

Advancements and Perspectives toward Lignin Valorization via O-Demethylation.

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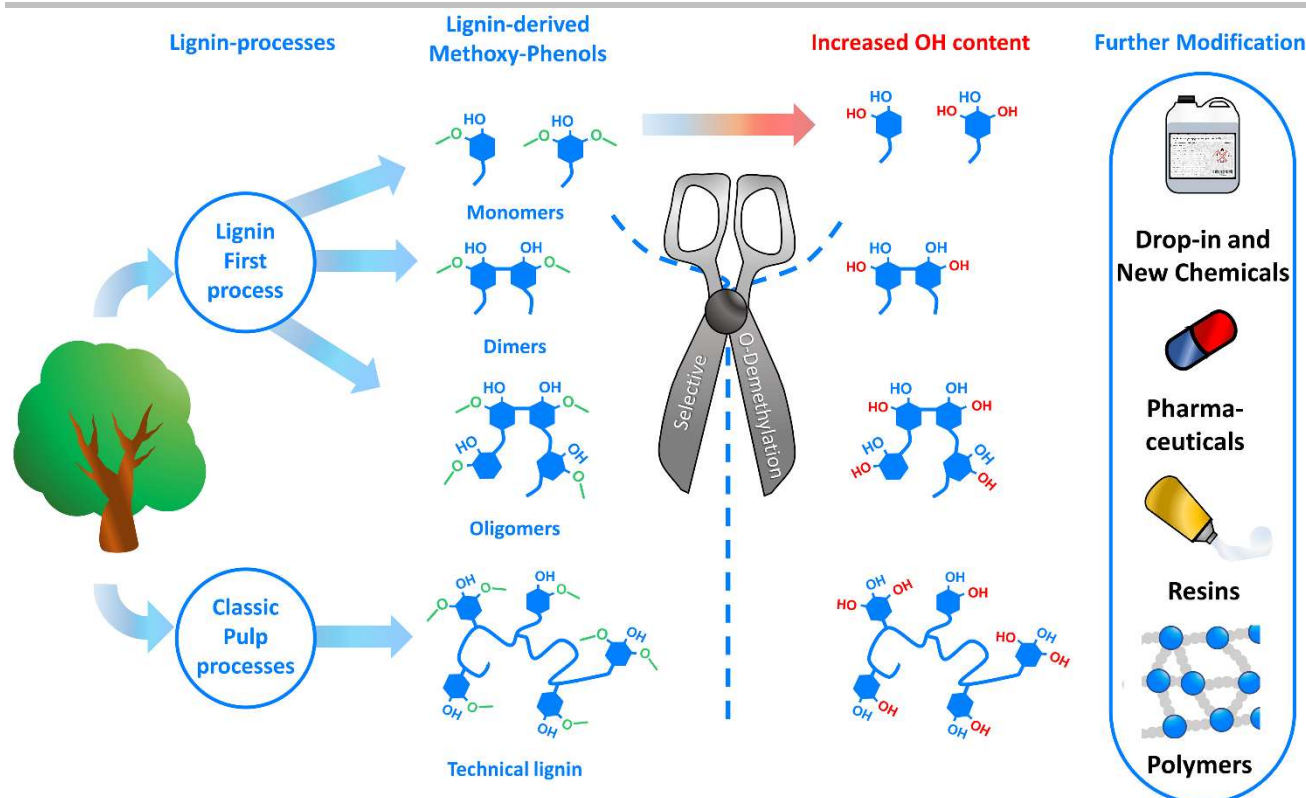
Abstract: Lignin represents the largest aromatic carbon resource in plants, holding significant promise as a renewable feedstock for bioaromatics and other cyclic hydrocarbons in the context of the circular bioeconomy. However, the methoxy groups of aryl methyl ethers, abundantly found in technical lignins and lignin-derived chemicals, limit their pertinent chemical reactivity and broader applicability. Unlocking the phenolic hydroxyl functionality through *O*-demethylation (ODM) has emerged as a valuable approach to mitigate this need and enables further applications. In this review, we provide a comprehensive summary of the progress in the valorization of technical lignin and lignin-derived chemicals via ODM, both catalytic and non-catalytic reactions. Furthermore, a detailed analysis of the properties and potential applications of the *O*-demethylated products is presented, accompanied by a systematic overview of available ODM reactions. This review primarily focuses on enhancing the phenolic hydroxyl content in lignin-derived species through ODM, showcasing its potential in the catalytic funneling of lignin and value-added applications. A comprehensive synopsis and future outlook are included in the concluding section of this review.

1. Introduction

A major societal challenge is to find sustainable alternatives to fossil-derived feedstocks for the production of chemicals, fuels, and materials. Lignocellulosic biomass, a plant-based non-edible feedstock, is a promising candidate for this purpose.^[1] Lignin is one of the major components of lignocellulose and represents the planet's largest source of renewable aromatics.^[2] Historically, the complexity and recalcitrance of lignin have been an almost insurmountable obstacle to successful lignin biorefining.^[3] However, a cutting-edge technology known as *lignin-first* has been recently established,^[4] which aims to efficiently extract lignin from the lignocellulose matrix and simultaneously depolymerize it into various low molecular weight species. The reactive species formed during this process are *in situ* stabilized with a specific chemical reaction (e.g. acetal protection, oxidation, and reduction), thus avoiding repolymerization into even more recalcitrant lignin.^[5] During reductive catalytic fractionation (RCF), the most commonly applied technique, the reactive species are stabilized *via* hydrogenation/hydrogenolysis using hydrogen (H₂) and transition metal catalysts.^[1c, 1d, 6] Accordingly, in such a process lignin is converted into a viscous lignin oil, essentially a mixture of lignin-derived methoxy-phenols consisting of

monomers, dimers, and oligomers.^[6] Meanwhile, the (hemi)cellulose part of the lignocellulose matrix mainly remains as a solid pulp.

Over the past years, many studies have demonstrated the possibility of controlling *lignin-first* products, and several attempts to scale up these approaches are currently underway.^[1c, 1d, 7] The RCF technology and its product separation are advancing with progressive improvement of the minimum selling prices and systematic reduction of the carbon footprint of its products.^[8] A foreseeable challenge for the lignin refinery is integrating its products into the current petrochemical market with a realistic price.^[9] Undoubtedly, phenols and, in general, aromatics are in great demand due to their applications in a wide range of products, such as chemicals, packaging, pharmaceuticals, dyes, thermal and electrical insulators, automotive vehicles, and others.^[2] The aromatics market, therefore, represents a large share of the chemical industry, which is expected to reach more than 300 billion USD by 2030.^[10] Currently, aromatics are predominantly produced from fossil sources, including commodity molecules such as BTX, (*i.e.* benzene, toluene, xylenes), phenol, and catechol.^[9] Compared to these commercial fossil-based aromatics, lignin-derived phenolic monomers are highly functionalized. There are three main groups present: a phenolic hydroxyl, *ortho*-methoxy(ies), and a *para*-alkyl group. In this respect, several strategies, such as hydrodeoxygenation and dealkylation (or transalkylation), have already been developed to defunctionalize lignin-derived compounds to produce fuel-grade hydrocarbons, typically referred to as catalytic funneling.^[1d, 11] In terms of lignin defunctionalization, *O*-demethylation (ODM) stands out as a critical chemical transformation. Indeed, ODM consists of converting an unreactive *ortho*-methoxy group (O-CH₃) into a reactive phenolic hydroxyl group (Ar-OH).^[11c] These functional group interconversions can potentially facilitate the synthesis of bio-derived catechols and pyrogallol moieties (**Scheme 1** top). In addition to the lignin monomer valorization, increasing the Ar-OH content in dimers and oligomers, also obtained from wood in the *lignin-first* approach can potentially unlock their usage for further applications in polymers.^[12] Furthermore, the low-value technical lignins produced from classical pulping would also benefit from an increased Ar-OH content. For instance, depolymerized and *O*-demethylated lignin possessing a large number of vicinal hydroxyl groups has improved reactivity towards cross-linking and other modifications in production of e.g. adhesives, carbon fibers, polyphenol-nanoparticles, and antibacterial/antioxidant compounds.^[12-13]



Scheme 1. Schematic representation of ODM of lignin-derived products from lignocellulosic biomass. The introduction of new Ar-OH functionalities on the arene via ODM in the lignin moieties, including technical lignin and *lignin-first* derived oligomers and monomers, provides building blocks to access new and/or more performant molecules for various applications.

