Check for updates

Stabilization strategies in biomass depolymerization using chemical functionalization

Ydna M. Questell-Santiago [1], *Maxim V. Galkin* [2], *Katalin Barta* [2,3 ✉] *and Jeremy S. Luterbacher* [1 ✉]

Abstract | A central feature of most lignocellulosic-biomass-valorization strategies is the depolymerization of all its three major constituents: cellulose and hemicellulose to simple sugars, and lignin to phenolic monomers. However, reactive intermediates, generally resulting from dehydration reactions, can participate in undesirable condensation pathways during biomass deconstruction, which have posed fundamental challenges to commercial biomass valorization. Thus, new strategies specifically aim to suppress condensations of reactive intermediates, either avoiding their formation by functionalizing the native structure or intermediates or selectively transforming these intermediates into stable derivatives. These strategies have provided unforeseen upgrading pathways, products and process solutions. In this Review, we outline the molecular driving forces that shape the deconstruction landscape and describe the strategies for chemical functionalization. We then offer an outlook on further developments and the potential of these strategies to sustainably produce renewable-platform chemicals.

[1]*Laboratory of Sustainable and Catalytic Processing, Institute of Chemical Sciences and Engineering, École Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland.*

[2]*Stratingh Institute for Chemistry, University of Groningen, Groningen, Netherlands.*

[3]*Institute of Chemistry, Organic and Bioorganic Chemistry, University of Graz, Graz, Austria.*

✉*e-mail: katalin.barta@uni-graz.at; jeremy.luterbacher@epfl.ch*

https://doi.org/10.1038/s41570-020-0187-y

Lignocellulosic biomass represents the bulk of terrestrial biomass and is a promising sustainable alternative to fossil carbon[1,2]. Lignocellulosic biomass is a feedstock comprised of three major biopolymers: cellulose (30–50%), hemicellulose (20–35%) and lignin (15–30%)[2,3]. The cellulose fraction is exclusively composed by anhydroglucose units (AGU) linked linearly through β-1,4-glycosidic bonds[4,5] (**2**) (FIG. 1). Each chain participates in hydrogen bonding and van der Waals interactions with nearby chains, such that the material exists as rigid and semi-crystalline fibres that are insoluble in most conventional solvents[6,7]. These cellulose polymer chains, in the case of woody biomass, can have a degree of polymerization up to 10,000 (REF.[8]). In contrast, hemicellulose is an amorphous heteropolymer with branches and short lateral chains, which may contain five different sugar monomers (D-galactose, D-mannose, D-glucose, L-arabinose and D-xylose), with xylose being the most abundant[9–11] (**1**) (FIG. 1). Other sugars, such as L-rhamnose and α-L-fucose, can be present in minor quantities, and some of the OH groups in the monomers can be acetylated. The degree of polymerization for hemicellulose is substantially lower than that of cellulose and varies between 50 to 300 anhydrosugar units[12]. Lignin is also an amorphous heteropolymer but is, instead, composed of methoxylated phenylpropanoid units[3,13] (**15**) (FIG. 2). Because of its lower O content

compared with cellulose and hemicellulose (30 wt% O in lignin versus 49 wt% O in cellulose), lignin accounts for about 40% of the biomass heating value[2,14].
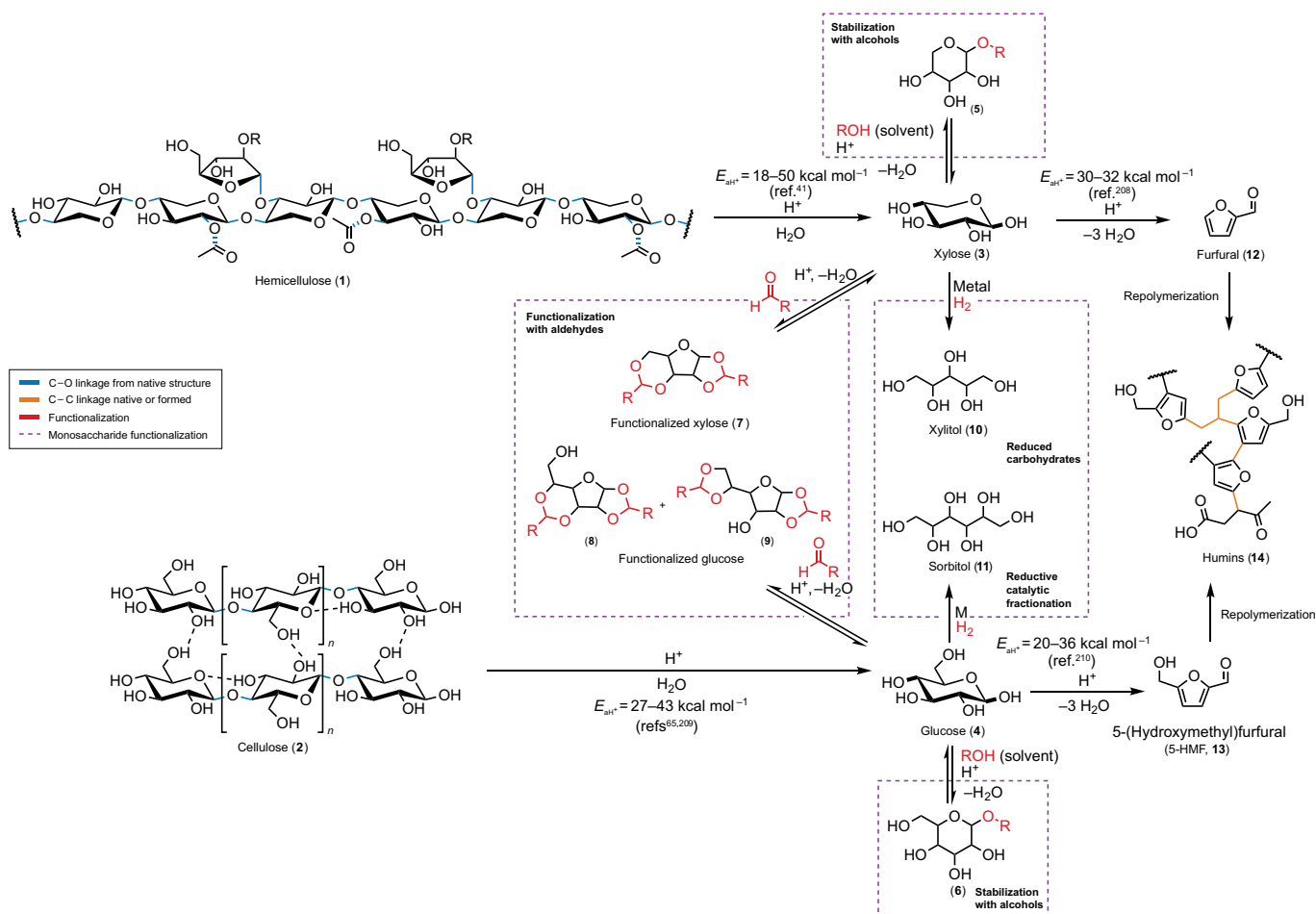
In the plant cell wall, lignin surrounds hemicellulose and cellulose, while cellulose fibres are interlaced with hemicellulose[15]. If one wishes to convert biomass, then, for two reasons, it is typical to begin by extracting lignin and some hemicellulose sugars. First, the hydrolysis reactions of hemicellulose and lignin tend to be kinetically more favourable than the hydrolysis of cellulose. Thus, most biomass-deconstruction methods remove hemicellulose and lignin before extensive cellulose depolymerization. Second, their removal increases the purity of the cellulose and its accessibility to further reagents, thereby, facilitating following processing. The depolymerization of the three constituents of lignocellulosic biomass affords small molecules — monophenols from the lignin and simple sugars from the polysaccharides that have each been explored as a feedstock to replace petroleum-based products, including fuels, materials and fine chemicals[16,17]. However, given the differences in the structures and reactivities of the small molecules, developing integrated approaches for the conversion of all three biomass fractions into well-defined monomers or other platform chemicals is challenging[18]. As we detail here, it has been especially challenging to upgrade lignin to well-defined platform molecules as part of an

Fig. 1 | **Depolymerization of polysaccharides in lignocellulosic biomass by conventional acid hydrolysis.** Acid hydrolysis of hemicellulose affords xylose[41], which can undergo dehydration to give furfural[208]. The problem is that furfurals readily participate in undesirable condensations that give humins. When acid hydrolysis is, instead, conducted on cellulose, one obtains glucose[65,209], the dehydration of which give 5-(hydroxymethyl)furfural (5-HMF)[210,211], which can repolymerize into humins. Ether, C–C, functionalization and H-bonds are highlighted in blue, orange, red and pink, respectively.

integrated method with cellulose and hemicellulose (for which many long-standing strategies exist). Thus, lignin valorization has attracted less attention than the other two polymers, despite it having aromatic moieties that could serve as substitutes for petrochemicals. Moreover, lignin has a low O content that sees it have a higher energy density compared with polysaccharides[19,20].

The initial step of biomass conversion generally involves transformation of the cellulose and hemicellulose biopolymers into single carbohydrates (for example, **3** and **4**) and conversion of lignin into phenylpropanoid monomers such as **20** through C–O bond cleavage[21]. The cleavage of C–O linkages in both polysaccharides and lignin can happen readily, even in inexpensive systems through hydrolysis, which may proceed either in pure H_2O (autohydrolysis) or dilute acid (pH = ~2.5)[22–24]. However, the scissile C–O bond in the glycosidic linkages is a hemiacetal, which is different to the alkyl aryl ether linkages in lignin[25], as reflected in their different bond-cleavage energies. These differences mean that we need targeted strategies to stabilize species released on solvolysis, so they do not undergo subsequent acid-catalysed reactions, such as

dehydration, condensation and uncontrolled repolymerization. These reactions afford polymers that contain extremely recalcitrant C–C bonds; the sugar-derived degradation products are called humins (**14**), while the lignin-derived degradation products are referred to as condensed or technical lignins (**28**)[26,27]. The balance between depolymerization and degradation kinetics for these three biopolymers has always governed the production of simple sugars and lignin monomers. Various depolymerization strategies have addressed these kinetic limitations but often have higher process costs because they require (often sacrificial) catalysts or biocatalysts that are often not fully compatible with all lignocellulose fractions. As a result, present biorefinery processes use technologies that lead to incomplete valorization of biomass[28,29]. We now discuss the kinetics of lignin and polysaccharide depolymerization and how these kinetics have shaped depolymerization methodologies.

Kinetics of lignin cleavage and degradation
Lignin is biosynthesized by radical coupling of coniferyl, sinapyl and *p*-hydroxyphenyl alcohol monomers, to give materials in which the monomers are connected by

several C–C or C–O linkages (or both)[13,19]. As we will cover in detail, it is lignin that is the most sensitive to typical biomass-deconstruction conditions, which generally focus on cleaving C–O linkages, rather than the much more recalcitrant C–C linkages. Approximately 60–80% of the linkages in a typical hardwood are ethers, while the value is 40–60% for a typical softwood[27] (**15**) (FIG. 2). Because the linkages are thought to be randomly distributed, and because each monolignol must be surrounded by two ether linkages to produce a monomer after depolymerization by ether cleavage, the theoretical monomer yield based on cleaving ether linkages is approximately the square of the fraction of linkages that are ethers (i.e. those present between C_9 units) in native lignin[19,27,30–32] (Eq. 1).

$$\text{Monomer yield} \approx 100\% \times (\text{Fraction of linkages that are ethereal})^2 \tag{1}$$

The ether linkages include all the different types of pure ether linkages in lignin (**16**) (FIG. 2) and are assumed to be randomly distributed throughout a linear polymer chain in which C_9 monomers are connected through either C–O or C–C linkages. More complicated structures and end-group effects are ignored (that is, lignin is assumed to be infinitely long)[31]. This correlation was first used to estimate the lignin monomer and dimer yields from the fraction of linkages in white birch that are ethereal[33]. Using Eq. 1, we can estimate a theoretical monomer yield of ~45–55% for hardwoods and ~20–30% for softwoods[31,33,34].

The bond-dissociation enthalpy (BDE) for each linkage in lignin falls in the range 42–83 kcal mol⁻¹ for C–O linkages and 54–118 kcal mol⁻¹ for C–C linkages[27,35–37] (**15**) (FIG. 2). Although these values give some indication of the difficulty of breaking C–C or C–O linkages in purely thermal processes, they are not indicative of the energy required to break C–O linkages in aqueous or acidic conditions. Under these conditions, the reaction does not proceed by single-step homolytic cleavage but, rather, by a multistep, acid-catalysed cleavage and/or modification of the molecule.

The most abundant linkage in lignin is the β-aryl ether unit referred to as the β-O-4′ linkage[3,13,30] (**16**) (FIG. 2). This linkage contains a benzylic secondary hydroxyl at the Cα position and a primary hydroxyl at the Cγ position. A combined experimental and theoretical study on a lignin dimer with a free phenolic OH and a β-O-4′ linkage estimated, under acidic conditions, that the activation energy (E_{aH^+}) for conversion of an α-OH group to give a benzylic carbocation (**18**) is ~3 kcal mol⁻¹ (REF.[38]). The relevance of this and related studies on lignin model compounds is difficult to assess because they do not use real lignin. However, even taking uncertainty into account, the activation energy for β-O-4′ cleavage through intermediate **19** is substantially higher at 11 kcal mol⁻¹, which demonstrates the favourability of condensation reactions. The Cα–OH BDE decreases with the degree of methoxylation (56 → 48 kcal mol⁻¹)[39] and is also lower for terminal β-O-4′ fragments with an aryl alcohol. Therefore, the barrier to modification can be higher for the middle of the lignin polymer than it

is for end units. Intermediates **18** and **19** can undergo cleavage through direct rehydration and C–O bond scission, which produces Hibbert ketones (a series of C9 guaiacyl or syringyl compounds featuring a keto group in the Cα or Cβ position), in which the C3 aliphatic moiety is maintained (C3 pathway, Supplementary Fig. 1). Alternatively, a deformylation step precedes C–O bond cleavage and rehydration (C2 pathway), in which case one obtains C2 aldehydes (2-arylacetaldehyde species such as **24**) that are prone to recondensation. The Hibbert ketones are the only carbonyl-containing products measured from lignin deconstruction by acidolysis, emphasizing the propensity of C2 aldehydes to undergo recondensation[40].

The energy barriers to the lignin-modification reactions illustrate how sensitive these linkages are under lignin extraction or pretreatment conditions. The reported activation energies for hemicellulose hydrolysis under acidic conditions (18–50 kcal mol⁻¹; see below)[41] (FIG. 1a) and cleaving lignin–carbohydrate linkages (19 kcal mol⁻¹) are substantially higher than the energy required for Cα–OH dehydration[42]. These differences clearly indicate that the rate of lignin-backbone modification is greater than that of any chemical extraction. The challenge is that this modification is problematic. If a benzylic carbocation is formed, condensation reactions are calculated to be substantially more favourable than cleavage of the ether linkage[38,43]. Condensation reactions can lead these fragments to rapidly form new C–C linkages, which are highly recalcitrant and greatly lower the depolymerization yields for these modified lignin structures[29,30,44,45]. Several catalytic strategies have been proposed to cleave C–C linkages in technical lignins, but strategies remain exploratory and will always face lower selectivity than ether cleavage in native lignin[27]. This competition between the cleavage of β-O-4′ linkages and the more favourable formation of new C–C bonds limits the yields of lignin-upgrading reactions. Despite these challenges, several strategies have been developed to fractionate biomass and extract lignin, while limiting its degradation. These strategies afford lignins with a wide variety of structural modifications.

