

Lignin Valorization and the Opportunities of Retaining its Natural Structure

Jean Behaghel de Bueren and Jeremy S. Luterbacher^{§,*}

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Abstract: The chemical industry's dependence on fossil carbon increasingly raises major sustainability concerns. Lignocellulosic biomass is a promising alternative resource, but it has been historically difficult to valorize to chemicals, especially in a way that is economically profitable. The lignin fraction has been particularly challenging to use even though it is nature's largest source of aromatic functionality, notably because conventional lignin extraction methods cause severe condensation, limiting subsequent depolymerization and functionalization. Recent lignin-first technologies address these challenges through active lignin stabilization during fractionation, enabling the high-yield production of oxygenated aromatic monomers. This review summarizes strategies for preserving native lignin structures and explores their conversion into chemicals, polymers, and bioactive molecules. We emphasize emerging opportunities to leverage lignin's intrinsic functionalities to enhance atom economy, reaction efficiency, and final product safety and performance. We suggest that leveraging natural functionality leads to these benefits, which go beyond simple circularity, and could ultimately push and enable adoption of this more sustainable feedstock in the chemical industry.

Keywords: Green chemistry · Lignin · Lignocellulosic biomass



Jean Behaghel de Bueren was born in Belgium in 1995. He received a BSc in Bioengineering from the Université Catholique de Louvain in 2016 and an MSc in Chemical Engineering from the École Polytechnique Fédérale de Lausanne in 2018. He then joined Prof. Jeremy Luterbacher's group, where he worked on the catalytic upgrading of lignocellulosic biomass using aldehyde-assisted fractionation and received his PhD in 2025.



Jeremy S. Luterbacher was born in Switzerland in 1984. He has been the head of the Laboratory of Sustainable and Catalytic Processing at EPFL since 2014 and an Associate Professor since 2021. Prior to this, he obtained his PhD from Cornell University in 2012 and was a Swiss National Science Foundation Postdoctoral Fellow at the University of Wisconsin-Madison between 2012 and 2014. Prior to

the Green & Sustainable Chemistry Award, he had received the Werner Prize from the Swiss Chemical Society and the University Latsis Prize in 2019.

1. The Chemical Industry's Reliance on Fossil Resources

The chemical industry consumes around 10% of global final energy, mostly from fossil resources.^[1] This fossil resource use is almost equally divided between energy used for processes (42%) and use as a carbon feedstock (58%).^[1] To avoid the release of CO₂ into the atmosphere, decarbonization of the energy supply is

often the preferred strategy.^[2] However, avoiding the use of fossil energy on its own will not make the chemical industry sustainable, as it cannot be completely decoupled from carbon.^[3] Recycling helps reduce carbon inputs, but losses still require fresh carbon.^[4] One alternative is to capture CO₂ from the atmosphere and convert it to chemicals - a process known as carbon capture and utilization (CCU).^[5] Promising technologies have been developed in this direction, but they still lack maturity and are unlikely to be affordable in the near future.^[4] Biomass is another interesting feedstock because it contains biogenic carbon.^[6] Owing to its high energy content and reduced carbon, biomass has long been directly combusted to produce heat or, more recently, converted into fuels and chemicals through biorefining processes.^[7] While first-generation biorefineries, defined by the use of edible feedstocks produced by agriculture, rely on well-established processes, their sustainability from environmental and socio-economic perspectives remains contentious.^[8] To address these challenges, so-called 'second-generation' biorefineries are being developed, focusing on substrates such as non-edible cellulose-based wastes and lignocellulose.^[9,10] The goal is to fractionate these materials and transform them into fuels, chemicals, or materials, thereby reducing competition with food production and enhancing sustainability. While this biorefinery concept holds promise for mitigating some of the environmental and social challenges of first-generation biorefineries, its development remains complex.^[11,12] This complexity arises from the heterogeneous chemical composition, polymeric nature, and recalcitrance of the targeted feedstocks.^[13]

2. Lignocellulosic Biomass Reactivity

Lignocellulose is mostly composed of two polysaccharides - cellulose and hemicellulose - and one aromatic polymer - lignin.^[14] The latter has historically been the most challenging fraction of biomass to valorize, due to its complex structure and

*Correspondence: Dr. J. Luterbacher, E-mail: jeremy.luterbacher@epfl.ch

Laboratory of Sustainable and Catalytic Processing, Institute of Chemical Sciences and Engineering, École Polytechnique Fédérale de Lausanne (EPFL), CH-1015 Lausanne, Switzerland.

