a homogeneous catalyst to a suitable support material. For example, the famous homogeneous *Grubbs* metathesis catalyst has been immobilised using a molecular linker that does not directly interfere with the catalytic performance, between the homogeneous catalyst and silica as support.^[37-38] Also, several polymeric support materials can be used to covalently link a catalytically active (organic) molecule to a suitable inert polymeric support.^[39-41]

2.3 State-of-the-art BD Production

Although catalysis has become an indispensable key technology in the chemical industry, there are still a few processes remain uncatalyzed. One of these processes is the thermal cracking of naphtha, a hydrocarbon mixture with chain lengths ranging from C_7 to C_{12} . Steam cracking of naphtha is currently the most important industrial process for the synthesis of BD.^[1] In a steam cracker, naphtha feedstock is fed into a tubular pyrolysis furnace, where long carbon chain molecules are “cracked” into shorter carbon chain length molecules at temperatures $T > 800$ °C.^[42] Steam is added to the mixture to suppress the formation of coke and to ensure a long time-on-stream (TOS) of the reactor.^[42] Thermal cracking of naphtha mainly results in a mixture of various chain length olefins.^[1, 16, 43] The main products of a steam cracking unit are ethene and propylene. BD and to some extent higher olefins, up to C_5 are also produced as by-product.^[19] A simplified flow-scheme of a steam cracking unit is visualised below in Figure 3.

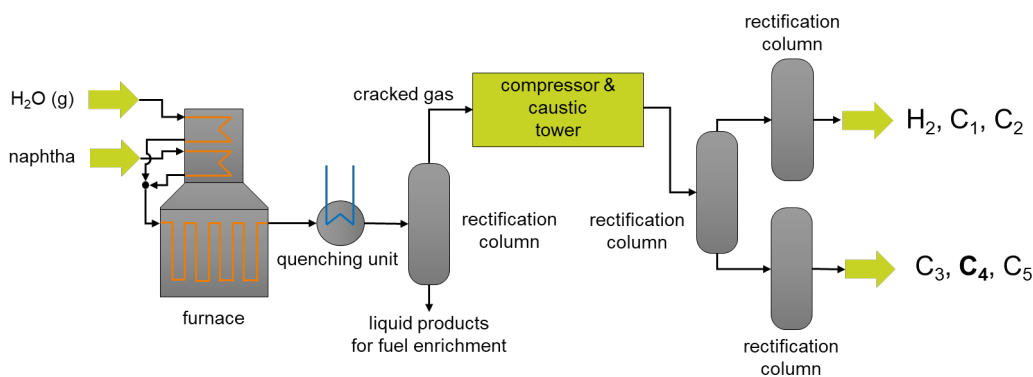


Figure 3: Schematic representation of a steam cracking unit, adapted from^[19].

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Depending on the desired products, either low- or high-boiling naphtha is fed into the tubular furnace arrangement of a steam cracker. The residence time inside the reactor, is kept very low, typically < 0.5 s, to prevent unwanted side-reactions like polymerisation and coking.^[19] With higher temperatures and short residence times of around 0.2-0.3 s, the so-called crack severity increases and more ethylene is produced. Consequently, the propylene-to-ethylene ratio decreases. For lower temperatures and longer residence times, more propylene is produced. After the tubular reactor arrangement, the high temperature pyrolysate is quickly quenched. This quenching takes place in two stages and prevents prevent the high temperature pyrolysate *i.e.* the highly reactive hydrocarbon mixture from further reacting.^[4] In the first stage, water is added which reduces the temperature of the pyrolysate to around 400 °C within 0.1 s. Quenching with water results in the production of large amounts of high-pressured steam, which can be recycled in the cracking process. In the second quenching stage, a quenching oil is used to further cool down the pyrolysate to around 200 °C. In the following rectifying units, liquid products for fuel enrichment and cracked gases are recovered, which need further purification.^[19]

Prior to purification *via* distillation, the cracked gases are compressed and subjected to a caustic treatment to remove hydrogen sulphide and carbon dioxide *i.e.* acidic gases. After a series of drying steps to remove residual water, low-boiling C_1 , C_2 and H_2 fractions are separated from the high-boiling C_3 to C_5 fractions. Ethylene is obtained after a set of cryogenic distillations. In order to obtain the C_4 hydrocarbon fraction containing BD, another set of distillations is required. Following this, the crude C_4 fraction is subjected to an extractive distillation (Figure 4).

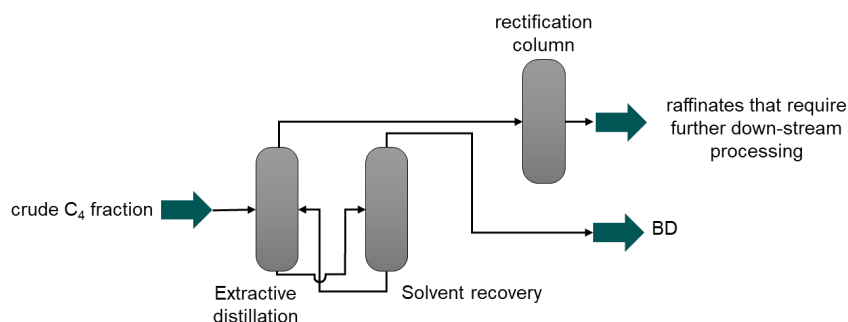


Figure 4: Schematic representation of the purification of the crude C_4 fraction to obtain BD as adapted from^[19].

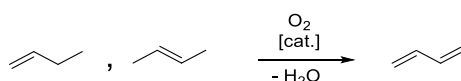
Around 50% of the crude C_4 stream is made up of BD. Besides BD, the C_4 stream contains *iso*-butylene, *iso*-butane as well as *n*-butene and *n*-butane. Due to the close boiling point of these compounds, as well as the fact that some of the compounds form azeotropes, a conventional distillation procedure is not possible. Hence, an extractive distillation is applied. Non-volatile, high-boiling solvents are added to the mixture in order to decrease the volatility of certain components in the mixture which makes them separable *via* distillation. In this specific case, solvents like dimethyl formamide or *N*-methyl pyrrolidone are added to the crude C_4 fraction to decrease the volatility of BD. The solvent/BD mixture is extracted from the bottom of the column, whereas the other components in the C_4 fraction are collected from the top fraction. In a second distillation unit, the solvent/BD mixture is separated to recover the solvent and obtain pure BD.^[1, 44] By using the extractive distillation approach, modern plants can reach up to 99-100% BD recovery from the crude C_4 stream.^[1, 3]

Based on the cracking conditions (*i.e.* crack severity) as well as the composition of the feedstock, the C₄ fraction contains varying amounts of BD.^[1, 3, 16] Whereas steam crackers using heavy feedstocks like naphtha and gas oils produce significant quantities of BD, steam crackers using lighter feedstocks like liquified petroleum gas and higher crack severities, produce only very low quantities of C₄ products that cannot be recovered economically.^[1, 16] As the main economic driving force of steam cracking remains the production of ethylene and propylene, many cracking operators seek to maximize the output of these lighter olefins at the expense of the heavier ones, including BD and other C₄₊ by-products. This has caused a shift in feedstock from heavier naphtha towards lighter ones.^[3-4] In the light of these unfavourable trends in naphtha-based BD production, as well as recent the developments in the methanol-to-olefin processes which do not generate BD, it is possible that a BD shortage may occur in the (near) future.^[1, 3] This would result in an associated increase in the BD price and, consequently, raise the cost in all products in the entire BD value chain.^[3, 45-46] Besides this, BD production is vastly unsustainable due to the energy intensive steam cracking process, the fossil based feedstock and the numerous purification steps needed to obtain pure BD. Consequently, the current situation poses a good starting point to explore the opportunities to develop and implement an on-purpose sustainable synthesis route to BD.^[5, 10, 47-48]

2.4 Alternative pathways to Butadiene

Besides the naphtha-based route for preparing BD, another fossil-derived production process is the so-called *Catadiene* process, where *n*-butane or a mixture of *n*-butane and *n*-butenes is catalytically dehydrogenated to BD.^[3-4, 49] Due to the increased efficiency in butane-rich liquefied petroleum gas extractions, the *Catadiene* could become increasingly important.^[10, 50] In the process, the feedstock is catalytically dehydrogenated at high temperatures of around 600-800 °C using supported chromium- or iron-based catalysts. Processes typically generate 30-40% BD yield and are mainly operated in China.^[50] The high temperatures, resulting in unwanted cracking reactions and coke formation, rapidly decreases the activity and selectivity of the catalysts, requiring frequent catalyst regeneration.^[50-51]

Another process for obtaining BD is the catalytic oxidative dehydrogenation (ODH) of butene (Scheme 2). This process is more promising compared to direct dehydrogenation *via* the *Catadiene* process.



Scheme 2: Schematic representation of the oxidative dehydration of *n*-butenes to BD.

As water is generated, the reaction is thermodynamically favourable. Furthermore, the reaction operates at much lower temperatures (300-400 °C), compared to the conventional dehydration.^[50] In the ODH, *n*-butenes or *n*-butane/*n*-butene mixtures are passed over vanadium oxide-based supported catalysts in fixed or fluidised bed reactors. These industrial processes, operated at near-ambient pressures by BASF-Linde or Mitsubishi Chemicals for example, run at 70-90% selectivity towards BD.^[52]

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Besides the already established industrial processes using (transition-)metal-based catalysts, research has been focussing on alternative catalyst.^[53-55] For example, *Schlögl* and co-workers reported 60% selectivity towards BD using commercially available carbon-nano tubes as catalyst.^[56]

However, the briefly reviewed alternative BD production processes are still reliant on butanes or butenes, which are predominantly obtained from steam cracking of naphtha and therefore do not serve the need for a sustainable alternative BD synthesis route. In order to achieve the objective of establishing a more sustainable chemical value chain, biomass is typically regarded as potential resource to replace fossil-based ones. In particular, bio-ethanol is currently already being manufactured on a large scale from renewable sources and biomass waste streams. It is regarded as a promising bio-fuel and alternative bio-based building block for a sustainable chemical industry.^[10]

2.5 Sustainably Sourced Butadiene from Ethanol

Bio-ethanol is predominantly obtained from the fermentation of agricultural biomass. In contrast to other renewable feedstocks, bio-ethanol is already a global commodity, with hundreds of billions of litres produced annually.^[3, 47] Currently, the US and Brazil are the largest producers of bio-ethanol, which is predominantly obtained from fermentation of sugar crops (corn and sugar cane respectively) *i.e.* first-generation biomass. Current production of bio-ethanol is therefore in competition with food production, which raises ethical concerns. On the other hand, second-generation biomass, which includes non-food lignocellulosic materials such as agricultural residues, can also be converted to bio-ethanol *via* fermentation, albeit in lower efficiencies. Third-generation biomass to ethanol fermentation focuses on algae, which grow faster and do not compete with food sources at all. Fourth-generation bio-ethanol relies on genetically modified algae to enhance production efficiency. Each generation shows technological advancements, with higher generations facing higher processing and production costs but lower environmental impacts.^[57-59]

Besides its use as drop-in fuel, bio-ethanol could become a versatile bio-based building block for the chemical industry. For example, bio-ethanol could have prominent use in the production of ethylene, using zeolite catalysts (e.g. H-ZSM-5) or γ -alumina.^[10, 60] Bio-ethanol can also be used as potential green building block for ethyl acetate and acetic acid.^[61-63] Another application is the production of *n*-butanol and other higher alcohols via the *Guerbet* reaction, which are used in detergents, cosmetics, and lubricants.^[63-67] Recently, the ethanol-to-butadiene pathway is re-gaining attention.

Historically, at the beginning of the 20th century before the era of petrochemistry, ethanol was the main feedstock for the catalytic BD production. *Lebedev* and *Ostromislensky* independently discovered that BD can be derived from ethanol and ethanol/acetaldehyde mixtures respectively. *Lebedev* showed that it was possible to convert ethanol into considerable amounts of BD, using a one-step process and a bifunctional catalyst with dehydrogenating and dehydrating activities.^[6-8]

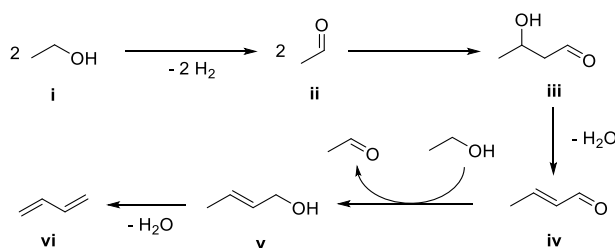


Scheme 3: Overall reaction scheme for the one-step *Lebedev* process for the production of BD from ethanol.

In the U.S., *Ostromislensky's* two step-process was intensively studied. Ethanol was first subjected to a partial dehydration to acetaldehyde using a copper catalyst, followed by the reaction of the ethanol/acetaldehyde mixture to yield BD.^[3, 5, 9] While the one-step *Lebedev* processes was commercialised in Russia, the two-step process was studied and commercialised by Union Carbide and Carbon Chemicals Corporation (UCC). One of the reasons for this, was that there were already sufficient catalysts available to dehydrogenate ethanol to acetaldehyde.^[68] Until the era of petrochemistry and the advance of naphtha steam cracking, starting in the years after the Second World War, both the *Lebedev* and *Ostromislensky* processes were economically viable. Currently, apart from a recently inaugurated demonstration plant in France, there are no industrial-scale *Lebedev* or *Ostromislensky* plants in operation, at least in the Western world.^[69]

2.5.1 Mechanistic Considerations for the Ethanol-to-BD Pathway

The generally accepted mechanism for both the one-step *Lebedev* or two-step *Ostromislensky* process is considered to be the same and is often referred to as *Toussaint–Kagan* pathway.^[9, 70-73] The mechanism consists of five steps and starts with the dehydrogenation of ethanol to acetaldehyde followed by the aldol condensation of acetaldehyde to 3-hydroxybutanal (acetaldol, **Scheme 4**, iii). Subsequently, the aldol product is dehydrogenated to 2-butenal (crotonaldehyde, **Scheme 4**, iv). *Toussaint* showed that direct addition of crotonaldehyde to the feed enhanced the formation of BD.^[74] Therefore, formation of crotonaldehyde is considered to be the rate-determining step. Crotonaldehyde is then reduced to 2-butenol (crotyl alcohol, **Scheme 4**, v). It has been debated in literature, if this reduction takes place using hydrogen as reductant or *via* a *Meerwein-Ponndorf-Verley* (MPV) reduction with ethanol as hydrogen donor. As it was found that the former reaction has a larger apparent activation energy together with the observation that the catalyst does not contain hydrogen activating functionalities, the MPV reduction remains most plausible. In the last step, crotyl alcohol is dehydrated to BD (**Scheme 4**, vi). Though this mechanism is generally accepted and widely used in thermodynamic considerations of the reaction and the process, it still remains under debate as for example acetaldol, one of the key-intermediates in the sequence, has never been observed *in-situ*.^[47, 75]

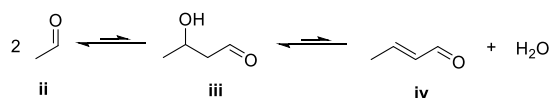


Scheme 4: Generally accepted *Toussaint–Kagan* pathway for the direct synthesis of BD (vi) from ethanol (i) over a heterogeneous catalyst.^[9, 70-73]

The fact that acetaldol is seldom detected in and has not been observed using *in-situ* spectroscopy, led *Cavani* to the development of a different mechanism.^[76] This is backed by an early observation of the engineers at UCC who showed that if acetaldol (**Scheme 4**, iii) was fed over the original Ta₂O₅/SiO₂ catalyst, it was converted back to acetaldehyde (ii) instead of being dehydrogenated to crotonaldehyde (**Scheme 4**, iv).^[77] Similarly, the self-aldolization of acetaldehyde (ii) was ruled out by *Meunier et al.* in their study on the gas-phase *Guerbet*

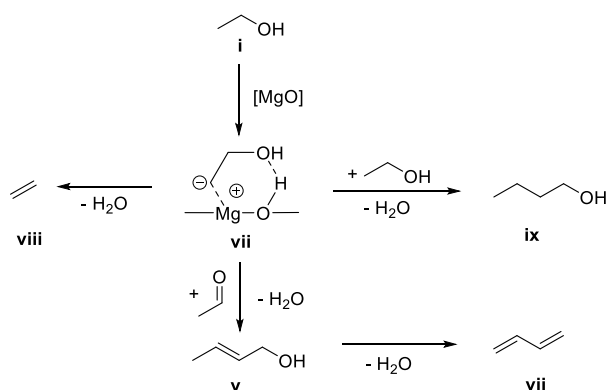
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reaction using a commercial hydroxyapatite catalyst.^[75] Therefore, according to *Cavani et al.* it is highly unlikely that the gas-phase *Guerbet* reaction or the *Lebedev* synthesis can have acetaldol (**iii**) as a key-intermediate (**Scheme 5**).^[3, 11, 47, 76, 78]



Scheme 5: For the reaction conditions used in the gas-phase *Guerbet* process, acetaldol, **iii** is mainly converted back to acetaldehyde, instead of being dehydrated to crotonaldehyde (**iv**).^[76, 78]

In order to gain insight into the ethanol-to-BD pathway, *Cavani* employed a combination of *in-situ* diffuse-reflectance infrared Fourier transform spectroscopy (DRIFTS), mass spectrometry (MS) and density functional theory (DFT). It was found that a carbanionic species of ethanol was formed as intermediate.^[76] This carbanionic species is thought to be stabilized by surface Mg cations (**Scheme 6, vii**).^[76, 78] The carbanion of ethanol can subsequently undergo a variety of reactions, including the dehydration to ethylene (**viii**), reaction with another molecule of ethanol to form 1-butanol (**Scheme 6, ix**) or reaction with a molecule of acetaldehyde, previously formed upon ethanol dehydrogenation, to afford crotyl alcohol (**v**). The crotyl alcohol would undergo dehydration into BD (**vii**) according to the same mechanism discussed earlier.^[9, 11, 48, 74, 76] The overall *Cavani* mechanism is shown in **Scheme 6**.^[76, 78]

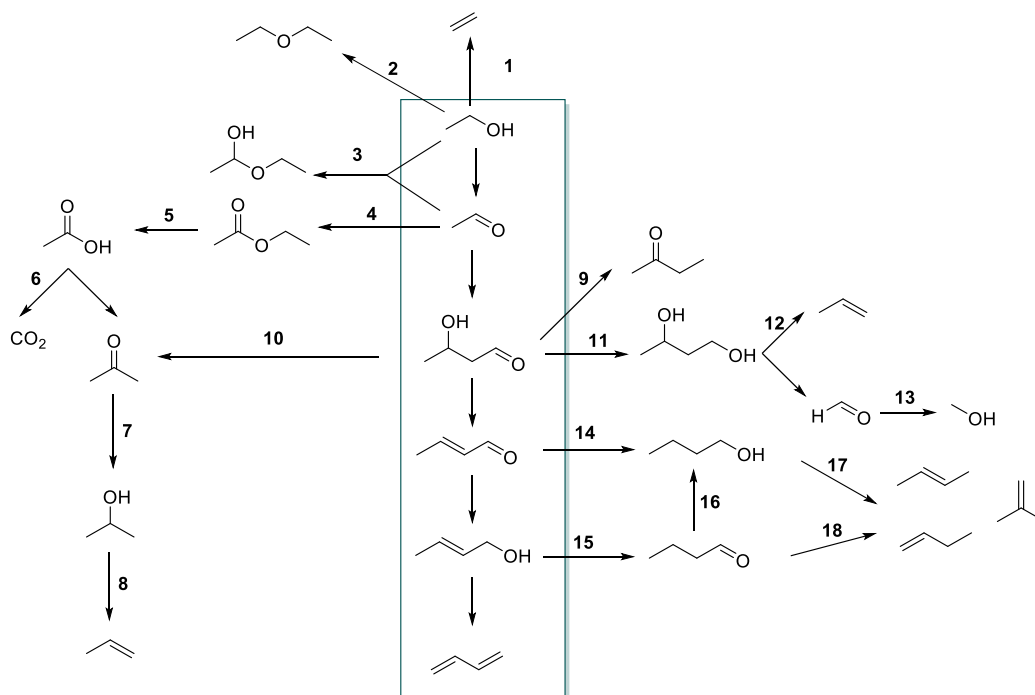


Scheme 6: Mechanism of the ethanol-to-butadiene pathway according to *Cavani*. The carbanion is stabilized by surface Mg cations. The need for formation of acetaldol as well as the MPV reduction, key intermediates and a key step in the earlier discussed *Toussaint-Kagan* pathway respectively, are omitted.^[76, 78]

As illustrated in the above scheme, the carbanion mechanism proposed by *Cavani* was suggested to take place on MgO containing catalysts. Within the reaction studies, ethylene and butanol were observed as main by-products.^[78] Regardless of the catalyst used, there are a number of by-products that emerge from a typical gas-phase ethanol-to-BD reaction.

2.5.2 By-product Spectrum of the Ethanol-to-BD Reaction

Already in the first studies carried out by *Quattlebaum*, *Toussaint* and *Dunn* at UCC, the quantification and identification of the by-products as well as their origin, received much attention.^[74] According to *Quattlebaum et al.* the by-products can be classified into two main groups. The first one consists side products that emerge upon dehydration and ester-forming reactions. The second class of side products consists of products formed *via* reactions similar to those in the generally accepted *Toussaint-Kagan* pathway (e.g. MPV reduction and dehydrogenation). A schematic overview of the most common by-products is shown in **Scheme 7**.



Scheme 7: Schematic overview of the reaction network in the ethanol-to-BD pathway. The boxed pathway represents the generally accepted *Toussaint-Kagan* pathway. The reaction network is adapted from^[5] and ^[11].

In the first category, ethylene as main by-product and diethyl ether can be found (**Scheme 7**, reaction **1** and **2**). Other by-products in the category are ethoxy ethanol (reaction **3**) as condensation product of ethanol and acetaldehyde, ethyl acetate as product of the *Tishchenko* reaction (**Scheme 7**, reaction **4**) and acetic acid as product of ethyl acetate hydrolysis (reaction **5**). As these reactions occur on acidic sites, they cannot be suppressed as the acidic sites and their dehydration activity are required for the formation of BD in the final step of the sequence. At reaction conditions, acetic acid can chemically decompose into CO₂ and acetone (reaction **6**). Formation of acetone as by-product is the most likely cause appearance of *iso*-propanol and ultimately propylene in the side product spectrum (reaction **7** and **8** respectively).

Methyl ethyl ketone (MEK, reaction **9**) can be grouped into the second category of by-products, as it can be formed from deoxygenation of acetaldol with subsequent rearrangement.^[79] Acetaldol can also be transformed into acetone, hydrogen and CO₂ in a reaction with lattice oxygen (reaction **10**).^[80-82] 1,3-Butanediol (1,3-BDO) can be formed upon acetaldol reduction (reaction **11**). Subsequently, 1,3-BDO can undergo cleavage into propylene and formaldehyde (**Scheme 7**, reaction **12**).^[79] Presence of methanol in the product spectrum can be explained by the dehydrogenation of formaldehyde (reaction **13**). Hydrogenation of croton aldehyde yields butanol (**14**). Butanol can be a result of the isomerization reaction of crotyl alcohol (**15**). Butanol can also be dehydrogenated to butanal (**16**). Dehydration of butanol as well as deoxygenation of butanal yield butenes (reaction **17** and **18** respectively).

Furthermore, aromatic compounds, soot and other hydrocarbon compounds can be formed upon decomposition and rearrangement reactions. For instance, aromatic compounds can be formed according to the methanol-to-olefins concept *via* ethers formed upon the reaction

with methanol.^[83] Among the other by-products not listed in the above scheme, soot is the most common and often considered as main cause of catalyst deactivation.^[12, 84-87]

Despite the complicated reaction mechanism and the numerous by-products that can be obtained, it is possible to direct the catalytic activity towards BD by carefully choosing the catalyst material, support and promoters which has resulted in some notable achievements in both *Lebedev* and *Ostromislensky* catalysis. Depending on various factors, like availability of substrate, investment costs for constructing an industrial plant as well as the geographic location (e.g. US, Brazil or Europe) either of the two could be more sustainable in a future setting.^[48, 88]

2.5.3 Catalytic Advances in the *Lebedev* Process

In the first patent by *Lebedev*, the catalyst was described as a mixture of zinc oxide and alumina, capable of yielding BD with a selectivity of 18%.^[6-8, 89] Further developments with respect to the catalyst, resulted in the industrial process with an apparent selectivity of up to 70% BD, although the exact composition of the catalyst remained undisclosed.^[90] It was not until after the Second World War, that an industrial *Lebedev* catalyst was analysed by UCC Carbide in the US and it was revealed that the industrial catalyst was composed of magnesia and silica (MgO-SiO₂), alongside numerous other elements in small amounts.^[9] Whilst screening multiple catalyst compositions, *Natta* and *Rigamonti* claimed to have disclosed the original *Lebedev* catalyst as a mixture of magnesium and silicon oxide prepared *via* wet-kneading. A yield of 42% at a selectivity of 51% was reported using a SiO₂/MgO/Cr₂O₃ catalyst at 400 °C, similar to earlier reports for the Russian process.^[6-8] Ethylene and butenes were observed as main by-products.^[91]

In the 1960s, the group around *Bhattacharyya* investigated the one-step *Lebedev* process and found that an Al₂O₃/ZnO catalyst was able to attain 56% BD yield at 425 °C. Furthermore, by changing the reactor from a packed-bed to a fluidized bed, the yield of BD could be increased to as high as 73%.^[92-93] *Bhattacharyya* reported an extensive preparation procedure for the catalyst, highlighting to avoid impurities like sodium and potassium hydroxides as precipitants and chloride or sulphate salts as precursors, as these compounds would leave impurities on the catalyst, negatively influencing its performance.^[92-93] On the contrary, *Kitayama* and *Michishita* reported that addition of as little as 0.1wt% sodium or potassium could substantially increase BD yield over MgO-SiO₂ catalysts.^[94-95] These beneficial effects contributed to an increase in BD yield to 87%.^[94]

Kvisle et al. compared single oxides of silica and magnesia, mechanically blended mixtures, and chemically mixed oxides. Their findings revealed that the chemically mixed MgO-SiO₂ catalyst exhibited higher activity and stability. Furthermore, chemically mixed catalysts were found to be more stable compared to single oxides with increasing time on stream.^[96] Also, it was found that in catalytic activity of the process strongly depends on the catalyst preparation.^[97] Despite these notable efforts, the catalytic activity of the pure MgO-SiO₂ materials did not exceed a productivity of 0.06 g_{BD}·g_{cat}⁻¹·h⁻¹ in the direct ethanol-to-BD process.^[5] It is considered, that the productivity of the catalyst should exceed 0.15 g_{BD}·g_{cat}⁻¹·h⁻¹ before becoming industrially relevant.^[11, 98] In this regard, higher productivities were reported for doped MgO-SiO₂ materials.^[98]

Very recently, *Winkelman et al.* reported a productivity of $0.12 \text{ g}_{\text{BD}} \cdot \text{g}_{\text{cat.}}^{-1} \cdot \text{h}^{-1}$ for a Na doped Ag/ZrO₂/SBA-16 catalyst at non-optimised reaction conditions, a 50% increase compared to the pristine Ag/ZrO₂/SBA-16 catalyst. Given the fact that the pristine Ag/ZrO₂/SBA-16 catalyst was able to attain a BD productivity of $0.4 \text{ g}_{\text{BD}} \cdot \text{g}_{\text{cat.}}^{-1} \cdot \text{h}^{-1}$ at optimised reaction conditions suggest that even higher productivities can be attained for the doped catalyst, though these experiments were not reported.^[99]

It has been demonstrated that promoters employed in mixed-oxide catalysts for the one-step process have the ability to suppress catalyst coking and reduce the undesirable ethanol to ethylene dehydration, resulting in an enhanced BD productivity. As pointed out earlier, the dehydration of ethanol to ethylene is the main substrate-competing reaction in the one-step process. In this regard, the two-step *Ostromislensky* process offers advantages as not pure ethanol but rather ethanol/acetaldehyde mixtures are subjected to the catalyst with dehydration properties (see Scheme 6).

2.5.4 Catalytic Advances in the *Ostromislensky* Process

Whereas the *Lebedev* process can be catalysed by MgO-SiO₂-based catalysts, investigations on the two-step *Ostromislensky* process, mainly focus on group 4 and 5 transition metal oxides doped or promoted with several other metals, like Zr^[100-101], Cr^[93, 100] or Ta^[100]. It is assumed that the Lewis acidic properties of group 4 and 5 transition metal oxides are the source of catalytic activity.^[5] In the industrialised *Ostromislensky* process, the first dehydration step proceeds over a Cu-based dehydration catalyst. Research mainly focusses on artificial ethanol/acetaldehyde mixtures and primarily targets the conversion of these mixtures to BD. Therefore, in this section, the catalytic achievements will mainly focus on the second step of the *Ostromislensky* process *i.e.* converting mixtures of acetaldehyde and ethanol to BD.

Historically, the two-step process was mainly operated in the US, where it was licensed by UCC in the 1940s. Researchers at UCC discovered that when a 3:1 ethanol/acetaldehyde mixture was fed into a fixed bed reactor with a silica gel-supported Ta₂O₅ catalyst at $T = 350^\circ\text{C}$ and ambient pressures, a BD efficiency of approximately 64% could be achieved. This resulted in the development of an industrial process with a capacity of 750,000 t BD in 1945.^[3, 5, 9, 102]

In the 1950s, *Corson et al.* found that Hf promoted SiO₂ was active in the two-step production of BD as well.^[100] Best results (64% BD yield) were attained when feeding a 2.75:1 ethanol/acetaldehyde mixture at 300 °C over a 2% HfO₂/SiO₂ catalyst in a fixed bed operation. Unfortunately, based on the data in the original publication, no catalyst productivity can be calculated.^[100]

In the light of the recent developments in the ethanol-to-BD research, the *Ostromislensky* process regained attention. For example, *Cadran and Chaumonnot* reported that Ta and Nb oxides supported on silica gel doped with zinc oxide, could improve BD production in both the *Lebedev* and *Ostromislensky* process to a maximum of $1.02 \text{ g}_{\text{BD}} \cdot \text{g}_{\text{cat.}}^{-1} \cdot \text{h}^{-1}$.^[3, 103]

Cheong et al. used a meso cellular silica foam (MCF) prepared in a urea hydrolysis method to avoid concentration gradients of the precipitants in the solution. Using this 2.7% Zr/MCF catalyst for converting a 1.38:1 ethanol/acetaldehyde mixture to BD, a BD productivity $1.4 \text{ g}_{\text{BD}} \cdot \text{g}_{\text{cat.}}^{-1} \cdot \text{h}^{-1}$ at a selectivity of 73% was reached.^[104] When using isolated Yt sites grafted

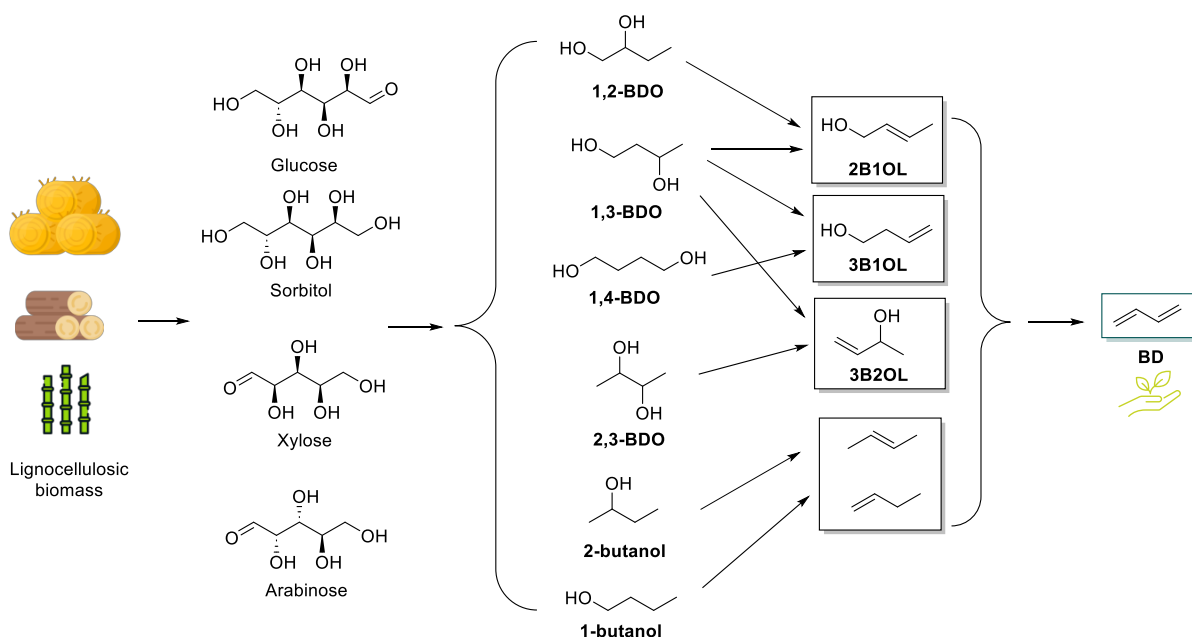
onto dealuminated β -zeolite, *Qi et al.* were able to attain a BD productivity of $6.6 \text{ g}_{\text{BD}} \cdot \text{g}_{\text{cat}}^{-1} \cdot \text{h}^{-1}$ with a BD selectivity of 64% at comparable reaction conditions to *Cheong* and co-workers.^[105] To the best of our knowledge, this productivity is the highest reported in literature for the two-step *Ostromislensky* process. However, the catalyst quickly deactivated, presumably due to extensive coking within the first 40 minutes TOS.

Besides the achievements made regarding the conversion of ethanol, ethanol/acetaldehyde mixtures and even aqueous ethanol^[106-109] to BD, recently, substantial work has gone into BD production from biomass derived diols.

2.6 Butadiene Derived from other Bio-Based C₄ Alcohols

Apart from ethanol as bio-based drop in alternative for BD synthesis, C₄ alcohols have gained increasing research interest in recent years as well. Various biomass derived alcohols like 1- and 2-butanol as well as 1,2- 1,3-, 2,3-, and 1,4-butanediol (BDO) have been studied as feedstock for BD production. The advantage of C₄ alcohols over ethanol that these alcohols already have a C₄ skeleton, hence no C–C bond formation is needed. Most of these C₄ alcohols are predominantly prepared from fossil resources.^[19, 110] For example, 1-butanol is an important solvent in the chemical industry and starting material for the synthesis of *n*-butyl phthalate. Currently, 1-butanol is prepared from the hydrogenation of the respective aldehyde, prepared through hydroformylation of propylene.^[19] 1,4-butanediol is also an important building block for the chemical industry, for example for the preparation of polyesters, polyurethanes and THF.^[19]

Apart from being produced from fossil resources, C₄ alcohols can also be prepared from the fermentation of sugars, obtained after hydrolysis of lignocellulosic biomass.^[111] Furthermore, *n*-butanol can be produced from fermentation of starch and glucose, using *Clostridium acetobutylicum* in the *ABE* fermentation.^[112-114] Also, acetogenic microorganisms can convert synthesis gas into alcohols like ethanol and 2,3-butanediol, when kept under anaerobic conditions.^[115] Recently, the preparation of 1,3-, 1,4- 2,3-BDO as well as 2-butanol from glucose has gained research interest. Especially these diols have great potential for being used as sustainable feedstock for the production of BD^[116-119] **Scheme 8** illustrates the synthesis of bio-based C₄ alcohols, starting from lignocellulosic biomass, and their potential conversion to BD.

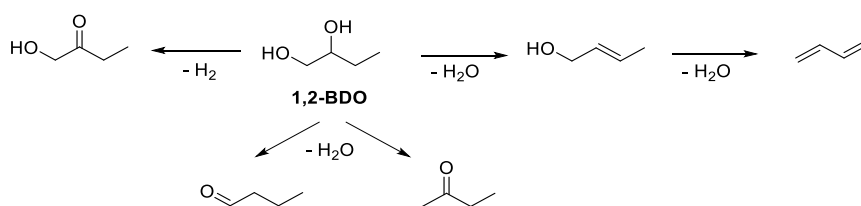


Scheme 8: Possible routes to sustainable BD prepared from biomass derived C₄ alcohols, as adapted from^[110] and^[120]. Lignocellulosic biomass (e.g. wheat straw, wood waste) is hydrolysed to various bio-based sugars that are fermented using metabolically engineered bacteria to produce the C₄ alcohols listed.

Among the microbial prepared C₄ alcohols, diols are considered as most suitable renewable feedstock for the on-purpose synthesis of BD. *Genomatica* and *Versalis* identified fermentation derived butanediols as most sustainable precursor for BD synthesis.^[121] As previously outlined in this work, the potential for converting butanols into BD *via* oxidative dehydration of butenes is already established on an industrial scale. In the following, the dehydration of various bio-based C₄ diols to produce BD will be highlighted.

2.6.1 Dehydration of 1,2-BDO

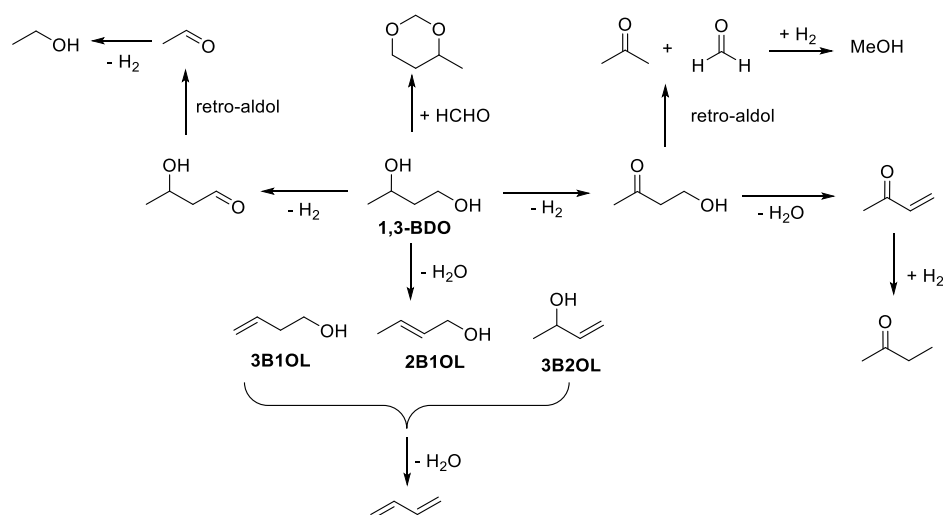
Among the possible routes to convert bio-based C₄ diols into BD, the least research effort has gone into converting 1,2-BDO to BD. For example, *Ott et al.* studied the 1,2-BDO dehydration in supercritical water. Although the main goal of the study was to investigate the dehydration of 1,2-BDO to *n*-butyraldehyde, it was put forward that BD oligomers might be among the reaction products, explaining operational problems (*i.e.* clogging) of the experimental setup.^[122] Recently, *Ai* and co-workers found that 1,2-BDO dehydration of H-Beta zeolite catalysts produced BD in a selectivity of 20% as well as butanal in a selectivity of 50%.^[123] Very recently, *Inaba et al.* reported a selectivity of almost 60% in the dehydration of 1,2-BDO to BD using a silica-supported caesium phosphate catalysts.^[124] A comprehensive reaction network for the dehydration of 1,2-BDO to BD and other identified side products is shown below in **Scheme 9**.



Scheme 9: Possible pathway to convert 1,2-BDO into BD as well as some of the by-products as identified in literature.^[122-124]

2.6.2 Dehydration of 1,3-BDO

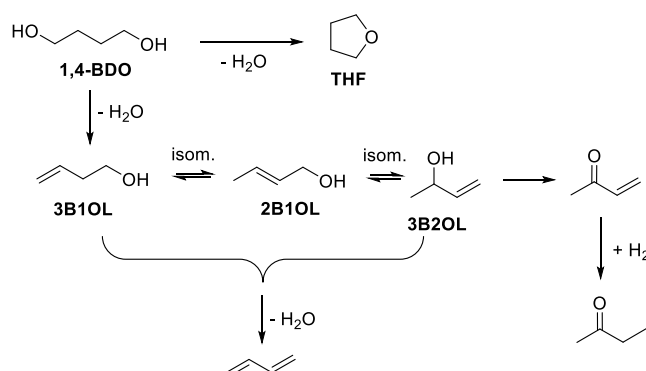
Compared to the dehydration of 1,2-BDO, the double dehydration of 1,3-BDO appears a more promising approach for the on-purpose synthesis of BD. In fact, the acid-catalysed double dehydration of 1,3-BDO has already been employed on an industrial scale to convert 1,3-BDO to BD in the acetylene-based route in the first half of the 20th century.^[5, 102] The reaction is catalysed by various (solid) acids, metal salts and acid anhydrides. Literature on 1,3-BDO dehydration to BD is ample.^[120, 125-127] For example, *Wellman* reported the gas-phase dehydration of 1,3-BDO over aluminium phosphate catalysts at 285 °C already in 1938.^[128] It was found that the reaction proceeds stepwise, *via* the unsaturated 3-buten-1-ol (3B1OL). By collecting and recycling the 3B1OL after the first dehydration step and recycling it back into the reactor, BD yields could be improved to up to 90%.^[128] By using different commercially available metal oxides, *Ichikawa et al.* showed that the catalytic activity was dependent on the acid strength. Strong acid metal oxide catalysts like SiO₂ and Al₂O₃ catalysed the dehydration of 1,3-BDO into the corresponding unsaturated alcohols 3B1OL, 2-buten-1-ol (2B1OL) and 3-buten-2-ol (3B2OL) which are further dehydrated into BD. Weaker acid catalysts like ZrO₂ and TiO₂ on the other hand also promoted side reactions such as hydrogenation and dehydrogenation, resulting in a complex product spectrum (**Scheme 10**).^[129-130]



Scheme 10: Schematic overview of the dehydration of 1,3-BDO into BD *via* the corresponding unsaturated alcohols 3B1OL, 2B1OL or 3B2OL, as well as some of the possible side products.^[120, 129-130]

2.6.3 Dehydration of 1,4-BDO

It is well-known that whenever 1,4-BDO is subjected to an acidic dehydration, THF is formed.^[131] The reaction has been demonstrated for numerous acid catalysts and is currently carried out on a commercial scale in the gas phase at temperatures between 250 and 320 °C using solid acid catalysts.^[126, 132-133] The production of BD from THF, is more endothermic and requires higher temperatures.^[134] A more straight-forward route is the double 1,2-elimination forming 3B1OL as intermediate using a suitable catalyst, to effectively dehydrate 1,4-BDO to the corresponding unsaturated alcohol (**Scheme 11**).^[120]



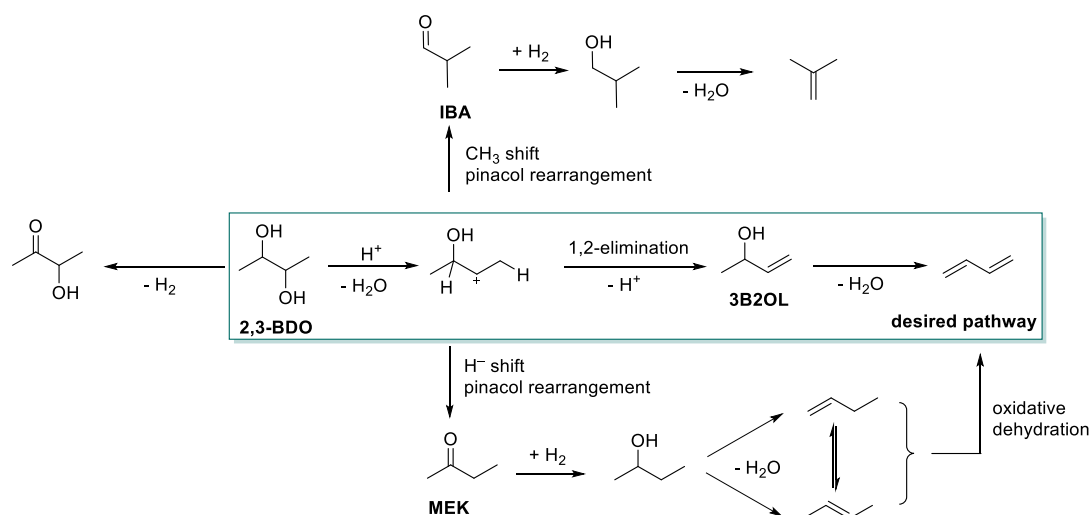
Scheme 11: Simplified overview of the double dehydration of 1,4-BDO into BD as well as some of the most probable side products.^[110, 135-137]

For example, neutral to basic phosphate catalysts are known for the dehydration of 1,4-BDO to the corresponding unsaturated 3B1OL, which can be readily dehydrated to butadiene over various other catalysts.^[120, 138] Furthermore, *Matsuda et al.* studied the double dehydration of 1,4-BDO over several rare-earth oxide (REO) catalysts. Especially, Y₂Zr₂O₇ prepared through hydrothermal aging (HT) resulted in complete conversion of 1,4-BDO with a BD selectivity of 93% at 360 °C. The Y₂Zr₂O₇ catalyst, calcined in air at 700 °C prior to the reaction, was found to have a stable performance over 10 h TOS using N₂ as carrier-gas in a fixed-bed reactor.^[136-137]

2.6.4 Dehydration of 2,3-BDO

Besides 1,4- and 1,3-BDO, 2,3-BDO is also extensively studied as renewable feedstock for BD. Among the C₄ diols mentioned earlier, especially the demand for 2,3-BDO is remarkably increasing. So far, 2,3-BDO can be readily prepared from synthesis gas fermentation by acetogenic organisms, also microbial production of 2,3-BDO from biomass (waste) streams is gaining attention.^[120, 139] Besides this, 2,3-BDO could be prepared *via* the self-acyloin condensation reaction of acetaldehyde. The latter could in theory be prepared from (bio-) ethanol.^[140-141]

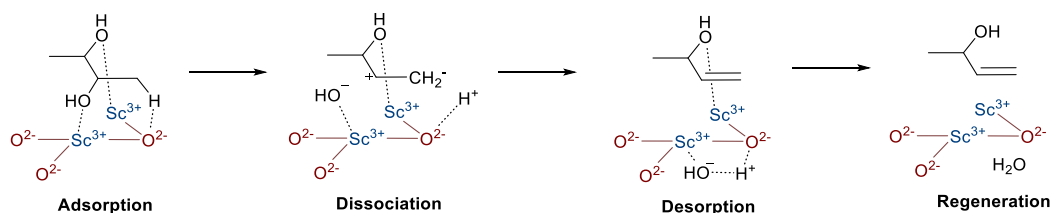
However, when it comes to the dehydration of 2,3-BDO, several hurdles have to be overcome. Owing to the nature of the molecular structure, dehydration of 2,3-BDO is more difficult compared to dehydration of 1,3- or 1,4-BDO. Most processes result in substantial amounts of 2-butanone (methyl ethyl ketone, MEK) or 2-methylpropanal (*iso*-butyraldehyde, IBA). Both side products emerge from the pinacol rearrangement of the formed carbocation after the first acid catalysed dehydration, in this case an H⁻ shift to eventually yield MEK or by a CH₃ shift to yield IBA. Unfortunately, both MEK and IBA cannot be easily converted into BD (**Scheme 12**).^[142-144] In case of MEK, a hydrogenation to 2-butanol and subsequent dehydration to the internal butenes would be possible. As discussed earlier, butenes can be converted to BD *via* oxidative dehydrogenation.^[145] Hence, in the BD production from 2,3-BDO, it is very important to suppress the formation of MEK and IBA as well as to promote the generation 3B2OL.^[120, 146-149]



Scheme 12: Possible reaction pathways for the dehydrogenation of 2,3-butanediol towards 1,3-butadiene *via* 3B2OL as intermediate as well as possible the unwanted side reactions that can occur, resulting in either 3-hydroxy-2-butanone (acetoin), methyl ethyl-ketone (MEK), *iso*-butylaldehyde (IBA), *iso*-butylene, butanols as well as butenes. As indicated in the above scheme, only the 1,2-elimination of H₂O proceeding *via* 3B2OL as intermediate results in the effective formation of BD.^[120, 146-148]

Already in 1945, *Winfield* described the catalytic dehydration of 2,3-BDO to BD over ThO₂ catalysts achieving 60% single pass-conversion with 80% selectivity to BD. Many years later, in 2014, *Duan et al.* discussed several REO catalysts for the selective dehydration of 2,3-BDO to 3B2OL.^[142] Apart from radioactive ThO₂ as catalytically active material, various REOs have been found to show activity in the dehydration of 2,3-BDO towards 3B2OL with Sc₂O₃, In₂O₃ and ZrO₂ showing the best results at $T > 300$ °C.^[142, 147, 150-152] Among them, Sc₂O₃ was found to have the highest activity and selectivity towards 3B2OL.

The mechanism for the dehydration of 2,3-BDO to 3B2OL was postulated by *Duan et al.* and involves both the acidic (cationic metals) and basic (oxide O²⁻) groups of the rare-earth metal oxide (**Scheme 13**).^[153]



Scheme 13: Postulated mechanism for the dehydration of 2,3-BDO to 3B2OL exemplarily illustrated using a Sc₂O₃ catalyst with acidic Sc³⁺ and basic O²⁻ concerted active sites.^[153]

As shown in **Scheme 13**, the mechanism of dehydration proceeds *via* four key steps: adsorption, dissociation, desorption and regeneration of the catalytically active site, liberating 3B2OL and H₂O. Initially, the hydroxide groups of 2,3-BDO interact with the Lewis acidic metal cation. The hydrogen atom from the methyl group interacts with the basic O²⁻ ion, forming a tridentate coordination. Followed by this, the basic O²⁻ abstracts the hydrogen atom from the methyl group, creating a CH₂⁻ anion followed by the elimination of the OH⁻ on the acidic Sc³⁺ site. It is assumed by *Duan et al.*, that the formation of the C⁺/C⁻ results in C=C bond formation resulting in 3B2OL production. The final step involves the liberation of the 3B2OL and the H₂O produced from acid-base pair sites.^[153] The mechanism remains speculative

though, and is not backed by computational calculations. Especially the formation of the C^+/C^- intermediate in the dissociation step (Scheme 13) is highly speculative.

Another possible mechanism involves the adsorption of both OH groups to form a bidentate adsorption on the acidic Sc^{3+} and O^{2-} site (exemplary for acid and basic sites). This pathway could explain the formation of MEK as well as IBA *via* acid catalysed formation of the respective carbocation during the dissociation step. In fact, when using (solid) acids as catalyst, for example zeolites with strong acidic sites, mainly MEK was observed upon 2,3-BDO dehydration.^[154] Hence, in order to obtain high BD yields from 2,3-BDO dehydration, it is necessary to promote the selective dehydrogenation to 3B2OL and to suppress the pinacol rearrangement.

Duan from the Sato group in Japan reported excellent 2,3-BDO conversion ($X > 99\%$) at a selectivity of $S = 94\%$ towards butadiene at $T = 318\text{ }^{\circ}\text{C}$ using commercially obtained and calcined Sc_2O_3 and as-obtained Al_2O_3 .^[155] However, a few years later, Zeng *et al.* were not able to reproduce these results. At comparable reaction conditions, BD was obtained in 30% selectivity. MEK was the main reaction product with about 55% selectivity at a 2,3-BDO conversion of $X > 99\%$. Zeng *et al.* reported a maximum in selectivity of 60% at $375\text{ }^{\circ}\text{C}$ for a dual bed catalytic system comprising of Sc_2O_3 in the first and Al_2O_3 in the second bed, using H_2 as flow-gas.^[151]

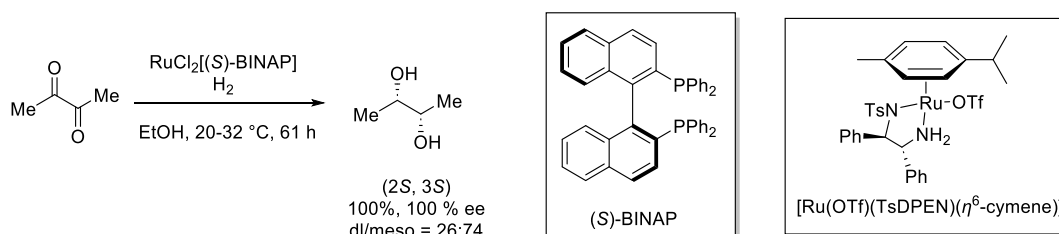
Following these contradictive results in literature, Nakazono, working at the same Sato group, reported a method for preparing Sc_2O_3 *via* hydrothermal synthesis (HT) of scandium-oxyhydroxide which is then annealed to Sc_2O_3 .^[147] Notably, in the same publication, Nakazono *et al.* were also unable to reproduce the earlier reported results with respect to 3B2OL selectivity using commercial-grade Sc_2O_3 as catalyst. This contradictive result was attributed to the lack of crystallinity in commercially obtained samples.^[147] Despite extensive catalyst development, characterisation and optimising the Sc_2O_3 catalyst obtained through HT synthesis and subsequent calcination in air at $800\text{ }^{\circ}\text{C}$, use of this HT-800- Sc_2O_3 catalyst in a dual bed catalytic approach was not reported by the group of Sato. Instead, they reported the direct preparation of BD ($Y = 80\%$) using the developed HT-800- Sc_2O_3 at a low weight-hour-space-velocity (WHSV) of 0.4 h^{-1} at a temperature of $411\text{ }^{\circ}\text{C}$. Furthermore, as flow gas for the reaction, N_2 was used at $1.8\text{ dm}^3\cdot\text{min}^{-1}$. When using H_2 as a flow gas, lower conversions and selectivities but longer catalyst stabilities were obtained. For the latter observation, an amendable explanation was given by the suspected suppression of coke formation due to the reductive atmosphere inside the reactor.^[147] On the contrary, for the dual bed catalytic dehydration of 2,3-BDO to BD over Sc_2O_3 and Al_2O_3 , investigations of different flow gases revealed that H_2 was beneficial for the productivity of the system.^[155] Being intensively studied, 2,3-BDO is regarded as promising substrate for the on-purpose BD synthesis.

2.7 Hydrogenation Reactions to Obtain Diols

As mentioned previously, 2,3-BDO is available from biomass (waste) streams through hydrolysis and subsequent fermentation of the obtained bio-based sugars. For the efficient fermentation of these sugars, genetically engineered bacteria are required.^[156] Fermentative processes to obtain 2,3-BDO are currently not competitive with the established petrochemical route, starting from 2-butene.^[19, 157]

On the other hand, diols can be readily obtained from the hydrogenation of corresponding diketones or hydroxy ketones. As these diols have chiral centres, the selective asymmetric hydrogenation as well as transfer hydrogenation of diketones and activated α -hydroxy ketones to yield chiral diols has received much research attention.^[158-160]

For example, *Noyori* and *Takaya* studied the asymmetric hydrogenation of acetylacetone using a homogeneous $\text{RuCl}_2[(R)\text{-BINAP}]$ catalyst in 1988. A 99:1 mixture of (2*R*,4*R*)-diol and *meso*-diol was obtained with a 1,3-diketone as substrate. With the [(*S*)-BINAP] ligand and 1,2-diacetyl as substrate, a 26:74 mixture of the (2*S*,3*S*)-BDO and *meso*-BDO was obtained (**Scheme 14**).^[161-162]

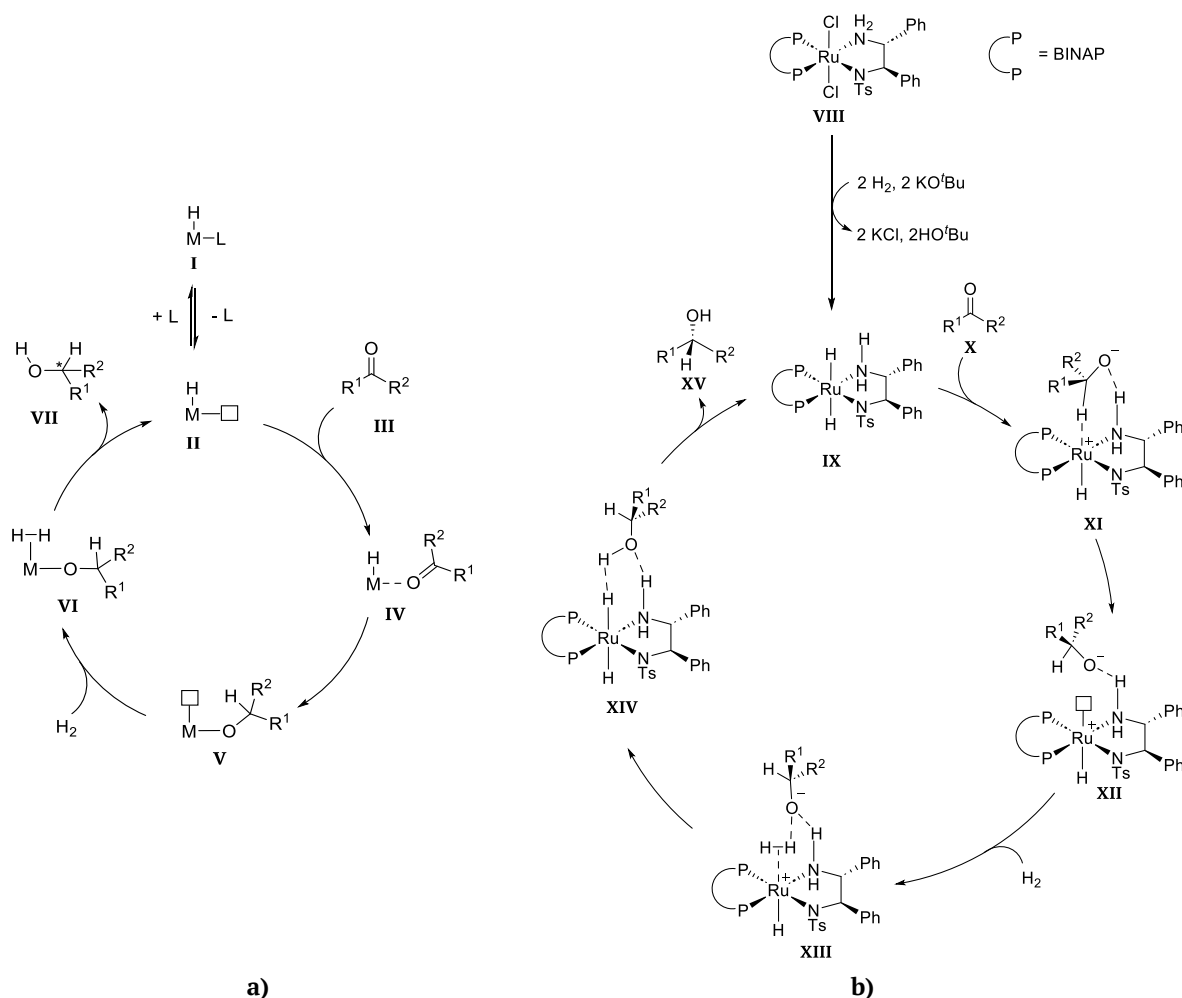


Scheme 14: Hydrogenation of diacetyl to (2*S*,3*S*)-BDO using a homogeneous $\text{RuCl}_2[(S)\text{-BINAP}]$ catalyst at ambient temperatures as reported by *Noyori* and *Takaya* on the left-hand side, as well as the $[\text{Ru}(\text{OTf})(\text{TsDPEN})(\eta^6\text{-cymene})]$ complex used by *Wang* and co-workers for a similar hydrogenation reaction.^[161-162]

Wang et al. used $[\text{Ru}(\text{OTf})(\text{TsDPEN})(\eta^6\text{-cymene})]$ (TsDPEN = *N*-tosyl-1,2-Diphenyl-1,2-ethylenediamine) which is commonly used in asymmetric transfer hydrogenation. The catalytic performance of $[\text{Ru}(\text{OTf})(\text{TsDPEN})(\eta^6\text{-cymene})]$ for the hydrogenation of aromatic 1,2-diketones was significantly higher than that of $\text{Ru}/[\text{BINAP}]$ catalyst, which mainly led to the formation of *meso*-products.^[162]

Wu et al. investigated a highly active Iridium/*f*-Amphox catalyst (*f*-Amphox = ferrocene aminophosphoxazoline) in the hydrogenation of various α -hydroxy ketones to afford the corresponding chiral diols with excellent results > 99% yield and > 99% *ee*. The catalytic system displayed extremely high activity, achieving a turn-over-number (TON) of 1 000 000.^[163]

In general, homogeneous hydrogenation reactions can proceed *via* two different mechanisms. Electron transfer is either facilitated through an inner sphere or outer sphere mechanism. This inner sphere mechanism, starting from a monohydride metal complex, is schematically shown in **Scheme 15a**. The representation of an outer-sphere mechanism, where the ligand environment assists in splitting of dihydrogen, e.g. the *Noyori-Ikariya*-mechanism, is shown in **Scheme 15b**.



