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de Vries, Johannes G.

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Catalytic Conversion of Renewable Resources into Bulk and Fine Chemicals

Johannes G. de Vries^{*,[a,b]}

ABSTRACT: Several strategies can be chosen to convert renewable resources into chemicals. In this account, I exemplify the route that starts with so-called platform chemicals; these are relatively simple chemicals that can be produced in high yield, directly from renewable resources, either via fermentation or via chemical routes. They can be converted into the existing bulk chemicals in a very efficient manner using multistep catalytic conversions. Two examples are given of the conversion of sugars into nylon intermediates. 5-Hydroxymethylfurfural (HMF) can be prepared in good yield from fructose. Two hydrogenation steps convert HMF into 1,6-hexanediol. Oppenauer oxidation converts this product into caprolactone, which in the past, has been converted into caprolactam in a large-scale industrial process by reaction with ammonia. An even more interesting platform chemical is levulinic acid (LA), which can be obtained directly from lignocellulose in good yield by treatment with dilute sulfuric acid at 200°C. Hydrogenation converts LA into gamma-valerolactone, which is ring-opened and esterified in a gas-phase process to a mixture of isomeric methyl pentenoates in excellent selectivity. In a remarkable selective palladium-catalysed isomerising methoxycarbonylation, this mixture is converted into dimethyl adipate, which is finally hydrolysed to adipic acid. Overall selectivities of both processes are extremely high. The conversion of lignin into chemicals is a much more complicated task in view of the complex nature of lignin. It was discovered that breakage of the most prevalent β -O-4 bond in lignin occurs not only via the well-documented C3 pathway, but also via a C2 pathway, leading to the formation of highly reactive phenylacetaldehydes. These compounds went largely unnoticed as they immediately recondense on lignin. We have now found that it is possible to prevent this by converting these aldehydes in a tandem reaction, as they are formed. For this purpose, we have used three different methods: acetalisation, hydrogenation, and decarbonylation. These reactions were first established in the tandem reactions of model compounds, but subsequently, we were able to show that this works equally well on organosolv lignin and even on lignocellulose.

Keywords: biomass, biomass conversion, catalysis, platform chemicals, renewable resources

1. Introduction

Although currently known reserves of fossil resources would be sufficient to cover the world's need for energy and chemicals for the coming 50 years,^[1] and probably much longer than that, it is clear that now is the time to convert to a sustainable economy based on renewable resources. Whereas for renewable energy a range of different resources can be explored, for chemicals we have to orient ourselves to the use of biomass as raw material.^[2] The most abundantly available source of biomass is

lignocellulose, the material that plant cell walls are made from.^[3] At the core of lignocellulose are the highly stable crystalline cellulose fibres, which are encased in lignin, whereas hemicellulose, an amorphous and partially branched carbohydrate polymer made from C5 and C6 sugars, fills up the empty spaces. The largest supplies are in the form of wood, but the waste streams of agriculture (straw, leaves, bagasse, corn stover, empty fruit bunches of palm trees), the paper industry, or even municipal waste are also interesting. In addition, smaller, but still substantial, amounts of raw materials are available in the form of vegetable and animal oils and their constituents, the fatty acids and glycerol, and a number of large-scale chemicals that are obtained by fermentation, such as the amino acids glutamic acid and lysine, and acids, such as citric acid, lactic acid, and succinic acid. Sucrose is particularly interesting as a raw material for fermentation, but it can also be chemically converted, as we will see later. However, sucrose and starch are important food sources and there is societal dislike of their use for the production of fuels (food vs. fuel), although this issue is much less important when it comes down to chemical production.

The chemical community has now been challenged to invent cost-effective methods to convert these raw materials into the chemicals we need to sustain our lives. Here, two strategies can be chosen. One strategy aims to replace current

^[a]Prof. Dr. J. G. de Vries
Department Catalysis with Renewables
Leibniz Institut für Katalyse e. V. an der Universität Rostock
Albert-Einstein-Strasse 29a
18059 Rostock (Germany)
E-mail: johannes.devries@catalysis.de

^[b]Prof. Dr. J. G. de Vries
Stratingh Institute for Chemistry
University of Groningen
Nijenborgh 4
9747 AG Groningen (The Netherlands)
E-mail: j.g.de.vries@rug.nl