high reactivity. This amorphous aromatic polymer is composed of phenylpropanoid units and is formed in the cell wall through the radical coupling of three natural monolignols: *p*-coumaryl alcohol, coniferyl alcohol, and sinapyl alcohol, which after incorporation into the lignin backbone form *p*-hydroxyphenyl (H), guaiacyl (G), and syringyl (S) aromatic residues, respectively.^[15,16] The end product of lignification is an amorphous and heterogeneous aromatic polymer composed of H, G, and S subunits linked through various C–O and C–C linkages, with the monomer composition and linkage distribution varying significantly across plant species. The most frequent linkage in all lignins is the β -O-4 (Fig. 1), which accounts for 40 to 85% of the total bonds.^[17] This linkage is also the main target for depolymerizing lignin and for tracking the structural changes of lignin during biomass pretreatment, as it is the easiest linkage to break.^[18] In the cell wall, lignin is physically tightly bound and chemically linked to polysaccharides, forming lignin-carbohydrate complexes (LCCs),^[19] which include phenyl glycoside, γ -ester, and benzyl ether bonds.^[20] LCCs provide stability to the cell wall and reduce the accessibility of cellulose to enzymatic attack, thereby affecting the efficiency of processes such as pulping and enzymatic hydrolysis.^[21]

The initial step for using biomass as chemical feedstock typically involves a fractionation step to isolate each biomass fraction, allowing specific upgrading processes to be applied to each.^[22] For this purpose, lignin is most often removed from the carbohydrate matrix, which requires relatively harsh conditions to hydrolyze the LCC linkages and solubilize the lignin.^[23] The pulp and paper industry is by far the largest operator of lignocellulose fractionation and the only industry to have systematically scaled these processes. The dominant fractionation process within this industry is the Kraft pulping process, which focuses on producing cellulose-rich pulp and then paper, cardboard, textiles, and other products, while lignin is considered a by-product.^[24] As a consequence, approximately 95% of the lignin extracted worldwide by this industry is burned for energy production, while only 5% is recovered and used in higher-value applications.^[25] Although producing pure cellulose fibers is profitable and efficient, the harsh conditions (pH, temperature) used to extract and solubilize lignin in all pulping processes leads to severe condensation of this biopolymer. Indeed, under the conditions required to release lignin from the carbohydrate matrix, the lignin also undergoes severe structural modifications.^[26] The reactions involved are complex and include both partial depolymerization of lignin and the generation of reactive species that subsequently repolymerize to form condensed structures.^[27] The different mechanisms have been previously reviewed by Lan *et al.*^[28]

The extensive condensation of technical lignins drastically limits their potential for depolymerization and valorization more generally by reducing the content of cleavable ether bonds, which become replaced by recalcitrant C–C bonds that are challenging to cleave selectively.^[29] Repolymerization reactions also reduce the linearity of lignin oligomers by introducing branching and crosslinking.^[30] This process leads to the disappearance of hydroxyl functional groups, which decreases the polymer's reactivity and limits opportunities for further functionalization.^[31] Condensation reactions also give isolated lignins a dark color through the formation of chromophoric groups.^[32] Furthermore, during the repolymerization of lignin, its oligomers often establish a diverse range of inter- and intramolecular noncovalent bonds, such as hydrogen bonds, CH– π interactions, and π – π stacking. These interactions are believed to impede the solubility and miscibility of lignin in various solvents and polymers.^[33,34] Finally, the use of sulfur in pulping leads to an unpleasant smell.^[35] Collectively, the consequences of these chemical alterations during lignin extraction limit its applicability in the production of chemicals and materials. Given the abundant availability and low cost of technical lignins – particularly Kraft lignin – overcoming these limitations to

find suitable applications is a longstanding research goal of wood chemistry.^[36] However, preserving the native structure of lignin during extraction could also open new avenues for the valorization of lignocellulosic biomass.

3. Preserving Lignin's Native Structure

Organosolv processes were developed to solubilize lignin in organic solvents under milder conditions and to limit the extent of lignin condensation.^[37] Acid catalysts are typically used to decrease the pH of the liquor and increase the solvolysis of hemicellulose and lignin by hydrolyzing the LCC bonds. Nevertheless, a tradeoff between extraction yields and the preservation of the native structure almost always exists: mild conditions preserve the native structure but limit the extraction yields, whereas more severe conditions improve delignification but also favor condensation through the formation of reactive carbocation intermediates (Fig. 1).^[38]

Recently developed lignin-first technologies have focused on overcoming this trade-off by mitigating lignin condensation during fractionation.^[39] Limiting condensation is achieved through the active stabilization of lignin *via* catalysis or protection chemistry, either by preventing the formation of reactive intermediates or by stabilizing these intermediates *in situ* once formed. These strategies adopt a more holistic approach by valuing both lignin and polysaccharide upgrading, and they enable a more complete valorization of biomass. An overview of current methods using these principles is presented in Fig. 1.