Unstabilized lignin extraction. Organosolv processes can extract lignin by solvolysis. Acid-catalysed organosolv processes feature added Brønsted (for example, H_2SO_4, H_3PO_4, CF_3SO_3H and AcOH)[46,47] or Lewis acids (for example, $FeCl_2$, $ZnCl_2$ and metal triflates)[48–50] that usually decrease the pH of organosolv liquor to 2–4, values at which solvolysis of the lignocellulosic matrix is substantially accelerated and both hemicellulose and lignin are removed. If no acid is used, the process will still be accompanied by a pH decrease from 7 to ~4 because deacetylation of hemicellulose (1–6% of the OH groups in hemicellulose (**1**) are acetylated) liberates acidic carboxylic acids. The degree of delignification and hemicellulose removal depends on the solvent system, severity of the process and nature of the acid catalyst. Delignification is quite sensitive to acidity at low temperatures (<120 °C)[51] but, at higher temperatures, solvolysis reactions rapidly occur and delignification is not substantially affected by pH[52]. The cellulose fraction usually
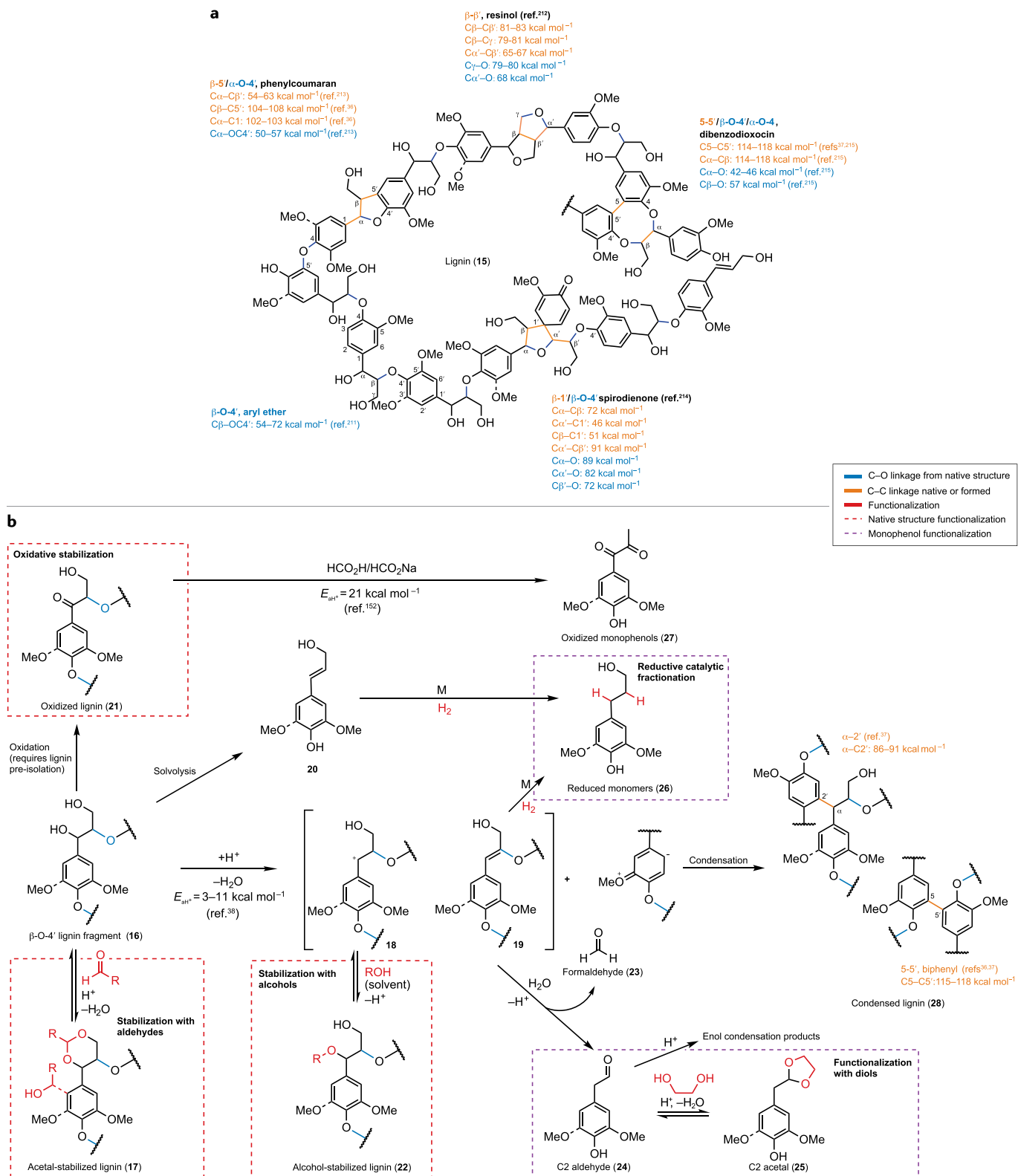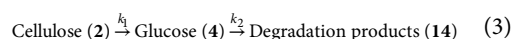
Fig. 2 | **Depolymerization of lignin in lignocellulosic biomass by conventional acid hydrolysis. a** | The illustrative structure of lignin depicts the diversity of C–O and C–C linkages present and the bond-dissociation energy of each (calculated using model compounds). **b** | The fragment **16** can undergo a variety of transformations. For example, if we consider dehydration of a model guaiacyl dimer, an activation energy (E_{aH^+}) of 3 kcal mol^{-1} or 11 kcal mol^{-1} is predicted to go to carbocation or alkene products, respectively. Likewise, calculations on an oxidized dimer show that HCO$_2$H-catalysed cleavage is facile and affords oxidized monophenols[152].

stays intact because organosolv conditions are generally too mild to cause cellulose fragmentation. As discussed above, any conditions harsh enough to extract lignin are generally harsh enough to dehydrate the β-O-4′ structure to give reactive intermediates that condense to afford C–C linkages. However, condensation reactions are not universally faster and it is possible to trap the reactive intermediates in stabilized forms. Furthermore, repolymerization can be minimized by conducting acidolysis under the mildest possible conditions, often by using organic solvents such as tetrahydrofuran, alcohols, 1,4-dioxane and γ-valerolactone (GVL) — liquids capable of solubilizing lignin fragments[49,53–55]. Once optimized, this approach can preserve up to 62% of the β-O-4′ linkages in native lignin[49]. Nevertheless, because aromatic monomer yields tend to be proportional to the square of the β-O-4′ ether bond content, this still leads to a rapid drop in yield. The first fraction of lignin (typically around 30% of the native lignin) extracted under mild conditions can typically be depolymerized almost quantitatively, but as the conditions are adjusted (for example, by increasing the reaction time or severity) to extract more lignin, potential monomer yields drop quickly[56].

In the same way, one can use a flow-through reactor to prevent condensation reactions and/or preserve the original structure of lignin by removing dissolved species from the heated zone to rapidly lower the solution temperature[3,35]. For example, a flow-through set-up at 190 °C using MeOH solvent afforded lignin monomer (**20**) yields of ~4 wt%[57], while pumping an acidified mixture of MeOH and H₂O through birch wood at 200 °C and rapidly dropping the temperature of the resulting solvent gives yields up to 21 wt% starting from the original Klason lignin[58]. Alternatively, pumping 72 wt% aqueous HCO_2H through poplar wood[59] induced ~90% delignification with preservation of up to 83% of the β-O-4′ moieties (compared with milled wood lignin). These methods do not include reagents to stabilize the intermediates, and lower the extent of undesirable condensations by using dilute conditions (1:50–1:100 biomass:solvent) to allow full lignin extraction at flow-through conditions. Unfortunately, the method uses large quantities of solvents and it is challenging and energy-intensive to isolate products from dilute solutions.

Kinetics of polysaccharide deconstruction

The vast majority of polysaccharide depolymerization processes are geared towards acid hydrolysis of glycosidic bonds in cellulose and hemicellulose. These reactions have frequently been described as pseudo-first-order sequential reactions (with respect to the reactant) that depend on $[H_3O^+]$, T and the chemical environment of the bond[60–66]:

$$\text{Hemicellulose (1)} \xrightarrow{k_1} \text{Xylose (3)}$$
$$\xrightarrow{k_2} \text{Degradation products (14)} \quad (2)$$

$$\text{Cellulose (2)} \xrightarrow{k_1} \text{Glucose (4)} \xrightarrow{k_2} \text{Degradation products (14)} \quad (3)$$
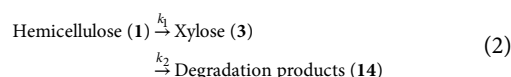
The rate constants of these models depend on acid concentration [HA] and system T according to a modified Arrhenius equation:

$$k_i = [\text{HA}]^{n_i} k_{0,i} e^{\frac{-E_{ai}}{RT}} \quad (4)$$

where i is the reaction in question (1, 2, …), n_i is the empirical acid exponent and [HA] is the concentration of acid (often H_2SO_4).

The activation energies computed using these hydrolysis models offer useful insights into the challenges of polysaccharide depolymerization and can be used to explain apparent kinetic trends. Nevertheless, other phenomena, such as mass-transfer effects, can also exert at least partial control over reactions of whole biomass, and more detailed analyses are required to fully account for such effects. The depolymerization of hemicellulose and cellulose involves heterogeneous substrates, and access to reactants and other species by diffusion can be limited. These effects are reflected in the estimated kinetic parameters varying a lot throughout the literature. In particular, estimated activation energies (E_{aH^+}) for depolymerization of hemicellulose and cellulose are reported to fall in the ranges 18–50 kcal mol⁻¹ and 27–43 kcal mol⁻¹, respectively (FIG. 1). Despite the large spread, these values are clearly higher than the activation energy associated with lignin modification, which further emphasizes the difficulty of preventing lignin degradation during biomass deconstruction. Furthermore, the ranges of activation energies for hemicellulose and cellulose depolymerization are usually within the same range as those of the dehydration reactions of their products xylose and glucose, which produce furfural (**12**) and 5-(hydroxymethyl)furfural (5-HMF, **13**), respectively (FIG. 1). The similarity of these E_{aH^+} values reflects the challenge of converting cellulose and hemicellulose to simple sugars without further dehydration. In practice, obtaining high monosaccharide yields from hemicellulose is much more straightforward than it is from cellulose. The activation energies in acidic solution for cellobiose and xylobiose (soluble dimers of glucose and xylose) hydrolysis are 31 and 33 kcal mol⁻¹, respectively. Hemicellulose undergoes depolymerization more readily because its heterogeneous structure is different, particularly in terms of its lack of crystallinity, which makes its glycosidic bonds much more susceptible to hydrolysis. The maximum monosaccharide yields predicted by the sequential reactions (Eqs 2, 3) illustrate this difference between the two polymers. Near-quantitative xylose yields from hemicellulose can be obtained within minutes at temperatures below 200 °C using dilute acid (≤3 wt%)[22,62]. In comparison, maximal glucose yields from cellulose treated for similar residence times are much lower (<60%), even when much higher temperatures (>220 °C) are used. Owing to these differences, maximizing the yield of both soluble carbohydrates necessitates either dual-stage hydrolysis processes or specific treatments of the cellulose fraction. This might involve first converting hemicellulose at a lower temperature and then cellulose under harsher or otherwise modified conditions.

The dehydration of sugars to furans produces highly reactive molecules that tend to react rapidly, most predominantly by aldol condensations to produce insoluble solid humins (**14**)[67]. Humin formation is sufficiently

favourable such that, if furans are targeted as a product, they must be removed from the reactive mixture by selective extraction or reactive distillation[68,69]. Humins are randomly crosslinked macromolecules (50–66 wt% C, 29–46 wt% O; balance H)[70,71] that exclusively feature C–C linkages, so the energy required for their cleavage can be approximated by their BDE, which is substantially higher than the activation energy for the cleavage of glycosidic bonds in acidic solution. In addition, as with condensed lignin, the condensations that afford humins are uncontrolled, such that any catalytic cleavage processes will face selectivity issues. For this reason, humins are presently used only to generate low-value heat and electricity by combustion. However, several studies have explored humin valorization to H_2 (REF.[70]) or activated C[71], but these strategies limit the valorization of cellulose into platform chemicals.

Cellulose depolymerization in hydrothermal and dilute acid systems. As we described above, cellulose depolymerization is challenging because the apparent activation energy for cellulose depolymerization is usually higher than that of glucose degradation, leading to lower monosaccharide yields at lower processing temperatures (<250 °C). Increasing the reaction temperature will accelerate the hydrolysis reaction more than the degradation reaction[22,63,72]. Data from many different studies indicate that, because of its higher activation energy, cellulose depolymerization only starts to outpace glucose degradation at around 350 °C in pure H_2O (REF.[73]). The kinetic model for cellulose (Eq. 3) predicts yields of 40% and 80% for systems at 350 °C/1 s and 450 °C/10 ms, respectively[2], and these values are consistent with experimental data[74–76].

Dilute acid hydrolysis processes accelerate depolymerization by the presence of mild $[H_3O^+]$[28,77] to give the same carbohydrate yield from polysaccharides as hydrothermal processes do, but at lower temperatures (for example, a 60% glucose yield can be obtained from cellulose in dilute acid at 240 °C in only 10 s)[2]. Despite dilute acid hydrolysis presenting practical difficulties, not least the high pressure drops and short residence times, several two-stage chemical hydrolysis processes have been commercialized[28,76,78–82]. A larger number of processes use single-stage dilute acid hydrolysis as a pretreatment, wherein lignin and hemicellulose undergo partial depolymerization and afford products that can be extracted, after which, the remaining cellulose is often hydrolysed by enzymes in a second step. Another approach to avoid harsh conditions is to decouple depolymerization and sugar degradation using flow-through reactors. These systems can afford high sugars yields because the soluble products are rapidly removed from the heated zone, before they can degrade, by flowing a solvent through the solid substrate[21,22,83]. The kinetics are decoupled because the solid that undergoes depolymerization has a much longer residence time than its soluble products, which are rapidly removed from the reactor. However, this method introduces a trade-off between product yield and concentration, such that, if one aims to convert cellulose into glucose in 70% yield, the concentration of glucose in the final solution is generally less than 1.5 wt%[22].

Depolymerization facilitated by organic solvents. The use of organic solvents can facilitate traditional dilute acid processes in several ways. Notably, organic solvents can remove lignin much more effectively by solubilizing extracted (usually condensed) lignin and avoiding its reprecipitation on the surface of cellulose[83–85]. Solvents, in particular, polar aprotic solvents, can also enhance the catalytic activity of an acid and lower the required acid loading and/or processing temperature[86,87]. This increased activity in polar aprotic solvents is generally due to the solvation effects, which increase the Gibbs free energy of the acid without substantially affecting that of the transition state for hydrolytic cleavage. In this way, one can use mild reaction temperatures (77–147 °C) and low catalyst loadings[87,88] — conditions that can, at least partially, preserve the β-O-4′ linkages in lignin. However, even with these benefits, degradation usually still occurs and substantially affects lignin upgradability[3,54]. The destabilization of the acid lowers the activation energy of both H^+-catalysed hydrolysis and dehydration reactions. However, depolymerization is accelerated to a greater degree, which disfavours degradation and humin formation[83,85,89,90]. Thus, introducing an organic solvent allows one to mitigate, if not overcome, rapid degradation of lignin and polysaccharides. Lignin still undergoes substantial degradation and cellulose remains challenging to depolymerize in simple reaction systems, with reasonable yields only attainable in the flow-through reaction set-ups described above. Of course, these systems lead to similar trade-offs between yield and concentration as those for pure H_2O systems (66–69% glucose at 2–1.7 wt% concentrations)[83]. However, the solvent can be easily separated from H_2O by adding liquid CO_2 or apolar solvents like C_6H_6 or PhMe to induce phase separation and leave a concentrated (up to 13 wt%) aqueous sugar solution[83,84,91]. The main disadvantages of the process remain the cost of solvent recovery, recycling and make-up, as well as risks associated with its stability and flammability[92,93]. Nevertheless, techno-economic analyses have shown that this process could be economically competitive with state-of-the-art technologies for EtOH, furan-2-carboxaldehyde (furfural) and pulp production[77,94].

Alcoholic co-solvents used for the depolymerization of polysaccharides partially incorporate as ethers at the anomeric positions of C_5 and C_6 carbohydrates. The main pathway for this is acid-catalysed hydrolysis, followed by Fisher glycosylation or transglycosylation — reactions that both yield α-alkyl monoglycosides and β-alkyl monoglycosides (**5** and **6**)[46,58,95]. Such monoglycosides are commonly formed in yields up to 47% in catalytic biomass fractionation under acidic conditions if the pulping medium is high in alcohol content[46,58,96]. Pure alcohol solvents in combination with Lewis or Brønsted acid catalysis have been widely applied in biomass and cellulose depolymerization. These solvent systems can substantially lower the apparent activation energy of the depolymerization reaction from ~27–43 kcal mol⁻¹ in H_2O to 13 kcal mol⁻¹ in EtOH (REF.[97]). For instance, cellulose depolymerization in MeOH produced methyl glucosides in 57% yield at 85% conversion. In contrast, hydrolysis of cellulose in H_2O under the same reaction

conditions (polyoxometalate catalyst, 147 °C)[98] resulted in a conversion of only 20% and a glucose yield of 7.1%.

Cellulose depolymerization in concentrated acid and ionic liquids. An alternative to using very high temperatures and short residence times in cellulose processing is to disrupt the crystallinity of cellulose, thereby, increasing the accessibility of its glycosidic bonds and rendering it similar in reactivity to hemicellulose and, thus, susceptible to hydrolysis. Concentrated mineral acids can swell and decrystallize cellulose[99–101], for example, by hydrogen bonding to cellulose OH groups and interfering with interchain interactions that hold the crystalline structure together[60,102,103]. As a result, cellulose is completely dissolves and assumes an amorphous structure that undergoes hydrolysis more quickly to give high yields of glucose. Although this was known already in the early 1800s[104,105], recent work has shown that ionic liquids (ILs) can also completely dissolve cellulose by breaking the hydrogen bonds between cellulose strands and forming stronger interactions to these separated strands. In addition, the activation energy of cellulose hydrolysis can also be decreased by the presence of ILs[106–108]. This is thought to arise because the strongly ionic environment of ILs stabilizes charged species such as oxocarbenium ions, which feature in the transition state ($E_a = 22$ kcal mol^{-1} in 1-ethyl-3-methylimidazolium chloride and MeSO$_3$H)[109]. Thus, the depolymerization of cellulose to glucose can proceed at temperatures where no reaction would have occurred in pure H$_2$O (REF.[106]). However, the hydrolytic depolymerization requires just the right concentration of H$_2$O — enough to facilitate hydrolysis but not too much because this might see cellulose chains re-establish their hydrogen bonds such that cellulose precipitates. After dissolution, the hydrolysis process is typically performed by slowly adding H$_2$O in the presence of acid to cleave the glycosidic bonds without precipitating the cellulose[107].

By using concentrated acids and ILs, it is possible to run processes at high reaction rates despite low temperatures and pressures[60,110,111]. However, such processes face high operating and capital costs because acids and ILs must be recovered and corrosion-resistant materials are required. A few commercial processes exploit concentrated acids, most notably HCl, which can be recovered thanks to its volatility[112,113]. ILs are much more expensive and harder to recover, although these problems are being addressed to attempt to lower production and recovery costs. However, such technologies remain prohibitively expensive[114–116].

Enzymatic hydrolysis of cellulose. The enzymatic hydrolysis of hemicellulose and cellulose involves cleavage of these polysaccharides to give soluble sugars, a reaction that occurs at catalytic acidic residues in cellulase or xylanase active sites[117]. Cellulase and xylanase enzymes are highly selective and active, so their reactions occur under mild conditions (~50 °C) and do not afford degradation products, despite leveraging similar chemistry to what occurs in traditional acid-catalysed hydrolysis. The enzymes' active sites lower the activation energy for hydrolysis (to as low as 1.2 kcal mol^{-1} for cellulose),

without affecting the activation energy of glucose degradation[118,119]. Unfortunately, a similarly simple enzymatic (but not necessarily hydrolytic) process for lignin depolymerization has yet to be discovered or developed. The kinetics of polysaccharide hydrolysis are largely governed by the extent to which glycosidic bonds are exposed, which can be measured as the surface area accessible to enzymes[120]. For this reason, a pretreatment process is almost always required to remove lignin and hemicellulose to expose more of the cellulose surface and decrease its crystallinity[28,84,121]. Enzymatic depolymerization does not give degradation products and proceeds under mild conditions, making this method the preferred industrial process in biorefineries. However, the method requires a two-step process, can suffer from slow kinetics and requires costly enzymes, so there remains interest in purely chemical alternatives.