Scheme 15a): Schematic representation of the inner-sphere hydride mechanism for the hydrogenation of a ketone with molecular hydrogen as well as **b)** The *Noyori-Ikariya* mechanism as example of an outer-sphere hydrogenation of a prochiral ketone. As opposed to the inner-sphere mechanism, hydrogen transfer is assisted by the ligand environment. The square represents a vacant coordination site at the metal centre. Depending on the R-groups R^1 and R^2 , a new stereo-centre (*) is generated. Mechanisms **a)** and **b)** as adapted from ^[158] and ^[164].

As can be seen in **Scheme 15a**, the catalytically active complex **II**, is generated upon ligand dissociation from the precursor **I**. Apart from ligand dissociation, this activation can also proceed by adding a strong basic co-catalyst, to generate a vacant coordination site by liberation of a halogen (X) from precursor **I**, in the case where $\text{L} = \text{X}$. The ketone **III** coordinates to the metal centre **IV** and undergoes migratory insertion into the $\text{M}-\text{H}$ bond to form intermediate **V**. Molecular hydrogen (H_2) coordinates to the vacant site (**VII**) and undergoes heterolytic bond cleavage to generate the hydrogenated product **VII** and the unsaturated metal complex **II** that can re-enter the catalytic cycle.^[158]

The outer sphere *Noyori-Ikariya* mechanism in **Scheme 15b**, starts with liberation of two Cl ligands by interaction with a strong base, like KO^tBu in the presence of H_2 . This ultimately yields the catalytically active complex dihydro complex **IX**. Due to the ligand environment, the complex is prochiral. Enantioselective addition of ketone **X** results in formation of complex **XI**. As opposed to the inner-sphere mechanism in **Scheme 15a**, the outer-sphere mechanism does not have direct a metal-O bond. Transfer of a hydride from the dihydrido complex to the carbonyl carbon atom, leads to formation of complex **XII** with cationic metal centre and a vacant coordination site. Molecular H_2 coordinates to the vacant site (**XIII**) and

undergoes bond cleavage (**XIV**). Ultimately, the hydrogenated chiral product **XV** is liberated and the prochiral dihydrido complex **IX** is regenerated.

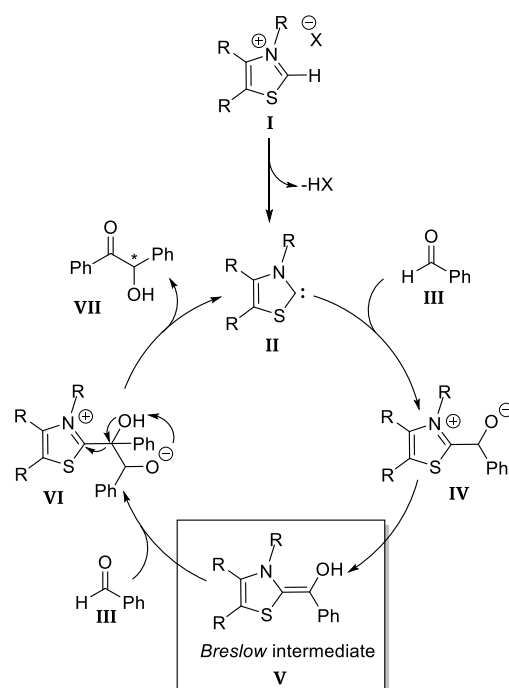
Apart from homogeneous transition metal complexes, several heterogeneous catalysts have been reported as well, even for the enantioselective hydrogenation of activated ketones. Chiral Pt nanoparticle catalyst developed by *Xue et al.* are able to attain excellent *ee* > 99% and conversions > 99% at low H₂ pressures and near ambient temperatures (*T* = 30 °C) in the hydrogenation of activated ketones (e.g. 1,1-dimethoxyacetone).^[165] Despite some of these notable advances in the asymmetric hydrogenation of (activated) ketones, *Tecnalia* has developed an alternative approach. A method for the non-stereospecific production of 2,3-BDO from 3-hydroxy-2-butanone (acetoin) has been patented.^[166] This method employs a carbon-supported ruthenium catalyst (Ru/C), which can be deployed in both batch and continuous-flow processes. Notably, this process attains 2,3-BDO yields > 99%, rendering it highly efficient for industrial applications.^[166] On the other hand, *Nakazono et al.* reported in 2022, that a nickel catalysts on SiO₂ support prepared through citric acid precipitation, outperformed a commercial Ru/C catalysts in the vapour phase pressureless flow hydrogenation of acetoin to 2,3-BDO. At temperatures of 150 °C, a 5wt% commercial Ru/C catalyst was able to attain 87% acetoin conversion at a 2,3-BDO selectivity of 88%, whereas the citric acid assisted precipitated 2wt% Ni/SiO₂ catalyst was able to attain 91% conversion at > 99.9% selectivity.^[167] Though the starting substance acetoin has been considered by the U.S. Department of Energy as potential platform chemical for a bio-based economy, its general use has been hampered by its high price.^[168]

2.8 Upgrading of Aldehydes to Acyloin Compounds

Acetoin, one of the simplest acyloin (*i.e.* α -hydroxy ketone) compounds, is commonly derived from fermentation processes.^[169-170] The most efficient acetoin production process with a capacity of 2 g·dm⁻³·h⁻¹, relies on a pathogenic bacterium, increasing production cost and consequently hindering the use of acetoin as bio-based platform chemical.^[169-171] A cost-effective, yet sustainable chemical route to attain higher productivities is underexploited in literature.

On the other hand, the preparation of α -hydroxy ketones in general, is well studied.^[172-177] In this context, *N*-heterocyclic carbene (NHC) catalysts are used to couple two aldehyde molecules at the α -position, hence inverting their classical reactivity in condensation reactions (*Umpolung*).^[178] NHC catalysed *Umpolung* reactions offer a mild and selective approach for preparing α -hydroxy ketones from aromatic and long-chain alkyl aldehydes. As the product of the reaction contains a newly formed stereo centre, the reaction has become a useful synthetic tool for enantioselective inter and intramolecular coupling reactions for the preparation of various biomolecules, antibiotics, α,β -dihydroxylated acids and other useful organic building blocks.^[179-180]

In particular, the NHC-catalysed benzoin condensation has been extensively studied. The postulated catalytic cycle is shown below in **Scheme 16**.^[175, 181-182]



Scheme 16: Mechanism of the *N*-heterocyclic carbene catalysed benzoin condensation as proposed by Breslow. As product of the benzoin condensation, a new stereo-centre (*) is generated.^[181-182]

Upon deprotonation of the thiazolium salt **I** with a suitable base, the catalytic active carbene species **II** is generated. The carbene acts as a nucleophile and attacks the aldehyde **III** at the carbonyl position to generate a thiazolium salt adduct **IV**. Subsequent deprotonation and re-protonation generate the resonance stabilized Breslow intermediate **V**. This nucleophilic synthon reacts with another aldehyde **III** to form intermediate **VI**. From this, the product **VII** is eliminated and the active carbene species **II** is regenerated.^[181-182]

The NHC-catalysed self-addition of acetaldehyde to form acetoin is barely exploited in literature. However, this reaction could fill the void in the need for a highly productive and cost-effective acetoin production process. For the acetaldehyde self-coupling it has already been shown that NHC-based catalysts offer efficient and to some extent even recyclable approaches: Zhang *et al.* reported that homogeneous thiazolium salts could be used for up to three cycles, using a solid-base to form a recyclable catalyst-base-adduct.^[140-141] However within the recycling pathway, yields towards acetoin decreased from 98% to 55%. On the other hand, polymeric (supported) imidazolium salts have been reported in literature for similar aldehyde self-coupling reactions for both batch and continuous-flow applications.^[183-185] Chen *et al.* have shown that polystyrene (PS) supported imidazolium salts can act as catalyst in the self-addition of 5-HMF to C₁₀-furoins.^[184] The system could be recycled for up to 10 times when an acid wash was included in-between recycling runs. When using a PS supported thiazolium salts in combination with K₂CO₃ as activating base in the acetaldehyde self-addition, acetoin yields quickly declined from 95% in the first run to < 10% in the second.^[140]

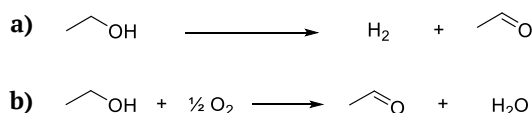
Nonetheless, findings in literature show that the NHC catalysed self-addition reaction of acetaldehyde to acetoin is feasible but lacks an adequate in-depth study for upscaling and process optimisation. Furthermore, for the developed supported NHC catalysts, continuous-flow applications of were not exploited.^[140, 184] The NHC catalysed self-addition reaction holds the potential to overcome the aforementioned hurdles encountered in the direct fermentative

preparation of acetoin, by starting from the (bio-)ethanol-derived building block acetaldehyde. Thus far, ethanol upgrading processes proceed *via* a number of different pathways like *Guerbet*- and aldol-type reactions as well as the earlier reviewed *Ostromislensky* process. All of these processes have one thing in common: the initial step being the dehydrogenation of ethanol to acetaldehyde.^[63, 186-189]

2.9 Dehydrogenation of Ethanol to Acetaldehyde

As described previously, the *Ostromislensky* process as operated by UCC used a supported Cu-based catalyst with 1-5% Cr to partially converted ethanol into acetaldehyde in the first step of the two-step ethanol-to-BD process.^[68] As was the case for the industrially established ethanol-to-BD processes, the dehydrogenation of ethanol to acetaldehyde became obsolete with the developments in the post-war petrochemical industry and the associated discovery of the *Wacker-Hoechst* process. This process enabled the production of acetaldehyde from petroleum derived ethylene in aqueous media *via* direct oxidation with air, using a homogeneous PdCl₂/CuCl₂ catalyst.^[190-191]

Currently, the *Wacker-Hoechst* process is still the main production process for acetaldehyde.^[19] With the rise of sustainably sourced ethanol, the direct dehydrogenation and oxidative dehydrogenation of ethanol have regained interest (**Scheme 17**).



Scheme 17: Possible routes to prepare acetaldehyde from ethanol *via* **a)** direct dehydration to produce acetaldehyde and pure hydrogen and **b)** oxidative dehydrogenation.^[192]

As previously described, the industrial direct dehydration of ethanol to acetaldehyde and hydrogen can be carried out using Cu-based catalysts.^[68, 193] Besides this, the route yields pure hydrogen as by-product which makes it more profitable for large scale applications. Some notable achievements in the field of Cu-catalysed ethanol dehydrogenation include the Cu/SiO₂ catalyst developed by *Zhang et al.* which is able to attain conversions > 90% and acetaldehyde selectivities > 98%. The catalyst was found to be stable for 500 h TOS in a fixed bed reactor.^[194] Various commercial catalyst have been reported for the direct dehydrogenation of ethanol as well: *Santacesaria et al.* tested various catalysts manufactured by BASF and were able to obtain 64% ethanol conversion at 88% acetaldehyde selectivity using a BASF-K310 CuO/ZnO/Al₂O₃ catalyst.^[195]

Besides Cu, Au nanoparticles show excellent performance in the direct dehydrogenation of ethanol as well. *Guan* and *Hensen* found that the particle size greatly affected the performance of the catalyst, with Au nanoparticles of about 6 nm being much more active than smaller ones.^[196] However, a long-term catalytic test was not reported. On the other hand, when using oxidative dehydrogenation conditions (**Scheme 17b**) particles with a diameter > 10 nm showed the highest activities. These findings reveal a clear structure sensitivity of the catalyst as well as the fact that both reactions occur *via* a different mechanism.^[196-197]

Although it is well studied, that homogeneous transition metal complexes are able to catalyse the dehydration of alcohols, ethanol has proven to be a more challenging substrate.^[61-62, 198-200]

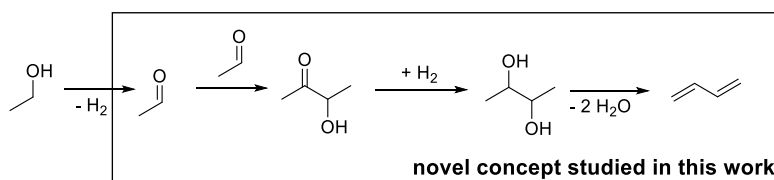
As shown by *Nielsen et al.* ethanol is oxidized to acetaldehyde using a Ru-MACHO catalyst via an outer-sphere dehydrogenation mechanism. As the acetaldehyde molecule stays in close proximity of the metal centre, another molecule of ethanol attacks the aldehyde and forms a hemi-acetal which ultimately results in the liberation of ethyl acetate.^[62]

A whole different, yet sustainable route to acetaldehyde was very recently described by *Koolen* and co-workers. A highly selective (92%) electrochemical conversion of CO₂ to acetaldehyde was reported, using Cu nanoclusters on carbonaceous support as catalyst.^[201]

3 Aim of Present Work – Conceptual Ethanol-to-BD Approach

Though the *Lebedev* and *Ostromislensky* process could play an important role in the on-purpose synthesis of BD from sustainably sourced ethanol, both processes have to overcome several hurdles before being re-adapted by the chemical industry. As pointed out previously, development of a suitable, industrially viable catalyst with high stability and a productivity is hampered by the complexity of the reaction network.^[98] Rather than carrying out the whole reaction sequence over a single catalyst, starting either from ethanol or ethanol/acetaldehyde mixtures, a decoupled strategy where each key-intermediate is prepared at optimised reaction conditions, is not exploited in literature so far and could potentially overcome the aforementioned industrial productivity barrier.

In such a novel, decoupled sequence, acetaldehyde, obtained from dehydrogenation of ethanol, can be converted to BD, *via* acetoin and 2,3-BDO respectively as mentioned in the previous chapter. The overall reaction scheme of the decoupled reaction sequence investigated in this work, is shown in **Scheme 18**.



Scheme 18: Decoupled reaction sequence for a novel ethanol-to-BD approach *via* acetoin and 2,3-BDO as key-intermediates. The boxed reactions are studied within this work.

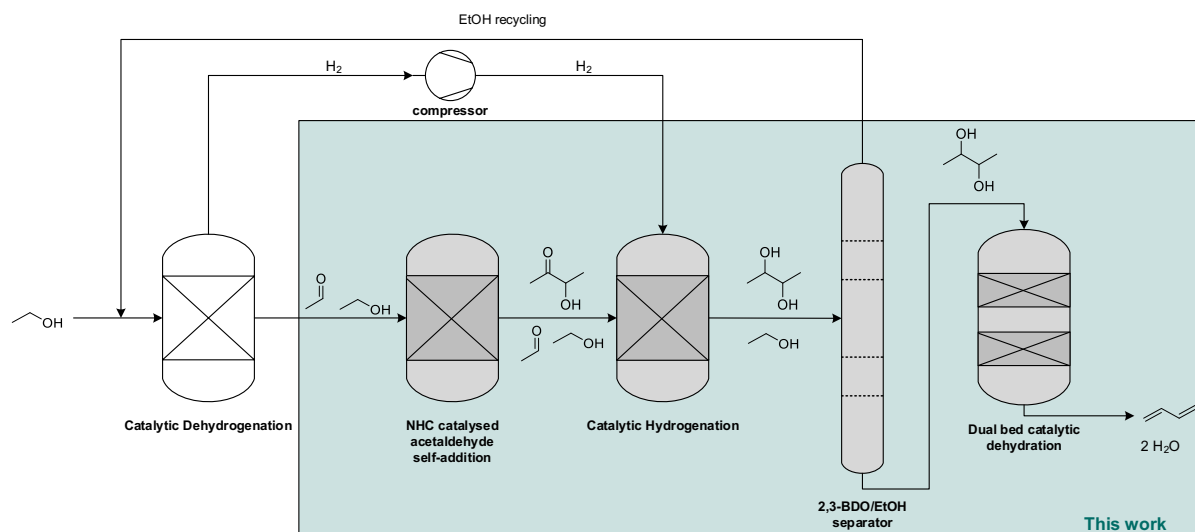
As part of the two-step *Ostromislensky* process, the ethanol-to-acetaldehyde dehydrogenation has already been commercialised on an industrial scale. To date, several industrial and commercially available catalysts exist for this reaction step.^[195, 202] Therefore, research discussed in this work will start with the self-addition of acetaldehyde to acetoin.

Initially, there seemed to be a significant gap in literature, regarding the availability and recyclability of a suitable catalysts for the acetaldehyde-to-acetoin reaction. To scale up the reaction effectively, it is essential to increase the total turnover number (TTON) of the catalyst whilst ensuring its stability and selectivity throughout continuous-flow operations for example. The use of the corresponding alcohol as a solvent was not reported either.^[140] Implementing the acetaldehyde self-addition reaction in ethanol would be particularly beneficial as this approach could pave the way for an integrated reaction system that allows for the direct synthesis of acyloin compounds from alcohols, without the need for purification of aldehydes or the removal of excess alcohol after the first alcohol-to-aldehyde dehydrogenation.

After obtaining the acetoin/ethanol/acetaldehyde mixture from the coupling reaction, a hydrogenation using suitable catalysts is needed to obtain a mixture of diol and ethanol. Patents by *Tecnalia* already disclose that acetoin can be hydrogenated to 2,3-butanediol using Ru/C supported catalysts.^[166] In this work, the possibility to use homogeneous catalysts will be investigated as well. Implementing hydrogenation directly after the coupling reaction without intermittent purification to obtain pure acetoin seems particularly advantageous as residual acetaldehyde from the coupling reaction, will most likely be converted into ethanol,

leaving a mixture of 2,3-BDO and ethanol after the catalytic hydrogenation. In order to obtain pure 2,3-BDO for the dual bed catalytic dehydration step, feasibility of implementing distillation as single purification strategy in the whole sequence will be investigated.

For the 2,3-BDO dehydration reaction, use of hydrothermally aged, calcined Sc_2O_3 , as reported by Nakazono, will serve as benchmark system for the first dehydration step of 2,3-BDO to 3B2OL^[147] By using a suitable second dehydration catalyst we aims to enhance the 2,3-BDO-to-BD conversion process in an isothermal dual bed catalytic reactor.



Scheme 19: Simplified process scheme of the conceptual novel ethanol-to-BD approach studied in this work. By using a combination of different transformations known in literature, a proof-of-concept for this novel approach will be given. Carrying out the acetaldehyde self-addition in ethanol as corresponding alcohol, allows for implementing only a single purification step in the sequence. In this work, the boxed processes were investigated with the goal of achieving near-industrial productivities of BD from ethanol/acetaldehyde mixtures.

In order to give an elaborate proof-of-concept for the proposed approach, small continuously operated miniplants will be used to scale-up the reactions and gain a deep knowledge of the performance of various catalysts in a continuously operated mode. Prior to this upscaling though, optimal reaction conditions have to be found in small scale batch experiments. Besides this, for the final step in the sequence, a suitable miniplant will be constructed in order to safely operate and handle the produced highly toxic BD in a controlled environment.

4 Design and Operation of a Miniplant

In order to carry out the gas-phase continuous-flow dehydration of 2,3-BDO to 1,3-BD, a miniplant was constructed. Initial planning and design of the miniplant was primarily done by the author of this work. Construction of the miniplant and first test-runs were carried out in collaboration with *J. Mannschott* and carried out as part of her master's thesis (TU Dortmund University, 2022). The idea and simplified piping and instrumentation diagram (P&ID) of the miniplant was derived from a flow diagram proposed by *Zeng et al.* for the heterogeneous catalysed dehydration of 2,3-BDO to 3B2OL.^[151] Using this as a basis, the miniplant was constructed and optimised as desired during catalytic experiments. As for the optimisations, care was taken to obey the *Hazard and Operability Study* (HAZOP, described in the appendix to this work in section A2). A full P&ID of the original miniplant as well as for the final miniplant can be found in the appendix to this work (**Figure A 1** and **Figure A 2**).

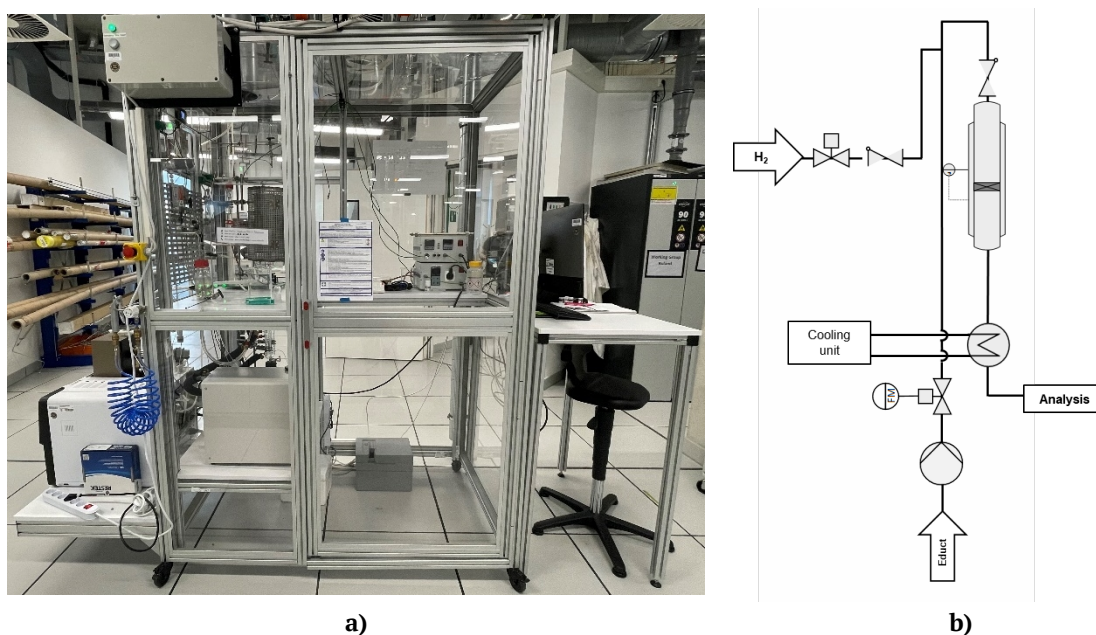


Figure 5: a) Miniplant enclosure in a custom-made *item* box as well as b) the simplified schematic representation of the BD miniplant.

4.1 Description of the Miniplant

Originally, the miniplant was designed to investigate the dual bed catalytic dehydration of 2,3-BDO to BD using two different catalyst beds at isothermal conditions and a continuous stream of H_2 as feed-gas with 2,3-BDO as substrate at a low weight-hour-space-velocity (WHSV) of 3.2 h^{-1} . However, as the work on the novel ethanol/acetaldehyde to BD pathway progressed, the miniplant was also used for continuous-flow (gas-phase) hydrogenation reactions of acetoin to 2,3-BDO at moderate temperatures ($150\text{ }^{\circ}\text{C}$) and pressures (up to 10 bar). The central unit of the miniplant is the downward facing tubular flow reactor, heated in a vertical tube-furnace. Initially, reactions were carried out using a custom-made glass reactor with a G3 frit, to hold the catalyst bed in place at a certain height inside the furnace. In a later stage of the investigations regarding the dual bed catalytic dehydration, reactions were carried out in a custom-made *Swagelok*-based reactor with two distinct catalyst chambers to hold the catalyst in place and prevent the two catalysts from swirling together (see section 7.6.2 for a more detailed description). The reactor is designed to be fed with liquid substrates as well as H_2 as feed- or Ar as inert gas. In order to set the desired reaction temperature and to prevent the oven from exceeding a certain safety temperature, a temperature control unit as well as circuit breaker (*Max-Planck-Institut für Kohlenforschung*) was used (Figure 6).

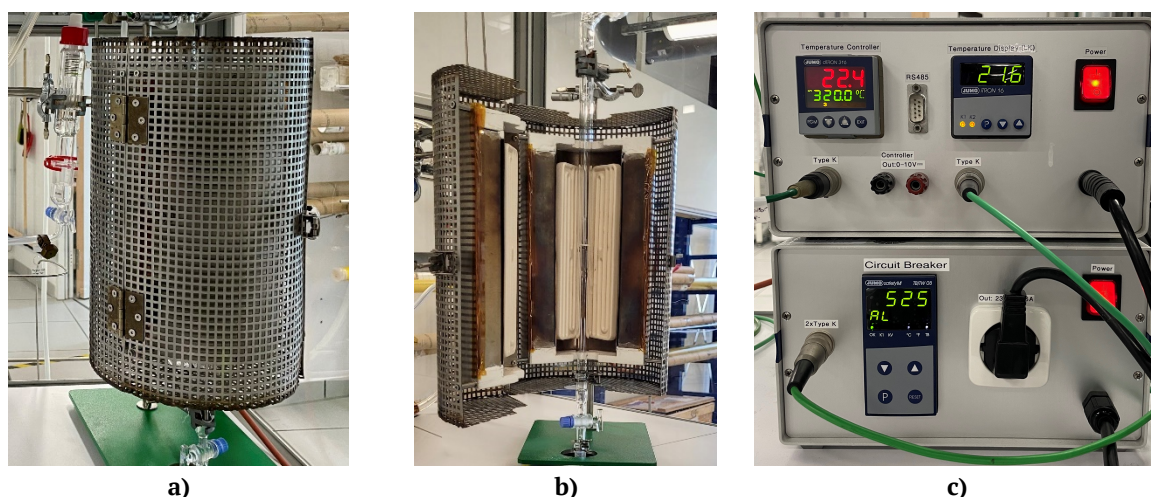


Figure 6: a) View of the tubular furnace used to heat the reactor in a) closed and b) open state as well as c) temperature controller (top) and circuit breaker (bottom) provided by the electrical workshop of the *Max-Planck-Institut für Kohlenforschung*.

Gases (H_2 or Ar) are fed into the reactor via $1/8''$ *Swagelok* pipes from low-pressure reducing valves in the range of 1-10 bar. Flow of H_2 is controlled using a *Bronkhorst* mass-flow-controller (MFC) with variable flow-speeds between $1\text{-}196\text{ mL}\cdot\text{min}^{-1}$ depending on the inlet pressure (Figure 7). Flow of Ar as inert-gas is not controlled using an MFC but only regulated with a low-pressure reducing valve. Both lines are connected to the reactor *via* a $3/2$ -way valve. The $3/2$ -way valve allows for a switch between the two gases during operation of the miniplant. Both lines are equipped with safety check-valves to ensure the desired flow direction.

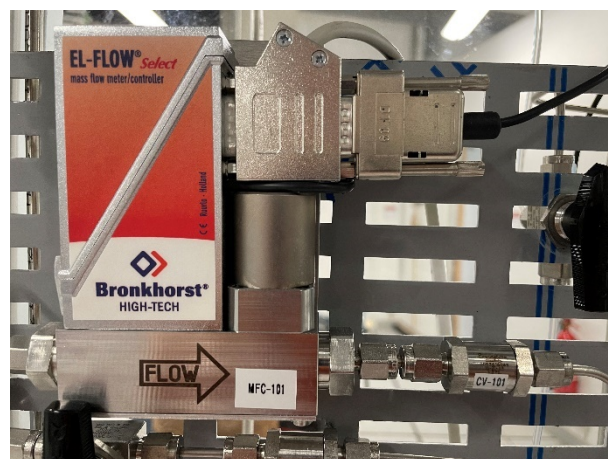


Figure 7: Bronkhorst EL-FLOW mass-flow-controller (MFC) installed in the H_2 line. The MFC is controlled via the Bronkhorst FlowSuite 2 software. Downstream of the MFC, a Swagelok check-valve can also be seen (CV-101).

Substrates are fed into the miniplant using either an *Aladdin AL-1000 SyringeONE* programmable syringe pump, or a *Shimadzu LC-10AD HPLC* pump. In case of using the syringe pump, a reusable 10 mL *Nemesys-S* piston syringe purchased from *CETONI* was used. In order to additionally determine the mass-flow of substrates into the reactor, a *Bronkhorst EL-FLOW* digital flow-meter was used (Figure 8).

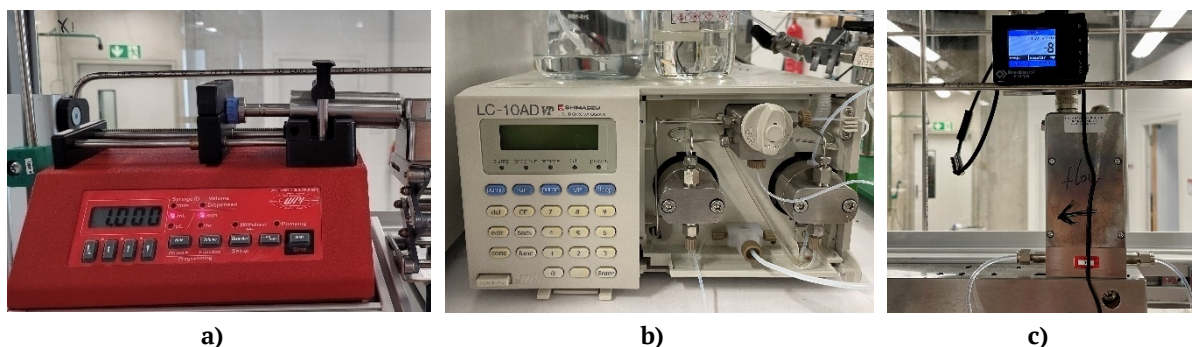


Figure 8: Substrate feed-line of the miniplant consisting either of **a)** an *Aladdin* syringe pump, **b)** a *Shimadzu* HPLC pump and **c)** the *Bronkhorst* flow-meter to additionally record the mass flow of liquid substrates into the reactor.

Substrates and flow-gases lines (1/8" Swagelok pipes) were connected to the reactor via a Swagelok T-piece and are fed into the reactor without pre-mixing or evaporating the substrates. After the reactor, effluent flow-gas and reaction products are quenched in a cooling circuit. Initially, a single *Duran®* intense condenser with ice-water as coolant was used. The coolant was pumped through the intense cooler using an *IKA HBC 5 basic* bath circulator (Figure 9). Occasionally, heated water was manually drained from the batch circulator and replaced with new ice-water to maintain a bath temperature between 1 and 5 °C which was governed using a thermometer. During the operation of the miniplant, especially for the 2,3-BDO dehydration experiments, it was found that this cooling capacity was not sufficient. Therefore, cooling capacity needed to be improved. For this purpose, the *IKA HBC 5 basic* bath circulator was replaced by an *IKA RC 2 Lite* compact recirculating chiller. The ice-water coolant was replaced with an *iPrOH/H₂O* mixture to ensure a cooling capacity down to -10 °C. The single intensive cooler was replaced by two intensive coolers, one for the downflowing and the other for the rising miniplant gas-stream. Both coolers were connected via a Claisen adapter. Condensable liquid products were collected from a collection flask placed inside a cold trap at -78 °C which was placed at the bottom of the condenser setup.

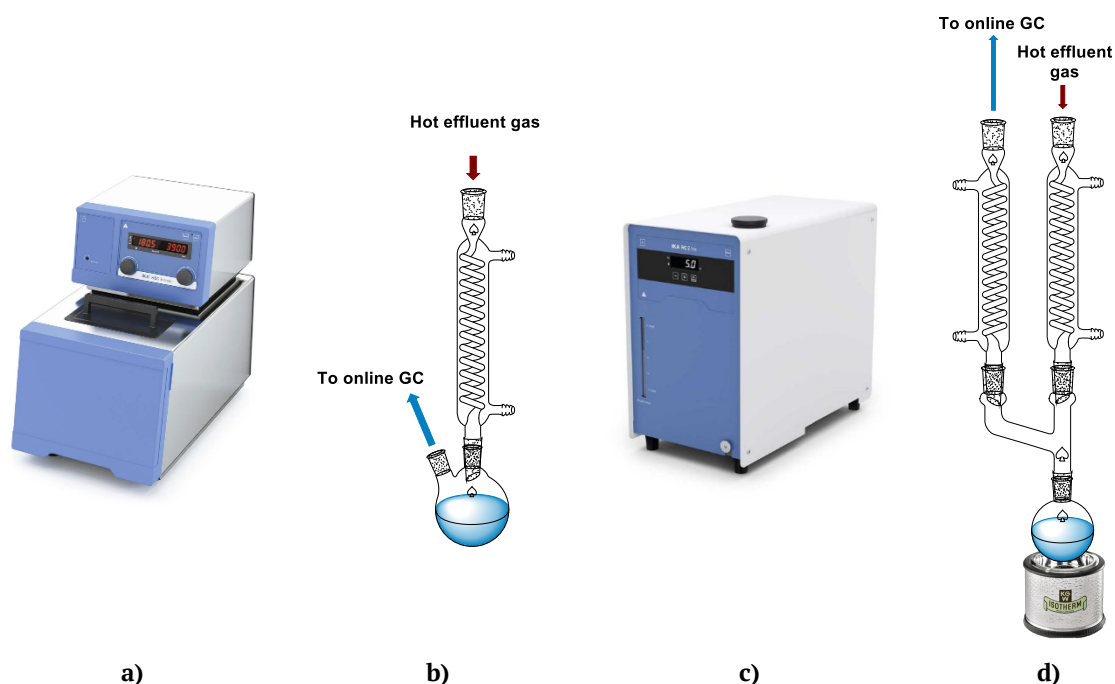


Figure 9: Overview of the initial and improved effluent gas quenching setup. **a)** IKA HBC 5 basic bath circulator and **b)** schematic representation of the single intensive cooler used in an initial version of the miniplant and **c)** an IKA RC 2 lite recirculating chiller ($T_{\min} = -10\text{ }^{\circ}\text{C}$) and two intensive coolers **d)** used to quench the hot miniplant gases and maximise the amount of condensable liquid products. Liquid products were collected from a cold trap at $-78\text{ }^{\circ}\text{C}$ from the bottom of the condenser setup.

In the initial version of the miniplant (Figure A 1), upstream of the on-line GC-FID headspace gas analysis instrument, an additional gas-sampling station was installed to facilitate gas sampling. Samples were collected in a custom-made gas collector with two double-end shutoff Swagelok quick-connectors, to prevent the sampled gas from exiting the collector after taking samples. Samples of gas were withdrawn from the gas collector *via* the PTFE-septum installed on one end of the collector using a syringe. Samples were manually injected into a GC-MS device, in order to qualitatively analyse and identify the components in the effluent reactor gas (Figure 10). In the final version of the miniplant, this custom-made gas collector was replaced by a gas sampling bag (SupelTM-Inert Multi-Layer Foil bag purchased from Sigma). Samples were collected of the effluent cooled miniplant gases, using a 3/2-way valve installed in the gas-line prior to the on-line GC instrument and analysed on a GC-MS instrument using the same specifications and column as the on-line instrument.



Figure 10: **a)** Custom-made Swagelok gas-collector with two double-end shutoff quick-connectors (red) and **b)** SupelTM gas sampling bag to collect effluent miniplant gas samples for qualitative off-line GC-MS analysis.

4.2 Process Safety

The BD miniplant is designed to operate at high temperatures, using flammable substrates to investigate the production of toxic butadiene. Therefore, the miniplant must be designed and operated in such a way, that the potential hazards and risks for the operator of the plant and other personnel is kept to an absolute minimum. In order to achieve this, several layers of safety were implemented. As a risk assessment methodology, the *Layer of Protection Analysis* LOPA was used.^[203]



Figure 11: Overview of the different levels within the Layers of Protection Analysis (LOPA) as adapted from R. J. Willey.^[203]

In the first layer of protection, the process design, care should be taken to ensure that small deviations can be tolerated or are inherently prevented. This can for example be achieved by using filters in liquid substrate feed-lines to prevent solid particle contamination of pumps and parts and by using check-valves to circumvent a reverse flow direction which could potentially damage equipment. Both measures were implemented into the design of the miniplant. Furthermore, regarding the double dehydration of 2,3-BDO to BD, the process was operated in a manner that ensures compliance with the MAK values for BD, even in the event of a complete conversion of the substrates to BD and subsequent release of the plant gas into the ambient air, provided that the exhaust air system is coupled to the miniplant system. This meant not exceeding a liquid 2,3-BDO substrate flow of $2.0 \text{ g}\cdot\text{h}^{-1}$ given a dimension of the miniplant enclosure (custom made *item* box) and the extraction capacity of $100 \text{ m}^3\cdot\text{h}^{-1}$. Furthermore, exhaust gases of the miniplant were washed, prior to being fed into the exhaust of the miniplant enclosure. Washing of gases was carried out in a pressure resistant *Duran® pressure plus+* bottle using water or glycerol. Another measure within this first layer of protection was selecting the piping size and length to be as short as possible with as few connections as possible. The process itself, predominantly the double dehydration of 2,3-BDO to BD, was further evaluated with respect to the potential hazards in a HAZOP study. A complete description and the results of the HAZOP study can be found in the appendix in section A2 and A3.

The second and third layer of protection includes the controls and alarms of the miniplant. To detect a possible leak as soon as possible, a hand-held acoustic H_2 warning device was placed inside the miniplant enclosure during operation. In order to prevent the tubular furnace from over-heating, a circuit breaker was used with a safety temperature set to 100 K above operating temperature. If the temperature exceeds the safety temperature, the power to the furnace controller is cut-off, preventing overheating. Also, the automated shut-down

of the pumps in case of overpressure or detected leakage falls within these layers and leads to the fourth layer of protection, automated shut-down.

As there are no high pressures and only low to moderate flows of H_2 as potentially explosive gas and BD concentrations below MAK values, the miniplant was not equipped with automatic gas shut-off valves controlled by an additional MCS warning system. Though this decision reduced the time required for designing and constructing the miniplant, it consequently meant that the miniplant cannot be operated unattended (*i.e.* no unmanned overnight experiments) and that the sounding of the acoustic signal from hand held warning device placed in the miniplant enclosure, must be followed by an immediate shut-down of the entire miniplant, via the emergency stop switch installed outside of the miniplant enclosure. In this extreme emergency case, all power to all devices is cut, resulting in a shut-down of the liquid feed pump, the oven and the MFC installed in the H_2 line. The MFC was chosen to be in a “normally closed” state, so that in case of complete power outage, gas supply is also automatically cut off.

The fifth layer of protection deals with the scenario that all previous layers of protection have failed and describes the physical protection of the miniplant setup. To prevent overpressure from the constant feed of H_2 as flow-gas (e.g. when downstream equipment is clogged), a pressure relief valve was installed in the H_2 line and connected to the exhaust to prevent damage to the glass reactor and equipment. Besides this, the whole plant was enclosed in a custom-made *item* box which is connected to an overhead ventilation system with a capacity of $100\text{ m}^3\cdot\text{h}^{-1}$. The box also serves as protection in case of equipment burst and therefore, was kept closed during operation of the miniplant (except for the time of sampling). Additionally, all electrical equipment is installed in such a way that a potential contact between leaking fluids and the devices is minimized.

The sixth and final level within the LOPA comprises of emergency measures outside the miniplant. In cases of a fire, fire extinguishers were located near the miniplant as well as presence of a fire alarm system and push-button detectors at site. In the event of personnel injury, a phone is located near the miniplant in the reactor hall, so that first aiders or the emergency services can be contacted.

5 Results and Discussion

Within this chapter, the individual reactions to convert ethanol/acetaldehyde mixtures into BD *via* acetoin and 2,3-BDO will be discussed. For each reaction step, optimal conditions were first identified through small-scale batch experiments before transitioning to continuous-flow reactions where possible.

As starting point of the investigations towards delivering a proof of concept for the novel acetaldehyde-to-butadiene approach, the NHC catalysed acetaldehyde self-addition to acetoin will be studied in more detail (chapter 5.1). Especially the discussions around the development of a suitable, yet stable and selective heterogeneous NHC catalyst will play a pivotal role in this chapter. In order to obtain a deeper knowledge about the system, advanced spectroscopic techniques were employed to study the catalyst and the changes it undergoes during catalysis. Parts of the work described in chapter 5.1 has already been published:

- *M. Belleflamme et al., ChemSusChem* **2024**, *17*, e202400647.^[204]
- *M. Belleflamme et al., Green. Chem.* **2025**, *27*, 14317-14327.^[205]
- *M. Belleflamme et al., Manuscript under review.*^[206]

In Chapter 5.2 the hydrogenation of acetoin to 2,3-BDO will be discussed in more details, starting with the development of a base-free, molecularly defined Ru-based catalytic system. Afterwards, this chapter will focus on using commercially available solid catalyst materials that allow for the possibility of conducting larger scale heterogeneously catalysed slurry-phase reactions. Also, gas-phase continuous-flow reactions using heterogeneous solid catalysts will be investigated. The gas-phase continuous-flow reactions were investigated using the constructed miniplant which was partially reconstructed for this purpose.

Finally, chapter 5.3 will focus on the double dehydration of 2,3-BDO to BD *via* 3B2OL as intermediate in the miniplant. In order to develop a suitable, highly productive dual bed catalytic system, the first dehydration reaction of 2,3-BDO to 3B2OL will be optimised with respect to the selectivity towards 3B2OL as well as the conversion of pure 2,3-BDO as substrate. Following this, the second dehydration step will be investigated in more detail to afford a highly selective dual bed catalytic system for the 2,3-BDO to BD reaction. Parts of the work described in chapter 5.3, was conducted by *J. Mannschott* (Master's Thesis, TU Dortmund, 2022).

5.1 Coupling of Acetaldehyde to Acetoin using NHC Catalysts

As described in section 2.8, *Zhang et al.* already reported several thiazolium salts as *N*-heterocyclic carbene (NHC) precursors in the self-addition of acetaldehyde to 3-hydroxy-2-butanone (acetoin).^[140-141] In order to identify the best performing NHC precursor, several homogeneous NHC precursors were screened prior to developing an innovative biphasic recycling strategy. Also, immobilisation of the best performing NHC precursor on a suitable support material was carried out. With the heterogeneous NHC precatalyst at hand, recycling as well as continuous flow strategies were investigated.

5.1.1 Screening of Homogeneous NHC Catalysts

As an initial step in investigating the self-addition of acetaldehyde to acetoin, a broad range of NHC precursors was evaluated under solvent-free conditions. The scope of precursors screened is shown in Figure 12a. The NHC precursors **NHC1-5** as well as **NHC7** and **NHC8** were obtained from *Sigma*. **NHC6** was prepared according to a procedure described in literature (see section 7.3.1).^[207] Reactions were conducted in a sealed, pressure-resistant glass vessel using a microwave reactor. Generation of the catalytically active species, *i.e.* the active carbene, was ensured by using Na_2CO_3 as mild base. The catalytic performance of the NHC precursors were tested at 100 °C using a 1:1.3 ratio of precatalyst to base. This ratio of precatalyst to base taken from literature.^[140-141] The catalytic performance of the various NHC precursors screened herein, are shown below in Figure 12. A more detailed experimental procedure can be found in section 7.4.1.

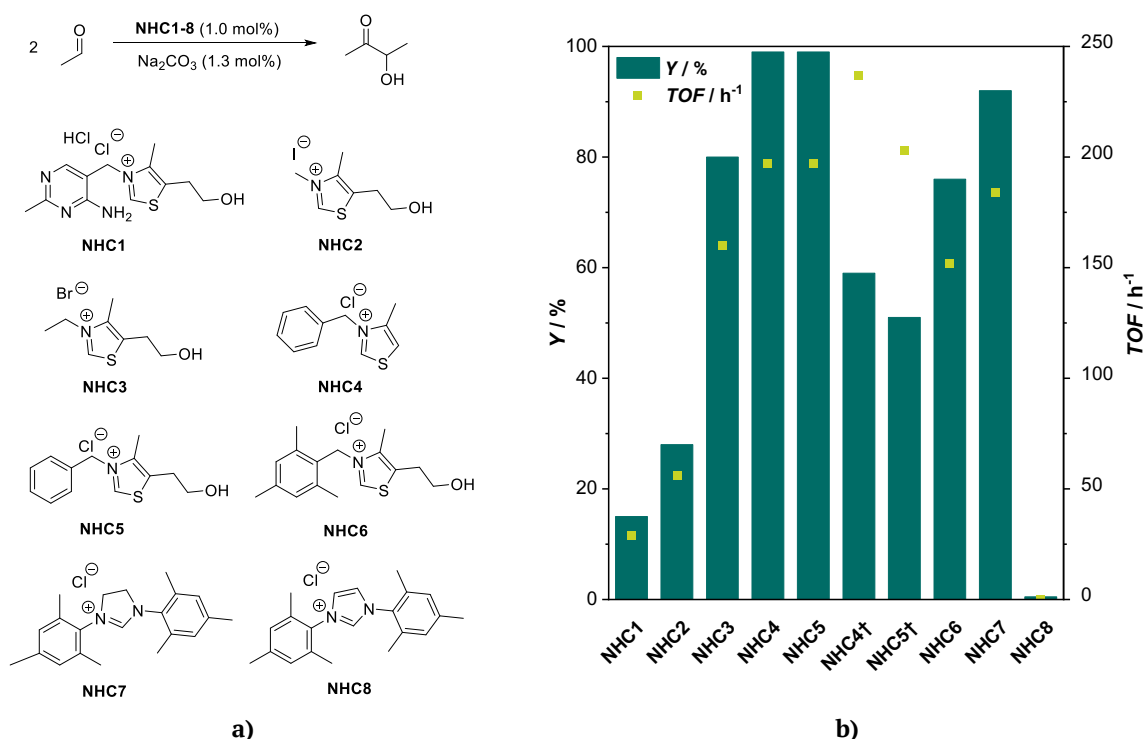


Figure 12: **a)** Overview of the *N*-heterocyclic carbenes catalyst precursors screened in the acetaldehyde self-addition. **b)** Catalytic results (yield of acetoin and turn-over-frequency) obtained with various NHC precursors **NHC1-8**. Reaction conditions: $V(\text{acetaldehyde}) = 2.0 \text{ mL}$, $n(\text{acetaldehyde}) = 36 \text{ mmol}$, $c(\text{NHC1-8}) = 1.0 \text{ mol\%}$, $c(\text{Na}_2\text{CO}_3) = 1.3 \text{ mol\%}$, $T = 100 \text{ }^\circ\text{C}$, $t = 30 \text{ min}$. †: $t = 15 \text{ min}$ at otherwise identical conditions. Yields as determined by GC-FID using mesitylene as an internal standard.

The use of thiamine hydrochloride (**NHC1**, Vitamin B1) as precatalyst in the acetaldehyde self-addition, yielded approximately 15% acetoin after 30 minutes. Although Na₂CO₃ used to active the catalyst *in-situ* was not removed prior to adding aldehyde and carrying out the reaction, no undesired formation of aldol by-products like 3-hydroxybutanal or crotonaldehyde was observed. This experiment demonstrates the exceptional ability of the system to afford high selectivities towards desired acetoin. Also, the result indicates that the use of Na₂CO₃ as a mild base is sufficiently strong to activate the catalyst while being too weak to catalyse undesired aldol side reactions of the highly reactive acetaldehyde. Alternatively, it is plausible that the rate of NHC catalysed acetoin formation exceeds that of base catalysed aldol reaction under these conditions. The latter could also explain the absence of aldol side products in the GC-FID chromatogram. Notably, when using NaOH as base, more aldol side products and higher molecular acetaldehyde condensation products were observed. Despite high selectivity, the catalytic activity of **NHC1** in the acetaldehyde self-addition is low. A reason for this could be the high steric demand of the side-group attached to the quaternary nitrogen, which makes the catalytically active centre, less accessible for substrates.

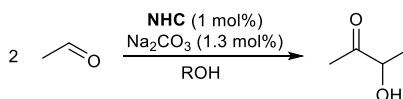
When 5-(2-hydroxyethyl)-3,4-dimethylthiazol-3-ium iodide (**NHC2**) is used as precatalyst, bearing but a methyl group at the quaternary nitrogen, an acetoin yield of 28% is attained. To further investigate the influence of the side-group attached to the quaternary nitrogen on the catalytic performance of the active catalyst, steric hindrance was systematically increased by introducing ethyl (**NHC3**) and benzyl groups (**NHC4** and **NHC5**). This increase in steric demand on the substituent at the quaternary nitrogen atom led to a notable enhancement in catalytic activity (**Figure 12b**). With **NHC3**, an acetoin yield of approximately 80% was achieved, whereas **NHC4** and **NHC5** facilitated nearly quantitative yields (> 99%) with a selectivity exceeding 99% after 30 minutes of reaction time for all precursors. In order to identify the most active catalyst in the reaction, the experiments with **NHC4** and **NHC5** were repeated with a shorter reaction time. After 15 minutes, the system with **NHC4** was able to attain 59% yield towards acetoin, whereas the **NHC1**/Na₂CO₃ catalytic system attained 51% yield. Again, excellent selectivity > 99% was observed.

Comparison of the different thiazolium salts used (**Figure 12a**), highlights the influence of the substituent on the quaternary nitrogen atom on catalytic performance. Varying the substituent at the [5] position of the thiazole ring (as in **NHC4** and **NHC5**) exhibited a less pronounced effect. This minor effect of the NHC backbone on the catalytic performance has also been shown for NHC catalysed *Stetter* reactions.^[208] Interestingly, further increasing the steric bulk of the side-group by replacing the benzyl group with a mesityl group (**NHC6**) did not result in enhanced catalytic performance; the **NHC6**/Na₂CO₃ catalytic system yielded 76% acetoin.

In addition to thiazolium salts, an imidazolidinium-based (**NHC7**) and an imidazolium-based compound (**NHC8**) were evaluated as precatalysts as well. The carbenes generated from these compounds are stabilized by the mesomeric effect of their mesityl groups.^[209] Imidazolidinium-based **NHC7** exhibited substantial catalytic activity, yielding 92% acetoin, whereas **NHC8** showed negligible product formation (< 1%). These observations suggest that electron delocalization within the NHC ring significantly influences the system's productivity.

To further intensify the process, additional experiments were conducted using **NHC5**, and **NHC7**. Notably, **NHC4** is more active compared to **NHC5**, but due to increased stability of **NHC5** (as per manufacturer specification) focus was put on **NHC5** rather than **NHC4**. First, the tolerance of the use of EtOH and MeOH as solvent was investigated using **NHC5**. Especially the use of EtOH as solvent for the reaction would be beneficial as this would lower the catalytic requirements of a potential upstream ethanol-to-acetaldehyde dehydrogenation reaction. The results of the experiments using either **NHC5** or **NHC7** as precatalyst in the acetaldehyde self-addition in EtOH and MeOH as solvent, are listed below in **Table 1**.

Table 1: Catalytic results of experiments using **NHC5** or **NHC7** as precatalyst in the self-addition of acetaldehyde in EtOH or MeOH as reaction solvent.^[a]



Entry	NHC catalyst	solvent	Y(acetoin) ^[b] (%)	ΣY(side products) ^[b,c] (%)
1.1	NHC5	EtOH	98	<< 0.1
1.2	NHC7	EtOH	15	7
1.3 ^[d]	NHC7	EtOH	48	5
1.4	NHC5	MeOH	38	8
1.5	NHC7	MeOH	9	3

[a] Reaction conditions: V(acetaldehyde) = 1.0 mL, n(acetaldehyde) = 18 mmol, V(solvent) = 5.0 mL, c(NHC) = 1.0mol%, c(Na₂CO₃) = 1.0mol%, T = 100 °C, t = 30 min. [b] As determined by GC-FID using mesitylene as internal standard. [c] Total yield of aldol products that were identified from GC-MS. [d] t = 4 h at otherwise identical conditions.

A comparison of the catalytic performances of **NHC5** and **NHC7** in ethanol as the solvent (**Table 1**, entries 1.1 and 1.2) reveals a significant difference. Using **NHC7** as precatalyst resulted a total acetoin yield of only 15%, whereas with **NHC5**, a near-quantitative yield of 98% was obtained, indicating substantially lower activity of the former when using EtOH as solvent. Furthermore, from the post reaction solution of the experiment in entry 1.2 formation of crotonaldehyde and 3-hydroxybutanal as side products (7%) were observed from GC-FID and GC-MS chromatogram. Formation of these side products are attributed to base-catalysed aldol reactions catalysed by Na₂CO₃. The moderate yield of **NHC7** when using EtOH as solvent could be remedied somewhat by applying longer reaction times (entry 1.3). In an experiment using 4 h of reaction time at otherwise identical 48% acetoin yield and 5% aldol side products were obtained.

Using MeOH as solvent for the **NHC5**/Na₂CO₃ catalysed acetaldehyde self-addition results in 38% of acetoin yield and 8% aldol side products (entry 1.4). Compared to the experiment in entry 1.1 where EtOH was used at otherwise identical conditions, the finding in entry 1.4 highlights the significant drop in catalytic activity of the system when MeOH is used. Also, the activity of the **NHC7**/Na₂CO₃ suffers from the use of MeOH as reaction solvent (9% acetoin, 3% side products, entry 1.5).

5.1.2 Development of a Recyclable Homogeneous NHC Catalysed System

Though both **NHC5** and **NHC7** are tolerable to the use of EtOH as solvent, the **NHC5**/ Na_2CO_3 system is more active which why further process intensification with **NHC5** was proposed. Nonetheless, comparing the molecular structures of **NHC5** and **NHC7** indicates that **NHC7** is probably less polar compared to **NHC5**. This could also explain the lower activity of **NHC7** when using polar solvents like EtOH and MeOH, as the solubility of **NHC7** might have been too low.

In this regard, the use of cyclohexane as non-polar solvent for the **NHC7** catalysed acetaldehyde upgrading was investigated (Table 2). When using cyclohexane as solvent, a partial miscibility of acetaldehyde and cyclohexane was observed prior to the reaction. After the reaction, two very distinct phases were observed. GC-FID analysis of both fractions revealed that one polar acetoin containing phase and one non-polar solvent phase was obtained. In the non-polar solvent phase, negligible contents of acetoin (< 2%) were attained. Also, using ^1H -NMR spectroscopy, evidence was found for the presence of the active **NHC7** catalyst in the cyclohexane-containing phase. Therefore *in-situ* extraction of the catalyst using cyclohexane as solvent, was used to develop a recyclable **NHC7** catalysed system.

Table 2: Catalytic results of the **NHC7**/ Na_2CO_3 catalysed acetaldehyde addition in cyclohexane as solvent, as well as the schematic representation of the biphasic recycling procedure carried out. In this schematic representation, cyclohexane and catalyst containing phase is represented in blue, acetaldehyde in yellow and the acetoin containing product phase is represented in orange.^[a]

$2 \text{ CH}_3\text{CHO} \xrightarrow[\text{cyclohexane (2 mL)}]{\text{NHC7 (1 mol\%)} \atop \text{Na}_2\text{CO}_3 \text{ (1.3 mol\%)}}$
 $\text{CH}_3\text{CH(OH)CH}_3$

Entry	Phase	Y(acetoin) ^[b] (%)
2.1 ^[c]	-	73
2.2	cyclohexane	< 2
2.3	product run 1	72
2.4	product run 2	73
2.5	product run 3	33

[a] reaction conditions: $V(\text{acetaldehyde}) = 2.0 \text{ mL}$, $n(\text{acetaldehyde}) = 36 \text{ mmol}$, $c(\text{NHC7}) = 1.0 \text{ mol\%}$, $c(\text{Na}_2\text{CO}_3) = 1.3 \text{ mol\%}$, $V(\text{cyclohexane}) = 2.0 \text{ mL}$, $T = 100^\circ\text{C}$, $t = 30 \text{ min}$. [b] As determined by GC-FID using mesitylene as internal standard added after the reaction to each phase separately. [c] Experiment carried out without additional solvent at otherwise identical conditions.

As previously shown in Figure 12b using the **NHC7**/ Na_2CO_3 catalytic system in the solvent-free acetaldehyde self-addition resulted in 73% acetoin yield (entry 2.1). By using cyclohexane as solvent, after the reaction two distinct phases were obtained, where the non-polar phase (entry 2.2) mainly consisting of the cyclohexane solvent and minor quantities of acetoin (< 2% yield). The polar phase that had a much larger acetoin content (72%, entry 2.3, product phase run 1). In order to test the recyclability of the active **NHC7** presumably retained in the cyclohexane phase, to the reaction vessel was added fresh acetaldehyde as substrate and the reaction was carried out as usual. Notably, after analysis of the product containing phase of this experiment (entry 2.4, product phase run 2) an acetoin yield of 73% was found. This finding strongly supports the aforementioned postulate that the active carbene catalyst is present in the cyclohexane phase, as opposed to the acetoin containing product phase. After

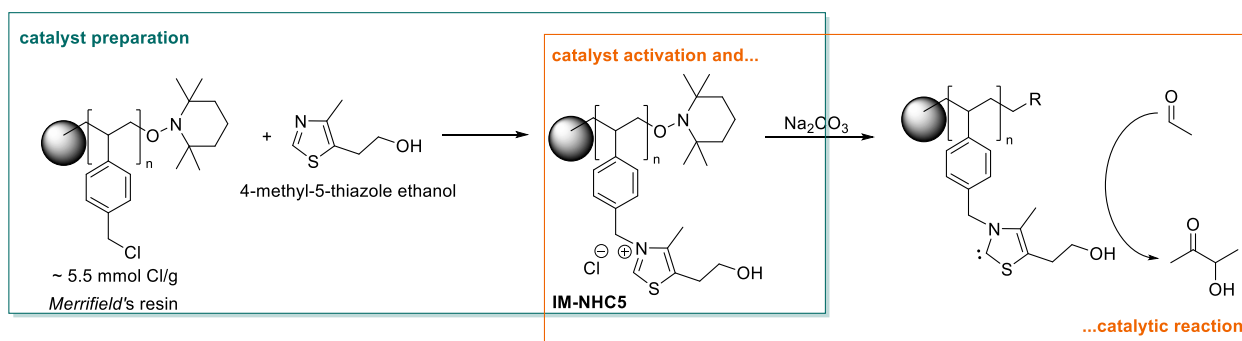
phase separation, the carbene/cyclohexane phase was again charged with fresh substrate, but unfortunately in the third run (entry 2.5) only 33% acetoin yield was attained in the product phase.

It has to be noted, that due to the nature of the experiments and the fact that the experiments were carried out in a micro-wave reactor, no inert atmosphere was used which might have caused premature deactivation of the active carbene due to oxygen or moisture intrusion. Nonetheless, the use of a non-polar organic solvent to extract the active carbene form of **NHC7** could benefit more experiments and different conditions as well as more detailed analysis of the reason for catalyst deactivation from run 2 to run 3. Similar extraction experiments with cyclohexane as solvent and the use of **NHC5** were far less promising, possibly owing to the lack of non-polar side-chains in **NHC5** and higher solubility of **NHC5** in the product containing acetoin phase.

In an attempt to yet come up with a recycling strategy for the **NHC5**/ Na_2CO_3 catalysed system, attempts were made to use distillation as recycling strategy. Unfortunately, these efforts too remained fruitless which could possibly due to the instability of the active carbenes at higher temperature.^[210] As extraction of **NHC7** nor *in-situ* distillation with **NHC5** led to the desired process intensification, a completely different approach for process intensification was studied: heterogenization of the NHC precursor on a suitable support material.

5.1.3 Development and Analysis of an Immobilised NHC Catalyst

In general, catalyst recycling *via* extraction or distillation is more demanding to the catalysts molecular structure compared to filtering-off the catalyst after completion of the reaction. Heterogenization by means of immobilisation of the catalytically active component is a topic well covered in literature.^[39-41, 211] Although using supported NHCs as ligand in (cross) coupling and metathesis reactions, is broadly studied in literature, there are but a few reports on the immobilisation and continuous-flow applications of reactions catalysed by the supported NHCs itself.^[38, 211-212] *Chen* and *Wang* investigated the self-addition of 5-HMF to C_{10} furoins using covalently linked imidazole compounds onto an organic polymer resin. The heterogeneous NHC precatalyst was used in batch recycling experiments with excellent performances.^[184] Inspired by these works, *Merrifield's* peptide resin with a defined content of Cl end groups, was chosen as support material. Covalently linking 4-methyl-5-thiazole ethanol onto the *Merrifield's* resin (chloromethyl polystyrene), affords a precatalyst which resembles the molecular structure of one of the best performing homogeneous NHC precursor, **NHC5** (Scheme 20). Similar to the homogeneous precatalyst, the prepared heterogeneous precatalyst **IM-NHC5** can presumably be activated using a mild base to generate the catalytically active, immobilised carbene species. Due to the nature of the *Merrifield's* resin, the final (pre) catalyst is obtained as small beads (16-50 mesh) which are easily separable after the reaction and can be tested in batch-recycling and continuous-flow applications for process intensification.



Scheme 20: Schematic representation of the synthesis of **IM-NHC5** by covalently linking 4-methyl-5-thiazole ethanol to Merrifield's polymer resin in an $\text{S}_{\text{N}}2$ reaction. Also, the proposed *in-situ* activation reaction with Na_2CO_3 as a base to yield the catalytically active immobilised carbene species and the catalytic reaction is shown.

Before subjecting the prepared **IM-NHC5** to catalysis, successful covalent linking of the heterogeneous precatalyst was verified using solid-state nuclear magnetic resonance (NMR) spectroscopy. These solid-state NMR experiments were carried out in collaboration with the group of Wiegand at the facilities of the *Magnetic Resonance Center* (MARC, Institut für Technische und Makromolekulare Chemie, Worringerweg 2, 52074 Aachen). For **IM-NHC5** and **NHC5**, solid-state ^1H - ^{13}C cross-polarisation (CP) spectra were acquired, whereas for 4-methyl-5-thiazole ethanol a solution state direct-pulsed ^{13}C spectrum was recorded (**Figure 13**).