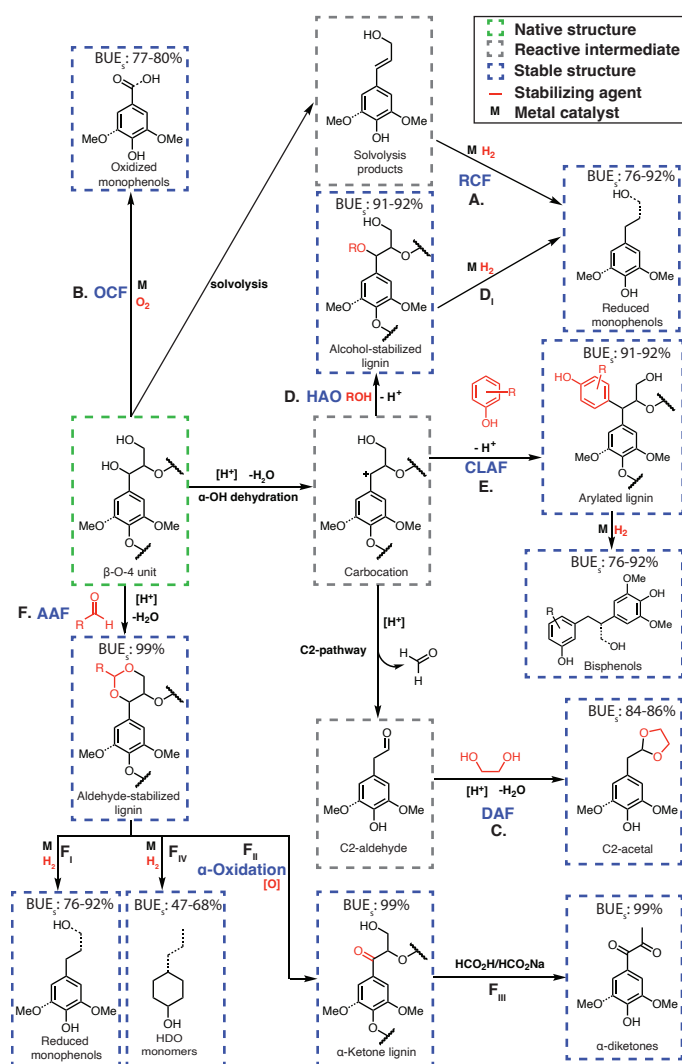


Fig. 1. Overview of different *lignin-first* technologies.

3.1 Direct Depolymerization from Biomass and in situ Stabilization of Reactive Intermediates

The most widely used and oldest lignin-first technology is known as reductive catalytic fractionation (RCF, Fig. 1A). This process involves the solvolysis of lignin in an organic solvent at high temperatures (200–250 °C) in the presence of a transition metal catalyst, under hydrogen pressure or with a hydrogen-donor solvent.^[40,41] Under these conditions, lignin depolymerizes through the action of heat and solvent, forming reactive fragments and monomers that can repolymerize if not stabilized (Fig. 1, solvolysis). The metal catalyst plays a crucial role in stabilizing these intermediates by hydrogenating the unsaturated fragments, thereby producing reduced, stable monomers (Fig. 1A).

Originally developed in the 1930s, RCF has so far never been industrialized for lignin monomer production.^[42] However, the ability of this approach to produce monomers from lignin in quantitative yields based on the ether content of the substrate has garnered significant interest over the past decade and piloting operations are underway. Substantial efforts have been made to improve the process, particularly with respect to the physical separation of the catalyst from the biomass, which does not affect monomer yields but enables catalyst recycling and prevents contamination of the carbohydrate pulp.^[43–46]