Hence, ODM is a vital chemical transformation to further widen the potential applications of lignin. The development of lignin-based biorefineries has reached an important development stage, where a foreseeable valorization of each refinery product for end-use applications is required to finally achieve an economically feasible process. This review focuses primarily on the chemical approaches for ODM of aryl methyl ether bonds (including catalytic and non-catalytic reactions) for upgrading both technical lignin and *lignin-first* derivatives. The C1 by-products of ODM, e.g. methanol and methane, may be potentially used as commodity chemicals, contributing to the reaction's atom economy. Biotechnological approaches for ODM, encompassing enzymes, bacterial systems, and wood-rotting fungi, have also undergone extensive research and are comprehensively summarized elsewhere. We advise the reader to consult these reviews for more details on that matter.^[13b, 14]

The scope of this review is to highlight the potential of ODM in lignin valorization by providing the reader with insights into lignin chemistry [*i.e.* cleavage (depolymerization) and functionalization], a comprehensive overview of the reported ODM works, the possible future applications of the reaction products, and qualitative green and cost metrics for ODM reactions.

2. Bio-derived Phenolics from Lignin.

2.1. Native Lignin in Lignocellulosic Biomass

Lignin co-exists with cellulose and hemicellulose in plants via a semi-interpenetrating solid polymer network.^[15] This

Lignocellulose is mainly composed of polysaccharide-based polymers, *i.e.* cellulose (30-50% on a dry weight basis), hemicellulose (20-30%), and an aromatic macromolecule, lignin (15-30%). Lignin is an irregular oxygenated *p*-propylphenol polymer composed of three phenolic units or monolignols: coumaryl-, coniferyl-, and syringyl alcohol. The arene moieties of these building blocks are referred to as *p*-hydroxyphenyl (H-), guaiacyl (G-), and syringyl (S-) units in native lignin, as shown in **Figure 1**.^[16] These monolignols are secreted in the plant's cell wall and undergo oxidative polymerization, forming carbon-carbon (C-C) and carbon-oxygen (C-O) linkages (e.g. β -O-4, β -O-5, and β - β). This process leads to an entangled, cross-linked polymer (native lignin), with 2500-10 000 g mol⁻¹ estimated molecular weight.^[14a, 17] Monolignols differ in the number of *ortho*-methoxy groups; no, one, and two methoxy moieties are present in the H-, G-, and S-units, respectively.

The distribution of the phenolic units (**Figure 1**) strongly depends on the plant species, tissues, and cell types. Generally, hardwood plants present a blend of G- and S-units in a 1 to 3 ratio (**Figure 1A**), while softwood species are rich in G-units (**Figure 1B**). Instead, herbaceous crops contain all three units H-, G-, and S- (*viz.* **Figure 1C**).^[6, 16] The *ortho*-methoxy groups in these units determine the reactivity of lignin, and they prevent their positions from participating in C-C bond formation. Varying the ratio of secreted monolignols, thus, allows the plant to control its lignin growth and structure, and consequently its macroscopic properties. It should be noted that the H units in hard and softwood and the S units in softwood lignin are usually less than 5%. Due to the absence of the methoxy groups, the H units are anyway outside the scope of ODM.

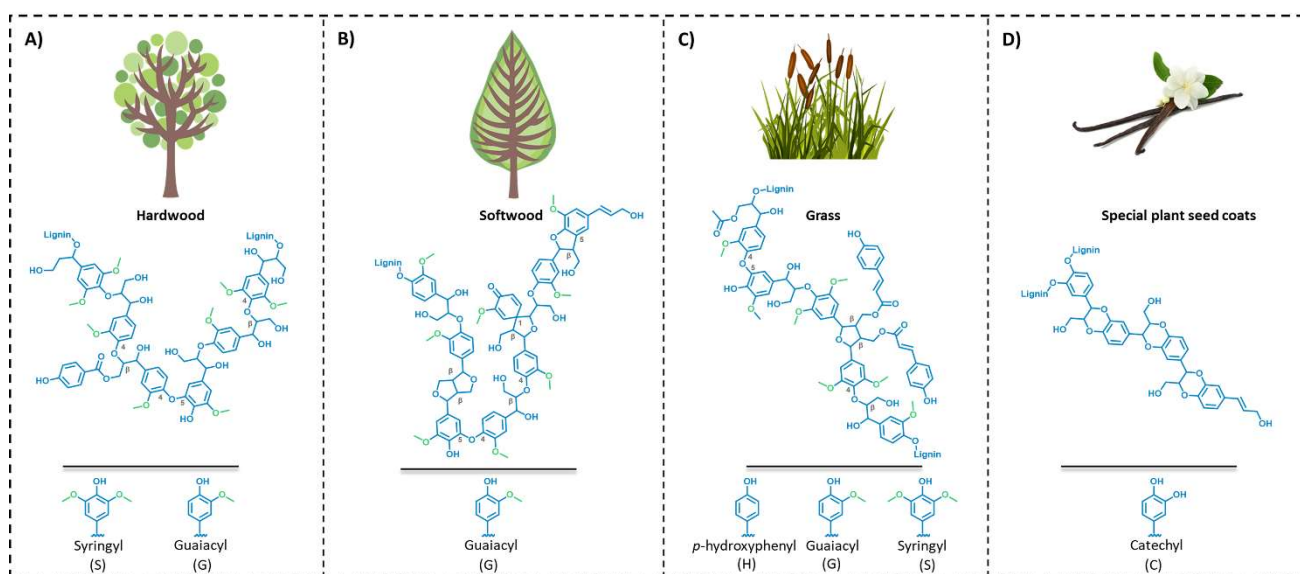


Figure 1. The representative models of lignin structures (A: hardwood; B: softwood; C: grass; D: special plant seed coats).^[16, 18] The methoxy functionalities are highlighted in green.

Recently, a novel type of native lignin, *i.e.* catechyl or C-lignin (**Figure 1D**), composed of the monolignol caffeyl alcohol as subunits and benzodioxane linkages was discovered.^[18] This C-lignin can be found in the seed coats of vanilla plants, castor plants, and several members of the cactaceae.^[19] The catechol monomers obtained via depolymerization of C-lignin contain two

hydroxyl groups and can be transformed into a plethora of useful chemicals. These are in fact the compounds that are typically targeted with ODM of lignin as discussed later. Given the majority of the lignin found in nature is of the G/S-type, ODM is essential to gain access to these hydroxyl-rich compounds.