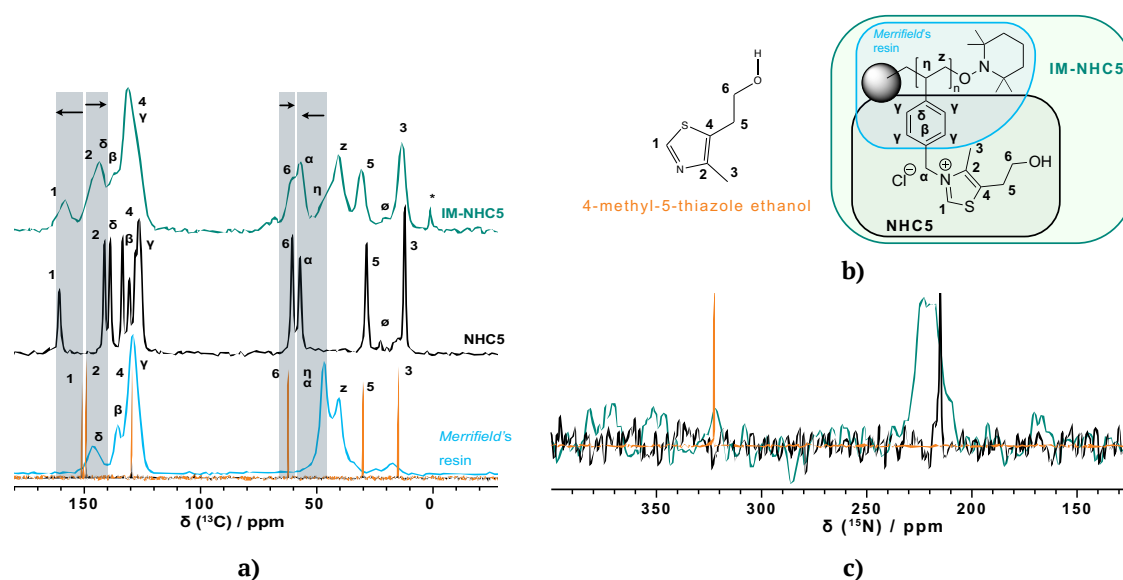


Figure 13: **a)** ^1H - ^{13}C cross-polarisation (CP) spectra of Merrifield's peptide resin (cyan spectrum), **NHC5** (black spectrum) and **IM-NHC5** (green spectrum). In case of 4-methyl-5-thiazole, a direct-pulsed ^{13}C spectrum is shown (orange spectrum). * denotes a resonance from a silicone sample spacer used. Ø denotes MAS sidebands. ^{13}C resonances experiencing significant chemical-shift (δ) changes upon catalyst immobilization are highlighted by grey rectangles. **b)** Atom labelling used and chemical structure of the measured compounds. **c)** ^{15}N NMR spectra of a 4-methyl-5-thiazole ethanol in solution, as well as solid **NHC5** and **IM-NHC5**.

Comparing the ^1H - ^{13}C CP spectra (**Figure 13a**) indicates that the spectrum of **IM-NHC5** (green) closely resembles the combined spectra of **NHC5** (black) and Merrifield's peptide resin (cyan), hinting successful covalent linking of 4-methyl-5-thiazole ethanol to the support material. Notably, comparing the ^{13}C spectrum of 4-methyl-5-thiazole ethanol with that of **IM-NHC5** reveals a significant change in chemical shift (δ), particularly for the carbon atoms within the thiazole ring, labelled as 1 and 2 in **Figure 13b**. These shifts ($\Delta\delta \approx 10$ ppm) are an indication of

covalent bond formation between the polymer and the nitrogen atom in 4-methyl-5-thiazole ethanol, rather than non-specific adsorption onto the polymer surface. Broadening of signals observed in the resonances of **IM-NHC5** can be attributed to structural disorder within the polymer matrix.

In addition to ^1H - ^{13}C CP spectra, **Figure 13c** shows the ^{15}N -NMR spectra of **IM-NHC5** as well as **NHC5**. For 4-methyl-5-thiazole ethanol, also shown in **Figure 13c**, a ^1H - ^{15}N insensitive nuclei enhanced by polarization transfer (INEPT) experiment was performed. Due to the low sensitivity of these experiments, long measurement times were necessary (25 to 78 h in this case). Nonetheless, the INEPT experiment provides valuable insight into the successful immobilisation. The nitrogen atom in the thiazole compound 4-methyl-5-thiazole ethanol resonates at approximately $\delta = 322$ ppm (orange spectrum in **Figure 13c**). Upon formation of a covalent bond with the *Merrifield's* resin, this resonance undergoes a pronounced low-frequency shift of about 108 ppm, as observed in the green spectrum of **Figure 13c**. Comparable shielding effects have been noted in ^{15}N -NMR spectra for sp^2 -hybridized nitrogen atoms upon protonation.^[213] This substantial chemical shift difference in the ^{15}N spectrum upon covalent bond formation, was further corroborated by density functional theory (DFT) calculations of the ^{15}N magnetic-shielding tensors for both 4-methyl-5-thiazole ethanol and the **NHC5** molecule. These calculations revealed an isotropic ^{15}N chemical-shift difference of $\Delta\delta(^{15}\text{N}) = 122.9$ ppm between the two compounds, closely matching the experimentally observed low-frequency shift (see section 7.2.3 for additional details).

The ^{15}N resonance of **IM-NHC5** is noticeably broadened, which is consistent with the chemical-shift distribution effects, commonly observed in polymeric species. Additionally, the nitrogen atom in **NHC5** is detected at 215 ppm, closely aligning with the **IM-NHC5** chemical shift. This observation further supports the successful covalent linking of 4-methyl-5-thiazole ethanol onto *Merrifield's* polymer resin, forming the grafted precatalyst.

Prior to developing recycling and continuous-flow applications with the **IM-NHC5** precatalyst, its activity in catalysis was verified (**Figure 12b**). Unfortunately, using the benchmark reaction conditions (**Figure 12b**, *i.e.* neat in acetaldehyde, 1.0mol% cat.) did not result in noticeable quantities of acetoin based on the GC-FID chromatogram (< 1%). However, when EtOH was introduced as solvent for the reaction at otherwise identical reaction conditions, around 18% of acetoin yield was attained (**Figure 14**, experiment 14.1). Absence of reactivity when carrying out the reaction in pure acetaldehyde, could be due to swelling behaviour of the *Merrifield* resin in EtOH as solvent.^[214] In pure acetaldehyde, a contracted resin is retained where catalytic centres might be entrapped in the contracted support structure. On the other hand, the homogeneous **NHC5** precatalyst was able to attain 87% yield (**Figure 14**, experiment 14.2). When performing the reaction in EtOH, some side products started to emerge. Among the side products were mainly 1,1-diethoxyethane and paraldehyde which were identified from GC-MS measurements.

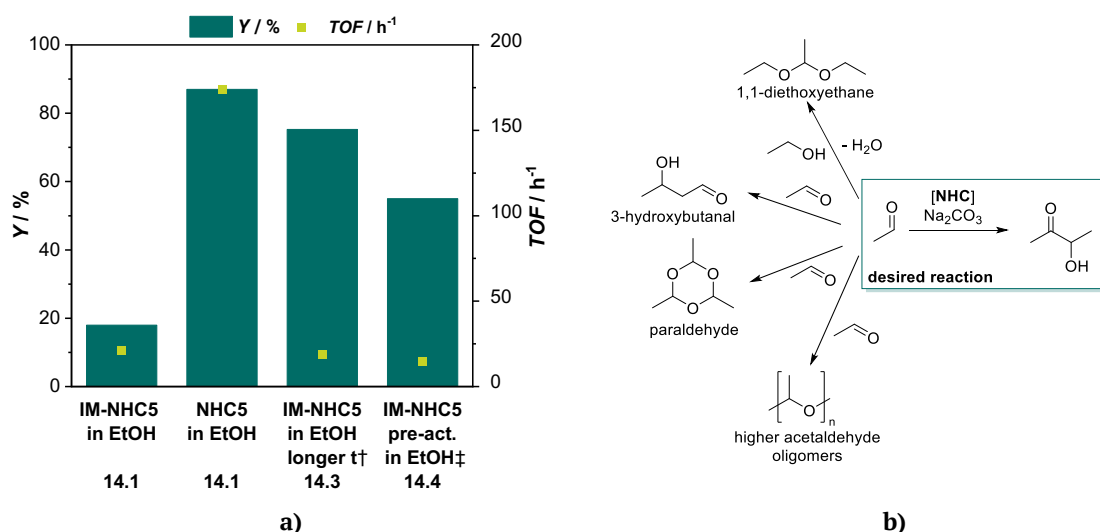


Figure 14: **a)** Catalytic results from various experiments with the **NHC5**/ Na_2CO_3 or **IM-NHC5**/ Na_2CO_3 in the self-addition of acetaldehyde to acetoin. **b)** Schematic representation of the formation of various side products that were identified using GC-MS and observed in minor quantities (<5 %). Reaction conditions: $V(\text{acetaldehyde}) = 1.0 \text{ mL}$, $n(\text{acetaldehyde}) = 18 \text{ mmol}$, $c(\text{cat}) = 1.0 \text{ mol\%}$, $c(\text{Na}_2\text{CO}_3) = 1.3 \text{ mol\%}$, $V(\text{EtOH}) = 5.0 \text{ mL}$, $T = 100^\circ\text{C}$, $t = 0.5 \text{ h}$. † $c(\text{IM-NHC}) = 1.0 \text{ mol\%}$, $c(\text{Na}_2\text{CO}_3) = 1.3 \text{ mol\%}$, $V(\text{EtOH}) = 1.0 \text{ mL}$, $T = 70^\circ\text{C}$, $t = 2 \text{ h}$. Yields determined by GC-FID using mesitylene as internal standard. ‡ pre-activated using equimolar amount of KO $^\text{i}$ Bu before adding substrate to avoid base catalysed side reactions at otherwise identical reaction conditions to † .

Carrying out experiment 14.1 for longer reaction times, resulted to an almost four-fold increase in yield from roughly 18% to 75% after 2 h of reaction time (14.3). For the experiment, an excellent selectivity of $S = 96\%$ towards acetoin was attained. Again, paraldehyde and 1,1-diethoxyethane (**Figure 14b**) were identified as main side products. Formation of base-catalysed condensation products like 1,1-diethoxyethane were also verified by various blind-experiments that were carried out in absence of catalyst but in presence of Na_2CO_3 . Although for these blind experiments, conversions of acetaldehyde were found to be very low (<3%), 1,1-diethoxyethane, some 3-hydroxybutanal (aldol-product), as well as negligible amounts of higher acetaldehyde oligomers were identified from GC-MS measurements. Blind experiments using pure acetaldehyde and Na_2CO_3 did not result in the formation of these side products.

In experiment 14.4, a pre-activation strategy was investigated. For this purpose, the catalyst was suspended in EtOH and to that was added KO $^\text{i}$ Bu as strong base. After pre-activating the catalyst for 30 minutes at room temperature, the catalyst was filtered-off and washed with EtOH, prior to adding acetaldehyde as substrate. Carrying out the reaction with pre-activated **IM-NHC5** at otherwise identical conditions afforded 55% acetoin yield. As opposed to the experiments where Na_2CO_3 resided in the system, presence of 1,1-diethoxyethane and other aldol products were found to be below detection limits of GC-FID. Especially for continuous-flow applications, a pre-activation step could be beneficial. However, pre-activation resulted in substantially lower acetoin yields. In addition, the **IM-NHC5**/ Na_2CO_3 catalytic system has an exceptional ease-of-use compared to the pre-activated system. Therefore, the pre-activation strategy was omitted in further recycling and continuous-flow applications.

5.1.4 Recycling and Continuous-flow Applications with IM-NHC5

Prior to developing the continuous-flow application with the **IM-NHC5**/ Na_2CO_3 system, the system was subjected to various batch-recycling experiments. As opposed to the experimental conditions in Figure 14, a lower temperature of 70 °C was used to minimise the impact of higher temperatures on the resin-based catalyst. Also, the concentration of the catalyst was elevated to 2mol% and the concentration of base was adjusted accordingly. The results of five consecutive recycling experiments are shown below in Figure 15.

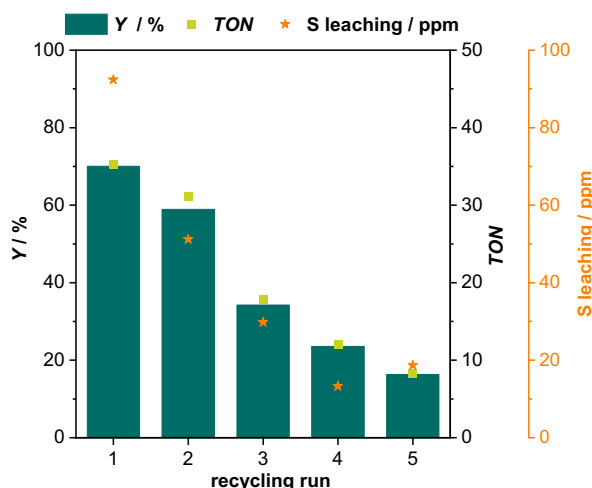


Figure 15: Catalytic results from batch recycling runs using the **IM-NHC5**/ Na_2CO_3 catalytic system in the acetaldehyde self-addition. As substrate containing stock-solution of acetaldehyde in EtOH was used (1:1). Reaction conditions: $V(\text{stock}) = 2.0 \text{ mL}$, $m(\text{IM-NHC5}) = 119.8 \text{ mg}$ (0.4 mmol, 2.0mol%), $m(\text{Na}_2\text{CO}_3) = 53.4 \text{ mg}$ (0.5 mmol, 2.6mol%), $T = 70 \text{ }^\circ\text{C}$, $t = 2 \text{ h}$. Yields determined by GC-FID using mesitylene as internal standard. Mass-balances $\Sigma Y > 92\%$ were obtained.

After each catalytic run, the post reaction solution was extracted from the reaction vessel *via* cannula filtration, ensuring that the catalyst beads remained inside the reactor. Fresh substrate containing stock-solution was added, without intermediary catalyst reactivation procedures that were described in literature for a similar catalytic system (re-protonation and de-protonation).^[184] To preserve the activity of the catalyst, all operations including filtration of the post reaction solution and the addition of fresh substrate, were conducted under inert atmosphere. The integrity of the **IM-NHC5** catalyst beads was maintained throughout the process, with no observable loss of solid catalyst. The limited solubility of Na_2CO_3 in EtOH allowed for a consistent base concentration, which was also confirmed *via* X-ray fluorescence (XRF) analysis after each run. Sodium levels in the post reaction solutions were consistently below 17 ppm. In the first catalytic run, 72% yield of acetoin was achieved (Figure 15). From post reaction XRF measurements, sulphur concentrations in the post reaction solution were already elevated after the first recycling run. By the second run, catalytic activity had declined, with a yield of approximately 60% acetoin. Over three consecutive runs, the catalytic activity further deteriorated, resulting in a yield of only 16% acetoin in the fifth run.

As depicted in Figure 15, elevated sulphur levels were detected in the post reaction solutions after each run. Given that each catalytically active centre in **IM-NHC5** contains a single sulphur atom (Scheme 20), suggests that presence of sulphur in the solution results from catalyst decomposition. To rule out the possibility that this degradation was caused by batch recycling procedures, the system was transitioned from a batch recycling to a continuous-flow

operation mode. The reaction conditions of the continuous-flow experiment were chosen to mimic the conditions of the batch recycling experiments, with an average residence time of $\tau = 2$ h inside the stirred tank reactor. A more detailed experimental procedure as well as the description of continuous stirred tank reactor (CSTR) miniplant that was used for these experiments, can be found in section 7.4.3. Conversion, yield, selectivity as well as the leaching-over-time behaviour of a typical continuous-flow experiment, are shown below in Figure 16.

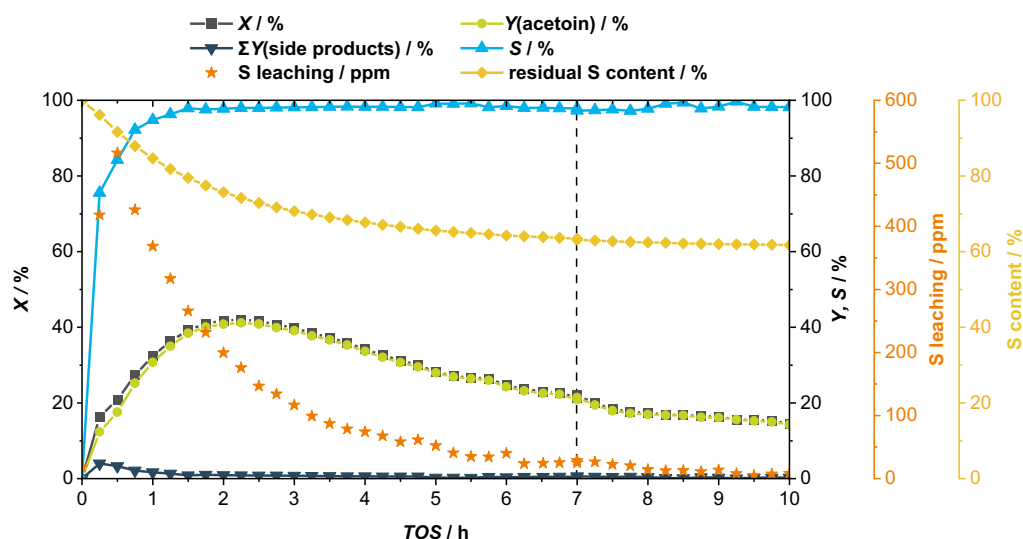


Figure 16: Catalytic results of the continuous-flow acetaldehyde self-addition, carried out in a CSTR miniplant for a total of duration of 10 h TOS. Graph indicates conversion X , yield Y and selectivity S towards acetoin over TOS as well as the calculated residual sulphur content (%) of the catalyst and the measured leaching of sulphur in ppm. Reaction conditions: stock-solution containing acetaldehyde (250 mL, 194.7 g, 4.4 mol), EtOH (250 mL, 196.4 g, 4.5 mol) and mesitylene (29.0 mL, 24.86 g), flow-rate(stock) = $0.475 \text{ mL} \cdot \text{min}^{-1}$, $m(\text{IM-NHC5}) = 1.7386 \text{ g}$ ($3.24 \text{ mmol} \cdot \text{g}^{-1}$, 5.63 mmol NHC , $2 \text{ mol}\%$), $m(\text{Na}_2\text{CO}_3) = 775.9 \text{ mg}$ (7.32 mmol , $2.6 \text{ mol}\%$), $T = 70^\circ \text{C}$, $\tau = 2 \text{ h}$. Mass-balances $\Sigma Y > 90\%$ were obtained. Dotted line at $t = 7 \text{ h TOS}$, indicates that the reaction was terminated over-night and re-started the next day.

As observed in Figure 16, the system reaches its maximum in catalytic activity after a start-up phase of approximately 2 h time-on-stream (TOS), achieving an acetoin yield of 41% at 42% acetaldehyde conversion resulting in a selectivity towards acetoin of $S > 97\%$. Compared to typical batch experiments (Figure 15, $Y(\text{acetoin}) = 70\%$ after 2 h), yields and conversions obtained in the continuous-flow experiment are notably lower. This can be attributed to the fact that the residence time, is only a resemblance for the average residence time of all substrates and products in the continuous-flow setup. Also, channelling may occur when catalyst and base are present in the system, as they were not introduced to the system when estimating the residence time distribution (section 7.4.4). This channelling might have resulted in a potential runaway of acetaldehyde. Nonetheless, an excellent selectivity ($S > 97\%$) was maintained throughout the experiment. In the initial 2 hours, minor side products such as paraldehyde, 1,1-diethoxyethane, and 3-hydroxybutanal (aldol product) were detected by GC-FID, with a combined yield of less than 2% after over 2.5 h TOS. Following the peak conversion and yield, the catalyst's activity gradually declines, reaching approximately 15% conversion and acetoin yield after 10 h TOS. In addition, Figure 16 also illustrates the residual sulphur content (%) and sulphur leaching (ppm) as determined from XRF measurements over time. Residual sulphur content of the spent catalyst was determined

from elemental analysis. The sulphur content in the catalyst decreased from $3.24 \text{ mmol}\cdot\text{g}^{-1}$ for the pristine **IM-NHC5** to $2.00 \text{ mmol}\cdot\text{g}^{-1}$ after the reaction, corresponding to a loss of approximately $1.24 \text{ mmol}\cdot\text{g}^{-1}$ or 38% of the sulphur content, *i.e.* catalytically active centres. Sulphur leaching exhibits an exponential trend, with more significant leaching observed at the beginning of the reaction compared to longer *TOS*. After 5 h of *TOS*, the leaching rate stabilizes, resulting in a steady decline in catalytic activity toward the end of the reaction. Interestingly, interrupting the reaction after 7 h *TOS* by quickly cooling the system to room temperature and resuming the experiment on the next day, did not significantly affect selectivity, which remained high. However, the decline in conversion and yield persisted, indicating that the system's reduced productivity is directly linked to the loss of catalytically active material. Despite transitioning to continuous operation mode, sulphur leaching was not suppressed. Nonetheless, the **IM-NHC5**/ Na_2CO_3 system was able to attain a total turn-over-number (TTON) of 111 at an average acetoin yield of 26% through single-pass conversion. Using this average acetoin yield, the given reactor volume of $V = 30.6 \text{ mL}$ (see section 7.4.4), the residence time $\tau = 2 \text{ h}$ and the concentration of acetaldehyde in the feed, affords a space-time-yield of $STY = 48 \text{ g}\cdot\text{L}^{-1}\cdot\text{h}^{-1}$.

As a starting point of developing a more profound knowledge about the apparent catalyst deactivation, an experiment was performed using the **IM-NHC5**/ Na_2CO_3 in the absence of acetaldehyde as substrate at otherwise identical conditions to experiment 14.3. The “post reaction” mixture was analysed using ESI-MS, solution-state ^1H NMR spectroscopy, and XRF. XRF analysis revealed approximately 320 ppm of sulphur in the post reaction content. From ESI-MS analysis, a prominent peak at $m/z = 144.1$ was identified, strongly indicating presence of 4-methyl-5-thiazole ethanol ($M = 143.21 \text{ g}\cdot\text{mol}^{-1}$). Further evidence was provided by the ^1H NMR spectrum (400 MHz, EtOD- d_6 , rt) of the “post reaction” solution. Signals were observed at $\delta = 8.62$ (s, 1H), 2.88 (t, $J = 6.7 \text{ Hz}$, 2H), and 2.28 (s, 3H) ppm. Comparison with the pure component spectrum and literature data, confirmed that these signals can be attributed to 4-methyl-5-thiazole ethanol in the “post reaction” solution (Figure 17).

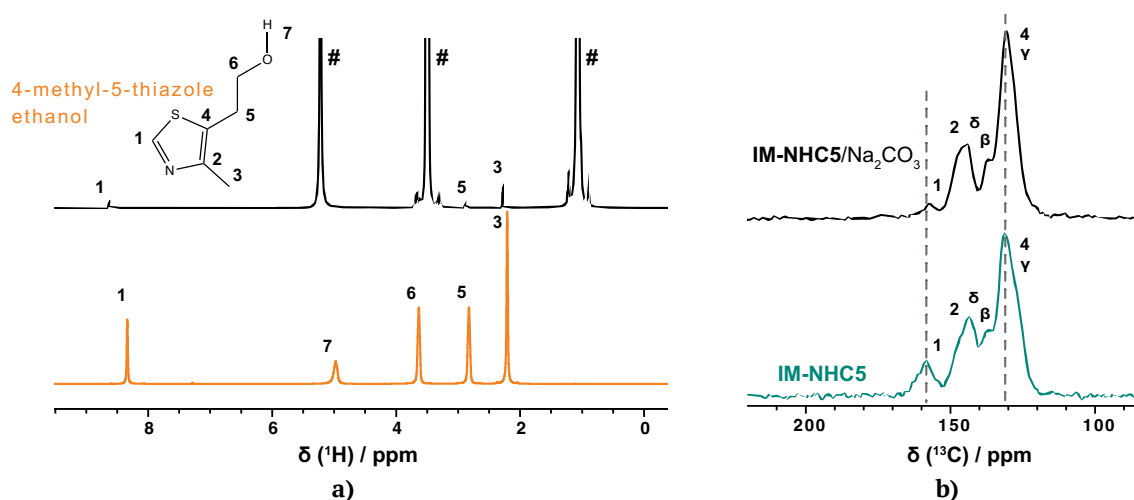
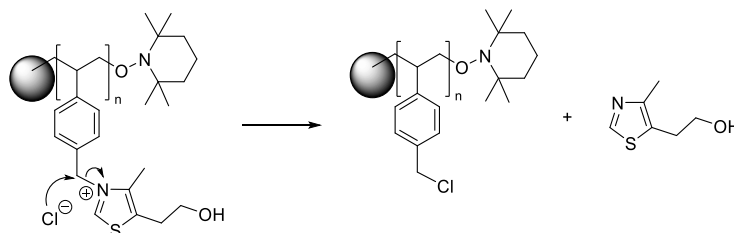


Figure 17: **a)** Comparison of ^1H NMR (400 MHz, EtOD- d_6 , rt) spectrum of the post reaction solution of a blind-experiment where **IM-NHC5**/ Na_2CO_3 was heated in EtOH for 2 h at 70 °C (top) as well as the pure component spectrum of 4-methyl-5-thiazole ethanol (bottom) including the assignments of resonances. **b)** ^1H - ^{13}C CP NMR spectra of spent **IM-NHC5**/ Na_2CO_3 after catalysis (black) and pristine **IM-NHC5** (as seen in Figure 17a, green). Spectra were recorded at 11.7 T and a MAS frequency of 14.0 kHz. # denote ^1H peaks of EtOH as reaction solvent.

Apart from the signals clearly hinting to presence of 4-methyl-5-thiazole ethanol, no other decomposition products were observed from ^1H NMR spectrum. Hence, the most probable pathway of decomposition of **IM-NHC5** is the degradation into 4-methyl-5-thiazole ethanol and most probably pristine *Merrifield*'s resin (**Scheme 21**).



Scheme 21: Mechanism of the reverse *Menshutkin* reaction where precatalyst **IM-NHC5** decomposes into pristine *Merrifield*'s resin and 4-methyl-5-thiazole ethanol. The chlorine counterion acts as nucleophile in the $\text{S}_{\text{N}}2$ reaction. Most likely, the reaction only occurs with the precatalyst **IM-NHC5** and does not take place as postulated for the activated carbene form of the catalyst.

The observed degradation pathway, also known as the reverse *Menshutkin* reaction, is well established in literature for imidazolium as well as thiazolium halide salts.^[210, 215-217] Verification experiments were carried out to show that the leached 4-methyl-5-thiazole ethanol had no catalytic properties in the self-addition of acetaldehyde. This is not surprising, as the compound cannot be converted to a carbene species by using Na_2CO_3 as a base. In a similar manner, it was shown that pristine *Merrifield* resin did not exhibit catalytic properties. Decomposition of **IM-NHC5** underlies a molecular-level degradation mechanism and might be mitigated by increasing the stability of the catalyst. Furthermore, the occurrence of the reverse *Menshutkin* reaction hints, that **IM-NHC5** is not fully converted to its active form. The probability of the *Menshutkin* reaction occurring from the active carbene catalyst is deemed to be unlikely. As the heterogeneous catalyst is activated by a solid base, an in-depth study on the role of base on the activation of **IM-NHC5** could provide a deeper understanding on the mechanism of activation of the precatalyst, as well as the mechanism of decomposition.

5.1.5 In-Depth Study on the Role of Na_2CO_3 on the Activity of **IM-NHC5**

During analysis of samples collected from a typical **IM-NHC5** experiment described earlier, it was found that sodium levels were below detection limits of the XRF instrument. This means that it is amendable that Na_2CO_3 is solid throughout the reaction, which raises the assumption that activation of **IM-NHC5** proceeds *via* a solid-solid interface reaction. Consequently, the amount of Na_2CO_3 present, and thus the available base surface might have an influence on the productivity of the system as well (**Table 3**).

Table 3: Results of the **IM-NHC5** catalysed acetaldehyde self-addition using different concentrations of Na_2CO_3 .^[a]

Entry	$c(\text{Na}_2\text{CO}_3)$ (mol%)	$Y(\text{acetoin})^{[b]}$ (%)	$\Sigma Y(\text{side products})^{[b,c]}$ (%)	$S(\text{acetoin})$ (%)
3.1	0	<0.1	38	<0.1
3.2	1.3	40	21	66
3.3	2.6	73	5	91
3.4	5.2	82	4	95
3.5	10.4	83	3	96
3.6	26.0	83	4	95

[a] Reaction conditions: experiments were carried out using a stock solution containing acetaldehyde, ethanol and mesitylene in a 1:1:0.1 volumetric ratio. $V(\text{stock}) = 2.0 \text{ mL}$, $n(\text{acetaldehyde}) = 18 \text{ mmol}$, $c(\text{IM-NHC5}) = 2 \text{ mol\%}$, $T = 70 \text{ }^\circ\text{C}$, $t = 2 \text{ h}$. [b] As determined by GC-FID using mesitylene as internal standard [c] Side products include 1,1-diethoxyethane, paraldehyde. The overview of identified side products is shown in **Figure 14b**.

As indicated in **Table 3** entry 3.1, in absence of Na_2CO_3 acetoin yields are found to be below detection limits of GC-FID. Instead, paraldehyde and 1,1-diethoxyethane are attained as main side products at a combined yield of 38%. Without base present in the system, the catalytically active carbene species cannot be generated, resulting in unwanted side reactions of the reactive acetaldehyde. In contrast, employing an under stoichiometric quantity of base (entry 3.2) resulted in an acetoin yield of already 40% and a combined side product yield of 21%. Comparison of the results in entry 3.2 and the benchmark experiment in 3.3 highlights the importance of presence of base as a deficiency of base leads to a decline in catalytic performance.

Elevating the base concentration to well above the precatalyst concentration (entry 3.4) leads to an increase in acetoin yield from 73 to 82%. This improvement may be attributed to the previously insufficient base concentration for effectively activating the heterogeneous **IM-NHC5** precatalyst. In this case, the higher base concentration provides an increased available base surface, which in turn facilitates greater activation of the **IM-NHC5** precatalyst, leading to an increased product yield. However, further elevating the base concentration to 10.4 mol% (entry 3.5) or even 26 mol% (entry 3.6) does not significantly enhance catalytic performance. Notably, at such high base concentrations, side product yields are found to be < 5% throughout. Based on the data presented in **Table 3**, the optimal catalyst-to-base ratio is determined to be 1:5.2.

Given the significant role of Na_2CO_3 in catalyst activation, it is plausible that particle size also influences catalytic productivity. A finer base particle size may enhance catalyst activation by providing a greater surface area. To investigate this hypothesis, a series of experiments were conducted using sodium carbonate (Na_2CO_3) sieved through defined mesh sizes, prior to use in catalysis (**Table 4**).

Table 4: Results of the **IM-NHC5**/ Na_2CO_3 catalysed acetaldehyde self-addition in EtOH as solvent using different mesh-fractions of Na_2CO_3 .^[a]

$$2 \text{ CH}_3\text{CHO} \xrightarrow[\text{EtOH}]{\text{IM-NHC5 (2.0 mol\%)}, \text{Na}_2\text{CO}_3 (2.6 \text{ mol\%})} \text{CH}_3\text{C(OH)(CH}_3\text{)}_2$$

Entry	sieve fraction d (μm)	Y(acetoin) ^[b] (%)	$\Sigma Y(\text{side products})^{[b,c]}$ (%)	S(acetoin) (%)
4.1	≥ 300	59	13	81
4.2	$200 < d < 300$	78	6	93
4.3	≤ 200	85	4	96

[a] reaction conditions: experiments were carried out using a stock solution containing acetaldehyde, ethanol and mesitylene in a 1:1:0.1 volumetric ratio. $V(\text{stock}) = 2.0 \text{ mL}$, $n(\text{acetaldehyde}) = 18 \text{ mmol}$, $c(\text{IM-NHC5}) = 2 \text{ mol\%}$, $c(\text{Na}_2\text{CO}_3) = 2.6 \text{ mol\%}$, $T = 70 \text{ }^\circ\text{C}$, $t = 2 \text{ h}$. [b] As determined by GC-FID using mesitylene as internal standard. [c] Side products include 1,1-diethoxyethane, paraldehyde and others.

When employing Na_2CO_3 with a coarse grain size of $\geq 300 \mu\text{m}$, an acetoin yield of 59% was achieved with a selectivity of 81% (entry 4.1). In contrast, using as-received Na_2CO_3 under identical conditions (Table 3 entry 3.3) resulted in a higher acetoin yield of 73% at 91% selectivity. This finding demonstrates that the activation efficiency of the **IM-NHC5** precatalyst is negatively impacted by larger Na_2CO_3 particle sizes, likely due to reduced surface availability. The results presented in Table 4, entry 4.2 further reinforce the hypothesis that the accessible base surface area plays a critical role in precatalyst activation. As the particle size is reduced ($200 \mu\text{m} < d < 300 \mu\text{m}$), a greater surface area becomes available, leading to an increased acetoin yield of 78% with an exceptional selectivity of 93%. A further reduction in Na_2CO_3 particle size ($d \leq 200 \mu\text{m}$) led to a significant improvement in catalytic performance, yielding 85% acetoin with a selectivity of 96% and minimal side product formation (entry 4.3).

The combined results from Table 3 and Table 4 indicate that an optimal catalytic performance is achieved with a Na_2CO_3 particle sizes $\leq 200 \mu\text{m}$ and a concentration of 5.2 mol%, relative to the substrate. To further investigate the effect of increased base concentration on system performance and catalyst stability under continuous-flow conditions, an experiment was conducted using a the CSTR miniplant setup (Figure 18). Initially, a base concentration of 2.6 mol% with a particle size $\leq 200 \mu\text{m}$ was employed during the first 5 h of TOS to allow for a direct comparison with system previously discussed in Figure 16. For reasons of comparison, key catalytic parameters of the **IM-NHC5**/ Na_2CO_3 catalysed system discussed in in Figure 16 are summarized in Figure 18 as well.

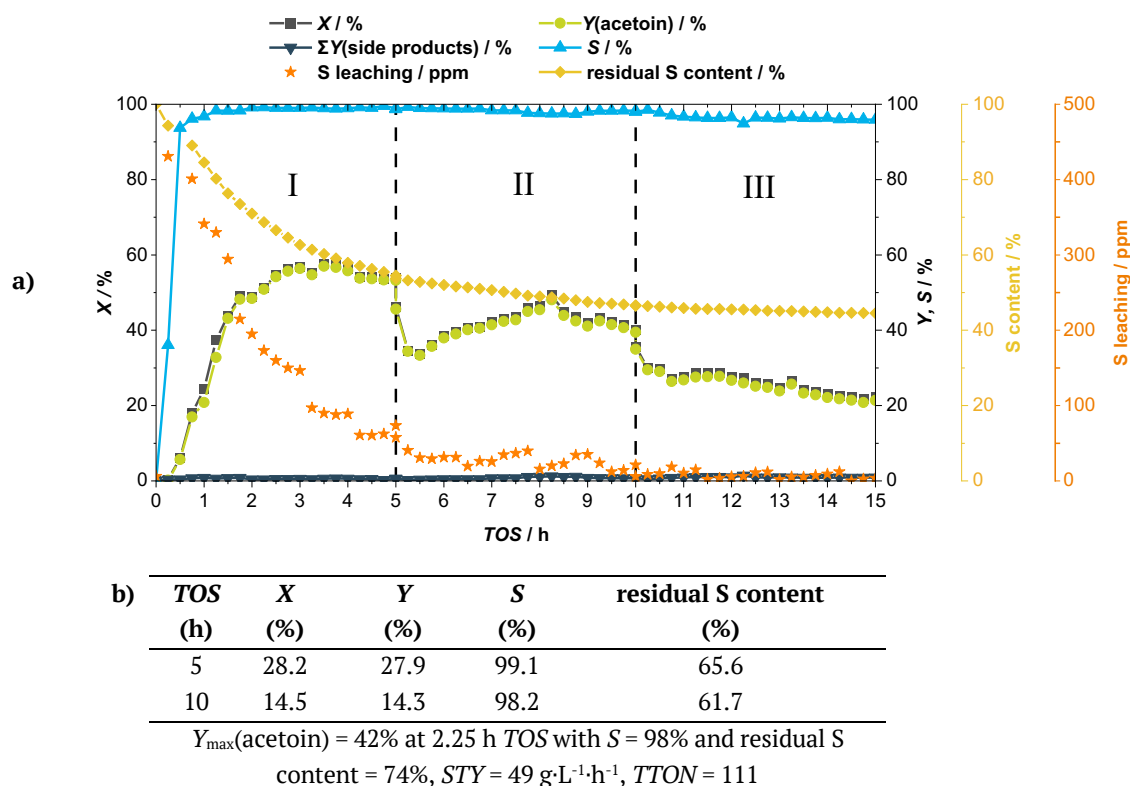


Figure 18: a) Catalytic results of the continuous-flow acetaldehyde self-addition in a CSTR setup over a total of 15 h TOS with intermittent Na_2CO_3 addition after 5 h TOS (2 cycles). Graph indicates conversion X , yield Y and selectivity S towards acetoin over TOS as well as the calculated residual sulphur content (%) of the catalyst and the measured leaching of sulphur in ppm. Reaction conditions: stock-solution containing acetaldehyde (350 mL, 274.8 g, 6.2 mol), EtOH (350 mL, 275.3 g, 6.0 mol) and mesitylene (40.0 mL, 33.94 g), flow-rate(stock) = $0.475 \text{ mL}\cdot\text{min}^{-1}$, $m(\text{IM-NHC5}) = 1.7403 \text{ g}$ ($3.24 \text{ mmol}\cdot\text{g}^{-1}$, 5.64 mmol NHC, 2mol%), $m(\text{Na}_2\text{CO}_3) = 779.6 \text{ mg}$ (7.36 mmol, 2.6mol%), $T = 70^\circ\text{C}$. Dotted lines indicate that the reaction was terminated over-night and re-started the next day. b) Tabular representation of the key catalytic results from Figure 16.

For the experiment in Figure 18a, an induction period was observed, which indicates a delayed catalyst activation and product generation. Nonetheless, the impact of the additional Na_2CO_3 crushing on the productivity of the system was particularly significant during the first 5 h TOS (Figure 18a, region I). A peak conversion and yield of 57% were achieved at 3.75 h TOS. In contrast, when employing as-received Na_2CO_3 , the maximum conversion and yield reached only 42% after 2.25 h (Figure 18b). Furthermore, XRF analysis after 5 h TOS revealed a 45% loss of catalytically active sites, a slightly greater decline than that found previously in Figure 16, where a 38% loss was attained under similar reaction conditions (Figure 18b). The first 5 h (Figure 18a, region I) underscore the influence of base properties on system performance, particularly when comparing the performance of the sieved Na_2CO_3 -based ($d \leq 200 \mu\text{m}$) system with that of the as-received Na_2CO_3 -system.

To accommodate a base concentration of 5.2mol%, the reaction was terminated after 5 h TOS. The reactor was rapidly cooled to ambient temperature, and the system was left undisturbed overnight. The next day, at the onset of region II (Figure 18a), an additional 2.6mol% Na_2CO_3 was introduced into the reactor. Starting up the reactor as usual and analysing the effluent stream, led to observing a partial recovery of catalytic activity between 5 h and 8.3 h TOS. A maximum conversion of 48% was observed at 8.25 h TOS before yields gradually declined to 40% at 10 h TOS. Notably, the addition of supplementary base did not affect the leaching

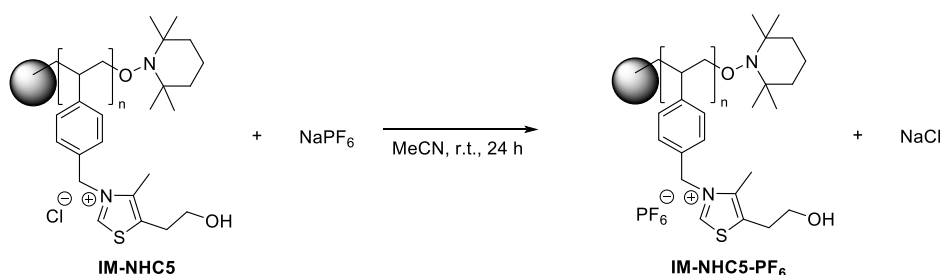
behaviour observed. Furthermore, acetoin selectivity remained consistently high, exceeding 96% throughout region II. Increasing the base concentration to 5.2mol%, as suggested by batch experiments (Table 3), proved advantageous for catalytic productivity. However, the additional base did not mitigate catalyst decomposition, as indicated by the sulphur leaching trend, which remained consistent throughout region II.

Following a second base addition after 10 h TOS (Figure 18a, beginning of region III), a moderate increase in catalytic activity was observed. However, after 12.5 h TOS, the rate of activity decline in region III was more pronounced than in region II. A slight reduction in overall selectivity was also noted, likely due to the combined effects of gradual catalyst degradation and the excessive base concentration, which may have blocked active catalytic sites, thereby reducing overall productivity. In region III, the formation of aldol condensation by-products increased relative to regions I and II. Despite this, residual catalytic activity remained above 20% with excellent selectivity (> 96%) throughout region III.

Overall for this experiment, a space-time-yield $STY = 56 \text{ g}\cdot\text{L}^{-1}\cdot\text{h}^{-1}$ and $TTON$ of 230 were attained, representing significant improvements over the system discussed in Figure 16. Nonetheless, though the intermittent addition of Na_2CO_3 combined with finer particle sizes, enhanced the productivity of the **IM-NHC5** based catalytic system, it did not improve its stability. Therefore, in order to suppress the reverse *Menshutkin* reaction, the molecular design of the catalyst needs to be addressed.

5.1.6 Structural Modifications of the IM-NHC5 Catalyst for Improved Stability

It has already been shown in literature, that the anion of certain homogeneous thiazolium precatalysts has a significant effect on their stability.^[210] A significant enhancement in thermal stability was observed when using larger, non-nucleophilic anions like OTf^- and BF_4^- , whereas precatalysts bearing simple halide anions like I^- and Br^- were found to be less thermally stable.^[210] In this context, it is hypothesised that by exchanging the nucleophilic Cl^- counterion in **IM-NHC5** with a non-coordinating, non-nucleophilic one like PF_6^- could result in a more stable heterogeneous catalyst. Starting from pristine **IM-NHC5**, an ion exchange procedure was carried out, commonly described in literature for halide-based ionic liquids (Scheme 22).^[218-219]



Scheme 22: Schematic representation of the ion exchange procedure with **IM-NHC5** and NaPF_6 in acetonitrile at room temperature to afford the PF_6 derivatised **IM-NHC5-PF₆** (see section 7.3.3 for detailed procedure).

After the ion exchange procedure, the loading of catalytically active compound was determined to be $2.27 \text{ mmol}\cdot\text{g}^{-1}$ whereas the loading of unmodified **IM-NHC5** used in this procedure, was determined to be $2.87 \text{ mmol}\cdot\text{g}^{-1}$. Loss of catalytically active component during the immobilisation procedure hints that the decomposition of **IM-NHC5** is catalysis

independent. To still account for the same concentration of catalytically active component, the mass of catalyst was adjusted in the experiments that will be discussed in this section. Notably, after the ion exchange procedure, the loading of PF_6^- in **IM-NHC5-PF₆** was determined to be $2.27 \text{ mmol}\cdot\text{g}^{-1}$, indicating that each Cl^- as anion to the quaternary N atom in every catalytically active centre was replaced with a non-nucleophilic PF_6^- counter ion.

After preparing and analysing the modified **IM-NHC5-PF₆** catalyst (see section 7.3.3) its performance was compared to that of the pristine **IM-NHC5** (Table 5).

Table 5: Catalytic results of two batch experiments carried out with **IM-NHC5-PF₆**/ Na_2CO_3 as well as the results of a comparable experiment carried out with unmodified **IM-NHC5**.^[a]

Entry	Catalyst	Y(acetoin) ^[b] (%)	Σ Y(side products) ^[c] (%)	TON (acetoin)	S leaching ^[d] (ppm)
5.1	IM-NHC5-PF₆	75	1.9	37	21
5.2	IM-NHC5	75	3.8	38	58

[a] Reaction conditions: $V(\text{acetaldehyde}) = 1.0 \text{ mL}$, $n(\text{acetaldehyde}) = 18 \text{ mmol}$, $V(\text{EtOH}) = 1.0 \text{ mL}$, $c(\text{cat.}) = 2\text{mol}\%$, $c(\text{base}) = 2.6\text{mol}\%$, $T = 70^\circ\text{C}$, $t = 2 \text{ h}$. [b] As determined by GC-FID using mesitylene as internal standard. [c] Side products include 1,1-diethoxyethane, paraldehyde and others aldol products. [d] Determined via XRF measurements of the filtered post reaction solution.

A comparison of the single-run catalytic performance of the modified **IM-NHC5-PF₆** catalyst (entry 5.1) with that of the unmodified **IM-NHC5** catalyst (entry 5.2) reveals that both catalysts afford a similar yield, selectivity, and turnover number. However, an analysis of sulphur leaching indicates a significantly lower degree of leaching when using **IM-NHC5-PF₆**. Specifically, after a typical reaction, the **IM-NHC5-PF₆** catalyst leaches approximately 21 ppm of sulphur into the solution, whereas the **IM-NHC5** catalyst leaches nearly three times this amount (58 ppm, entry 5.2). Considering the extent of sulphur leaching as a measure for catalyst stability already indicates that the **IM-NHC5-PF₆** catalyst has improved stability and thus holds potential for a more elaborate investigations in both batch recycling and continuous-flow applications.

5.1.7 Recycling and Continuous-flow Applications with **IM-NHC5-PF₆**

Owing to the presumed greater stability of **IM-NHC5-PF₆**, batch recycling as well as continuous-flow applications seem more promising with this second generation, immobilised NHC precatalyst. Batch recycling experiments were carried out using the same experimental procedure as for the developed **IM-NHC5**/ Na_2CO_3 system. Below in Figure 19, a graphical representation of the results of several batch recycling experiments with **IM-NHC5-PF₆** is shown. Also, Figure 19 includes a tabular representation of the results earlier discussed for the unmodified **IM-NHC5**-based catalytic system as seen in Figure 15 for reasons of comparison.

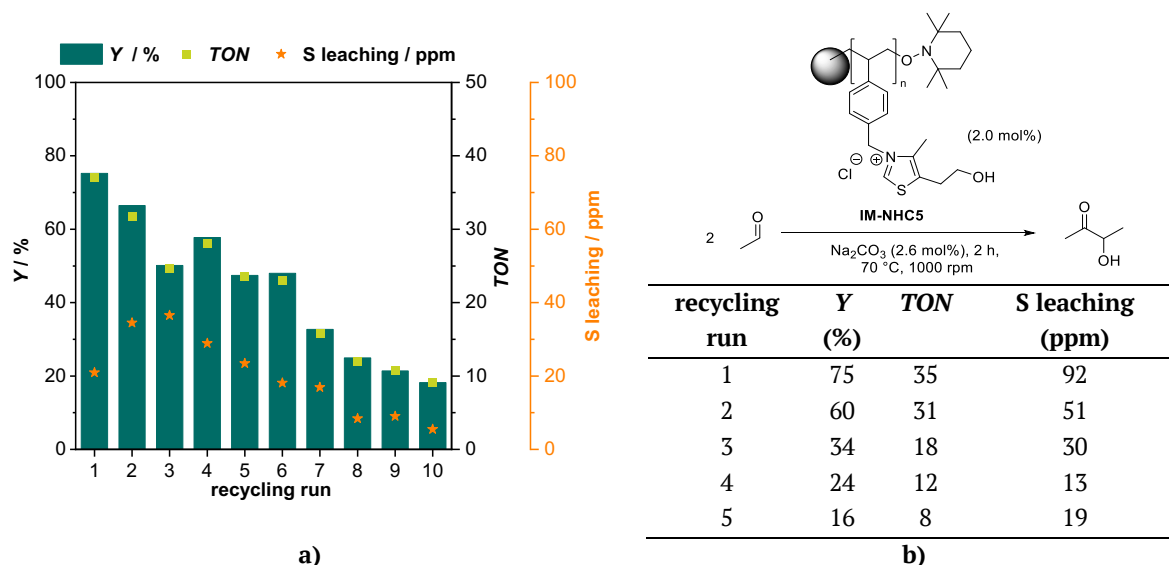


Figure 19: a) Graphical representation of the catalytic results obtained from ten consecutive recycling runs using the **IM-NHC5-PF₆/Na₂CO₃** catalyst system in the acetaldehyde self-addition to acetoin. **b)** Tabular representation of the results obtained by the pristine **IM-NHC5/Na₂CO₃** system discussed in **Figure 15**. Reaction conditions: $m(\text{IM-NHC5-PF}_6) = 156.2 \text{ mg}$ ($2.27 \text{ mmol} \cdot \text{g}^{-1}$, 0.4 mmol , $2.0 \text{ mol}\%$), $m(\text{Na}_2\text{CO}_3) = 53.6 \text{ mg}$ (0.5 mmol , $2.6 \text{ mol}\%$), $T = 70^\circ \text{C}$, $t = 2 \text{ h}$, yields determined by GC-FID using mesitylene as internal standard. Mass-balances $\Sigma Y > 90\%$ were obtained.

During the first catalytic run with **IM-NHC5-PF₆**, 75% acetoin was produced. In the second run, a slight decay in acetoin yield was observed to 66%. From the third to the sixth run, the acetoin yield stabilised at around 50%, with a minor increase to 57% in the fourth run. After the sixth run, the catalytic activity began to decline. Nevertheless, even after ten consecutive batch recycling experiments, with an added total of 20 hours TOS, a yield of 20% acetoin was still attained. Over these ten runs with the **IM-NHC5-PF₆/Na₂CO₃** system, a total turnover number of $TTON = 216$ was attained. The unmodified **IM-NHC5** catalyst showed significant decomposition, allowing only five consecutive runs (**Figure 15** and **Figure 22b**). In contrast, the PF₆-modified catalyst demonstrated greater stability indicated by lower sulphur leaching, maintaining a higher residual catalytic activity resulting in approximately 60% acetoin yield after five runs.

All in all, comparison of single-run catalytic experiments as well as batch recycling, suggest that the **IM-NHC5-PF₆** catalyst is more stable and less prone to decomposition. To further verify this, the catalyst was recovered after the 10th recycling experiment analysed using solid-state NMR spectroscopy. This investigation aimed to identify any spectroscopic evidence of catalytically active species, *i.e.* free carbenes, even after ten consecutive batch experiments. An overlay of several ¹H-¹³C and ¹H-³¹P CP spectra is shown in **Figure 20**. For reasons of comparison, the spectrum of pristine **IM-NHC5-PF₆** is also shown in **Figure 20**.

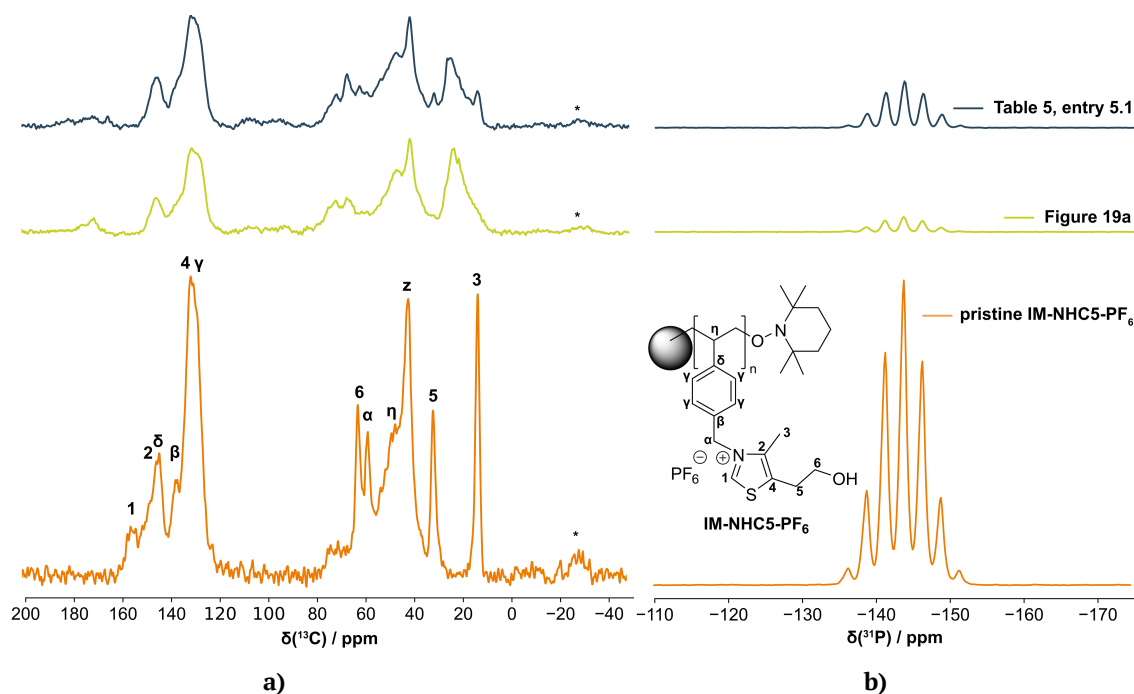


Figure 20: a) ^1H - ^{13}C and b) ^1H - ^{31}P CP spectra of **IM-NHC5-PF₆** subjected to different reaction conditions. In both a) and b), the grey spectra (top) correspond to **IM-NHC5-PF₆** after 2 h TOS (Table 5, entry 5.1), standard experiment with 2mol% cat, 2.6mol% Na_2CO_3 , the green spectra (bottom) correspond to **IM-NHC5-PF₆** after a total of 10 recycling runs in batch (Figure 19a). * indicates MAS sidebands. Spectra were recorded at 14.0 kHz MAS frequency and a static magnetic-field strength of 16.4 T.

Both the ^1H - ^{13}C CP MAS spectra of the spent catalyst, exhibit several notable changes, compared to the spectrum of the pristine **IM-NHC5-PF₆** (Figure 20a, bottom orange spectrum). An additional resonance, between 80 and 120 ppm appears in the spectra of the spent catalyst. This suggests formation of a yet unexplained structural or electronic modification of the catalyst during catalysis. Also, the resonance at 160 ppm in the ^1H - ^{13}C CP spectrum, attributed to carbon 1 undergoes de-shielding and an associated shift to around $\delta = 175$ ppm. Dipolar dephasing CP-MAS (DD-CPMAS) experiments were carried out that indicated that this resonance corresponds to a quaternary carbon atom which can potentially be linked to the activated carbene species. This finding supports the catalyst's high stability, as spectroscopic evidence for activated carbene species is found in the spent catalyst after ten batch recycling experiments.

The signal of the PF_6^- anion detected in ^1H - ^{31}P CP-experiments (Figure 20b) decreases with longer catalyst reaction times. This can likely be explained by the fact that the PF_6^- anion is washed out of the catalyst upon activation with Na_2CO_3 as NaPF_6 is soluble in EtOH. Evidence for the decreasing amount of PF_6^- was also found by elemental analysis of the respective spent catalysts.

Given the exceptional performance of **IM-NHC5-PF₆** in batch recycling experiments as well as the proven higher stability by means of solid-state NMR experiments, the **IM-NHC5-PF₆** catalyst appears highly promising for extended performance testing in the CSTR miniplant. Over the course of the study, the catalyst was maintained on-stream for more than 60 hours, during which various reaction conditions were explored keeping the catalyst in the closed system (Figure 22).

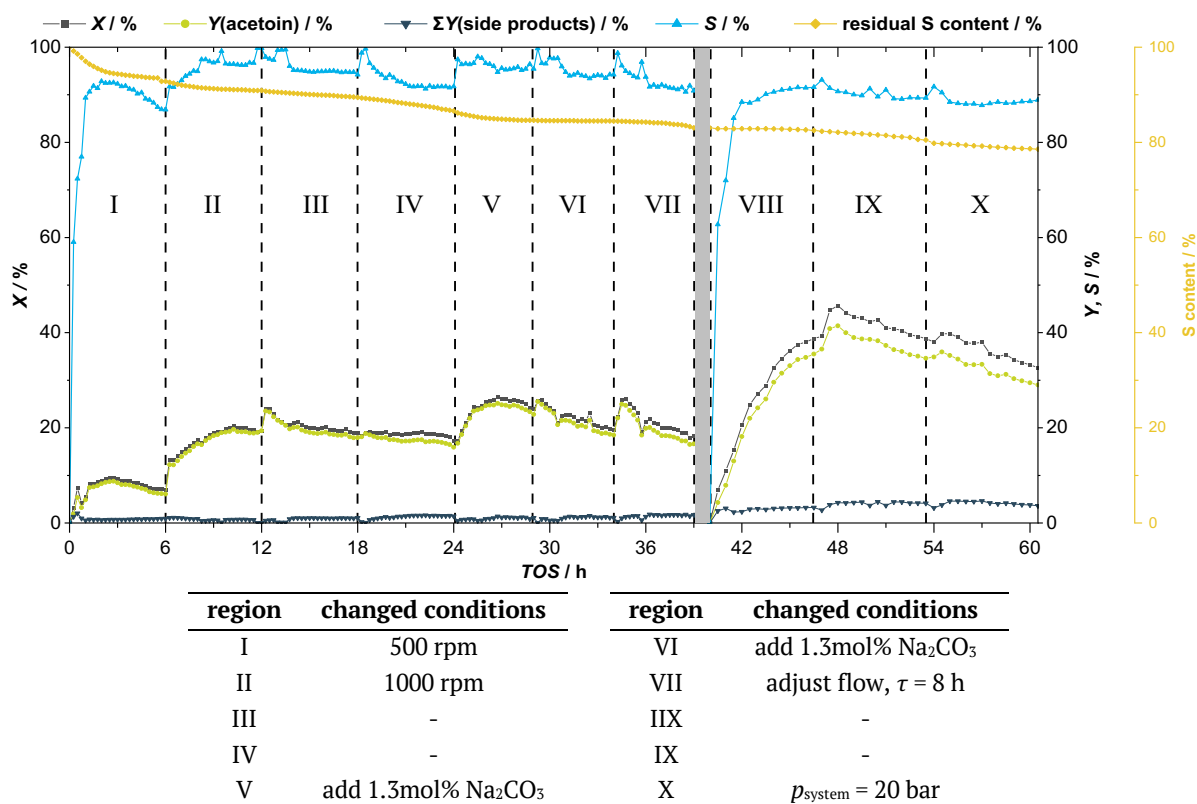


Figure 21: Results of the continuous-flow acetaldehyde self-addition over a total of 60 h. Graph indicates conversion X , yield Y and selectivity S towards acetoin over TOS as well as residual sulphur content (%) over time. Reaction conditions: stock-solution containing acetaldehyde EtOH and mesitylene, flow-rate(stock) = $0.475 \text{ mL} \cdot \text{min}^{-1}$, for $0 \text{ h} < TOS < 39 \text{ h}$, flow-rate(stock) = $0.148 \text{ mL} \cdot \text{min}^{-1}$ for $TOS > 39.5 \text{ h}$, $m(\text{IM-NHC5-PF}_6) = 2.49 \text{ g}$ ($2.27 \text{ mmol} \cdot \text{g}^{-1}$, 5.65 mmol NHC , $2 \text{ mol}\%$), $m(\text{Na}_2\text{CO}_3) = 775.0 \text{ mg}$ (7.31 mmol , $2.6 \text{ mol}\%$), $T = 70^\circ \text{C}$, $\tau = 2 \text{ h}$ for $0 \text{ h} < TOS < 39 \text{ h}$, $\tau = 8 \text{ h}$ for $TOS > 39.5 \text{ h}$. Mass-balances $\Sigma Y > 89\%$ were obtained. Dotted lines indicate that the reaction was terminated over-night and re-started the next day and/or changes were made with regard to the flow-rate of the substrate containing stock solution. Grey masked area at around 39 h indicates flushing of the reactor with EtOH: flow-rate(EtOH) = $3.0 \text{ mL} \cdot \text{min}^{-1}$.

During the first 6 h into the experiment, the conversions of acetaldehyde and yields of acetoin (10%) with the **IM-NHC5-PF₆** system are substantially lower compared to the unmodified **IM-NHC5** system (Figure 16). Notably, the selectivity reached a maximum of 92% before steadily decreasing to 85% after 6 h. This deviation from earlier observed trend, can be attributed to the reduced stirring speed of 500 rpm that was employed during this phase. The reduced catalytic activity observed under these conditions underscores the importance of strong mixing (*i.e.*, higher rpm) to ensure effective dispersion of solid Na₂CO₃ and optimal catalyst activation. During this period, only 8% of the initial amount of the catalytically active component (as indicated by residual sulphur content) was lost. In contrast, the earlier discussed CSTR experiments with the unmodified **IM-NHC5/Na₂CO₃** system, showed nearly 30% sulphur leaching into the solution within the same timeframe (Figure 16).