More recently, and by analogy with RCF, oxidative catalytic fractionation (OCF, Fig. 1B) was developed. Under strongly alkaline aerobic conditions in the presence of a copper-based catalyst, near-theoretical yields of aldehyde-substituted monomers were produced (18 wt% for softwood, 30 wt% for hardwood).^[47,48] This process remains difficult to operate, as the products rapidly degrade under depolymerization conditions.^[49] A neutral process was developed to overcome this product-stability issue and to prevent degradation of polysaccharides. By heating poplar at 190 °C in acetone with a heterogeneous, non-precious-metal (cobalt-based) catalyst in the presence of oxygen, 15 wt% (vs. lignin content) of aldehyde- or carboxylic-acid-functionalized monomers were produced.^[50] Although these yields are lower than those observed for RCF, the functionality of these monomers complements those of the monomers obtained *via* the reductive pathway, enriching the portfolio of platform chemicals that can be produced from lignin. A two-step process using polyoxometalate catalysts in a methanol-water mixture allowed the production of 46 wt% oxygenated monomers from hardwood sawdust, albeit with lower selectivity, yielding a mixture of aldehydes and methyl esters.^[51] Recently, the use of CuO nanoparticles has proven effective in fractionating lignocellulose under mild aqueous basic conditions, significantly increasing the carbon efficiency of the process (>80%).^[52] The monomer yield even surpasses the theoretical maximum, due to the cleavage of bonds other than β -O-4, with impressive selectivity towards aromatic aldehydes. Simultaneously, hemicellulose is converted into small carboxylic acids, while 80% of the cellulose is retained as a high-purity, crystalline pulp.

Another method consists in stabilizing the reactive intermediates formed during the acid-catalyzed depolymerization of lignin to prevent their repolymerization. Initially developed using isolated lignin or model compounds, this strategy leverages the ability of diols (typically ethylene glycol) to form stable acetals with the reactive phenylacetaldehyde structures produced by the C2-hydrolytic pathway, catalyzed by triflic acid or metal triflates (Fig. 1, C2-pathway).^[53–56] This approach has proven effective in depolymerizing isolated lignins but is limited by the loss of β -O-4 linkages during the extraction process. Building on this concept, a lignin-first strategy was developed by treating lignocellulose directly under acidic hydrolysis conditions while adding ethylene glycol as a stabilizing agent in the pretreatment liquor.^[57] This method, known as diol-assisted fractionation (DAF, Fig. 1C), results in near-quantitative C2-acetal monomer

yields from lignin (77–98% of the maximum yield based on β -O-4 content).

3.2 Quenching of the Carbocation

Another strategy involves quenching the carbocation formed by acid-catalyzed dehydration of the α -OH of the β -O-4 moiety (Fig. 1, α -OH dehydration) before its condensation with another lignin fragment.

One particular type of Organosolv pretreatment uses an alcohol-rich mixture (>95% alcohol) as the solvent (high-alcohol Organosolv, HAO, Fig. 1D).^[58] Compared to Organosolv pretreatments using a larger proportion of water (~50%), these conditions allow a higher retention of β -O-4 units. This is notably achieved through the quenching of reactive carbocations by alcohol nucleophiles to form a stable ether. Lignin is extracted in good yields, and the subsequent depolymerization can reach 15–20% of the theoretical yield, which is around four times higher than the yield of technical lignin extracted from the same biomass (Fig. 1D).^[38] These results indicate that condensation was not completely suppressed but was significantly reduced through α -etherification of β -O-4 units. Interestingly, these etherified lignins can be isolated rather than depolymerized, and they can be further functionalized for material applications or deprotected to regenerate the native β -O-4 linkages, which become a promising substrate for the selective oxidation of α - or β -hydroxyls to carbonyl groups.^[14,59,60]

Alternatively, catalytic lignin arylation fractionation (CLAF, Fig. 1E) was recently developed using a similar approach. Lignin-derived phenols were used as carbocation-scavenging agents,^[61] leading to the controlled formation of C–C bonds between the phenols added to the pretreatment mixture and the lignin rather than lignin condensing with itself. After depolymerization, arylated lignin yields high yields of bisphenols that could advantageously replace petroleum-derived bisphenols thanks to lower toxicity and high performance.

3.3 Preventing Carbocation Formation

To prevent the dehydration of the α -position in β -O-4, another type of Organosolv pretreatment, known as aldehyde-assisted fractionation (AAF, Fig. 1F), was developed using aldehydes as stabilizing agents. First reported with formaldehyde, this approach exploits the formation of cyclic acetals with β -O-4 diols, allowing the isolation of a stable lignin at high yields and with near complete suppression of β -O-4 condensation.^[62] After hydrogenolysis, 47 wt% monomers could be produced from beech lignin, matching the performance of RCF on the same substrate (Fig. 1F). To date, this is the main scalable method that allows near-theoretical yields of monomers from isolated lignin. However, highly reactive formaldehyde partially hydroxymethylates the electron-rich aromatic moieties of lignin, increasing the complexity of the final monomer mixture, which is partially methylated. The method was extended to other aldehydes to prevent hydroxymethylation, and propionaldehyde allowed the extraction of uncondensed lignin with similar yields (48 wt%) of non-methylated monomers.^[63,64] Propionaldehyde-stabilized lignin (PA-lignin) can also be deprotected and selectively oxidized to a ketone at the α -position (Fig. 1F_{II}).^[65] α -Ketone lignin is a stable substrate that can be isolated, as the α -position cannot dehydrate once oxidized, preventing the formation of carbocations. After formic-acid-induced depolymerization, birch lignin produced 31 wt% aromatic monomers with high selectivity (>90%) towards highly functionalized aryl- α -diketones (Fig. 1F_{III}).^[65,66]