Dedicated to Prof. Ryoji Noyori for being an inspiration throughout my scientific career

bulk chemicals by biosimilars (replacement strategy). The advantage is that relatively short routes can be devised from biomass. However, the disadvantage is that market penetration can be extremely slow. An example is the replacement of phthalic acid by 2,5-furan-dicarboxylic acid.^[4] A second strategy aims at so-called drop-ins; these are basically the same bulk chemicals that are currently made from fossil resources. The attraction is that the market is already there and does not need to be developed. The only limitation here is that the cost price should be the same as, or ideally, somewhat lower than, the current fossil-based price. In view of the fact that the price of bulk chemicals is largely dominated by the cost of the raw materials, this is by no means impossible. Biomass, in particular, lignocellulose, is relatively cheap. The next aspect to focus on is the selectivity of the conversion(s) of the raw material into the desired bulk chemical. This is an important aspect that is often neglected. For instance, the fermentation of sugars to (bio)ethanol proceeds with a selectivity of only 40%. It is clear that we can do much better with chemical conversions, although we may need more than one step. For the conversion of lignocellulose into chemicals, a variety of methods have been developed (Scheme 1). The simplest one is pyrolysis;^[5] however, this yields a mixture of compounds that is rather unstable and needs further deoxygenation to be used as fuel. Catalytic pyrolysis methods offer more possibilities, as these can lead to mixtures of hydrocarbons that can be used as the raw materials for today's crackers.^[6] Although this seems very attractive from a hardware point of view, as little needs to be changed, selectivities of these conversions are much too low to be economically interesting.

A second approach is the use of gasification of biomass, which leads to the formation of a mixture of CO and H₂, in addition to CO₂ and some carbon.^[7] The CO/H₂ mixture can be catalytically converted to methanol as is currently done, and methanol can be converted in a process known as methanol-to-gasoline (MTG) to a mixture of hydrocarbons.

Another option is to use the CO/H₂ mixture as raw material for a Fischer–Tropsch process to produce alkenes and/or alkanes. These two options again suffer from relatively low

Scheme 1. Conversion of lignocellulose into chemicals.

selectivity. A number of chemicals can be produced in good yield by fermentation using sucrose or hydrolysed starch as raw materials. Many companies are trying to extend the range of fermentation products, but fermentative production of desirable bulk chemicals, such as adipic acid or caprolactam, fails because of low titres, low production rates, and/or poor selectivity. In addition, the microbiological constructs that are created are relatively weak and easily infected with natural strains.

The strategy which we believe is the most sustainable in the long run is based on the use of a limited number of platform chemicals that can be obtained in high yield from biomass, either chemically or by fermentation. These platform chemicals can be converted in multiple highly selective chemical steps, which will rely, to a large extent, on the use of homogeneous^[8] and heterogeneous catalysis,^[9] into the desired chemicals. In a report published by the U.S. Department of Energy, 12 groups of platform chemicals have been named.^[10] In the meantime, a few more can be added (Scheme 2; additions in red by me).

2. HMF to Caprolactam

A very interesting platform chemical is 5-hydroxymethylfurfural (HMF), which can be made by the dehydration of fructose (Scheme 3).^[11] HMF is not stable in water and is further converted into levulinic acid and formic acid. Use of

Johannes G. de Vries received his Ph.D. from the University of Groningen in the Netherlands in 1979. After a postdoc at Brandeis University, Waltham, USA, his first job was as a medicinal chemist with Sandoz in Vienna and in London. From 1988–2013, he worked for DSM in Geleen, The Netherlands, lastly as a Principal Scientist in the area of homogeneous catalysis. In 1999, he was appointed part-time professor of homogeneous catalysis at the University of

Groningen. In 2014, he commenced a new career as head of the Department of Catalysis with Renewables at the Leibniz Institute for Catalysis in Rostock, Germany. His research interests are in the area of homogeneous hydrogenation, metal-catalysed C–C and C–X bond formation, combinatorial catalysis, nanocatalysis, and catalytic conversion of renewable resources and platform chemicals. He is the recipient of the 2013 Paul N. Rylander Award from the Organic Reactions Catalysis Society.

Scheme 2. Platform chemicals: the new raw materials for the chemical industry.

DMSO or ionic liquids gives good yields in the dehydration, but it is impossible to isolate HMF economically from these reactions. The current best method for its synthesis is in aqueous/organic mixtures, leading to yields around 75%. Avantium has developed the dehydration of fructose in methanol to produce the methyl ether of HMF, which is much more stable than HMF and can be easily isolated.^[12] Mascal and Nikitin have developed the synthesis of 5-chloromethyl-furfural (CMF) by treatment of fructose, glucose, and even cellulose or lignocellulose with concentrated HCl/LiCl using a chlorinated solvent.^[13] CMF can be hydrolysed to HMF or levulinic acid. Avantium has further converted the methyl ether of HMF into dimethyl 2,5-furan-dicarboxylate.^[14] Reaction of this with ethylene glycol leads to the polyester PEF (polyethylene furanoate), which is foreseen as the replacement of PET (polyethylene terephthalate); for instance, in soda bottles.^[4] Converting

Scheme 3. Preparation of HMF from renewable resources.