Stabilization of intermediates
Each of the approaches discussed above influences polysaccharide depolymerization kinetics by perturbing the kinetics of glycosidic bond cleavage. Yet, these approaches almost always lead to lignin degradation, so an alternative approach is to trap reactive intermediates as stable derivatives before they degrade. As we will discuss, this strategy can lead to the simultaneous valorization of both polysaccharides and lignin.

Reductive fractionation: lignin first
The dominant lignin valorization strategy — known as reductive catalytic fractionation (RCF), catalytic upstream biorefining (CUB) or lignin first — involves lignocellulose solvolysis, extracting reactive lignin fragments and stabilizing them by catalytic hydrogenation/hydrogenolysis over a heterogeneous metal-containing catalyst, such as Pd-C, Ni-C or Raney Ni[3,19,122,123]. These reactions can be performed with H$_2$ itself or by transfer hydrogenation from an external donor (for example, MeOH, *i*PrOH) or an internal donor from biomass (for example, HCO$_2$H, reducing carbohydrates)[3,19,122,123].

The solvolysis pathway depends on the nature of the pulping media: solvent properties (protic, aprotic, polar etc.), nature of any acid present (strong, weak, Lewis or Brønsted) and overall acidity[46,124–126]. In protic solvents under pH-neutral or low-acidity conditions, solvolysis predominantly gives unsaturated lignin monomers (**18/19** to **20**)[58,127–131]. At higher acidity, the same systems tend to yield acidolysis products (**18/19** to **24** and Hibbert ketones), the selectivity for which can be increased by switching from protic to polar aprotic or non-polar solvents[40,126]. Products of both homolysis and acidolysis reactions are prone to condensation but can be rapidly stabilized if their unsaturated groups are catalytically hydrogenated. When a protic solvent is present in high concentrations, a competing incorporation of the solvent into the α-position of the β-O-4′ moieties is observed (**18/19** to **22**), which could inhibit cleavage pathways but assist lignin solubilization[132,133].

Any lignin oligomers liberated by solvolysis can have their linkages further (catalytically) cleaved if the fragments are small enough to reach the surface of a metal catalyst. The β-O-4′ linkage can undergo various

transformations, depending on the nature of the metal catalyst and the availability of H$_2$ (or its equivalent)[134]. At low H$_2$ pressures (for example, 0–1 bar), the β-O-4′ moiety can undergo hydrogen-neutral C–O bond cleavage via its corresponding ketone intermediate (**21**)[135]. However, direct hydrogenolysis is favoured if excess H$_2$ is available.

A plethora of cleavage mechanisms have been proposed based on model compound studies, with the most favourable pathway depending on the reaction conditions and, importantly, on the nature of the catalytic sites[134]. The bond strengths in lignin follow the order: α-O-4′ < β-O-4′ < 4-O-5′ << C–C[36,136,137]. In general, the weakest linkages are most susceptible to hydrogenolysis, with the reaction being most enthalpically favourable at α-O-4′ and β-O-4′ bonds. Recent work has sought to elucidate mechanisms of lignin biosynthesis according to the monomers released by RCF. For example, it is now thought that monomer transport during this biosynthesis may control the formation of C–C and C–O linkages[138].

The complexity of lignin and the wide variety of conditions used to effect its conversions mean that either solvolysis or hydrogenolysis of lignin fragments can be rate-determining. Under typical RCF conditions (H$_2$, Ni-C, MeOH), the apparent activation barriers for hydrogenolysis (40 kcal mol^{-1}) and acid-catalysed hydrolysis (36 kcal mol^{-1}) of lignin β-O-4′ model compounds (arylglycerol-β-aryl ethers) are very similar and much higher than that for lignin extraction (~15 kcal mol^{-1})[139,140]. However, for the same model compounds under different conditions (H$_2$, 1,4-dioxane–H$_2$O, Pd-C), the apparent E_a of the hydrogenolysis step was nearly twice as low (19 kcal mol^{-1}) and closer to what was observed for lignin extraction[141].

Even though the hydrogenolysis reactions can be slow, the hydrogenation and hydrogenolysis of reactive intermediates generated in lignin conversion proceed in preference to condensation reactions, which are almost fully curtailed. Indeed, RCF produces monomers in yields that are close to the theoretical maximum of 50%.

Of the carbohydrate fractions, cellulose can be almost fully recovered as a solid (up to 97% cellulose recovery), while the retention of hemicellulose in solid pulp varies substantially with conditions (5–95%)[46,142–144]. In most cases, hemicellulose can be valorized to give alkyl glycosides (**5** and **6**), polyols (**10** and **11**) and other products, such that these processes retain reasonable carbon balances[29,125]. However, these fractionation methods are limited by technical difficulties that include catalyst and solvent recovery, catalyst deactivation, mass-transfer limitations, pulp contamination and high energy demand. Promising economic and sustainability projections are currently being made for RCF technologies[145]. However, the aforementioned difficulties are not yet well understood and result in the high operational and capital costs that have, so far, limited the scale-up and potential commercialization of this approach.

Lignin oxidation

Oxidation of the Cα–OH secondary alcohol in β-O-4′ motifs affords a product that cannot undergo dehydration to give reactive species such as benzylic carbocations, which are susceptible to condensation reactions. This oxidation strategy has been an attractive route to activating β-O-4′ linkages towards new cleavage mechanisms[146,147]. Specifically, oxidation of the secondary benzylic hydroxyl (α-OH, **16 → 21**) (FIG. 2) leads to a lowering in the BDE of the Cβ–O ether from 68.2–71.8 kcal mol^{-1} to 55.9–57.1 kcal mol^{-1}. This activation is comparable to that resulting from oxidation of the primary alcohol (Cγ–OH), after which, the Cβ–O BDE is 56.7–59.1 kcal mol^{-1} (REF.[146]). In addition, both these transformations make the Cβ–H group more acidic[148] and, thereby, promote other depolymerization routes, such as the retro-aldol[149] and deformylation reactions[150]. Indeed, once the Cα–OH group has been oxidized, the lignin (**21**) Cβ–H group can be deprotonated to give a diketone product (**27**)[151] (FIG. 2). The HCO$_2$H-catalysed cleavage of an oxidized model lignin dimer was calculated to have an activation energy of 21 kcal mol^{-1}, a value comparable to that for carbohydrate hydrolysis[152].

Selective oxidation of the Cα–OH group in the β-O-4′ lignin motif has been widely studied, including with typical reagents such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[56,146,153] or (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO)[154] analogues, N-hydroxyphthalimide (a catalyst for oxidation with O$_2$)[155], oxovanadium complexes and metalloporphyrins[147]. A more challenging reaction is the selective oxidation of the Cγ–OH group, which can be effected by Cu–TEMPO, TEMPO or Ir complexes[150,156,157]. The subsequent cleavage or depolymerization step can take the form of a hydrolysis, oxidation (for example, Baeyer–Villiger)[147], reduction (for example, photo-reductions, Zn/NH$_4$Cl reductions)[158–160] or redox-neutral reaction (such as photocatalyzed[155], retro-aldol[156], NH$_2$OH-mediated[161] or HCO$_2$H/HCO$_2$Na-mediated reactions[151,152]). Due to the weakening of the β-O-4′ ether bond, the cleavage reaction can be performed under mild conditions to afford high yields, especially in model studies (67% cleavage yield for Cα–OH motifs and 100% for their oxidized equivalents)[160,162].

The main drawback of the lignin oxidation strategy is its incompatibility with lignocellulose fractionation, such that lignin must be extracted prior to oxidation. Therefore, all oxidation methods, when tested on structurally modified lignins obtained by conventional fractionation, led to either low yields of monomers or poor product selectivity[56,150,162]. Notably, high yields (52 wt%) of oxygenated monomer mixtures can be obtained when oxidation is performed on enzymatically extracted lignin, which has a near-native structure[151]. However, the enzymatic extraction of lignin is not considered to be industrially feasible because it requires several conventional ball-milling and enzymatic treatments.

Oxidation of lignin could play an essential role in producing high-value compounds that include functionalized phenol derivatives not available through other depolymerization strategies. Therefore, further developments should address either the integration of mild oxidations into pretreatment or combining oxidations with another stabilizing approach to preserve lignin during extraction. The following sections describe such stabilization approaches.
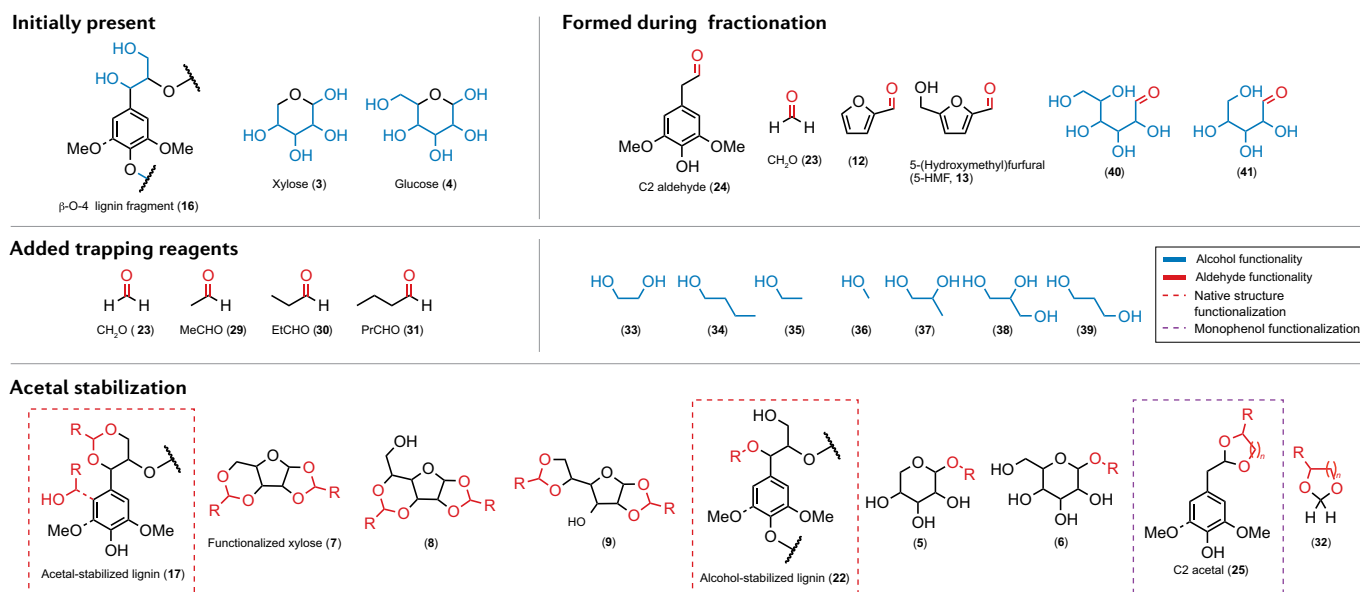
Fig. 3 | **Lignin structures and their stabilized products.** Representative structures of lignin fragments, sugars, reagents and their products, with functionalities (or masked functionalities) highlighted.

High-alcohol organosolv

Alcohols have been used in biomass fractionation for close to a century, but certain benefits of their use in lignin extraction have only recently become clear[163]. During lignin extraction, the β-O-4′ motif undergoes conversion to a benzylic carbocation intermediate (**18**) (FIG. 2), which can be intercepted by alcohol nucleophiles to give ethers (**22**). This reaction is, of course, promoted in alcohol-rich (>95%) solvent mixtures, with the resulting ethers being much less prone than the carbocations to undergo condensation reactions and/or β-O-4′ bond cleavage[132,164–167]. Interestingly, the BDE of Cα–OMe ether groups is substantially lower (70 kcal mol⁻¹) than the corresponding alcohol Cα–OH (89 kcal mol⁻¹)[168]. Nevertheless, other factors, such as Le Chatelier's principle and lignin's hydrophobicity, could be the driving force for the more effective stabilization of carbocations in alcohols relative to in aqueous media. Both model studies and butanosolv biomass fractionation demonstrated that the benzylic ether Cα–OR is less reactive than the parent benzyl alcohol Cα–OH. Preservation of the (etherified) β-O-4′ motifs can be confirmed using NMR spectroscopy, with the fraction of intact β-aryl ether bonds increasing from 3–17% for lignin isolated using a conventional method (for example, the kraft or soda method) to 63% and 51% in the case of ethanosolv and butanosolv isolation, respectively[164,169]. Lignins stabilized in such a way could be selectively depolymerized to monomers in yields of up to 35% (for 18% of the lignin extracted), which is 15–20% of theoretical yields based on the original lignin but fourfold higher than what was obtained with technical lignin from the same biomass species[49,164–166].

Lignins stabilized by etherification at Cα are valuable substrates for further modification. The reversible nature of the etherification reaction means that one can 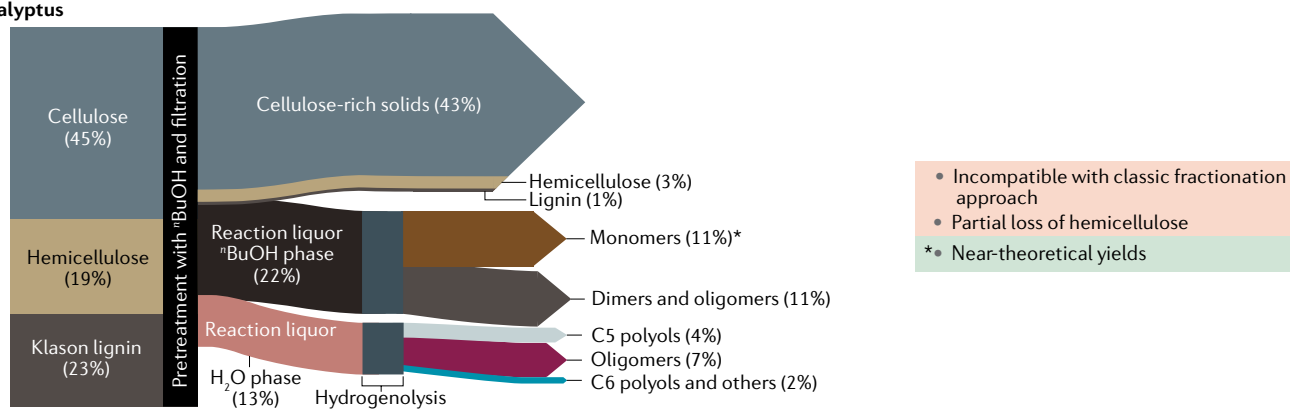readily regenerate native-like lignin, notably by subjecting the ether to mildly acidic dioxanosolv conditions (0.1 M HCl, 100 °C; albeit with some degradation in the form of a 30% decrease in β-O-4′ linkages). Interestingly, these α-alkylated β-O-4′ motifs can be considered protected versions of the Cα–OH species, so one can now perform selective oxidation of the Cγ–OH group and, thereby, open alternative defunctionalization pathways[96,150].

As with organosolv processing, fractionation with aliphatic alcohols preserves most of the carbohydrate fraction. For example, the solid residue obtained from HCl-catalysed butanosolv beech wood fractionation has been subjected to enzymatic hydrolysis to give ~70 wt% yields of reducing sugars (based on the original carbohydrate content in biomass)[164]. Part of the more labile hemicellulose reacts with the solvent during the fractionation process to give the corresponding alkyl glycosides in detectable quantities.