After 6 h TOS (beginning of region II, Figure 22) stirring speed was increased to 1000 rpm, leading to improved mixing within the reactor. The enhanced mass transfer resulted in increased conversion and yield, which rose to 20% with a selectivity of 96% towards acetoin in region II. In Regions III and IV, no changes were made to the reaction conditions, and both conversion and yield gradually declined to approximately 16%, while selectivity decreased to 91%. Despite this decrease, the **IM-NHC5-PF₆** catalyst remained active at the end of region

IV (24 h TOS), retaining approximately 86% of its initial sulphur content. These observations indicate that the PF₆-modified catalyst is significantly less prone to decomposition *via* the reverse *Menshutkin* reaction compared to its unmodified predecessor **IM-NHC5**. However, in terms of catalytic performance, the PF₆ modified catalyst exhibited a slightly lower activity.

Regions I to IV were conducted using the established catalyst-to-base ratio of 1:1.3. To evaluate the effect of intermittent base addition, 1.3 equivalents of solid Na₂CO₃ were introduced at the beginning of region V, increasing the base concentration from 2.6mol% to 5.2mol%. This base addition significantly boosted system productivity, while its impact on catalyst leaching behaviour remained negligible.

At the start of regions VI and VII, another 1.3 equivalents of base were added. Interestingly, the productivity increase in region VI was less pronounced than in region VII. Despite this, a gradual decline in productivity was evident from approximately 27 h TOS (mid-region V) through the end of region VII. Nevertheless, the modified catalyst still remained active after 39 h TOS, achieving a conversion of 20%, an acetoin yield of 18%, and a selectivity of 90%, with a residual sulphur content of 83%.

Between 39 h TOS and 39.5 h TOS, the system was flushed with EtOH. Afterwards, feed of substrate was re-initiated at a rate of 0.148 mL·min⁻¹ to achieve an averaged residence time of $\tau = 8$ h. The relationship between the flow-rate of substrate and the averaged residence time of substrates in the reactor is described in section 7.4.4. In region VIII as well as in the beginning of region IX, conversion increased, reaching a maximum of 46% at 48 h TOS (region IX, **Figure 22**), with approximately 80% of the initial sulphur content retained in the catalyst. The extended residence time enhanced the productivity of the system but also increased the likelihood of side reactions occurring, leading to greater formation of by-products. After achieving a maximum acetoin yield of 41% at 48 h TOS, catalytic activity gradually declined to approximately 35% by the end of region IX.

In region X, the system pressure was increased from 7 bar to 20 bar. This change had no noticeable effect on the trends in activity or catalyst decomposition. After nearly 60.5 h TOS, the system still achieved a 29% acetoin yield at a 32% substrate conversion, with a total turnover number of 600. In the above experiment, for 0 h < TOS < 39 h, *i.e.* where $\tau = 2$ h and an average yield of 18%, a STY of 34 g·L⁻¹·h⁻¹ was attained. For TOS > 39.5 h, with an average residence time of $\tau = 8$ h, average acetoin yield of 30% and STY = 14.2 g·L⁻¹·h⁻¹ resulted. The catalyst retained 78% of its initial sulphur content after 60.5 h TOS, underscoring the significant stability improvements achieved through the ion-exchange procedure.

Keeping in mind that in **Figure 22** not one single optimal reaction parameter was probed, combined with the fact that enzymatically produced acetoin has a production capacity of 2 g·L⁻¹·h⁻¹ leaves to wonder what a fully optimised immobilised NHC precatalyst might be able to attain.^[169-171] Nonetheless, these results highlight the robustness of the **IM-NHC5-PF₆** catalyst while leaving room for extended investigations on its use in continuous-flow applications, especially regarding the stability of the immobilised catalyst with respect to decomposition. Other non-nucleophilic anions like BPh₄, BArF or triflates could aid in the stability of the catalyst as well. Especially BPh₄ might be of interest as it impedes the use of fluorinated compounds and their exposure to the environment.

5.2 Hydrogenation of Acetoin to 2,3-Butanediol

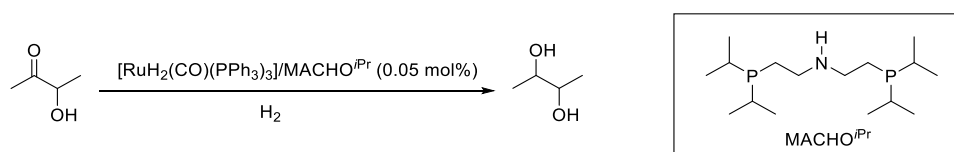
Developing a tandem catalysed one-pot acetaldehyde-to-2,3-BDO approach using a combination of NHC catalysed acetaldehyde self-addition and hydrogenation of acetoin to 2,3-BDO, seemed very interesting. Therefore, a catalytic system needed to be developed which would be tolerable with the optimal reaction conditions for the NHC/ Na_2CO_3 catalysed acetaldehyde self-addition.

5.2.1 Homogeneous Base-Free Hydrogenation of Acetoin Using a Ru-based Catalyst

As shown previously, the NHC catalysed acetaldehyde self-addition is reliant on a weak base (Na_2CO_3) to generate the catalytically active species. When using much stronger bases like NaOEt or KO^tBu , a vast polymerisation of the reactive acetaldehyde occurred. Unfortunately, conventional homogeneous hydrogenation catalysts, are often reliant on such strong basic co-catalyst to generate the catalytically active complex.^[158] Therefore, a base-free catalytic system needs to be developed, in order to allow for the possibility to combine the homogeneous NHC catalysed acetaldehyde self-addition with the hydrogenation of acetoin to 2,3-BDO in a single reactor. Though *Nielsen et al.* reported the dehydrogenation of ethanol to ethyl acetate and pure hydrogen using a base-free catalytic system, the hydrogenation properties of the ruthenium complex investigated therein, were not reported.^[62]

Intrigued by these findings in literature, the catalytic properties of the *in-situ* generated $[\text{RuH}_2(\text{CO})(\text{PPh}_3)_3]/\text{MACHO}^{\text{iPr}}$ catalyst were investigated in the hydrogenation of acetoin to 2,3-BDO with H_2 at elevated temperatures and pressures. A preliminary batch experiment carried out in a 10 mL autoclave at 90 °C revealed presence of 2,3-BDO in the GC-MS measurement of a reaction aliquot after 5 h of reaction time with 20 bar of H_2 . As a first step in the optimisation of the base-free $[\text{RuH}_2(\text{CO})(\text{PPh}_3)_3]/\text{MACHO}^{\text{iPr}}$ catalysed hydrogenation, the reaction was repeated for 24 h of reaction time in an attempt to attain higher yields and facilitate quantitative analysis. The results of these experiments and the temperature screening carried out, are listed in Table 6.

Table 6: Catalytic results for the temperature screening carried out with the *in-situ* generated $[\text{RuH}_2(\text{CO})(\text{PPh}_3)_3]/\text{MACHO}^{\text{iPr}}$ catalytic system in the base- and solvent free homogeneous hydrogenation of acetoin.^[a]



Entry	<i>T</i> (°C)	Y(2,3-BDO) ^[b] (%)	TON
6.1	90	22	439
6.2	100	24	487
6.3	110	25	492
6.4	120	25	496
6.5 ^[c]	90	27	542

[a] Reaction conditions: $V(\text{acetoin}) = 3.0 \text{ mL}$, $n(\text{acetoin}) = 34 \text{ mmol}$, $c(\text{Ru}) = 0.05\text{mol}\%$, $c(\text{MACHO}^{\text{iPr}}) = 0.05\text{mol}\%$, $p = 20 \text{ bar}$ at r.t., $t = 24 \text{ h}$, 800 rpm. [b] As determined by GC-FID using mesitylene as internal standard [c] $p = 60 \text{ bar}$ at r.t. at otherwise identical conditions.

As can be seen from **Table 6**, variation of reaction temperature does not have a significant effect on the yield of 2,3-BDO and *TON* of the $[\text{RuH}_2(\text{CO})(\text{PPh}_3)_3]/\text{MACHO}^{\text{iPr}}$ catalytic system. There is but a mere hint that the yield and *TON* increase with rising temperature. However these differences are too small to make a finite statement about the relationship between reaction temperature and yield. Carrying out an experiment with a higher pressure of H_2 at 90 °C (**Table 6**, entry 6.5) does not directly support this assumption. With 60 bar of H_2 , again only 27% acetoin yield was attained. The underlying reason for the comparable results achieved with 20 bar of H_2 at various reaction temperatures might be more complex.

One reason, besides low H_2 pressure for the 20 bar experiments, might be that the reactions were carried out in absence of solvent. When investigating cationic Rh complexes in the hydrogenation of various aldehydes, including acetoin, and ketones, *Burk et al.* pointed out that protic solvents have a beneficial effect on catalysis and are needed to achieve full conversion.^[220] In this regard, use of ethanol as solvent was investigated. As opposed to the experiments in **Table 6**, a reaction system with 60 bars of H_2 and a reaction time of 6 h was chosen with a catalyst concentration of 0.1 mol%. Again, reactions were carried out in 10 mL stainless steel autoclaves at a temperature of 100 °C.

Table 7: Results of the catalytic hydrogenation of acetoin to 2,3-BDO in EtOH as solvent using various combinations of $[\text{RuH}_2(\text{CO})(\text{PPh}_3)_3]$ and $\text{MACHO}^{\text{iPr}}$ to verify the activity of the *in-situ* generated complex.^[a]

Entry	$c(\text{[Ru]})$ (mol%)	$c(\text{MACHO}^{\text{iPr}})$ (mol%)	$Y(2,3\text{-BDO})^{[b]}$ (%)	<i>TON</i>
7.1	0.1	0.1	90	898
7.2	0.1	-	26	256
7.3 ^[c]	-	0.1	< 0.1	-
7.4 ^[d]	0.1	0.1	> 99.9	1000

[a] Reaction conditions: $V(\text{acetoin}) = 1.0 \text{ mL}$, $n(\text{acetoin}) = 11.5 \text{ mmol}$, $V(\text{EtOH}) = 2.0 \text{ mL}$, $p = 60 \text{ bar}$ at r.t., $T = 100 \text{ °C}$ $t = 6 \text{ h}$. [b] As determined by GC-FID using mesitylene as internal standard. [c] No hydrogenated products were observed from the GC-FID chromatogram. [d] Acetoin was used as solid dimer $m(\text{acetoin-dimer}) = 1.01 \text{ g}$, $n(\text{acetoin}) = 11.5 \text{ mmol monomer}$.

Indeed, when using EtOH as solvent and higher catalyst concentrations, 90% acetoin yield at a *TON* of 898 can be attained (**Table 7**, entry 7.1), highlighting that protic solvents are indeed beneficial for the productivity of the system thereby confirming findings in literature. As the reaction system in entry 7.1 were already very promising, the conditions used were set as benchmark reaction conditions. Several verification experiments were carried to confirm the activity of the *in-situ* generated $[\text{RuH}_2(\text{CO})(\text{PPh}_3)_3]/\text{MACHO}^{\text{iPr}}$ catalyst.

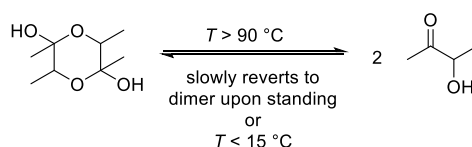
Based on the experimental result in **Table 7**, entry 7.2, when only the Ru precursor ($[\text{RuH}_2(\text{CO})(\text{PPh}_3)_3]$) is added, a moderate 2,3-BDO yield of 26% at *TON* = 256 is obtained. This result highlights the beneficial effect of the $\text{MACHO}^{\text{iPr}}$ ligand. In absence of Ru, with only $\text{MACHO}^{\text{iPr}}$ ligand is present in the system, no hydrogenation products are observed at all (**Table 7**, entry 7.3).

For the experiments listed in **Table 6** and **Table 7** (entries 7.1-7.3) liquid, monomeric acetoin was used as substrate. However, acetoin as purchased from *Sigma* comes as a mixture of

monomer and dimers. It was observed that monomeric, liquid acetoin slowly converts to solid dimeric acetoin. In order to obtain monomeric acetoin, the dimer was heated to 90 – 100 °C under reflux, to convert the dimeric acetoin into monomers. Subsequently monomeric acetoin was stored at room temperature under Ar, as it was found that keeping the monomer under inert gas, could substantially slow down crystallisation into the corresponding dimer.

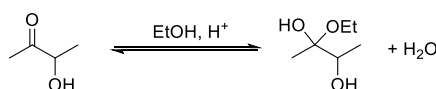
In order to see if using solid dimer as opposed to liquid monomer as substrate for the hydrogenation would make a difference, an experiment was carried out at otherwise identical conditions (Table 7, entry 7.4). Indeed, when using solid dimeric acetoin as opposed to liquid monomeric acetoin, a near quantitative yield (>99.9%) at corresponding $TON = 1000$ can be attained, which is significantly higher compared to the experiment with liquid acetoin monomer as substrate (90%, entry 7.1).

The observed difference in reactivity is rather unique and seemingly strange at first, since at the given reaction temperatures of 100 °C dimeric acetoin should quickly convert into its monomeric counterpart. However, when the molecular structures of both dimer and monomer are studied, some noteworthy differences can be seen (Scheme 23).



Scheme 23: Structures of dimeric (left) and monomeric acetoin (right) as well as the conditions to convert dimeric acetoin to monomer and back.

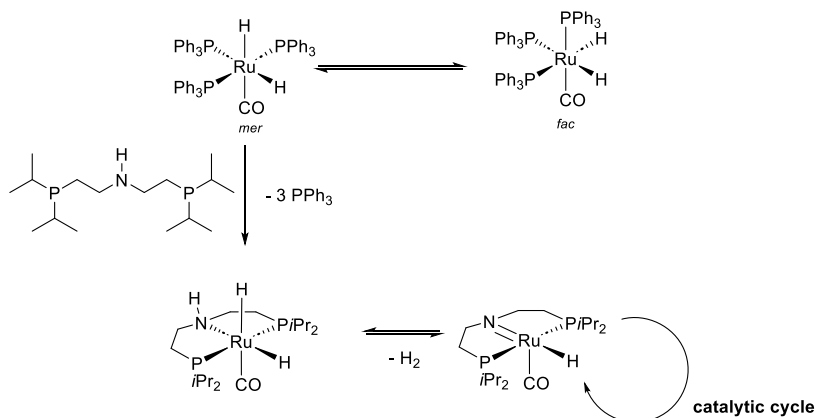
Whereas the monomer is an α -hydroxy-ketone, the dimeric structure has two hemiketal groups. Due to this structural difference, the former C=O bond in the monomeric structure can be regarded as more activated due to a shift in bonding electrons away from the C=O bond into a new C-O-C bond. It is generally acknowledged that in order for a C=O bond to be hydrogenated, the bond has to be activated at first. In dimeric acetoin, this bond is ‘naturally’ activated which could be a possible explanation of the observed difference in reactivity. In order to further verify the hypothesis, that C=O bond activation through formation of a hemiketal moiety changes the reactivity, an experiment was carried out where a small amount of Brønsted acid was added to the reaction solvent to actively induce hemiketal formation with the alcoholic solvent according to the following equilibrium reaction (Scheme 24).



Scheme 24: Formation of a hemiketal from the reaction of monomeric acetoin in the presence of EtOH as solvent and H^+ from in this case, a few drops of HCl as catalyst.

The experiment was carried out at identical reaction conditions to the experiment listed in Table 7, entry 7.2, *i.e.* in absence of $MACHO^{iPr}$ ligand (Table 8, entry 8.1). At the time, there were some issues with the reproducibility of the experiments discussed in Table 6 owing to different Ru precursors obtained from different vendors. Although the same $[RuH_2(CO)(PPh_3)_3]$ precursor was purchased, extensive $^{31}P\{^1H\}$ -NMR characterisation revealed that different vendors sold different isomers of the precursor. Whereas previously, *mer*- $[RuH_2(CO)(PPh_3)_3]$ obtained from *Sigma* was employed in catalysis, a new batch also purchased

from *Sigma*, had a larger content of *fac*-[RuH₂(CO)(PPh₃)₃] which caused reproducibility errors in the experiments conducted with the MACHO^{iPr} ligand. This might be associated with the isomerisation of the *fac*-[RuH₂(CO)(PPh₃)₃] complex to its corresponding *mer* form, that has to take place prior to MACHO^{iPr} coordination (**Scheme 25**).



Scheme 25: Proposed mechanism of isomerisation of *fac*-*fac*-[RuH₂(CO)(PPh₃)₃] into *mer*-*fac*-[RuH₂(CO)(PPh₃)₃] prior to tridentate coordination of the MACHO^{iPr} ligand. Upon generation of the Ru-MACHO-complex, loss of H₂ generates the catalytically active species.

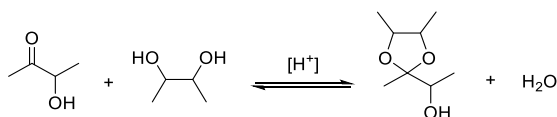
In order to circumvent the problems in reactivity with different batches of Ru-precursors and MACHO^{iPr} ligands, experiments that are not listed herein, were carried out that focused on identifying the best performing [RuH₂(CO)(PPh₃)₃] precursor in absence of additional ligand. Afterwards, choice was made to conduct further investigations on the homogeneous hydrogenation in absence of additional ligand and solely use [RuH₂(CO)(PPh₃)₃] obtained from *TCI* as best performing precursor.

Table 8: Results of the catalytic hydrogenation of acetoin in either acidified EtOH as solvent or non-acidified EtOH only using [RuH₂(CO)(PPh₃)₃] as a catalyst.^[a]

Entry	Solvent	Y(2,3-BDO) ^[b] (%)	Y(ketal) ^[b] (%)	TON(2,3-BDO)
8.1	acidified EtOH ^[c]	97	1	964
8.2	EtOH	72	< 1	730

[a] reaction conditions: V(acetoin) = 1.0 mL, *n*(acetoin) = 11.5 mmol, *c*([Ru]) = 0.1mol%, V(acid. EtOH) = 2.0 mL, *p* = 60 bar at r.t., *T* = 100 °C, *t* = 6 h. [b] As determined by GC-FID using mesitylene as internal standard. [c] acidified using a few drops of H₂SO₄.

As seen in **Table 8**, entry 8.1 using acidified EtOH as solvent results in around 97% 2,3-BDO is reached, whereas when using non-acidified ethanol (**Table 8**, entry 8.2) only 72% 2,3-BDO is attained. Furthermore, in absence of acid, no ketal side products were identified from the GC-FID chromatogram. The C₈ cyclic ketal (1-(2,4,5-trimethyl-1,3-dioxolan-2-yl)ethanol) was identified from the *m/z* fragmentation in the GC-MS chromatogram at higher retention times. Presence of this ketal indicates that 2,3-BDO and acetoin can undergo a consecutive reaction to form the ketal compound. This reaction is most probably catalysed by presence of an acid as indicated in **Scheme 26**.



Scheme 26: Reaction between acetoin and 2,3-BDO to form a cyclic ketal in acidic conditions.

As the yield is significantly increased when acidified EtOH is used as solvent, this experiment (entry 8.1) indicates that C=O bond activation of the keto-moiety by means of hemiketal formation indeed plays a significant role in promoting the catalytic activity of the system. However, when regarding the possibility to implement a tandem catalytic reaction with the homogeneous NHC/ Na_2CO_3 catalysed acetaldehyde coupling and [Ru]-based base-free homogeneous hydrogenation, using Brønsted acids to induce hemiketal formation for C=O bond activation of the acetoin, is not possible. Instead, a Lewis acid can be used to induce a similar C=O bond activation whilst not interfering with the Brønsted base (Na_2CO_3) needed for the generation of the catalytically active carbene catalyst in the self-addition reaction. Bond activation by means of Lewis acid additives, is a common practice in CO_2 hydrogenation for example.^[221-223]

To the reaction system in **Table 8**, entry 8.2, catalytic amounts (0.2mol%) of $\text{Al}(\text{OTf})_3$ (OTf = trifluoromethanesulfonate) as a Lewis acid (LA) were introduced into the catalytic system (**Table 9**).

Table 9: Catalytic results of the experiments using $\text{Al}(\text{OTf})_3$ as a Lewis acidic (LA) additive in the hydrogenation of monomeric acetoin in EtOH using $[\text{RuH}_2(\text{CO})(\text{PPh}_3)_3]$ as catalyst.^[a]

Entry	<i>t</i> (h)	Y(2,3-BDO) ^[b] (%)	Y(ketal) ^[b] (%)	TON(2,3-BDO)
9.1	6	99	1	1013
9.2	3	96	4	957
9.3	1.5	92	8	918

[a] Reaction conditions: $V(\text{acetoin}) = 1.0 \text{ mL}$, $n(\text{acetoin}) = 11.5 \text{ mmol}$, $c([\text{Ru}]) = 0.1 \text{ mol\%}$, $c(\text{Al}(\text{OTf})_3) = 0.2 \text{ mol\%}$, $V(\text{EtOH}) = 2.0 \text{ mL}$, $p = 60 \text{ bar}$ at r.t., $T = 100 \text{ }^\circ\text{C}$. [b] As determined by GC-FID using mesitylene as internal standard.

Using the conditions established in **Table 8**, entry 8.2 with the addition of 0.2mol% LA, improved the yield of 2,3-BDO from 72 to 99% and 1% ketal by-product formation (**Table 9**, entry 9.1) at near quantitative conversion of acetoin ($X > 99.9\%$). Hence, use of LA additive also results in an improvement of the catalytic performance of the system. For a decreased reaction time of 3 h (entry 9.2), a 2,3-BDO yield of 96% and 4% ketal by-products was attained. Again, near full conversion of acetoin was achieved as only trace amounts were identified from the GC-FID chromatogram. Further reducing the reaction time to 1.5 h still resulted in an almost complete conversion of the acetoin. However, the product spectrum again shifted a little bit, 2,3-BDO yields were calculated to be 92% and ketal by-product was present in a total of 8% (entry 9.3).

Experimental results described in **Table 8** indicate that decreasing reaction time, yield of ketal in the post reaction mixture increases, at the expense of 2,3-BDO yield. Hence, selectivity is somewhat shifted with shorter reaction times. As formation of the cyclic ketal is an

equilibrium reaction (**Scheme 26**), it is possible that upon the reverse reaction, formed acetoin can undergo hydrogenation to 2,3-BDO before formation of the ketal can reoccur.

Based on the results of the investigated $[\text{RuH}_2(\text{CO})(\text{PPh}_3)_3]/\text{Al}(\text{OTf})_3$ reaction system, the best trade-off in ketal by-product formation and relatively short reaction times, is attained after 3 h. Comparing the results of the $[\text{RuH}_2(\text{CO})(\text{PPh}_3)_3]/\text{Al}(\text{OTf})_3$ with those of the *in-situ* generated $[\text{RuH}_2(\text{CO})(\text{PPh}_3)_3]/\text{MACHO}^{\text{iPr}}$ reaction system (**Table 7**) reveal that even higher productivities and even shorter reaction times could be reached by using the $[\text{RuH}_2(\text{CO})(\text{PPh}_3)_3]/\text{MACHO}^{\text{iPr}}$ reaction system in combination with $\text{Al}(\text{OTf})_3$.

5.2.2 Exploring the Tandem Catalytic One-Pot Acetaldehyde-to-2,3-BDO Approach

Before combining the homogeneous LA-assisted hydrogenation with the NHC catalysed acetaldehyde self-addition in a tandem catalytic approach, tolerance of LA on the NHC/ Na_2CO_3 system has to be investigated at first. For the purpose of these experiments, one of the best-performing homogeneous NHC precursors 3-Benzyl-5-(2-hydroxyethyl)-4-methyl-thiazoliumchlorid, **NHC5** was used. As pointed out earlier, the **NHC5**/ Na_2CO_3 system was able to attain near quantitative acetoin yields at 100 °C and only 30 minutes of reaction time (**Table 1**, entry 1.1, section 5.1.1). Various amounts of LA were introduced to the **NHC5**/ Na_2CO_3 system and the results are displayed in **Table 10**.

Table 10: Catalytic results of the **NHC5**/ Na_2CO_3 catalysed acetaldehyde self-addition in EtOH as solvent with $\text{Al}(\text{OTf})_3$ as additive.^[a]

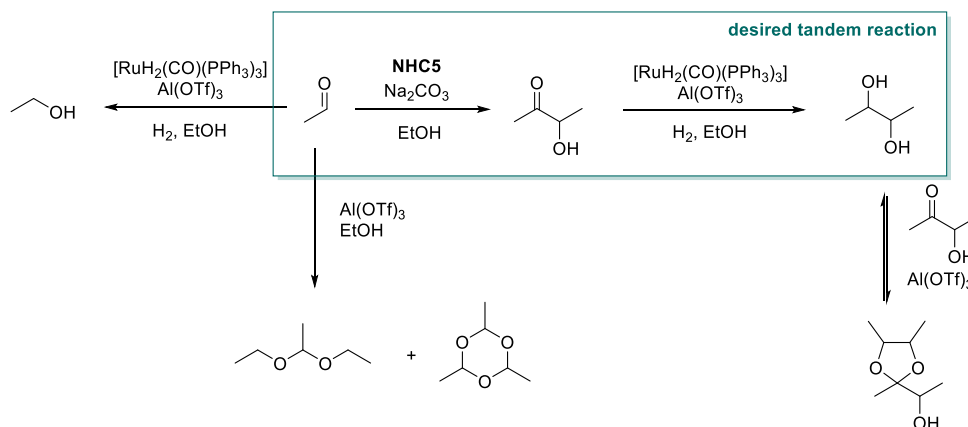
Entry	$c(\text{Al}(\text{OTf})_3)$ (mol%)	$Y(\text{acetoin})^{[b]}$ (%)	$\Sigma Y(\text{side products})^{[b,c]}$ (%)
10.1 ^[d]	-	98	-
10.2	0.5	12	41
10.3	0.1	45	42
10.4 ^[e]	0.1	68	27

[a] Reaction conditions: $V(\text{acetaldehyde}) = 1.0 \text{ mL}$, $n(\text{acetaldehyde}) = 18 \text{ mmol}$, $c(\text{NHC5}) = 1.0 \text{ mol\%}$, $c(\text{Na}_2\text{CO}_3) = 1.3 \text{ mol\%}$, $V(\text{EtOH}) = 5.0 \text{ mL}$, $T = 100 \text{ °C}$, $t = 30 \text{ min}$. [b] As determined by GC-FID using mesitylene as internal standard. [c] By-products observed were 1,1-diethoxyethane and paraldehyde which were identified by GC-MS. [d] As seen and discussed in **Table 1**, entry 1.1, section 5.1.1. [e] $c(\text{NHC5}) = 2.0 \text{ mol\%}$, $c(\text{Na}_2\text{CO}_3) = 2.6 \text{ mol\%}$ at otherwise identical conditions.

As discussed previously in this work, the **NHC5**/ Na_2CO_3 catalytic system reaches near quantitative conversions and yields (98%) after 30 minutes of reaction time with negligible amounts of side products identified from GC-FID (**Table 10** entry 10.1 and **Table 1**, entry 1.1, section 5.1.1.). Introducing 0.5mol% LA (entry 10.2) results in a drastic decrease in catalytic activity, reflected in a yield of 12% acetoin as well a shift in product spectrum towards unwanted side products (41%). Formation of 1,1-diethoxyethane from acetaldehyde and 2 equivalents of ethanol as well as the condensation of three molecules of acetaldehyde to form paraldehyde compete with the formation of the desired acetoin. Formation of 1,1-diethoxyethane it known to be catalysed H^+ , making it amendable that $\text{Al}(\text{OTf})_3$ as LA can also serve as catalyst for this reaction.^[224]

HYDROGENATION OF ACETOIN TO 2,3-BUTANEDIOL

Decreasing the amount of LA to 0.1mol% resulted in an improved acetoin yield from 12 to 45% (entry 10.3) but yield of side products remain unchanged (42%). When increasing the concentration of the NHC/ Na_2CO_3 catalytic system to 2.0mol% and 2.6mol% respectively, at otherwise identical conditions, formation of desired acetoin increases from 45% to 68% whereas by-products yield is decreases from 41% to 27% (entry 10.4). As doubling the concentration of the NHC/ Na_2CO_3 system does not directly go hand-in-hand with the doubling of acetoin yield, it is amendable that addition of LA does have a negative influence on the overall productivity of the carbene catalysed acetaldehyde self-addition. A possibility could be the formation Lewis acid-base pair. The Al serves as acid metal centre and the activated carbene form of **NHC5** can acts as Lewis base which together could form a stable Lewis pair. Formation of such a Lewis pair would render parts of the carbene inactive in catalysis and could explain the low activity of the system when LA is introduced.^[225] Nonetheless, as acetoin is still produced in acceptable yields of 68%, the experiment in **Table 10** entry 10.4 was used as starting point for the investigations regarding the tandem catalytic one-pot acetaldehyde to 2,3-BDO reaction (**Table 11**). When considering a tandem catalytic one-pot reaction for producing acetoin directly from acetaldehyde, it has to be kept in mind that acetaldehyde can undergo hydrogenation to ethanol. This reaction is competing for substrate with the NHC catalysed acetaldehyde self-addition. Also, several other unwanted side reactions can occur. An overview of the possible reactions that can occur in a tandem catalysed one-pot reaction starting from acetaldehyde in EtOH as solvent, using a combination of **NHC5**/ Na_2CO_3 and the developed [Ru]-LA assisted hydrogenation system, is shown in **Scheme 27**.



Scheme 27: Possible reactions that can take place when acetaldehyde is reacted with H_2 in presence of $[\text{RuH}_2(\text{CO})(\text{PPh}_3)_3]$ as hydrogenation catalyst, $\text{Al}(\text{OTf})_3$ as LA additive and the **NHC5**/ Na_2CO_3 catalytic system in EtOH as solvent.

Table 11: Catalytic results for the tandem catalytic acetaldehyde self-addition and subsequent acetoin hydrogenation using **NHC5**/ Na_2CO_3 as catalyst for the acetoin formation and $[\text{RuH}_2(\text{CO})(\text{PPh}_3)_3]/\text{Al}(\text{OTf})_3$ system for the base-free LA promoted hydrogenation of acetoin to 2,3-BDO.^[a]

Entry	Y(acetoin) ^[b] (%)	Y(2,3-BDO) ^[b] (%)	ΣY(side products) ^[b,c] (%)
11.1	64	2	2

[a] reaction conditions: $V(\text{acetaldehyde}) = 2.0 \text{ mL}$, $n(\text{acetaldehyde}) = 36 \text{ mmol}$, $c(\text{NHC}) = 2.0 \text{ mol\%}$, $c(\text{Na}_2\text{CO}_3) = 2.6 \text{ mol\%}$, $n([\text{Ru}]) = 18 \text{ }\mu\text{mol}$, $n(\text{Al}(\text{OTf})_3) = 18 \text{ }\mu\text{mol}$, $V(\text{EtOH}) = 2.0 \text{ mL}$, $p = 60 \text{ bar}$ at r.t., $T = 100 \text{ }^\circ\text{C}$, $t = 3 \text{ h}$.

[b] Determined *via* GC-FID using mesitylene as internal standard. [c] Main by-products observed were 1,1-diethoxyethane and paraldehyde which were identified by GC-MS.

As can be seen from the above **Table 11**, when the NHC catalysed acetaldehyde self-addition is combined with the $[\text{RuH}_2(\text{CO})(\text{PPh}_3)_3]$ catalysed hydrogenation of acetoin, only 2% of the acetoin is hydrogenated to 2,3-BDO. After the reaction, acetoin is obtained in a yield of 64% as determined from GC-FID. Hence, the total yield of the acetaldehyde self-addition to acetoin is 66%. This yield is relatively similar compared to the yield obtained with the **NHC5**/ Na_2CO_3 system where the same amount of LA was used as additive (**Table 10**, entry 10.4, 68%). Apparently, the acetaldehyde self-addition catalysed by **NHC5**/ Na_2CO_3 is not negatively influenced if the $[\text{Ru}]$ complex and 60 bar of H_2 are introduced to the system. Notably, side product yields are much lower compared to the **NHC5**/ Na_2CO_3 /LA systems discussed earlier. Also, merely of 1,1-diethoxyethane and some ketal side products were observed, as paraldehyde was found to be below detection limits.

Unfortunately, addition of $[\text{RuH}_2(\text{CO})(\text{PPh}_3)_3]$ as hydrogenation catalyst did not lead to high yields of 2,3-BDO. As discussed earlier, in absence of **NHC5**/ Na_2CO_3 though, the $[\text{RuH}_2(\text{CO})(\text{PPh}_3)_3]/\text{Al}(\text{OTf})_3$ gave some very good results. This remarkable drop of catalytic activity could be due to the formation of a Ru complex bearing the carbene form of **NHC5** as ligand, which could make the complex catalytically inactive. Generally, carbenes are stronger σ -ligands compared to PPh_3 .^[226-229] Therefore, formation of a Ru-NHC complex by displacement of PPh_3 is hypothesised. In order to verify this, several solution-state NMR spectra were recorded.

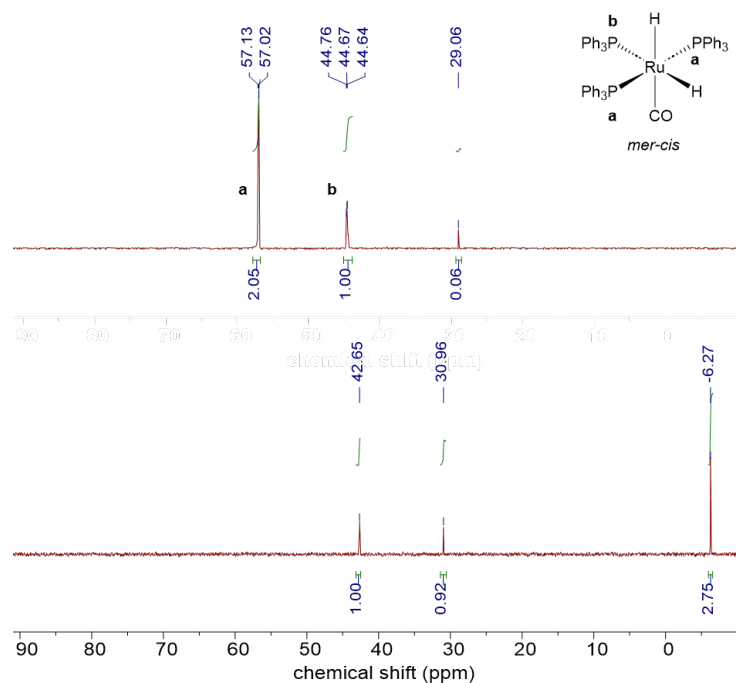


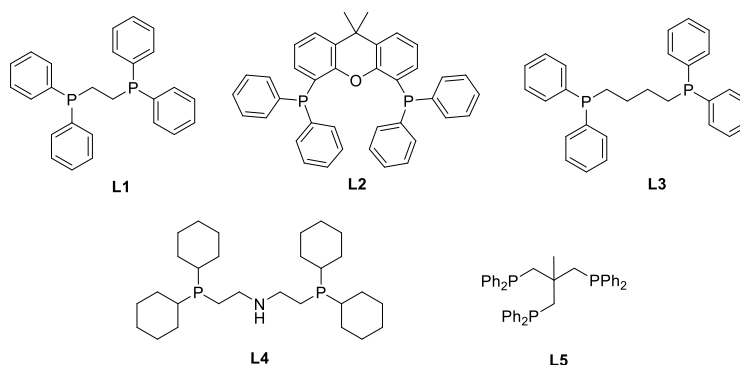
Figure 22: $^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, CDCl_3 , r.t.) spectra of pure $[\text{RuH}_2(\text{CO})(\text{PPh}_3)_3]$ (top) and post reaction solution of the tandem experiment discussed in **Table 11**, entry 11.1 (bottom).

In the spectrum of the pure $[\text{RuH}_2(\text{CO})(\text{PPh}_3)_3]$ complex (**Figure 22**, top), three signals can be observed at $\delta = 57.02$, (d, 2P, 2 x PPh_3), 44.64 (t, 1P, PPh_3) and 29.06 (s, $\text{O}=\text{PPh}_3$) ppm. The two signals at $\delta = 57.13$ and 57.02 ppm belong to the P atoms in equatorial plane of the complex that are adjacent to each other. The triplet at $\delta = 44.6$ ppm belongs to the P of a PPh_3 -ligand in the mirror-plane of the meridional complex. The pure component spectrum of $[\text{RuH}_2(\text{CO})(\text{PPh}_3)_3]$ reveals no presence of free PPh_3 -ligand (expected at negative δ). Minor quantities of oxidised PPh_3 ligand are however present, as indicated by the resonance at $\delta = 29.06$ ppm. The spectrum of the post reaction solution (**Figure 22**, bottom), exhibits different resonances at $\delta = 42.7$ (s), 30.1 (s) and -6.3 (s) ppm. The singlet at $\delta = -6.3$ ppm can be assigned to free PPh_3 ligand in solution. Based on the integral ratio of the signals, free PPh_3 is the most pronounced species in the post reaction solution. The singlet at around $\delta = 30.1$ ppm can be assigned to triphenylphosphine oxide and the observed chemical shift is in accordance with values obtained from literature.^[230] The singlet at $\delta = 42.7$ ppm can be assigned to a PPh_3 ligand bonded to the Ru metal centre. From the post reaction spectrum, no peaks are observed in the $\delta = 57$ ppm region which would belong to PPh_3 ligands in the equatorial position of the pure complex. Hence, the post reaction spectrum of the tandem experiment indicates indeed, that PPh_3 ligands get replenished and either get slowly oxidised to $\text{O}=\text{PPh}_3$ or remain as free PPh_3 in solution. Assumed formation of carbene-Ru complex would change the chemical environment of the remaining (axial) PPh_3 ligand which causes the PPh_3 ligand to be slightly more shielded and show up at lower chemical shift which causes the remaining PPh_3 ligand to resonate at $\delta = 42.7$ ppm rather than at $\delta = 44$ ppm. Also, the fact that there is no splitting of the signal supports the assumption that the Ru complex in the post reaction solution of the tandem experiment has but one PPh_3 ligand.

In order to overcome the suspected PPh_3 /carbene ligand replacement and make the Ru complex less susceptible to carbene-complex formation, multidentate phosphine ligands with chelating properties were introduced to overcome the strong donor affinity of the carbene.

5.2.3 Ligand Screening in the Tandem Catalysed Acetaldehyde-to-2,3-BDO Approach

Initially, ligand-screening experiments were carried out in absence of LA additive. For one, this allows the experiments to be comparable with the results of the earlier discussed *in-situ* generated $[\text{RuH}_2(\text{CO})(\text{PPh}_3)_3]/\text{MACHO}^{i\text{Pr}}$ system. Secondly, the absence of LA suppresses the side-reactions induced in the acetaldehyde self-addition. The earlier postulated carbene-phosphine ligand exchange is supposed to be unaffected by presence of LA. A broad variety of phosphine-based ligands was screened and tested in the tandem catalytic approach (Scheme 28).

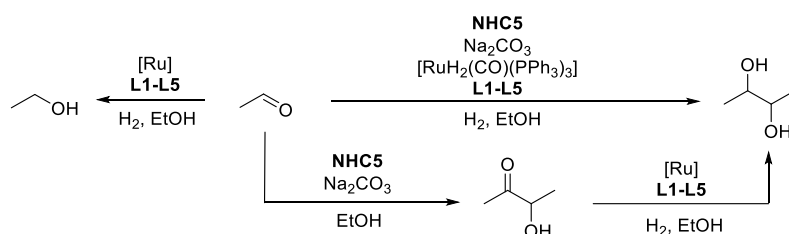


Scheme 28: Overview of the phosphine-based ligands tested in the tandem catalytic acetaldehyde self-addition/acetoin hydrogenation reaction.

Experiments were carried out using *in-situ* formation of the hydrogenation complex with $[\text{RuH}_2(\text{CO})(\text{PPh}_3)_3]$ as precursor. Ligands were added equimolar and the amount of the precursor (0.1mol%, as seen in Table 9) was based the assumption that acetaldehyde is completely converted to acetoin formation by the NHC catalytic system. For the latter, 1.0mol% of **NHC5** and 1.3mol% of Na_2CO_3 was used. Reactions were again carried out in EtOH as solvent for 6 h using 60 bar of H_2 in 10 mL autoclaves. The catalytic results of the ligand screening experiments with ligands **L1-L5** are listed below in Table 12. For all experiments, quantitative conversion of acetaldehyde was attained. It can therefore be assumed, that acetaldehyde that did not get converted to acetoin, was hydrogenated to ethanol. As described earlier, the both reactions compete for substrate. As ethanol was used as solvent, the additional generation of ethanol from acetaldehyde hydrogenation is difficult to quantify. The discussion on the ligand screening experiments will therefore only focus on the ability of the [Ru]-based hydrogenation catalyst to convert acetoin into 2,3-BDO rather than accounting for the activity in hydrogenation of acetaldehyde towards ethanol.

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Table 12: Catalytic result of the phosphine-based ligand screening experiments in the tandem acetaldehyde self-addition/acetoin hydrogenation reaction.^[a]



Entry	Ligand L	Y(acetoin) ^[b] (%)	Y(2,3-BDO) ^[b] (%)
12.1	MACHO ^{iPr}	22	35
12.2 ^[c]	-	45	6
12.3	L1	55	14
12.4	L2	53	1
12.5	L3	36	16
12.6	L4	49	11
12.7	L5	79	1
12.8 ^[d]	-	30	34

[a] Reaction conditions: $V(\text{acetaldehyde}) = 2.0 \text{ mL}$, $n(\text{acetaldehyde}) = 36 \text{ mmol}$, $c(\text{NHC}) = 1.0 \text{ mol\%}$, $c(\text{Na}_2\text{CO}_3) = 1.3 \text{ mol\%}$, $n([\text{Ru}]) = 18 \text{ }\mu\text{mol}$, $n(\text{L}) = 18 \text{ }\mu\text{mol}$, $V(\text{EtOH}) = 2.0 \text{ mL}$, $p = 60 \text{ bar}$ at r.t., $T = 100 \text{ }^\circ\text{C}$, $t = 6 \text{ h}$. [b] Determined via GC-FID using mesitylene as internal standard. [c] Experiment carried out using $[\text{RuH}_2(\text{CO})(\text{PPh}_3)_3]$ ($18 \text{ }\mu\text{mol}$) without additional ligand. [d] Experiment carried out with Ru-MACHO[®]-BH ($18 \text{ }\mu\text{mol}$) without additional ligand at otherwise identical conditions.

Conducting a tandem catalytic approach using the *in-situ* generated $[\text{RuH}_2(\text{CO})(\text{PPh}_3)_3]$ /MACHO^{iPr} system discussed in Table 7 and the NHC5/ Na_2CO_3 , results in an acetoin yield of 22% and a 2,3-BDO yield of 35% (Table 12, entry 1). In absence of any ligand, i.e. only using the $[\text{RuH}_2(\text{CO})(\text{PPh}_3)_3]$ (entry 2) results in 45% acetoin yield and 6% yield of hydrogenation product 2,3-BDO. As pointed out earlier in Table 7, the sole $[\text{RuH}_2(\text{CO})(\text{PPh}_3)_3]$ complex has a lower hydrogenation activity compared to the *in-situ* generated $[\text{RuH}_2(\text{CO})(\text{PPh}_3)_3]$ /MACHO^{iPr} system. Furthermore, large excess of activated carbene present in the reaction solution might result in formation of inactive Ru-carbene complexes like previously discussed.

When using 1,2-bis(diphenylphosphino)ethane **L1**, an acetoin yield of 55% is attained and 14% of 2,3-BDO is observed as hydrogenation product (entry 3). With the Xantphos ligand **L2**, no improvement in the yield of 2,3-BDO was attained ($Y = 1\%$, entry 4). The 1,2-bis(diphenylphosphino)butane ligand **L3** gave a yield of 16% 2,3-BDO which is comparable for the yield of 2,3-BDO when using structurally similar **L1** (entry 3).

Using a MACHO ligand with cyclohexyl groups bounded to the P atoms (MACHO^{Cy}, **L5**) resulted in a yield of 2,3-BDO of 11% alongside 49% acetoin (entry 4). Still, the total yield of acetoin and 2,3-BDO is 60% and hence comparable to the summed yield of the experiment with MACHO^{iPr} (entry 1, 58%). This result indicates that the overall performance of the tandem catalytic system is roughly the same with both MACHO-type ligands.

With the tridentate Triphos (Triphos = 1,1,1-Tris(diphenylphosphinomethyl)ethane) ligand (**L6**) high acetoin yield of 79% were attained but only small amounts of acetoin were hydrogenated to 2,3-BDO as yields were found in the 1% range (entry 8). Preliminary screenings with the $[\text{RuH}_2(\text{CO})(\text{PPh}_3)_3]$ /Triphos *in-situ* generated catalyst in the

hydrogenation of acetoin in absence of LA, suggested that the **L6** might be a good alternative to **MACHO**^{iPr} since conversions/yields around 60% were attained. Though the **NHC5**/ Na_2CO_3 catalysed acetaldehyde self-addition does not seem to be negatively influenced by the presence of the Triphos Ligand, the absence of 2,3-BDO as desired hydrogenated product indicates that there are some severe cross interactions when combining the **NHC5**/ Na_2CO_3 system with the *in-situ* $[\text{RuH}_2(\text{CO})(\text{PPh}_3)_3]/\text{Triphos}$ catalyst, preventing the latter to be active in the acetoin hydrogenation reaction.

Using commercially available Ru-MACHO®-BH as hydrogenation catalyst led to an almost 1:1 ratio of acetoin to 2,3-BDO (30% and 34% respectively, Table 12 entry 8). This result adds up to a total acetoin yield of 64%. The obtained result indicates that the performance of the **NHC5**/ Na_2CO_3 comparable in presence of Ru-MACHO®-BH compared to the experiments using *in-situ* generated catalysts with MACHO ligands (entries 12.1 and 12.8). Using Ru-MACHO®-BH is mostly beneficial for the hydrogenation of generated acetoin.

Despite a remarkable 1:1 ratio of acetoin and 2,3-BDO, combining both reactions in a single reactor comes with a decrease in catalytic activity for both catalyst systems. Whereas both reactions run at almost quantitative conversions and yields when separated, combining the two does not lead to a high-yield single-step preparation of 2,3-BDO from acetaldehyde. Furthermore, as hydrogenation of acetaldehyde competes for substrate with the acetaldehyde self-addition, combining both reactions in a single reactor is probably not the most efficient way. Therefore, further research on a tandem-catalytic approach in the one-pot acetaldehyde-to-2,3-BDO was not continued. Instead, to optimise the conceptual ethanol/acetaldehyde-to-BD approach (Scheme 19), a hydrogenation strategy is proposed using a heterogeneous catalyst for improved recyclability and separation of substrates.

5.2.4 Heterogeneously Catalysed Slurry-Phase Hydrogenation of Acetoin to 2,3-BDO

In order to find the most active hydrogenation catalyst for converting the acetoin/acetaldehyde mixture obtained from the continuous-flow acetaldehyde self-addition experiment (Figure 21) into 2,3-BDO and EtOH, a broad variety of commercially available heterogeneous hydrogenation catalysts were tested. The screening experiments were carried out using artificially prepared mixtures of acetoin and EtOH, in order to identify the most suitable catalyst, prior to converting the product mixture from Figure 21 on bigger scale. The results of several low-pressure slurry batch experiments, carried out in H_2 atmosphere (10 bar) and temperatures of 100 °C are shown in Table 13.

Table 13: Results of the catalyst screening experiments in the hydrogenation of acetoin to 2,3-butanediol and the corresponding ketal which was found to be present in minor quantities in nearly all experiments with heterogeneous catalysts.^[a]

Entry	catalyst	X(acetoin) ^[b] (%)	Y(2,3-BDO) ^[b] (%)	Y(ketal) ^[b] (%)	S(2,3-BDO) (%)
13.1	5wt% Ru/C	71	68	3	97
13.2	5wt% Ru/C ^[c]	84	84	< 1	> 99
13.3	2wt% Ru/Al ₂ O ₃	18	18	< 1	> 98
13.4	2wt% Ru/Al ₂ O ₃ ^[c]	18	18	> 0.1	> 99
13.5	5wt% Ru/SILP ^[231]	18	17	> 1	98
13.6	1wt% Pd/TiO ₂	5	3	2	63

[a] Reaction conditions: $V(\text{acetoin}) = 1.0 \text{ mL}$, $n(\text{acetoin}) = 11.5 \text{ mmol}$, $2.2\text{wt}\% < c(\text{catalyst}) < 12\text{wt}\%$ in order to keep the amount of catalytically active material constant, $V(\text{EtOH}) = 2.0 \text{ mL}$, $p(\text{H}_2) = 10 \text{ bar}$ at r.t., $t = 1.5 \text{ h}$, $T = 100 \text{ }^\circ\text{C}$, 800 rpm. [b] As determined by GC-FID using mesitylene as standard added after the reaction. Mass-balances $\Sigma Y > 90\%$ were obtained. [c] Freshly reduced samples, reduction conditions: $p(\text{H}_2) = 60 \text{ bar}$ at r.t., $T = 150 \text{ }^\circ\text{C}$, $t = 69 \text{ h}$.

Entry 13.1 shows the catalytic results of commercially available 5wt% Ru/C (*Sigma*) where 71% of initial substrate is converted to 68% 2,3-BDO and around 3% ketal-based side products resulting in a very high selectivity of 97%. Freshly reducing described Ru/C catalyst (entry 13.2) in H₂ before employing in a catalytic reaction results in an enhanced catalytic activity (84% yield/conversion) and exceptional selectivity. Switching from activated carbon to Al₂O₃ as support material (entry 13.3) results in a substantial decrease in catalytic activity as 18% conversion/yield is observed. Although Al₂O₃ is generally considered to be acidic in nature, the acid catalysed ketal by-product formation is not enhanced.^[232-233] Studying the influence of reduction on the 2wt% Ru/Al₂O₃ did not result in an improvement of catalytic activity (entry 13.4). A 5wt% Ru/SILP catalyst, applied by the group of *Bordet* in functional group hydrogenation as well as hydrodeoxygenation reactions (entry 13.5) affords 18% conversion/yield in 1.5 h of reaction time.^[231, 234] Furthermore, a commercial Pd/TiO₂ catalyst sample was tested (entry 13.6) Although Pd catalysts are readily applied in industry for the hydrogenation of various types of bonds, ketones and aldehydes the ability of Pd to act as catalyst in the hydrogenation of aldehydes and ketones is usually much lower and requires harsher conditions, ultimately resulting in bond-cleavage rather than hydrogenation.^[235] Hence, only 5% acetoin is converted at a moderate 2,3-BDO selectivity of 63%.

In order to investigate the hydrogenation of the EtOH/acetaldehyde/acetoin mixture from the long-time catalytic experiment with the **IM-NHC5-PF₆**/Na₂CO₃ a 5wt% Ru/C catalyst (Table 13, entry 13.1) was chosen as go-to method. The upscaling of the slurry phase hydrogenation of acetoin/ethanol mixture was studied in more detail using a *Parr* reactor in batch operation mode with continuous H₂ feed. Experiments in the *Parr* reactor setup were carried out at 100 °C with a continuous pressure of 100 bar of H₂. Using the *Parr* reactor setup at such a scale, allowed for taking reaction samples which were directly analysed *via* GC-FID to determine the course of the reaction. A more detailed description of the *Parr* reactor used can be found in section 7.5.2. The conversion of acetaldehyde to ethanol over time as well as the generation

of 2,3-BDO over time using either different amounts of a 5wt% Ru/C catalyst and the product solution from the IM-NHC5-PF₆ experiment (Figure 21) as feedstock, is shown in Figure 23.

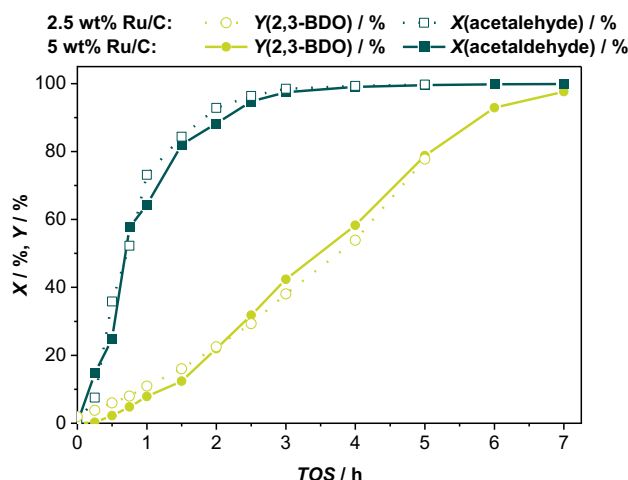


Figure 23: Conversion of acetaldehyde and yield of 2,3-BDO over time using either 2.5wt% (open symbols) or 5.0wt% (filled symbols) of a 5wt% Ru/C catalyst, where the mass of catalyst was based on the mass of acetoin containing product solution from the acetaldehyde self-addition experiment described in **Figure 21**, section 5.1.7, page 54. Reaction conditions: $m(\text{Ru/C}) = 2.5 \text{ g}$ or 5.0 g , $m(\text{stock}) = 100 \text{ g}$, $p(\text{H}_2) = 100 \text{ bar}$, $T = 100 \text{ }^\circ\text{C}$, 1500 rpm. Samples were collected and analysed using GC-FID. Yields and conversions were calculated based on the relative changes in area of the peak in the GC-FID chromatogram.

In both cases, acetaldehyde is quickly converted to EtOH and full acetaldehyde conversion is attained after roughly 3 h into the reaction. The hydrogenation of acetoin to 2,3-BDO appears to be much slower. After 5 h into the reaction, about 80% of the acetoin is hydrogenated to 2,3-BDO. As the reaction rate does not seem to be influenced by the increasing amount of catalyst, it is amendable that the reaction system suffers from mass-transport limitations, which were not further investigated. Instead, the experiments shown in **Figure 23** serve to show that direct hydrogenation of the acetaldehyde/acetoin/EtOH product mixture from **Figure 21**, to a 2,3-BDO/EtOH containing product mixture, is also possible.

After delivering a proof of concept that the slurry phase hydrogenation of the acetaldehyde /acetoin/EtOH containing product mixture can be carried out on bigger scale, the separation of the obtained 2,3-BDO/EtOH mixture was investigated. Due to the large difference in boiling points ($T_{\text{bp}}(\text{EtOH}) = 78 \text{ }^\circ\text{C}$ whereas $T_{\text{bp}}(2,3\text{-BDO}) = 177 \text{ }^\circ\text{C}$), separation *via* distillation was proposed. Prior to separating the 2,3-BDO/EtOH mixture after hydrogenation, preliminary distillations of artificially prepared mixtures of ethanol (~90 g) and 2,3-BDO (~10 g), were carried out. EtOH was recovered from the top of the column at $T = 78 - 80 \text{ }^\circ\text{C}$. Once the temperature had dropped to below $78 \text{ }^\circ\text{C}$, the distillation was terminated, and the top and bottom fraction were analysed. GC-FID analysis revealed that pure EtOH was recovered in 96wt% of the initially weighed EtOH from the top of the column, leaving around 4wt% of EtOH remaining in the bottom containing 2,3-BDO fraction, resulting in 83% pure 2,3-BDO in the bottom flask.

Applying the procedure to the hydrogenated EtOH/2,3-BDO mixture (**Figure 23**) resulted in the isolation of pure EtOH from the top of the column. As opposed to the artificially prepared mixture though, around 75% pure 2,3-BDO in EtOH, as determined *via* GC-FID analysis remained as bottom fraction. Further purification of this mixture using an additional Vigreux

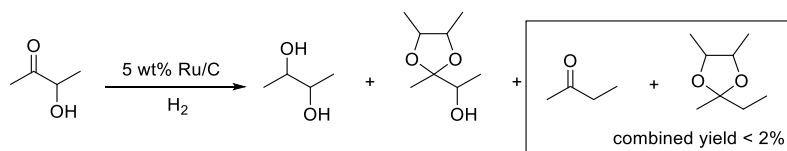
column and applying higher temperatures and carrying out the distillation for longer times, led to the isolation of 95% pure 2,3-BDO in EtOH. Further purification of this mixture using hybrid extractive distillation as for example proposed by *Subudhi et al.* was not investigated, but might be applied to obtain highly pure 2,3-BDO (> 99.9%) which can directly be used in the double dehydration to afford 1,3-BD from 2,3-BDO.^[236-237]

5.2.5 Pressureless Gas-Phase Flow Hydrogenation of Acetoin to 2,3-BDO

As opposed to the slurry phase hydrogenation of the acetaldehyde/acetoin/EtOH containing product mixture in a stirred tank reactor, using the PFR-type reactor in the BD miniplant (chapter 4) with the same feedstock seemed far less promising. In a set of parameter screening-experiments using a tubular quartz-glass reactor in the BD miniplant, a mixture of acetoin and ethanol was fed into the reactor which contained a single bed of 5wt% Ru/C catalyst. Unfortunately, these experiments proved to be unfruitful as only very low (< 5%) 2,3-BDO yields were attained. Therefore, use of a PFR type reactor to convert the acetoin/acetaldehyde/ EtOH mixtures of the earlier discussed continuous-flow acetaldehyde self-addition reactions to 2,3-BDO/EtOH mixtures was not further investigated.

Nonetheless, investigating the continuous-flow hydrogenation of pure acetoin to 2,3-BDO in a pressureless stream of H₂ seems promising. As described earlier, pure acetoin can be obtained by carrying out the acetaldehyde self-addition in absence of solvent, or by using fermentative processes.^[169-170] By using pressureless or low pressured H₂ streams, the reaction could serve as model reaction for more elaborate investigations on low pressure continuous-flow hydrogenation reactions in general. This would be beneficial as it would reduce the need for high pressure compatible equipment and it would make use of pressureless H₂ streams that are often regarded as “waste-streams” by industry. It has already been shown in literature, that the hydrogenation of acetoin to 2,3-BDO can be carried out in a H₂ flow without the need for high pressure compatible equipment.^[167] However, the potential of scaling up the reaction beyond the 20 $\mu\text{L}\cdot\text{min}^{-1}$ scale, was not discussed by *Nakazono*.

For the process intensification regarding the pressureless flow hydrogenation of acetoin, the BD miniplant was slightly reconstructed (see section 7.5.3). An HPLC pump was used to feed pure liquid acetoin monomer (for synthesis, > 98%, *Sigma*) into the reactor (**Figure 8**). Mass-flow of feed was additionally governed using a digital flow-meter. Experiments were carried out using a single bed of 5wt% Ru/C as catalyst in a H₂ flow of 80 mL·min⁻¹. Liquid reactor effluent was collected for the whole duration of the experiment. After a typical experiment with 2 h TOS a single-pass conversion of 82% (**Table 14**, entry 14.1) was attained. However, despite high conversion, the selectivity towards 2,3-BDO is rather low due to the high content of ketal side products as well as dehydration side products (2-butanone, methyl ethyl ketone, MEK) and its corresponding ketal that were observed. The combined yields of the latter two side products however, was found to be <2 % in most of the experiments.

Table 14: Catalytic results of the flow hydrogenation of acetoin to yield 2,3-BDO and a variety of other products catalysed by a 5wt% Ru/C catalyst.^[a]

Entry	Flow-rate(H ₂) (mL·min ⁻¹)	X(acetoin) ^[b] (%)	Y(2,3-BDO) ^[b] (%)	ΣY(sides) ^[c] (%)	S(2,3-BDO) (%)
14.1	80	82	40	43	48
14.2	40	74	31	42	42
14.3	120	35	16	18	47

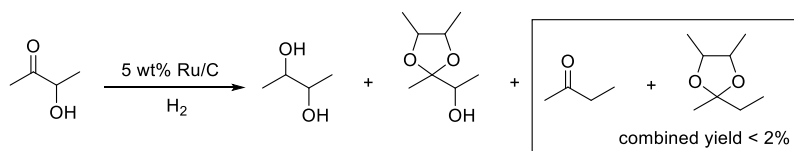
[a] Reaction conditions: flow-rate(acetoin) = 0.125 mL·min⁻¹, *T* = 150 °C, samples collected for 2 h TOS after equilibrating the reactor for 1 h in H₂ flow, *m*(Ru/C) = 2.0 g. [b] As determined by GC-FID using mesitylene as standard added after the reaction. Mass-balances ΣY > 95% were obtained. [c] Side products include various C₈ ketals, MEK and others.