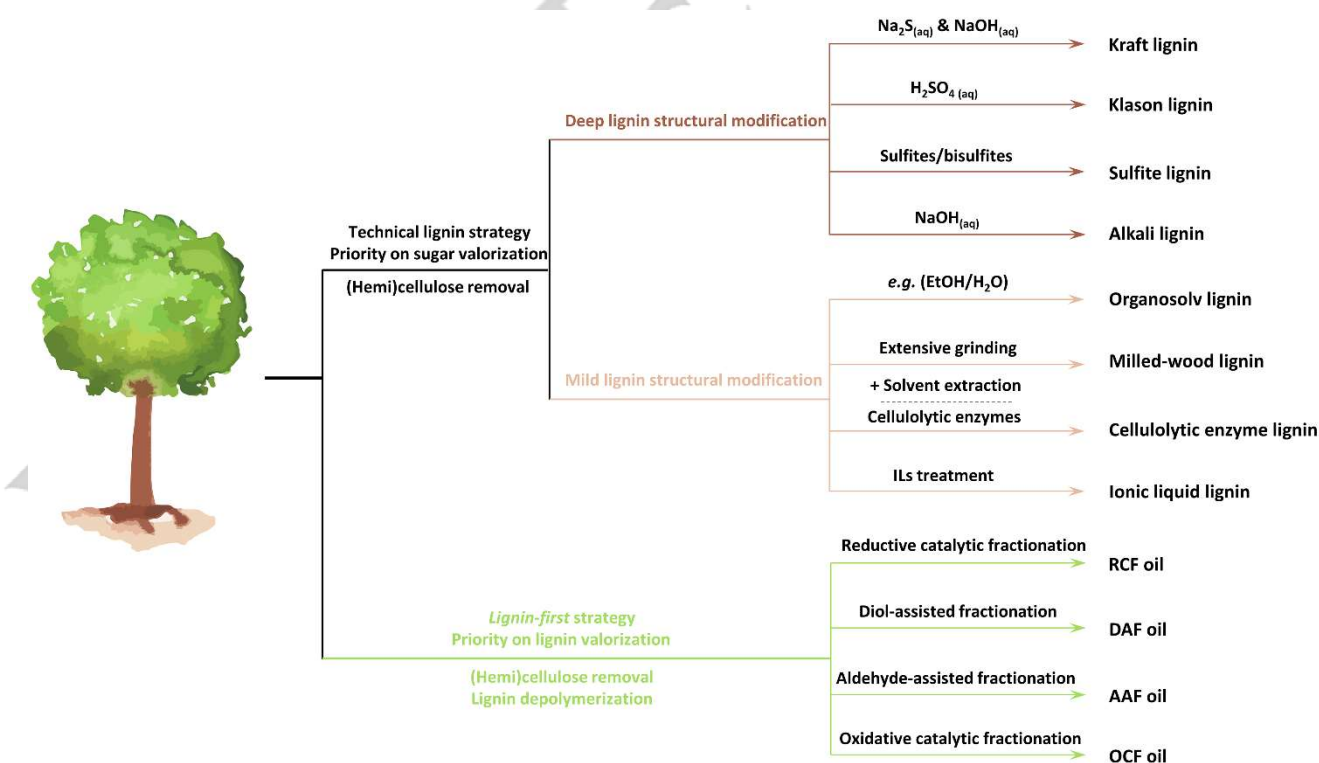


Figure 2. Schematic representation of technical lignin production (Top) and *lignin-first* strategy (Bottom). Mild structure modification: more α -aryl ether and β -aryl ether bonds are preserved in technical lignin and fewer repolymerization reactions during the pulping process; Deep structural modification: a large amount of inorganic acid, base, and/or salts are used during the pulping process, leading to the cleavage of α -aryl ether and β -aryl ether bonds along with extensive repolymerization forming C-C bonds.^[2a]

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2.2. Technical Lignin: (Hemi)cellulose Removal

Technical lignin is a broad category that refers to a wide class of native lignin derived polymers obtained after the removal of cellulose and hemicellulose from the lignocellulose matrix. Its structure and properties are altered, and vary with the biomass feedstock and fractionation process selected.

The pulp and paper industry currently provides technical lignins on an industrial scale, by adapting five standard technologies, *i.e.* kraft, alkali, sulfite, enzymatic hydrolysis, and organosolv processes.^[20] In addition, technical lignin is also a by-product in second generation bioethanol production.^[21] The structure of the by-product lignins from these processes differs from the in planta lignin present in plants and is therefore referred to as technical lignin irrespective of the process applied.

The chemical structure of native lignin alters during the fractionation process. As cellulose receives priority attention in these standard biorefineries, technical lignin is usually burned as low-grade fuel in the facilities for energy recovery, *e.g.* to dry the pulp *etc.*^[22] Therefore, while present, they may not always be as accessible as one thinks as it has a crucial function in the biorefinery.

The technical lignins obtained via treatments under relatively harsh conditions, such as low pH (1-5) and high temperature (150-250 °C) (Figure 2), usually have lower ether contents, but abundant more recalcitrant lignin-uncommon C-C bonds.^[23] Besides, technical lignins can also contain various organic and inorganic impurities, for instance, sulfur and sodium salts.^[21] According to the sulfur content, technical lignin can be classified into sulfur-containing lignin (lignosulfonates and kraft lignin) and sulfur-free lignin (organosolv lignin, alkali lignin, enzymatically hydrolyzed lignin, ionic liquid lignin, milled wood lignin, and the second generation biorefinery lignin).^[21] The sulfur-free lignins are normally produced with a mild structural modification (except the alkali lignin), and the sulfur-containing lignin has profound structural modifications (*viz.* Figure 2). The technical lignins with structures close to native lignin are obtained by applying less harsher conditions.

Regardless of the severity of the applied production process, abundant methoxy groups are always preserved in most technical lignins.^[23a, 24] For instance, methoxy groups correspond to approximately 11.0 and 14.1 wt% of kraft lignin and organosolv lignin, respectively.^[25] While several technical lignins are produced on a commercial scale, there remains a need for an efficient pathway to incorporate them into the production of renewable chemicals or materials without the need for depolymerization into monomers.^[23a] After all, its macromolecular form provides a stage to serve as a versatile material with potential applications as binding agents, carbon fiber precursors, co-polymer materials, and battery electrodes.^[13d, 26] The selective increase of phenolic hydroxyl functionalities would benefit these applications and unlock new ones.

2.3. Lignin-First Strategy: (Hemi)cellulose Removal and Lignin Depolymerization

Recently, a new biorefinery paradigm called *lignin-first* has been developed that prioritizes the extraction and conversion of native lignin from wood. In *lignin-first*, active stabilization strategies are applied to prevent lignin repolymerization during the (hemi)cellulose extraction and lignin depolymerization process.^{[1c,}

1d, 2a, 6, 7b, 23a, 27] This allows to both valorize the sugar and lignin fractions of wood. Stabilization strategies can be classified into reductive catalytic fractionation (RCF), diol-assisted fractionation (DAF), aldehyde-assisted fractionation (AAF), and oxidative catalytic fractionation (OCF), which rely on catalysis and *in situ* lignin derivatization chemistry.^[1c, 2a, 4e, 6, 23a, 28] Accordingly, a handful of phenolic monomers are produced in high yield by avoiding undesired polymerization that produces more recalcitrant compounds.^[6] Some of the most representative *lignin-first* monomers obtained are represented in Figure 3, including guaiacyl (G)-, syringyl (S)-, and *p*-hydroxyphenyl (H)- units. The abundance of each product can vary based on several factors, including the type of feedstock used, the type of *lignin-first* approach, the type of catalyst, solvent, and process conditions.^[6, 7b, 29]

For example, RCF of birch (hard) wood over Ru/C produces a lignin oil containing a mixture of monomers with a 4-propylsyringol to 4-propylguaiacol ratio of 3 to 1, representing more than 50 wt% of the native lignin content.^[7b, 27] Notably, pine sawdust (softwood) delivers an exceptionally high selectivity (95%) in 4-propylguaiacol corresponding to the total *lignin-first* monomers under the same RCF conditions, representing approximately 16 wt% of the native lignin content.^[11a, 30] Apart from lignin monomers, also di-, tri-, and oligomers featuring methoxy functionalities are present in RCF lignin oils.^[1c, 31] The content can be up to 50 wt% of the RCF lignin oil, depending on the biomass and catalytic process conditions.^[6, 11a, 31b, 32] The ODM of such typical *lignin-first* products, including mono- (G-type and S-type), di-, and oligomers is discussed in the following sections.

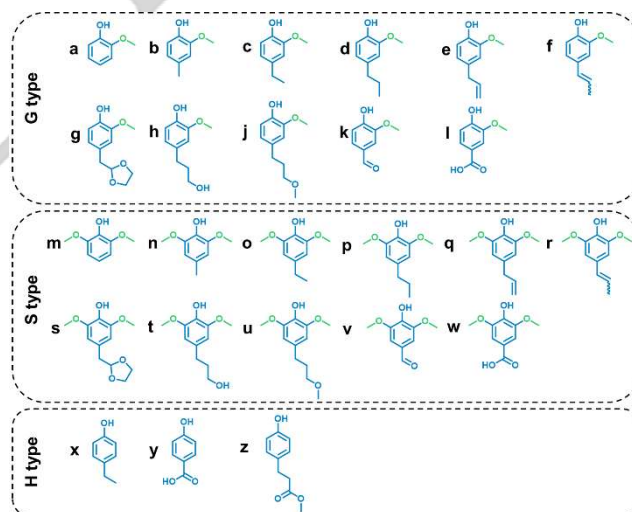
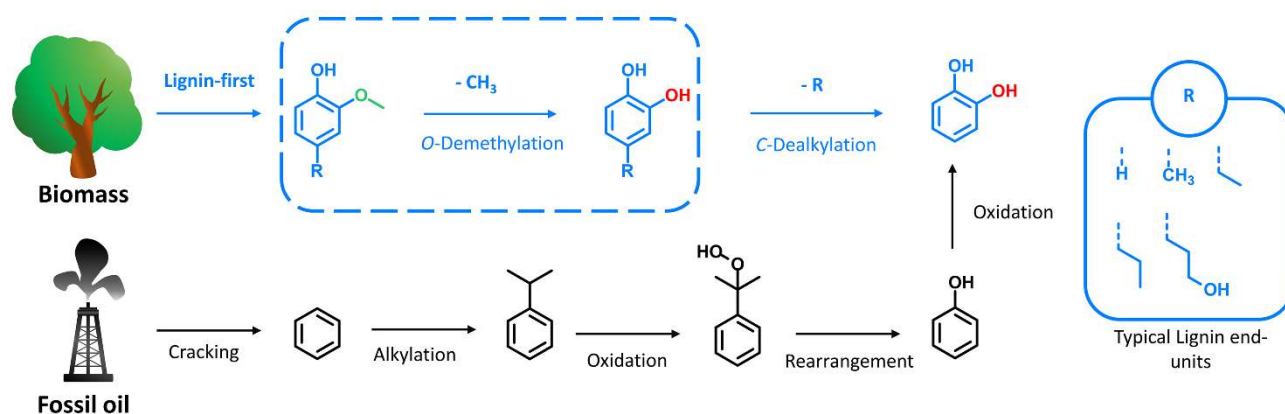


Figure 3. A summary of representative lignin monomers obtained in *lignin-first* approaches and classified based on the aromatic unit type, respectively G-, S-, and H-type. RCF: a-f, h, j, m-r, t, u, x; DAF: g and s; AAF: a-f, h, j, m-r, t, u, x; OCF: k, l, v, w, y and z.