Functionalization with acetals

Another even more common reversible functionalization reaction is acetal formation, which often involves a diol reacting with a carbonyl compound to liberate H₂O and give a cyclic acetal or ketal. The reaction is particularly favourable in the case of aldehydes and, thus, could be an interesting means to prevent degradation reactions because a diol or aldehyde trapped in an acetal ring cannot dehydrate or condense. Lignin's β-O-4′ linkage (**16**) has a diol structure, as do many polysaccharide functionalities (**3** and **4**). These diols may be reacted with aldehydes (**23**, **29**, **30**, **31**) (FIG. 3) to give acetals prior to lignin fragmentation. Additionally, one lignin-degradation mechanism features reactive aldehyde intermediates. Here, we can also stabilize these functionalities by converting them into their corresponding acetals, for example, using diols (**33–39**) (FIG. 3) before or after lignin fragmentation. We now review studies focused on lignin functionalization before

a Eucalyptus

Cellulose (45%)

Hemicellulose (19%)

Klason lignin (23%)

Pretreatment with ⁿBuOH and filtration

Cellulose-rich solids (43%)

Hemicellulose (3%)
Lignin (1%)

Reaction liquor ⁿBuOH phase (22%)

Monomers (11%)*

Dimers and oligomers (11%)

Reaction liquor

H₂O phase (13%)

Hydrogenolysis

C5 polyols (4%)
Oligomers (7%)
C6 polyols and others (2%)

- Incompatible with classic fractionation approach
- Partial loss of hemicellulose
*• Near-theoretical yields

b Birch

Minor sugars (3%)
Acid-soluble lignin (3%)
Extractives (3%)

Glucan (32%)

Xylan (18%)

Klason lignin (18%)

Acetyl (6%)
Ashes (0.15%) and other (11%)
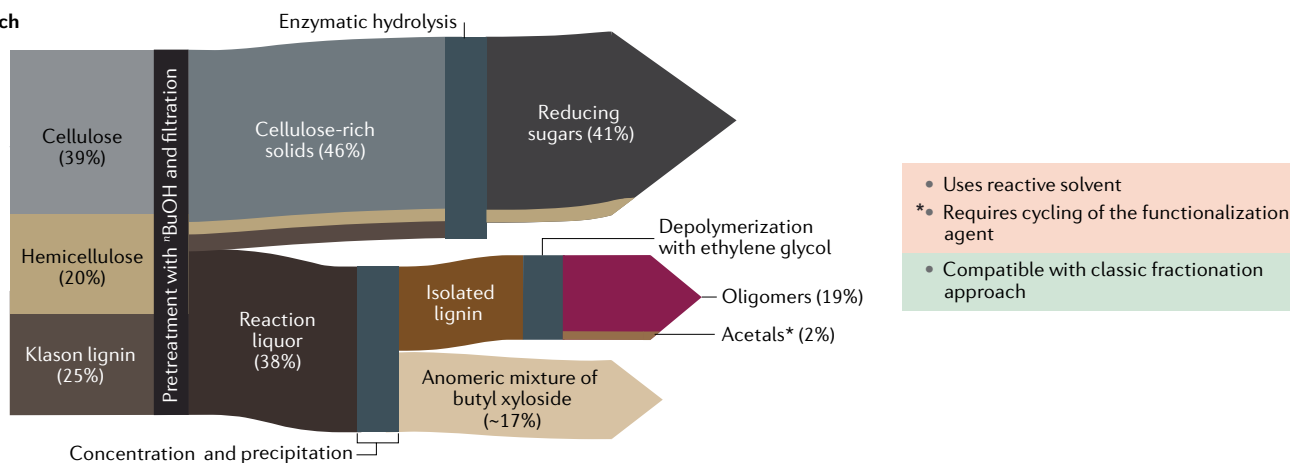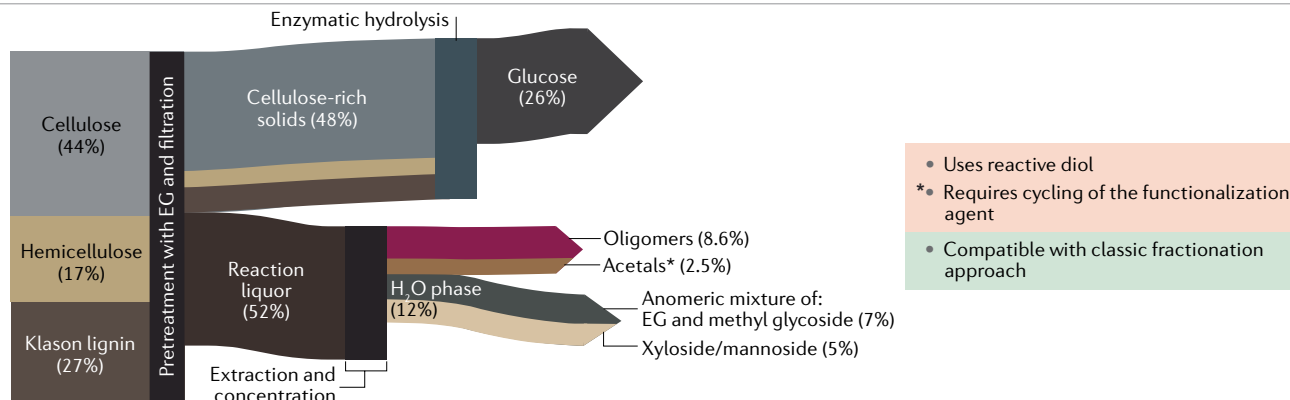Hydration (6%)

Extraction and drying

Pretreatment with PA and filtration

Enzymatic hydrolysis

Cellulose-rich solids (39%)

Glucose (30%)

Xylose (4%)

Propionaldehyde-stabilized lignin* (19%)

Monomers (8%)*,**

Hydrogenolysis

Reaction liquor (52%)

Liquor (33%)

Dipropylxylose* (11%)

Furfural (1%)
5-HMF (0.28%)

Precipitation and trituration

Neutralization, concentration and precipitation

- Uses reactive aldehyde
*• Requires cycling of the functionalization agent
- Compatible with classic fractionation approach
**• Near-theoretical yields

c Beech

Cellulose (39%)

Hemicellulose (20%)

Klason lignin (25%)

Pretreatment with ⁿBuOH and filtration

Enzymatic hydrolysis

Cellulose-rich solids (46%)

Reducing sugars (41%)

Reaction liquor (38%)

Isolated lignin

Depolymerization with ethylene glycol

Oligomers (19%)

Acetals* (2%)

Anomeric mixture of butyl xyloside (~17%)

Concentration and precipitation

- Uses reactive solvent
*• Requires cycling of the functionalization agent
- Compatible with classic fractionation approach

d Pine

Cellulose (44%)

Hemicellulose (17%)

Klason lignin (27%)

Pretreatment with EG and filtration

Enzymatic hydrolysis

Cellulose-rich solids (48%)

Glucose (26%)

Reaction liquor (52%)

H₂O phase (12%)

Oligomers (8.6%)
Acetals* (2.5%)

Anomeric mixture of:
EG and methyl glycoside (7%)
Xyloside/mannoside (5%)

Extraction and concentration

- Uses reactive diol
*• Requires cycling of the functionalization agent
- Compatible with classic fractionation approach

◄ Fig. 4 | **Overall mass balances of the main stabilization approaches. a** | The composition of eucalyptus and overall mass balance for its reductive catalytic fractionation[125]. **b** | Similarly, birch starting material can be subjected to biomass fractionation and treatment with propionaldehyde (PA; EtCHO) as part of acetal stabilization[51]. **c** | Another means of stabilization is the conversion of alcohols to ethers[164]. For example, treating beech with nBuOH eventually affords n-butyl ethers. **d** | A related approach is to form (cyclic) acetals using ethylene glycol (EG), an approach to converting C2 aldehydes into stable derivatives[126]. The thickness of each arrow is proportional to the composition and yield of the products. 5-HMF, 5-(hydroxymethyl)furfural.

describing the functionalization of polysaccharides. It is important to not forget the holistic picture of the fates of all biomass components, along with overall mass balances. These are described here for four stabilization routes beginning with different woods (FIG. 4).

Lignin. As discussed above, the C_{aryl}–O ether bonds, particularly those in the β-O-4′ motifs, readily undergo modifications that lead to degradation, often through benzylic carbocation intermediates that condense with a variety of nucleophiles (**18–28**) (FIG. 2). A possible means to prevent these undesired processes is to stabilize the substrate prior to carbocation formation. Specifically, a β-O-4′ linkage has a 1,3-propanediol group (**16**) (FIG. 2) that readily reacts with aldehydes, including CH_2O and most linear aldehydes, such as MeCHO or EtCHO (**29–31**), to form cyclic 1,3-dioxanes (**17**)[34]. Trapping the diol in the form of a cyclic acetal prevents its dehydration and subsequent degradation. Though acetal formation is a reversible reaction that liberates H_2O, the acetal form can be highly favoured when the H_2O concentration is low (<20 wt%). Furthermore, computational studies on model lignin dimers have predicted acetal formation to be far more favourable than condensation reactions, with the former reaction having an activation barrier 7.6 and 4.8 kcal mol⁻¹ lower in the case of MeCHO and EtCHO, respectively[170].

2D ^{1}H–^{13}C heteronuclear single-quantum coherence NMR has been used to show that aldehyde-stabilized lignin has almost all its native β-O-4′ linkages trapped as cyclic acetals[34,44]. The extracted lignin can then be further upgraded — either directly in the pretreatment liquor or isolated from the other biomass components. In particular, this aldehyde-stabilized lignin, which is soluble in polar solvents such as ethers and alcohols, can be depolymerized by hydrogenolysis over heterogeneous metal catalysts such as Pd, Ru or Ni to give monomers in 42–50% yield based on the original lignin content in a typical wild-type hardwood[34,44,51] (FIG. 4b). Even after isolation, overall monomer yields are often comparable (within 5%) to the yields obtained by RCF. These yields are close to the theoretical maximum monomer yields attainable through ether cleavage.

The present aldehyde-protection method can be combined with the oxidative depolymerization approach described earlier[56]. Specifically, lignin can be condensed with propionaldehyde to give an acetal that can later be deprotected and the Cα–OH group oxidized in a single step using DDQ and HNO_3 catalysts under O_2. A HCO_2H/HCO_2Na-mediated cleavage of the oxidized lignin's β-O-4′ ether bonds resulted in a 31–36 mol% (depending on whether a catalytic or stoichiometric quantity of the catalyst was used) yield of monophenolic

compounds with >90% selectivity for diketone products[56]. However, the yields remain 10–20% lower than those obtained when the same protected lignin is depolymerized using hydrogenolysis[44].

Acetals can also be formed later in lignin extraction as a means to stabilize monomeric depolymerization products. For example, as we have discussed, the fractionation of lignocellulosic biomass acidic solution affords reactive benzylic carbocations and unsaturated intermediates (**18** and **19**)[165]. These species can condense with nucleophiles but also undergo either H⁺ abstraction (C3 pathway) or loss of CH_2O through Cβ–Cγ bond cleavage as part of the C2 pathway (**24**). This pathway yields a single type of aldehyde, while the C3 pathway affords a group of products known as Hibbert ketones. Monomeric products from model acid hydrolysis studies were almost exclusively derived from the C3 pathway, suggesting that the aldehydes rapidly condensed under these conditions.

We have, so far, described how the diol functionalities in the lignin backbone might be trapped by reaction with external aldehydes. Likewise, the above monomeric C2 aldehydes that form during acid-catalysed lignin depolymerization can be trapped with external diols (**33–39**) to form stable acetals (**25**). Subjecting simple β-O-4′ model compounds to acidolysis in 1,4-dioxane at 140 °C using CF_3SO_3H in the presence of ethylene glycol affords protected aldehydes (**25**) in up to quantitative yields (in the case of arylethanol-β-aryl ethers)[171]. Apart from ethylene glycol (**33**), other potentially bio-derived species such as 1,3-propanediol, 1,2-butanediol and glycerol can be used to give the corresponding 1,3-dioxolanes or 1,3-dioxanes, respectively. Notably, using glycerol results in the formation of regioisomers (both 1,3-dioxolane and 1,3-dioxane) and several diastereomers. When more complex arylglycerol-β-aryl ether models are studied, one observes a 55% decrease in C2 acetal yields because the C3 pathway competes and carbocation intermediates undergo condensations (**18 → 28**)[165]. Hibbert ketones formed through the C3 pathway could also be protected in the form of ketals. When more complex models were used, the CH_2O released through the C2 pathway (**23**) was trapped by ethylene glycol to form 1,3-dioxolane (**32**; up to 85% yield) and can be quantified[166]. This ethylene glycol stabilization method was further tested on 28 lignins from different biomass sources and obtained by different isolation techniques, using various metal triflates instead of CF_3SO_3H. The yield of the targeted C2 acetals was proportional to the quantity of β-O-4′ linkages in the starting lignin and was as high as 8.4 wt% based on the original Klason lignin in biomass[49] (FIG. 4c). The fate of more complex lignin models featuring a combination of β-O-4′, β-5′ and β-β′ linkages has been studied and acetal formation was observed in the case of models containing β-O-4′ and β-5′ motifs, while a model containing a β–β′ linkage undergoes acid-catalysed epimerization.

Acid-catalysed fractionation of cedar wood meal has allowed for detection of up to 4.8 wt% (based on Klason lignin) stable monomeric C2 dimethyl acetals in PhMe/MeOH (REF.[172]). Recently, the acid-catalysed fractionation of pine lignocellulose in the presence of ethylene glycol

afforded C2 acetals (8.8 wt% based on Klason lignin)[126] (FIG. 4d). The remaining cellulose-rich solids were enzymatically digestible (up to 85% yield), while part of the cellulose and hemicellulose were dissolved during processing to give stable alkyl glycosides. After these alkyl glycosides are hydrolysed, the total overall glucose yield can reach 77 wt%, with the yield of hemicellulose sugars being ~30 wt%, according to the weight of the original cellulose and hemicellulose.

Polysaccharides. There are many ways, aside from conversion into stabilized derivatives, to avoid carbohydrate degradation to humins. However, in recent years, carbohydrate-stabilization techniques have emerged in parallel with analogous techniques developed for lignin. For example, the acetal strategy we described above for lignin is also appropriate for carbohydrates, which can feature 1,2-diol and 1,3-diol groups that can attack a carbonyl group. Indeed, carbohydrates react with both aldehydes and ketones under acid catalysis to give acetals (3 → 7, 4 → 8/9) (FIG. 1b) and ketals with extrusion of H_2O (REFS[173,174]). As mentioned above, the reversibility of the process means that it works best when the solvent mixture contains <20 wt% H_2O, as is the case in most organosolv processes. Aprotic solvents are the most suitable because OH groups in the solvent can compete with the diols for aldehyde substrates, limiting functionalization of the biomass-derived species. The removal of the acetal and recovery of simple sugars readily proceeds in aqueous solution with an acid catalyst[21,34,44,175].

Acetals are thought to form through a hemiacetal intermediate, which can convert to an oxocarbenium species in a rate-limiting step[175–177], after which attack by the second alcohol group gives the product. The rate of sugar functionalization appears to be substantially faster than its dehydration, which limits degradation to less-desirable humins[21]. For comparison, a similar reaction that converts glycerol and CH_2O into an acetal (32) has an apparent activation energy of 14 kcal mol^{-1} (REF.[178]), which is notably lower than what has been observed for sugar dehydration (FIG. 1a,b). Acetal functionalization as a means to trap intermediates has been used in the depolymerization of both hemicellulose and cellulose. However, given that cellulose requires high temperatures (>180 °C) to undergo acid organosolv processes, the degradation of functionalized sugars, which can equilibrate with unprotected sugars, is not insignificant and can lower yields of monosaccharides[21].

We recently reported that, when an aldehyde is introduced to an acid organosolv pretreatment (using an aprotic co-solvent), hemicellulose-derived sugars and lignin react with the aldehyde to give xylose acetal (7) and stabilized lignin fragments (17) in near-theoretical yields[21,34,44]. In the case of cellulose, using an aldehyde in a flow-through set-up with GVL solvent produced glucose acetal isomers (8, 9) that resisted degradation, such that glucose recovery and concentration are increased by 2–3-fold compared with the same system run in the absence of an aldehyde. This increase allowed us to obtain products in ~70% yield with equivalent glucose concentrations close to 5 wt%. Degradation was

attenuated because the modified carbohydrates cannot undergo dehydration, the primary pathway to humin formation. Aldehydes other than CH_2O can afford a new stereogenic centre in the acetal product, thereby generating two isomers[51]. Of course, this stereogenic centre is lost upon deprotection.

Just as biomass-derived carbohydrates can be stabilized as acetals, they can also be converted to their corresponding ketals[21,34,44,179–181]. Ketalization of biomass-derived carbohydrates can be conducted using, for example, organosolv pretreatments with 70–90% Me_2CO and dilute mineral acids[180]. The ketal sugars are similar to the acetals in that they do not readily undergo dehydration and degradation[180,181]. This method has been used to improve the quality of bio-oil by protecting carbohydrates in the form of C_5 and C_6 ketals[179]. More recently, the ketal approach was used in acid organosolv biomass pretreatment (along with other protecting groups), but this led to similar carbohydrate yields to those in control experiments[44]. The lack of a substantial increase in carbohydrate yields could be attributed to the protection and degradation reactions having similar rates, which likely limited the merits of stabilization here.

Sugars that have been converted into acetal or ketal forms are robust towards dehydration and can be converted back to simple sugars, but may also serve as useful intermediates for further reactions. Indeed, they can be produced in high yields and could be interesting platform molecules. Recent work has shown that they have unique reactivity and separation properties and, thus, could be part of new upgrading schemes within biorefineries. For example, diformylxylose (formaldehyde-stabilized xylose 7) can be converted to furfural (12) through a unique mechanism that does not require a Lewis acid but only a Brønsted acid and heating at 160 °C (REF.[21]). Additionally, diformylxylose is sufficiently volatile to be purified by distillation and upgraded into xylitol (10), thereby eliminating one of the most expensive and complex steps in typical xylitol-production schemes — purification by chromatography[182].

Sustainability of stabilization approaches

The development of economically successful biorefineries will require sustainable and easily implementable catalytic methods to depolymerize all major biopolymers. The economic viability and sustainability will require us to isolate individual molecules in high yields, which means avoiding substantial mass loss. It is particularly bad if the products feature substantially fewer C atoms than the raw biomass, because photosynthesis is such an energy-intensive process. High yields lead to lower process costs and environmental impacts, with the latter also being lowered by implementing 'green' processing steps. For this reason, we first briefly compare selected stabilization methods: RCF (FIG. 4a), stabilization with reactive aldehydes (FIG. 4b), stabilization with alcohols (FIG. 4c) in alcohol-rich media, as well as stabilization with diols in aprotic media (FIG. 4d). Our comparison involves assessing each method according to the main principles of green chemistry[183]. We will then discuss sustainable upgrading and how these stabilized monomers might be used.

Comparison of stabilization approaches

RCF and aldehyde stabilization can transform lignin into monomers in near-theoretical yields (FIG. 4a,b), while etherification with alcohols (FIG. 4c) usually gives lower yields of monophenolic compounds, based on the original Klason lignin content, because lignin extraction is inefficient and intermediate trapping is incomplete. However, some of the carbohydrate fraction in RCF is converted to polyols (**10**, **11**) (FIGS 1,5b), which may be desirable but limits upgrading possibilities. Reacting sugars, lignin or lignin monomers with aldehydes affords products that can either be more desirable or that can introduce complications, depending on the application.

In considering the reagents for stabilization, RCF uses H_2, which is typically less expensive than the aldehydes or alcohols used (FIG. 3) and is essentially integrated into the final product, which is attractive in terms of atom economy. In principle, the acetal strategy and the alcohol functionalization strategy (FIG. 4b–d) use carbonyl compounds as protecting reagents to preserve the β-O-4′ moiety. Derivatization is not ideal from a sustainability perspective (eighth principle of green chemistry)[183], so either deprotection needs to be extremely efficient, which is usually easier for alcohol stabilization due to the lower stability of this functionality, or the functionalized intermediate be directly useful, obviating the need to cycle the stabilization agent. In any case, these stabilization agents (H_2, H atom donors, carbonyl compounds, alcohols) should be produced from renewable resources, which is technically possible but not necessarily performed industrially.