Interestingly, functionalized aldehydes can also be used to tune the properties of extracted lignin, and especially its solubility.^[67] For instance, lignin stabilized with fatty aldehydes (octanaldehyde, dodecanaldehyde) is soluble in apolar toluene, while glyoxylic-acid fractionation produces lignin that is completely soluble in water, even at neutral pH. This water solubility can be leveraged

to produce hydrodeoxygenated (HDO) monomers from lignin in a single step by performing tandem depolymerization-HDO in an aqueous environment (Fig. 1F_{IV}).^[67] Beyond depolymerization, AAF-lignin can be directly used as a polymer in various applications, as recently reviewed.^[68] This method ensures a high retention of biogenic atoms while preserving the native lignin structure and the associated characteristics that make it attractive for certain uses.

4. Valorization of Lignin Monomers

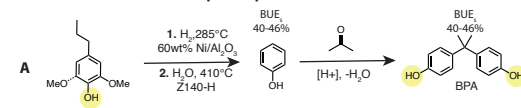
The *lignin-first* technologies described above enable the production of monomers (or dimers, in the case of CLAF) at high yields from lignin, providing a renewable platform for the synthesis of biobased chemicals. To evaluate the retention of renewable atoms in these platforms, we calculated their theoretical biomass utilization efficiencies (BUEs), which represent the percentage of the initial biomass present in the final product assuming 100% yield (Fig. 1).^[69] This metric can be calculated using the stoichiometry of the reaction, by dividing the molecular weight corresponding to the biogenic atoms in the final structure by the molecular weight of the biomass monomer - the native β -O-4 unit, in our case. Although not perfect, this indicator allows us to highlight routes that maximize the utilization of the feedstock in alignment with the atom-economy principle of green chemistry.^[70] Note that, as the BUE does not take yields into account, it is indicative of the potential of a route to maintain biogenic structures rather than a measure of its actual efficiency.

All the monomers produced through *lignin-first* technologies generally have high BUEs (76–99%, except for HDO monomers at 47–68%; see Fig. 1). This efficiency is achieved by maintaining the functionality present in natural lignin and yielding aromatic monomers with a more complex functionalization than their petroleum-derived counterparts. These are promising new platforms that can be adapted to a variety of applications using (bio)catalytic pathways.^[71] Below we review some of the more prominent categories of chemicals that have been targeted as applications for lignin monomers.

4.1 Lignin to Bisphenols

One possible strategy to produce platform chemicals already manufactured by petrochemistry - such as phenol and then classic bisphenols - is to defunctionalize lignin monomers. To this end, several routes have been reported for the demethoxylation and dealkylation of lignin monomers produced by hydrogenolysis.^[72–77] Liao *et al.* proposed an integrated biorefinery concept using this pathway (Fig. 2A).^[78] After conducting a techno-economic analysis (TEA) and a life-cycle assessment (LCA), they predicted economic competitiveness and a lower CO₂ footprint compared to fossil-based phenol. This method offers the advantage of producing a platform product already used by the chemical industry, which can serve as a drop-in replacement. This greatly facilitates its implementation within existing infrastructure - for example, to produce bisphenol A (BPA) through condensation with acetone (Fig. 2A).^[79] However, monomer defunctionalization results in a drastic drop in BUE, from 83–85% for RCF monomers to 40–46% for phenol, depending on the initial methoxy substitution of the lignin (S to G ratio). This effect can be mitigated by valorizing the propylene cleaved off during the dealkylation, as proposed by Liao *et al.*^[78] Importantly, BPA raises severe concerns due to its adverse effects on human health and the environment, primarily because of its estrogenic endocrine disruption.^[80] Current substitutes proposed by the chemical industry, such as bisphenol S (BPS) and bisphenol F (BPF), are considered ‘regrettable substitutions’ because they have not significantly reduced xenoestrogenic activity.^[81–83] Interestingly, methoxy substitution, which is naturally present in lignin-derived molecules, has been reported to effectively minimize the estrogenic activity of bisphenols.^[84–86]