3. ODM Products: Properties and Their Applications

3.1. Chemical- and Physical Properties of *Ortho*-hydroxyphenols



Scheme 2. Process for the production of catechol. (Bottom) The current established process for industrial catechol production (black). (Top) Possible route for catechol production from biomass involving an ODM reaction (blue).

The ODM of G- and S- units leads to mono and di-*ortho*-hydroxyphenolic moieties known as catechols (**Figure 4 a-f**) and pyrogallols (**Figure 4 g-j**), respectively.

Their chemical-physical properties are correlated with the presence of the vicinal hydroxyl groups that allow these molecules to form strong non-covalent interactions, such as H-bonding, and metal-ion complexation. Additionally, the aromatic cores can bind via π - π and metal- π interactions.^[33] These properties are fundamental for interaction with biological macromolecules, such as proteins, peptides, and DNA/RNA.^[34] For these reasons, catechol and pyrogallol moieties are widespread in natural products, e.g. myricetin and fisetin, and used as a building block for various active pharmaceutical ingredients (APIs), e.g. Erlotinib and dopamine.^[35] The vicinal Ar-OHs can be oxidized to form quinone and hydroxyquinone from catechol and pyrogallol, respectively. This oxidation occurs quickly under near-physiological conditions in a reversible manner, as a result of which catechol and pyrogallol moieties can act as antioxidants and stabilizers.^[36] Moreover, the redox switch between the aromatic 1,2-diol and quinone opens avenues for a variety of reactions, such as Michael addition and Schiff base formation.^[37] In addition, the Ar-OHs are reactive moieties for chemical functionalization with reactions such as esterification, etherification (*i.e.* alkylation), arylation, addition (e.g. urethanization), and silylation reactions.^[38] Importantly, phenolics are ambident nucleophiles and can therefore also react on carbon rather than oxygen, hence the tendency of lignin fragments to C-C repolymerize.

From all the above properties, it is clear that ODM products such as catechol and pyrogallol have unique physicochemical properties, valuable in a wide range of applications including as building blocks for materials, agrochemicals, pharmaceuticals, and fragrances.^[30a, 39]

3.2. Lignin-first Monomer Upgrading toward Drop-in and New Chemicals

Catechols and pyrogallols have been known for a long time with well-established synthetic procedures and applications.^[30a, 36, 39-40] Therefore, ODM of lignin-derived monomers may open up new sustainable and potentially shorter routes for these target compounds as well as new chemicals (including derivatives). The

following sections discuss the production routes of ODM products derived from guaiacols and syringols present in lignin oil.

3.2.1. Catechols

The simple 1,2-benzenediol, or catechol, is undoubtedly the most important representative among the catechols. Catechol is used as an antioxidant and to a small extent as a photographic developer.^[40] It is mainly used as a building block in the chemical industry for the synthesis of pesticides, pharmaceuticals, fragrances, stabilizers (polymerization inhibitors), and dyes.^[40] Catechol is also used for the industrial production of vanillin and guaiacol, which can be alternatively produced directly from lignin.^[41]

The chemical commodity, catechol produced from fossil fuels (*viz.* **Scheme 2** bottom), had an annual global production of 40 kilotons in 2017 and is expected to grow in the foreseeable future with an estimated market price of about 2000 USD per ton.^[42] Benzene is converted into phenol via the Hock process, and phenol is then further oxidized to catechol with H_2O_2 .^[40] Ube Industries adds additional methyl isopropyl ketone (MIBK) to enhance catechol selectivity and suppress hydroquinone formation.^[43] *para*-Hydroxylation providing hydroquinone cannot be avoided. The concentration of H_2O_2 is kept low, so more than 95% of the used phenol is not converted and recycled afterward.

As an alternative to fossil feedstock, catechol may be better synthesized from RCF-derived monomers with a two-step process consisting of ODM followed by C-dealkylation (*viz.* **Scheme 2** top).^[30a] In this respect, Sels *et al.* recently reported the synthesis of catechol from 4-propylguaiacol, one of the major RCF products of wood.^[30a] Maes *et al.* showed that also other biorenewable platform molecules, such as eugenol and ferulic acid, present in clove and rice bran respectively, can be transformed into catechol involving a sequence of ODM and C-dealkylation.^[44] Given the potential of reaching a market price as low as 1100 USD per ton for bio-catechol,^[42a, 42b] its production from renewables can be profitable. Direct synthesis of catechols without additional ODM has also been reported from C-lignin, but the feedstock availability poses challenges.^[45]

A selection of substituted catechols (**a-f**) and pyrogallols (**f-j**) derivable from *lignin-first* monomers via ODM is shown in **Figure 4**. For instance, 4-methylcatechol (**a**) and 4-propylcatechol (**b**) have been used as the precursor for bio-based bis-phenol A analogues, to replace fossil-based and endocrine disruptive

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bisphenol A,^[46] and to prepare 3-alkylmuconic acids and 3-alkyllevulinic acids not accessible from sugars (xylan/cellulose).^[47]

Additionally, **a** has pharmacological activity as an anti-tumoral agent.^[48] Similarly, **b** and hydroxychavicol (**c**) have shown promising anti-malarial activity.^[49] **c** has also shown cytotoxic properties versus tumoral cells.^[50] In addition, protocatechuic aldehyde (**e**) and acid (**f**) can be derived from vanillin and vanillic acid, which are typical products of OCF or broadly oxidative depolymerization of lignin.^[28a, 28g, 41c] Although primarily of interest for their functional end-unit, **e** and **f** also have pharmacological potential for use in various diseases, including diabetes, cancer, and pulmonary fibrosis.^[51]

3.2.2. Pyrogallols

The ODM of syringols could lead to the formation of di-*ortho*-hydroxyphenols known as pyrogallols. Similarly to catechols, pyrogallols are widespread in nature and present in wood barks, mainly in the form of tannins derived from gallic acids.^[52] The simplest representative is benzene-1,2,3-triol, known as pyrogallol (**Scheme 3**). Pyrogallol occurs naturally in plants, especially in oak, eucalyptus, and other hardwoods.^[53] Pyrogallol is the oldest photographic developer and is applied in lithography, as an antioxidant, and in hair dyes.^[53]

To date, several processes already exist to produce pyrogallol (**Scheme 3**). The most common method is to produce it from biomass rich in tannins or gallic acid. Gallic acid is obtained by ester hydrolysis of the tannins or directly extracted from them, and subsequently, decarboxylated thermally with release of CO₂. Despite its easiness, the pathway is expensive due to the high feedstock cost. Accordingly, pyrogallol can also be produced from fossils in a manner analogous to the production of catechol, though, to the best of our knowledge, not used industrially.^[54]

Compared to catechols, there is little information in the literature on pyrogallols. For example, 5-propylpyrogallol (**Figure 4 g**) has not yet been reported in any application. Due to the similar interaction with biological components, 5-allylpyrogallol (**h**) presents similar anti-malarial properties to its catechol counterpart (**c**), with a higher IC₅₀ value.^[49] Furthermore, gallic aldehyde (**i**) and gallic acid (**j**) are potential compounds of ODM

of typical OCF products from wood such as syringaldehyde and syringic acid.^[28a, 28g]