HMF to other interesting bulk chemicals is a highly active current field of research.^[11,15]

We were interested in converting HMF into caprolactam, the monomer for nylon-6. The carbon count for this conversion is already correct; what remains to be done is the adjustment of the oxidation state and the introduction of the nitrogen atom. We decided to opt for a reductive approach (Scheme 4).^[16] It should be possible to convert HMF into 1,6-hexanediol by hydrodeoxygenation, although this reaction was not really known. In the next step, a double dehydrogenation should lead to the formation of caprolactone. This chemistry was successfully developed by Murahashi for the C4 and C5 diols using $\text{Ru}(\text{H})_2(\text{PPh}_3)_3$ as the catalyst.^[17] The reaction was remarkably accelerated by using acetone as the hydrogen acceptor, and indeed, in this case, it is an Oppenauer oxidation, as acetone is reduced to isopropanol. However, the dehydrogenation of 1,6-hexanediol was not reported in this publication. The final step, the reaction between caprolactone and ammonia to form caprolactam was already known, and indeed, has been used industrially in one of the first caprolactam processes, where caprolactone was obtained via a Bayer-Villiger reaction of cyclohexanone.^[18]

We screened a range of hydrogenation catalysts in an attempt to convert HMF directly to 1,6-hexanediol.^[16] Most reactions gave 2,5-tetrahydrofuran-dimethanol (THFDM) as the major product, but at higher temperatures and pressures, varying amounts of 1,6-hexanediol, 1,5-hexanediol, and 1,2,6-hexanetriol, as well as 1,5-pentanediol were also observed. Best results (4% 1,6-hexanediol) were obtained with a mixture of copper chromite and Pd/C as the catalyst as reported earlier by Utne *et al.* (Scheme 5a).^[19] We assumed that the C5 product was caused by decarbonylation, and for this reason, it seemed prudent to first reduce the aldehyde to prevent this side reaction. In any event, reduction of HMF by Ra-Ni with 90 bar H_2 at 100°C gave a quantitative yield of THFDM (Scheme 5b).^[16]

At this stage, we were helped by a timely publication of Tomishige and coworkers who had reported the highly selective hydrogenation of 2-furyl-methanol to 1,5-pentanediol using a Rh-Re/ SiO_2 catalyst.^[20] Application of this catalyst in the hydrogenation of the very similar 1,5-tetrahydrofuran-dimethanol led to the formation of a mixture of 1,2,6-

Scheme 4. Synthetic plan for the conversion of HMF into caprolactam via a reductive pathway.

Scheme 5. Hydrogenation of HMF.

hexanetriol, 1,6-hexandiol, and 1,5-hexanediol (Table 1).^[21] And although the triol could presumably be further converted, 1,5-hexanediol is an unwanted side product, the formation of which needs to be prevented, as otherwise no economic process can be developed. Luckily, hydrogenation at lower temperatures led to the almost exclusive formation of 1,2,6-hexanetriol, albeit at incomplete conversion. This latter aspect is not really problematic; most bulk chemical processes are run at incomplete conversion of the starting material and the unconverted starting material is simply recycled.

With the conversion of HMF to 1,2,6-hexanetriol secured in good selectivity, the next assignment was its selective conversion into 1,6-hexanediol.^[22] Use of the Tomishige catalyst allowed the hydrogenation of 1,2,6-hexanetriol into a mixture of 1,6- and 1,5-hexanediol (73: 27). Use of other catalysts did not improve matters.

Interestingly, the hydrogenolysis reaction we were attempting is probably not a true hydrogenolysis, but rather a dehydration followed by the hydrogenation of the formed alkene. The dehydration can of course be accelerated by acid catalysis, and we would expect that such a carbonium ion mechanism would strongly prefer the formation of the secondary carbocation, and thus, lead to the formation of the desired product. Surprisingly, attempted hydrogenation of 1,2,6-hexanetriol using Rh-Re/SiO₂ in the presence of 10 mol% trifluorosulfonic acid led to the exclusive formation of tetrahydropyran-2-methanol (2-THPM). Apparently, the hydrogenation catalyst is fully deactivated by the acid. Possibly,

Table 1. Hydrogenation of 1,6-THF-dimethanol.

Entry	T (°C)	t (h)	THFDM conv. (%)	Selectivity (%)		
				1,2,6-HT	1,6-HD	1,5-HD
1	120	4	55	77	15	5
2	120	20	81	61	28	10
3	180	4	83	54	30	15
4	80	20	21	97	0	0

Scheme 6. Ring-closure of 1,2,6-hexanetriol to 2-tetrahydroxyranmethanol and hydrogenolysis thereof to 1,6-hexanediol.

the rhenium is dissolved by the acid, although this aspect was not further investigated. The formation of this new adduct presented new opportunities, as this compound possesses the same cyclic ether-hydroxymethyl motif that was present in tetrahydrofuran-2-methanol and -2,5-dimethanol.