A very important issue in terms of sustainability and green chemistry (fifth principle)[183] for any process is the nature, recyclability and amount of solvent used. In this regard, several stabilization strategies offer possibilities for the use of bio-derived and non-toxic reaction media. The process solvent demand is reflected in the biomass:liquor ratio, a measure by which stabilization strategies are comparable to present conventional fractionation processes (1:10–1:20 versus 1:3–1:10, depending on the biomass origin). RCF systems predominantly utilize alcohol–H_2O solutions (50–100% MeOH, EtOH or *n*BuOH) and the high alcohol-fractionation process similarly relies on bio-derivable alcohols. Stabilization of diols can be performed by transesterification with dimethyl carbonate, a renewable, non-toxic reagent[184]. The conversion of diols to acetals has mostly been performed in 1,4-dioxane (a fossil-based, non-green solvent) but has also been performed with GVL, which is green and relatively easy to produce from glucose[34]. The aldehydes used are currently largely fossil-based and would ideally be produced from renewable feedstocks. All methods generally involve handling flammable organic solvents, which poses additional engineering problems when considering scale-up. RCF would pose the most demanding problem when run with H_2 because it often requires elevated operating pressures and the gas must be recycled. Biomass loading and discharging of solid carbohydrate residues must be compatible with a H_2 atmosphere, which requires specialized infrastructure (for example, reaction vessels that are not prone to hydrogen embrittlement) that adds to the high capital costs.

To improve process sustainability, we may need to design alternative solvents that can both effect depolymerization and then convert monomers into stabilized derivatives. This concept has been applied to arylethanol-β-aryl ether model compounds for the stabilization of reactive C2 aldehydes in an acid–IL solvent system that sees the aldehydes stabilized as their ethylene glycol acetals in up to 60% yield. Alternatively, one can use a Brønsted acid–Ru nanoparticle–IL system to effect acidolysis and then catalytic hydrogenation of the monomers to give C2 alcohols in 64% yield[185]. In this case, both the depolymerization and the stabilization reaction are performed by the reaction medium.

Let us now consider the energy balance and efficiency of selected processes. Those focused on lignin structure preservation using alcohols or aldehydes (FIG. 4b,c) are the mildest and can be conducted at 80 °C (5 h) and 90 °C (6 h), respectively, but only over long reaction times. The RCF and stabilization with diols are substantially shorter (1–2 h) processes but demand higher temperatures of ~200 °C and ~140 °C, respectively. However, the latter two processes directly deliver monophenols, whereas the former two need an additional depolymerization step. On the other hand, the aldehyde stabilization process (acetal formation, FIG. 4b) involves the isolation of the three biomass fractions, allowing for the subsequent use of a broader range of lignin and carbohydrate valorization methods, as well as the independent optimization of the fractionation and valorization steps. These advantages have to be weighed against the need to cycle the stabilizing reagent, which will undoubtedly increase process complexity.

The methods that use alcohols or aldehydes to stabilize biomass-derived species are essentially compatible with established organosolv pulping methods, and, thus, only require adjustment of solvents and/or reaction conditions. With RCF, near-theoretical yields are obtained from the lignin fraction, but the conditions necessary for high delignification see C_5 sugars partially degraded or lost, while catalyst recycling is another key challenge that remains unsolved on the industrial scale. On the laboratory scale, catalyst recycling has been proposed to involve physical separation of the catalyst in a different compartment[57,58,186], or catalyst caging and flowing newly solubilized lignin to the catalyst surface[187], isolation of the magnetically active solid catalyst using a magnet[187] or integrating a second catalytic step to fully convert all process residues to predominantly liquid products[188].

Renewable atom balance and applications

Each of the stabilization methods described here allows access to several platform chemicals in high yield and selectivity (FIG. 5). To assess the extent of renewable atom retention in these components and their subsequent use (FIG. 5a), and to make our comparison quantitative, we have calculated the biomass utilization efficiency (BUE, see calculation details in the supplementary information)[189] for each process. The BUE is the percentage of initial biomass that is in the end product, according to the molar mass of the reactant (the native biomass monomer in this Review) and target bio-based product. More specifically, BUE_S designates the theoretical

a

b

c
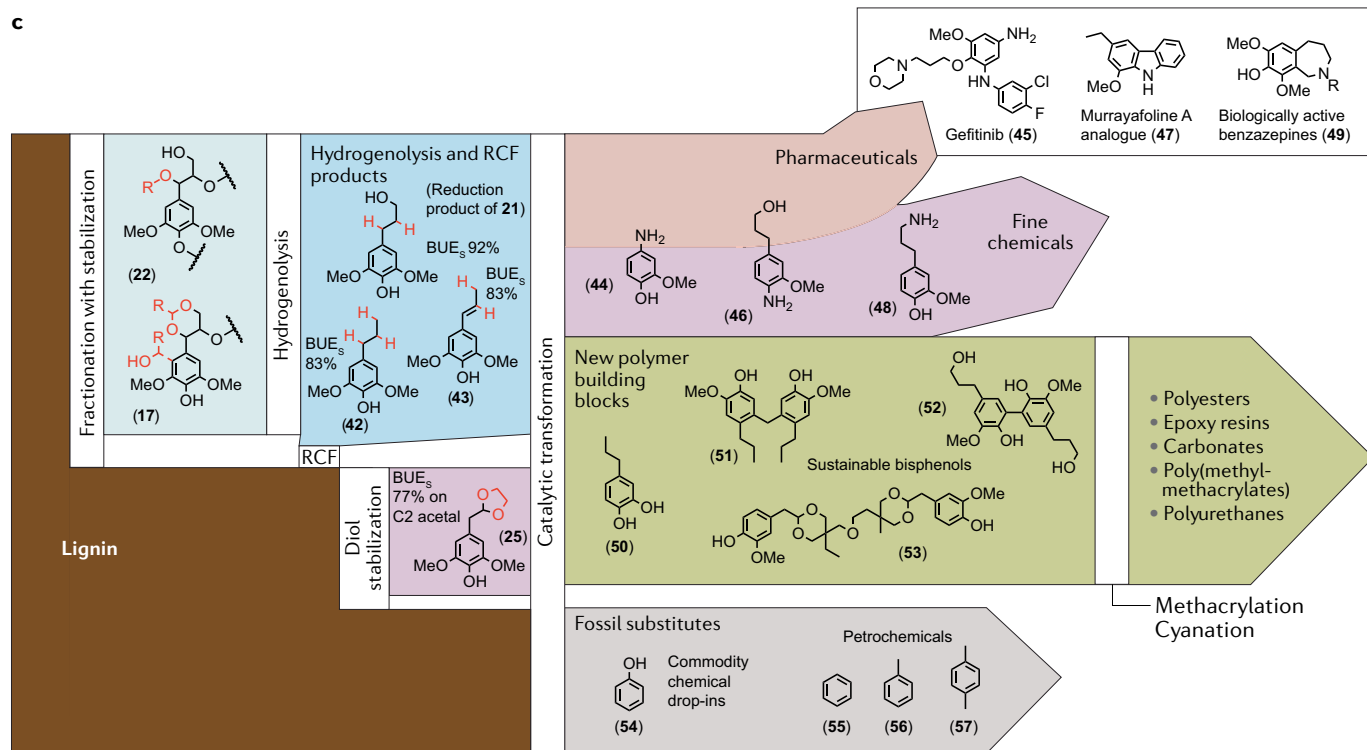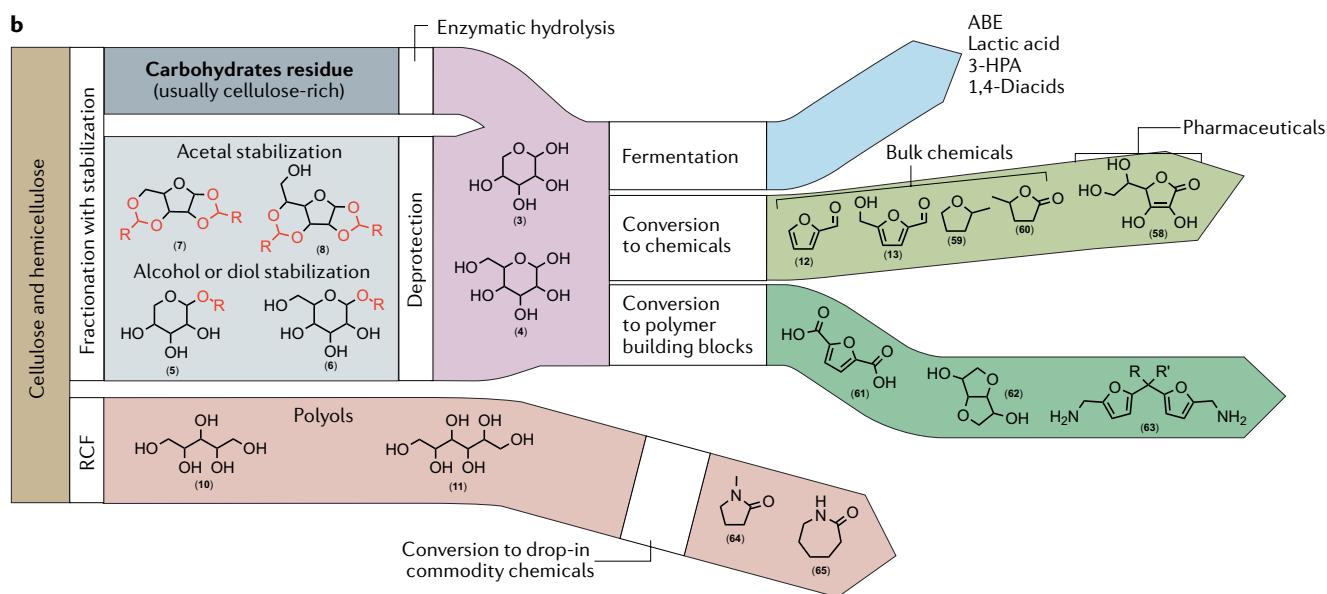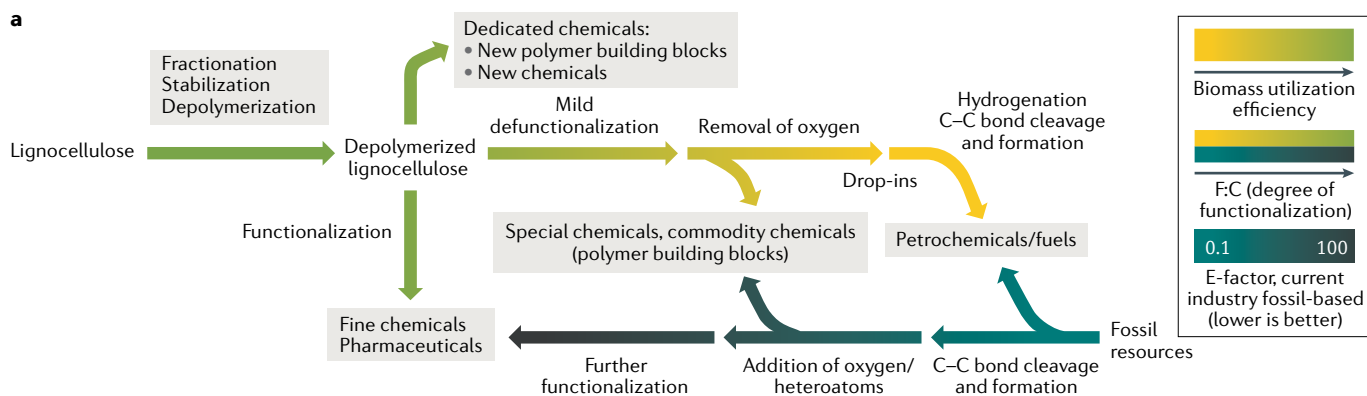
Fig. 5 | **Upgrading strategies for lignin-derived and polysaccharide-derived products. a** | The general approach to upgrading and the products that are available. Several species can serve as replacements for fossil-derived chemicals, while other 'dedicated' products are bio-based chemicals with no fossil counterpart (see further definitions in the supplementary information). **b** | Upgrading routes for carbohydrate-based molecules. **c** | Upgrading routes for lignin-based molecules. Arrow thicknesses are not proportional to yield. 3-HPA, 3-hydroxypropionaldehyde; ABE, acetone/butanol/ethanol; BUE, biomass utilization efficiency; RCF, reductive catalytic fractionation.

value describing the percentage of reactant ending up in the product only based on the chemical reaction itself. While not without limitations[189], the concept of maximizing the BUE is analogous to the classical definition of atom economy emphasized in the second principle of green chemistry. The BUE values for the molecular products of the stabilization methods clearly reflect a very high renewable atom retention (FIG. 5b,c).

What becomes clear is that novel stabilization methods can deliver high yields of well-known platform chemicals from hemicellulose and cellulose fractions, for which several established conversion strategies exist (FIG. 5b). Simultaneously, the novel lignin depolymerization–stabilization methods have made available previously unforeseen aromatic monomers that are structurally more complex than the simple molecules usually generated under harsher processes, such as pyrolysis or liquefaction[14,190]. These new molecules could participate in further atom-economical transformations, many of which are still only at the demonstration stage (FIG. 5c). Very recently, great progress has been made regarding the synthesis of novel polymers starting from aromatics (for example, **21**)[35,44,123,165,172] (FIG. 2b) obtained by the aforementioned stabilization strategies. Specifically, propyl guaiacol (**42**) can be a source of bisphenols either by demethylation of the OMe group (**42** to **50**) or by acid-catalysed condensation with CH_2O (**42** to **51**) (FIG. 5c). These have been used for the manufacture of bio-based polyesters[191–193], polycarbonates[191–193], polycyanurates[191–193] and epoxy nanocomposites[194]. Furthermore, propanol guaiacol (**21**) and a depolymerization mixture obtained by RCF, which is rich in lignin oligomers (such as **52**), can be glycidylated (i.e. addition of an epoxy function by forming a glycidyl ether or ester from a hydroxyl) to give epoxy resins that could substitute up to 75% of bisphenol A diglycidyl ether in several formulations[195]. Isoeugenol (**43**) obtained by RCF has been used in epoxy-resin synthesis by transforming it into diglycidyl ether through glycidylation and then epoxidation of the double bond[196]. Products of C2 acetal stabilization can also be used to prepare bisphenols through transacetalization (**25** to **53**) (FIG. 5c) and subsequent glycidylation reactions, for example, using lignocellulose-derived protected C2 acetal as an aromatic monomer[197]. In all cases, the mechanical and thermal properties of the bio-based polymers compared favourably to those of conventional materials or were even superior[193].

The emerging lignin-based bisphenols have high BUE values (83–92%) and represent sustainable alternatives to bisphenol A (BPA). For comparison, producing the BPA precursor PhOH from lignin would lead to more than a 50% loss of the native monomer

structure (BUE = 47%, FIG. 5c). The high BUE numbers of these monoaromatics show that it is preferable to find strategies to incorporate these monomers into novel products with little structural modification. This approach holds enormous potential in terms of green chemistry because it allows the manufacture of novel sustainable products with potentially superior biodegradability and lower toxicity relative to present materials. Lower toxicity has already been demonstrated for some of the new polymer building blocks in the case of BPA analogues, where the best examples demonstrate no detectable oestrogenic activity[191,198].

The higher O content of lignin-derived monophenolic compounds offers great opportunities for the design of waste-free coupling pathways[188,199], including heteroatom insertion through the hydrogen-borrowing strategy or by activating aromatic OH and OMe groups[200–202]. Such transformations could lead to a marked reduction in waste associated with the production of fine chemicals and pharmaceutical intermediates, and could open the way for the design of novel biologically active compounds (FIG. 5c; see Supplementary Fig. 4 for detailed synthesis strategies). The monophenols will also need to be amenable to the incorporation of N atoms, which are prevalent in bioactive compounds. Encouragingly, the phenols can be converted to their corresponding anilines, as was demonstrated for propyl guaiacol (**42**) and ethyl guaiacol (obtained by RCF), which were oxidized to the corresponding benzoquinone ketal before reaction with glycine methyl ester hydrochloride. In the case of ethyl or propyl guaiacol, this strategy affords building blocks that can be converted to valuable carbazoles in a single step (**47**) (Supplementary Fig. 4). Alternatively, aniline derivatives were obtained from ethyl guaiacol by Ni-catalysed Buchwald–Hartwig amination via the corresponding pseudohalides, a method whose atom economy depends on the nature of the pseudohalide. Therefore, catalytic strategies for the direct activation of aromatic OH and OMe groups for use in Buchwald–Hartwig amination or cross-coupling reactions are interesting future research directions[200–202]. Another interesting study used propyl guaiacol as the core building block to synthesize the anticancer drug gefitinib[203] (**42** → **45**) (FIG. 5c). Introduction of N was carried out through a Beckmann rearrangement that gave dialkoxyanilines that were further converted to the desired drug molecule.