Lowering the flow-rate of H₂ from 80 mL·min⁻¹ to 40 mL·min⁻¹ (entry 14.2) and thus theoretically halving the contact time of the educt with the catalytically active material, did not result in an improved selectivity. Comparable conversions and yields were attained (74% and 31% respectively) as in the experiment with 80 mL·min⁻¹. The lower flow-rate of H₂ and consequently the longer residence time of the generated 2,3-BDO in the reactor, might have been parts of the reason why side product yields are relatively high. It can be assumed that the consecutive reaction of 2,3-BDO and acetoin to the corresponding ketal, is much slower compared to the hydrogenation of acetoin to 2,3-BDO. Hence, a longer residence time in the reactor, could have been the reason for a higher yield in the corresponding ketal side products. This hypothesis could not be verified by carrying out the reaction at a flow of H₂ of 120 mL·min⁻¹. Due to a lower single-pass conversion of 35%, 18% ketal side products were obtained. Though the yield of ketal side products is much lower compared to the other experiments, due to the lower acetoin conversion, a comparable selectivity of 47% was found (entry 14.3).

The experiments listed above hint that with increasing flow-rate of H₂, a decrease in desired product yield is attained, especially when comparing entry 14.1 and 14.3. Albeit selectivity is still rather low as ketals are observed. It might be, that the selectivity issue observed here, is associated with high concentrations of unconverted acetoin in vicinity of generated 2,3-BDO. The formation of the corresponding ketal is not suspected to be directly catalysed by the Ru/C catalyst. In order to decrease the concentration of unconverted acetoin inside the reactor, the volumetric flow of acetoin was reduced at a H₂ flow-rate of 80 mL·min⁻¹ and otherwise identical reaction conditions (Table 15). In theory, the decrease in volumetric flow-rate of acetoin should go hand-in hand with an increase in conversion and decrease in side product yield.

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Table 15: Catalytic results of the flow hydrogenation of acetoin to yield 2,3-BDO at different acetoin flow-rates, catalysed by a single bed of 5wt% Ru/C which was used without pre-treatment ^[a]



Entry	Flow-rate(acetoin) (mL·min ⁻¹)	X(acetoin) (%) ^[b]	Y(2,3-BDO) (%) ^[b]	ΣY(sides) (%) ^[c]	S(2,3-BDO) (%)
15.1	0.125	82	40	43	48
15.2	0.050	93	64	30	68
15.3	0.025	93	68	25	73

[a] reaction conditions: flow-rate(H₂) = 80 mL·min⁻¹, *T* = 150 °C, samples collected for 2 h TOS after equilibrating the reactor for 1 h in H₂ flow *m*(Ru/C) = 2.0 g. [b] As determined by GC-FID using mesitylene as standard added after the reaction. Mass-balances ΣY > 95% were obtained. [c] Side products include various C₈ ketals, MEK and others.

At first glance, decreasing the flow-rate of acetoin indeed results in higher yields and higher selectivities towards 2,3-BDO. For an acetoin flow-rate of 0.050 mL·min⁻¹ (entry 15.2) and 0.025 mL·min⁻¹ (entry 15.3), comparable conversion is attained while selectivities rise somewhat. Still, for the lowest feed-rate of 0.025 mL·min⁻¹ (Table 15, entry 15.3) tested in these experiments, the selectivity towards 2,3-BDO is only 73% at 93% acetoin conversion. Varying the feed-rate of substrate and thereby the contact time with the catalyst as well as the concentration of generated 2,3-BDO in the reactor, has an influence on the observed product spectrum. In order to get a deeper knowledge of the system, the total TOS of the experiment was increased from 2 h to 5 h and samples were taken from the cold trap every hour. Besides this, an acetoin flow-rate of 0.022 mL·min⁻¹ at otherwise identical conditions was adapted in order to allow for comparison with a system described in literature.^[167]

For the experiments discussed thus far, the yield of MEK and the corresponding ketal of MEK and acetoin, was found to be <2%. Hence, in the discussion of the following conversion-time profiles, the term 'side products' refers primarily to the C₈ ketals of acetoin and 2,3-butanediol. The obtained conversion/time profile for the gas-phase hydrogenation of acetoin to 2,3-BDO using a pressure less stream of H₂ is shown Figure 24.

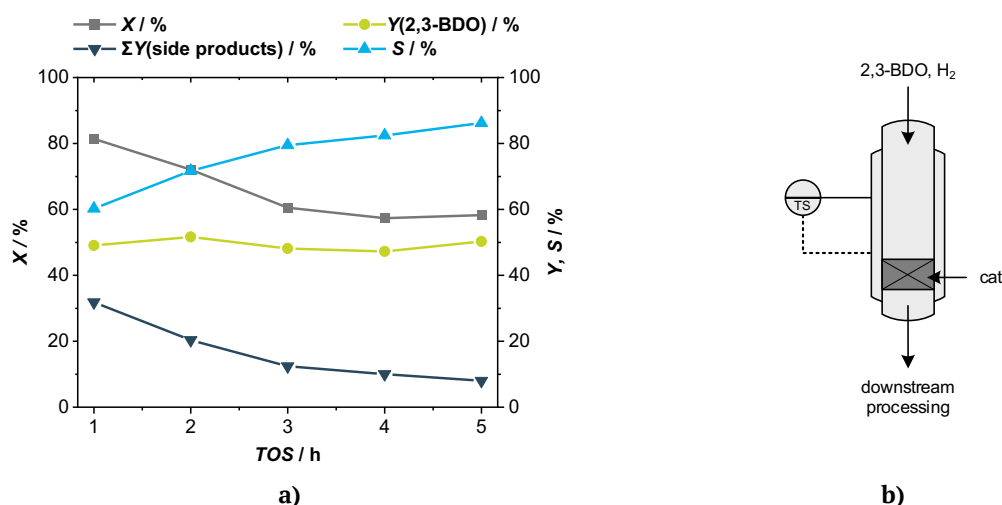


Figure 24: **a)** Catalytic results of a flow hydrogenation experiment carried out for a total of 5 h TOS where samples were collected for a duration of 1 h. Reaction conditions: $m(\text{Ru/C}) = 0.125$ g, $\text{flow-rate}(\text{H}_2) = 30$ mL·min⁻¹, $\text{flow-rate}(\text{acetoin}) = 0.022$ mL·min⁻¹, $T = 150$ °C, $\text{WHSV} = 11$ h⁻¹. The 5wt% Ru/C catalyst was freshly reduced prior to catalysis, reduction conditions: $p(\text{H}_2) = 60$ bar at r.t., $T = 150$ °C, $t = 69$ h. Yields were determined by GC-FID using mesitylene as standard added after the reaction. Side products include various C₈ ketals, MEK and others. **b)** Schematic representation of the reactor cross section, where the grey marked area indicates the catalyst bed.

After preheating the catalyst for 1 h in a H₂ stream, feed of substrate was initiated which marks the beginning of the experiment and 0 h TOS. After collection of samples, analysis was carried out *via* GC-FID using mesitylene as standard. In the first hour, an acetoin conversion of 80% is obtained. 2,3-BDO is obtained in a yield of 49% and the residual of the converted substrate has reacted with 2,3-BDO in a consecutive reaction resulting in 31% ketal yield. Based on the trend of conversion-over-time, the obtained time profile suggests a decay in catalytic performance over the first 3 h into the reaction, before the conversion of acetoin levels out at around 60%. Formation of side products decreases with increasing TOS whereas the yield of 2,3-BDO stays rather constant at around 45%. Due to the fact that the side product formation (*i.e.* C₈ ketals) decreases, but the yield of acetoin stays rather constant, selectivity rises with increasing TOS. Averaged over the whole duration of the experiment, an average conversion of $\bar{X} = 66\%$ and an averaged selectivity of $\bar{S} = 76\%$ is obtained. Though Nakazono *et al.* investigated the same reaction conditions, they were able to attain an averaged conversion of $\bar{X} = 86\%$ with an averaged selectivity of $\bar{S} = 88\%$ using a commercial Ru/C catalyst.^[167] A possible explanation of this deviation from the literature value could be the missing information on reactor dimensions and consequently the height of the catalyst bed which might have an influence on the performance of the system.

From this first continuous-flow experiment, a few flaws were noted that needed to be optimised. As seen in **Figure 24b**, liquid substrate fed from the top of the reactor, is not vaporised prior coming in contact with the catalyst bed. Therefore, liquid droplets hitting the catalyst bed get vaporised upon impact with the hot catalyst as the reactor temperature is above the boiling point of acetoin ($T_{\text{bp}} = 147$ °C). This had caused a visible disruption of the catalyst bed which was observed after the experiment and in turn might have affected the catalytic performance of the system.

To afford an even distribution of the (liquid) substrate onto the catalyst bed, a layer (2 cm) of glass beads ($m = 5.0$ g, $d = 1$ mm, Hecht Assistant®) was introduced into the system. The

addition of the glass beads on top of the catalyst bed can not only act as vaporising zone for the substrate, but might also facilitate mixing of acetoin vapour with the H_2 flow-gas. The plot of conversion, yield and selectivity towards 2,3-BDO for this experiment using glass beads on top of the catalyst bed at otherwise identical reaction conditions, is shown below (Figure 25).

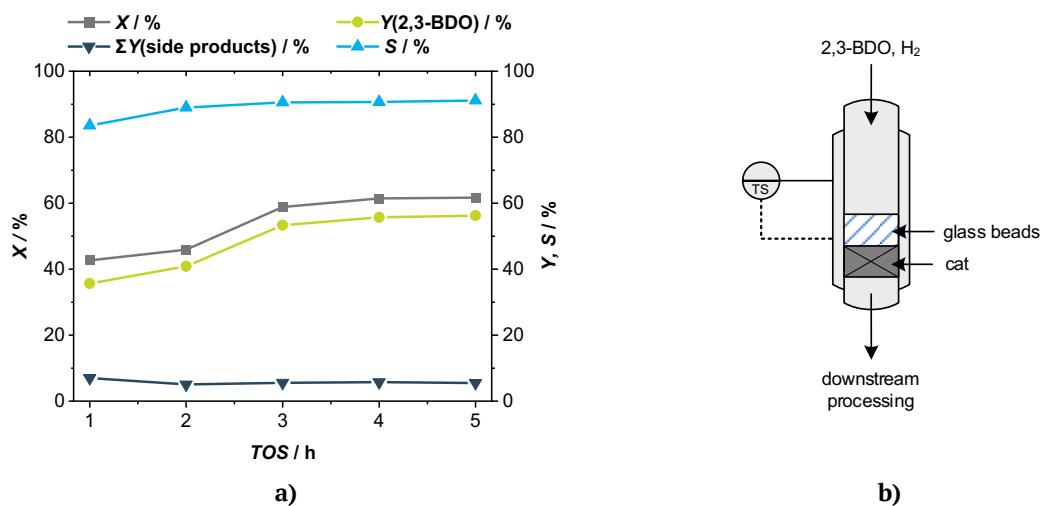


Figure 25: **a)** Catalytic results of the flow hydrogenation using glass beads on top of the catalyst bed as pre-heat/vaporising zone. Reaction conditions: $m(\text{Ru/C}) = 0.125 \text{ g}$, $\text{flow-rate}(H_2) = 30 \text{ mL}\cdot\text{min}^{-1}$, $\text{flow-rate}(\text{acetoin}) = 0.022 \text{ mL}\cdot\text{min}^{-1}$, $T = 150 \text{ }^\circ\text{C}$, $WHSV = 11 \text{ h}^{-1}$. Yields were determined by GC-FID using mesitylene as standard added after the reaction. Side products include various C_8 ketals, MEK and others. **b)** Schematic representation of the reactor cross section, where the grey marked represents the catalyst bed and the blue marked area the glass beads added on top of the catalyst bed.

As can be seen from Figure 25, for the experiment carried out with glass beads, the yield of side products stays more or less constant, resulting in an average yield of $\bar{Y}(\text{side products}) = 6\%$. As opposed to the experiment without glass beads, conversion as well as yields follow the same trend, rising for the first 3 h TOS and levelling out at 61% conversion and 55% yield respectively, resulting in an average conversion of $\bar{X} = 54\%$ and $\bar{Y}(2,3\text{-BDO}) = 48\%$ at an average selectivity of $\bar{S} = 90\%$. Compared to the conversion/yield/selectivity-time plots observed in Figure 24, addition of glass beads on top of the catalyst bed has an influence on the selectivity of the reaction as the yields of side products are found to be very low. Based on this observation, the experiment was repeated, with two instead of one catalyst contacts. Half of the desired catalyst weight, was used in the first layer which was consecutively topped off with half the amount of glass beads and on top of that the other half of the catalyst with the other half of glass beads. With this approach, the contact time of the substrate with the catalyst bed is halved. Due to the implementation of two layers, the $WHSV$ (based on the flow of acetoin as substrate) can be maintained, in order to achieve comparable results. Also, two distinct layers of glass beads might facilitate effective mixing of unconverted acetoin after the first bed with H_2 flow-gas to attain higher conversions in the second bed. The results as well as a visual representation of the reactor packing is visualised below (Figure 26).

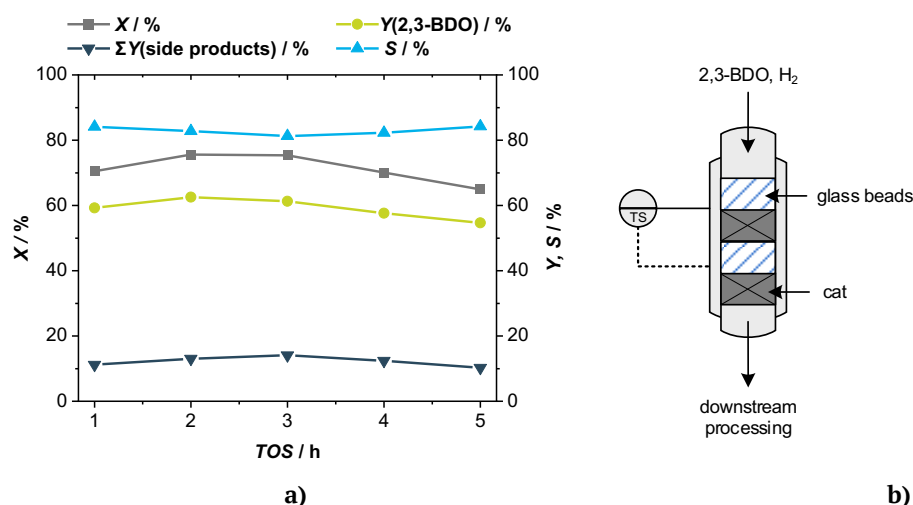


Figure 26: a) Catalytic results of the flow hydrogenation using a dual bed catalytic approach, carried out for a total of 5 h TOS where samples were collected for a duration of 1 h. Reaction conditions: $m(\text{Ru/C}) = 0.125 \text{ g}$ distributed equally over the two beds, $\text{flow-rate}(\text{H}_2) = 30 \text{ mL}\cdot\text{min}^{-1}$, $\text{flow-rate}(\text{acetoin}) = 0.022 \text{ mL}\cdot\text{min}^{-1}$, $T = 150 \text{ }^\circ\text{C}$, $\text{WHSV} = 11 \text{ h}^{-1}$. Yields were determined by GC-FID using mesitylene as standard added after the reaction. Side products include various C₈ ketals, MEK and others. **b)** Schematic representation of the reactor cross section, where the grey marked represents the catalyst bed and the blue marked area represents the glass beads added to separate the reactor contacts.

In this dual bed flow hydrogenation experiment an average conversion of $\bar{X} = 71\%$ was attained, affording 2,3-BDO with an average yield of $\bar{Y}(2,3\text{-BDO}) = 59\%$. Both conversion and yield, stay relatively constant during the first 3 h TOS before declining a bit. This is contradictory to the findings for the single bed approach, where conversion and yield changed during the initial 3 h TOS. Compared to the single bed experiment, the averaged selectivity is somewhat lower ($\bar{S} = 90\%$) but the averaged acetoin conversion as well as total 2,3-BDO yield is higher for the dual bed catalytic approach.

A closer examination of the two reactors after the reaction, revealed that although great care was taken to ensure distinctly separation of catalyst layers prior to the experiment, after a typical dual bed flow hydrogenation reaction, the two catalyst beds were not separated anymore. As it seemed, catalyst was dragged from the top layer into the separation layer and possibly also into the next bed of catalyst. Comparison of the catalyst beds before and after a typical reaction can be seen in Figure 27a and b respectively.

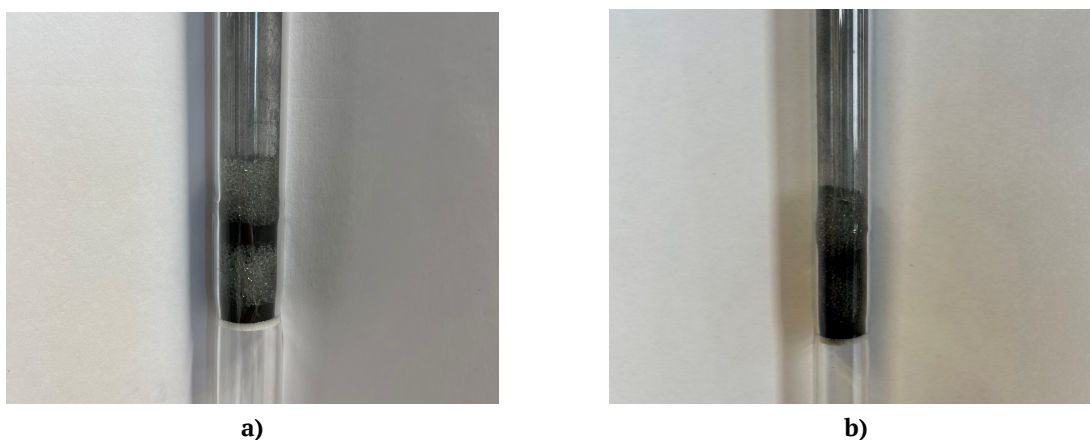


Figure 27: Comparison of the packed reactor before a) and after b) a typical dual bed catalytic flow hydrogenation using Ru/C as catalyst and glass beads as inert filling material.

As there is no information on the timeframe of the apparent redistribution of catalyst/glass beads during the reaction, the trends observed in Figure 26 have to be considered with great care as the behaviour of the system in the studied 5 h TOS might not be representative for more prolonged time-frames as it is possible that the swirling of the catalyst layers has an influence on the obtained results. In order to rule out the observed redistribution of catalyst throughout the course of the experiment and to better understand its influence, a reference experiment was carried out where the catalyst was thoroughly mixed with the glass beads as filling material prior to the reaction. The conversion/yield/selectivity-over-TOS profile of this reference experiment is shown in Figure 28a.

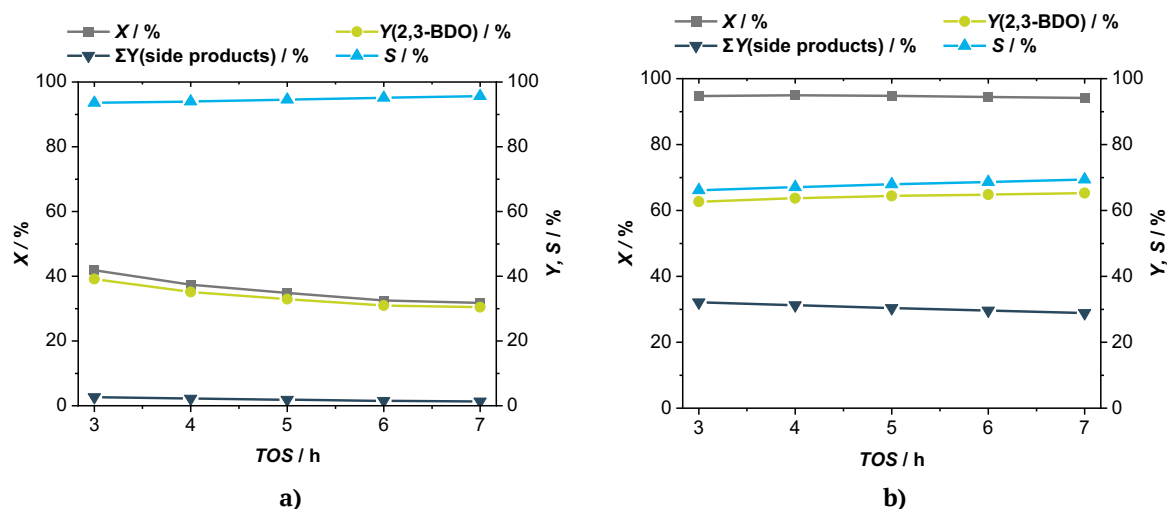


Figure 28: Comparison of the catalytic results of the flow hydrogenation using a catalyst bed where the powdered 5wt% Ru/C catalyst was well-mixed with the glass beads prior to the reaction for **a)** an experiment at standard reaction conditions and **b)** experiment with the double amount of Ru/C catalyst at otherwise identical conditions. Experiments were carried out for a total of 7 h TOS where samples were collected for a duration of 1 h after a start-up phase of 2 h. Reaction conditions: $m(\text{Ru/C}) = 0.125 \text{ g}$ in **a)** and 0.250 g in **b)**, $\text{flow-rate}(\text{H}_2) = 30 \text{ mL}\cdot\text{min}^{-1}$, $\text{flow-rate}(\text{acetoin}) = 0.022 \text{ mL}\cdot\text{min}^{-1}$, $T = 150 \text{ }^\circ\text{C}$. Yields were determined by GC-FID using mesitylene as standard added after the reaction. Side products include various C_8 ketals, MEK and others.

Comparing the time-profile obtained for the mixed catalyst in Figure 28a with that of the initially separated catalyst bed (Figure 26) shows a higher overall selectivity towards 2,3-BDO ($\bar{S} > 94\%$) for the whole duration of the experiment. In Figure 28a, the trend in yield/conversion declines with rising TOS. Mass-transfer limitations might play a role, as the generated 2,3-BDO is in the liquid phase at reaction conditions. Generation of liquid 2,3-BDO could have caused saturation of pores of the Ru/C catalyst and subsequently preventing acetoin from access to the catalytically active sites. In order to find out if the system could be pushed to higher conversions and to investigate underlying mass-transfer issues, the amount of catalyst was doubled at otherwise identical conditions (Figure 28b). It can be assumed that the double amount of catalyst does not have a significant influence on the residence time inside the reactor, as this is most likely influenced by the amount of inert glass beads which was kept constant in both experiments. As seen in Figure 28b, doubling the amount of catalyst led to an increase in conversion/yield. The amount of converted substrate is more than twice as high, compared to the experiment in Figure 28a. However, the yield towards the desired 2,3-BDO does not rise accordingly. It has to be kept in mind, that unconverted acetoin can undergo a consecutive reaction to form ketals. It can also be assumed that doubling the catalytically active material, has resulted in an increased formation of 2,3-BDO. When considering this, it

can be assumed that the concentration of 2,3-BDO in the overall catalyst bed/reactor is higher whenever there is more catalyst present. The ‘volume’ of the catalyst bed inside the reactor, is mostly affected by the amount of filling material. The higher concentration of 2,3-BDO could favour the consecutive reactions with acetoin resulting in the formation of about 30% ketals. It is suggested that the amount of filling material used *i.e.* the ratio of filling material to catalyst, influences the product spectrum of the system. More filling material results in a lower concentration of 2,3-BDO in the reactor and consequently less formation of ketal side products. On the other hand, the amount of catalyst is the governing factor for acetoin conversion. Therefore, the ratio of catalyst to filling material might be of importance. To verify this, the experiment in Figure 28b was recreated with twice the amount of glass beads. This in turn should facilitate a high conversion of acetoin to 2,3-BDO, while at the same time decreasing the concentration of 2,3-BDO in the reactor. Again, catalyst and glass beads were mixed well before reaction. The obtained conversion/time profiles of this experiment are visualised in Figure 29.

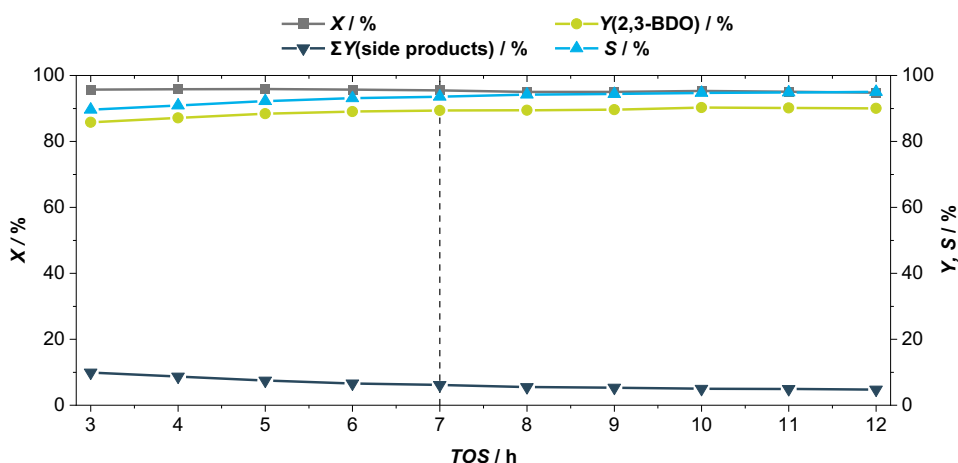


Figure 29: Catalytic results of the pressureless flow hydrogenation where a powdered 5wt% Ru/C catalyst was well-mixed with the glass beads prior to the reaction. Experiments were carried out for a total of 12 h TOS where samples were collected for a duration of 1 h after a start-up phase of 2 h. After 420 min TOS, the reaction was terminated for the night and re-started the next day. For that purpose, flow of H₂ as well as substrate flow were stopped and the reactor was allowed to cool to r.t.. The next day, the reactor was heated to the desired reaction temperature in H₂ flow and educt feed was initiated after a stable temperature was reached. Reaction conditions: $m(\text{Ru/C}) = 0.250 \text{ g}$, $m(\text{glass beads}) = 20 \text{ g}$, $\text{flow-rate}(\text{H}_2) = 30 \text{ mL}\cdot\text{min}^{-1}$, $\text{flow-rate}(\text{acetoin}) = 0.022 \text{ mL}\cdot\text{min}^{-1}$, $T = 150 \text{ }^\circ\text{C}$. Yields were determined by GC-FID using mesitylene as standard added after the reaction. Side products include various C₈ ketals, MEK and others.

Doubling the amount of filling material and restoring the ratio of catalyst to filling material as seen in Figure 28a has beneficial effect on the catalytic performance of the system, especially when regarding the selectivity towards side product *i.e.* ketal formation, which proves the aforementioned hypothesis regarding the need for lowering the concentration of 2,3-BDO in the reactor. Over the course of the reaction, yields towards desired 2,3-BDO seems to increase a bit from around 85% to 90%, at constant acetoin conversions of 94%. Consequently, side product yields decline throughout the reaction resulting in an overall high average selectivity of $\bar{S} = 93\%$. Increasing the amount of glass beads from 10 to 20 g suggest that a greater dispersion of the powdered catalyst is beneficial for the reaction. As far as the residence time or contact time of the substrates with the catalyst is concerned, doubling the amount of glass beads does not seem have a significant influence since the initial sample mass collected after

a total time of 3 h TOS was roughly the same for all experiments listed herein where glass beads were used. In the experiment shown **Figure 29**, the reaction was terminated after a total of 7 h TOS. Afterwards flow of substrates was terminated and the reactor was allowed to come to ambient temperature whilst maintaining a flow of H₂ and kept under Ar for the night. The next day, the reactor was heated to the reaction temperature in H₂ flow and substrate feed was reinitiated after a constant temperature was achieved. Samples were again collected for 1 h TOS. The samples collected on the second reaction day (TOS 7 to 12 h) demonstrate the high stability and performance of the system. The system shown in **Figure 29** already meets the set criteria of achieving a stable, highly active flow hydrogenation catalytic system based on a commercial 5wt% Ru/C catalyst, the drawback is its throughput of only 0.022 mL acetoin per minute and consequently a low productivity of $P = 4.8 \text{ g}_{2,3\text{-BDO}} \cdot \text{g}_{\text{cat.}}^{-1} \cdot \text{h}^{-1}$

5.2.6 Low-Pressure Continuous-Flow Hydrogenation of Acetoin to 2,3-BDO

In an attempt to scale up the reaction, *i.e.* increase the amount of product per unit catalyst and time, the glass reactor was exchanged for a pressure resistant stainless-steel *Swagelok* reactor and a *Gentec* back-pressure-regulator (BPR) was installed downstream of the reactor. With these adjustments, carrying out the flow hydrogenation at ambient pressures (< 15 bar) was possible. With the modified reactor setup, the experiment shown in **Figure 29** was recreated with a H₂ pressure of 10 bar and substrate flow of 0.11 mL·min⁻¹ at otherwise identical reaction conditions. The results of the experiment, which was again carried out for two experimental days, is shown below in **Figure 30**.

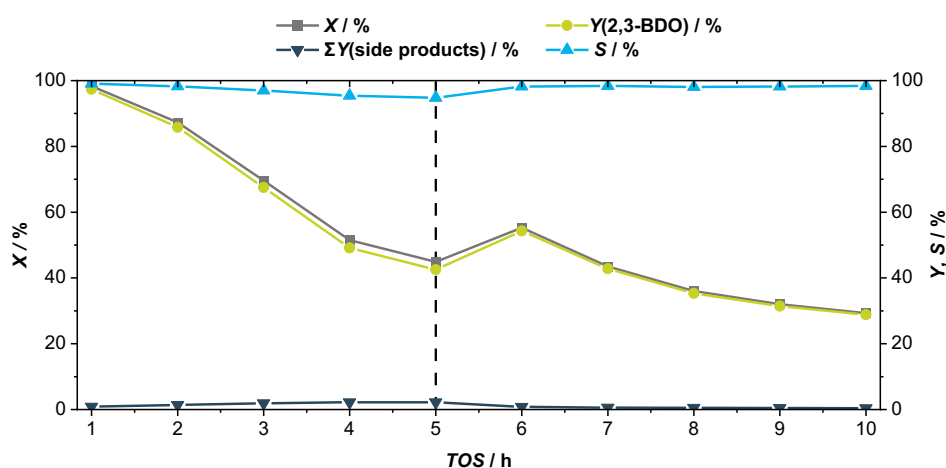


Figure 30: Catalytic results of the low-pressure flow hydrogenation of acetoin to 2,3-BDO. Experiment was carried out for a total of 10 h TOS where samples were collected for a duration of 1 h after a start-up phase of 1 h. After 5 h TOS, the reaction was terminated for the night and re-started the next day. After 5 h, the flow of educt was stopped, but the H₂ flow was raised to 90 mL·min⁻¹ for 1 h at 10 bar of H₂ and a reactor temperature of $T = 250 \text{ }^{\circ}\text{C}$. The next day, the reactor was heated to the desired reaction temperature before flow of H₂ was started. Once reaching the desired pressure, the flow of educt was re-initiated as well. Reaction conditions: $m(\text{Ru/C}) = 0.250 \text{ g}$, $m(\text{glass beads}) = 20 \text{ g}$, $\text{flow-rate}(\text{H}_2) = 30 \text{ mL}\cdot\text{min}^{-1}$, $p(\text{H}_2) = 10 \text{ bar}$, $\text{flow-rate}(\text{acetoin}) = 0.11 \text{ mL}\cdot\text{min}^{-1}$, $T = 150 \text{ }^{\circ}\text{C}$. Yields were determined by GC-FID using mesitylene as standard added after the reaction. Side products include various C₈ ketals, MEK and others.

Unfortunately, the conversion/yield-time profile shows a vast decline in performance over the first 3 h into the reaction and continued to decline during the first experimental day. Both yield and conversion rapidly decline, although the selectivity of the reaction seems to be

rather constant. Preliminary analysis of samples collected during the first 3 h *TOS* already revealed the declining conversions and yields on the first experimental day. Therefore, in an attempt to partially re-store the catalytic activity of the system, an *in-situ* reduction of the contained catalyst was attempted after 5 h *TOS*. Reduction was carried out at a temperature of 250 °C and an increase H_2 flow of $90 \text{ mL}\cdot\text{min}^{-1}$ for 1 h at 10 bar of system pressure in absence of substrate feed. Afterwards, the reactor was allowed to come to ambient temperature whilst maintaining a flow of H_2 . The reactor was vented and stored under Ar for the night. As can be seen from the sample collected for 6 h *TOS* (second experimental day after achieving a steady state of the reactor) carrying out the *in-situ* reduction of the Ru/C catalyst was indeed able to partially restore the activity of the catalyst. Despite this, the observed decaying trend in catalytic activity, reflected in a decrease in conversion and yield for 2,3-BDO, persisted on the second experimental day. Selectivity towards 2,3-BDO however, remains unchanged and stays > 95% throughout the experiment. The low concentration of ketal side product formation might again be associated with the concentration of generated 2,3-BDO in the reactor which is kept low by the increased volume of the reaction zone due to the filling material present.

Unfortunately, carrying out the continuous-flow hydrogenation in a PFR-type reactor using a moderate pressure of 10 bar did not lead to the desired effect of achieving a stable, high throughput continuous acetoin-to-2,3-BDO hydrogenation. Whilst cleaning the reactor after the reaction, it was observed that the catalyst bed had clogged together. It is amendable that the clogged bed had a negative influence on the catalytic performance. Therefore, the experiment was recreated, without using glass beads. Instead, a single bed of Ru/C catalyst was used between two small plugs of glass wool. This was done to keep the catalyst bed in place during the reaction and to provide the necessary surface area for distribution and mixing of the liquid substrate with the H_2 stream (Figure 31).

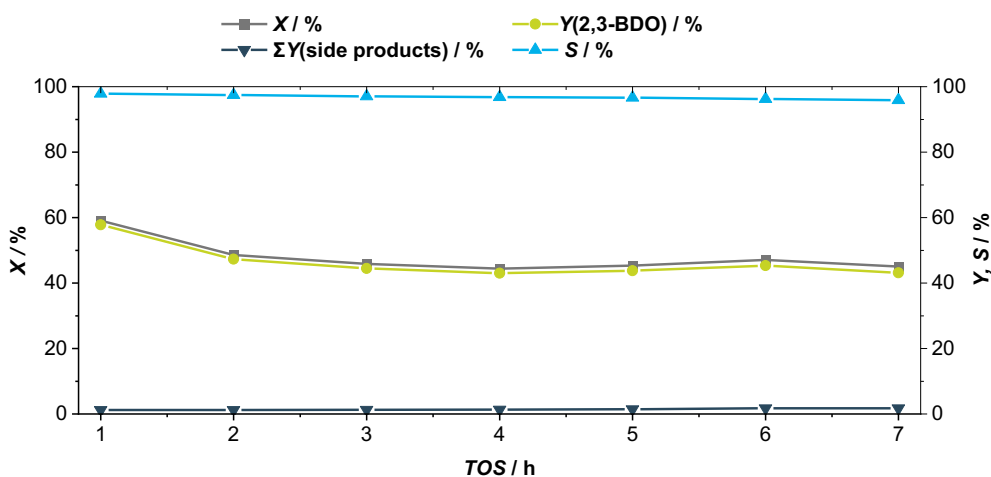


Figure 31: Catalytic results of the low-pressure flow hydrogenation of acetoin to 2,3-BDO. Experiment was carried out for a total of 7 h *TOS* where samples were collected for a duration of 1 h after a start-up phase of 1 h. Reaction conditions: $m(\text{Ru/C}) = 0.250 \text{ g}$, $\text{flow-rate}(\text{H}_2) = 30 \text{ mL}\cdot\text{min}^{-1}$, $p(\text{H}_2) = 10 \text{ bar}$, $\text{flow-rate}(\text{acetoin}) = 0.11 \text{ mL}\cdot\text{min}^{-1}$, $T = 150 \text{ }^\circ\text{C}$. Yields were determined by GC-FID using mesitylene as standard added after the reaction. Side products include various C_8 ketals, MEK and others.

Notably, the continuous-flow low-pressure hydrogenation of acetoin to 2,3-BDO in absence of glass beads as filling material, has a much more constant conversion/yield-over-*TOS* trend as compared to the experiment with added glass beads (Figure 30). This result contradicts the

observations and assumptions raised based on the results from the pressureless continuous-flow hydrogenation. There it was found that use of glass beads as a filler material have a promoting effect on catalytic activity as well as aided in suppressing consecutive ketal formation. In **Figure 31**, an average 2,3-BDO yield of 46% was attained, at a selectivity $S > 96\%$ at a productivity of $12.3 \text{ g}_{2,3\text{-BDO}} \cdot \text{g}_{\text{cat}}^{-1} \cdot \text{h}^{-1}$. Notably, the productivity for the pressured system is about 3 times higher compared to the pressureless system.

All in all, the results obtained with pressureless and low-pressure continuous-flow hydrogenation of acetoin to 2,3-BDO suggest that there are many more underlying factors that affect the performance of the system. Some factors that might play an additional role are the flow behaviour in the reactor, especially when inert filling material is added, as well as the packing density and pressure hysteresis due to the inherent BPR function. The experiments discussed above deliver a proof of concept that both pressureless and low-pressure continuous-flow hydrogenation of acetoin to 2,3-BDO using a commercially available Ru/C catalyst is possible with the designed PFR miniplant setup but also leave plenty of room for further studies and scale up. Also, the results discussed show that a commercial Ru/C catalyst is able to attain the same excellent performance in the pressureless continuous-flow hydrogenation compared to elaborately manufactured Ni/SiO₂ catalyst discussed by Nakazono and co-workers (91% conversion at $> 99.9\%$ selectivity averaged over 5 h TOS).^[167]

In general, when looking into literature on hydrogenation catalyst used in industry, Ru/C catalysts are among the lesser mentioned and their application is in most cases research laboratory oriented (small reactors, small amounts of catalyst, batch mode etc.). Probably also owing to the bad mechanic stability of charcoals, industrialised hydrogenation catalysts often use more stable support materials as well as cheaper catalytically active materials.

5.2.7 Catalyst Screening in the Low-Pressure Continuous-flow Hydrogenation of Acetoin to 2,3-BDO

The earlier developed Ru/C systems (**Figure 31**) can serve as benchmark system when screening other commercially available catalysts. For the screening of different commercially available hydrogenation catalysts, we were kindly provided with three industrial catalyst samples from *Johnson Matthey*. Although the catalysts were developed to catalyse the reduction of aldehydes to alcohols in the liquid phase, it is reasonable to assume that they also show activity in the hydrogenation of ketones to alcohols. Therefore, each catalyst was tested under conditions comparable to the earlier Ru/C experiment (**Figure 31**). As all catalyst samples were received as extrudates, the extrudates were ground to powder prior to testing. Catalytic runs were carried out using a single bed of catalytically active material without any other fill material for a duration of 5 h TOS. Again, the catalyst was held in place between two small plugs of glass wool. The results of several commercial catalysts samples are shown in **Figure 32**.

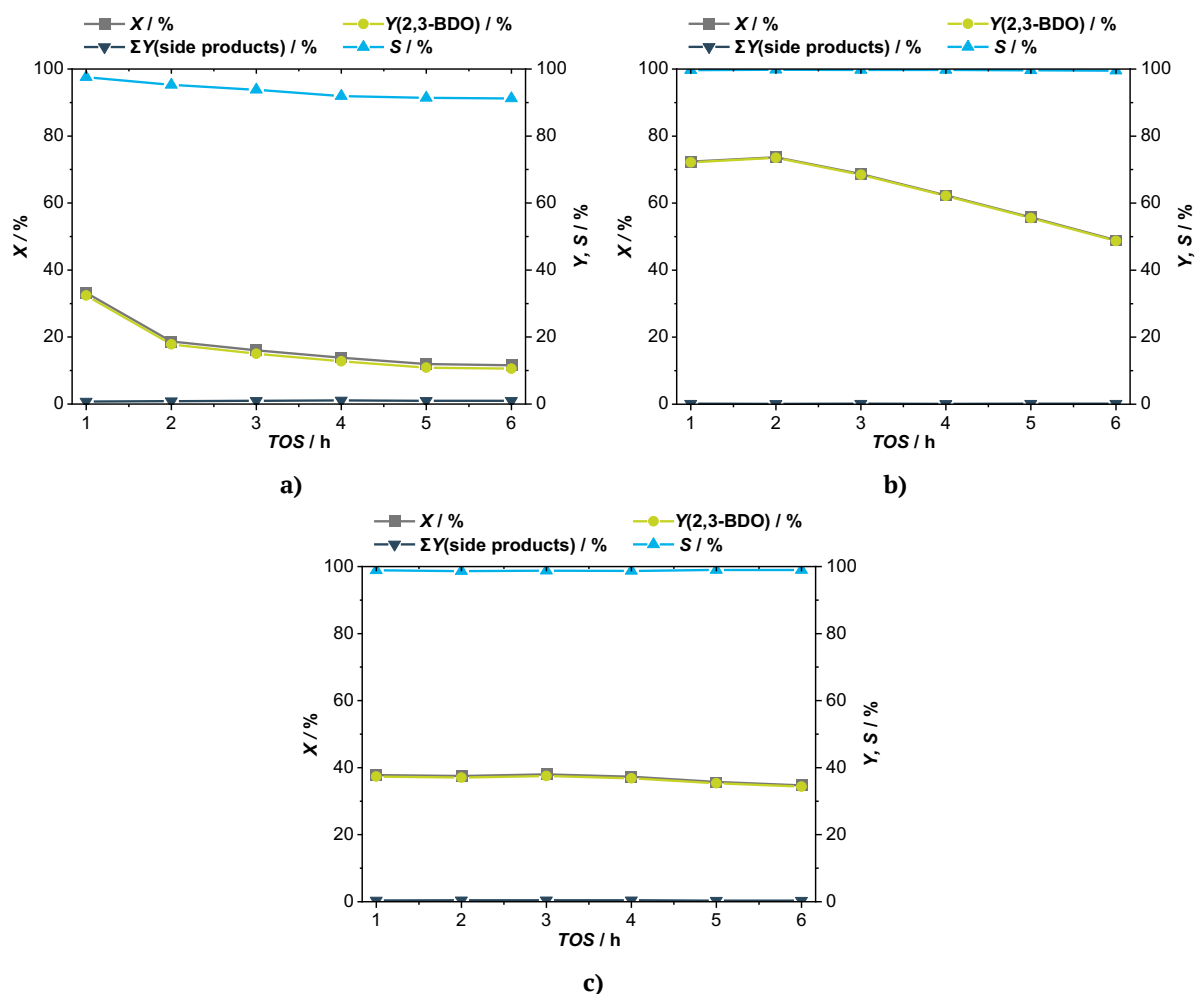


Figure 32: Catalytic results of the low-pressure flow hydrogenation of acetoin to 2,3-BDO using **a)** a CuO/Alox, **b)** a Ni/NiO/Alox and **c)** a Ni/NiO/Alox/Celite as catalyst. Commercial samples were supplied by *Johnson Matthey*. Experiments were carried out for a total of 5 h TOS where samples were collected for a duration of 1 h after a start-up phase of 1 h. Reaction conditions: $m(\text{cat.}) = 0.250 \text{ g}$, $p(\text{H}_2) = 10 \text{ bar}$, $\text{flow-rate}(\text{H}_2) = 30 \text{ mL} \cdot \text{min}^{-1}$, $p(\text{H}_2) = 10 \text{ bar}$, $\text{flow-rate}(\text{acetoin}) = 0.11 \text{ mL} \cdot \text{min}^{-1}$, $T = 150 \text{ }^\circ\text{C}$. Yields were determined by GC-FID using mesitylene as standard added after the reaction. Side products include various C_8 ketals, MEK and others.

As can be seen above, the time profiles of both the CuO/Alox and Ni/NiO/Alox based catalysts in **Figure 32 a)** and **b)** respectively do not look very satisfactory at first sight. Both conversion and yield values decline rather quickly over time, although the CuO-based catalyst has a much higher initial catalytic activity (more than twice as high compared to Ni/NiO catalyst). Whereas the selectivity of the reaction declines over time when using CuO/Alox as catalyst, the selectivity stays constant at very high levels $> 99\%$ when using the Ni/NiO/Alox catalyst. Lower selectivity of the Ni/NiO/Alox catalyst was also observed in the liquid phase aldehyde-to-alcohol reduction carried out by *Vossen*. In the case of *Vossen*, aldol side products were identified whereas for the gas phase hydrogenation experiments, only the usual ketal by-products were observed. Interestingly, the Ni/NiO/Alox/Celite catalyst displayed in **c)** shows a very stable trend at around 37% conversion/yield resulting in a productivity of $9.9 \text{ g}_{2,3\text{-BDO}} \cdot \text{g}_{\text{cat.}}^{-1} \cdot \text{h}^{-1}$. Also, exceptionally high selectivities $> 99\%$ were attained with this particular Ni/NiO/Alox/Celite catalyst. Intrigued by these findings and an experiment was carried with twice the amount of catalyst as well as a longer TOS (**Figure 33**).

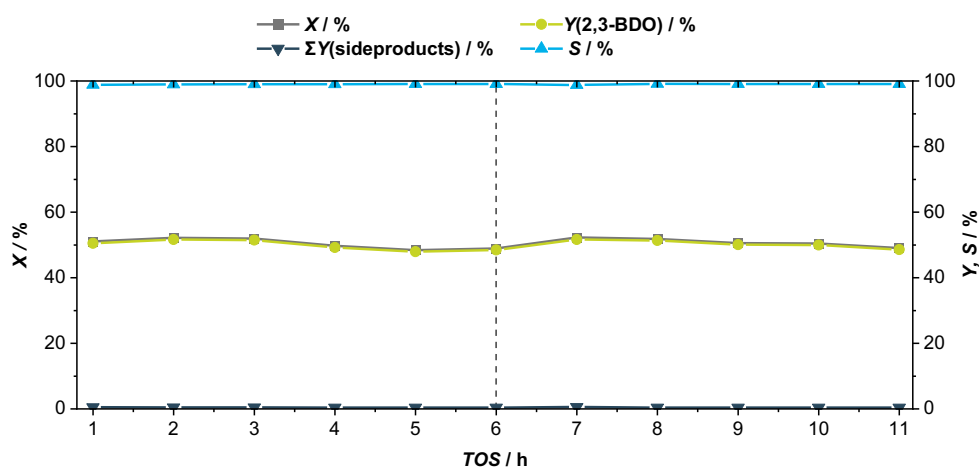


Figure 33: Catalytic results of the long-time low-pressure flow hydrogenation of acetoin to 2,3-BDO using a commercial Ni/NiO/Alox/Celite catalyst supplied by *Johnson Matthey*. Experiment was carried out for a total of 11 h TOS where samples were collected for a duration of 1 h after a start-up phase of 1 h. After 6 h TOS, the reaction was terminated for the night and re-started the next day. The flow of educt was stopped and the reactor was allowed to cool over-night without performing an *in-situ* reduction procedure. The next day, the reactor was heated to the desired reaction temperature before flow of H₂ was started. Once reaching the desired pressure, feed of educt was re-initiated as well. Reaction conditions: $m(\text{cat.}) = 0.500 \text{ g}$, $\text{flow-rate}(\text{H}_2) = 30 \text{ mL}\cdot\text{min}^{-1}$, $p(\text{H}_2) = 10 \text{ bar}$, $\text{flow-rate}(\text{acetoin}) = 0.11 \text{ mL}\cdot\text{min}^{-1}$, $T = 150 \text{ }^\circ\text{C}$. Yields were determined by GC-FID using mesitylene as standard added after the reaction. Side products include various C₈ ketals, MEK and others.

A comparison of Figure 32c) with Figure 33 shows that the catalyst not only shows stable performance in a single run of 6 h, but is also able to maintain stable performance after a nightly interruption of the reaction process. Whereas the experiment with 0.25 g catalyst (Figure 32) resulted in an averaged conversion/yield of 37%, the experiment with double the amount of catalyst gave stable results around 50%. Both experiments exhibit a very high selectivity towards the desired 2,3-BDO as $S > 99.9\%$ throughout the experiments. For this experiment, a productivity of about $6.7 \text{ g}_{2,3\text{-BDO}}\cdot\text{g}_{\text{cat.}}^{-1}\cdot\text{h}^{-1}$ is calculated. Though the double amount of catalyst was used, the conversion/yield did only increase by about 40%, revealing that the reaction might suffer from underlying mass transport limitations. Still, there is room for improvement with respect to the conversion/yield. Also, the separation of the obtained acetoin/2,3-BDO mixture needs to be investigated in more detail, in order to afford pure 2,3-BDO that can be used in the dehydration to BD. On the other hand, as elucidated earlier, carrying out the hydrogenation of acetoin/EtOH mixtures in a stirred tank reactor, results in a mixture of 2,3-BDO and EtOH that can easily be separated *via* distillation.

5.3 Double Dehydration of 2,3-Butanediol to 1,3-Butadiene

The final step in the proposed ethanol-to-butadiene pathway, is the double dehydration of 2,3-BDO to produce BD. As described in the section 2.6.4, it is essential that the reaction proceeds *via* 3B2OL as intermediate. Various rare-earth-oxide materials like Sc_2O_3 as well as In_2O_3 and ZrO_2 are known to exhibit catalytic activity towards the desired 3B2OL.^[147, 150, 152, 155] In order to make use of the catalytic properties of these oxides and to afford an effective “one-pot” process, *Duan et al.* proposed a vapour phase isothermal dual bed catalytic approach using a combination of Sc_2O_3 and Al_2O_3 to attain BD selectivity of 94% at > 99.9% 2,3-BDO conversion.^[155] Motivated by this seemingly simple, yet effective approach to convert 2,3-BDO to BD, an experiment was carried out, using the constructed miniplant (chapter 4). According to the procedure described in literature, Sc_2O_3 was calcined in air at 800 °C prior to use and H_2 was used as flow-gas.^[155] Al_2O_3 (Sigma) was used without pre-treatment. The reaction was carried out for 4.5 h and samples were collected from 1 h TOS onward. The constructed miniplant allowed for a direct on-line analysis of the gaseous products containing BD. Liquid samples obtained from the condenser were analysed using off-line GC-FID. The catalytic results of a typical experiment as well as a simplified reaction mechanism, are shown below in Figure 34.

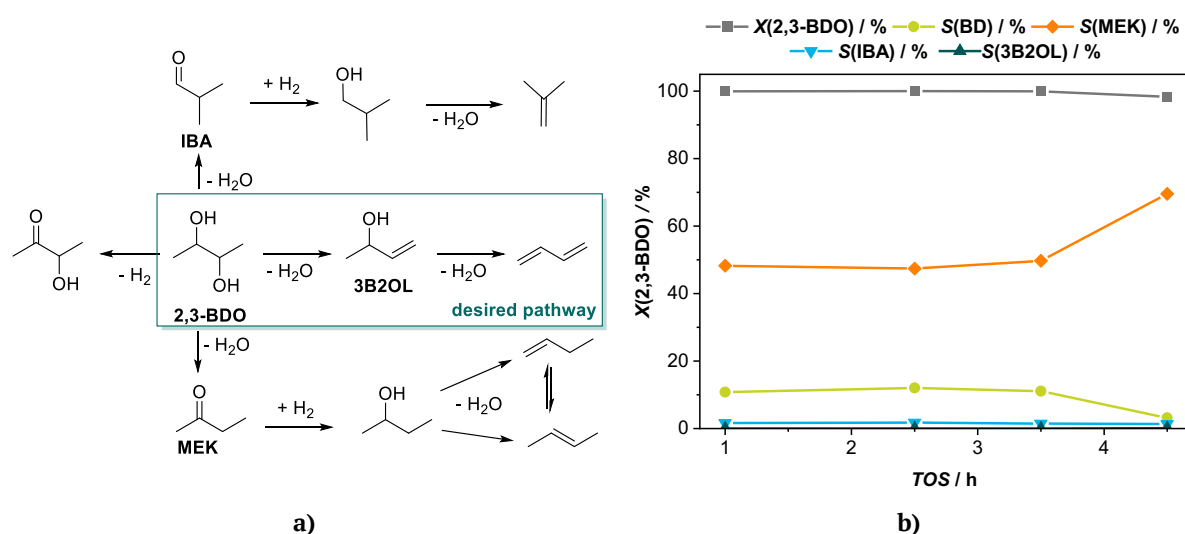


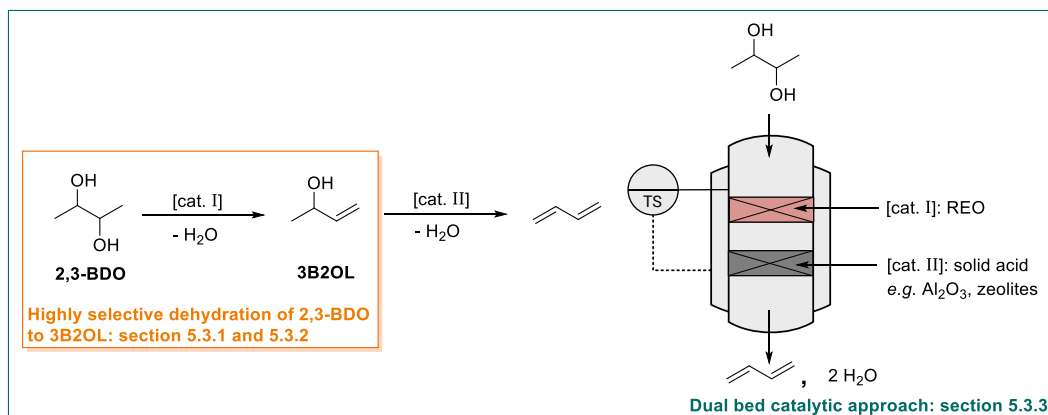
Figure 34: a) simplified reaction scheme of the double dehydration of 2,3-BDO to BD, highlighting the desired reaction pathway which proceeds *via* 3B2OL as key intermediate. The full reaction mechanism is shown in **Scheme 12**, section 2.6.4, page 18. Catalytic results of the dual bed dehydration of 2,3-BDO to BD using commercially, calcined (800 °C) Sc_2O_3 and Al_2O_3 . Reaction conditions: $m(\text{Sc}_2\text{O}_3) = 1.0$ g, $m(\text{Al}_2\text{O}_3) = 1.0$ g, catalysts separated with a small plug of glass-wool, flow-rate(H_2) = 1.8 $\text{dm}^3\cdot\text{h}^{-1}$, flow-rate(2,3-BDO) = 2.1 $\text{g}\cdot\text{h}^{-1}$, $T = 320$ °C, $\text{WHSV} = 1.1$ h^{-1} . Selectivities of liquid products were determined by GC-FID using mesitylene as standard added after the reaction.

As low carbon balances were obtained from the individual measurements in the experiment shown above, the results should be interpreted with caution. Nonetheless, as can be seen from **Figure 34 b)**, selectivity towards BD is around 12% between 1 and 3.5 h TOS before declining to 3%. At the same time, MEK selectivity is high, around 50% and even increases to 70% after 4.5 h TOS at the expense of BD production. Selectivities towards other side products like IBA or 3B2OL as intermediate, were found to be < 2% throughout the experiment. One of the reasons for low carbon mass-balance ($\Sigma Y_c \approx 65\%$), could be the insufficient cooling of the

DOUBLE DEHYDRATION OF 2,3-BUTANEDIOL TO 1,3-BUTADIENE

effluent miniplant gas. Condensation of liquid in the gas-analysis line was identified as persisting problem which was remedied in a later improved version of the miniplant setup. Also, literature on the topic indicates that the inherent activity of commercially obtained, calcined Sc_2O_3 might be too low, as described earlier (section 2.6.4). Nonetheless, the first experiments considering the dual bed catalytic approach, already delivered a proof of concept that 2,3-BDO can be converted into BD and MEK, albeit with rather low selectivity towards desired BD.

In order to further optimise the dual bed catalytic approach and afford $S(\text{BD}) > S(\text{MEK})$, the dual bed catalytic approach needs to be ‘decoupled’ before attempts can be made to carry out both dehydration reactions in the isothermal dual bed catalytic reactor. For that purpose, section 5.3.1 and 5.3.2 will focus on optimising the dehydration of 2,3-BDO to the corresponding unsaturated 3B2OL, before section 5.3.3 will again cover the combined dual bed catalytic approach using the best performing catalyst from section 5.3.1 and 5.3.2 (Scheme 29).



Scheme 29: Schematic representation of the ‘decoupled’ 2,3-BDO-to-BD reaction *via* the selective dehydration of 2,3-BDO to 3B2OL, which will be studied in section 5.3.1 and 5.3.2. The best performing catalyst that meets the requirements in terms of 3B2OL selectivity and conversion of 2,3-BDO will then be combined with a suitable second dehydration catalyst (section 5.3.3) to convert the generated 3B2OL into BD.

5.3.1 Dehydration of 2,3-BDO to 3B2OL Using Sc_2O_3 Catalysts

As starting point of the investigations regarding the gas-phase dehydration of 2,3-BDO to 3B2OL, the activity of commercially obtained, calcined Sc_2O_3 was investigated in more detail. Furthermore, in collaboration with the group of *Heumann* a hydrothermally synthesised (HT), calcined (800 °C) Sc_2O_3 catalyst (HT-800- Sc_2O_3) was prepared and its performance benchmarked against the performances of a commercially obtained Sc_2O_3 catalyst. A detailed procedure on the preparation of the HT-800- Sc_2O_3 catalyst can be found in section 7.3.4. Following the preparation and calcination of the HT-800- Sc_2O_3 catalyst, its catalytic performance in the dehydration of 2,3-BDO to 3B2OL was investigated at 320 °C using H_2 as flow-gas. In **Figure 35**, the results of three different catalytic dehydration reactions using different batches of HT-800- Sc_2O_3 catalysts and a commercially obtained, calcined Sc_2O_3 catalyst at otherwise identical reaction conditions are visualised.

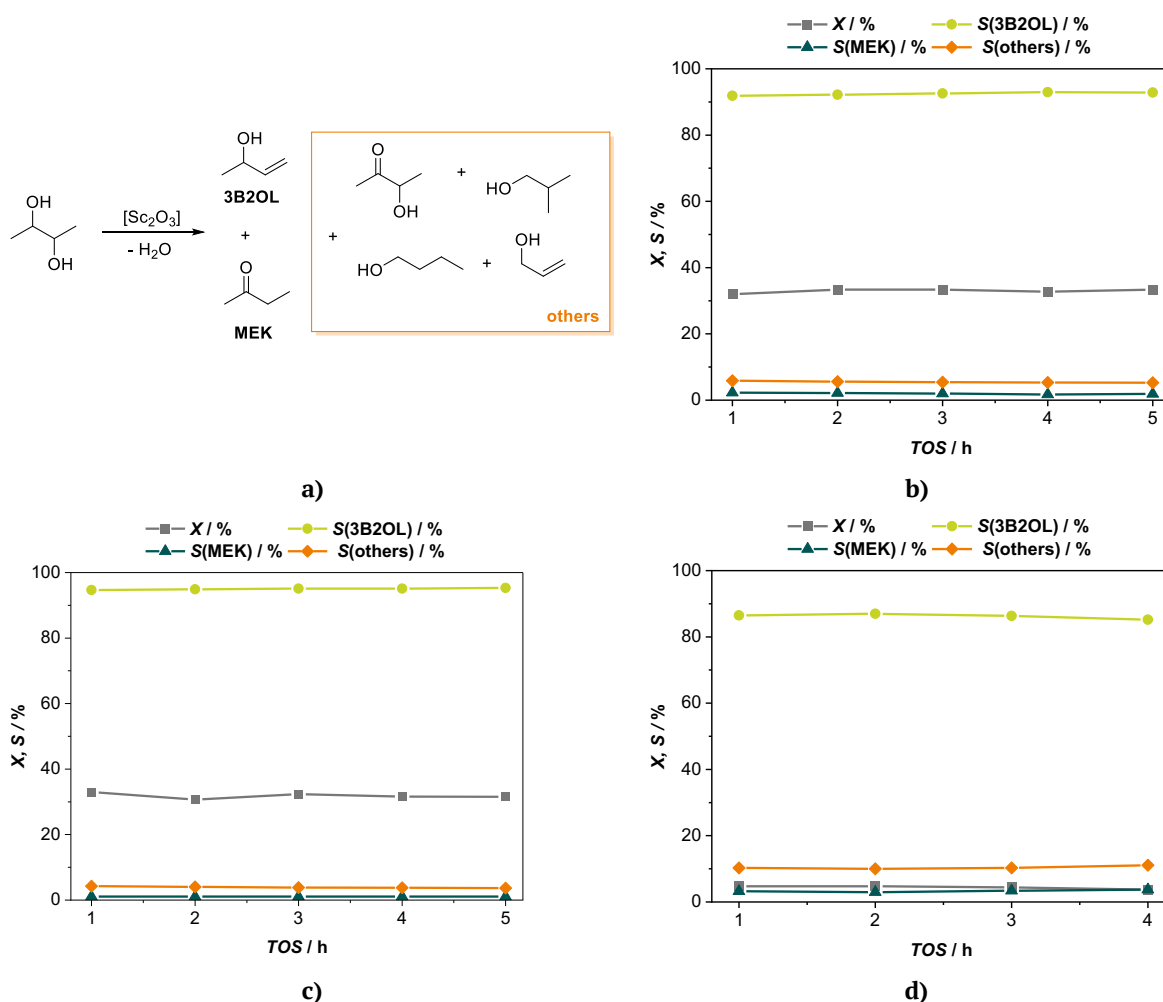


Figure 35: **a)** Reaction scheme of the Sc_2O_3 catalysed dehydration of 2,3-BDO to 3B2OL and several other side products of the reaction were identified by GC-MS. **b)** Overview of the conversion X of 2,3-BDO and selectivity S using the first batch of HT-800- Sc_2O_3 . **c)** Catalytic results of a second and larger batch of HT-800- Sc_2O_3 and **d)** commercially available Sc_2O_3 (*Sigma*), calcined at 800 °C in air and denoted as 800- Sc_2O_3 . Reaction conditions: $m(\text{cat}) = 0.5 \text{ g}$, $\text{flow-rate}(\text{H}_2) = 1.8 \text{ dm}^3\cdot\text{h}^{-1}$, $\text{flow-rate}(2,3\text{-BDO}) = 1.6 \text{ g}\cdot\text{h}^{-1}$, $T = 320 \text{ °C}$, $\text{WHSV} = 3.2 \text{ h}^{-1}$. Yields determined by GC-FID using mesitylene as standard added after the reaction.