Defunctionalization to drop-in replacement of BPA



Retention of lignin functional groups to produce alternatives to BPA

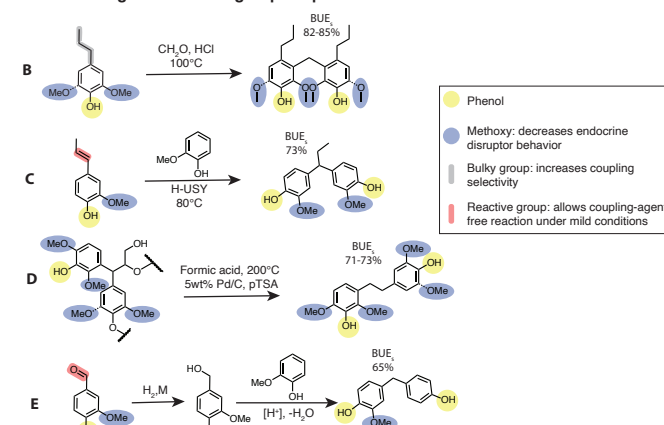


Fig. 2. Strategies for the synthesis of bisphenols from lignin. We highlight the lignin functional groups that are leveraged to design efficient conversion methods or to increase the safety of the final product.

This feature offers the opportunity to produce bisphenols from lignin that can substitute for the function of BPA without replicating the exact structure of these petrochemicals, thereby allowing potential improvements in the safety of the final products.

Several routes have been reported to produce bisphenols directly from lignin monomers. 4-Propyl-guaiacol (PG) and 4-propyl-syringol (PS) were efficiently dimerized to bisphenols through acid-catalyzed condensation with formaldehyde (Fig. 2B).^[87,88] Interestingly, the alkyl chain was shown to significantly reduce unwanted oligomerization during the coupling through a steric effect. By avoiding defunctionalization, these bisguaiacols retain high BUEs of between 82 and 85%. Polycarbonates, cyanate ester resins, and aromatic polyesters produced from them exhibited good thermomechanical properties. More recent studies have demonstrated the selective alkylation between lignin-derived alkenes such as isoeugenol and biobased arenes (*e.g.* guaiacol) over the Hydrogen-form of the ultra-stable zeolite Y (H-USY) to produce bisphenols (Fig. 2C).^[89] The BUE of *p,p'*-bisguaiacol resulting from the alkylation of guaiacol by isoeugenol is 73%, slightly lower than previously reported for bisphenols, because of the dealkylation of guaiacol. However, this approach compares favorably with former routes, as it does not require a volatile organic coupling agent thanks to the presence of a reactive unsaturation in the substrate. This route also uses a stable zeolite catalyst and is less prone to oligomerization than formaldehyde-based coupling routes. The syntheses were performed on a multigram scale, and a family of polymers (polyesters, polycarbonates, and epoxy resins) was produced, exhibiting promising thermomechanical properties.

Another route to produce bisphenols involves the depolymerization of arylated lignin produced by CLAF, as described above (Fig. 2D). During the catalytic depolymerization of lignin with formic acid as the hydrogen donor, aryl migration is observed, and the most abundant bisphenol products feature a methylene bridge. The BUE when syringol is used as the arylating agent varies between 71 and 73%.

Alternatively, bisguaiacol F (BGF) can be produced through the Brønsted-acid-catalyzed condensation of vanillyl alcohol and guaiacol (Fig. 2E).^[85,90–93] Guaiacol is a lignin-derived monomer,^[94] while vanillyl alcohol can be produced by the hydrogenation of lignin-derived vanillin.^[95] Interestingly, this reaction is more selective towards *p,p'*-coupling than the BPF synthesis,

which predominantly yields *o,p'*-isomers. C–C cleavage during the oxidative depolymerization of lignin to vanillin, which results in the loss of two carbons, combined with the dealkylation required to obtain guaiacol, leads to a drop in BUE to 65%.

Importantly, all these lignin-derived bisphenols exhibit much lower transactivation activity of human estrogen receptors thanks to their methoxy substitution. Concentrations one to two orders of magnitude higher were required to trigger a response, and the maximum effect on the receptors was reduced. In summary, preserving lignin's native motifs enhances atom economy, selectivity, and product safety, extending the benefits of structure retention beyond simple carbon circularity.