Another elegant method to introduce N atoms into lignin-derived monophenols (**21**) is the Ru-catalysed amination of the primary alcohol in dihydroconiferyl and dihydrosynapyl alcohol by means of the hydrogen-borrowing approach. The resulting secondary amines were subjected to the Pictet–Spengler reaction to give seven-membered N-heterocycles (**49**), with H_2O being the only by-product[199]. The modular synthesis strategy allowed access to a library of linear and cyclic amines that showed promising antimicrobial and anticancer properties in initial tests.
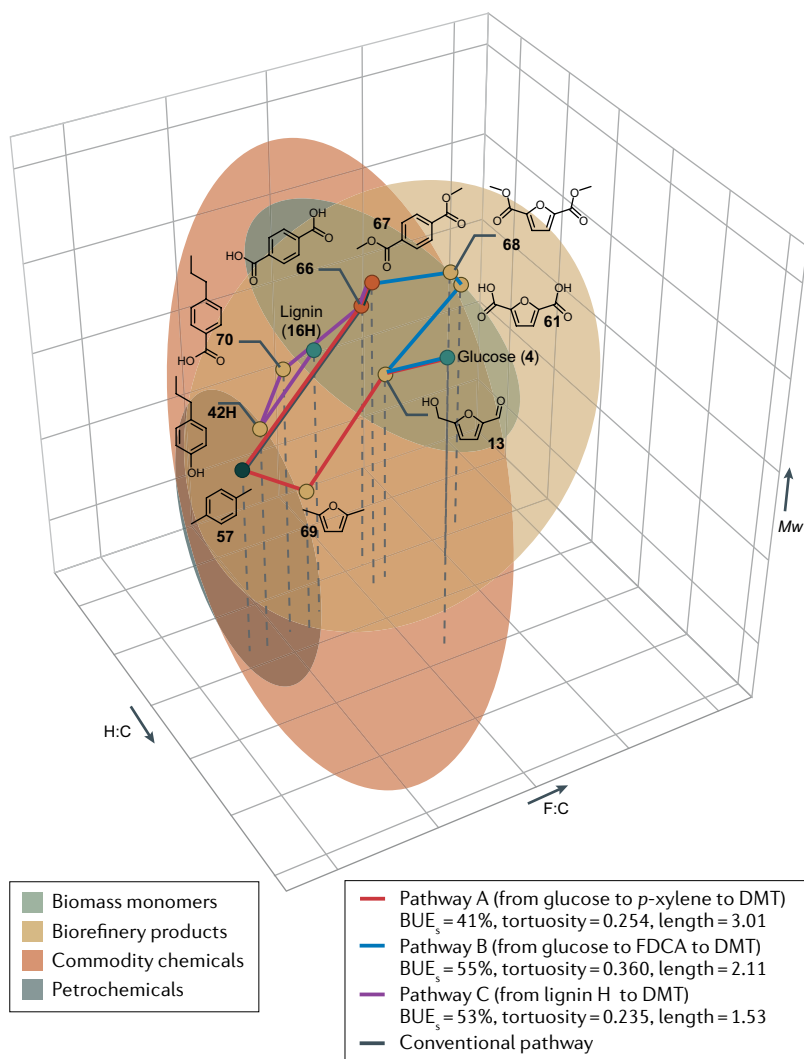
Of course, lignin-derived monophenols can also be subjected to 'defunctionalization' reactions to produce direct drop-in substitutes for petrochemicals, which means that a fossil-derived chemical can, instead, be

made using a renewable bio-based approach. Using drop-in chemicals is, of course, convenient for current industries, but the BUE values are low and, if the compounds require refunctionalization, then our present methods to do so are frequently highly polluting. Moreover, these challenging transformations usually require the cleavage of strong C–O and C–C bonds and, therefore, a high energy input.

To illustrate the trade-offs between defunctionalizing bio-based molecules and producing direct drop-in substitutes for fossil-based molecules, we depict the various production routes in a modified 3D van Krevelen plot (FIG. 6). The tortuosity of a specific route through this space represents the change in functionality and of the original carbon skeleton, and, as a result, the overall efficiency of the transformation[204]. Therefore, transformations with the fewest steps that minimize reactant alteration will show less tortuosity and are reflected in a shorter distance between starting materials and ultimate products.

An illustrative example is the synthesis of dicarboxylic acids and their methyl esters as part of the preparation of polyesters: fossil-based dimethyl terephthalate (DMT, **67**) from terephthalic acid (PTA, **66**) for polyethylene terephthalate (PET) production or its renewable analogues (FIG. 6). Fossil-based DMT is obtained from PTA, which, in turn, is available from *p*-xylene (**57**) through oxidation. However, while *p*-xylene is a basic petrochemical building block, producing it from glucose[204,205] requires three steps, and two additional steps will be needed to transform *p*-xylene to DMT (synthetic route A, Supplementary Fig. 6). This requires a total of 2.4 tons of glucose for each ton of biomass incorporated into DMT. An alternative four-step route to DMT starts from lignin[206], where lignin monophenols produced by RCF were converted into 4-alkylbenzoic acids (**70**) through selective demethoxylation, followed by carbonylation. Subsequent oxidation yielded PTA, which was esterified to DMT (synthetic route C, Supplementary Fig. 6). This route demands 1.8–2.3 tons of monomer (depending on its structure, Supplementary Fig. 3) to produce 1 ton of final product. Another, recently commercialized strategy targets an alternative polymer based on 2,5-furandicarboxylic acid (FDCA, **61**). FDCA can be co-polymerized with ethylene glycol to give a product with properties comparable to and, in some respects, better that those of conventional PET[207]. Among the presented alternatives, synthetic routes that include a direct (drop-in) substitution of DMT have a higher tortuosity (by about 1 unit) and greater length (0.25 and 3.0, respectively)[204], especially in comparison to the production of the alternative building block dimethyl 2,5-furandicarboxylate (DMFC, 0.44 and 1.8). The same conclusion comes from calculating BUE values for these various routes. The most atom-economical approach among these options will be the same — production of DMFC for polyethylene furanoate (PEF) synthesis ($4 \rightarrow 68$), which will result in preserving the most biomass-derived atoms and, therefore, lower the demand for the starting material to only 1.5 tons of glucose per ton of biomass incorporated into the monomer. This analysis illustrates how producing indirect replacements such as FDCA allow for the most efficient biomass utilization and the fewest processing steps. In general, we see that it is important to best exploit the biomass structures that are already available.

Opportunities and outlook

The stabilization chemistry reviewed here has afforded new opportunities in biomass conversions. Older approaches were mostly shaped by unfavourable depolymerization kinetics, where these reactions were outpaced by degradation reactions. In particular,

Fig. 6 | **Modified 3D van Krevelen plot and pathways to terephthalic acid starting from both biomass and fossil fuels.** The three parameters that define the chemical space are: functional groups density (F:C), which characterizes the ratio between C and heteroatoms, as well as degree of unsaturation (for a detailed definition of the F parameter, see the supplementary information)[216], number of H atoms for each C atom (H:C) and molecular weight (Mw). Different subclasses, such as biomass-derived monomers, petrochemicals and biorefinery products, occupy separate areas of the plot due to their different H content and functional-group density. Compounds with low or no functionality and high H content are petrochemicals such as benzene, toluene, xylenes, ethylene and hexane. Compounds with moderate functionality include present commodity chemicals and biorefinery products. Compounds with the highest functionality and lowest H content are presently derived from lignocellulose (C_6 and C_5 carbohydrates and G, H and S lignin monomers). BUE, biomass utilization efficiency; DMT, dimethyl terephthalate, FDCA, 2,5-furandicarboxylic acid.

biomass-conversion schemes were largely focused on creating favourable kinetics for polysaccharide conversion by using concentrated acids, ILs or enzymes. These traditional approaches usually ignored lignin, which always had the most unfavourable depolymerization kinetics. The introduction of stabilization strategies has allowed processes to run under conditions that were previously unfavourable by trapping reactive intermediates and preventing undesirable degradation or repolymerization reactions. The strategies allow the depolymerization of lignin in its more native form in high yields and simultaneously open new routes to sugar production. For example, one can produce lignin-derived monoaromatics along with carbohydrates or polyols that largely retain all the atoms originally in the plant, such that the conversion processes have high atom economy. Some of these lignin-derived monoaromatics are known as 'dedicated' bio-based products because they are only available through these processes. This has spawned new valorization routes to value-added compounds such as bulk polymer precursors or high-value pharmaceuticals, which can even have properties, including reduced toxicity, superior to their fossil-derived counterparts.

Up to now, industry has not been willing to adapt to using new products, which have high initial registration and regulation costs. Instead, industry has largely favoured direct drop-in replacements, despite these compounds usually requiring more processing and being less atom-economical. At the same time, stabilization strategies systematically involve the use of an external functionalization agent to stabilize reactive intermediates. This agent and the non-aqueous solvent both need to be produced and/or recycled throughout the process. These requirements will inherently drive up costs and lower process sustainability, but can be mitigated with emerging strategies. For example, one can integrate the stabilization reagent into the desired product to improve atom economy or instead use an alternative reaction medium that incorporates the stabilization function and/or facilitates product separation.

Overall, stabilization strategies have widened the panoply of attainable bio-based molecules, while offering opportunities to drastically improve the atom economy of their production routes. In addition to considering the principles of green chemistry, any scale-up will need to be economically viable and relatively easy to operate to compete with conventional refineries. Eventual industrial implementation will require similar progress geared towards the process-development and engineering phases that lie ahead.

Published online 22 May 2020

1. Muradov, N. in *Liberating Energy from Carbon: Introduction to Decarbonization* (ed. Muradov, N.) 141–184 (Springer, 2014).
2. Luterbacher, J. S., Alonso, D. M. & Dumesic, J. A. Targeted chemical upgrading of lignocellulosic biomass to platform molecules. *Green Chem.* **16**, 4816–4838 (2014).
3. Schutyser, W. et al. Chemicals from lignin: an interplay of lignocellulose fractionation, depolymerisation, and upgrading. *Chem. Soc. Rev.* **47**, 852–908 (2018).
4. Heinze, T. in *Cellulose Chemistry and Properties: Fibers, Nanocelluloses and Advanced Materials* (ed. Rojas, O. J.) 1–52 (Springer, 2016).
5. Rojas, O. J. (ed.) *Cellulose Chemistry and Properties: Fibers, Nanocelluloses and Advanced Materials* (Springer, 2016).
6. Nishiyama, Y., Langan, P. & Chanzy, H. Crystal structure and hydrogen-bonding system in cellulose Iβ from synchrotron X-ray and neutron fiber diffraction. *J. Am. Chem. Soc.* **124**, 9074–9082 (2002).
7. Nishiyama, Y., Sugiyama, J., Chanzy, H. & Langan, P. Crystal structure and hydrogen bonding system in cellulose Iα from synchrotron X-ray and neutron fiber diffraction. *J. Am. Chem. Soc.* **125**, 14300–14306 (2003).
8. Azizi Samir, M. A. S., Alloin, F. & Dufresne, A. Review of recent research into cellulosic whiskers, their properties and their application in nanocomposite field. *Biomacromolecules* **6**, 612–626 (2005).
9. Scheller, H. V. & Ulvskov, P. Hemicelluloses. *Annu. Rev. Plant. Biol.* **61**, 263–289 (2010).
10. Gírio, F. M. et al. Hemicelluloses for fuel ethanol: a review. *Bioresour. Technol.* **101**, 4775–4800 (2010).
11. Wilkie, K. C. B. in *Advances in Carbohydrate Chemistry and Biochemistry* Vol. 36 (eds Tipson, R. S. & Horton, D.) 215–264 (Academic, 1979).
12. Jones, D., Ormondroyd, G. O., Curling, S. F., Popescu, C.-M. & Popescu, M.-C. in *Advanced High Strength Natural Fibre Composites in Construction* (eds Fan, M. & Fu, F.) 23–58 (Woodhead, 2017).
13. Ralph, J., Lapierre, C. & Boerjan, W. Lignin structure and its engineering. *Curr. Opin. Biotechnol.* **56**, 240–249 (2019).
14. Zakzeski, J., Bruijnincx, P. C. A., Jongerius, A. L. & Weckhuysen, B. M. The catalytic valorization of lignin for the production of renewable chemicals. *Chem. Rev.* **110**, 3552–3599 (2010).
15. Bajpai, P. *Pretreatment of Lignocellulosic Biomass for Biofuel Production* (Springer, 2016).
16. Werpy, T. & Petersen, G. Top value added chemicals from biomass: volume I — Results of screening for potential candidates from sugars and synthesis gas (US Department of Energy, 2004).
17. Holladay, J. E., White, J. F., Bozell, J. J. & Johnson, D. Top value-added chemicals from biomass: volume II — Results of screening for potential candidates from biorefinery lignin (US Department of Energy, 2007).
18. van Putten, R.-J. et al. Hydroxymethylfurfural, a versatile platform chemical made from renewable resources. *Chem. Rev.* **113**, 1499–1597 (2013).
19. Rinaldi, R. et al. Paving the way for lignin valorisation: recent advances in bioengineering, biorefining and catalysis. *Angew. Chem. Int. Ed.* **55**, 8164–8215 (2016).
20. Putro, J. N., Soetaredjo, F. E., Lin, S.-Y., Ju, Y.-H. & Ismadji, S. Pretreatment and conversion of lignocellulose biomass into valuable chemicals. *RSC Adv.* **6**, 46834–46852 (2016).
21. Questell-Santiago, Y. M., Zambrano-Varela, R., Amiri, M. T. & Luterbacher, J. S. Carbohydrate stabilization extends the kinetic limits of chemical polysaccharide depolymerization. *Nat. Chem.* **10**, 1222–1228 (2018).
22. Lee, Y. Y., Iyer, P. & Torget, R. W. in *Recent Progress in Bioconversion of Lignocellulosics* (ed. Tsao, G. T.) 93–115 (Springer, 1999).
23. Carvalheiro, F., Silva-Fernandes, T., Duarte, L. C. & Gírio, F. M. Wheat straw autohydrolysis: process optimization and products characterization. *Appl. Biochem. Biotechnol.* **153**, 84–93 (2009).
24. Bobleter, O. Hydrothermal degradation of polymers derived from plants. *Prog. Polym. Sci.* **19**, 797–841 (1994).
25. Loerbroks, C., Rinaldi, R. & Thiel, W. The electronic nature of the 1,4-β-glycosidic bond and its chemical environment: DFT insights into cellulose chemistry. *Chem. Eur. J.* **19**, 16282–16294 (2013).
26. van Zandvoort, I. et al. Formation, molecular structure, and morphology of humins in biomass conversion: influence of feedstock and processing conditions. *ChemSusChem* **6**, 1745–1758 (2013).
27. Guadix-Montero, S. & Sankar, M. Review on catalytic cleavage of C–C inter-unit linkages in lignin model compounds: towards lignin depolymerisation. *Top. Catal.* **61**, 183–198 (2018).
28. Moriarty, K. L., Milbrandt, A. R., Warner, E., Lewis, J. E. & Schwab, A. A. 2016 bioenergy industry status report (US Department of Energy, 2018).
29. Renders, T., Van den Bosch, S., Koelewijn, S.-F., Schutyser, W. & Sels, B. F. Lignin-first biomass fractionation: the advent of active stabilisation strategies. *Energy Environ. Sci.* **10**, 1551–1557 (2017).
30. Shuai, L., Talebi Amiri, M. & Luterbacher, J. S. The influence of interunit carbon–carbon linkages during lignin upgrading. *Curr. Opin. Green Sustain. Chem.* **2**, 59–63 (2016).
31. Phongpreecha, T. et al. Predicting lignin depolymerization yields from quantifiable properties using fractionated biorefinery lignins. *Green Chem.* **19**, 5131–5143 (2017).
32. Talebi Amiri, M., Bertella, S., Questell-Santiago, Y. M. & Luterbacher, J. S. Establishing lignin structure-upgradeability relationships using quantitative ^{1}H–^{13}C heteronuclear single quantum coherence nuclear magnetic resonance (HSQC-NMR) spectroscopy. *Chem. Sci.* **10**, 8135–8142 (2019).
33. Yan, N. et al. Selective degradation of wood lignin over noble-metal catalysts in a two-step process. *ChemSusChem* **1**, 626–629 (2008).
34. Shuai, L. et al. Formaldehyde stabilization facilitates lignin monomer production during biomass depolymerization. *Science* **354**, 329–333 (2016).
35. Lan, W. & Luterbacher, J. S. Preventing lignin condensation to facilitate aromatic monomer production. *Chimia* **73**, 591–598 (2019).
36. Kim, S. et al. Computational study of bond dissociation enthalpies for a large range of native and modified lignins. *J. Phys. Chem. Lett.* **2**, 2846–2852 (2011).
37. Rinaldi, R. in *Lignin Valorization: Emerging Approaches* (ed. Beckham, G. T.) 108–127 (Royal Society of Chemistry, 2018).
38. Sturgeon, M. R. et al. A mechanistic investigation of acid-catalyzed cleavage of aryl-ether linkages: implications for lignin depolymerization in acidic environments. *ACS Sustain. Chem. Eng.* **2**, 472–485 (2014).
39. Parthasarathi, R., Romero, R. A., Redondo, A. & Gnanakaran, S. Theoretical study of the remarkably diverse linkages in lignin. *J. Phys. Chem. Lett.* **2**, 2660–2666 (2011).
40. Miles-Barrett, D. M. et al. The synthesis and analysis of lignin-bound Hibbert ketone structures in technical lignins. *Org. Biomol. Chem.* **14**, 10023–10030 (2016).
41. Shi, S. *Fundamental Study on Kinetics of Hemicellulose Hydrolysis and Bioconversion of Hemicellulose Hydrolysate Mixture into Lactic Acid*. Thesis, Auburn Univ. (2015).
42. Chum, H. L., Johnson, D. K., Black, S. K. & Overend, R. P. Pretreatment-catalyst effects and the combined severity parameter. *Appl. Biochem. Biotechnol.* **24**, 1 (1990).

43. Shimada, K., Hosoya, S. & Ikeda, T. Condensation reactions of softwood and hardwood lignin model compounds under organic acid cooking conditions. *J. Wood Chem. Technol.* **17**, 57–72 (1997).

44. Lan, W., Amiri, M. T., Hunston, C. M. & Luterbacher, J. S. Protection group effects during α,γ-diol lignin stabilization promote high-selectivity monomer production. *Angew. Chem. Int. Ed.* **57**, 1356–1360 (2018).

45. Li, N. et al. An uncondensed lignin depolymerized in the solid state and isolated from lignocellulosic biomass: a mechanistic study. *Green Chem.* **20**, 4224–4235 (2018).

46. Renders, T. et al. Influence of acidic (H_3PO_4) and alkaline (NaOH) additives on the catalytic reductive fractionation of lignocellulose. *ACS Catal.* **6**, 2055–2066 (2016).