When comparing **Figure 35 b)** and **Figure 35 c)**, it can be seen that for different synthetic batches of HT-800- Sc_2O_3 , very similar catalytic results are obtained. Both batches of catalyst exhibit exceptional selectivity towards 3B2OL ($S > 95\%$) as well as a maintaining a stable conversion

of $X = 32\%$. Although the observed selectivity towards 3B2OL matches the literature value of 95.1% reported by *Nakazono* and co-workers, the conversion is not in agreement with literature as *Nakazono* obtained 68.8% 2,3-BDO conversion. It has to be noted, that the experiment by *Nakazono* was carried out in a flow of N_2 rather than H_2 . It is reported that the flow-gas has a tremendous influence on the activity of an HT- Sc_2O_3 catalyst in the dehydration of 2,3-BDO especially in the beginning of catalyst life time.^[147] On the other hand, it is also reported in literature that use of H_2 as flow gas is beneficial for the second catalyst bed, where 3B2OL is dehydrated to BD.^[155] It is assumed that use of H_2 can to some extent suppress deposition of coke on the catalyst, thereby extending its lifetime. Therefore, the choice was made to the use of H_2 as flow-gas for the reaction. Nonetheless, even when comparing the results to the experiment by *Nakazono* carried out in H_2 flow, the obtained conversion of roughly 32% is not in line with the results reported in literature. On the other hand, the conversion in H_2 flow studied by *Nakazono* decreases rapidly during the first 10 h TOS, whereas here, a stable conversion throughout the duration of the experiment (5 h) was observed.

In **Figure 35 d)** the results of an experiment carried out with commercial grade and calcined Sc_2O_3 are shown. The catalyst was calcined in air at 800 °C prior to the reaction (800- Sc_2O_3). Despite the fact that the 3B2OL selectivity is around 90%, the conversion of this 800- Sc_2O_3 catalyst is rather low ($X = 5\%$). Based on the evaluated reaction conditions, the use of commercially obtained calcined Sc_2O_3 is not feasible for a dual bed catalytic approach. As the conversion of 2,3-BDO is low, large portions of 2,3-BDO would most probably result in large quantities of MEK (compare **Scheme 12**, section 2.6.4) in the second catalyst bed. The low 2,3-BDO conversion might be remedied by using more catalytically active material, but as the catalyst tested was used in a fine powdered form, increasing the catalyst mass would likely cause issues on the process level (e.g. pressure built up, clogging of the catalyst bed inside the reactor). The low dehydration activity of commercially obtained Sc_2O_3 is one of the reasons why the dual bed catalytic approach reported earlier did not lead to satisfactory results with respect to BD selectivity ($S(BD) \approx 10\%$, **Figure 34d**) and explains why more the MEK is produced compared to BD. Unconverted 2,3-BDO passing the Sc_2O_3 catalyst is mainly dehydrated to MEK as the Al_2O_3 catalyst promotes the pinacol rearrangement and H^- shift upon generation of the carbocation (**Scheme 12**).

One factor for the significant difference in catalytic activity of the commercially obtained Sc_2O_3 and the prepared HT-800- Sc_2O_3 catalyst, could be crystallinity of the catalyst, as a greater amount of (nano) crystalline regimes present in the HT-800- Sc_2O_3 catalyst can be associated with an increased productivity, as described by *Nakazono*.^[147] At first glance, the commercial, as-obtained and calcined 800- Sc_2O_3 catalyst has a rather homogeneous surface, whereas HT-800- Sc_2O_3 exhibits larger Sc_2O_3 particles as seen in the comparison of the SEM images (**Figure 36**).

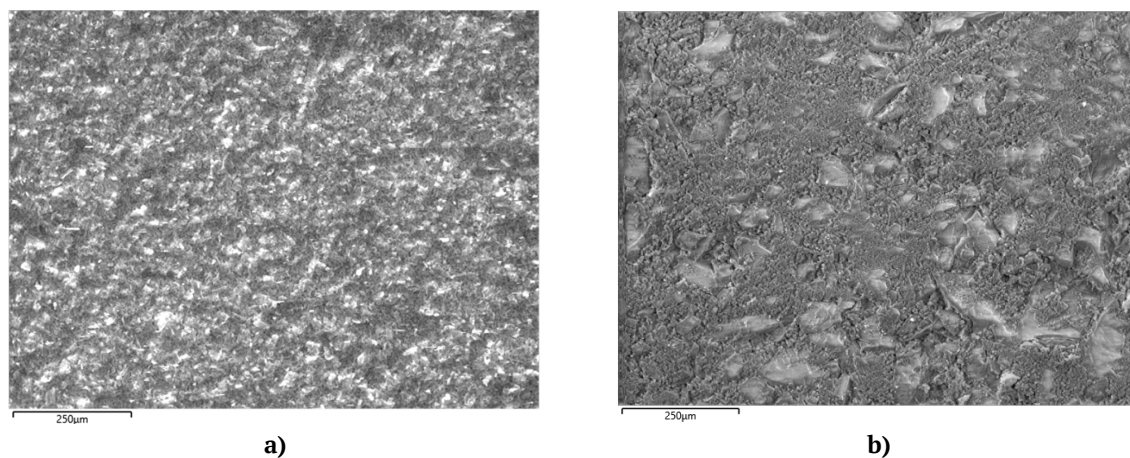


Figure 36: SEM images recorded of different Sc_2O_3 samples. **a)** Commercially obtained (*Sigma*), and calcined (800 °C) Sc_2O_3 (800- Sc_2O_3) as well as **b)** hydrothermally aged and calcined (800 °C) Sc_2O_3 (HT-800- Sc_2O_3).

Despite the fact that the larger particles are visible in the SEM images of HT-800- Sc_2O_3 (Figure 36 b) compared to the commercially obtained and calcined 800- Sc_2O_3 (Figure 36 a) does not directly corroborate the presence of larger crystalline regimes. In order to find out the size of crystallites (nano-crystallinity) several XRD measurements (Figure 37a) were performed for various scandium oxide samples. The size of crystallite regimes was calculated after the *Rietveld* refinement procedure and shown in Table 16 as part of Figure 37 b).

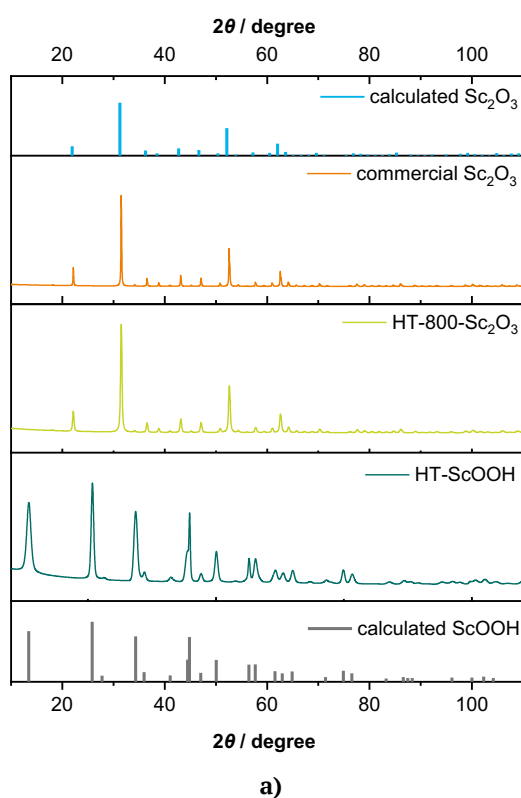


Table 16: Estimation of crystallite size based on *Rietveld* refined X-ray diffractograms for various scandium oxide samples.

Entry	Catalyst	D_{XRD} (nm)
16.1	HT-ScOOH	11
16.2	HT-800- Sc_2O_3	24
16.3	800- Sc_2O_3	65

Figure 37: **a)** XRD patterns obtained from different catalyst samples as well as an overview of the theoretical/literature-based reflexes for ScOOH (precipitation product) and pure Sc_2O_3 . **b)** Overview of the obtained crystallinity of the samples as determined from the *Rietveld* refinement method. Calculated XRD data for Sc_2O_3 was obtained from^[238]. XRD Data for ScOOH was obtained from^[147] and^[239].

As can be seen from the XRD patterns, after the HT treatment of the obtained precipitate, Sc is only present in its oxy-hydroxide form, rather than the oxide. The XRD pattern obtained for the ScOOH is in accordance with the theoretical XRD for orthorhombic ScOOH as well as

the XRD of as-prepared not calcined HT-ScOOH shown in literature.^[147] The HT-ScOOH catalyst has crystalline regimes with 11 nm in size (entry 16.1). *Nakazono et al.* did not mention the size of crystallites in their HT-ScOOH, but rather assumed that due to the fact that sharper XRD reflexes were attained for the calcined compound, sintering of particles into larger agglomerates had occurred.^[147] Upon calcination of the HT-ScOOH catalyst, the orthorhombic ScOOH is fully converted to cubic bixbyite Sc₂O₃. Based on the diffractogram, the intensity of the peaks for the HT-800-Sc₂O₃ is sharper compared to that of the HT-ScOOH indeed suggesting a larger crystallinity. This finding is in accordance with findings in literature. When evaluating the size of crystallites after carrying out the *Rietveld* refinement method, a crystallite size of $D_{\text{XRD}} = 24$ nm follows, which corroborates a growth/sintering of the ScOOH into Sc₂O₃ crystallites during calcination (entry 16.2). For commercially obtained Sc₂O₃ calcined at 800 °C, very sharp reflexes were obtained from the XRD, and a crystallite size of $D_{\text{XRD}} = 65$ nm was calculated (16.3). Comparison with theoretical reflexes of Sc₂O₃ (cubic bixbyite Ia-3 space group) reveal that both HT-800-Sc₂O₃ and commercially obtained, calcined 800-Sc₂O₃ are present in the same phase and that there are not noticeable differences in the XRD from HT-800-Sc₂O₃, commercial Sc₂O₃ and literature values for Sc₂O₃. Based on the XRD patterns recorded and the calculated crystallite sizes of HT-ScOOH, HT-800-Sc₂O₃ and commercially obtained, calcined 800-Sc₂O₃, no enhanced effect of increased crystallite size on catalytic activity of Sc₂O₃ in the dehydration of 2,3-BDO to 3B2OL can be drawn. Based on the XRD measurements, $D_{\text{XRD}}(800\text{-Sc}_2\text{O}_3) > D_{\text{XRD}}(\text{HT-800-Sc}_2\text{O}_3)$ was found. This is not in agreement with the assumption put forward in literature by *Nakazono*. It has to be noted at this point, that *Nakazono* only investigated D_{XRD} for various hydrothermally synthesised and calcined catalysts and did not mention D_{XRD} of the commercially obtained, calcined Sc₂O₃ catalyst.

A second possible reason for the higher performance of the HT aged Sc₂O₃ catalyst, could be funded in the HT synthesis step itself. As the HT aging step is carried out in water at high temperatures and pressures, a hydrophilic catalyst surface is generated. This hydrophilic surface should enhance the adsorption of hydrophilic/polar (OH) groups onto the surface of the catalyst (compare **Scheme 13** for the mechanism on the 2,3-BDO dehydration to 3B2OL). Furthermore, upon generation of the less hydrophilic 3B2OL, an effective removal of reaction product could also be assumed. To get an indication for the hydrophilicity of the catalyst surface, quantitative ¹H NMR spectroscopy was used to determine the number of exchangeable protons on the surface of the catalyst. Though not as exact as temperature programmed NH₃ desorption (TPD) for example, a ¹H NMR measurement yields a fast and qualitative indication for the amount exchangeable protons present on the catalyst surface. The exchangeable protons present in these groups can be attributed to hydroxy or carboxylic acid groups, which in turn can be correlated to the hydrophilicity of the catalyst. Prior to measurement, a known amount of catalyst sample was suspended in a known amount of D₂O. The suspension was subsequently agitated in an ultrasonic bath for a certain amount of time, kept constant for each sample. During this time, proton/deuterium exchange will take place, increasing the concentration of protons in the D₂O. By using an additional standard (DMF) added after the proton exchange step, the total amount of protons/-OH groups in the D₂O can be calculated. By subtracting the residual H content in D₂O obtained from earlier measurements with DMF as standard, and by performing quantitative ¹H NMR experiments

(i.e. complete relaxation) the concentration of exchangeable H/-OH groups can now be estimated. The procedure is described in more detail in section 7.2.3. **Figure 38** provides an overview of the integrated (OH resonance) and processed spectra of these ^1H NMR experiments for different catalyst samples.

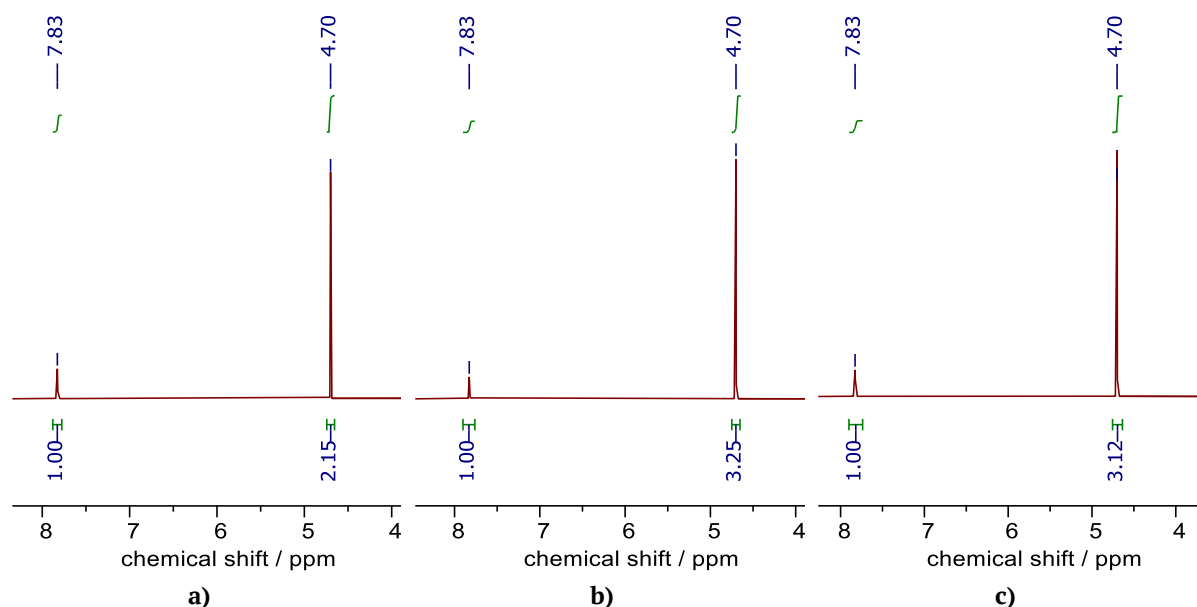


Figure 38: Overview of quantitative ^1H NMR(500 MHz, D_2O , r.t.) experiments for different catalyst samples. **a)** As-obtained calcined (800 °C) Sc_2O_3 **b)** as-prepared HT-ScOOH (prior to calcination) and **c)** HT-800- Sc_2O_3 prior to use in catalysis. Based on the residual proton content in D_2O , the content of exchangeable protons in the catalyst samples is as follows: commercial, as-obtained Sc_2O_3 **a)**: 3.30 $\text{mmol}\cdot\text{g}^{-1}$, HT- Sc_2O_3 **b)**: 44.8 $\text{mmol}\cdot\text{g}^{-1}$ and HT-800- Sc_2O_3 **c)**: 30.5 $\text{mmol}\cdot\text{g}^{-1}$.

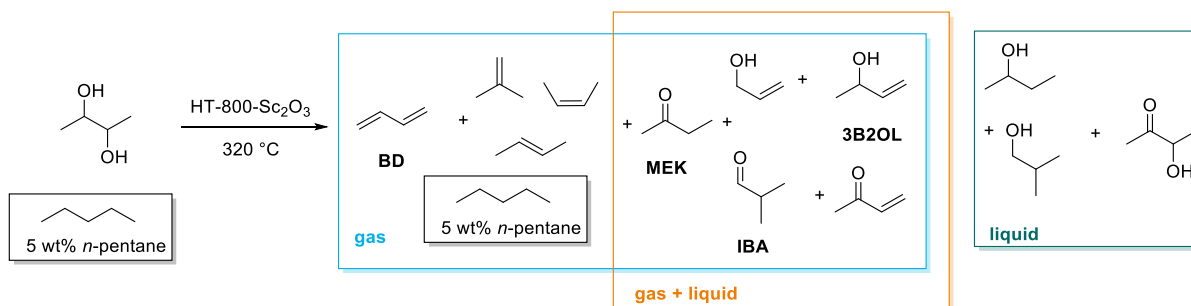
Commercial, as obtained and calcined (800 °C) Sc_2O_3 expectedly has the lowest -OH group content of 3.30 $\text{mmol}\cdot\text{g}^{-1}$. For the HT-ScOOH (prior to calcination) a content of 44.8 $\text{mmol}\cdot\text{g}^{-1}$ is obtained. This value is a little over one order or magnitude larger compared to the as-obtained oxide and indicates that the HT-ScOOH has a significantly higher concentration of exchangeable groups, which is expected due to the nature of the ScOOH. After calcining the HT-ScOOH **b** in air at 800 °C, an exchangeable group content of 30.5 $\text{mmol}\cdot\text{g}^{-1}$ remains, which is within the margin of error for the method, implying that the exchangeable surface group did not undergo large changes during the annealing. The residual concentration is still significantly larger compared to the commercially available oxide and strongly supports the aforementioned hypothesis. Though the analysis of exchangeable -OH groups using ^1H NMR gives a rough estimate of the actual surface basicity/acidity, a more precise determination could be given by using NH_3 or CO_2 TPD measurements.

Nonetheless, the catalytic dehydration of 2,3-BDO to 3B2OL over HT-800- Sc_2O_3 offers a significant advance over the use of commercially obtained, calcined Sc_2O_3 in terms of conversion. Therefore, HT-800- Sc_2O_3 was investigated in more detail and optimized to attain higher 2,3-BDO conversions. In order to see if the reaction suffers from mass-transfer limitations, the experiment in **Figure 35b)** was repeated with double the amount of catalyst as well as longer reaction times at otherwise identical conditions (**Figure 39**). It is described in literature that HT-800- Sc_2O_3 also exhibits activity towards the double dehydration of 2,3-BDO to BD at high temperatures (> 375 °C). To verify the significance of BD production at the lower investigated temperature of 320 °C, a slight modification of the miniplant setup was carried

out. In order to ensure sufficient cooling of effluent reactor gas a double helix cooler was installed. Also, the *IKA* bath circulator was replaced by an *IKA* recirculating chiller capable of achieving temperatures down to $-10\text{ }^{\circ}\text{C}$ (Figure 9, section 4.1). Unless stated otherwise, the temperature of the recirculating chiller was set to $-5\text{ }^{\circ}\text{C}$. Liquid products were collected in a cold trap at $-78\text{ }^{\circ}\text{C}$ every hour. Effluent gas passing out on top of the second cooler was analysed by an on-line GC (Figure A 2).

In an attempt to evaluate amount of gaseous products produced, *n*-pentane was used as internal standard. Based on several benchtop HPLC-vial experiments with *n*-pentane and other alkanes, a 5wt% *n*-pentane in 2,3-BDO solution was found to be completely miscible and stable over the course of a few days. Judging from a test-experiment in the dehydrogenation miniplant setup, negligible amounts of *n*-pentane were found in the liquid products cold trap. Presumably, this is caused by the high vapour pressure of *n*-pentane and the fact that there is a constant stream of H_2 as flow-gas. Hence, the amount of *n*-pentane fed into the reactor can in good approximation be regarded as internal standard in the head-space GC-FID analysis to accurately calculate the yield of gaseous products. Furthermore, *n*-pentane is not suspected to undergo molecular changes when passing over the catalyst, nor does it overlap with any relevant products in the gas phase.

The results of the experiment using double the amount of HT-800- Sc_2O_3 catalyst and the *n*-pentane/2,3-BDO feedstock for a total of 10 h time-on-stream (*TOS*) is shown below in Figure 39. An overview of the identified reaction products using off-line GC-MS measurements from both gas and liquid phase, is given in Scheme 30.



Scheme 30: Reaction network of the HT-800- Sc_2O_3 catalysed dehydration of 2,3-BDO. Products were identified from off-line GC-MS measurements of both liquid and gaseous samples.

As can be seen in Scheme 30 several reaction side products like MEK and IBA are present in both liquid and gaseous phase. The *n*-pentane standard was used to quantitatively analyse the contents of the head-space gas, whereas mesitylene was used as standard for quantitative liquid analysis using GC-FID.

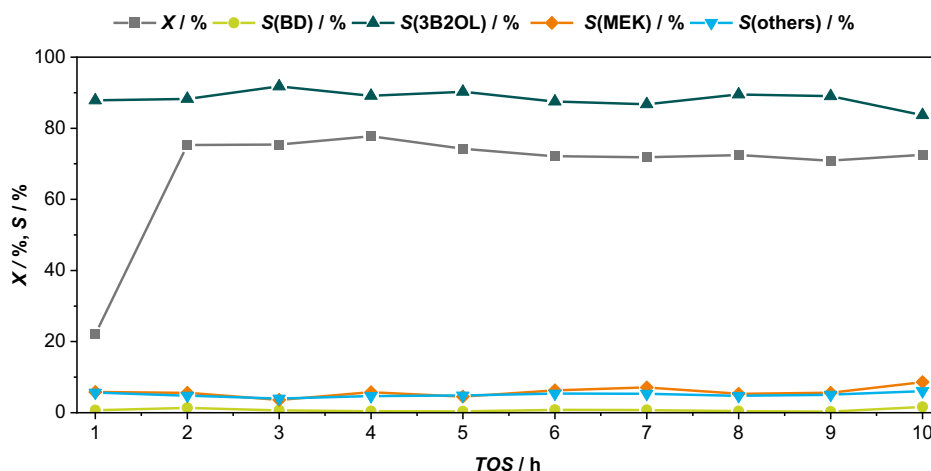


Figure 39: Catalytic results of the dehydration of 2,3-BDO using HT-800-Sc₂O₃ as catalyst and a 5wt% *n*-pentane in 2,3-BDO feedstock solution. Reaction conditions: $m(\text{cat}) = 1.00 \text{ g}$, $\text{flow-rate}(\text{H}_2) = 1.8 \text{ dm}^3 \cdot \text{h}^{-1}$, $\text{flow-rate}(2,3\text{-BDO}) = 1.6 \text{ g} \cdot \text{h}^{-1}$, the mass of pentane fed has been accounted for, $T = 320 \text{ }^\circ\text{C}$, $\text{WHSV} = 1.6 \text{ h}^{-1}$. Mass-balances (carbon-based) $\Sigma Y_C > 92\%$ were obtained. Yields determined by GC-FID using mesitylene as standard added after the reaction. $S(\text{others})$ include methyl vinyl ketone (MVK), butanol, acetoin and *iso*-butyraldehyde (IBA).

During the first hour after the start-up phase of the reactor, some issues were experienced with the substrate feed pump. A liquid flow exceeding $1.6 \text{ g} \cdot \text{h}^{-1}$ during the first hour was the result of a malfunction during the initial start-up phase of the reactor where a higher pump velocity was used (see section 7.6.1 for a detailed procedure of the reactor start-up). Hence, more substrate was fed through the catalyst bed in the initial start-up phase of the reactor and the reactor and catalyst bed got oversaturated with substrate. Consequently, this caused a higher sample volume collected in the cold trap after one hour which also mainly consisted of unconverted 2,3-BDO. Notably, this oversaturation of the catalyst bed with substrate did not negatively influence the selectivity towards 3B2OL (88%). Nonetheless, from the second hour onward, the conversion is rather constant at around 75% with a slight decreasing trend over the course of 10 h. When looking on the trends in product and side product selectivity, the HT-800-Sc₂O₃ catalyst seems to be very stable in that regard. Notably, this behaviour of rather constant conversion and constant selectivity towards the desired 3B2OL was also found in the experiments with a lower catalyst mass and consequently higher weight hourly space velocity. As put forwards in literature, lower product feed velocity or higher catalyst mass may ultimately result in a higher conversion. Based on the selectivity in the product spectrum for the experiment with lower catalyst mass (Figure 35) and the experiment with a higher catalyst mass, no influence of the catalyst mass on the product spectrum was observed. For both the experiments in Figure 35 a) and Figure 35 b) as well as in Figure 39, very similar product selectivities are attained. Nonetheless, the unconverted 2,3-BDO (around 25% in Figure 39) might result in higher quantities of MEK when carrying out the dual bed catalytic approach. Nonetheless, the reaction conditions used in Figure 39 *i.e.* $\text{WHSV} = 1.6 \text{ h}^{-1}$ seem a good trade-off between 2,3-BDO throughput and the amount of hydrothermally aged catalyst needed for each experiment.

As briefly mentioned, the HT-800-Sc₂O₃ catalyst showed minor signs of deactivation over the 10 h TOS. As possible re-activation strategy, re-calcination as well as re-aging was investigated. Unfortunately, re-aging *i.e.* subjecting the spent catalyst to another

hydrothermal treatment in H₂O at high temperatures and pressures, resulted in a significant over-pressure of the HT autoclave. This might have something to do with the lack of solubility of the spent HT-800-Sc₂O₃ in the aq. NH₃ solution used for the HT aging step. On the other hand, some of the catalyst used in the experiment described in **Figure 39** was subjected to a calcination cycle at 800 °C for 3 h. The recalculated catalyst was then used at the earlier described benchmark conditions for the HT-800-Sc₂O₃ system described in **Figure 35**. The key catalytic parameters for the re-calcined catalyst compared to the pristine HT-800-Sc₂O₃ catalyst are shown below in **Table 17**.

Table 17: Key catalytic parameters of the HT-800-Sc₂O₃ catalysed dehydration of 2,3-BDO.^[a]

Entry	Catalyst	$X^{[b]}$ (%)	$S(3B2OL)^{[b]}$ (%)	$S(MEK)^{[b]}$ (%)	$S(others)^{[b]}$ (%)	$c_{exch.}(OH)$ (mmol·g ⁻¹)
17.1	as-obt. HT-800-Sc ₂ O ₃	32	95	1	4	30.5
17.2	re-calc. HT-800-Sc ₂ O ₃	39	92	3	5	13.1

[a] reaction conditions: $m(cat) = 0.5$ g, $flow-rate(H_2) = 1.8$ dm³·h⁻¹, $flow-rate(2,3-BDO) = 1.6$ g·h⁻¹, the mass of pentane in the feed has been accounted for, $T = 320$ °C, $WHSV = 3.2$ h⁻¹. Yields determined by GC-FID using mesitylene as standard added after the reaction. $S(others)$ include butanol, acetoin and IBA. [b] Averaged values over 5 h TOS.

Comparing the key catalytic parameters for both catalysts in entry 17.1 and entry 17.2, reveal that the overall performance of the catalyst in its as-obtained (entry 17.1) and in its spent, re-calcined (800 °C) form, is very similar. In order to better understand the effect of the catalytic dehydration reaction on the amount of exchangeable -OH groups (**Table 17**, $c_{exch.}$) NMR analysis was carried out of a spent catalyst sample from **Figure 39**. The concentration of exchangeable H/-OH groups of spent HT-800-Sc₂O₃ after 10 h of reaction time was calculated to be 13.1 mmol·g⁻¹. Whereas the concentration of exchangeable H/-OH groups on pristine HT-800-Sc₂O₃ was found to be 30.5 mmol·g⁻¹. This indicates substantial loss of surface H/-OH groups during catalysis and 10 h TOS at reaction conditions. From this point of view, the re-calcination strategy to restore catalytic surface does not seem promising. As elucidated previously, H/-OH group content could also decrease during the calcination step, though the observed difference in exchangeable group content was found to be within the error margin of the method. Nonetheless, it is amendable that upon calcination, some surface OH group content is lost, which would result in even smaller concentrations of exchangeable H/-OH groups and consequently lower surface hydrophilicity for the re-calcined catalyst (re-calc., entry 17.2). The fact that very comparable key catalytic parameters were found for the as-obtained (entry 17.1) and re-calcined (entry 17.2) HT-800-Sc₂O₃ catalyst might have something to do with the shorter reaction time of 5 h. Unfortunately, no NMR characterisation was carried out of a catalytic sample after 5 h of reaction time (e.g. entry 17.1 post catalysis).

For the experiment in entry 17.2, again a 5/95wt% *n*-pentane/2,3-BDO feedstock solution was used, which was also used for the experiment shown in **Figure 39**. During these and several other testing experiments not described in this work, little bubbles of gas were noticed in the PTFE feed-lines when using a pentane containing stock solution, especially during the summer months. In previous experiments with pure 2,3-BDO, this was not observed. Small gas bubbles in the feed line could be an indication for the separation of the pentane and the 2,3-BDO. Therefore, instead of a continuous co-feed of substrate and standard, a plug flow-like state is reached with alternating pentane (gaseous) and 2,3-BDO (viscous liquid) plugs. This in turn negatively influences the actual amount of pentane fed into the reactor and hence

the accuracy of the evaluation method which is heavily reliant on the amount of pentane fed. Although the total carbon mass-balance averaged over the whole experiment was an acceptable $\Sigma Y_C = 102\%$, the deviations between the individual carbon mass balances of each liquid sample and gas-phase measurement ranged between $\Sigma Y_C = 76\%$ and $\Sigma Y_C = 120\%$. The co-feeding pentane as headspace GC-FID standard is therefore most likely not beneficial for the accuracy of the data evaluation. Hence, for the dual bed catalytic approach, a true carbon-based data evaluation is proposed for the dual bed catalytic approach.

5.3.2 Screening of In_2O_3 -Based Catalysts in the Dehydration of 2,3-BDO to 3B2OL

Besides the extensive testing done with various Sc_2O_3 catalysts, several In_2O_3 -based catalysts were provided by *Schühle* and co-workers from Friedrich-Alexander-Universität Erlangen-Nürnberg. In this section, the catalytic activity of several supported In_2O_3 catalysts will be tested and benchmarked against the results obtained in the HT-800- Sc_2O_3 catalysed dehydration of 2,3-BDO, before continuing with the discussion of the dual bed isothermal approach to afford BD from 2,3-BDO in a single reactor, using two distinct catalyst beds. The supported catalysts provided by *Schühle* were obtained as catalyst pellets and crushed prior to performance testing in the catalytic dehydration of 2,3-BDO to 3B2OL. It is described by *Sanyal et al.* that calcined In_2O_3 catalysts exhibit activity in the dehydration of 2,3-BDO to 3B2OL at temperatures around 300 °C, however supported In_2O_3 catalysts have remain unexploited in literature in the 2,3-BDO dehydration.^[152] Despite the fact that In_2O_3 was reported to have the highest $S(3\text{B2OL})$ at temperatures < 300 °C, the reaction was carried out at the benchmark conditions established for HT-800- Sc_2O_3 (as seen in Figure 35).^[152] The results of the averaged conversion of 2,3-BDO as well as the other supported oxides tested are listed below in Table 18.

Table 18: Catalytic results of various supported REOs in the flow dehydration of 2,3-BDO to 3B2OL. The full conversion-time profiles can be found in the appendix to this report (Figure A 3).^[a]

Entry	Catalyst	$X^{[b]}$ (mol%)	$S(3\text{B2OL})^{[b]}$ (mol%)	$S(\text{MEK})^{[b]}$ (mol%)	$S(\text{others})^{[b]}$ (mol%)	ΣY_C (mol%)
18.1	HT-800- Sc_2O_3	32	95	1	4	85
18.2	400- In_2O_3 ^[c,d]	3	30	3	67	98
18.3	$\text{In}_2\text{O}_3/\gamma\text{-Al}_2\text{O}_3$ ^[c]	56	29	5	66	74
18.4	$\text{In}_2\text{O}_3/\text{TiO}_2$ ^[d]	76	12	52	36	55
18.5	$\text{In}_2\text{O}_3/\text{ZrO}_2$ ^[e]	3	30	3	67	96
18.6	$\text{In}_2\text{O}_3/\text{SiO}_2$ ^[f]	< 1	7	30	63	91

[a] reaction conditions: $m(\text{cat}) = 0.5$ g, flow-rate(H_2) = 1.8 dm³·h⁻¹, flow-rate(2,3-BDO) = 1.6 g·h⁻¹, $T = 320$ °C, $WHSV = 3.2$ h⁻¹. Yields determined by GC-FID using mesitylene as standard added after the reaction. No evaluation of headspace gas was carried out. $S(\text{others})$ include, butanol, acetoin and IBA. [b] Averaged values over 5 h TOS. [c] Experiment carried out for 5 h TOS, but values for calculation averaged over 1-4 h TOS as the 5th h TOS was regarded as outlier value. [d] Visible coking of the catalyst after the experiment. [e] Stable production of reactor was attained after 2 h TOS, values averaged over 2-5 h TOS. [f] Almost no 2,3-BDO conversion observed at all.

Unfortunately, the as-obtained and calcined 400- In_2O_3 catalyst (entry 18.2) shows only a minor activity as the conversion of 2,3-BDO is only around 3mol%. Also, the catalytic performance is characterised by a low selectivity towards the desired 3B2OL. Looking closer into the composition of the side product spectrum ($S(\text{others}) = 67\text{mol}\%$) reveals, that mainly acetoin as dehydrogenation product is obtained. Despite the fact that the catalyst showed

visible coking (as indicated by the colour change of pale yellow to light grey after the reaction), still a high carbon balance is obtained ($\Sigma Y_C = 98\text{mol}\%$). The $\gamma\text{-Al}_2\text{O}_3$ supported In_2O_3 catalyst on the other hand (entry 18.3) exhibits a much higher conversion of 2,3-BDO (56mol% averaged over 5 h). Unfortunately, the selectivity towards desired 3B2OL is much lower (29mol%) compared to the benchmark experiment carried out with HT-800- Sc_2O_3 (95mol%, entry 18.1). As was the case for the unsupported In_2O_3 catalyst, the side product composition was dominated by acetoin as dehydrogenation product. Surprisingly, despite the fact that Al_2O_3 was used as support material, the MEK content was found to be very low (5%) which seems promising when considering Al_2O_3 for the dual bed catalytic double dehydration. Unfortunately, the catalyst showed visible coking after the reaction, which might be an explanation for the lower carbon balance obtained from this experiment (74mol%) compared to the experiment with HT-800- Sc_2O_3 .

For the TiO_2 supported catalyst (entry 18.4) an averaged conversion of 76mol% is attained, much higher compared to the benchmark experiment with HT-800- Sc_2O_3 (32mol%, entry 18.1). However, the catalyst is not very suitable for selective 3B2OL production. For the 7.5wt% $\text{In}_2\text{O}_3/\text{TiO}_2$ supported catalyst (entry 18.4), a high selectivity towards MEK was found (52mol%) based on the quantitative analysis of the liquid phase. Also, the catalyst had visibly coked as it turned grey after catalysis. This assumed coke formation might also have caused a low carbon mass-balance of only 55mol%. Regarding the carbon balance, better results are obtained when using ZrO_2 as support material (entry 18.5, $\Sigma Y_C = 96\text{mol}\%$). However, when In_2O_3 is immobilised on ZrO_2 , the activity in dehydration is very low as only 3mol% of substrates are converted. Also, the $\text{In}_2\text{O}_3/\text{ZrO}_2$ catalyst has a rather low selectivity towards 3B2OL (30mol%). When using SiO_2 as support material (entry 18.6) conversions $< 1\text{mol}\%$ were found. Most of 2,3-BDO was obtained in the liquid cold trap with a good mass-balance of $\Sigma Y_C = 91\text{mol}\%$. Due to the low conversion, calculated values for selectivity are to be interpreted with caution.

In short, based on the scandium and indium oxides tested, the HT-800- Sc_2O_3 catalyst system developed and discussed in **Figure 39**, using $WHSV = 1.6 \text{ h}^{-1}$ seems promising for further use in a dual bed catalytic reactor. Unfortunately, the approach of using a 5wt% *n*-pentane in 2,3-BDO feedstock did not result in an improvement in the accuracy of data evaluation, due to the observed separation of the pentane and the 2,3-BDO in the feedline, especially with rising temperatures in the reactor hall during the summer months.

5.3.3 Dual bed Catalytic Dehydration of 2,3-BDO to BD

As starting point of the investigations towards the development of an isothermal, dual bed catalytic dehydration of 2,3-BDO to BD with high $S(\text{BD})$, the design of the reactor was revised. Instead of using a glass reactor with a solid-impermeable frit, a steel *Swagelok* reactor with two distinct chambers was constructed. This was done in order to ensure that the two catalysts can be filled into and removed from the reactor with ease. Also, cross contamination of the two solid catalyst is avoided by having two distinctly separated catalyst chambers. Instead of using a frit at the end of each chamber, the catalyst was fixed between two glass wool plugs.

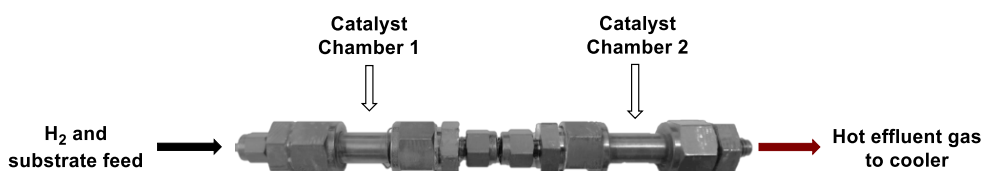
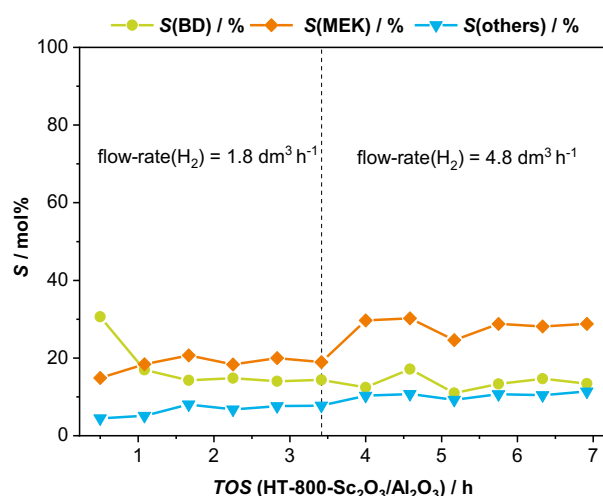


Figure 40: Schematic representation of the dual chamber downward flow reactor, constructed using Swagelok pipes and connection pieces.

As previously described, the studied dual bed catalytic approach as proposed by *Duan et al.* with a combination of commercially obtained, calcined Sc_2O_3 and Al_2O_3 , did not result in high selectivities towards BD. On the other hand, the HT-800- Sc_2O_3 system gave very promising results with respect to 2,3-BDO conversion and selectivity towards 3B2OL. Replacing commercially obtained Sc_2O_3 by the improved HT-800- Sc_2O_3 catalyst, seems like a good starting point for the investigations regarding the isothermal dual bed catalytic double dehydration of 2,3-BDO to BD. Using the two-chamber reactor with 1.0 g HT-800- Sc_2O_3 in the upper chamber and 0.5 g Al_2O_3 in the bottom chamber with a H_2 flow of $1.8 \text{ dm}^3 \cdot \text{h}^{-1}$ at a reaction temperature of 320°C resulted in notable quantities of desired BD already from the first headspace GC measurement (0.5 h TOS, **Figure 41**). In this experiment, headspace gas measurements were conducted every 35 minutes (duration of a single measurement). The liquid products were collected in the cold trap (-78°C) for the whole duration of the experiment. This decision was made to afford a higher accuracy in determining the mass-balance for the whole reaction and to correctly evaluate the mass of gaseous products generated. Previous experiments with the HT-800- Sc_2O_3 indicated that its catalytic performance and hence its conversion over time is rather stable. Therefore, averaging the conversion of 2,3-BDO and residual selectivity towards 3B2OL found in the liquid cold trap is justified. Since $X(2,3\text{-BDO})$ and $S(3\text{B2OL})$ have been averaged over the entire duration of the experiment, the subsequent discussions concerning the dual bed catalytic approach shows these catalytic indicators in a tabular format rather than as graphical representations. If not stated otherwise, this procedure was applied for all dual bed catalytic experiments that will be discussed herein.



$X(2,3\text{-BDO})^{[a]}$ (mol%)	$S(3\text{B2OL})^{[a]}$ (mol%)
> 99	43

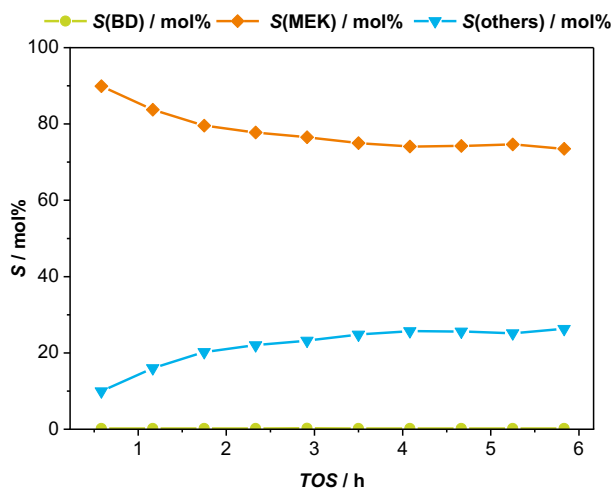
Figure 41: Catalytic results of the dual bed catalytic dehydration of 2,3-BDO to BD, MEK and others *via* 3B2OL as intermediate using a HT-800-Sc₂O₃ catalyst in the first and an Al₂O₃ catalyst in the second bed. Headspace gas measurements were taken every 35 minutes, liquid sample was collected from the cold trap (-78 °C) after completion of the experiment. Reaction conditions: $m(\text{HT-800-Sc}_2\text{O}_3) = 1.00$ g, $m(\text{Al}_2\text{O}_3) = 0.50$ g, flow-rate(H₂) = 1.8 dm³·h⁻¹ or 4.8 dm³·h⁻¹, flow-rate(2,3-BDO) = 1.6 g·h⁻¹, $T = 320$ °C, $WHSV = 1.1$ h⁻¹. Yields of liquid products were determined by GC-FID using mesitylene as standard added after the reaction. *S(others)* include, butanols, acetoin, butenes, IBA and MVK. [a] Averaged over the whole duration of the experiment.

As shown in **Figure 41**, the selectivity towards BD is relatively high (*S*(BD) 30mol%) in the beginning, but decreases quickly to around 15% within the first 3.5 h TOS. At the same time, the selectivity towards MEK increases. During the experiment, this trend was already indicated by acquisition of head-space GC data. Therefore, in order to see if the flow-speed of H₂ has an influence on the product spectrum, the flow of H₂ was increase after roughly 3.5 h TOS (dotted line in **Figure 41**). With 4.8 dm³·h⁻¹ instead of 1.8 dm³·h⁻¹, selectivity towards MEK increases substantially. Therefore, the flow of H₂ will be kept at 1.8 dm³·h⁻¹ for all following experiments.

Based on the analysis of the liquid products after roughly 7 h TOS, almost full conversion was attained ($X > 99\text{mol}\%$). However, the residual selectivity towards 3B2OL was calculated to be 43%. This observation indicates that the second catalytic dehydration of 3B2OL to BD over Al₂O₃ seems to fall short. This finding is not in agreement with reports in literature. A possible explanation for this could be that *Duan et al.* used a different Al₂O₃ (JRC-ALO-6) catalyst with a specific surface area of 180 m²·g⁻¹ supplied by the *Reference Catalyst Division*, of the *Catalysis Society of Japan*.^[155, 240] Unfortunately, this specific catalyst could not be obtained from the *Catalysis Society of Japan* which is why it was not possible to exactly reproduce the experiment.

Nonetheless, already from this dual bed catalytic experiment it was shown that BD can be produced with an average selectivity of 15mol%, a single pass 2,3-BDO conversion of > 99% and a selectivity of 43mol% towards 3B2OL. Considering this, the tested dual bed system would be able to attain a theoretical maximum selectivity of almost 60mol% BD. Theoretical maximum BD selectivity is calculated as sum of residual 3B2OL selectivity, assuming full 3B2OL-to-BD conversion in the second bed, and the already determined BD selectivity from gas-phase measurements.

In order to better understand and verify the apparent lack of dehydrogenation activity of the Al_2O_3 catalyst used, an experiment was carried out using only Al_2O_3 (0.5 g) at otherwise identical conditions (Figure 42).



$X(2,3\text{-BDO})^{[a]}$ (mol%)	$S(3\text{B2OL})^{[a]}$ (mol%)
28	< 1

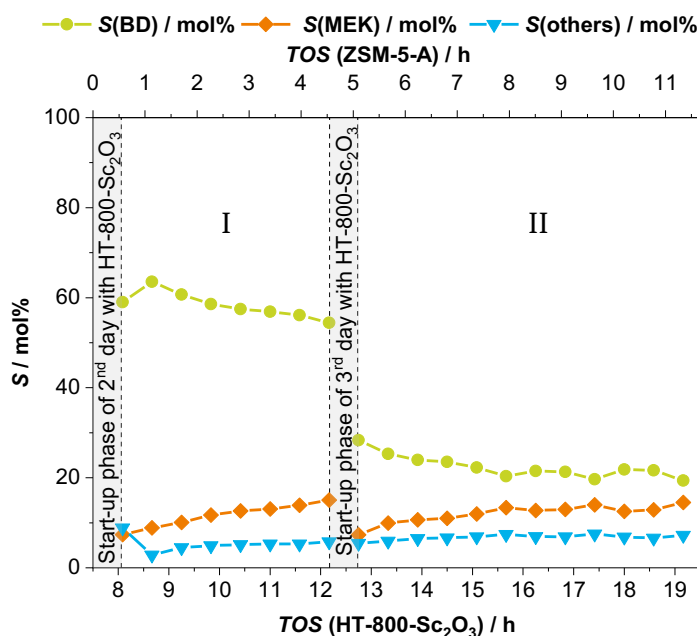
Figure 42: Results of the single bed catalytic dehydration of 2,3-BDO using a $\gamma\text{-Al}_2\text{O}_3$ catalyst. For this experiment, the dual bed setup was used and the first catalyst chamber was kept empty. Reaction conditions: $m(\text{Al}_2\text{O}_3) = 0.50$ g, $\text{flow-rate}(\text{H}_2) = 1.8 \text{ dm}^3\cdot\text{h}^{-1}$, $\text{flow-rate}(2,3\text{-BDO}) = 1.6 \text{ g}\cdot\text{h}^{-1}$, $T = 320$ °C, $WHSV = 3.2 \text{ h}^{-1}$. Yields of liquid products were determined by GC-FID using mesitylene as standard added after the reaction. $S(\text{others})$ include, butanols, acetoin, butenes, IBA and MVK. [a] averaged over the whole duration of the experiment.

As indicated in the above selectivity-time profile (Figure 42) a high MEK selectivity is attained for the dehydration of 2,3-BDO over an Al_2O_3 catalyst. This experiment shows the importance of achieving a high $X(2,3\text{-BDO})$ in the first bed, as this would otherwise be converted to MEK. Also, low $S(\text{BD})$ when using Al_2O_3 (< 1%) is in accordance with literature.^[120, 146-148] The results obtained in this experiment indicate the tendency of Al_2O_3 to promote the pinacol rearrangement. This reaction pathway, associated with a H^- or CH_3 shift to stabilise the carbocation generated upon the removal of one H_2O molecule, results in the formation of MEK or IBA (the latter accounted for in $S(\text{others})$ in Figure 42) which are both *dead-ends* for the BD production (compare Figure 34 a) and Scheme 12).^[120, 146-148] Notably, for the experiment with Al_2O_3 a low single-pass conversion $X(2,3\text{-BDO}) = 28\text{mol}\%$ is obtained which indicates an intrinsic low dehydration activity of Al_2O_3 .

All in all, the choice for Al_2O_3 as catalyst in the second bed does not seem promising, as a low dehydration activity is observed. Also, no stable selectivity-over-time behaviour is attained at the investigated reaction conditions. The low catalytic activity of the Al_2O_3 catalyst might have something to do with the tendency of Al_2O_3 to adsorb water. In the dehydration of both methanol and ethanol, it is well known that the activity of Al_2O_3 decreases when water, the inevitable by-product of the dehydration reaction, is adsorbed during the reaction resulting in lower conversions with increasing time-on-stream.^[241-242] On the other hand, zeolites, such as ZSM-5 have a higher hydrophobicity, and consequentially less tendency to adsorb water. Water adsorption correlates with the ratio of Si:Al, where higher ratios result in less water adsorption. In the dehydration of methanol and ethanol, it is assumed that this is the main cause for the observed higher activities in the dehydration reaction.^[242-245] Considering this, a zeolite type catalyst with a high Si:Al ratio might be a more suitable catalyst for the second

bed. In this regard, a 200-400:1 mole ratio $\text{SiO}_2\text{:Al}_2\text{O}_3$ (*Alfa Aesar* 400 $\text{m}^2\cdot\text{g}^{-1}$) was tested and will be discussed in the following.

As was previously shown in **Figure 39**, the HT-800- Sc_2O_3 exhibits stable catalytic activity well over 7 h TOS with only minor signs of deactivation. Hence, in order to minimise the use of HT-800- Sc_2O_3 , the first catalyst bed from the experiment described in **Figure 41** was re-used. At the beginning of the dual bed experiment, the HT-800- Sc_2O_3 catalyst had already been employed for 7 h TOS. The second catalyst chamber was charged with the zeolite catalyst, ZSM-5-A (200-400:1 mole ratio $\text{SiO}_2\text{:Al}_2\text{O}_3$ *Alfa Aesar* 400 $\text{m}^2\cdot\text{g}^{-1}$). In the following graph, both TOS for the HT-800- Sc_2O_3 catalyst as well as for the ZSM-5-A catalysts are indicated. Hence, the first region in **Figure 43** spans a time-frame of around 0-4.5 h TOS for the dual bed catalytic system with ZSM-5-A and 7-12.5 h TOS for the HT-800- Sc_2O_3 catalyst. At the end of region I, the content of the liquid cold trap was analysed and the conversion of 2,3-BDO and residual selectivity towards 3B2OL (*i.e.* after the dual bed reactor) was determined from GC-FID measurements. Consequently, as $X(2,3\text{-BDO})$ and $S(3\text{B2OL})$ were averaged over the experiment's duration, these indicators are listed tabularly rather than shown graphically (**Figure 43**).



Region	$X(2,3\text{-BDO})^{[a]}$ (mol%)	$S(3\text{B2OL})^{[a]}$ (mol%)
I	86	25
II	86	59

Figure 43: Catalytic results of the dual bed catalytic dehydration of 2,3-BDO to BD, MEK and others via 3B2OL as intermediate using a HT-800- Sc_2O_3 catalyst in the first and a ZSM-5-A with 200-400:1 $\text{SiO}_2\text{:Al}_2\text{O}_3$ catalyst in the second bed. The HT-800- Sc_2O_3 catalyst was previously used in the experiment in **Figure 41** and the total TOS for the HT-800- Sc_2O_3 catalyst is indicated in the bottom. The TOS of the second ZSM-5-A (200-400:1 $\text{SiO}_2\text{:Al}_2\text{O}_3$) catalyst is indicated at the top. Headspace gas measurements were taken every 35 minutes, liquid sample was collected from the cold trap ($-78\text{ }^\circ\text{C}$) after completion of the experiment. Reaction conditions: $m(\text{HT-800-Sc}_2\text{O}_3) = 1.00\text{ g}$, $m(\text{ZSM-5-A}) = 0.50\text{ g}$, flow-rate(H_2) = $1.8\text{ dm}^3\cdot\text{h}^{-1}$, flow-rate(2,3-BDO) = $1.6\text{ g}\cdot\text{h}^{-1}$, $T = 320\text{ }^\circ\text{C}$, $\text{WHSV} = 1.1\text{ h}^{-1}$. Yields of liquid products were determined by GC-FID using mesitylene as standard added after the reaction. $S(\text{others})$ include, butanols, acetoin, butenes, IBA and MVK. [a] Averaged over the whole duration of the experiment.

As shown in the selectivity-time profile above (**Figure 43**), an exceptional selectivity towards BD $> 60\text{mol}\%$ is attained in the first 2 h TOS after the exchange of Al_2O_3 from **Figure 41** with ZSM-5-A. Furthermore, the selectivity towards MEK is significantly lower, compared to the

dual bed experiment with Al_2O_3 . As opposed to the experiment with Al_2O_3 , where a rather constant $S(\text{MEK})$ was observed at constant flow-gas speed, (Figure 41) $S(\text{MEK})$ seems to increase with TOS when using ZSM-5-A in the second catalyst chamber. The increase in MEK selectivity goes hand-in-hand with a decrease in BD selectivity. In Figure 43, region I, a low 3B2OL selectivity of 25mol% is obtained (averaged over the experiment) which indicates that that ZSM-5-A is more active in the dehydration of 3B2OL to BD compared to Al_2O_3 ($S(3B2OL) = 43\text{mol\%}$, Figure 39). As far as conversion of 2,3-BDO is concerned, a lower value is obtained here. Using a dual catalytic approach with HT-800- Sc_2O_3 and ZSM-5-A results in 86mol% 2,3-BDO conversion, as opposed to the experiment in Figure 41, where $> 99\text{mol\%}$ 2,3-BDO conversion was attained for the combination of HT-800- Sc_2O_3 and Al_2O_3 . It should be noted though that for the experiment in Figure 41 fresh, pristine HT-800- Sc_2O_3 catalyst was used, whereas for the experiment in Figure 43, the same HT-800- Sc_2O_3 from Figure 41 was re-used, which might have undergone some deactivation due to coke deposition.

After a total TOS of 12.5 h for the HT-800- Sc_2O_3 catalyst and around 4.5 h for the ZSM-5-A catalyst, the experiment was terminated. The reactor was shut down until the next day. This 'break' is indicated in the above graph as grey marked are. The end of the start-up-phase of the reactor on the next day (see detailed procedures section 7.6.2), marks the beginning of region II. Though no reaction conditions were altered, a sharp decrease in BD selectivity as was found (around 30mol%). Like on the preceding day in region I, MEK selectivity increases during 5 to 8 h TOS for the ZSM-5-A catalyst (12.5-15.5 h for the HT-800- Sc_2O_3 catalyst), but all-in-all still more BD than MEK is produced during the second day. The side product selectivity seems unaffected by the nightly shutdown of the reactor and stays rather constant in the $< 10\text{mol\%}$ range. Results from liquid phase analysis on the second reaction day (region II in Figure 43) a 2,3-BDO conversion of 86mol% is attained, which is the same as in region I. However, $S(3B2OL)$ is much higher in region II compared to region I (59mol% for the latter, 25mol% for the former). Based on the combination of these observations, it can be assumed that the activity of the ZSM-5-A catalyst in the dehydration of 3B2OL to BD has substantially decreased, whereas the activity of the HT-800- Sc_2O_3 catalyst has remained unchanged. One of the reasons for this could be the accumulation of coke deposits as the spent ZSM-5-A catalyst sample obtained from the reactor after 11.5 h TOS was visibly coked as indicated by a dark gray colour. However, other mechanisms of catalyst deactivation, like sintering and loss of specific surface area and/or pore-volume might play a role as well. Nonetheless, ZSM-5-A has superior catalytic performances compared to Al_2O_3 and seems not to exhibit a high selectivity towards undesired MEK. Based on the results obtained in this experiment with the ZSM-5-A zeolite type catalyst, testing other zeolite-type catalyst seems promising in order to find the optimal $\text{SiO}_2:\text{Al}_2\text{O}_3$ ratio to effectively facilitate the dehydration of 3B2OL to BD.

In this context, an experiment was carried out using a zeolite catalyst with a different $\text{SiO}_2:\text{Al}_2\text{O}_3$ ratio (30:1, referred to as ZSM-5-B). Furthermore, in order to see if a higher mass of acidic zeolite catalyst in the second catalyst chamber results in less residual 3B2OL and consequently more BD, the experiment was carried out using twice the amount of zeolite catalyst in the second chamber. Like in the earlier discussed experiment with ZSM-5-A, the HT-800- Sc_2O_3 was recycled after another experiment, not listed herein, carried out for total TOS of 14 h (Figure 44).

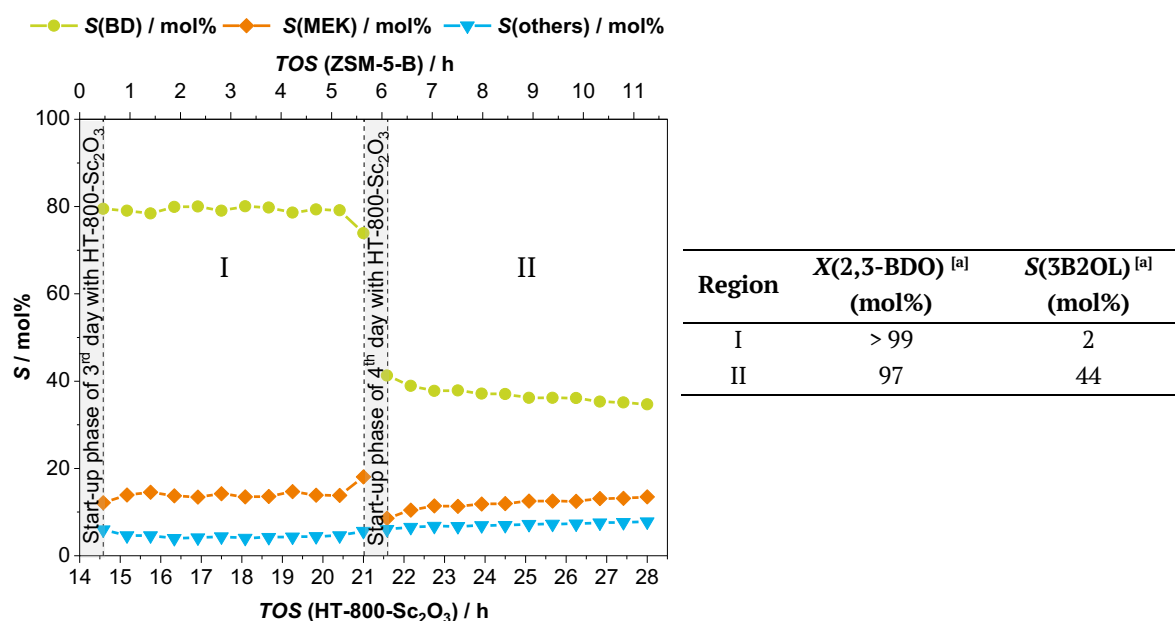


Figure 44: Catalytic results of the dual bed catalytic dehydration of 2,3-BDO to BD, MEK and others via 3B2OL as intermediate using a HT-800-Sc₂O₃ catalyst in the first a new fresh loading of ZSM-5-B (30:1 SiO₂:Al₂O₃) catalyst in the second bed. Headspace gas measurements were taken every 35 minutes, liquid sample was collected from the cold trap (-78 °C) after completion of the experiment. Reaction conditions: $m(\text{HT-800-Sc}_2\text{O}_3) = 1.00$ g, $m(\text{ZSM-5-B}) = 1.00$ g, flow-rate(H₂) = 1.8 dm³·h⁻¹, flow-rate(2,3-BDO) = 1.6 g·h⁻¹, $T = 320$ °C, $WHSV = 0.8$ h⁻¹. Yields of liquid products were determined by GC-FID using mesitylene as standard added after the reaction. $S(\text{others})$ include, butanols, acetoin, butenes, IBA and MVK. [a] Averaged over the whole duration of the experiment.