Treatment of 1,2,6-hexanetriol with trifluorosulfonic acid in sulfolane led to the clean formation of tetrahydropyran-2-methanol. This allowed the isolation of this compound in > 99% yield. Subjecting the product to hydrogenation with Rh-Re/SiO₂ indeed led to the exclusive formation of 1,6-hexanediol at 17% conversion (Scheme 6).

Thus, we had finally developed a route from HMF to 1,6-hexanediol with extremely high overall selectivity. Although the selectivities were very good, 4 steps were needed for this conversion, which translates to building 4 large-scale plants. An obvious shortcut presents itself, as we use the same conditions for steps 2 and 4 of this sequence. If we could combine these steps with step 3, the acid-catalysed dehydration, we could reduce the sequence to 2 steps. As we assumed the incompatibility of the acid catalyst with the hydrogenation catalyst is due to dissolution of the rhenium, an obvious solution would be the use of a solid-acid catalyst. We screened 12 different solid-acid catalysts and obtained the best results with the use of NafionTM.^[16] In this case, we were able to achieve 86% selectivity from tetrahydrofuran-2-methanol to 1,6-hexanediol at full conversion (Scheme 7). Although fine-tuning of the reaction conditions should allow further improvement of these results, this selectivity is already good enough to serve as the basis for a bulk chemical process.

Scheme 7. One-step conversion of tetrahydrofuran-2-methanol into 1,6-hexanediol.

Scheme 8. Dehydrogenation of 1,6-hexanediol to caprolactone.

Next, we examined the dehydrogenation of 1,6-hexanediol to caprolactone.^[23] In fact, this is a dehydrogenation, followed by the formation of the cyclic hemiacetal, which is dehydrogenated again (Scheme 8). Initial tests using the conditions of Murahashi with $\text{RuH}_2(\text{PPh}_3)_3$ in the absence of an oxidant resulted in the formation of a multitude of products. Attempting the use of oxygen or air as the oxidant in these reactions did not make things better. However, we found that the Oppenauer oxidation reaction did lead to varying amounts of caprolactone upon testing a number of different heterogeneous and homogeneous redox-active catalysts (Table 2).

Since with acetone as the oxidant the reactions proceeded very slowly, we switched to the use of methyl *iso*-butylketone as the oxidant, allowing the oxidation to take place at higher temperatures without having to resort to the use of pressurised equipment. Use of the heterogeneous catalysts led to slow or poorly selective reactions, and the best results were obtained with a catalyst that was prepared *in situ* from $[\text{Ru}(\text{cymene})\text{Cl}_2]_2$ and a bidentate phosphine. To maximize the selectivity, we tested a range of bidentate phosphines in combination with the ruthenium catalyst precursor (Table 3). This led to the finding that use of 1,1'-bis(diphenylphosphino)ferrocene (dppf) results in complete conversion and full selectivity to the desired caprolactone.^[23]

Table 2. Catalyst screening for the conversion of 1,6-hexanediol into caprolactone.

Entry	Catalyst	Conv. (%)	Sel. (%)
1	—	0	0
2	$[\text{Cp}^*\text{IrCl}_2]_2$	44	33
3	$\text{RuCl}_2(\text{PPh}_3)_3$	31	81
4	Ru/C	—	—
5	Ru/TiO_2	3	90
6	$[\text{Ru}(\text{p-cymene})\text{Cl}_2]_2$ and DPPP ^[a]	54	87
7	RuCl_3 and DPPP ^a	3	90
8	$\text{Ru}(\text{acac})_3$	0	0

[a] DPPP = 1,3-diphenylphenylphosphinylpropane.

Table 3. Ligand screening for the conversion of 1,6-HD into caprolactone.

Entry	Ligand	Yield (%) ^[b]
1	—	0
2	$\text{Ph}_2\text{P}(\text{CH}_2)_5\text{PPh}_2$	74
3	$\text{Ph}_2\text{P}(\text{CH}_2)_4\text{PPh}_2$	70
4	$\text{Ph}_2\text{P}(\text{CH}_2)_3\text{PPh}_2$	79
5	$\text{Ph}_2\text{P}(\text{CH}_2)_2\text{PPh}_2$	88
6	$\text{Ph}_2\text{P}(\text{CH}_2)\text{PPh}_2$	79
7	1,1'-Bis-(diphenylphosphinyl)-ferrocene	100
8	X-Phos ^[a] (1 eq)	54
9	X-Phos ^[a] (2 eq)	71
10	Cy_3P	50
11	Tris(2,4-di- <i>tert</i> -butylphenyl)phosphite	15
12	<i>rac</i> -Monophos ^[b]	29
13	<i>rac</i> -3,3'-Dimethyl-Monophos ^[c]	54

[a] 2-Di-*t*-butylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl. [b] (3,5-Dioxa-4-phosphacyclohepta[2,1-a;3,4-a']dinaphthalen-4-yl)dimethylamine. [c] (2,6-Dimethyl-3,5-dioxa-4-phosphacyclohepta[2,1-a;3,4-a']dinaphthalen-4-yl)dimethylamine.