47. Ouyang, X., Huang, X., Hendriks, B. M. S., Boot, M. D. & Hensen, E. J. M. Coupling organosolv fractionation and reductive depolymerization of woody biomass in a two-step catalytic process. *Green Chem.* **20**, 2308–2319 (2018).

48. Deuss, P. J. et al. Metal triflates for the production of aromatics from lignin. *ChemSusChem* **9**, 2974–2981 (2016).

49. Deuss, P. J. et al. Phenolic acetals from lignins of varying compositions *via* iron(iii) triflate catalysed depolymerisation. *Green Chem.* **19**, 2774–2782 (2017).

50. Parsell, T. et al. A synergistic biorefinery based on catalytic conversion of lignin prior to cellulose starting from lignocellulosic biomass. *Green Chem.* **17**, 1492–1499 (2015).

51. Talebi Amiri, M., Dick, G. R., Questell-Santiago, Y. M. & Luterbacher, J. S. Fractionation of lignocellulosic biomass to produce uncondensed aldehyde-stabilized lignin. *Nat. Protoc.* **14**, 921–954 (2019).

52. Chesi, C., de Castro, I. B. D., Clough, M. T., Ferrini, P. & Rinaldi, R. The influence of hemicellulose sugars on product distribution of early-stage conversion of lignin oligomers catalysed by Raney nickel. *ChemCatChem* **8**, 2079–2088 (2016).

53. Wan, G. & Frazier, C. E. Lignin acidolysis predicts formaldehyde generation in pine wood. *ACS Sustain. Chem. Eng.* **5**, 4830–4836 (2017).

54. Luterbacher, J. S. et al. Lignin monomer production integrated into the γ-valerolactone sugar platform. *Energy Environ. Sci.* **8**, 2657–2663 (2015).

55. Yokoyama, T. Revisiting the mechanism of β-O-4 bond cleavage during acidolysis of lignin. Part 6: A review. *J. Wood Chem. Technol.* **35**, 27–42 (2015).

56. Lan, W., de Bueren, J. B. & Luterbacher, J. S. Highly selective oxidation and depolymerization of α,γ-diol-protected lignin. *Angew. Chem. Int. Ed.* **58**, 2649–2654 (2019).

57. Anderson, E. M. et al. Flowthrough reductive catalytic fractionation of biomass. *Joule* **1**, 613–622 (2017).

58. Kumaniaev, I. et al. Lignin depolymerization to monophenolic compounds in a flow-through system. *Green Chem.* **19**, 5767–5771 (2017).

59. Zhou, H. et al. Rapid flow-through fractionation of biomass to preserve labile aryl ether bonds in native lignin. *Green Chem.* **21**, 4625–4632 (2019).

60. Wijaya, Y. P. et al. Comparative study on two-step concentrated acid hydrolysis for the extraction of sugars from lignocellulosic biomass. *Bioresour. Technol.* **164**, 221–231 (2014).

61. Timell, T. E. The acid hydrolysis of glycosides: I. General conditions and the effect of the nature of the aglycone. *Can. J. Chem.* **42**, 1456–1472 (1964).

62. Esteghlalian, A., Hashimoto, A. G., Fenske, J. J. & Penner, M. H. Modeling and optimization of the dilute-sulfuric-acid pretreatment of corn stover, poplar and switchgrass. *Bioresour. Technol.* **59**, 129–136 (1997).

63. Jin, Q., Zhang, H., Yan, L., Qu, L. & Huang, H. Kinetic characterization for hemicellulose hydrolysis of corn stover in a dilute acid cycle spray flow-through reactor at moderate conditions. *Biomass Bioenerg.* **35**, 4158–4164 (2011).

64. Fagan, R. D., Grethlein, H. E., Converse, A. O. & Porteous, A. Kinetics of the acid hydrolysis of cellulose found in paper refuse. *Environ. Sci. Technol.* **5**, 545–547 (1971).

65. Saeman, J. F. Kinetics of wood saccharification - hydrolysis of cellulose and decomposition of sugars in dilute acid at high temperature. *Ind. Eng. Chem.* **37**, 43–52 (1945).

66. Wyman, C. E. & Yang, B. in *Hydrothermal Processing in Biorefineries* (eds Ruiz H. A., Hedegaard Thomsen, M. & Trajano, H. L.) 161–180 (Springer, 2017).

67. Patil, S. K. R., Heltzel, J. & Lund, C. R. F. Comparison of structural features of humins formed catalytically from glucose, fructose, and 5-hydroxymethylfurfuraldehyde. *Energy Fuels* **26**, 5281–5293 (2012).

68. Chiang, Y. et al. Separation and purification of furans from n-butanol by zeolitic imidazole frameworks: multicomponent adsorption behavior and simulated moving bed process design. *ACS Sustain. Chem. Eng.* **7**, 16560–16568 (2019).

69. Metkar, P. S. et al. Reactive distillation process for the production of furfural using solid acid catalysts. *Green Chem.* **17**, 1453–1466 (2015).

70. Hoang, T. M. C., Lefferts, L. & Seshan, K. Valorization of humin-based byproducts from biomass processing - a route to sustainable hydrogen. *ChemSusChem* **6**, 1651–1658 (2013).

71. Kang, S. et al. Valorization of humins by phosphoric acid activation for activated carbon production. *Biomass Convers. Biorefin.* **8**, 889–897 (2018).

72. Rogalinski, T., Liu, K., Albrecht, T. & Brunner, G. Hydrolysis kinetics of biopolymers in subcritical water. *J. Supercrit. Fluids* **46**, 335–341 (2008).

73. Peterson, A. A. et al. Thermochemical biofuel production in hydrothermal media: a review of sub- and supercritical water technologies. *Energy Environ. Sci.* **1**, 32–65 (2008).

74. Sasaki, M., Fang, Z., Fukushima, Y., Adschiri, T. & Arai, K. Dissolution and hydrolysis of cellulose in subcritical and supercritical water. *Ind. Eng. Chem. Res.* **39**, 2883–2890 (2000).

75. Cantero, D. A., Bermejo, M. D. & Cocero, M. J. Kinetic analysis of cellulose depolymerization reactions in near critical water. *J. Supercrit. Fluids* **75**, 48–57 (2013).

76. Kilambi, S. & Kadam, K. L. Production of fermentable sugars and lignin from biomass using supercritical fluids. US patent US9359560B2 (2018).

77. Wagemann, K. & Tippkötter, N. in *Biorefineries* (eds Wagemann, K. & Tippkötter, N.) 1–11 (Springer, 2019).

78. Stuart, E. Advanced biorefinery process. European patent EP2069406A2 (2010).

79. Genta, M. et al. Biomass hydrothermal decomposition apparatus and method. US patent US9238827B2 (2010).

80. South, C. R., Wyman, C. E. & Martin, R. L. Two-stage method for pretreatment of lignocellulosic biomass. US patent US20100279361A1 (2010).

81. Nguyen, Q. A., Keller, F. A. & Tucker, M. P. Ethanol production with dilute acid hydrolysis using partially dried lignocellulosics. US patent US20030199049A1 (2003).

82. Tao, L. et al. *NREL 2012 achievement of ethanol cost targets: biochemical ethanol fermentation via dilute-acid pretreatment and enzymatic hydrolysis of corn stover* (US Department of Energy, 2014).

83. Luterbacher, J. S. et al. Nonenzymatic sugar production from biomass using biomass-derived γ-valerolactone. *Science* **343**, 277–280 (2014).

84. Shuai, L., Questell-Santiago, Y. M. & Luterbacher, J. S. A mild biomass pretreatment using γ-valerolactone for concentrated sugar production. *Green Chem.* **18**, 937–943 (2016).

85. Ghosh, A., Bai, X. & Brown, R. C. Solubilized carbohydrate production by acid-catalyzed depolymerization of cellulose in polar aprotic solvents. *ChemistrySelect* **3**, 4777–4785 (2018).

86. Shuai, L. & Luterbacher, J. Organic solvent effects in biomass conversion reactions. *ChemSusChem* **9**, 133–155 (2016).

87. Mellmer, M. A. et al. Solvent-enabled control of reactivity for liquid-phase reactions of biomass-derived compounds. *Nat. Catal.* **1**, 199–207 (2018).

88. Mellmer, M. A. et al. Effects of chloride ions in acid-catalyzed biomass dehydration reactions in polar aprotic solvents. *Nat. Commun.* **10**, 1132 (2019).

89. Mellmer, M. A. et al. Solvent effects in acid-catalyzed biomass conversion reactions. *Angew. Chem. Int. Ed.* **53**, 11872–11875 (2014).

90. Mellmer, M. A., Alonso, D. M., Luterbacher, J. S., Gallo, J. M. R. & Dumesic, J. A. Effects of γ-valerolactone in hydrolysis of lignocellulosic biomass to monosaccharides. *Green Chem.* **16**, 4659–4662 (2014).

91. Motagamwala, A. H., Won, W., Maravelias, C. T. & Dumesic, J. A. An engineered solvent system for sugar production from lignocellulosic biomass using biomass derived γ-valerolactone. *Green Chem.* **18**, 5756–5763 (2016).

92. Borand, M. N. & Karaosmanoğlu, F. Effects of organosolv pretreatment conditions for lignocellulosic biomass in biorefinery applications: a review. *J. Renew. Sustain. Energy* **10**, 033104 (2018).

93. Han, J., Luterbacher, J. S., Alonso, D. M., Dumesic, J. A. & Maravelias, C. T. A lignocellulosic ethanol strategy via nonenzymatic sugar production: process synthesis and analysis. *Bioresour. Technol.* **182**, 258–266 (2015).

94. Alonso, D. M. et al. Increasing the revenue from lignocellulosic biomass: maximizing feedstock utilization. *Sci. Adv.* **3**, e1603301 (2017).

95. Jérôme, F., Marinkovic, S. & Estrine, B. Transglycosylation: a key reaction to access alkylpolyglycosides from lignocellulosic biomass. *ChemSusChem* **11**, 1395–1409 (2018).

96. Panovic, I., Lancefield, C. S., Phillips, D., Gronnow, M. J. & Westwood, N. J. Selective primary alcohol oxidation of lignin streams from butanol-pretreated agricultural waste biomass. *ChemSusChem* **12**, 542–548 (2019).

97. Yu, F. et al. Fast catalytic conversion of recalcitrant cellulose into alkyl levulinates and levulinic acid in the presence of soluble and recoverable sulfonated hyperbranched poly(arylene oxindole)s. *Green Chem.* **19**, 153–163 (2017).

98. Deng, W., Liu, M., Zhang, Q., Tan, X. & Wang, Y. Acid-catalysed direct transformation of cellulose into methyl glucosides in methanol at moderate temperatures. *Chem. Commun.* **46**, 2668–2670 (2010).

99. Kanchanalai, P., Temani, G., Kawajiri, Y. & Realff, M. J. Reaction kinetics of concentrated-acid hydrolysis for cellulose and hemicellulose and effect of crystallinity. *BioResources* **11**, 1672–1689 (2016).

100. Moe, S. T. et al. Saccharification of lignocellulosic biomass for biofuel and biorefinery applications - a renaissance for the concentrated acid hydrolysis? *Energy Procedia* **20**, 50–58 (2012).

101. Cuzens, J. E. & Farone, W. A. Method of strong acid hydrolysis. US patent US5562777A (1998).

102. Liu, Z.-S., Wu, X.-L., Kida, K. & Tang, Y.-Q. Corn stover saccharification with concentrated sulfuric acid: Effects of saccharification conditions on sugar recovery and by-product generation. *Bioresour. Technol.* **119**, 224–233 (2012).

103. Ioelovich, M. Study of cellulose interaction with concentrated solutions of sulfuric acid. *Int. Sch. Res. Notices* **2012**, 428974 (2012).

104. Braconnot, H. Action de l'acide sulfurique sur la sciure de bois de charme. *Ann. Chim. Phys.* **12**, 172–195 (1819).

105. Stern, A. L. X. - Contributions to the chemistry of cellulose. I. Cellulose-sulphuric acid, and the products of its hydrolysis. *J. Chem. Soc. Trans.* **67**, 74–90 (1895).

106. Binder, J. B. & Raines, R. T. Fermentable sugars by chemical hydrolysis of biomass. *Proc. Natl Acad. Sci. USA* **107**, 4516–4521 (2010).

107. Swatloski, R. P., Spear, S. K., Holbrey, J. D. & Rogers, R. D. Dissolution of cellose with ionic liquids. *J. Am. Chem. Soc.* **124**, 4974–4975 (2002).

108. Samayam, I. P., Hanson, B. L., Langan, P. & Schall, C. A. Ionic-liquid induced changes in cellulose structure associated with enhanced biomass hydrolysis. *Biomacromolecules* **12**, 3091–3098 (2011).

109. Dee, S. J. & Bell, A. T. A study of the acid-catalyzed hydrolysis of cellulose dissolved in ionic liquids and the factors influencing the dehydration of glucose and the formation of humins. *ChemSusChem* **4**, 1166–1173 (2011).

110. Bergius, F. Conversion of wood to carbohydrates. *Ind. Eng. Chem.* **29**, 247–253 (1937).

111. Shahbazi, A. & Zhang, B. in *Bioalcohol Production* (ed. Waldron, K. W.) 143–158 (Woodhead, 2010).

112. BlueFire Renewables. Our technology. *BlueFire* https://bfreinc.com/our-technology/ (2011).

113. van Groenestijn, J. W., Hazewinkel, J. H. O. & Bakker, R. R. Pre-treatment of ligno-cellulose with biological acid recycling (the Biosulfurol process). *Int. Sugar J.* **110**, 689–692 (2008).

114. Gschwend, F. J. V., Brandt-Talbot, A., Chambon, C. L. & Hallett, J. P. in *Ionic Liquids: Current State and Future Directions* Vol. 1250 (eds Shiflett, M. B. & Scurto, A. M.) 209–223 (American Chemical Society, 2017).

115. Zhou, J. et al. Recovery and purification of ionic liquids from solutions: a review. *RSC Adv.* **8**, 32832–32864 (2018).

116. Konda, N. M. et al. Understanding cost drivers and economic potential of two variants of ionic liquid pretreatment for cellulosic biofuel production. *Biotechnol. Biofuels* **7**, 86 (2014).

117. Davies, G. & Henrissat, B. Structures and mechanisms of glycosyl hydrolases. *Structure* **3**, 853–859 (1995).

118. Jeoh, T., Cardona, M. J., Karuna, N., Mudinoor, A. R. & Nill, J. Mechanistic kinetic models of enzymatic

cellulose hydrolysis - a review. *Biotechnol. Bioeng.* **114**, 1369–1385 (2017).

119. Moreira, L. R. S. & Filho, E. X. F. Insights into the mechanism of enzymatic hydrolysis of xylan. *Appl. Microbiol. Biotechnol.* **100**, 5205–5214 (2016).

120. Luterbacher, J. S., Parlange, J.-Y. & Walker, L. P. A pore-hindered diffusion and reaction model can help explain the importance of pore size distribution in enzymatic hydrolysis of biomass. *Biotechnol. Bioeng.* **110**, 127–136 (2013).

121. Singh, N. et al. Overview of the process of enzymatic transformation of biomass. *IntechOpen* https://doi.org/10.5772/intechopen.85036 (2019).

122. Galkin, M. V. & Samec, J. S. M. Lignin valorization through catalytic lignocellulose fractionation: a fundamental platform for the future biorefinery. *ChemSusChem* **9**, 1544–1558 (2016).

123. Sun, Z., Fridrich, B., de Santi, A., Elangovan, S. & Barta, K. Bright side of lignin depolymerization: toward new platform chemicals. *Chem. Rev.* **118**, 614–678 (2018).

124. Huang, X. et al. Selective production of mono-aromatics from lignocellulose over Pd/C catalyst: the influence of acid co-catalysts. *Faraday Discuss.* **202**, 141–156 (2017).

125. Renders, T. et al. Catalytic lignocellulose biorefining in *n*-butanol/water: a one-pot approach toward phenolics, polyols, and cellulose. *Green Chem.* **20**, 4607–4619 (2018).

126. De Santi, A., Galkin, M. V., Lahive, C. W., Deuss, P. J. & Barta, K. Lignin-first fractionation of softwood lignocellulose a mild dimethyl carbonate and ethylene glycol organosolv process. *ChemSusChem* https://doi.org/10.1002/cssc.201903526 (2020).

127. Li, S., Lundquist, K. & Westermark, U. Cleavage of arylglycerol β-aryl ethers under neutral and acid conditions. *Nord. Pulp Pap. Res. J.* **15**, 292–299 (2000).

128. Nimz, H. A new type of rearrangement in the lignin field. *Angew. Chem. Int. Ed.* **5**, 843 (1966).

129. Kishimoto, T. & Sano, Y. Delignification mechanism during high-boiling solvent pulping. IV. Effect of a reducing sugar on the degradation of guaiacylglycerol-β-guaiacyl ether. *J. Wood Chem. Technol.* **23**, 233–248 (2003).

130. Sano, Y. & Kishimoto, T. Delignification mechanism during high-boiling solvent pulping. V. Reaction of nonphenolic β-*O*-4 model compounds in the presence and absence of glucose. *J. Wood Chem. Technol.* **23**, 279–292 (2003).

131. Omori, S., Aoyama, M. & Sakakibara, A. Hydrolysis of lignin with dioxane–water XIX. Reaction of β-*O*-4 lignin model compounds in the presence of carbohydrates. *Holzforschung* **52**, 391–397 (1998).

132. Zijlstra, D. S. et al. Extraction of lignin with high β-*O*-4 content by mild ethanol extraction and its effect on the depolymerization yield. *J. Vis. Exp.* **143**, e58575 (2019).

133. Jasiukaitytė-Grojzdek, E., Kunaver, M. & Crestini, C. Lignin structural changes during liquefaction in acidified ethylene glycol. *J. Wood Chem. Technol.* **32**, 342–360 (2012).