3.3. Upgrading Oligomers and Technical Lignin for Application as Macromolecules.

Increasing the value of technical lignins and *lignin-first* oligomers is critical to the development of efficient future biorefineries. This requires a deep understanding of their structure due to their complexity, heterogeneity, and strong dependence on the type of feedstock and the process conditions for cleavage employed.^[6, 11a, 31b, 32]

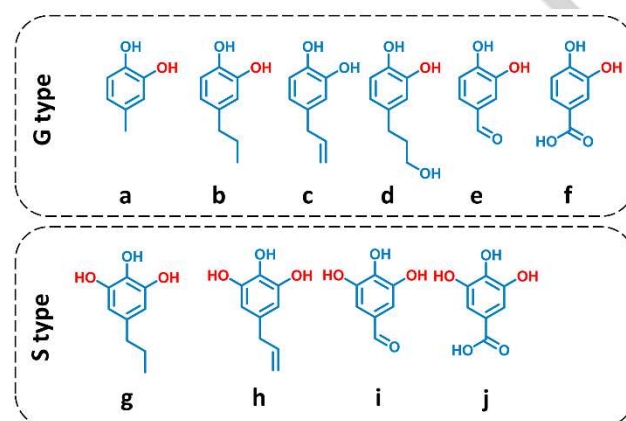
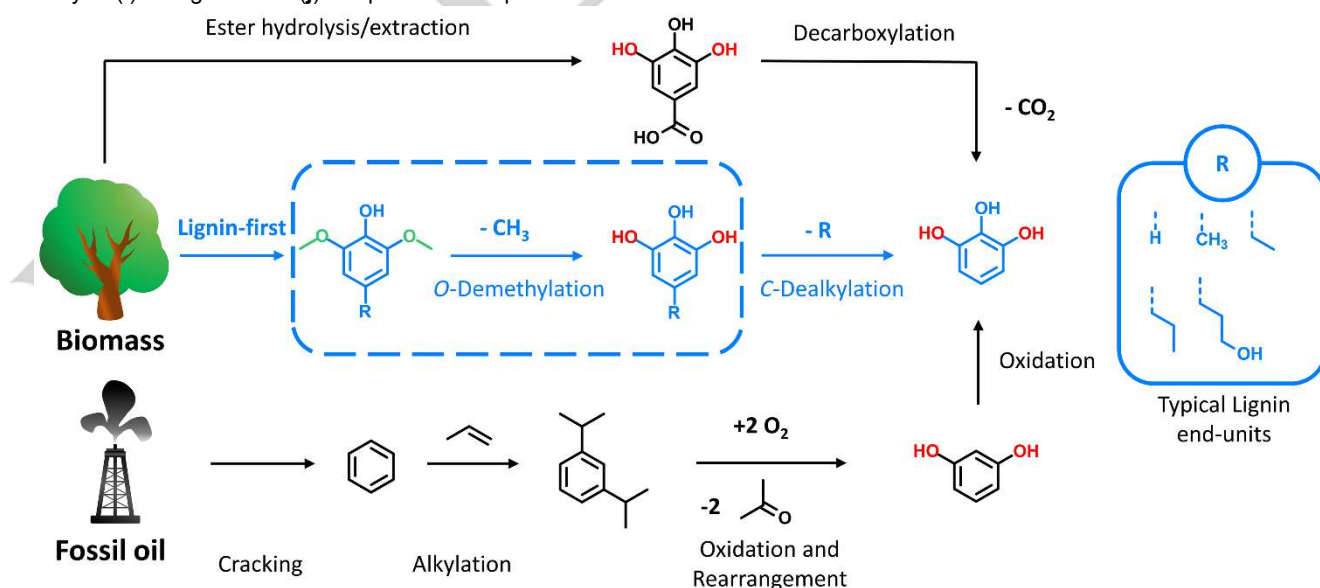


Figure 4. Catechols (Top) and pyrogallols (Bottom) derived from ODM of *lignin-first* monomers.

Among the applications, their direct use as macromolecules is promising for the synthesis of renewable carbon-based materials, including carbon fibers, adhesives, polymers, and phenolic resins.^[13d, 26a, 26b, 26e, 38] In this context, increasing the hydroxyl content in their structure by ODM can be a suitable tool for broadening their application range and improving the final performance of the target materials.



Scheme 3. Process for the production of pyrogallol. (Top and Bottom) The current established process for industrial pyrogallol production from oil and biomass (Black). Biomass rich in tannins is used (roots, seeds, barks, wood, and leaves) (Center) Possible route for pyrogallol production from biomass involving an ODM reaction (Blue).

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One major field of interest for technical lignin as a macromolecule is the replacement of bisphenol A to produce bio-based polycarbonate and phenolic resins.^[31a] Phenolic resins have a substantial global market of approximately 14 billion USD in 2021, which is projected to grow in the following years.^[55] In the synthesis of epoxy resins, the phenolic functionality is exploited as a reactive site.^[56] The total number of Ar-OHs has been highlighted as one of the most critical features of technical lignin to increase the cross-linking density of the resins resulting in improved thermal resistance, mechanical properties, and more favorable epoxide equivalent weight.^[57] For technical lignin upgrading, ODM is seen as a mandatory step for improving lignin's properties in the field of epoxy resins.^[57] In addition to Ar-OH, the presence of aliphatic alcohols can also modify the epoxy resin properties.^[31a, 57] The aliphatic alcohols are abundant in RCF lignin oils, processed in the presence of Pd catalysts.^[7b]

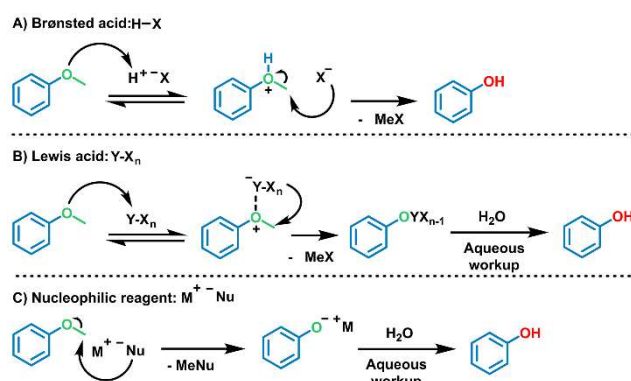
Furthermore, oligomers and technical lignin can also be used as a sustainable alternative to petrochemical diols and polyols in synthetic polymers.^[58] The Ar-OHs can be used as reactive moieties directly or after modification (e.g. hydroxyalkylation) to synthesize lignin-based polyurethanes and poly-esters.^[26a, 58a] In such applications, ODM can provide more reactive products with an increased Ar-OH content. In addition, due to its low cost and environmental compatibility, technical lignin is also receiving growing interest as an adsorbent material for heavy metal ions in water.^[59] The adsorption capacity of oligomers and technical lignin varies widely depending on the lignin type and source. However, there are no studies that address the correlation between their structure and performance. Nevertheless, the vicinal -OH moieties of catechol and pyrogallol units could improve the adsorption performance of oligomers and technical lignin.^[60] Indeed, the chelating properties of these substrates are higher when compared to the corresponding methoxyphenols. Due to its structure, lignin also has antioxidant properties, mainly due to the presence of the phenol moiety that allows for proton-coupled electron transfer and radical stabilization.^[61] Furthermore, the number of hydroxyl groups has been identified among the significant parameters to increase the anti-oxidative efficiency of lignin.^[61] In this context, it is clear that catechol and pyrogallol moieties present a higher anti-oxidative performance when compared with methoxyphenols. Therefore, ODM is of growing interest for promotion of antioxidant performances.

4. ODM of *Ortho*-methoxyphenols

4.1. ODM reactions

In synthetic organic chemistry, ethers are common functionalities that are also used as protection groups for alcohols and phenols.^[62] In an ODM reaction, the methyl group is replaced by hydrogen, thereby transforming an ether into an alcohol function. There are three groups of classical reagents (catalytic and/or stoichiometric) that are used for ODM of aryl methyl ethers (**Scheme 4**): Brønsted acids (A), Lewis acids (B), and nucleophilic reagents (C). In addition, some other reaction systems based on alkali metals, enzymes, and photoredox catalysis also exist.^[63] For reaction types (A) and (B), the reaction steps are quite similar: protonation/coordination of the ether oxygen followed by a nucleophilic attack. Reaction type (C) occurs without prior substrate activation for the nucleophile to attack. In all cases, the

nucleophilic attack proceeds via an S_N2 - and not an S_N1 -mechanism, due to the high instability of the methyl carbenium ion.