Using a different zeolite-type catalyst with a 30:1 SiO₂:Al₂O₃ ratio (ZSM-5-B) results in a very stable and highly selectivity towards BD of around 80mol% during the first 6 h into the experiment. Overall, a very high conversion of 2,3-BDO is attained (> 99%) and only 2mol% of 3B2OL is residually found in the collected liquid fractions. It has to be noted, that the HT-800-Sc₂O₃ catalyst had already been on-stream for 14.5 h at the beginning of the experiment. A stable MEK selectivity of around 12mol% was found throughout the first experimental day with ZSM-5-B and other side products were found to be < 10mol% as well (Figure 44, region I). Based on these promising results obtained on the first day, the reactor was re-started on the next day and the experiment was continued to run for another 7 h TOS (region II). A sharp decrease in BD selectivity can be observed in Figure 44, region II, although the overall performance of the dual bed catalytic reaction is relatively stable as only a minor declining trend in BD selectivity can be observed. On the other hand, MEK selectivity seems to be relatively similar in both regions and thus unaffected from the shut-down and start-up of the reactor. Based on the analysis of the liquid products in the cold trap, a much higher residual 3B2OL content was found in region II (44mol%) compared to region I (2mol%), whereas in both regions (*i.e.* both experimental days), almost full 2,3-BDO conversion was attained (97 and > 99mol% respectively).

This sharp switch in product selectivity was already observed in Figure 43 with ZSM-5-A. The results obtained with zeolite catalysts suggest that shutting down, *i.e.* cooling down the and heating up the reactor again on the next day, causes extensive decay in catalytic activity which is more prominent for ZSM-5-A compared to ZSM-5-B. In this regard, it would have been better to keep the plant continuously operated during day and night, to acquire more data and get a better understanding of the true performance and lifetime of the dual bed system.

Unfortunately, this would significantly impair the miniplant's HAZOP and LOPA, as it is explicitly stated therein, that the plant cannot be operated unsupervised, as no adequate automated safety shutdown precautions have been taken when designing the miniplant. Such an experiment would only be possible when implementing an MCS gas warning system and automated gas shut-off valves, that prevent exposure of BD and H₂ to the direct environment of the miniplant in case of emergency.

A reason for the sharp deactivation after shutting down and re-starting the reactor, might be a consequence of the temperature change of nearly 300 °C when shutting down the oven and reapplying heat the next day. During shutdown of the reactor, still gaseous 2,3-BDO and H₂O can condense in the pores/on the surface of the porous zeolite catalyst when cooling down. When heating the catalyst bed on the next day, this condensate will start to become gaseous again as temperatures well above boiling points of the individual components are applied. This abrupt gasification of condensed products and or water as formed by-product, could have caused destruction of the pore-system of the zeolite, causing a loss of surface area and pore-volume, which might be an explanation for the loss in catalytic activity.^[246] In order to see if the surface area and pore volume of the employed ZSM-5-A and ZSM-5-B catalysts changed during the reaction, several N₂ physisorption measurements were carried out (Table 19).

Table 19: N₂ physisorption results from both a pristine as well as a spent zeolite type ZSM-5-A[†] and ZSM-5-B[‡] catalyst samples used in the dual bed gas phase dehydration of 2,3-BDO to BD.^[a]

Entry	Sample	Pore Volume / cm ³ ·g ⁻¹ [a]	Surface Area m ² ·g ⁻¹ [a]
19.1	as-obtained ZSM-5-A	0.22	427
19.2	as-obtained ZSM-5-B	0.21	364
19.3	spent ZSM-5-A ^[b]	0.05	72
19.4	spent ZSM-5-B ^[c]	0.02	12

[a] Measured using a *QuadraSorb* instrument and evaluated using *Quantachrome QuadraWin* v 7.1. † 200-400:1 mole ratio SiO₂:Al₂O₃ obtained from *Alfa Aesar*, ‡ 30:1 mole ratio SiO₂:Al₂O₃ obtained from *Alfa Aesar*. [b] Catalyst sample measured after the reaction shown in Figure 43 [c] Catalyst samples measured after the reaction shown in Figure 44.

Pristine, as-obtained ZSM-5-A (entry 19.1) and ZSM-5-B (entry 19.2) have a comparable pore volume of 0.2 cm³·g⁻¹ and a surface area of around 400 m²·g⁻¹. The latter is in good agreement with the manufacturer's specifications. However, after the use of the catalysts in the experiments described in Figure 43 and Figure 44 respectively (entry 19.3 and 19.4) both pore volume and surface area are drastically lower compared to the pristine zeolite catalyst. This significant change in pore volume and surface area supports the aforementioned destruction of the pore-system and loss of surface area upon shutting down and re-starting the reactor which can be a consequence of the abrupt gasification of substrates and reaction products during the start-up phase of the reactor. Decrease of surface area and pore volume can be regarded as reason for the switch in selectivity and reactivity as the activity of the heterogeneous catalyst is highly dependent on the surface area and pore volume. In order to obtain more detailed information about the deactivation of the zeolite catalysts, it seems promising to conduct experiment with a longer time-on-stream and no intermittent nightly shutdown of the reactor. As previously describe, this however would require some extensive modifications and safety precautions of the miniplant setup.

The dual bed catalytic system based on HT-800-Sc₂O₃/ZSM-5-B described in Figure 44, region I shows very promising results and paves the way for the development of an efficient 2,3-BDO-

to-BD process with high conversion of 2,3-BDO and high selectivity of BD that can be tested on small scale using an automated miniplant setup, capable of running unsupervised by an operator. When regarding the first region of the HT-800-Sc₂O₃/ZSM-5-B, the near quantitative conversion of 2,3-BDO (99.7%), the total mass of catalysts and the average selectivity of 79% towards BD (**Figure 44**, region I), a productivity of $0.63 \text{ g}_{\text{BD}} \cdot \text{g}_{\text{cat.}}^{-1} \cdot \text{h}^{-1}$ can be calculated. As described earlier in section 2.5.3 and 2.5.4, this productivity value obtained for the dual bed HT-800-Sc₂O₃/ZSM-5-B catalytic system is greater compared to the productivities attained in the one-step *Lebedev* process and sits somewhere in the middle between the highest productivity values attained in the one-step *Lebedev* process and the lower end of the productivity values attained in the *Ostromislensky* process. It has to be considered though, that in both processes, different feedstocks are used compared to the process studied here.

6 Conclusion and Outlook

Over the last years, the production of butadiene (BD) from steam-cracking of naphtha has faced drastic changes, as more steam-crackers are shifting from heavier naphtha feedstocks towards the lighter ones, less or even none BD per unit of feedstock is produced. As a result, the on-purpose synthesis of BD has gained increasing interest. In this regard, the historic one-step *Lebedev* and two-step *Ostromislensky* processes have regained attention. Both processes became obsolete with the advent of the post-war petroleum era. However, there is currently a need to develop new synthesis routes based on sustainable raw materials in order to make the petrochemical value chain more sustainable. Although both the *Lebedev* and *Ostromislensky* process can be used to convert bio-based, sustainably sourced ethanol into butadiene, adequate developments of a revitalised industrial process to sustain in the current industrial setting, have been hampered by the complexity of the underlying reaction network and the industrial productivity barrier of at least $0.15 \text{ g}_{\text{BD}} \cdot \text{g}_{\text{cat.}}^{-1} \cdot \text{h}^{-1}$.^[11, 98] This work serves to deliver a proof of concept for a novel ethanol-to-butadiene approach, where ethanol-derived acetaldehyde is used as main building block. In the self-addition reaction of acetaldehyde, 3-hydroxy-2-butanone (acetoin) is afforded as key intermediate. Hydrogenation will be used to convert the acetoin to the corresponding 2,3-butanediol, leaving double dehydration as final step in the sequence to attain 1,3-butadiene from ethanol-derived acetaldehyde.

Especially when regarding the literature on the upgrading of acetaldehyde to acetoin, there was a significant research gap in academic literature for this specific acyloin reaction. In this regard, the present work studied the *N*-heterocyclic carbene (NHC) catalysed acetaldehyde self-addition to acetoin, using a mild base like Na_2CO_3 to generate the catalytically active carbene catalyst. Although the base persisted in the reaction vessel, excellent selectivities were attained using various carbene precursors. Best results were achieved by using thiazolium-based NHC precursors, bearing bulky, but not too bulky side groups on the quaternary nitrogen atom. Whereas a thiazolium precursor with a benzyl side group gave near quantitative conversions/yield of acetoin already after 30 minutes of reaction time, NHC precursors bearing bulkier mesityl side group resulted in 76% conversion/yield. Despite excellent performance of the homogeneous NHC precursors that were tested, their recyclability (e.g. extraction or distillation) proved to be far less promising. Hence, a heterogeneous immobilised NHC precatalyst was developed and analysed using extensive solid-state nuclear magnetic resonance (NMR) spectroscopy. Solid-state NMR spectroscopy proved successful grafting of the precursor to *Merrifield's* polymer resin to afford an immobilised NHC precatalyst. With this heterogeneous NHC precatalyst at hand, recycling and continuous-flow applications were investigated.

Although the catalyst could be recycled for up to five consecutive runs, the catalytic activity quickly decayed, reflected in a decrease in acetoin yield from 72% to about 16% in the fifth run. Despite a decay in catalytic activity, an excellent selectivity towards acetoin > 95% was attained throughout the recycling experiments. The decay of catalytic activity was attributed to the loss of catalytically active centres, as found by elaborate analysis of the post reaction solution.

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Still, the system was transitioned to a continuous operation mode where the active carbene catalyst was kept from moisture and oxygen at all times. With the continuous-flow system, the developed heterogeneous catalyst was able to attain a maximum acetoin yield of 41% at a selectivity of > 97%. As was the case in batch recycling, catalytic activity decayed over the course of 10 h time-on-stream (TOS).

A more detailed study on the catalyst deactivation revealed that the catalyst decomposed in its pristine building blocks, causing the earlier grafted compound to leach into solution. This so-called reverse *Menshutkin* reaction was found to be invariant of catalysis and was caused by an underlying molecular ‘flaw’ in the structure of the catalyst. An elaborate study on the role of solid base to *in-situ* activate the catalyst was carried out, attempting to also mitigate catalyst decomposition. Although studying the role of base in catalysis led to an improvement in catalytic activity, decomposition could not be suppressed. Still, this led to the development of a continuously operated system attaining a space-time-yield of $56 \text{ g}\cdot\text{L}^{-1}\cdot\text{h}^{-1}$ and average single-pass conversion of 37%.

To improve the stability of the catalyst, *i.e.* prevent nucleophilic decomposition reaction, an ion exchange with a non-nucleophilic PF_6^- ion was carried out. Apart from several batch recycling experiments, this allowed for investigating the improved catalyst for a total of 60 h TOS in a continuously operated CSTR miniplant setup. When the average residence time $\tau = 2 \text{ h}$ an average acetaldehyde conversion of 19% at 94% selectivity towards acetoin was attained resulting in a space-time-yield of $34 \text{ g}\cdot\text{L}^{-1}\cdot\text{h}^{-1}$. Considering the state-of-the-art biological production process for acetoin with a space-time-yield of $2 \text{ g}\cdot\text{L}^{-1}\cdot\text{h}^{-1}$, indicates that both first- and second-generation catalyst are superior, at least in terms of space-time-yield. An overview of the achievements attained regarding the NHC catalysed acetaldehyde self-addition reaction is shown in Figure 45.

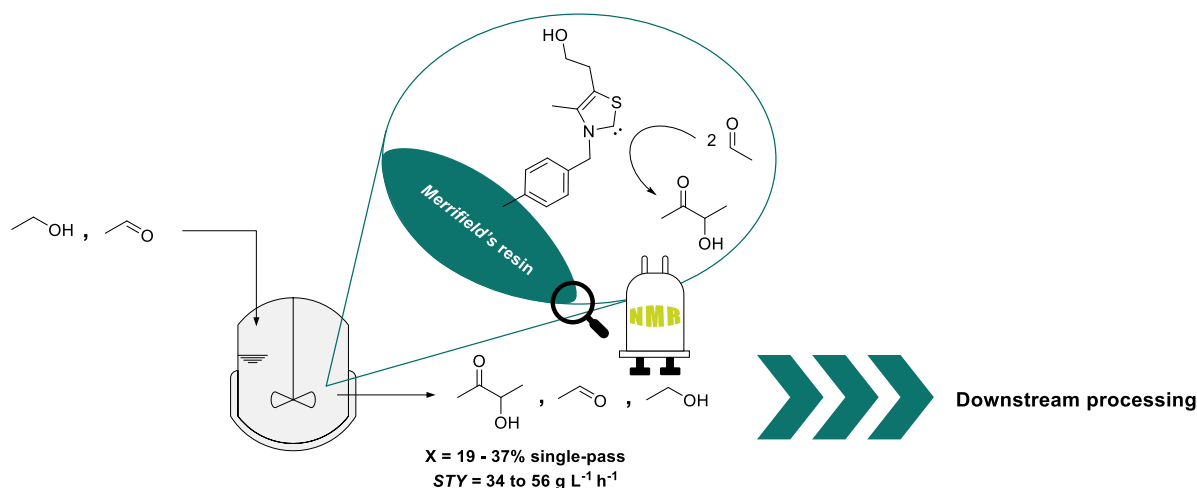


Figure 45: Schematic representation of achievements made regarding the continuous-flow acetaldehyde self-addition using an immobilised NHC catalyst grafted on *Merrifield's* resin. For the unmodified best performing catalyst, a time-yield of $STY = 56 \text{ g}\cdot\text{L}^{-1}\cdot\text{h}^{-1}$ was attained. Analysis of the immobilised NHC catalysts was carried out using advanced solid-state NMR techniques.

Following successful preparation of an acetoin in continuous-flow from acetaldehyde in ethanol, hydrogenation of the obtained acetoin/acetaldehyde/ethanol mixture was studied. Preliminary screening experiments using a broad variety of (commercially) available catalysts

showed that a 5wt% Ru/C catalyst gave the best results in slurry phase batch experiments. The hydrogenation of the acetoin containing product solution was therefore also carried out in a batch operation mode. Applying the reaction on bigger scale, using a commercial Ru/C catalyst and molecular H₂ led to obtaining a product solution containing mainly ethanol and 2,3-butanediol. Distillation of this mixture led to the isolation of 2,3-BDO in 95% purity (Figure 46).

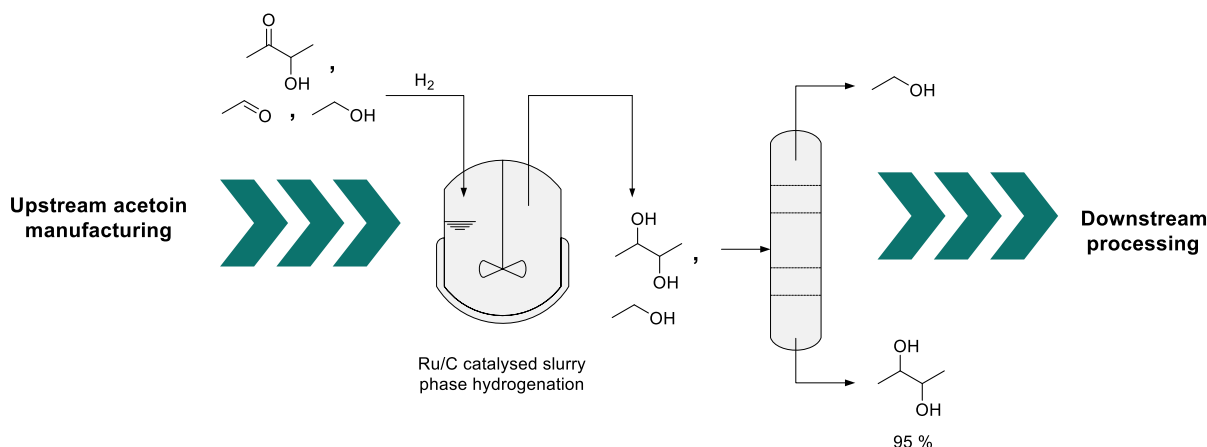


Figure 46: Catalytic hydrogenation of an acetoin/acetaldehyde/EtOH containing mixture from the continuous-flow acetaldehyde self-addition (Figure 45). A commercial 5wt% Ru/C catalyst was used for the reaction and after complete conversion of acetoin to 2,3-BDO was attained, the mixture EtOH/2,3-BDO was purified using distillation resulting in the isolation of 2,3-BDO in a purity of 95%.

Unfortunately, the gas-phase continuous-flow hydrogenation using the same acetoin containing product mixture in a continuously operated PFR-type reactor, was far less promising. Instead, better results with regard to conversions and selectivities were attained if pure acetoin was used as feedstock. Investigations regarding the pressureless flow hydrogenation of pure acetoin showcased the potential of using pressureless H₂ ‘waste streams’ for this model reaction. In the best performing system, 94% single-pass conversion at a selectivity of 93% was attained. The system was found to be stable over a total of 12 h TOS, attaining a productivity of $4.8 \text{ g}_{2,3\text{-BDO}} \cdot \text{g}_{\text{cat.}}^{-1} \cdot \text{h}^{-1}$ using a 5wt% Ru/C catalyst. Apart from pressureless flow hydrogenation, low-pressure continuous-flow hydrogenation was investigated as well. In this regard, a Ni/NiO/Alox/Celite catalyst gave the best results attaining a productivity of $9.9 \text{ g}_{2,3\text{-BDO}} \cdot \text{g}_{\text{cat.}}^{-1} \cdot \text{h}^{-1}$ at a single pass conversion of 37%. Unfortunately, for the gas-phase pressureless continuous flow hydrogenation as well as for the low-pressure continuous-flow hydrogenation, pure acetoin had to be used as substrate. Feeding an acetoin containing product mixture from the heterogeneous acetaldehyde self-addition reaction (e.g. Figure 45) into the flow-hydrogenation, resulted in a broad variety of unwanted side-reactions and consequently low selectivity towards 2,3-BDO. Hence, for the aforementioned continuous-flow hydrogenation reactions to be implemented in the process, an upstream isolation of the acetoin is mandatory (Figure 47). On the other hand, in a batch hydrogenation procedure, the acetoin/acetaldehyde/EtOH containing product mixture from Figure 45 for example, can be easily converted into a 2,3-BDO/EtOH containing product mixture. This would bring the total amount of purification steps down to one single simple distillation procedure (Figure 46) in the whole process, to obtain pure 2,3-BDO.

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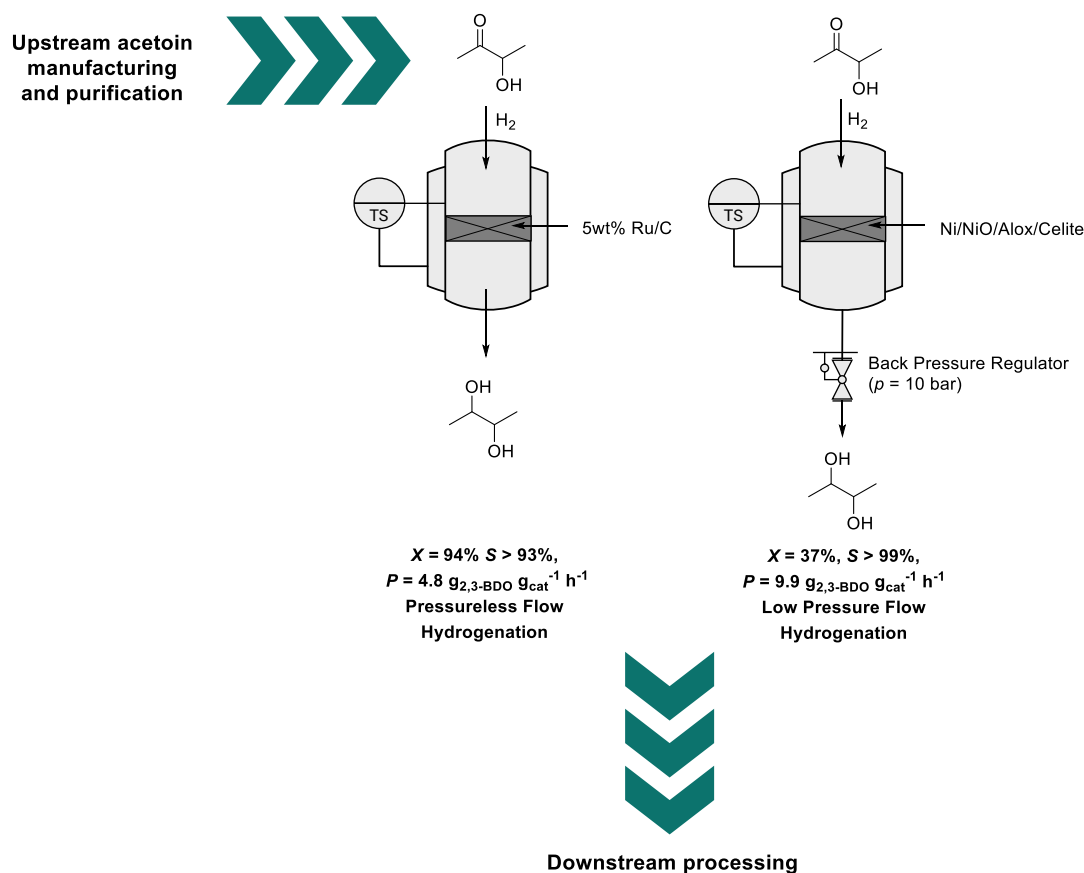


Figure 47: Catalytic advances in the pressureless (left) and low-pressure (right) continuous-flow hydrogenation of pure acetoin to 2,3-BDO in a PFR-type reactor. After generation of the acetoin, due to incomplete conversion of substrate, a purification of the generated 2,3-BDO is mandatory.

In order to convert 2,3-BDO to BD and to close the loop towards the novel acetaldehyde-to-BD process, a dual bed isothermal catalytic double dehydration was proposed. In the system, the essential reaction intermediate 3-butene-2-ol (3B2OL) was selectively prepared in a first catalytic bed, consisting of hydrothermally synthesised calcined Sc_2O_3 (HT-800- Sc_2O_3). With this specially prepared, non-porous HT-800- Sc_2O_3 catalyst, a high selectivity towards 3B2OL ($> 90\%$), relatively high conversion of 70% and long-time stability $> 10 \text{ h TOS}$ was demonstrated in a specially constructed miniplant. The exceptional reactivity of the HT-800- Sc_2O_3 catalyst was attributed to its synthetic preparation. During the hydrothermal synthesis, a hydrophilic catalyst surface is generated which promotes the catalytic reaction. Combining this HT-800- Sc_2O_3 catalyst with a suitable zeolite catalyst (ZSM-5, 30:1 $\text{SiO}_2\text{:Al}_2\text{O}_3$) afforded near full 2,3-BDO conversion with a high selectivity of 79% BD in the isothermal dual bed catalytic approach. The dual bed system was found to exhibit stable catalytic performance for at least 8 h TOS , resulting in a BD productivity of $0.63 \text{ g}_{\text{BD}} \cdot \text{g}_{\text{cat}}^{-1} \cdot \text{h}^{-1}$ (**Figure 48**). The productivity attained with this system is around four times higher than the industrial productivity barrier broadly discussed in literature.

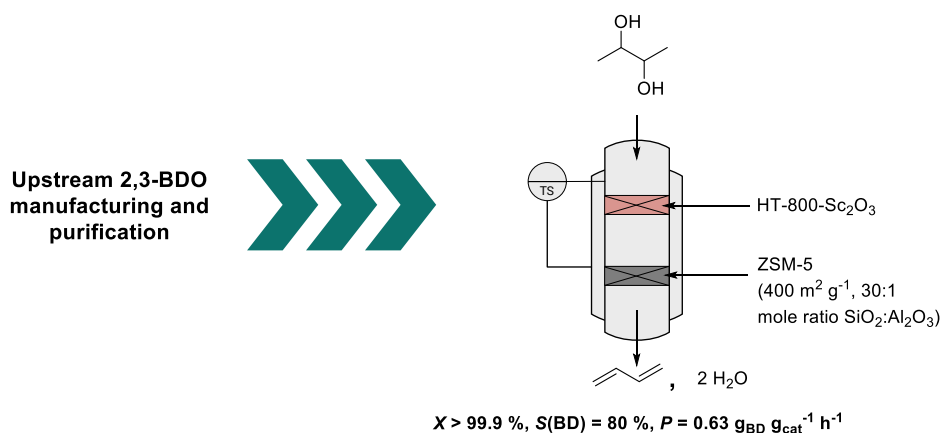


Figure 48: Schematic representation of the most productive isothermal dual bed catalytic system discussed in this work, using a combination of hydrothermally synthesised and calcined Sc₂O₃ (HT-800-Sc₂O₃) for the selective dehydration of 2,3-BDO to the 3B2OL and ZSM-5 for the subsequent dehydration of 3B2OL to BD.

Apart from the efforts that were made to deliver the proof-of-concept for the novel acetaldehyde-to-butadiene process, more research is necessary to bring this process to its full potential. Nonetheless, if the aforementioned processes are joined together, and the process is expanded by a dehydration step of ethanol to acetaldehyde with 50% catalytic efficiency towards acetaldehyde, from 1 kg of EtOH, ultimately 84 g BD will be attained. To put this in perspective, assuming quantitative conversion of 2,3-BDO to BD with a selectivity $S > 99.9\text{mol}\%$ would result in a maximum amount of 106 g BD. Based on the assumption of a 50% ethanol-to-acetaldehyde dehydration in the first step, this translates to a BD efficiency of 8.4 wt% based on EtOH. When considered that within this work, acetaldehyde was used as starting substrate, this translates to a process efficiency of around 17% in this specific acetaldehyde-to-BD pathway. A schematic overview of the investigated pathway, as well as a schematic representation of the chemical flows and potential EtOH recycling loop that could be implemented in a novel ethanol-to-BD pathway is shown in Figure 49.

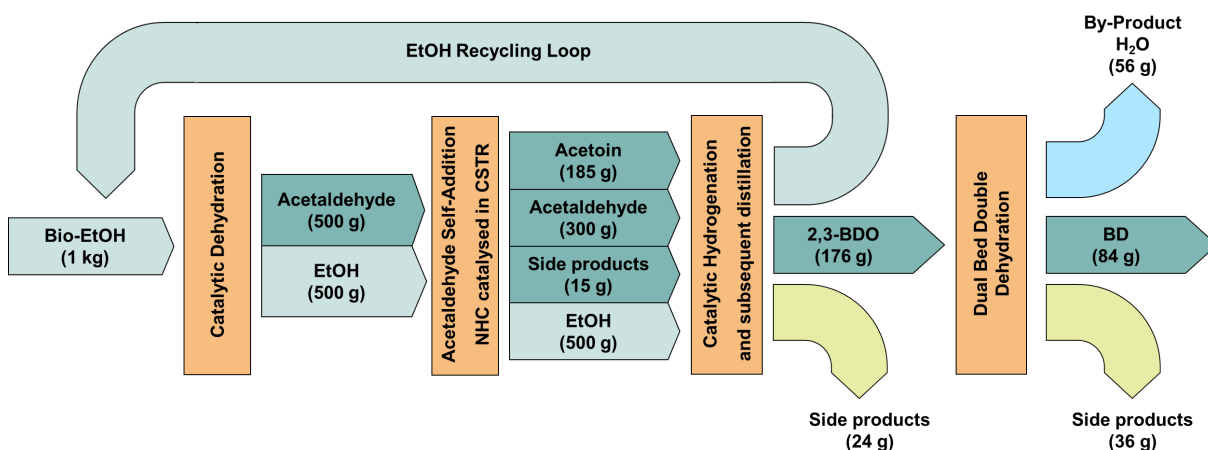


Figure 49: Schematic overview of the investigated ethanol/acetaldehyde-to-BD pathway. The catalytic parameters of the best performing systems discussed Figure 45, Figure 46 and Figure 48 respectively, were used to calculate the chemical flows, which are indicated in the above figure. The arrows are not accurate to size and serve merely as indication. Ethanol as residual educt after catalytic dehydration (first unit process, not investigated herein) is used as solvent in the acetaldehyde self-addition and subsequent hydrogenation. For the catalytic dehydration of ethanol to acetaldehyde, a process efficiency of 50% was assumed.

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In order to improve the efficiency of the overall process, the NHC catalysed acetaldehyde addition has to be greatly improved. In this regard, conversion of acetaldehyde could be improved by developing a more active heterogeneous catalyst. Also, higher conversions can be attained for longer residence-times and by using more catalytically active material as well as re-feeding the reactor effluent back into the process. The moderate to low single-pass conversion of the heterogeneous NHC catalysed acetaldehyde addition is largely responsible for the calculated low overall efficiency of the process.

Nonetheless, the flaws in converting acetaldehyde to acetoin, can be mitigated when coupling this unit process with the robust Ru/C catalysed slurry-phase batch hydrogenation. This process does not only convert acetoin to 2,3-BDO but also can be used to convert residual acetaldehyde in the feed to EtOH. In turn, a mixture of EtOH, 2,3-BDO and some side products results, which can be separated *via* distillation (Figure 46). EtOH can be fed back into the beginning of the process. Carrying out the hydrogenation reaction in a continuously operated mode is not advised, as it would not reduce the components in the system and increase complexity of separation. In a continuous hydrogenation setup, no quantitative conversion is attained which causes unconverted acetoin to be part of the reactor effluent, resulting in a product mixture containing acetoin, 2,3-BDO, side products (ketals, higher ethers) and EtOH.

Though the dual bed catalytic dehydration of 2,3-BDO to BD already gave excellent results ($X > 99.9\%$, $S = 80\%$) more research is necessary to attain even higher productivities. In this regard, the process could benefit from using the HT-800-Sc₂O₃ catalyst on a porous support to limit its use and provide a greater surface area for the catalytically active species. Egg-shell catalysts should be investigated as well to limit the use of precious Sc. This study found that the productivity towards BD was greatly influenced by the different Si:Al ratios in the zeolite catalyst in the second catalyst bed. Therefore, testing more zeolite catalysts with different Si:Al ratios might seem promising to attain higher BD selectivities. Also, the long-time stability of the zeolites > 8 h TOS has to be investigated. The dual dehydration of 2,3-BDO, produces pressureless BD and offers further opportunities for downstream processing. For instance, the implementation of palladium-catalysed telomerisation to convert (low pressured) BD into C₈ chemicals or surfactants could be considered. Moreover, the direct conversion of *in-situ* generated BD into value-added chemicals through tandem catalysis minimizes its exposure to the environment, aligning with the principles of *Green Chemistry* by reducing exposure and isolation of toxic intermediates and chemicals.

7 Experimental

Within this chapter, relevant experimental procedures, analytical methods and synthetic techniques applied as well as the detailed information regarding the continuous-flow CSTR- and PFR-type miniplant setups will be discussed. Some general remarks apply to all chapters and will be described in the following.

7.1 General Information

Handling air- and/or moisture-sensitive chemicals, the *Schlenk*-technique was applied using argon as inert gas with a purity of 99.999% either supplied by *AirLiquide* or *Westfalen AG*. A *Leybold Trivac D8B* rotary vane pump capable of $< 1 \times 10^{-3}$ mbar was used. For some synthesis and catalyst workups, deionised water was used obtained from a *MilliQ IQ 700* device. The water content of substances and solvents were, if needed determined by *Karl Fischer Titration* using an automatic *Titrande 851* from *Metrohm*. If the synthesis or work-up required the use of deionised water, this is explicitly stated. All commercially available chemicals were purchased from *Sigma Aldrich*, *Acros Organic*, *abcr*, *Alfa Aesar*, *TCI*, *Carl Roth*, *Berlin Catalysts GmbH* or *Johnson Matthey* and used without further purification. If needed, liquid chemicals were degassed by flowing argon through the liquid after which the liquid was stored under argon. An exception to this was 4-methyl-5-thiazole ethanol, which was degassed by using three freeze-pump-thaw cycles. Afterwards, the chemical was stored over dried and activated molecular sieves (4 Å). If dry solvents were required for synthesis, conventional molecular sieves (*Carl Roth*) 3 Å or 4 Å were used to dry and store solvents.

7.2 Analytical Methods

In the following chapters, the most important parameters and procedures for analysing products and identifying side products are described.

7.2.1 Gas Chromatography (GC)

Offline liquid GC measurements were carried out using a *Shimadzu Nexis GC-2030* instrument equipped with a 30 m *Rtx-1701* column purchased from *Restek* and flame ionisation detector (FID). Quantitative analysis was carried out by correlating the corrected signal intensity to the known amount of standard which was added prior or after the reaction. If not stated otherwise, a known amount of mesitylene (> 99.8%, additionally dried over MgSO_4) was used. Correction factors for acetaldehyde, acetoin and 2,3-butanediol were determined by calibrating a stock-solution with known concentration. For the non-calibrated side products, the *Sternberg* method was used to approximate the correction factors.^[247] Side product were identified using a *Shimadzu Nexis GC-2010 Plus* equipped with an *OPTIMA 1701* (33 m) column purchased from *Machery-Nagel* and *Shimadzu MS-QP2020* mass spectrometer.

Offline head-space gas measurements in the 2,3-BDO dehydration experiments were carried out using a *Shimadzu Nexis GC-2030* instrument equipped with a *Restek Rt-Q-Bond* column (30 m) and *MS-QP2020-NX* mass spectrometer.

Quantification of gaseous products in (double) dehydration experiments were carried out using an on-line *Shimadzu Nexis GC-2030* instrument equipped with a 30 m *Restek Rt-Q-Bond* column and FID. In an attempt to more precisely quantify the amount of gaseous products, in

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some experiments (explicitly stated) a known amount of standard was fed into the flow-reactor. For this purpose, a stock-solution containing 5wt% *n*-pentane in 2,3-BDO was used as feedstock and gaseous products were correlated to the amount of *n*-pentane found in the gas-phase. Additional details to the general procedures of the dehydration experiments carried out in a miniplant can be found in chapter 7.6.

For all GC measurements whether off-line or on-line and regardless of the detector, He with a purity of 99.999% either supplied by *AirLiquide* or *Westfalen AG* was used as flow-gas with a linear velocity of 35 cm·s⁻¹.

7.2.2 Elemental Analysis

In order to determine the content of catalytically active component grafted on the polystyrene-supported NHC catalysts and its residual content after catalysis, elemental analysis was carried out for a wide variety of samples by *Mikroanalytisches Laboratorium Kolbe*, Osterfelder Str. 3, 46047 Oberhausen. Elemental contents of carbon, hydrogen, nitrogen and sulphur (CHNS) were determined using an *Elementar vario MICRO cube*. Contents for chlorine and fluorine were determined using ion-chromatography carried out on a *Metrohm 930 Compact IC Flex Oven/SeS/PP/Deg* after complete combustion of the sample in a *Mitsubishi AQF-2100H* automatic quick furnace. Oxygen contents were determined using an *Elementar rapid OXY cube*.

7.2.3 Nuclear Magnetic Resonance (NMR) Spectroscopy

Solution-state NMR spectra were recorded using a *Bruker AvanceNEO 400*-spectrometer (¹H: 400 MHz) or a *Bruker AVANCE III HD 500* (¹H: 500 MHz) with PRODIGY cryo-probe head (82 K; Broadband decoupler, ¹H/¹⁹F- and 2D-Lock-channel). The unit was connected to a BCU II tempering-unit, capable of measuring from -40 °C to +80 °C. Measurements on the *Bruker AVANCE III HD 500* instrument were carried out by the group of *Weyhermüller*. If not stated otherwise, measurements were carried out at ambient temperatures (*i.e.* 296 K) and pressures. Chemical shift (δ) is given in ppm (parts per million). For ¹H NMR spectroscopy, the residual solvent signal was used for referencing to trimethyl silane (TMS) as internal standard for (Table 20). Multiplicities are reported as s (singlet), br (broad singlet), d (doublet), t (triplet), q (quartet), or m (multiplet).

Table 20: Chemical shifts and multiplicities of the deuterated solvents.^[248-249]

Solvent	δ (¹ H) / ppm (multiplicity)
CDCl ₃	7.26 (s)
DMSO- <i>d</i> ₆	2.50 (s)
D ₂ O	4.79 (s)
EtOD- <i>d</i> ₆	3.55 (br)

J-coupling constants refer to ¹H-¹H-*J*-coupling. If not stated otherwise, sample preparation was carried out as follows, 20 mg to 50 mg of substance were dissolved in 0.5 mL of deuterated solvent and transferred to the NMR tube. *MestReNova v14.0.1* was used to process and evaluate NMR spectra. Prior to evaluation, the NMR spectra were subjected to exponential apodisation (1.3 Hz) and zero-filling with four times the number of recorded data points. Additionally, a manual phase correction and a baseline correction with a polynomial fit were conducted.

Quantitative evaluation of the spectra was carried out using mesitylene as standard. In case of quantitative NMR (qNMR) evaluation, the respective signals of the compound as well as of the standard were manually integrated after spectral processing. Prior to carrying out qNMR, complete relaxation of the nuclei was ensured in a series of experiments with different D_1 times. The amount of analyte in the sample was determined using the equation (1).

$$m(\text{analyte}) = \frac{N_{\text{nuclei}}(\text{standard}) \cdot I(\text{analyte})}{N_{\text{nuclei}}(\text{analyte}) \cdot I(\text{standard})} \cdot m(\text{standard}) \quad (1)$$

$m(i)$: mass of component i

$N_{\text{nuclei}}(i)$: Number of nuclei corresponding to the signal of component i

$I(i)$: Integral of component i

In order to determine the amount of exchangeable protons/OH-groups of the solid-state Sc_2O_3 -based catalyst, a known amount of catalyst sample, around 5–10 mg was suspended in D_2O (0.4 mL) in an ultrasonic bath for 15 minutes. Afterwards, the solids were filtered through a 0.45 μm syringe filter, except for the ScOOH samples which had to be separated by centrifuge (7000 rpm, 3 min) and filled into a standard NMR tube. To that DMF (11.0 mg, 0.15 mmol) was added as internal standard. The residual number of protons in D_2O was determined using a blank NMR sample, containing only DMF and D_2O (0.4 mL). qNMR experiments were carried out on a *Bruker AVANCE III HD 500* (^1H : 500 MHz) by the group of Weyhermüller. A pulse width of 12.000 s and relaxation delay of 10.000 s were used in these experiments. The number of interchangeable protons in the samples (in $\text{mmol} \cdot \text{g}^{-1}$) were calculated using a modified version of equation (1), accounting for the number of residual protons in the D_2O .

$$c(\text{H}_{\text{exch.}}) = \frac{(I_{\text{H}}(\text{analyte}) - I_{\text{H}}(\text{residual H in D}_2\text{O})) \cdot n_{\text{H}}(\text{standard})}{m(\text{sample}) \cdot I_{\text{H}}(\text{standard})} \quad (2)$$

$c(\text{H}_{\text{exch.}})$: concentration of interchangeable protons in the analyte

$I_{\text{H}}(i)$: integral of protons in component i

$n_{\text{H}}(i)$: molar amount of protons in i

$m(i)$: mass of component i

Solid-state NMR spectra were recorded by the group of Wiegand at the facilities of the Magnetic Resonance Center (MARC) at the Institute for Technical and Macromolecular Chemistry, Worringerweg 2, 52074 Aachen. The solid-state NMR experiments were recorded using 4.0 mm double resonance and 3.2 mm triple-resonance *Bruker* probes at a *Bruker Avance III HD* spectrometer with a field strength of 11.7 T or 16.4 T. The spectra were either processed with *Topspin v3.6.4* and *v4.1* or *ssNake v1.5*. In case of processing with *ssNake*, gaussian apodization of 100 Hz was used as defined in the software.^[250] Where possible, experimental parameters were optimized directly on the samples. ^{13}C spectra were referenced to TMS using the methylene resonance of solid adamantane as an external standard (38.56 ppm). ^{15}N spectra were referenced with respect to liquid NH_3 using NH_4Cl set to 39.3 ppm.^[251] ^{31}P spectra were referenced to 85% H_3PO_4 using *O*-phospho-L-serine resonance as an external standard.^[252] The spectra have been recorded at a probe temperature of 293 K using a *Bruker BCU-II*. For ^{15}N experiments with low signal-to-noise ratios, ^{15}N labelled glycine ethyl ester was used to setup the experiment.

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For referencing the obtained ^{15}N NMR spectra, Ab initio calculations were also carried out by the group of Wiegand. The procedure as well as the details, have also been published in M. Belleflamme *et al.*, *ChemSusChem* **2024**, e202400647.^[204]

The initial geometries for 4-methyl-5-thiazole ethanol and 3-benzyl-5-(2-hydroxyethyl)-4-methyl thiazolium chloride were built using *Avogadro*.^[253-254] Geometry optimization of the initial structures was carried out with *TURBOMOLE* v7.5.1^[255-256] on a DFT meta-GGA r²SCAN-3c^[257] level of theory, applying the D4^[258] dispersion correction and a def2-mTZVPP^[259] basis set. For all calculations, the default self-consistent field (SCF) energy convergence criterion of $10^{-7} E_h$ was used together with an integration grid of *m4*^[260] and the resolution of identity (RI)^[260-261] approximation.

The calculations of the ^{15}N magnetic shielding tensors were based on the optimized geometries and carried out in the *ORCA*^[262-263] program package v5.0.4 with the Gauge Including Atomic Orbital^[264] (GIAO) method employing the PBE0^[265] functional and the triple- ξ pcSseg-2^[266] basis set with resolution of identity for Coulomb and exchange integrals (RIJK)^[267] and auxiliary basis sets automatically generated with the *AutoAux*^[268] algorithm. The DFT meta-GGA optimized structures used to calculate the GIAO ^{15}N magnetic-shielding tensors are shown in **Figure 50**.

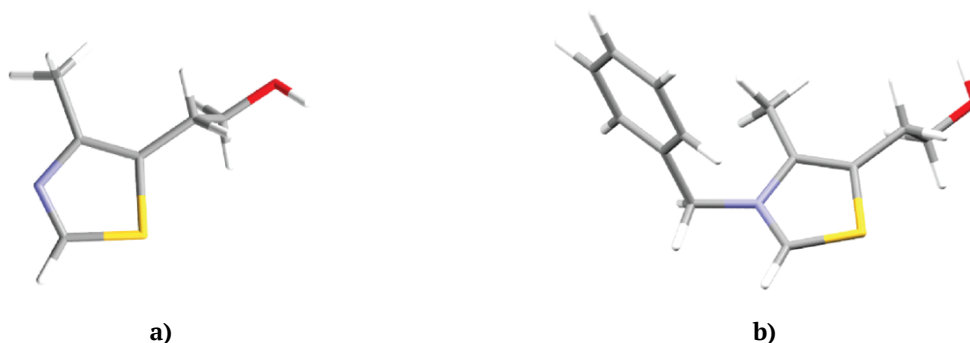


Figure 50: Structures of **a)** 4-methyl-5-thiazole ethanol and **b)** 3-benzyl-5-(2-hydroxyethyl)-4-methyl thiazolium chloride optimized using DFT meta-GGA (r2SCAN-3c)^[257] level of theory, applying the D4^[258] dispersion correction and a def2-mTZVPP^[259] basis set. Structures were used to calculate the GIAO^[264] ^{15}N magnetic-shielding tensors.

7.2.4 Mass Spectrometry (MS)

Substance identification was conducted using mass spectrometry. Measurements were performed on an *Advion Expression CMS*. All samples were analysed using the atmospheric pressure chemical ionization (APCI) method. A capillary temperature of 200 °C and a source gas temperature of 350 °C were used. Samples were introduced manually into the instrument using an atmospheric solids analysis probe (ASAP) with melting point capillary insert for both solid and liquid samples.

7.2.5 X-Ray Fluorescence (XRF)

XRF analysis was carried by *Gurowski* and *Jakubowski* using a *Spectro Xepos C* instrument. The instrument is equipped with a Co-Pd-alloy X-ray source and a silicon-drift-detector. For a typical measurement, 1.0 mL of sample was filled into a cuvette with an outer diameter of 20 mm and an inner diameter of 16 mm. The cuvette is covered with a 12 μm thick Prolene® foil. Measurements were carried out for 600 seconds in a mixed He/Air atmosphere at an Energy-

level (E) of 3 keV to 19 keV. Recalibration of the device was carried out daily, using a glass tablet with a certain elemental composition, used for referencing.

7.2.6 X-Ray Diffraction (XRD)

XRD patterns were recorded by the group of *Heumann* using a third generation *Malvern Panalytical Empyrean* diffractometer in a Bragg-Brentano geometry, Cu-K α radiation and 1Der detector. An automatic *iCore* module with 0.6 mm diverging diaphragm, 0.03 rad Soller and 14 mm mask was used. The flat sample holder was rotated with a frequency of 0.25 Hz. The diffracted X-rays (secondary beams) are treated with an 8 mm stray beam diaphragm and 0.04 rad Soller. The X-ray tube is operated at 40 kV and 30 mA. The range of measurement is 10–120° 2 θ with a step size of 0.016 or 0.03° and a measurement time of 100–200 seconds per point (depending on the crystallinity of the sample). *Rietveld* refinements of the crystalline constituents were done using the software *DIFFRAC.TOPAS v7* software developed by *Bruker*. The instrumental profile function was obtained from an X-ray powder pattern of LaB₆ NIST 660c line-shape standard.

7.2.7 X-Ray Photoelectron Spectroscopy (XPS)

Oxidation states and surface chemical composition of several solid oxide catalyst samples used in the dehydration of 2,3-BDO were determined using XPS in collaboration with the group of *Hetaba*. Material was thinly deposited on a carbon-tape and measured in ultra-high vacuum (UHV). A SPECS Phoibos 150 R5 electron energy analyser and MCD-9 channel Detector were used. A SPECS XR50 non-monochromatic Al X-ray source was used (Al K α , $h\nu$ = 1486.6 eV). The size of the measured range was manually set on the analyser using an iris, depending on the size of the sample. Typically, the opening was set between 5 and 10 mm in size. Survey scans were recorded using a step size of 1 eV and a pass energy of 100 eV. High resolution scans were recorded using a step size of 0.1 eV and a pass energy of 20 eV.

7.2.8 N₂ Physisorption

In order to determine the surface area as well as pore-volume of heterogeneous catalysts, N₂-physisorption measurements were carried out in collaboration with the group of *Ruland*. Prior to the measurements, samples were degassed under vacuum at 120 °C for 4 h using a *Quantachrome MasterPrep™* vacuum and flow degasser. Measurements were carried out using a *Quantachrome evo™* surface area and pore analyser. Raw-data was analysed using the *Quantachrome QuadraWin™ v7.1* software. Specific surface areas of the samples were determined according to the BET model in the range $0.05 \leq p/p_0 \leq 0.2$. For the analysis of the total pore volume, the highest relative pressure points $p/p_0 = 0.95$ were used. If applicable, micropore volumes were obtained by using the t-plot model in the range $0.2 \leq p/p_0 \leq 0.4$.

7.2.9 Electron Microscopy

Scanning electron microscopy with energy dispersive X-ray spectroscopy (SEM/EDX) was conducted using a *Hitachi S-3500N* operating at 30 kV. Samples were prepared for measurement by depositing the powder onto tape and flattening it out to create an even surface for analysis. Transmission electron microscopy (TEM) and scanning transmission electron microscopy (STEM) in high-angle annular dark-field (HAADF) mode, combined with energy dispersive X-ray spectroscopy (EDX) if applicable, were performed on a *FEI Talos*

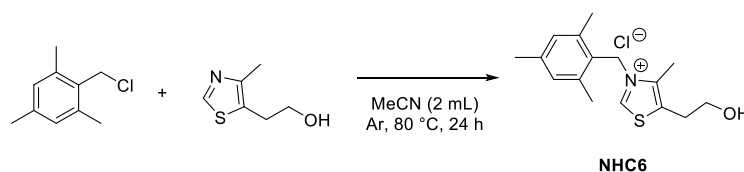
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F200X operating at 200 kV and equipped with a *SuperX* system (4 Bruker SDD EDX detectors). All measurements were performed at the *Max-Planck-Institut für Kohlenforschung*, Kaiser-Wilhelm-Platz 1, 45470 Mülheim an der Ruhr.

7.3 Synthesis of Compounds and Catalysts

Apart from commercially available chemicals, some chemicals and catalysts were prepared and purified by the author of this work. Relevant synthetic procedures and analysis of the products are described in this section.

7.3.1 Preparation of 5-(2-hydroxyethyl)-4-methyl-3-(2,4,6-trimethylbenzyl)thiazol-3-ium chloride (NHC6)



Inside a glovebox, a 10 mL Schlenk tube was charged with 2,4,6-trimethylbenzyl chloride (0.341 g, 2.02 mmol, 1.0 eq) and MeCN (2.0 mL, dried, degassed). Outside of the glovebox, in Ar counterflow, 4-methyl-5-(2-hydroxyethyl)-thiazole (0.321 g, 2.24 mmol, 1.1 eq, dried, degassed) was added and the reaction was stirred under Ar for 24 h at 500 rpm and 80 °C in an oil-bath. After completion of the reaction duration, the solvent was removed *in vacuo*. A white solid was obtained as crude reaction product. The solid was washed with little MeCN (2 x 2.5 mL) and recrystallised from warm (60 °C) MeCN (5.0 mL). Afterwards the Schlenk flask was placed inside a freezer set to -25 °C overnight. After removing the volatiles *in vacuo*, the product was recovered was a white, fluffy solid (0.3221 g, 1.033 mmol, 51.1%)

$T_{\text{mp}} = 172.0\text{ °C}$

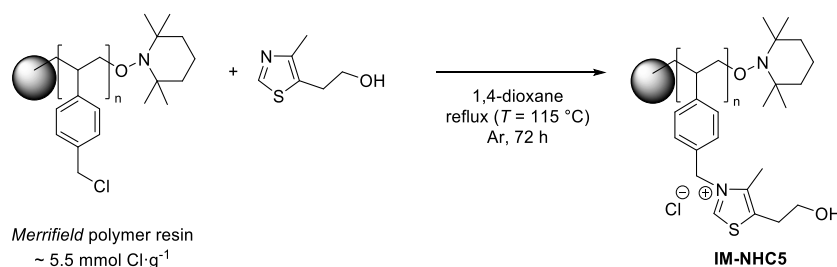
ESI-MS (positive, m/z): $[M-\text{Cl}]^+$ Calc: 276.1422; Found: 276.2.

^1H NMR (400 MHz, $\text{DMSO}-d_6$, r.t.): $\delta = 9.04$ (s, 1H), 7.04 (s, 2H), 5.56 (s, 1H), 3.65 (t, $J = 5.6$ Hz, 2H), 3.08 (t, $J = 5.6$ Hz, 2H), 2.63 (s, 3H), 2.29 (s, 3H), 2.20 (s, 6H) ppm.

^{13}C -APT NMR (100 MHz, $\text{DMSO}-d_6$, r.t.): $\delta = 154.2, 142.2, 139.2, 138.6, 136.0, 129.6, 125.0, 61.2, 59.5, 51.3, 29.4, 20.7, 19.1, 11.6$ ppm.

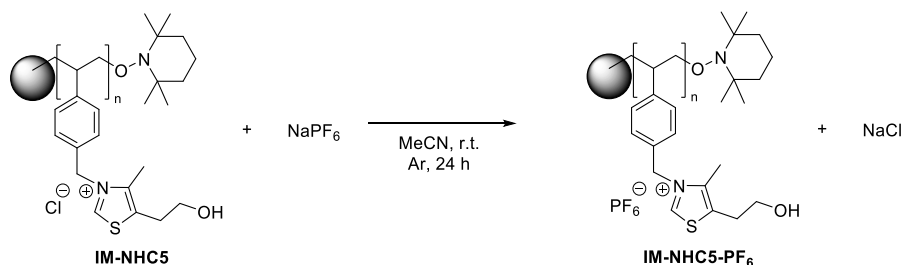
Further analytical details can be found in the publication by Terashima.^[207]

7.3.2 Preparation of (chloromethyl) 4-methyl-5-thiazole ethanol, grafted on Merrifield polymer resin (IM-NHC5)



A typical procedure for preparing **IM-NHC5** was carried out as follows. To an oven-dried 500 mL *Schlenk* flask was added (chloromethyl) polystyrene (10 g, ~ 55.5 mmol Cl, 1.0 eq) as well as 1,4-dioxane (200 mL) and 4-methyl-5-thiazole ethanol (19.99 g, 138.7 mmol, 2.5 eq). The mixture flushed with Ar for at least 10 minutes before heating up to reflux in Ar atmosphere. During the reaction (72 h) a steady stream of Ar was applied to ensure exclusion of Air and moisture. Furthermore, the reflux condenser was equipped with an oil-filled bubbler. After duration of the reaction, the contents of the flask were allowed to slowly cool to rt whilst maintaining the Ar atmosphere. The residual solvent was filtered off *via* cannula filtration. Subsequently, the polystyrene beads were washed with DCM (dried, degassed, 2 x 60 mL, 1 x 80 mL). Between washing cycles, residual DCM was also removed *via* cannula filtration. The reaction product was dried *in vacuo* for several hours and stored in the glovebox until use in catalysis. The collected filtrates were reduced *in vacuo* to afford 10.521 g, 73.5 mmol unreacted 4-methyl-5-thiazole ethanol. The precatalyst **IM-NHC5** was obtained as pale-yellow beads with a loading of 3.36 mmol·g⁻¹ as determined by gravimetric analysis. Apart from gravimetric determination of the precatalyst loading, elemental composition was determined by *Mikroanalytisches Laboratorium Kolbe* (see section 7.2.2). The loading of 4-methyl-5-thiazole ethanol was determined to be 3.24 mmol·g⁻¹ which is in good agreement with the value obtained *via* gravimetry. For the catalytic experiments carried out in this work **IM-NHC5**, the 4-methyl-5-thiazole ethanol *i.e.* precatalyst loading as determined by *Mikroanalytisches Laboratorium Kolbe* was used. For different batches of **IM-NHC5** prepared, slightly different loadings of catalytically active component were obtained.

7.3.3 Ion exchange procedure with IM-NHC5



Inside the glovebox, **IM-NHC5** (7.88 g, 2.78 mmol·g⁻¹, 21.9 mmol, 1.0 eq) was suspended in MeCN (120 mL) in a 500 mL round bottom flask. Outside of the glovebox, was added NaPF₆ (6.67 g, 39.6 mmol, 1.8 eq) in Ar counterflow. The reaction was carried out of 24 h at room temperature using a low stirring speed of 100 rpm to avoid abrasion of the **IM-NHC5** catalyst beads. Afterwards the duration of the reaction, a white precipitate was observed. Residual solvent was removed *in vacuo* and H₂O (40 mL) was added to extract precipitated NaCl and

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unconverted NaPF_6 . The brine was removed *via* cannula filtration in Ar counterflow and the obtained beads were washed with anhydrous MeOH (4 x 10 mL). After washing, the precatalyst beads were dried *in vacuo* and stored in the glovebox until further use. The washing solution was reduced *in vacuo* and subjected to NMR analysis and ESI-MS. The loading of the catalyst after ion exchange was determined to be $2.27 \text{ mmol}\cdot\text{g}^{-1}$ and the amount of PF_6 was found to be $2.27 \text{ mmol}\cdot\text{g}^{-1}$ as well, indicating complete ion exchange of the grafted catalyst. The loading of the PF_6 -modified catalyst is somewhat lower compared to the pristine **IM-NHC5** which indicates that some 4-methyl-5-thiazole ethanol ($M = 143.21 \text{ g/mol}$) was washed off-during the ion exchange procedure. This was also confirmed by detailed analysis of the washing solution. ^1H - ^{13}C CP solid-state NMR spectrum of the **IM-NHC5-PF₆** compound resembles the spectrum of the non-modified, pristine **IM-NHC5**. The ^1H - ^{31}P CP-spectrum shows the expected septet line shape for the PF_6^- counter ion. The fact that the PF_6^- can be observed in such a CP spectrum points to its successful immobilization.

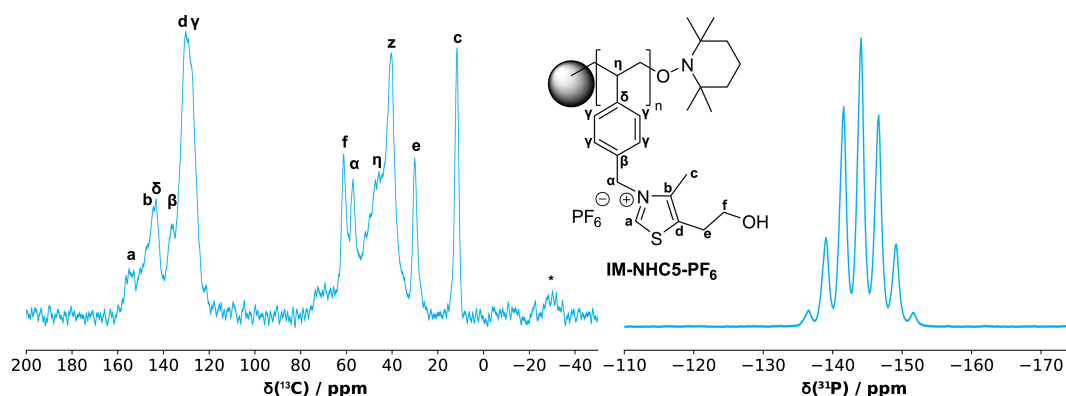


Figure 51: ^1H - ^{13}C (left) and ^1H - ^{31}P (right, a zoom into the spectrum is shown) CP spectra of **IM-NHC5-PF₆** recorded at a MAS frequency of 14.0 kHz using a magnetic field of 16.4 T in strength. For the annotation of the resonances in the left spectrum see the chemical structure. * indicates MAS sidebands.

Analysis of washing-solution after ion exchange procedure:

ESI-MS (positive, m/z): Calc: 143.21; Found: 144.0

^1H NMR (400 MHz, D_2O , r.t.): $\delta = 9.94$ (s, 1H), 4.25 (t, $J = 6.07 \text{ Hz}$ 2H), 3.5 (t, $J = 5.6 \text{ Hz}$, 2H), 2.89 (s, 3H) ppm.

^{31}P NMR (162 MHz, D_2O , r.t.): $\delta = -144.9$ (hept, $J = 706 \text{ Hz}$, 1P) ppm.

^{19}F NMR (376 MHz, D_2O , r.t.): $\delta = -72.6$ (d, $J = 706 \text{ Hz}$, 6F) ppm.

7.3.4 Preparation and analysis of hydrothermally synthesised, calcined Sc_2O_3

Synthetic procedure of HT-800- Sc_2O_3 was freely adopted from Nakazono *et al.*^[147] and carried out in collaboration with M. Müller of the group of Heumann. In a typical catalyst preparation, $\text{Sc}(\text{NO}_3)_3 \cdot x \text{H}_2\text{O}$ (5.0 g, x determined by TG, usually $x \approx 1.8$) was dissolved in H_2O (50 mL) and aq. 25wt% ammonia solution was added until a pH value of 9.8 was reached. During addition of the aq. ammonia solution, pH was continuously measured by a Mettler Toledo SevenExcellence™ Multiparameter pH meter. Upon the addition of the aq. ammonia, a very fine milky white suspension was obtained, indicating the formation of the respective hydroxide. The suspension was transferred to multiple 40 mL Teflon-lined autoclaves. Hydrothermal aging was carried out at 200 °C for 8 h. Afterwards, the precipitate was recovered via centrifuge (7000 rpm, 5 min) and washed with distilled water (3 x 50 mL). The precipitate was allowed to dry in an oven at 110 °C for 24 h. Afterwards, the solid was crushed into a fine powder with a mortar and calcined in air at 800 °C for 3 h. Following the preparation of the sample, SEM-EDX, BET, XRD and Raman measurements were carried out. The finished catalyst was denoted HT-800- Sc_2O_3 . After carrying out the preparation and analysis of the HT-800- Sc_2O_3 catalyst, the catalyst was kept in air until employing in catalytic reactions. Each batch of HT-800- Sc_2O_3 was characterised and results of analysis, mainly XRD measurements were awaited before combining different batches of HT-800- Sc_2O_3 . In general, the characterisation results obtained from different batches of catalyst were insignificantly different and for that purpose, in some cases combined to attain the desired catalyst mass for a typical experiment.

7.4 Acetaldehyde Self-Addition Experiments

7.4.1 Self-addition of acetaldehyde using homogeneous NHC precursors

To a 10 mL thick-walled borosilicate glass tube, purchased from *AntonPaar* with a tic-tac stir bar was added precatalyst, base, ethanol (Rotisolv® HPLC Gradient, <0.1% H₂O) as solvent (if described), mesitylene as internal standard and acetaldehyde as substrate. After addition of the aldehyde, the tube was quickly sealed and the reaction vessel was placed in the MAS 24 autosampler of an *AntonPaar Monowave 450* microwave reactor. The reaction was carried out for a given amount of time at a given temperature. After the reaction, post reaction solution was retrieved using a syringe and filtered through a 0.45 µm syringe filter prior to analysis via GC-FID. Typical GC-FID samples were prepared from approximately 200 mg of filtered post reaction solution and approximately 800 mg *i*PrOH as solvent. Response factors of acetoin and acetaldehyde were determined by calibration using mesitylene as internal standard and *i*PrOH as solvent.