4.2 Vanillin

To this day, vanillin remains the only commercially available lignin monomer, and is produced through the oxidative depolymerization of liginosulfonate.^[96] Beyond vanillin's use in flavoring and fragrance applications, the presence of two reactive groups in its structure (a phenol and an aldehyde, highlighted in yellow and red in Fig. 3) offers significant potential for catalytic upgrading. Consequently, extensive research has been conducted in recent years to transform vanillin into high-performance polymers and value-added products (Fig. 3).^[71,97] Bisphenols suitable for polycarbonate synthesis can be produced through electrochemical coupling (Fig. 3A).^[98] Vanillin can also be dimerized through iron-catalyzed $\text{Na}_2\text{S}_2\text{O}_8$ -based oxidative coupling at high yield (87.5%).^[99] After treatment with epichlorohydrin and curing with diamines, degradable epoxy resins were produced (Fig. 3B). These bisphenols are also significantly safer thanks to their methoxy substitution. The aldehyde functionality can also be used to form acetals with long-alkyl-chain 1,2-diols to produce non-ionic surfactants (Fig. 3C).^[100] For the production of polyethylene terephthalate (PET) analogues, vanillin can be converted into acetylated ferulic acid through a Perkin reaction between acetic anhydride and the aldehyde group of vanillin. Acetylated ferulic acid is then hydrogenated to acetyldihydroferulic acid, which can be polymerized into poly(dihydroferulic acid), exhibiting a glass transition temperature (T_g) and melting temperature (T_m) similar to those of fossil-based PET.^[101] Finally, the free *ortho* position of vanillin adjacent to the phenolic group makes it a suitable candidate for the synthesis of 1,3-benzoxazine upon reaction with formaldehyde and aniline. The resulting product can be polymerized into polybenzoxazine, which has desirable properties for some applications, such as low water absorption, excellent stability, and a high T_g .^[102] Interestingly, the pendant aldehyde group

can be further reacted to functionalize the polymer and tune the properties of the final material.

These methods illustrate the versatility of the vanillin platform for producing a wide range of products, primarily due to the retention of the highly reactive aldehyde group in its structure, which can participate in various reactions. However, these pathways are intrinsically constrained by the limited BUE of vanillin (77%), with over 20% of the biogenic atoms being lost during the C–C cleavage that occurs during the oxidative depolymerization of lignin. More importantly, the overall yields from biomass are limited by the low yields of vanillin from liginosulfonates (~5%),^[103] due to condensation during pulping and its potential uncontrolled depolymerization, the mechanism of which is still under debate.^[96]

4.3 Bioactive Molecules from Lignin

Another interesting pathway for the valorization of lignin monomers is to harness their functionalization and natural motifs to design more efficient and sustainable syntheses of bioactive ingredients, particularly compared with the multi-step processes required when starting from non-functionalized petrochemicals.^[104] Such approaches could allow the pharmaceutical industry to achieve its goals of reducing E-factors (the ratio of the total waste produced by a process to the mass of the desired product), limiting the extensive use of solvents, and incorporating the principles of green chemistry into their production processes.^[105] This approach has been thoroughly explored and reviewed in recent literature^[104,106] and we choose to just highlight several representative examples here.

Dihydroconiferyl (POHG) and dihydrosinapyl (POHS) alcohols produced by reductive depolymerization of lignin can be converted into a benzoxepine scaffold through an *oxa*-Pictet-Spengler reaction (Fig. 4A).^[107] From the same substrates, tetrahydro-2-benzazepines are accessible by amination of the aliphatic hydroxyl followed by Pictet-Spengler cyclization (Fig. 4B).^[108] These molecules have shown promising antibacterial or anticancer activities, and their synthesis from lignin monomers compares favorably with conventional approaches that require more steps, employ stoichiometric reagents, and generate more solvent waste.

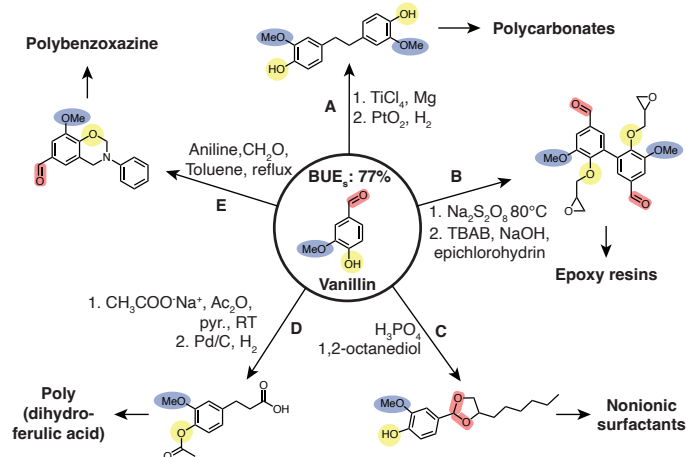


Fig. 3. Vanillin upgrading towards polymers and surfactants. The functional groups and their fate in the final product are highlighted in red for the aldehyde, yellow for the phenol, and blue for the methoxy. Inspired by Wu *et al.*^[71]