Scheme 4. The three main classical reaction types for aryl methyl ether cleavage. A. Brønsted acid mediated cleavage. B. Lewis acid mediated cleavage. C. Nucleophilic reagent mediated cleavage.

The ODM of aryl methyl ethers with Brønsted acids (A) starts with the protonation of the ether oxygen. In the second step, the generated weak nucleophile attacks the methyl group, thereby breaking the C-O bond, and generating the phenolic product. Alternatively, the solvent, water, can also act as a nucleophile. This reaction can be performed with catalytic amounts of acid. This requires water to act as a nucleophile or by-product MeX to react with water. For Lewis acid mediated reactions the mechanism is very similar (B). Here, the weak nucleophile is generated from the Lewis acid during the reaction. For instance with BBr_3 , bromide is released yielding $ArOBBR_2$ as a product, which upon work-up with water forms the Ar-OH target. In another frequently applied approach, catalytic Lewis acid is combined with (super)stoichiometric nucleophile. In the ODM of aryl methyl ethers with nucleophilic reagents, without substrate activation, the strong nucleophile performs a direct attack on the methyl group (C). This breaks the C-O bond, with formation of phenoxide anion. Various nucleophilic reagents, such as sodium thiolates, are reported to be active in this reaction.^[62]

In the reactions of aryl methyl ethers with Brønsted and Lewis acids, oxonium salts are formed as intermediates. Collie *et al.* were the first to propose the onium theory, that explains the high reactivity of the cleavage of alkyl ethers.^[64] It is important to note that the proton based cleavage mechanism in dilute aqueous solution fundamentally differs from that in anhydrous conditions.^[65] A bimolecular nucleophilic displacement is solely responsible for ether cleavage in dilute aqueous acids. With hydroiodic acid and hydrobromic acid, iodide and bromide are respectively involved in the ODM. These ions are sufficiently nucleophilic in water in contrast to chloride, released from hydrochloric acid. Accordingly, cleavage of aryl methyl ethers is not feasible when using anhydrous hydrochloride (HCl), even at 220 °C.^[66] Water molecules themselves are only weakly nucleophilic and not capable to O-demethylate aryl methyl ethers. However, at high temperatures (under pressure), the reactivity of water increases, and dilute aqueous HCl becomes suitable.^[40, 67] The primary by-product of ether cleavage with HI and HBr are the corresponding methyl halides that will transform with water into methanol. The HX by-product of this reaction allows catalytic use.

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In aqueous HCl, methanol will be generated directly. Compared to other acids, HF has rarely been used to break ether bonds in accordance with its corrosive nature and the low nucleophilicity of fluoride in water.^[62a] For Lewis acids, similar to Brønsted acids, the acid strength affects its ability in ether-cleavage.^[68] While dialkyl ethers have two alkyl groups which can be cleaved via nucleophilic attack, alkyl aryl ethers (such as the aryl methyl ethers present in lignin and its derivatives) are only attacked by the halide or water on the methyl moiety. On the one hand, the oxygen basicity is very different as in an aryl methyl ether it is in conjugation with the arene, making it substantially less Lewis and Brønsted basic. On the other hand, the electron-rich arene ring in aryl methyl ethers can potentially react with acids, generating oxonium indirectly via conjugation.^[44]

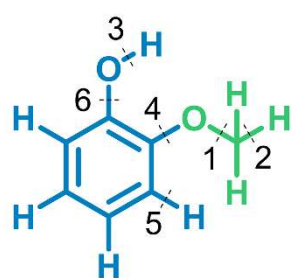


Figure 5. Bond dissociation energies in guaiacol as a lignin-derived model monomer.^[69]

1. C-O: 241.6 kJ/mol
2. C-H: 399.8 kJ/mol
3. O-H: 342.1 kJ/mol
4. C-O: 376.8 kJ/mol
5. C-H: 466.8 kJ/mol
6. C-O: 455.9 kJ/mol

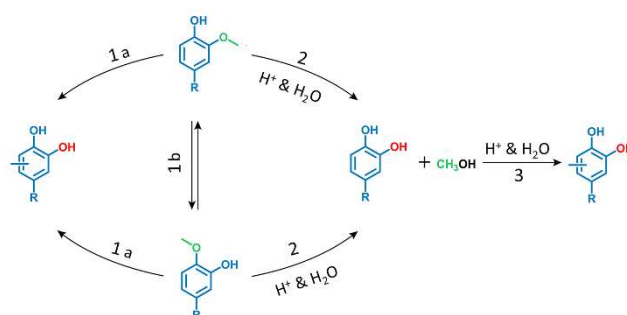
Guaiacol (2-methoxyphenol) is the most simple representative of a lignin-derived monomer. The bond dissociation energies of guaiacol are profiled in **Figure 5**. The structure comprises three C-O bond types, i.e. the Me-OAr, Ar-OMe, and Ar-OH.

Me-OAr is the weakest bond with an estimated bond dissociation energy (BDE) of 220–250 kJ mol⁻¹, which is lower than that of Ar-OMe (350–400 kJ mol⁻¹) and Ar-OH (415–460 kJ mol⁻¹) (**Figure 5**).^[65, 69a, 70] Even without activation, Me-OAr is therefore already the weakest bond. A similar reasoning is valid for S units. The thermal stability of alkyl phenyl ethers (~ 400 °C) is higher than that of benzylic ethers (~ 300 °C) but lower than simple alkyl ethers (> 500 °C), indicating that the presence of a benzylic functionality reduces the thermal stability.^[66]

The ODM of ethers transforms G- and S- phenolic monomers into catechols and pyrogallols, respectively. The transformation of Ar-OCH₃ into Ar-OH promotes the reactivity of the aryl ring in electrophilic substitution due to its stronger *ortho-para* directing ring activating effect.^[67a] The higher reactivity provides opportunities for synthesis (e.g. thermoplastics),^[46a, 67, 71] but the higher reactivity of catechols- and pyrogallols can also lead to undesired by-products, such as ring methylation or char formation.^[72]

Among the undesired reactions, C-methylation on the arene ring is inevitable and can occur via two different reaction pathways: O to C-transmethylation and C-methylation with methanol (viz. **Scheme 5**). To this respect, Gates *et al.* proposed a reaction network for the catalytic reactions of guaiacol over Lewis acidic Al₂O₃, suggesting that transfer of methyl groups involves both uni- and bimolecular parallel reaction pathways.^[73] Notably, intramolecular O to O-transmethylation is more favorable on

zeolites than intermolecular O to C-transmethylation considering pore sizes.^[30a]



Scheme 5. Reaction pathways involved in acid-catalyzed guaiacols ODM (R = H, CH₃, CH₂CH₃, and CH₂CH₂CH₃). 1a. Bimolecular O to C-transmethylation with a substrate or product molecule. 1b. Unimolecular O to C-transmethylation. 2. Bimolecular ODM. 3. Bimolecular C-methylation.^[30a, 39, 74]

In a recent report by Lercher *et al.*, the reverse reaction of C/O-ethylation of phenol with ethanol over ZSM-5 zeolites showed a similar activation energy of around 104 kJ mol⁻¹, caused by the formation barrier of ethyl carbenium ion via the activation of ethanol over hydronium ions.^[75] Overall, C-alkylation (*ortho* and *para* positions) has a slightly higher pre-exponential factor than O-alkylation, implying that the aromatic carbon is more reactive than the phenolic oxygen.^[75] The study suggested that the reaction rate of alkyl groups with phenol catalyzed by zeolites is completely determined by the formation of the alkyl carbenium ion, as exemplified by ethanol.^[75] However, conversion of 4-propylguaiacol in the presence of zeolites led to predominantly intramolecular O to O-transmethylation to 5-propylguaiacol, while C-methylated 4-propylguaiacol was formed less.^[30a] Similarly, this O to O-transmethylation reaction involving isomerization of 4- to 5-alkylguaiacol was also observed over a Ni catalyst supported on TiO₂-anatase.^[76] These studies confirm the existence of O to O-transmethylation and its dominance over C/O-methylation due to the vicinal orientation of the two phenolic oxygens not present in phenol, and the higher thermodynamic stability of 5-alkylguaiacol.

4.2. ODM of Lignin-first Products

An overview of ODM for upgrading *lignin-first* derived phenolics is listed in **Table 1** (can be found at the end, after the references). The recent advancements in the ODM of these products will be treated in three major sections with a distinct focus on guaiacols, syringols, as well as dimers, and oligomers.