From the patent literature, we surmised that the industrial process that was used in the past to convert caprolactone to caprolactam proceeded in around 90% selectivity. Thus, the overall selectivity for the process from HMF to caprolactone is 85% and to caprolactam 77%. Once HMF is available on a large scale from lignocellulose, this would obviously be a very good procedure to convert it into this important nylon monomer. In addition, 1,6-hexanediol and caprolactone are important monomers for polyesters in their own right.

3. Adipic Acid from Levulinic Acid

Another even more interesting platform chemical is levulinic acid (LA). LA can be obtained directly from biomass via reaction with dilute (4%) sulfuric acid at 200°C without any pretreatment (Scheme 9).^[24] Reported yields vary between 45% and 83% with respect to the C6 sugars, depending on the source, the temperature, and the type of acid used.^[25,26] Side products are furfural (from the C5 sugars), formic acid, and

Scheme 9. Levulinic acid from agro waste.

Scheme 10. Conversion of bio-based levulinic acid into adipic acid.

humines (a tar-like material). LA is currently produced on the ton-scale by two different companies, GFBiochemicals in Italy^[27] and the Golden Race Group in China,^[28] and is expected to break through as a platform chemical in the next few years. Levulinic acid can be converted into a multitude of other products.^[29] We were interested to find a short and efficient route from levulinic acid to adipic acid. A number of different routes can be envisaged for this conversion. We decided on the route, shown in Scheme 10, which starts with the hydrogenation of LA to γ -valerolactone (GVL).^[30] This can be ring-opened at high temperatures using an acid catalyst to yield an isomeric mixture of pentenoic acids.^[31] If the ring opening is performed in the gas phase, in the presence of methanol, a mixture of isomeric methyl pentenoates is formed.^[32] This opens up two possibilities: either the mixture of acids is subjected to an isomerising hydroxycarbonylation to yield adipic acid directly, or the mixtures of esters is subjected to an isomerising methoxycarbonylation to obtain dimethyl adipate, which now, in an extra step, needs to be hydrolysed to adipic acid. Although the acid route would seem to be preferred on first sight, we decided for the ester route for the following reasons. There is a separation problem in the process in which GVL is converted to the pentenoic acids, as the boiling point of some of the isomeric acids comes very close to that of GVL, making it almost impossible to separate off GVL completely. This problem is not encountered with the esters. The second issue is related to the recycling of the catalyst of the carbonylation step. In the aqueous system, adipic acid is purified via crystallisation from the aqueous product mixture. The question that pops up is what would happen to the relatively lipophilic catalyst, which needs to be recycled: will it remain in the aqueous phase or will it be (partially) attached to the product? Again, this problem cannot occur in the ester process, as here the product is

distilled off and the organic residue containing the catalyst is recycled back to the reactor. Nevertheless, almost simultaneously with our work, the aqueous process was developed by researchers from ICES A-Star in Singapore.^[33]

Hydrogenation of LA has been reported many times.^[34] We found that hydrogenation with Ru/C at (20 bar H₂ and 130°C) gave a virtually quantitative yield of GVL. In addition, we have examined the possibility of a gas phase hydrogenation process using a copper catalyst.^[35] Gas-phase conversion of GVL with methanol over a solid-acid catalyst leads to ring opening with concomitant esterification, resulting in an isomeric mixture of methyl pentenoates. This reaction was reported earlier by BASF,^[32] at DSM we screened a range of solid-acid catalysts to optimize the selectivity. In the end, alumina silicates turned out to be good catalysts for this reaction, and at 220°C, a good overall selectivity of 95% to the mixture of pentenoates was obtained. In this reaction, the acidity of the catalyst had to be finely tuned so as to not produce too much dimethyl ether as a side product. The lifetime of the catalyst could be significantly extended by co-dosing with small amounts of acid, such as methanesulfonic acid.^[36] Presumably this helps to keep the catalyst's surface clean.