7.4.2 Experiments using IM-NHC5 precatalyst and base

A typical recycling experiment with **IM-NHC5** and base was carried out in a thick-walled glass pressure tube (*ACE*, 20 mL) with a crosshead stir bar. Inside an Ar-filled glovebox, precatalyst **IM-NHC5** (119.8 mg, 3.24 mmol·g⁻¹, 0.4 mmol, 1.0 eq, 2.0mol%) as well as Na₂CO₃ (53.4 mg, 0.5 mmol, 1.3 eq, 2.6mol%) were added to the pressure tube. Outside of the glovebox was added either an acetaldehyde and mesitylene containing stock-solution in ethanol or acetaldehyde, ethanol and mesitylene separately in Ar counterflow. Apart from acetaldehyde, liquid reagents were degassed, dried and stored under Ar over molecular sieves. In order to ensure Ar counterflow for the addition of liquid reactants and solvents, the pressure tube containing precatalyst and base, was carefully lowered into a 100 mL Schlenk tube and the lid was removed in Ar counterflow. After addition of liquid reagents or stock solution, the tube was tightly closed in Ar counterflow and heated in an oil-bath and stirred for the indicated time. After completion of the reaction duration, the tube was retrieved from the oil-bath and allowed to come to room temperature, before submerging in an ice-bath for at least 15 minutes. Afterwards, the tube was opened and the liquid content was retrieved using a syringe and filtered over a 0.45 µm syringe filter, prior to GC-FID and XRF analysis (if desired).

In case of batch recycling experiments, after completion of the reaction and cooling the pressure tube in an ice-bath, the lid of the pressure tube was opened in Ar counterflow. Liquid contents of the pressure tube were retrieved using a syringe and 0.45 µm syringe filter. In order to prevent solid precatalyst and base from being removed during filtration, the filter was washed down with fresh substrates (Figure 52).

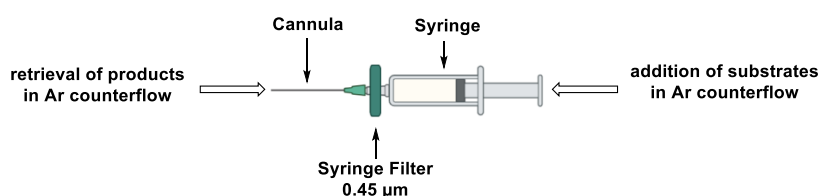


Figure 52: Schematic representation of the cannula filtration setup for retrieving and adding substrates to the reaction vessel in Ar counterflow, without losing solid catalyst and base on the filter.

After completing the reaction or recycling procedures, the residual catalyst was dried *in vacuo* to remove the volatiles before adding little H₂O and HCl until the bubbling had seized to decompose the Na₂CO₃. The acid washing solution was removed *via* cannula filtration. The spent catalyst was washed with MeOH (3 x 5 mL), dried *in vacuo* and stored under Ar for further analysis.

7.4.3 General procedures of a continuous-flow experiment

Prior to the experiment, a stock solution was prepared by mixing acetaldehyde, ethanol and mesitylene as internal standard. Ethanol (Rotisolv® HPLC Gradient, <0.1% H₂O) and mesitylene were added to a Schott bottle with a stir bar and refrigerated at 4 °C for at least 1 h before adding the acetaldehyde. Meanwhile, the aluminium heating mantle of the reaction vessel was pre-heated to the desired reaction temperature.

Inside an Ar filled glovebox, the desired amount of precatalyst and base was weighed, based on volume of the continuous-flow reactor $V(\text{CSTR}) = 30.6 \text{ mL}$ and the content of the previously prepared stock solution.

Outside of the glovebox, precatalyst and base were added to the dry reactor to which a crosshead stir bar had been added. The reactor was partially filled with stock solution using a syringe (20 mL). Afterwards, the reactor was sealed and the pump was started to further fill the reactor. The flow rate was first set to $\dot{V}(\text{stock}) = 2.5 \text{ mL} \cdot \text{min}^{-1}$. Once the reactor was filled, the pump rate was set to the desired value and the reactor was placed inside the preheated heating cone. The first reaction sample is taken when the first product droplet leaves the system behind the back-pressure regular (see section 7.4.4, Figure 53), marking the start of the experiment. If not stated otherwise, samples were taken every 15 minutes for a duration of 4 minutes.

At the end of the experiment, the reactor is removed from the heating cone and cooled in a water bath. Once the reactor had come to room temperature, the pump was switched off. In case of multi-day experiments, the reactor was kept sealed until the next day. Starting up the reaction on the next day consisted of pre-heating the aluminium cone and once heated, placing the reactor inside. The pump was started to initiate the flow of substrates. The first sample was collected after 15 minutes for a duration of 4 minutes.

In case of intermittent base-addition experiments, experiments were carried out for at least two consecutive days. After the first day, the experiment was terminated as previously described. On the second day, whilst pre-heating the cone, the desired amount of base was added through a 1/4" ball valve installed on the reactor head. If necessary, this procedure was repeated on the next day. Sample collection remain unaffected from intermittent base-addition experiments.

All collected samples were measured by GC-FID and XRF. GC-FID samples were prepared from approximately 200 mg of collected sample and 800 mg of *i*PrOH, whereas XRF samples were measured directly from the outlet collected samples of the miniplant.

After completion of the experiment, the cooled reactor was opened and the catalyst was transferred into a *Schlenk* tube. Residual substrates and products were removed *in vacuo*. Little H₂O as well as a small amount of HCl were added until bubbling had seized. Afterwards, the

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washing solution was removed *via* cannula filtration. The catalyst was washed with MeOH (3 x 10 mL), dried *in vacuo* and stored under Ar for further analysis.

7.4.4 Description and characterization of the continuous stirred tank reactor (CSTR) miniplant

The CSTR miniplant used to carry out the continuous-flow experiments as described in section 7.4.3 was built and characterised by *J. Hommes* (Master's Thesis, RWTH Aachen University, 2022) The miniplant consists of a 30.6 mL stainless-steel autoclave (R-201) which was heated on a stirring hot-plate and custom aluminium heating cone. Substrate was fed from a storage tank (T-102) *via* a 1/8" perfluoro alkoxy alkane (PFA) capillary through a *Shimadzu LC-10AD* HPLC pump (P-201) and into the reactor *via* a 1/16" stainless steel capillary. In order to prevent acetaldehyde from evaporating and to ensure a uniform feed-concentration, the storage tank was stirred and cooled in an ice-water bath (T-101). The product solution is passed through a 4-micron filter (F-201) into a riser tube, consisting of a 1/8" PFA capillary to a back-pressure regulator (BPR-301). The BPR is used to adjust the pressure of the system and to prevent run-away of acetaldehyde at reaction temperatures. If not explicitly stated otherwise, the pressure was manually set to $p = 8$ bar and kept constant throughout the experiments. After the BPR, the product stream is passed through a 1/8" PFA capillary cooled in an ice-water bath (C-301) to the collection vessel (T-301) where samples can be withdrawn and product can be stored. The process flow diagram of the CSTR miniplant is shown below in **Figure 53**.

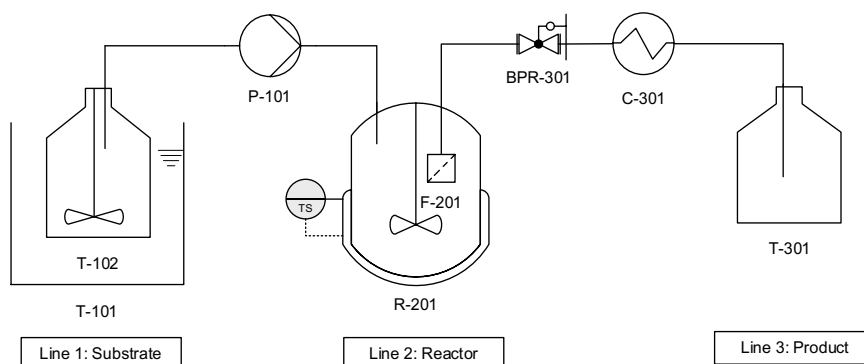


Figure 53: Process flow diagram of the continuous stirred tank reactor setup used in the continuous-flow acetaldehyde self-addition experiments.

Prior to the experiments, the residence time of the continuous stirred tank reactor (CSTR) miniplant setup were determined. The general setup in **Figure 53** was slightly modified and a 6/2-way valve (V-101) from *Shimadzu* model *FCV-20AH2* was installed between the pump P-101 and the reactor R-201. At V-101, a syringe (S-111) with a volume of 100 μL was used to introduce a tracer substance into the sample loop (L-121). Ink was used as tracer, which was first evaporated and dissolved in *MilliQ* water. Excess tracer was collected in vessel T-131. By switching the 6/2-way valve, tracer substance was fed into the reactor (R-201) and through the BPR-301. In order to detect the tracer substance, a UV-VIS detector of a *Shimadzu* HPLC was used (D-301).

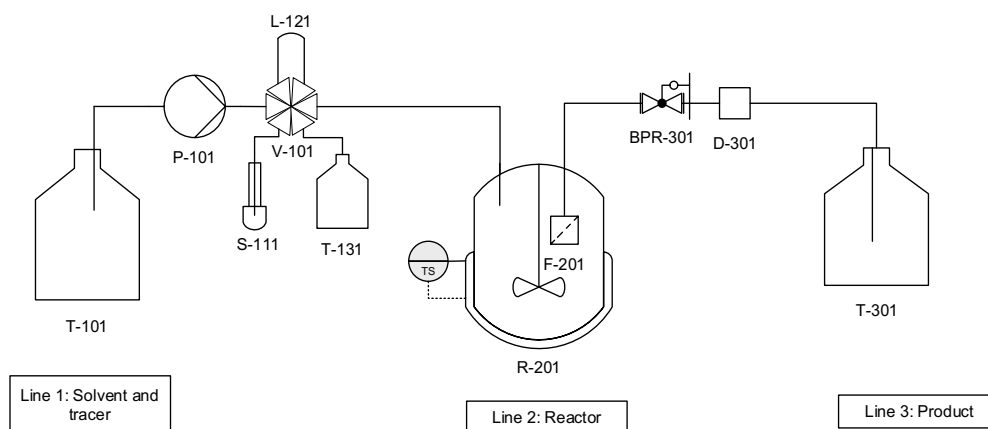


Figure 54: Process flow diagram of the modified CSTR setup to determine the residence-time distribution of the system.

All measurements were performed under reaction temperatures and pressures. For this purpose, the reactor was pre-heated and once reaction temperature was reached, the solution was pumped through the system until it had reached the collection tank T-301. The system was then purged for an additional 15 minutes. Afterwards, the residence time measurement was started by switching the 6/2-way valve through the sample loop and starting the measurement in the *LabSolutions* software.

Residence-time distributions were measured at various flows, ranging from 0.05 to 1.00 mL·min⁻¹. To determine the average residence time of the CSTR setup, the exponential decay of the UV-VIS signal was investigated for the various flows and fitted according to equation (3).^[19]

$$f(x) = y_0 + A \cdot e^{-\frac{x}{\tau}} \quad (3)$$

τ : average residence time in min

To determine the required flow ($\dot{V}$) for a certain residence time (τ) based on the measured data, the formula shown in equation (4) was obtained by power regression.

$$\dot{V} = 26.348 \cdot \tau^{-0.839} \quad (4)$$

$\dot{V}$: flow-rate in mL·min⁻¹

τ : average residence time in min

7.5 Hydrogenation of acetoin to 2,3-BDO

Hydrogenation of acetoin to 2,3-BDO was carried out using various homogeneous as well as heterogeneous catalyst. Also, the gas-phase continuous-flow hydrogenation of acetoin to 2,3-BDO was investigated using a slightly modified version of the PFR miniplant originally conceptualized for the double dehydration of 2,3-BDO to BD. This chapter describes the general procedure of the experiments. All information regarding the design, safety and operating procedure of the miniplant can be found elsewhere in this work (see Chapter 4).

7.5.1 General procedures for 10 mL and 20 mL autoclave reactors

Batch hydrogenation reactions using homogeneous and heterogeneous catalysts systems were carried out in 10- and 20-mL finger autoclaves respectively (**Figure 55**). The autoclaves were made of stainless steel (material number 1.4571) by the mechanical workshop of the *Max Planck Institute for Chemical Energy Conversion*, Stiftstr. 34-36, 45470 Mülheim an der Ruhr. Experiments were carried out in borosilicate glass inlets equipped with a magnetic stir bar, to minimize the effects of the reaction on the autoclave material. After each experiment, glass inlets were thoroughly cleaned and replaced if necessary.

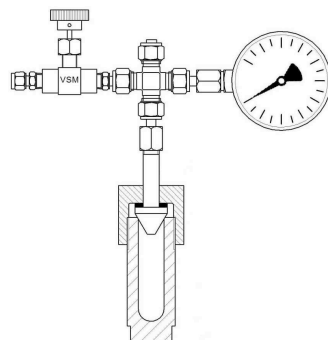


Figure 55: Profile drawing of the finger autoclaves used for batch hydrogenation experiments.

For homogeneously catalysed hydrogenation reactions with or without additives, catalyst, ligand and additive were weighed into the borosilicate autoclave inlet inside an Ar filled glovebox. Substrates and solvents were added outside the glovebox through a valve at the top of the reactor while applying Ar counterflow from the Schlenk-line using the autoclave's needle valve. Reactions were conducted with a total liquid volume of 3 mL.

Heterogeneously catalysed experiments were carried out in 20 mL autoclaves and the catalyst was weighed directly into the borosilicate glass inlet if catalyst was reported to be stable in air. Substrates and solvents (if applicable) were also added directly into the glass inlet. Reactions were conducted on a 5-10 mL scale. In case of air- and moisture-sensitive catalyst materials (e.g. Ru/SILP) catalyst was weighed into the autoclave inlet inside an Ar filled glovebox. Substrates and solvents were added to the reactor outside of the glovebox in Ar counterflow from the Schlenk-line.

Pressurisation with H₂ was carried out on a *Maximator* pressure station. Autoclaves were heated in preheated aluminium cones, fitted on stirring hotplates. After completion of the reaction, the autoclaves were placed in a water bath for cooling. Remaining gas was carefully vented and postreaction solution was retrieved using a syringe and passed through a syringe filter (0.45 µm), prior to analysis in GC-FID with mesitylene as internal standard.

7.5.2 General procedures for 150 mL and 300 mL Parr Instrument Reactors

Hydrogenation of the reaction mixture obtained after a continuous-flow experiment using **IM-NHC5-PF₆** was carried out in a 150 mL or 300 mL stainless steel reactor supplied by the *Parr Instrument Company* (Figure 56)

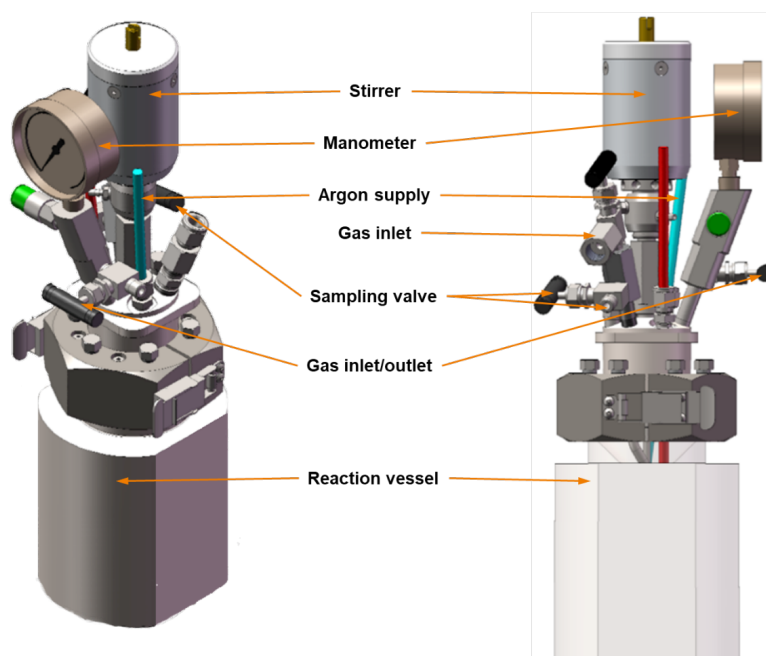


Figure 56: Schematic representation of the *Parr* reactors used for batch hydrogenation reactions. Important features of the reactor are labelled accordingly.

Based on the amount of substrate containing stock-solution, the catalyst was weighed into the reaction vessel. Usually, between 2.5 and 10wt% of catalyst was used. The reactor was pressurized with about 20 bar of H₂ once and the pressure was slowly released again to remove air from the reactor to avoid unwanted oxidation reactions of the acetoin. Afterwards, the reactor was heated to the reaction temperature of 100 °C using a heating jacket and 200 rpm of stirring. Both the heating jacket and the overhead stirring motor were controlled using a *Parr 4848 Reactor Controller*. Once the reactor had reached reaction temperature, H₂ was applied and a system pressure $p = 100$ bar was set on the *Maximator* pressure station. Stirring speed was increased to 1500 rpm. This marked the beginning of the reaction. Reactions were carried out until all of the acetoin had been converted to 2,3-butanediol which was determined from intermittent samples taken in regular intervals from the sampling valve. Samples were analysed using GC-FID. Depending on the amount of substrate containing stock-solution and the amount of residual head-space gas-volume of the reactor, this was usually between 7 and 24 h. During sampling, stirring of the reactor was reduced to 200 rpm. Solid catalyst particles were prevented from exiting through the sampling tube by installing a 4.0-micron filter at the end of the sampling dip-tube, custom made by *Parr Instrument Company*.

After completion of the experiment, the reactor was allowed to come to room temperature, the heating jacket was removed and the pressure was vented. The product containing liquid phase was decanted and the residual, wetted catalyst phase was separated from the remaining product containing liquid phase by centrifuging for at least 20 minutes using a *Hettich Rotofix*

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46 centrifuge. Afterwards, the product was removed from the catalyst *via* a syringe. In case of recycling of the catalyst, new substrate containing solution was added to the reactor and the catalyst was washed into the reactor with fresh substrate containing solution. The reaction was then carried out as usual.

7.5.3 Continuous-flow gas phase hydrogenation of acetoin

Continuous-flow gas phase hydrogenation reactions were carried out in the PFR miniplant, originally designed for the (double) dehydration of 2,3-BDO to BD (see Chapter 4)

In order to perform the gas phase continuous-flow hydrogenation reactions, the miniplant was slightly modified. For the hydrogenation reactions in a pressureless system, a custom-made circular glass reactor of 52.0 cm in length, $\varnothing = 20.0$ mm in diameter and a wall thickness of 1.6 mm with a G3-frit (16–40 μm pores) at 31.5 cm from the top of the reactor was used. Catalyst was filled on top of the frit. If not stated otherwise, in a usual single bed reaction, to prevent disruption of the catalyst bed, 5.0 g glass beads (*Hecht Assistent*, 1.0 mm) were placed on top of the catalyst. After filling the catalyst and glass beads into the reactor, the glass reactor was placed inside the vertical tube furnace and the stream of H_2 was initiated. After performing a leak check, the system was heated to the desired reaction temperature, usually 150 °C. Once the reaction temperature had been reached and maintained for at least 30 minutes, the flow of substrate was initiated. This marks the start of the experiment and a catalyst time-on-stream of $\text{TOS} = 0$ h. Gaseous product stream was passed over a single coil cooler. Liquid products were collected from a flask at the bottom. If not stated otherwise, samples were collected every hour from the liquid collection flask. Conversions and yields were determined *via* GC-FID using mesitylene as internal standard.

In case of multi-day experiments, H_2 stream as well as substrate feed was terminated after the first experimental day and the reactor was allowed to slowly come to room temperature. The reactor was then flushed with Ar for 15 minutes and left to stand over Ar for the night. The next day, the reactor was heated to the desired reaction temperature before starting the flow of H_2 and educts.

Upscaling reactions as well as commercial catalyst reactions were carried out under pressure using the same miniplant, but changing the glass reactor for a stainless steel 1/2" *Swagelok* pipe. In order to maintain a certain pressure in the system, a back-pressure regulator (BPR, *GENTEC® R72SL* 0–17 bar inlet pressure) was used to control the pressure of the system. Experiments were usually carried out at a system pressure of up to $p = 10$ bar. The desired amount of catalyst was weighed and filled into the reactor. Commercial catalyst samples from were ground into a fine powder. The catalyst bed was held in place between two small plugs of glass wool. The initiation of the reaction was the same as for the pressureless hydrogenation experiments carried out in a glass reactor. If not stated otherwise, catalytic tests were carried out using a single bed of catalytically active material without any filling material for a duration of 5 h TOS. Downstream of the BPR, liquid products were condensed using a single coil cooler and collected at the bottom of the cooler. If not stated otherwise, samples were collected every hour. Conversions and yields were determined *via* GC-FID using mesitylene as internal standard.

7.6 Double dehydration of 2,3-BDO to BD

Dehydration experiments of 2,3-BDO were carried out in a miniplant specifically conceptualised and designed for this purpose. More detailed information regarding this miniplant can be found elsewhere in this work (see Chapter 4). Within this chapter, the general procedures for performing (dual bed) catalytic gas phase dehydration reactions are described.

7.6.1 Catalytic dehydration of 2,3-BDO to 3B2OL using various (supported) REOs

Continuous-flow single bed catalytic dehydration reactions of 2,3-BDO to 3B2OL were performed in a custom-made circular glass reactor with a G3-frit (16–40 μm pores) to hold the solid oxide catalyst bed in place. The reactor was 52.0 cm in length with a diameter of $\varnothing = 20.0$ mm and a wall thickness of 1.6 mm and the frit was positioned at 31.5 cm from the top of the reactor. Solid catalyst was directly loaded on top of the frit. If needed, catalyst samples of supported REOs obtained from the group of *Schühle* (Department of Chemical and Biological Engineering, Egerlandstr. 3a, 91058 Erlangen) were ground into a fine powder using pestle and mortar prior to use in catalysis. A small glass wool plug was placed on top of the catalyst bed to avoid disruption. The reactor was placed into the vertical tube furnace and a leak-test of all connections was performed using H_2 as flow-gas. The catalyst bed was heated in H_2 stream to the desired reaction temperature and pre-heated for at least 30 minutes. Afterwards, the flow of substrates was initiated by switching on the pump. Prior to the reaction, it was made sure that the feed pump and all substrate containing capillaries were flushed with substrate. Switching on the feed pump marks the start of the experiment and a catalyst time-on-stream of $TOS = 0$ h. The total mass fed into the reactor was measured by a *Bronkhorst El-FLOW* which was set to reset to 0 (if needed) after the start-up phase of the reactor.

Liquid products were collected from the cold trap at -78°C every hour and analysed using GC-FID. Quantitative analysis was carried out by correlating the corrected signal intensity to the known amount of mesitylene as standard, added after sample collection. Correction factors for 2,3-butanediol and acetoin were determined by calibrating a stock-solution with known concentration. For all non-calibrated side products, the Sternberg method was used to approximate the correction factors.^[247]

After completion of the reaction, the feed pump and tube furnace were shut down and the reactor was allowed to come to room temperature whilst maintaining the flow of H_2 . Afterwards, the reactor was flushed with Ar for at least 15 minutes. The catalyst was retrieved from the reactor and stored for further analysis. After each catalytic reaction, the condenser was cleaned using *i*PrOH and acetone. After removal of the catalyst bed, the reactor was thoroughly cleaned in an ultrasonic bath to remove any traces of solid oxide material in the pores of the G3 frit.

7.6.2 Catalytic dual bed dehydration of 2,3-BDO to BD

The vapour-phase ambient pressure catalytic double dehydration of 2,3-BDO was performed in a fixed-bed downward flow-reactor with two catalyst chambers made of 10.0 cm 3/4" Swagelok pipe each, connected with a 6.5 cm 1/4" Swagelok pipe (see Figure 57).

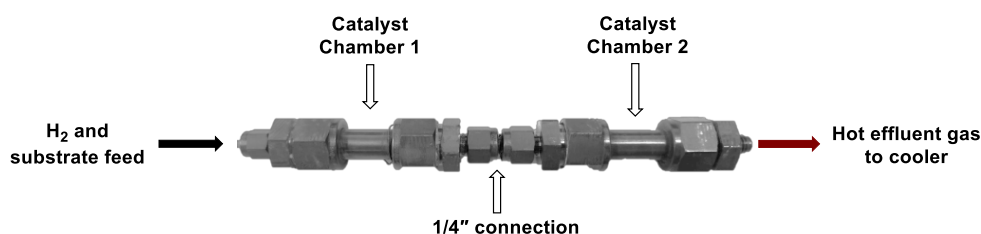


Figure 57: Schematic representation of the dual chamber downward flow reactor, constructed using Swagelok pipes and connection pieces. The reactor is vertically positioned in the tube furnace. Important features of the reactor are labelled accordingly.

The desired catalysts were filled into each chamber separately and secured between two small plugs of glass wool before assembling the reactor. The reactor was placed into the tube furnace and connected to the H₂ and substrate feed-line as well as to the gas cooler. A leak-test of the reactor and all connected parts was performed using H₂ as flow-gas. If needed, connections were tightened until the leak-test had been passed. Afterwards, the reactor and catalyst beds were heated in H₂ stream to the desired reaction temperature and pre-heated for at least 30 minutes. Afterwards, the flow of substrates was initiated by switching on the feed pump. As for the single bed catalytic experiments using the glass reactor (*vice infra*) it was made sure that the feed pump and all substrate containing capillaries were flushed with substrate or substrate-containing stock-solution. Switching on the feed pump marks the start of the experiment and a catalyst time-on-stream of *TOS* = 0 h. The total mass fed into the reactor was measured by a Bronkhorst El-FLOW. At *TOS* = 0 h, the first on-line headspace gas GC-FID measurements was performed. Following this, headspace effluent gas was analysed every 35 minutes (duration of one single measurement) using an online GC-FID (see section 7.2.1 for details). After a typical duration of 10-15 on-line GC measurement cycles, the experiment was terminated and the condensable liquid products were collected from the cold trap at -78 °C. Mesitylene was added to the samples and serves as standard to determine the amount of collected liquid products. Quantitative analysis was carried out by correlating the corrected signal intensity to the known amount of standard. Correction factors for 2,3-butanediol and acetoin were determined by calibrating a stock-solution with known concentration. For the non-calibrated side products, the Sternberg method was used to approximate the correction factors.^[247] Unless stated otherwise, the conversion was averaged for the whole duration of the experiment. In case of obtaining two distinct phases from the cold trap, both phases were analysed separately.

For experiments ranging over one day, the feed of substrate was terminated at a time after injecting a headspace GC measurement. Afterwards, the oven was shut down as well and the reactor was allowed to slowly come to room temperature, while maintaining a flow of H₂. After the reactor had completely cooled down in H₂ stream, the miniplant was flushed with Ar for at least 15 minutes and kept under Ar overnight. On the next day, the reaction was started again as described above.

If not stated otherwise, conversions, yields and selectivities were calculated using the carbon-based 100% method, assuming negligible amounts of carbon deposition during the experiments. The conversion (X) of 2,3-BDO is calculated as:

$$X = \frac{n(2,3\text{-BDO, in}) - n(2,3\text{-BDO, out})}{n(2,3\text{-BDO, in})} \cdot 100\text{mol\%} \quad (5)$$

$n(i)$: molar amount of compound i

where $n(2,3\text{-BDO, in})$ is calculated from the read-out value of the *Bronkhorst EL-FLOW* and $n(2,3\text{-BDO, out})$ is determined from quantitative GC-FID analysis of the collected liquid sample. In order to ensure maximum condensation of liquid products from the gas stream exiting the reactor, a double helix cooler setup was installed. Based on the amount of $n(2,3\text{-BDO, in})$ and quantitative analysis of the liquid products, the amount of moles of carbon in the gaseous products can be calculated:

$$n_c(\text{gas}) = n_c(2,3\text{-BDO, in}) - n_c(\text{liq.}) \quad (6)$$

$n_c(i)$: molar amount carbon in i

Using the corrected GC-FID areas of the headspace measurement, with BD as reference for the *Sternberg* method, the moles of carbon in the products identified in headspace GC-FID measurements can be calculated. Following this, the selectivity of the identified products in headspace gas is calculated as:

$$S(i) = \frac{n_c(i)}{X \cdot n_c(2,3\text{-BDO, in})} \cdot 100\text{mol\%} \quad (7)$$

$S(i)$: selectivity of component i in mol%

$n_c(i)$: molar amount of carbon component i

X : conversion in mol%

$n_c(2,3\text{-BDO, in})$: molar amount of carbon in the 2,3-BDO feed

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Appendix

A1. Miniplant P&IDs

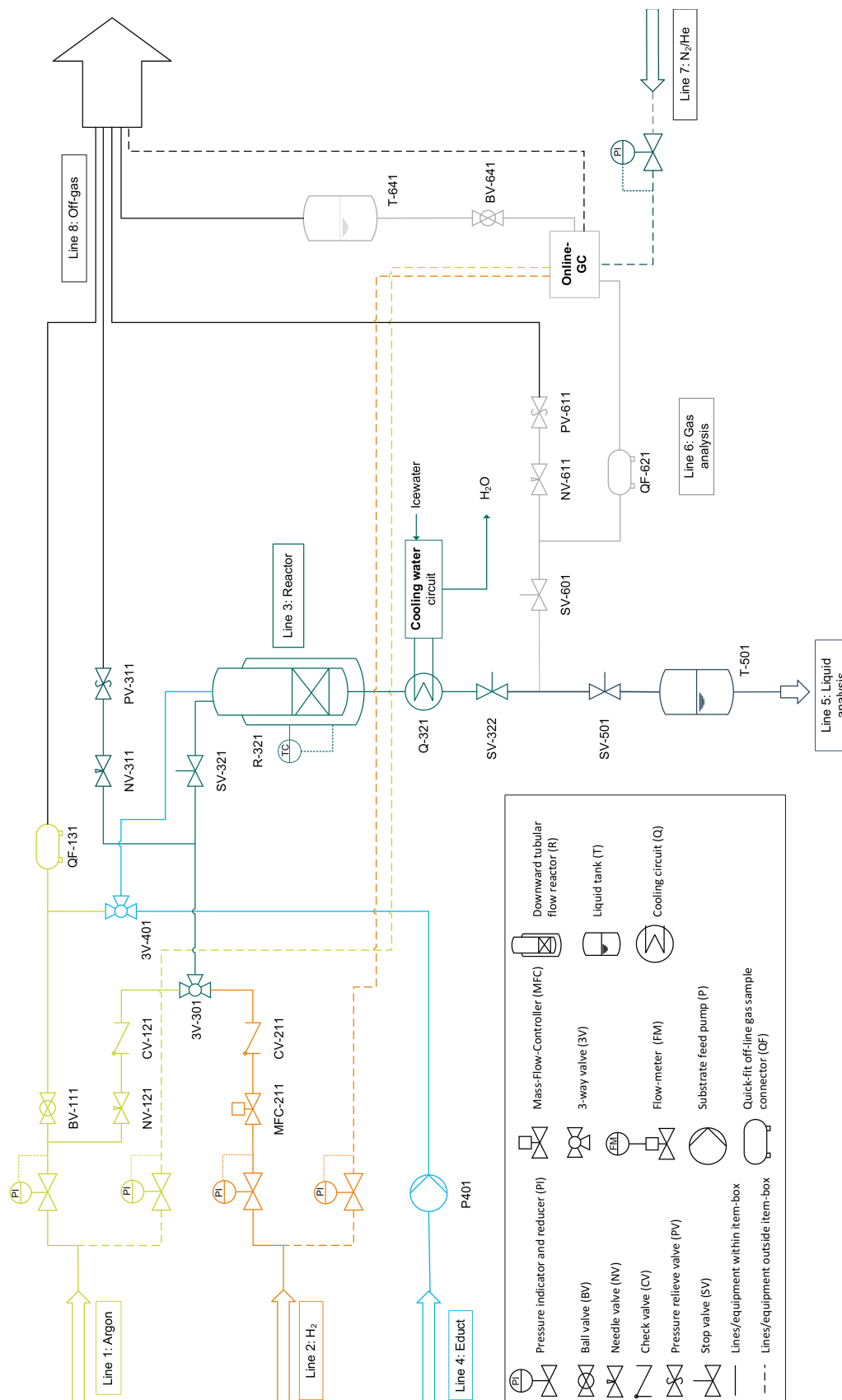


Figure A 1: Initial version of the P&ID of the BD miniplant conceptualised for the continuous ambient pressure flow (dual bed) dehydration of 2,3-BDO to BD as constructed in collaboration with *J. Mannschott*.

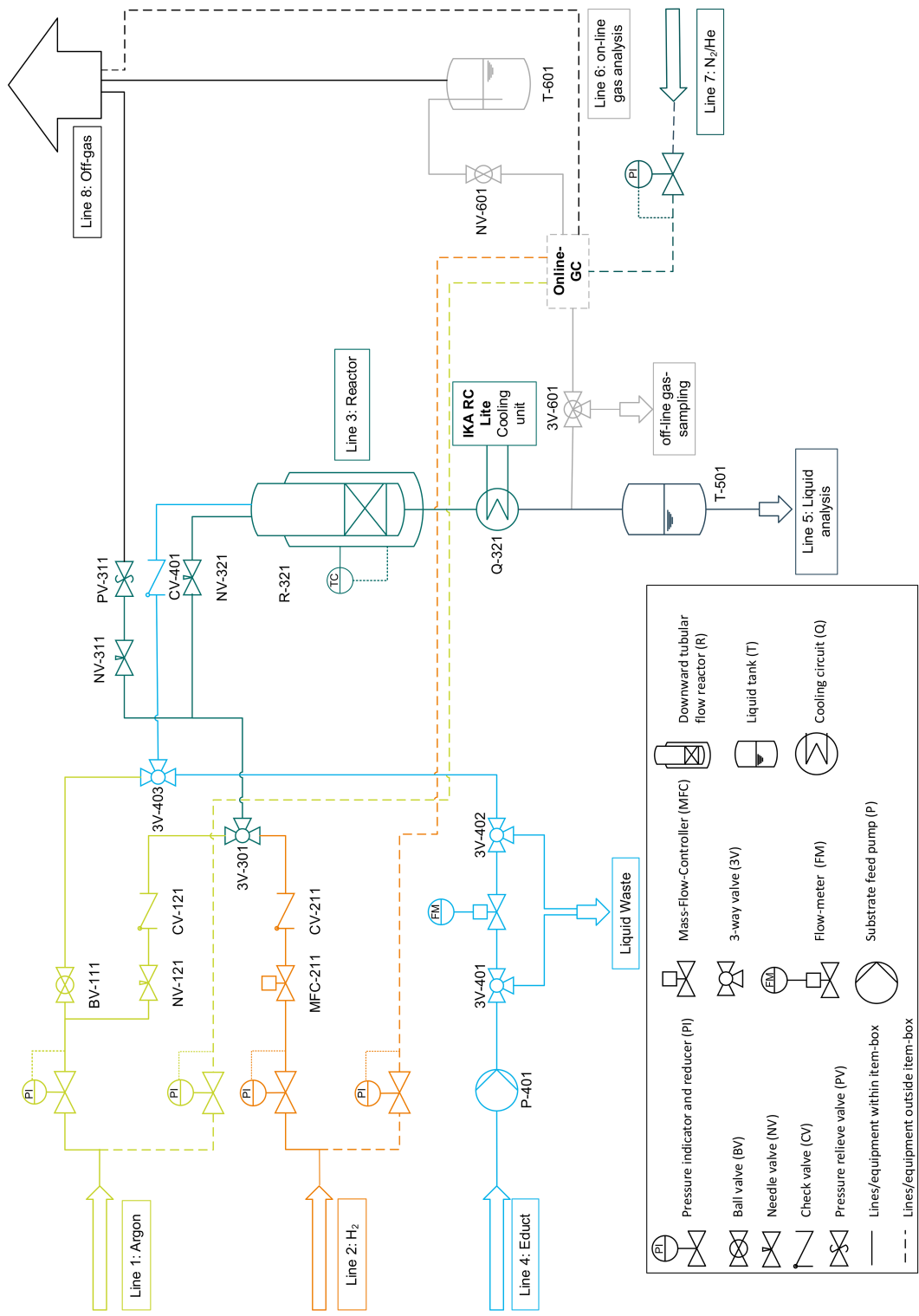


Figure A 2: Final version of the P&ID of the BD miniplant used in the continuous ambient pressure flow (dual bed) dehydration experiments using 2,3-BDO as feedstock H₂ as feed gas with on-line headspace GC-FID analysis.

A2. Miniplant Hazard and Operability Study (HAZOP)

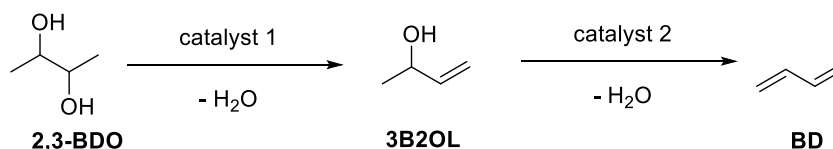
A so-called *Hazard and Operability Study* (HAZOP) is a methodological approach to identify possible problems during the operation of the miniplant. HAZOP is one of the most widely-used approaches in process industries to identify hazards and involves the planning of appropriate safety measures prior to construction.^[269]

In order to perform a HAZOP study, it is necessary to divide the miniplant P&ID into a number of discrete modules or lines. In this particular instance, eight distinct lines serving different functionalities were identified, as illustrated in the P&ID of the miniplant. Subsequently, an analysis of each line is conducted in four stages. First, the normal operating state of the module is described, and potential deviations are defined. In order to achieve this, a variety of parameters (e.g. temperature, pressure, flow, fill level, etc.) are subjected to analysis using a range of guide words (e.g. inverse-flow, high-flow, and no-flow). Once a deviation has been identified, the underlying cause is analysed. At this stage, any existing countermeasures are excluded. The third step is to estimate the potential consequences of the deviation from standard operating mode, again without considering any existing countermeasures. Finally, the aim is to identify potential countermeasures that could either prevent the scenario from occurring or minimise the damage to the miniplant.^[269]

A3. Results of the HAZOP

Process description

The miniplant will be primarily used to study the dual bed catalytic dehydration of 2,3-BDO to BD according to the following reaction schematics:



Possible side products include, but are not limited to: methyl-ethyl-ketone (MEK), *iso*-butyraldehyde (IBA), butyraldehyde, butanols, *iso*-butene, butenes and acetoin.

Reaction conditions:

- flow-speed(H_2) = $80 \text{ mL} \cdot \text{min}^{-1}$
- flow-speed(2,3-BDO) < $0.036 \text{ mL} \cdot \text{min}^{-1}$
- $T_{\text{oven}} = 320 \text{ }^\circ\text{C}$
- $p = 1 \text{ bar}$
- $t = 5\text{-}10 \text{ h}$
- $T_{\text{quencher}} = -10 \text{ to } 8 \text{ }^\circ\text{C}$ (depending on the type of cooler used)

The reaction will proceed stepwise in two different catalyst beds, using small glass-wool plugs on top and between the beds to facilitate separation. The whole system will run at isothermal conditions for a various amount of time using various flow-rates of H_2 as flow/carrier gas and 2,3-BDO as liquid substrate.

Though originally designed for the 2,3-BDO dual bed dehydration, the design of the miniplant also offers room to carry out the gas-phase continuous-flow hydrogenation reactions of acetoin to 2,3-BDO using H_2 as flow-gas and substrate. For these reactions, the the glass reactor is exchanged for a pressure resistant steel one, and a back-pressure regulator is installed after the reactor, prior to the cooler, to facilitate a decompression of the reaction mixture and ensure a certain elevated system pressure.

Line 1: Argon

- Inert-gas supply for miniplant

Line 2: H_2

- Supply of H_2 as flow-gas, controlled by a Mass-Flow-Controller
- Flow speed is controlled from the *Bronkhorst FlowSuite*

Line 3: Reactor

- Control of addition of substrates and flow-gases through extra valves
- Quencher installed after the reactor to quickly cool down the reactor gases

Line 4: Educt

- Addition of educts to the reactor using an appropriate pump
- Flow of educt separately measured using a *Bronkhorst EL-FLOW*

Line 5: Liquid analysis

- Collection tank installed after Line 3: Reactor
- Cooled in *i*PrOH/dry-ice at -78 °C in the final stage of the miniplant
- Allows for sampling/collecting of liquid products for various catalyst time-on-stream

Line 6: On-line gas analysis

- Headspace gas-analysis using an on-line GC-FID instrument
- Collection of samples in gas sampling bags and other custom gas collectors possible (for off-line quantification of effluent gas)
- Gas-treatment using a *Duran pressure plus+* bottle where gas is bubbled through water prior to being fed into off-gas line (line 8)

Line 7: N₂/He

- Supply of gases for the on-line GC-FID instrument

Line 8: Off-gas

- all gas-containing lines of the miniplant are fed directly into an exhaust line, connected to the ventilation system installed onto the miniplant enclosure (item box)

Operating Limits and Background Data:					
	Line number in P&ID				Container or vessel
	1	2	3	4	
$T_{\max}$ / °C	Room temperature	Room temperature	300-400	Room temperature	
$T_{\min}$ / °C	Room temperature	Room temperature	Room temperature	Room temperature	
$p_{\max}$ / bar	10	10	1.3	10	
$p_{\min}$ / bar	1	1	1	1	
Contents of line or vessel	Ar	H ₂	H ₂ , Ar, 2,3-BDO, catalyst 1, catalyst 2, glass wool, BD, MEK, IBA, butyraldehyde, butanols, <i>iso</i> -butene, butenes and acetoin	2,3-BDO, Ar	

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	Line number in P&ID				Container or vessel
	5	6	7	8	
$T_{\max} / ^\circ\text{C}$	Room temperature	Room temperature	300-400	Room temperature	
$T_{\min} / ^\circ\text{C}$	Room temperature	Room temperature	Room temperature	Room temperature	
$p_{\max} / \text{bar}$	10	10	1.3	10	
$p_{\min} / \text{bar}$	1	1	1	1	
Contents of line or vessel	H ₂ O, BD, BD-polymers, acetoin, MEK, IBA, butanols, 3B2OL	BD, MEK, IBA, Butene, Butyraldehyde, H ₂ , Ar	N ₂ , He	H ₂ , Ar, BD, MEK, IBA, butenes, butyraldehyde, N ₂ , He	

Checklist for operability	Line number indicated on P&ID												Container or Vessel		
	1			2			3			4					
Problem? Tick yes/no If yes-complete HAZOP noting form	Yes	No	Ref. no	Yes	No	Ref. no	Yes	No	Ref. no	Yes	No	Ref. no	Yes	No	Ref. no
HIGH FLOW		X			X		X		3.1		X				
LOW FLOW		X			X		X		3.2	X		4.1			
NO FLOW		X			X		X		3.2	X		4.1			
REVERSE FLOW	X		1.1	X		2.1		X			X				
HIGH LEVEL		X			X		X		3.3		X				
LOW LEVEL		X			X			X		X		4.2			
NO LEVEL		X			X			X		X		4.2			
HIGH PRESSURE	X		1.2	X		2.2	X		3.4		X				
LOW PRESSURE		X			X			X			X				
VACUUM		X			X		X		3.5		X				
HIGH TEMPERATURE		X			X		X		3.6		X				
LOW TEMPERATURE		X			X			X		X		4.3			
PROPERTY CHANGE (pH, density, viscosity)		X			X		X		3.1	X		4.4			
COMPOSITION CHANGE		X		X	X		X		3.3		X				
CONTAMINATION		X			X		X		3.7		X				
PRESSURE RELIEF		X			X		X		3.8		X				
INSTRUMENTATION		X			X		X		3.9	X					
SAMPLING		X			X			X			X				
CORROSION/EROSION		X			X		X		3.10	X					
DEAD ENDS		X			X			X			X				
SERVICE FAILURE		X		X		2.3		X	3.11	X					
PROTECTION PHILOSOPHY		X			X			X			X				
MAINTENANCE		X			X			X			X				
IGNITION		X		X		2.4	X		3.7		X				
SPARE EQUIPMENT or spares		X			X			X			X				
SAFETY		X			X		X		3.12	X					
SHUTDOWN SEQUENCE		X			X			X		X					
EFFLUENT		X			X		X		3.13		X				
POLLUTION		X			X			X			X				
Does the process controller have adequate detecting devices? Should any of the abovementioned deviations occur?	No/No														
Are line specifications suitable for temperature, pressure and product?	Yes/Yes*														
Are relief valves for flow and pressure changes?	Yes/Yes														

* No final solution for H₂ detection and automatic shutdown. Therefore, mobile hand-held warning device and operation of the system only under continuous supervision.

APPENDIX

Checklist for operability	Line number indicated on P&ID												Container or Vessel		
	5			6			7			8					
Problem? Tick yes/no If yes-complete HAZOP noting form	Yes	No	Ref. no	Yes	No	Ref. no	Yes	No	Ref. no	Yes	No	Ref. no	Yes	No	Ref. no
HIGH FLOW	X		5.1		X			X			X				
LOW FLOW		X			X			X			X				
NO FLOW	X		5.2	X		6.1		X			X				
REVERSE FLOW		X		X		6.2		X			X				
HIGH LEVEL	X		5.3		X			X			X				
LOW LEVEL		X			X			X			X				
NO LEVEL		X			X			X			X				
HIGH PRESSURE		X		X		6.1		X			X				
LOW PRESSURE	X		5.4		X			X			X				
VACUUM		X			X			X			X				
HIGH TEMPERATURE	X		5.5		x			X			X				
LOW TEMPERATURE		X			X			X			X				
PROPERTY CHANGE (pH, density, viscosity)		X			X			X			X				
COMPOSITION CHANGE		X			x			X			X				
CONTAMINATION	X		5.6		x			X			X				
PRESSURE RELIEF		X			x			X			X				
INSTRUMENTATION		X			x			X			X				
SAMPLING	X		5.7	X		6.3		X			X				
CORROSION/EROSION		X			X			X			X				
DEAD ENDS		X			X			X			X				
SERVICE FAILURE		X			X			X			X				
PROTECTION PHILOSOPHY		X			X			X			X				
MAINTENANCE		X			X			X			X				
IGNITION		X			X			X			X				
SPARE EQUIPMENT or spares		X			X			X			X				
SAFETY	X		5.8		X			X			X				
SHUTDOWN SEQUENCE		X			X			X			X				
EFFLUENT		X		X		6.4		X			X				
POLLUTION		X			X			X							
Does the process controller have adequate detecting devices? Should any of the abovementioned deviations occur?	No/No														
Are line specifications suitable for temperature, pressure and product?	Yes/Yes*														
Are relief valves for flow and pressure changes?	Yes/Yes														

* No final solution for H₂ detection and automatic shutdown. Therefore, mobile hand-held warning device and operation of the system only under continuous supervision.

Ref. No	Guide words or failure mode	Causes / underlying reasons which led to the failure mode (Point out the primary and secondary causes as applicable)	Incident detector (How does the operator know there is a deviation or danger?)	Design protective devices (trips, alarms, guards, instructions, design criteria or specific standard use)	Potential effect if designer's protection fails as described in manual	Action taken to reduce hazard to acceptable limits (state who must take action)
1.1/2.1	REVERSE FLOW	Downstream pipes have a higher pressure → backflow system gas	-	Check Valve RV-121 RV-211	Contamination of the purge gas Ar / flow gas H ₂	-
1.2/2.2	HIGH PRESSURE	Gas supply → pressure in system too high, or pressure build-up over catalyst beds	Pressure gauge	Pressure relief PV-311 PV-611	Glass bevels are pulled apart, glass breaks, tubes burst off	Set Pressure relief valve correctly using dosing valves, but do not close completely
2.3	SERVICE FAILURE	Power failure	Status LED	EL_FLOW MFC normally closed	Unregulated gas flow into the system → HIGH FLOW in Line 3	-
2.4	IGNITION	Combustible gas is introduced	-	Inert in normal operation, oxygen can only be in the line during the start-up process → Warm-up phase	Explosive mixture on the filament of heating mantle / tubular furnace	-
3.1	HIGH FLOW/ PROPERTY CHANGE	Substrate is added too quickly → condensate does not form, no reaction (cooling capacity is not sufficient because heat transfer is too low)	- Syringe pump display - Syringe pump - HPLC Pump - EL-FLOW	- Setting the pump - Glass wool - Intensive cooler - Ice water	HIGH PRESSURE in Line 3 because reactant clumps in catalyst	Increase cooling rate
3.2/3.1	LOW/NO FLOW	Gas flow in the reactor too low	Pressure relief valve in Line 3 PV-311	Pump adjustment, glass wool - P-401	Substrate/product phase is not removed from the reactor and clogs the downstream lines	-
3.3	COMPOSITION CHANGE	Without H ₂ catalyst bed might clump when using other gases	Discolouration of the catalyst after reaction	-	- HIGH PRESSURE in Line 3 - Avoid coking of catalyst	-
3.4	HIGH PRESSURE	Gas volume supplied cannot be discharged	Pressure relief valve PV-311	Pressure relief valve -PV-311	Bursting glass appliances, clamps on glass appliances slip apart	Miniplant enclosure serves as shatter protection
3.5	VACUUM	Cooling to room temperature in the sealed state	Pressure relief valve PV-311	Vacuum-proof glass appliances	Bursting glass appliances, clamps on glass appliances slip apart	Miniplant enclosure serves as shatter protection

APPENDIX

Ref. No	Guide words or failure mode	Causes / underlying reasons which led to the failure mode (Point out the primary and secondary causes as applicable)	Incident detector (How does the operator know there is a deviation or danger?)	Design protective devices (trips, alarms, guards, instructions, design criteria or specific standard use)	Potential effect if designer's protection fails as described in manual	Action taken to reduce hazard to acceptable limits (state who must take action)
3.6	HIGH TEMPERATURE	-Heater can heat higher than the respective ignition temperatures -Hoses and plastic clamps can melt -Risk of burning above the heating jacket -Effluent gas does not condense	-Temperature controller -Clamps -Condensate on the inside of the quencher	-Temperature sensor for reactor and heating jacket -temperature limitation -Mobile infrared thermometer -Ice water cooling	-Screw threads wear out -ignition temperatures can be reached -Effluent gas condenses in the gas analysis line and blocks the line	-Set temperature limits -Only use plastic hoses at lower temperature points and observe maximum operating temperature -Do not install valves above the heating jacket
3.7	CONTAMINATION/ IGNITION	Contamination with oxygen can form an ignitable atmosphere	-	Circuit breaker	-	Put under inert gas
3.8	PRESSURE RELIEF	In the event of overpressure, system gas is fed into the exhaust air via the two pressure relief valves	Pressure relief valve PV-311 and PV-611	Pressure relief valve PV-311 and PV-611	HIGH PRESSURE in Line 3	-
3.9	INSTRUMENTATION	Misinterpreting the syringe pump display (units)	-	-	HIGH FLOW in Line 3	-
3.10	CORROSION/EROSION MAINTENANCE	Reaction mixture and temperature attack grinding grease and screw connection	Visually due to discoloration on glass, ground joints and hoses	-As few greased valves as possible -PTFE gaskets	-Leakage -Discoloration on hoses -By-product formation	Regularly wipe PTFE seals and clean glass joints
3.11	SERVICE FAILURE	Power failure	State of Duran pressure plus+ bottle	No power switches off all devices → No reactant supply	Hot reactor is no longer supplied with flow gas	-
3.12	SAFETY	-Glass wool in the reactor -Leakage in the reactor cover	-Gas alarm (mobile) -Leak detector (mobile)	-mobile gas detector in item box -personal protective mask for filling/emptying the reactor	-Leakage -Itching on skin -Breathing difficulties	Replace seal in the reactor cover regularly and check again for leaks
3.13	EFFLUENT	Reaction mixture leaks from syringe pump	-	-steel syringe, suction Shut-off valve	-	Only screw on the syringe when the valve is closed
4.1	NO FLOW	-Formation of solids in reactant -Too high viscosity of the reactant -Leakage -Piston pushes into the syringe barrel jacket at an angle	-no uniform droplet formation -there is liquid on the piston	-Larger cables -Heat gun -Sealing rings -Tie wrap and mini lifting platform	-substrate solidifies in syringe and in pipes -educt does not pass through the system	-Only fill the syringe with pure substrate after several hours in a 60°C heating oven, preheat syringe -Clean the educt line regularly -Replace sealing rings regularly

Ref. No	Guide words or failure mode	Causes / underlying reasons which led to the failure mode (Point out the primary and secondary causes as applicable)	Incident detector (How does the operator know there is a deviation or danger?)	Design protective devices (trips, alarms, guards, instructions, design criteria or specific standard use)	Potential effect if designer's protection fails as described in manual	Action taken to reduce hazard to acceptable limits (state who must take action)
4.2	LOW/NO LEVEL	Syringe runs dry	Adhesive tape markings on syringe plungers	Adhesive tape markings	Syringe pump malfunction	-Regularly check the level of the syringe and refill manually if necessary
4.3	LOW TEMPERATURE	-Ambient temperature too low	Thermometer	Germ-free filling of the syringe	Crystallization of the reactant	-
4.4	PROPERTY CHANGE	-Crystallization of the reactant	-no uniform drop rate	See 4.3 LOW TEMPERATURE	See 4.1 NO FLOW	See 4.1 NO FLOW
4.5	SAFETY	Refill educt syringe and valve not closed	Noise in syringe pump block	Check position of valve 3V-401	Gas contact and reactant reverse flow	-
5.1	HIGH FLOW	Gas does not condense out and is led past the liquid outlet, no sufficient heat transfer	-Liquid in the gas pipe in Line 3 -No condensate above the drain valve	-Intensive cooling/quench -Ice water cooling	Blockage in the pipe results in overpressure leading to HIGH PRESSURE in 3.4	-
5.2	LOW FLOW	-Gas flow too low -Clogged reactor	State of Duran pressure plus+ bottle	-	Liquid remains in the reactor	-
5.3	HIGH LEVEL	High Flow 5.1, condensate can overflow	Optical, condensate level	Liquid drain valve	Gas analysis line blocked (Line 6)	Regular draining
5.4	LOW PRESSURE	No pressure difference in the valve of the liquid outlet	Liquid does not sink through the drain in the valve	Septum cannula screw cap: draw up system gas with syringe to suck liquid under valve	No liquid sample can be taken	Replace septum regularly
5.5	HIGH TEMPERATURE	No condensation of the liquid	Optical detection by the operator	Ice water-cooled intensive cooler	Blocked gas pipe because liquid condenses elsewhere	-
5.6/5.7	CONTAMINATION/SAMPLING	Contaminated cannula	-	Disposable cannulas	Liquid sample contamination	Use waste garbage cans
5.8	SAFETY	Leaking septum during sampling	Liquid sinks automatically below the valve outlet	-	Gas contact possible	Replace septum regularly
6.1/6.3	NO FLOW/HIGH PRESSURE/SAMPLING	Gas sampling/liquid sampling	State of Duran pressure plus+ bottle	Second overpressure bubbler behind reactor	Glass breakage due to gas back pressure	Miniplant enclosure serves as shatter protection
6.2	REVERSE FLOW	Potential difference between Duran pressure plus+ bottle and online GC	Liquid level of Duran pressure plus+ bottle	Shut-off valve	Liquid in headspace gas GC Line 6	Close the shut-off valve at the end of the test
6.4	EFFLUENT	Condensate containing solvent	-	Personal protective equipment (PPE), extraction system	-	Professional disposal
6.5	SHUTDOWN SEQUENCE	-Relays of the online GC not closed -Close shut-off valve SV-641 between online GC and Duran pressure plus+ bottle	-PC -optical detection by the operator	-PC -Shut-off valve SV-401 -Relays to GC	-Accumulation of plant gas -Water in online GC -Condensable liquid (by-) products in GC lines	-

APPENDIX

Ref. No	Guide words or failure mode	Causes / underlying reasons which led to the failure mode (Point out the primary and secondary causes as applicable)	Incident detector (How does the operator know there is a deviation or danger?)	Design protective devices (trips, alarms, guards, instructions, design criteria or specific standard use)	Potential effect if designer's protection fails as described in manual	Action taken to reduce hazard to acceptable limits (state who must take action)
8.1	SERVICE FAILURE	Power failure	Mobile gas warning device alarm sounds	-Emergency unit -enclosure of miniplant (item box)	System gas is not withdrawn by ventilation and is distributed in the interior of the item box	Keep the door closed until power is restored and ventilation is back online

A4. (X,t) -Profiles of Various Catalysts in the Dehydration of 2,3-BDO to 3B2OL

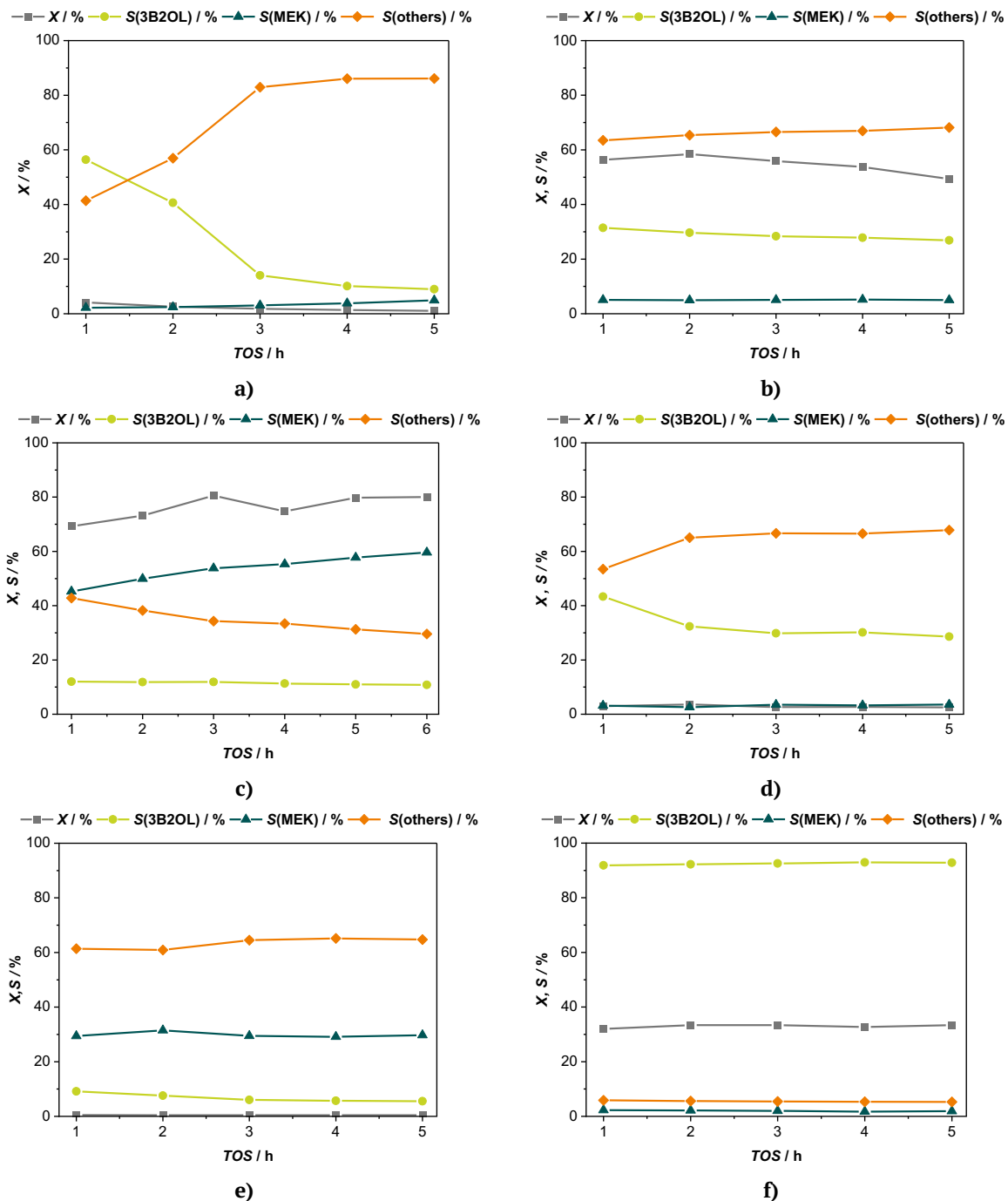


Figure A 3: Catalytic results of various (supported) REOs in the dehydration of 2,3-BDO to 3B2OL using **a)** an In_2O_3 catalyst calcined at 400 °C, **b)** a 7.5wt% $\text{In}_2\text{O}_3/\gamma\text{-Al}_2\text{O}_3$ **c)** a 7.5wt% $\text{In}_2\text{O}_3/\text{TiO}_2$ **d)** 7.5wt% $\text{In}_2\text{O}_3/\text{ZrO}_2$ **e)** 7.5wt% $\text{In}_2\text{O}_3/\text{SiO}_2$ **f)** benchmark experiment using a HT-800- Sc_2O_3 catalyst. Reaction conditions were identical for every experiment: $m(\text{cat}) = 0.5 \text{ g}$, $\text{flow-rate}(\text{H}_2) = 1.8 \text{ dm}^3 \cdot \text{h}^{-1}$, $\text{flow-rate}(2,3\text{-BDO}) = 1.6 \text{ g} \cdot \text{h}^{-1}$, $T = 320 \text{ }^\circ\text{C}$, $\text{WHSV} = 3.2 \text{ h}^{-1}$. Yields determined by GC-FID using mesitylene as standard added after the reaction. No evaluation of headspace gas was carried out. Solid pellets of supported cats were crushed prior to use.