4.2.1. ODM of Guaiacols

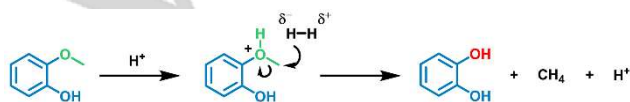
Guaiacols contain a single aromatic methoxy substituent that can be O-demethylated to yield catechols. Despite the numerous research works focusing on the cleavage of aryl methyl ethers, the available literature on the conversion of *lignin-first* monomers to O-demethylated products is surprisingly scarce.^[62b, 77] The first example of ODM of guaiacol can be traced back to the production of catechol from guaiacol in aqueous 48 wt% HBr, with CH₃Br as main by-product, which is distilled off, reported by Dakin and Taylor (**Scheme 4 A**).^[78] In subsequent research, acid-catalyzed/mediated approaches dominate the realm of ODM of

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aryl methyl ethers. For instance, stirring 4-propylguaiacol in aqueous 48 wt% HBr at 115 °C for 16 to 19 hours yielded 94–97% of *O*-demethylated 4-propylcatechol, needing only an extraction as purification step.^[79] Additionally, aqueous 40 wt% HBr has recently also been used for the ODM step in the synthesis of dopamine hydrochloride from softwood lignin.^[35b] With HBr, the product yield reached 94.5%, whereas only 50.1% was obtained with aqueous HI and 0% with aqueous HCl under similar conditions.

It is imperative to use high-temperature pressurized water when utilizing aqueous HCl. Maes *et al.* have demonstrated that this mineral acid (**Scheme 4A**; Entry 1, 24, 39, 40, and 58, **Table 1**) is a cheap catalyst to efficiently cleave the aryl methyl ether bond of guaiacols (including lignin oil rich in 4-propylguaiacol obtained from pine wood) (at 250 °C).^[39] The reaction on 4-propylguaiacol was scaled and performed on 150 mmol providing 92% product (autogenic pressure sufficed). In this report, Lewis acid FeCl₃ (Entry 41, **Table 1**) has also been observed to *O*-demethylate guaiacols and is assumed to produce Brønsted acid *in situ* by reaction with water. Aqueous H₂SO₄ can also be used, but it requires a longer reaction time or higher loadings compared to other mineral acids. When unsaturated side chains are present in the substrate, for example with eugenol and ferulic acid, additional *C*-dealkylation occurs under the reaction conditions.^[44] This tandem defunctionalization is a highly efficient strategy in the catalytic funneling of unsaturated lignin monomers towards catechol. A high loading (320 mol%) of aqueous 85 wt% H₃PO₄ was also able to *O*-demethylate guaiacol in 90% yield, unfortunately no temperature was indicated.^[80]

The reaction system comprised of heating a substrate with aqueous acid underwent several further innovations. For example, HX can also be obtained *in situ* via an elimination reaction in alkyl halides.^[81] Based on this observation, Duan *et al.* developed an efficient procedure to cleave the methyl group of guaiacol with a high yield of catechol (91%) using iodocyclohexane (5.0 equiv.) in DMF under relatively mild reaction conditions (reflux; Entry 7, **Table 1**).^[82] Due to the slow formation of HI from iodocyclohexane, undesired side reactions, that occur when using concentrated HI, can be minimized. Aqueous HCl has also been used in combination with H₂ to convert guaiacol into catechol with a high yield (89%) by heating at 280 °C for 3 h.^[83] Low pH and increased H₂ pressure proved essential to boost the reaction rates. The reaction follows an unusual aryl methyl ether hydrogenolysis pathway employing H₂ as a reactant rather than a classical ODM in which a nucleophile is involved. It is hypothesized that the charged reaction intermediate causes polarization of H₂, allowing it to react with the protonated intermediate, thereby generating catechol and methane (**Scheme 6**).



Scheme 6. ODM via an unusual aryl methyl ether hydrogenolysis reaction with polarization of H₂.^[83]

Waghmode *et al.* reported that the ODM rates of aryl methyl ethers such as 2-methoxynaphthalene over aqueous HBr were accelerated by adding aliquat-336, a so-called phase transfer catalyst (PTC). The ODM of guaiacol by heating with 4.5 equiv. of

47 wt% HBr and 10 wt% Aliquat-336 as catalyst at 105 °C for 6 h gave 78% yield of catechol (Entry 5, **Table 1**).^[84] For 2-methoxynaphthalene a significant acceleration of the reaction was observed by using aliquat-336. For guaiacol, however, the difference is minimal, since 85% of catechol was obtained in 7 h by Dakin and Taylor without additional aliquat-336,^[78] although no direct kinetic comparison has been done. We suspect that aliquat-336 functions more like a surfactant than as a PTC, thereby improving the interaction between the aqueous and organic phases. Guaiacol is sufficiently soluble in water, so no separate organic phase is formed and thus the surfactant has no effect on the reaction rate here. The presence of electron-withdrawing groups at the *ortho* and *para* positions of anisole turned out to accelerate the rate of ODM. Accordingly, electron-donating groups were found to retard the rate of reaction. Furthermore, substitution at *para* and *ortho* positions gave similar ODM rates. Combinations of mineral acids with halide nucleophiles have also been disclosed. Notably, the acidic concentrated lithium bromide (ACLB) system (53 wt% LiBr, 6 wt% HBr in water), was also shown to be active in the ODM of 4-methylguaiacol, yielding more than 80% of 4-methylcatechol at 100 °C in 4 h.^[12, 44] This is a significant enhancement compared to aq. 48 wt% HBr, yielding only 68% of 4-methylcatechol at 120 °C in 20 h. Similarly, an ACLB system (61.7 wt% LiBr, 1.5 M HCl in water) has been used to convert 4-propylguaiacol into 4-propylcatechol, reaching a yield of 96% in 2 h at 110 °C.^[85] Under these conditions LiBr forms a hydrated molten salt, where Li⁺ coordinates three water molecules, leaving Br⁻ more “naked” and free in solution to act as a nucleophile. In addition, H⁺ is more active (loosely hydrated) as well, which increases the acidity of the acid. Interestingly, the ODM of dihydroconiferyl alcohol under these conditions led to additional substitution of the aliphatic hydroxyl group by the halides. The apparent activation energy of ODM of 4-propylguaiacol over ACLB system, using the rate constants from Pan’s subsequent research,^[85] is estimated to be 81.6 kJ mol⁻¹ (0.1 mmol 4-propylguaiacol, 2.5 mL ACLB with 61.7% LiBr, and 1.5 M HCl in water).

Interestingly, the ODM of guaiacol and isomer 4-methoxyphenol show faster reaction rates than that of anisole, potentially due to the electron-donating effect of the additional hydroxyl substituents.^[85] In contrast, lower ODM rates were observed when 4-propylguaiacol was used as substrate compared to guaiacol, indicating other factors than electronics play a role. The reduced reaction efficiency can be explained by the lower solubility of these compounds in ACLB. In addition, a comparison between 4-nitroanisole and anisole revealed that electron-withdrawing substituents significantly reduce the ODM rate. These results are in contrast with the study of Waghmode *et al.*, where electron withdrawing substituents retarded the ODM reaction, and vice versa for electron donating substituents (*vide supra*).^[84]

Lewis acids with *in situ* nucleophile generation have also been used (**Scheme 4B**). The Lewis acid boron tribromide (BBr₃; 1.1 equiv.) is more reactive in guaiacol ODM than iodotrimethylsilane (TMSI; 1.1equiv), exhibiting 100 and 67% conversion, respectively, under the similar reaction conditions (halogenated solvent, room temperature).^[86] If no nucleophile is produced *in situ*, external addition is possible: e.g. aluminum chloride in combination with nucleophiles, such as KI, NaI, or Me₂S has also been found to be a practical and convenient system for the cleavage of aryl methyl ether bonds of guaiacols with various functional groups.^[87] Unfortunately, under these conditions, HCl is