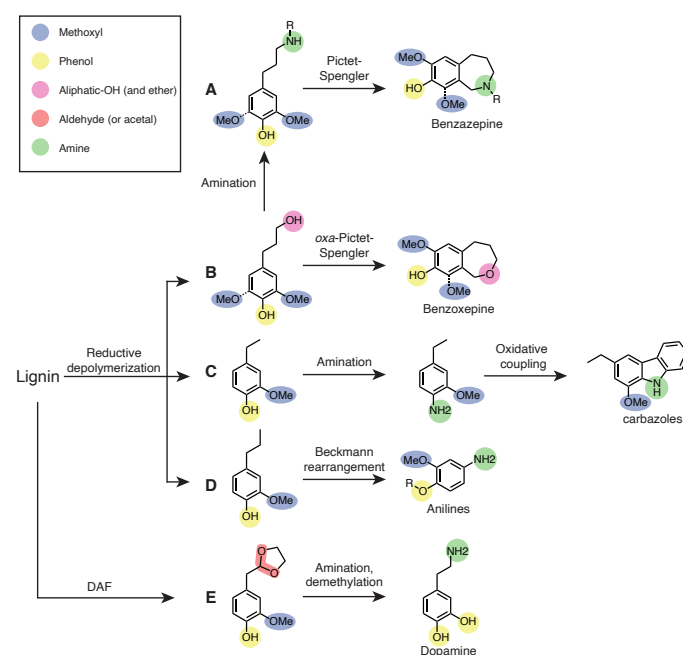


Fig. 4. Examples of synthetic routes from lignin monomers to bioactive compounds. The oxygenated functional groups of the lignin-derived monomers, as well as their fate in the bioactive molecules, are highlighted with colors.

Ethylguaiaicol (EG), which is also produced within RCF mixtures, can be used to produce naturally occurring carbazole alkaloids with antibacterial and antifungal properties (Fig. 4C).^[104,109,110]

Similarly, PG produced by RCF can be converted into aromatic amines through a four-step synthesis involving a Beckmann rearrangement (Fig. 4D).^[111] This strategy was efficiently used to produce drugs such as gefitinib, prazosin, and alfuzosin, and agrochemicals such as diethofencarb. Starting from lignin monomers made it possible to move away from the hazardous reagents and solvents used in the traditional benzene-based route and performed similarly or better with respect to process mass intensity (PMI), even at the unoptimized discovery stage of this route.

Recently, the production of dopamine from C2-acetals produced by DAF was reported at high yields (83% over four steps).^[112,113] These two molecules were used to synthesize a wide array of bioactive compounds with aminoalkylguaiaicol, tetrahydroisoquinoline, quinazolinone, or 3-arylindole structures, allowing both the production of known substances such as tetrahydropapaveroline and the rapid identification of frontrunners for key therapeutic applications.^[112]

These syntheses illustrate how preserving reactive oxygenated functional groups (such as hydroxyl groups and aldehydes) enables the design of efficient routes to highly functionalized molecules through atom-efficient transformations. In contrast, petrochemical alternatives often require multistep syntheses under harsh conditions to incorporate functional groups onto an unactivated hydrocarbon backbone. Additionally, the presence of natural motifs (such as methoxy substitution) can facilitate the direct production of natural or bioactive molecules.

5. Concluding Remarks

Over the past decades, significant efforts have been dedicated to the development of lignin-first technologies that prevent lignin condensation through active stabilization. Using this approach, a new class of oxygenated lignin monomers can be obtained in high yields. In the short term, defunctionalizing these biobased aromatics to produce drop-in replacements for fossil feedstocks is a promising path to integrating renewable carbon into existing processes.

Alternatively, these oxygenated monomers can be directly converted into useful products that replace current petrochemicals by fulfilling the same functions with a modified structure. The presence of reactive oxygen functionalities can then be leveraged as an advantage, enabling the design of more efficient transformation routes compared to traditional methods that start from less reactive hydrocarbons. Moreover, the presence of natural motifs offers opportunities for more direct syntheses of natural and bioactive compounds that are otherwise challenging to access. These motifs can also impart desirable properties to the final product, such as reduced toxicity or increased biodegradability. Overall, using largely unmodified biobased motifs can provide more than carbon circularity. It can simplify production processes, lead to safer products, and even promote the development of new and innovative molecular products.

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