134. Li, H. & Song, G. Ru-catalyzed hydrogenolysis of lignin: base-dependent tunability of monomeric phenols and mechanistic study. *ACS Catal.* **9**, 4054–4064 (2019).

135. Nichols, J. M., Bishop, L. M., Bergman, R. G. & Ellman, J. A. Catalytic C–O bond cleavage of 2-aryloxy-1-arylethanols and its application to the depolymerization of lignin-related polymers. *J. Am. Chem. Soc.* **132**, 12554–12555 (2010).

136. He, J., Zhao, C. & Lercher, J. A. Ni-catalyzed cleavage of aryl ethers in the aqueous phase. *J. Am. Chem. Soc.* **134**, 20768–20775 (2012).

137. Jiang, L., Guo, H., Li, C., Zhou, P. & Zhang, Z. Selective cleavage of lignin and lignin model compounds without external hydrogen, catalyzed by heterogeneous nickel catalysts. *Chem. Sci.* **10**, 4458–4468 (2019).

138. Anderson, E. M. et al. Differences in S/G ratio in natural poplar variants do not predict catalytic depolymerization monomer yields. *Nat. Commun.* **10**, 2033 (2019).

139. Anderson, E. M., Stone, M. L., Hülsey, M. J., Beckham, G. T. & Román-Leshkov, Y. Kinetic studies of lignin solvolysis and reduction by reductive catalytic fractionation decoupled in flow-through reactors. *ACS Sustain. Chem. Eng.* **6**, 7951–7959 (2018).

140. Sarkanen, K. V. & Hoo, L. H. Kinetics of hydrolysis of erythro-guaiacylglycerol β-(2-methoxyphenyl) ether and its veratryl analogue using Hcl and aluminum chloride as catalysts. *J. Wood Chem. Technol.* **1**, 11–27 (1981).

141. Li, Y. et al. Kinetic and mechanistic insights into hydrogenolysis of lignin to monomers in a continuous flow reactor. *Green Chem.* **21**, 3561–3572 (2019).

142. Anderson, E. M. et al. Reductive catalytic fractionation of corn stover lignin. *ACS Sustain. Chem. Eng.* **4**, 6940–6950 (2016).

143. Schutyser, W. et al. Influence of bio-based solvents on the catalytic reductive fractionation of birch wood. *Green Chem.* **17**, 5035–5045 (2015).

144. Galkin, M. V. et al. Hydrogen-free catalytic fractionation of woody biomass. *ChemSusChem* **9**, 3280–3287 (2016).

145. Liao, Y. et al. A sustainable wood biorefinery for low–carbon footprint chemicals production. *Science* **367**, 1385–1390 (2020).

146. Guo, H. et al. Unravelling the enigma of lignin^ox: can the oxidation of lignin be controlled? *Chem. Sci.* **9**, 702–711 (2018).

147. Vangeel, T., Schutyser, W., Renders, T. & Sels, B. F. Perspective on lignin oxidation: advances, challenges, and future directions. *Top. Curr. Chem.* **376**, 30 (2018).

148. Dawange, M., Galkin, M. V. & Samec, J. S. M. Selective aerobic benzylic alcohol oxidation of lignin model compounds: route to aryl ketones. *ChemCatChem* **7**, 401–404 (2015).

149. Mottweiler, J., Rinesch, T., Besson, C., Buendia, J. & Bolm, C. Iron-catalysed oxidative cleavage of lignin and β-*O*-4 lignin model compounds with peroxides in DMSO. *Green Chem.* **17**, 5001–5008 (2015).

150. Zhang, J., Lahive, C. W., Zijlstra, D. S., Wang, Z. & Deuss, P. J. Sequential catalytic modification of the lignin α-ethoxylated β-O-4 motif to facilitate C–O bond cleavage by ruthenium-Xantphos catalyzed hydrogen transfer. *ACS Sustain. Chem. Eng.* **7**, 12105–12116 (2019).

151. Rahimi, A., Ulbrich, A., Coon, J. J. & Stahl, S. S. Formic-acid-induced depolymerization of oxidized lignin to aromatics. *Nature* **515**, 249–252 (2014).

152. Qu, S., Dang, Y., Song, C., Guo, J. & Wang, Z.-X. Depolymerization of oxidized lignin catalyzed by formic acid exploits an unconventional elimination mechanism involving 3c–4e bonding: a DFT mechanistic study. *ACS Catal.* **5**, 6386–6396 (2015).

153. Zhang, C. et al. Promoting lignin depolymerization and restraining the condensation via an oxidation–hydrogenation strategy. *ACS Catal.* **7**, 3419–3429 (2017).

154. Rahimi, A., Azarpira, A., Kim, H., Ralph, J. & Stahl, S. S. Chemoselective metal-free aerobic alcohol oxidation in lignin. *J. Am. Chem. Soc.* **135**, 6415–6418 (2013).

155. Bosque, I., Magallanes, G., Rigoulet, M., Kärkäs, M. D. & Stephenson, C. R. J. Redox catalysis facilitates lignin depolymerization. *ACS Cent. Sci.* **3**, 621–628 (2017).

156. Dabral, S., Hernãndez, J. G., Kamer, P. C. J. & Bolm, C. Organocatalytic chemoselective primary alcohol oxidation and subsequent cleavage of lignin model compounds and lignin. *ChemSusChem* **10**, 2707–2713 (2017).

157. Lancefield, C. S., Teunissen, L. W., Weckhuysen, B. M. & Bruijnincx, P. C. A. Iridium-catalysed primary alcohol oxidation and hydrogen shuttling for the depolymerisation of lignin. *Green Chem.* **20**, 3214–3221 (2018).

158. Magallanes, G. et al. Selective C–O bond cleavage of lignin systems and polymers enabled by sequential palladium-catalyzed aerobic oxidation and visible-light photoredox catalysis. *ACS Catal.* **9**, 2252–2260 (2019).

159. Lancefield, C. S., Ojo, O. S., Tran, F. & Westwood, N. J. Isolation of functionalized phenolic monomers through selective oxidation and C–O bond cleavage of the β-*O*-4 linkages in lignin. *Angew. Chem. Int. Ed.* **54**, 258–262 (2015).

160. Galkin, M. V., Dahlstrand, C. & Samec, J. S. M. Mild and robust redox-neutral Pd/C-catalyzed lignol β-O-4' bond cleavage through a low-energy-barrier pathway. *ChemSusChem* **8**, 2187–2192 (2015).

161. Li, H. et al. NH$_2$OH-mediated lignin conversion to isoxazole and nitrile. *ACS Sustain. Chem. Eng.* **6**, 3748–3753 (2018).

162. Guo, H. et al. Is oxidation–reduction a real robust strategy for lignin conversion? A comparative study on lignin and model compounds. *Green Chem.* **21**, 803–811 (2019).

163. Muurinen, E. *Organosolv Pulping: A Review and Distillation Study Related to Peroxyacid Pulping.* Thesis, Univ. Oulu (2000).

164. Lancefield, C. S., Panovic, I., Deuss, P. J., Barta, K. & Westwood, N. J. Pre-treatment of lignocellulosic feedstocks using biorenewable alcohols: towards complete biomass valorisation. *Green Chem.* **19**, 202–214 (2017).

165. Deuss, P. J. et al. Aromatic monomers by in situ conversion of reactive intermediates in the acid-catalyzed depolymerization of lignin. *J. Am. Chem. Soc.* **137**, 7456–7467 (2015).

166. Lahive, C. W. et al. Advanced model compounds for understanding acid-catalyzed lignin depolymerization: identification of renewable aromatics and a lignin-derived solvent. *J. Am. Chem. Soc.* **138**, 8900–8911 (2016).

167. Dong, C. et al. Diol pretreatment to fractionate a reactive lignin in lignocellulosic biomass biorefineries. *Green Chem.* **21**, 2788–2800 (2019).

168. Zhang, C. et al. Cleavage of the lignin β-*O*-4 ether bond *via* a dehydroxylation–hydrogenation strategy over a NiMo sulfide catalyst. *Green Chem.* **18**, 6545–6555 (2016).

169. Constant, S. et al. New insights into the structure and composition of technical lignins: a comparative characterisation study. *Green Chem.* **18**, 2651–2665 (2016).

170. Mu, X., Han, Z., Liu, C. & Zhang, D. Mechanistic Insights into formaldehyde-blocked lignin condensation: a DFT study. *J. Phys. Chem. C* **123**, 8640–8648 (2019).

171. Greene, T. W. & Wuts, P. G. M. *Protective Groups in Organic Synthesis* 3rd edn (Wiley, 1999).

172. Kaiho, A., Kogo, M., Sakai, R., Saito, K. & Watanabe, T. *In situ* trapping of enol intermediates with alcohol during acid-catalysed de-polymerisation of lignin in a nonpolar solvent. *Green Chem.* **17**, 2780–2783 (2015).

173. Miljković, M. in *Carbohydrates: Synthesis, Mechanisms, and Stereoelectronic Effects* (ed. Miljkovic, M.) 143–167 (Springer, 2009).

174. Robyt, J. F. *Essentials of Carbohydrate Chemistry* (Springer, 1998).

175. Pētursson, S. Protecting groups in carbohydrate chemistry. *J. Chem. Educ.* **74**, 1297–1303 (1997).

176. Adkins, H. & Broderick, A. E. Hemiacetal formation and the refractive indices and densities of mixtures of certain alcohols and aldehydes. *J. Am. Chem. Soc.* **50**, 499–503 (1928).

177. Lewis, E. S. (ed.) *Investigation of Rates and Mechanisms of Reactions. Part I. General Considerations and Reactions at Conventional Rates* 3rd edn (Wiley, 1974).

178. Agirre, I. et al. Glycerol acetals, kinetic study of the reaction between glycerol and formaldehyde. *Biomass Bioenerg.* **35**, 3636–3642 (2011).

179. Batalha, N. et al. Gasoline from biomass through refinery-friendly carbohydrate-based bio-oil produced by ketalization. *ChemSusChem* **7**, 1627–1636 (2014).

180. Paszner, L. & Chang, P.-C. Organosolv delignification and saccharification process for lignocellulosic plant materials. US patent US4409032A (1983).

181. Chernyavskaya, N. A. Method of continuous acid hydrolysis of cellulose containing substances. Patent WO2009116885A1 (2009).

182. Questell-Santiago, Y. M., Yeap, J. H., Talebi Amiri, M., Le Monnier, B. P. & Luterbacher, J. S. Catalyst evolution enhances production of xylitol from acetal-stabilized xylose. *ACS Sustain. Chem. Eng.* **8**, 1709–1714 (2020).

183. Anastas, P. T. & Warner, J. C. *Green Chemistry: Theory and Practice* (Oxford Univ. Press, 2000).

184. Fiorani, G., Perosa, A. & Selva, M. Dimethyl carbonate: a versatile reagent for a sustainable valorization of renewables. *Green Chem.* **20**, 288–322 (2018).

185. Scott, M., Deuss, P. J., de Vries, J. G., Prechtl, M. H. G. & Barta, K. New insights into the catalytic cleavage of the lignin β-*O*-4 linkage in multifunctional ionic liquid media. *Catal. Sci. Technol.* **6**, 1882–1891 (2016).

186. Van den Bosch, S. et al. Integrating lignin valorization and bio-ethanol production: on the role of Ni-Al$_2$O$_3$ catalyst pellets during *lignin-first* fractionation. *Green Chem.* **19**, 3313–3326 (2017).

187. Ferrini, P. & Rinaldi, R. Catalytic biorefining of plant biomass to non-pyrolytic lignin bio-oil and carbohydrates through hydrogen transfer reactions. *Angew. Chem. Int. Ed.* **53**, 8634–8639 (2014).

188. Sun, Z. et al. Complete lignocellulose conversion with integrated catalyst recycling yielding valuable aromatics and fuels. *Nat. Catal.* **1**, 82–92 (2018).

189. Iffland, K. et al. *Definition, calculation and comparison of the "biomass utilization efficiency (BUE)" of various bio-based chemicals, polymers and fuels* (nova-Institut, 2015).

190. Pandey, M. P. & Kim, C. S. Lignin depolymerization and conversion: a review of thermochemical methods. *Chem. Eng. Technol.* **34**, 29–41 (2011).

191. Koelewijn, S.-F. et al. Sustainable bisphenols from renewable softwood lignin feedstock for polycarbonates and cyanate ester resins. *Green Chem.* **19**, 2561–2570 (2017).

192. Koelewijn, S.-F. et al. Promising bulk production of a potentially benign bisphenol a replacement from a hardwood lignin platform. *Green Chem.* **20**, 1050–1058 (2018).

193. Feghali, E. et al. Thermosetting polymers from lignin model compounds and depolymerized lignins. *Top. Curr. Chem.* **376**, 32 (2018).

194. Zhao, S. & Abu-Omar, M. M. Biobased epoxy nanocomposites derived from lignin-based monomers. *Biomacromolecules* **16**, 2025–2031 (2015).

195. van de Pas, D. J. & Torr, K. M. Biobased epoxy resins from deconstructed native softwood lignin. *Biomacromolecules* **18**, 2640–2648 (2017).

196. François, C. et al. Diglycidylether of iso-eugenol: a suitable lignin-derived synthon for epoxy thermoset applications. *RSC Adv.* **6**, 68732–68738 (2016).

197. Kaiho, A. et al. Construction of the di(trimethylolpropane) cross linkage and the phenylnaphthalene structure coupled with selective β-O-4 bond cleavage for synthesizing lignin-based epoxy resins with a controlled glass transition temperature. *Green Chem.* **18**, 6526–6535 (2016).

198. Peng, Y., Nicastro, K. H., Epps, T. H. & Wu, C. Evaluation of estrogenic activity of novel bisphenol A alternatives, four bioinspired bisguaiacol F specimens, by in vitro assays. *J. Agric. Food Chem.* **66**, 11775–11783 (2018).

199. Elangovan, S. et al. From wood to tetrahydro-2-benzazepines in three waste-free steps: modular synthesis of biologically active lignin-derived scaffolds. *ACS Cent. Sci.* **5**, 1707–1716 (2019).

200. Tobisu, M. & Chatani, N. in *Organometallics for Green Catalysis* (eds Dixneuf, P. H. & Soulé, J.-F.) 103–140 (Springer, 2019).

201. Deuss, P. J. & Barta, K. From models to lignin: transition metal catalysis for selective bond cleavage reactions. *Coord. Chem. Rev.* **306**, 510–532 (2016).

202. Bender, T. A., Dabrowski, J. A. & Gagné, M. R. Homogeneous catalysis for the production of low-volume, high-value chemicals from biomass. *Nat. Rev. Chem.* **2**, 35–46 (2018).

203. Blondiaux, E. et al. Bio-based aromatic amines from lignin-derived monomers. *ACS Sustain. Chem. Eng.* **7**, 6906–6916 (2019).

204. Lie, Y., Ortiz, P., Vendamme, R., Vanbroekhoven, K. & Farmer, T. J. BioLogicTool: a simple visual tool for assisting in the logical selection of pathways from biomass to products. *Ind. Eng. Chem. Res.* **58**, 15945–15957 (2019).

205. Orazov, M. & Davis, M. E. Catalysis by framework zinc in silica-based molecular sieves. *Chem. Sci.* **7**, 2264–2274 (2016).

206. Song, S., Zhang, J., Gözaydın, G. & Yan, N. Production of terephthalic acid from corn stover lignin. *Angew. Chem.* **131**, 4988–4991 (2019).

207. Eerhart, A. J. J. E., Faaij, A. P. C. & Patel, M. K. Replacing fossil based PET with biobased PEF; process analysis, energy and GHG balance. *Energy Environ. Sci.* **5**, 6407–6422 (2012).

208. Choudhary, V., Sandler, S. I. & Vlachos, D. G. Conversion of xylose to furfural using Lewis and Brønsted acid catalysts in aqueous media. *ACS Catal.* **2**, 2022–2028 (2012).

209. Rinaldi, R. & Schüth, F. Acid hydrolysis of cellulose as the entry point into biorefinery schemes. *ChemSusChem* **2**, 1096–1107 (2009).

210. Tan-Soetedjo, J. N. M. et al. Experimental and kinetic modeling studies on the conversion of sucrose to levulinic acid and 5-hydroxymethylfurfural using sulfuric acid in water. *Ind. Eng. Chem. Res.* **56**, 13228–13239 (2017).

211. Huang, J.-b et al. Theoretical study of bond dissociation energies for lignin model compounds. *J. Fuel Chem. Technol.* **43**, 429–436 (2015).

212. Elder, T. Bond dissociation enthalpies of a pinoresinol lignin model compound. *Energy Fuels* **28**, 1175–1182 (2014).

213. Younker, J. M., Beste, A. & Buchanan, A. C. Computational study of bond dissociation enthalpies for lignin model compounds: β-5 arylcoumaran. *Chem. Phys. Lett.* **545**, 100–106 (2012).

214. Elder, T., Berstis, L., Beckham, G. T. & Crowley, M. F. Density functional theory study of spirodienone stereoisomers in lignin. *ACS Sustain. Chem. Eng.* **5**, 7188–7194 (2017).

215. Elder, T. Bond dissociation enthalpies of a dibenzodioxocin lignin model compound. *Energy Fuels* **27**, 4785–4790 (2013).

216. Dusselier, M., Mascal, M. & Sels, B. F. in *Selective Catalysis for Renewable Feedstocks and Chemicals* (ed. Nicholas, K. M.) 1–40 (Springer, 2014).

Author contributions

J.S.L. and K.B. designed the review. Y.M.Q.-S. and M.V.G. wrote initial drafts of the document and prepared initial figures. All authors edited the manuscript.

Competing interests

The authors declare competing interests. J.S.L. is an inventor on European patent applications (EP16165180, EP19203000 and EP19202957) and has co-founded a spin-off company (Bloom Biorenewables) that seeks to produce lignin and sugars using methods described in this Review.

Publisher's note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Supplementary information

Supplementary information is available for this paper at https://doi.org/10.1038/s41570-020-0187-y.