Palladium-catalysed isomerising methoxycarbonylation of methyl 3-pentenoate had already been developed earlier by chemists from Shell, BASF, and Dupont, as part of their attempts to convert butadiene into adipic acid.^[37] The best results were obtained using the ligand originally developed by Moulton and Shaw,^[38] and used by ICI (later Lucite), for the methoxycarbonylation of ethylene to methyl propionate *en route* to methyl methacrylate.^[39] The methoxycarbonylation of methyl 4-pentenoate should have been even more facile.^[40] It was the presence of methyl 2-pentenoate in this mixture that worried us, as back in the 1990s we had found, during our research on the development of a new caprolactam process based on butadiene, that methyl 2-pentenoate was a catalyst poison in the rhodium-bisphosphite-catalysed isomerising hydroformylation of methyl 3-pentenoate, slowing down the reaction and leading to the formation of the hydrogenated product. This is due to the increased stability of the metal-alkyl complex in the α -position to the ester functionality. Since a similar intermediate could be formed in the palladium-catalysed methoxycarbonylation, we feared that the presence of this isomer could cause problems.

In any event, methoxycarbonylation of the mixture of methyl pentenoates proceeded very well, and yielded dimethyl adipate (DMA) in 98% selectivity upon use of the Shaw ligand (Scheme 11).^[41] Close to one hundred ligands, mostly bidentate phosphines, were screened, but none led to better results. Methanesulfonic acid was used as the acid in these reactions. However, it was also possible to use Lewis acids instead of Brønsted acids in this reaction, and especially, metal triflates performed well.^[42] We were able to perform

Scheme 11. Isomerising methoxycarbonylation of methyl pentenoates to dimethyl adipate.

this methoxycarbonylation with a substrate/catalyst ratio of 2000, and although the reaction had a turnover frequency of around 165 h^{-1} , our calculations showed that a higher reaction rate was necessary for an economic process. The required rate could easily be obtained by either doubling the palladium concentration or by raising the temperature from 50 to 100°C (Scheme 12a). However, in both cases, the formation of palladium black was observed.

This is a well-known phenomenon in palladium-catalysed reactions. The formation of palladium black is accelerated by high concentrations of palladium, higher temperatures, and high acid and high methanol concentrations. The loss of ligands from a $\text{Pd}(0)$ intermediate leads first to dimers, then to nanoparticles, and eventually, when the palladium crystals exceed a certain size, they will precipitate (Scheme 13). These nanoparticles are still in equilibrium with the monomeric catalyst, and for this reason, it is sufficient to stabilise them with ligands (e.g., by a polar soluble polymer such as poly-vinyl-

pyrrolidinone) to prevent their further growth via Ostwald ripening.^[43] This way, a steric barrier is created between the nanoparticles, preventing their fusion. Tetra-alkylammonium salts can also be used. Here, the anion usually binds to the metal, but the cations form a second layer around the nanoparticles, acting as a charge barrier to further fusion. Although these concepts are very effective, the presence of an extra entity in a bulk chemical process is not very attractive. Additional recycling is needed and the stability of the stabiliser also becomes an issue. Luckily, it was found that the product of the reaction, dimethyl adipate, is an excellent stabiliser for palladium nanoparticles.^[44] Thus, starting the methoxycarbonylation of the methyl pentenoate mixture in the presence of 25 mol% dimethyl adipate allowed both the use of the double concentration of palladium, as well as a reaction temperature of 100°C (Scheme 12b). In addition, the rate of the reaction is accelerated due to the reduced catalyst deactivation.

Hydrolysis of dimethyl adipate under acidic conditions allowed the formation of adipic acid in $> 99\%$ selectivity.

Thus, we have shown that levulinic acid can be converted into adipic acid with an exceptional overall selectivity of 92%. Although long-term catalyst stability of the palladium catalyst still needs to be ascertained, it is clear that this process can easily compete with the current benzene-based adipic-acid process when it comes to variable cost. Two companies are currently producing levulinic acid on a large scale. Once these productions are scaled up to the 100 kiloton level, it is expected that the cost of levulinic acid will drop below $\text{€}0.50 \text{ kg}^{-1}$.

Scheme 12. a) Rate of formation of DMA as function of reaction parameters. b) Effect of addition of DMA on the rate of formation of DMA.

Scheme 13. Mechanism of catalyst deactivation in palladium-catalysed methoxycarbonylation.

Scheme 14. Lignin, its monomers, and the three most prevalent types of bonds. (Lignin bond code: α, β, γ refers to the positions on the side chain; the numbers to the aromatic substitution pattern.)

These two examples do show that it is possible to convert biomass-based platform chemicals with excellent selectivity into existing bulk chemicals using multiple catalytic steps.

4. Fine Chemicals from Lignin

The previous two examples have shown that it is possible to convert sugar-based platform chemicals into existing bulk chemicals in excellent yield. However, a large part, up to 40%, of lignocellulose consists of lignin. For a truly sustainable economy, it would be highly preferable to also use the lignin as a raw material.^[45] However, converting lignin into chemicals is no easy matter. First of all, lignin is a polymeric compound that is produced by nature via the random radical polymerisation of three different monomers (Scheme 14). Secondly, those monomers are interconnected through several different types of bonds. The most prevalent connection, present in most lignins (up to 40%), the β -O-4 bond, is a single bond, but all other types of linkages between the monomers (such as the β -5 or β - β connections) are based on multiple bonds (2 for β -5 and 4 for β - β , respectively) (Scheme 14). For these reasons, it is deemed impossible to recover bulk aromatic compounds, such as phenol, from lignin on a large scale in an economic manner. Nevertheless, it is feasible to isolate aromatic compounds from lignin in smaller amounts, as long as these compounds can be used for higher value-added products. Thus, although the yield is less than 0.5%, vanillin is produced from Kraft lignin in an economic manner by the company Borregaard.^[46] The acid-catalysed depolymerisation of lignin was researched extensively in the first half of the 20th century, for a large part by Harold Hibbert.^[47] The products of the cleavage of the β -O-4 bond that were reported at the time are mostly

ketones (shown in red in Scheme 15). The mechanism of their formation is readily explained: not surprisingly, a carbonium ion is formed in the benzylic position. This cation can react in intramolecular fashion to form a benzofuran. It can also react at another position in the lignin molecule, leading to increased condensation. It can also lose a proton to form an aryl enol ether, which can hydrolyse or first rearrange and hydrolyse to form the Hibbert ketones (the so-called C3 route in which all three carbon atoms of the side chain are retained). However, there is a second mechanism that proceeds via a retro-aldol reaction, in which formaldehyde is formed (C2 route), leading to another aryl enol ether, which hydrolyses to the phenylacetaldehyde (shown in green in Scheme 15). This aldehyde has only ever been detected in trace amounts in model studies.^[48]

Scheme 15. Products of the acid-catalysed cleavage of the β -O-4 bond in lignin. (Products in red: the C3 route leading to the formation of Hibbert ketones; product in green: the C2 route.)

Scheme 16. Acid-catalysed cleavage of lignin model compound **1a**.

We have reinvestigated the acid-catalysed cleavage of lignin at moderate temperatures.^[49] Our investigations started with model compound **1a**. Reaction of **1a** with 10 mol% triflic acid at 140 °C produced guaiacol **3a** in good yield and varying amounts of phenylacetaldehyde **2a** (Scheme 16). Following the reaction over time showed that all phenylacetaldehyde had disappeared after 2 hours. Investigation of the reaction mixture by ¹H and ¹³C NMR showed formation of the expected aldol condensation products. And indeed, it is well known that phenylacetaldehyde **2a** is a very reactive compound. It is clear that if such compounds are formed from lignin, their fate will be an immediate recondensation on lignin, leading to the formation of higher condensed products. For this reason, these compounds had rarely been noticed before as cleavage products from lignin. In addition, they may well be the reason that recondensation has been such a major problem in all attempts at the depolymerisation of lignin.

To prevent this recondensation chemistry, we decided to investigate the possibility of scavenging the reactive aldehyde function in a tandem reaction.^[49a] Thus, the reaction of model compound **1a** with 10 mol% triflic acid in the presence of 1.5 eq. of ethylene glycol resulted in the formation of the acetal in 99% yield (Scheme 17). This high yield is surprising, as the reaction is carried out in a closed vessel at 140 °C, well above the boiling point of the solvent dioxane. As a consequence, the water that results from the formation of the acetal remains in the solution, and thus, an equilibrium between aldehyde and acetal would have been expected. Reactions with other diols,

Scheme 17. Tandem dehydration acetalisation strategy.

Scheme 18. Tandem dehydration hydrogenation strategy. (Reprinted with permission from Ref. [49a]. Copyright 2015 American Chemical Society.)

such as 1,3-propanediol and glycerol, were also successful, and gave the acetals in good yields. Reaction of the more realistic model compounds **1b** and **1c** led to a 35–40% yield of the acetal (Scheme 17). Here, the C3 pathway, leading to the acetals of the Hibbert ketones, is also operative.

A second strategy that we pursued was the *in situ* hydrogenation of the aldehyde (Scheme 18). This initially leads to formation of the 2-phenylethanol. However, under the reaction conditions, this compound is also dehydrated, and the resulting styrene is further hydrogenated to ethylbenzene. Hydrogenation at higher temperatures also led to the formation of ethylcyclohexane, which may have some relevance for the formation of fuels from lignin. The relative ratio of these three compounds was strongly influenced by the temperature of the reaction: whereas at 130 °C mostly 2-phenylethanol is formed, at 140 °C, a mixture of 2-phenylethanol and ethylbenzene is formed. At 160 °C, ethylcyclohexane becomes the major product.

The third strategy we successfully applied was a tandem dehydration/decarbonylation reaction. Use of a catalyst prepared *in situ* from [Ir(COD)Cl]₂ and PPh₃ at 120 °C led to the formation of toluene in 73% yield (Scheme 19).^[50] Thus, we have developed three different methods that would allow the isolation of the respective acetals, 2-phenylethanol,

Scheme 19. Tandem dehydration decarbonylation strategy.

Scheme 20. Preparation of dioxosolv lignin from walnut shells.

ethylbenzene, ethylcyclohexane, and toluenes from the unstable aldehydes that result from the C2 dehydration pathway. However, the most important question still needed to be answered: does it also work on lignin? To answer this question we isolated dioxosolv lignin from walnut shells (Scheme 20). Dioxosolv lignin is of much better quality than the usual ethanosolv lignin, as we find that in the latter, most benzylic alcohol functions have been replaced by ethyl ethers. With the dioxosolv lignin, we have performed five different reactions (Scheme 21). Two of these were control reactions with triflic acid in dioxane at 120°C (24 h) and 140°C (4 h). In one reaction at 140°C (4 h), we added 1.5 eq. of ethylene glycol. In one reaction at 120°C (24 h), we added Ru/C and applied

hydrogen pressure of 20 bar. And in another reaction at 120°C (24 h), we added $[\text{Ir}(\text{COD})\text{Cl}]_2$ and PPh_3 . At the end of the reactions, the insolubles were removed in two steps, resulting in a fraction that contained only monomers and dimers (Scheme 21). These fractions were analysed by GPC to confirm that they were indeed monomers and dimers. In addition, extensive GC-MS analysis was performed, allowing the assignment of most of the peaks. Scheme 22 shows the relative weights of the different fractions.

It is immediately visible that the strategy has worked and that our tandem reactions have reduced the size of the high-molecular-weight fractions substantially as a result of recondensation prevention. In addition, the size of the

Scheme 21. Three different tandem reactions on lignin (including controls) and purification scheme. (Reprinted with permission from Ref. [49a]. Copyright 2015 American Chemical Society.)

Scheme 22. Dry weight analysis of the different fractions obtained according to Scheme 21 upon solvent evaporation and drying. (Reprinted with permission from Ref. [49a]. Copyright 2015 American Chemical Society.)

Scheme 23. GC-FID of the monomer/dimer fraction of reaction B, the tandem dehydration acetalisation reaction. (Reprinted with permission from Ref. [49a]. Copyright 2015 American Chemical Society.)

fractions containing monomers and dimers is much larger in the tandem reactions than in the control reactions. Scheme 23 shows the GC of the monomer/dimer fraction of the tandem dehydration/acetalisation reaction. It is clear that the three acetals resulting from the C2 pathway are the major products. In later work, we have shown that this methodology can be applied to a variety of lignins. Better still, we have now shown that the tandem dehydration-acetalisation strategy also works on wood. Here, the type of wood chosen is of great importance, as the relative ratio of the three monomers varies greatly between species. Pine tree, for instance, contains lignin that is solely made from coniferyl alcohol, allowing the isolation of a single acetal in substantial amounts.

5. Summary and Outlook

In this account, I have shown the feasibility of converting platform chemicals that are easily obtained from renewable resources in economic yields into bulk chemicals with excellent overall selectivity. Although these studies are merely proof of principle and further process development will be needed, prospects are bright for this marriage between platform chemicals and catalysis, as the cost price of bulk chemicals is dominated by the price of the raw material and the selectivities of the conversions. These platform chemicals are produced from C6 sugars, or from the C6 sugars present in lignocellulose. The lignin part of lignocellulose deserves more attention than it has received so far. Converting lignin into useful products is a harder nut to crack, but many new approaches are being invented as we speak. Fine chemicals can certainly be produced from lignin in an economic manner. Further understanding of the reactivity of lignin under various reaction conditions will help to develop new strategies that allow the selective production of chemicals in higher overall yields than currently possible.

Looking ahead, we can detect a clear need to develop other chemistry beyond dehydration to convert sugars into interesting new platform chemicals. We have recently published a selective oxidation reaction that could serve as a tool in this direction.^[51] Fatty acids are certainly interesting platform chemicals, although most chemistry currently seems to revolve around oleic acid. Use of other fatty compounds, such as cardanol, a component from cashew-nutshell liquid, opens up new opportunities.^[52] Apart from the production of vitamins and flavour and fragrance compounds, terpenes remain underutilised as a source of renewable chemicals. Here also, new chemistry needs to be developed to allow the selective reaction at a single position of these polyene compounds.^[53]

Thus far, much chemical research has been aimed at fuels and bulk chemicals. Interestingly, there is a growing market demand for renewable raw materials in everyday products, like cosmetics, paints, and glues. As these are performance materials, the need to use existing well-defined chemicals is much less stringent, and market introduction could be very swift. Many new developments are expected in this area in the next 10 years.

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