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generated during the reaction, which leads to undesired side-reactions with acid-labile groups. Therefore, an acid scavenger, such as 1,3-diisopropylcarbodiimide (DIC) or calcium oxide (CaO), can be added to the AlCl_3 -NaI system.^[87a] Under these conditions, eugenol could be converted into hydroxychavicol in 99 % yield in 18 h at 80 °C. Additionally, AlI_3 has also been used extensively for this purpose. The ODM of eugenol with AlI_3 in combination with tetrabutylammonium iodide gives an additional reduction of its double bond.^[88] Pyridine,^[89] DMF-DMA,^[90] DIC,^[91] CaO,^[92] and DMSO have been used as acid scavengers to keep the double bond of eugenol intact during the ODM.^[93] The reaction with DIC has even been performed in EtOAc instead of MeCN, which is the usual solvent for this reaction.^[94] For the reaction with DMSO, it is proposed that *in situ* formed aluminum oxide iodide is the reactive species.^[93] A one-pot method, comprised of mixing aryl alkyl ether substrates, aluminum powder, iodine, and an acid scavenger (if needed) in acetonitrile, without preparing aluminum triiodide beforehand, can also efficiently cleave the ether bonds of aryl alkyl ethers.^[95] Furthermore, $\text{BF}_3\text{-Me}_2\text{S}$,^[96] AlI_3 , and BCl_3 in combination with TBAI,^[97] as well as the SiCl_4 - NaI couple were used for the demethylation of lignin-derived monomers.^[98] Catalytic $\text{B}(\text{C}_6\text{F}_5)_3$ with various organosilanes was able to convert the methoxy group of guaiacols into an Ar-OSiR group, to give the corresponding catechols after a subsequent hydrolysis step.^[99] The water-tolerant Lewis acids indium triflate ($\text{In}(\text{OTf})_3$), scandium triflate, ytterbium triflate, and indium chloride have been shown to catalyze the hydrolysis of guaiacol in water at 250 °C.^[100] $\text{In}(\text{OTf})_3$ displayed a higher catalytic performance for the cleavage of the C-O bond in guaiacol in comparison with HCl in high temperature water under an H_2 atmosphere.^[83, 100] It might be that under these conditions the corresponding Brønsted acid (*i.e.* HOTf) is formed *in situ*, which is the case for FeCl_3 (*vide supra*), and catalyzes the reaction. Yang *et al.* determined an activation energy of $134 \pm 5 \text{ kJ mol}^{-1}$ for the hydrolysis of guaiacol over indium triflate ($\text{In}(\text{OTf})_3$; Entry 15, **Table 1**).^[100]

Transition metal catalyst based systems have also appeared. In a recent study, Han *et al.* reported the complete conversion of guaiacol to catechol using a Ru-Co bimetallic catalyst with triphos ligand, and Lil in 1,3-dimethyl-2-imidazolidinone, under an atmosphere of CO_2 and H_2 .^[101] Lil is responsible for the ODM step, providing MeI. The Ru-Co catalytic system then catalyzes the carbonylation of MeI with CO, giving ethanal, that is subsequently reduced to yield 41% ethanol. The CO is *in situ* formed via a reverse water-gas shift reaction from CO_2 and H_2 . Lil is capable of ODM, but good conversions were only obtained when all the other reagents were present.^[101] Guaiacol and vanillic acid have been converted into catechol with more than 90 % yield using $\text{Pd}(\text{OAc})_2/[\text{Na}]^+[7,8\text{-bis(aminomethyl)-nido-dicarba-undecaborane(11)}]^-$ (*viz.* **Figure 6**) in 1 M aq. K_2CO_3 and DMA (1:2) at 240 °C in 4 h, the latter involving additional C-decarboxylation.^[102]

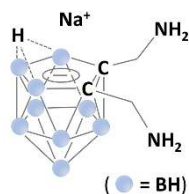


Figure 6. $[\text{Na}]^+[7,8\text{-bis(aminomethyl)-nido-dicarba-undecaborane(11)}]^-$.^[102]

Various ionic liquids, with or without transition metal catalyst, have been used for the ODM of aryl methyl ethers, but only a few have been applied to lignin-derived monomers. Guaiacol was converted into catechol (~ 70 % yield) by catalytic MeReO_3 in $[\text{Bmim}]\text{Cl}$ in 5 minutes under microwave irradiation.^[103] Methylimidazolium bromide has been used to demethylate vanillin in 83 % yield, in 5 h at 110 °C.^[104] Butylpyridinium bromide could demethylate vanillin as well, in 97 % yield in 2 minutes under microwave irradiation.^[105] HCl in combination with pyridine, which forms pyridinium hydrochloride, could be used to demethylate guaiacol in 96 % yield.^[106] Finally, nucleophilic inorganic salts such as LiCl in DMF under reflux were used in the demethylation of eugenol (50 % yield) but this system is not suitable for electron rich substrates.^[107]

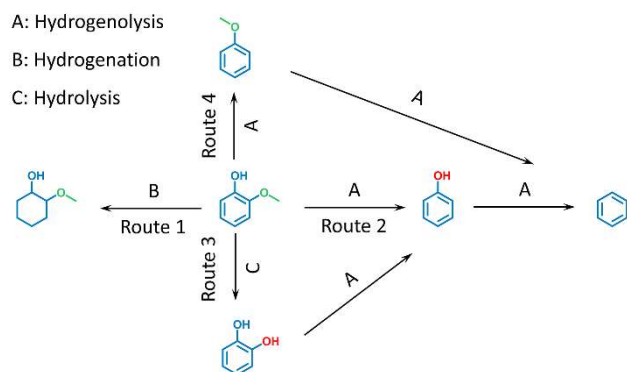
Various heterogeneous metal oxides (Entry 13 and 44-46, **Table 1**) such as Al_2O_3 , ZrO_2 , and TiO_2 (both rutile and anatase polymorphs), are catalytically active in the cleavage of C-O bonds, but with low catalytic activity.^[30a, 108] These liquid phase reactions are typically conducted at high H_2 pressure and temperature targeting various phenolic products starting from guaiacols. Strikingly, a distinct catalytic behavior of TiO_2 -anatase has been reported.^[108b] Almost no guaiacol conversion occurs using TiO_2 -anatase in toluene under 6.5 MPa of H_2 (initial pressure) at 300 °C within 2 h. When this oxide is decorated with Au nanoparticles (NPs) the conversion increases to 43%, though with phenol being the major product. Supporting Au NPs on other metal oxides (*e.g.* TiO_2 -rutile, Al_2O_3 , ZrO_2 , and SiO_2) showed selectivity shifts towards catechol as major product, but only Al_2O_3 showed acceptable, but still moderate (45%) conversion. A similar catalytic behavior was reported for Au NPs on layered acidic Nb_2O_5 (Entry 46, **Table 1**), but with water as solvent.^[108a] Under 6.5 MPa H_2 , 4-propylguaiacol was converted completely, mainly into propylphenols however, while under 6.5 MPa N_2 solely 4-propylcatechol (85%) was formed. Note that under N_2 atmosphere, Nb_2O_5 without Au NPs was even more efficient (92% yield of 4-propylcatechol). Only this last example can be considered as an efficient and selective ODM strategy for guaiacols. Guaiacol can also be converted into catechol over $\alpha\text{-MoC}_{1-x}/\text{C}$ catalyst in water (Entry 14, **Table 1**) but not in organic solvents.^[109] This is attributed to the structural transformation of Mo_{1-x}C into Lewis acidic MoO_2 in hot liquid water.

The acidic zeolite HZSM-5 presented a meager guaiacol conversion and catechol yield (< 1% in water at 200 °C for 40 min).^[65] When the reaction was carried out in benzene under 50 bar H_2 at 350 °C for 2 h, 54% of guaiacol was converted yielding 31% catechol. The authors observed a transalkylation of the methyl group from guaiacol to benzene.^[110] More recently, Sels and Maes *et al.* reported that the solid acid zeolites, preferably HBEA (Entry 48, **Table 1**) exhibited excellent performance in the conversion of 4-propylguaiacol into 4-propylcatechol (around 90% yield) in water at 275 °C.^[30a, 110] Also dihydroconiferylalcohol could be transformed into dihydrocaffeylalcohol.^[110] These represent the first published attempts to use zeolites as catalysts for the selective cleavage of aryl methyl ether bonds of guaiacols. The zeolite stability in such circumstances is limited, and therefore research for more stable versions such defect-free or superhydrophobic zeolites is currently done.^[111] Nevertheless, the high 4-propylcatechol yield shows great potential for ODM, even on real lignin oil, rich in 4-propylguaiacol.

Metallic catalysts, such as CoMo sulfides^[112], Ir (or Cu)/C,^[113] Ru/ZSM-5,^[114] MoRe carbides,^[115] Pt/ SiO_2 ,^[116] Pt/HBeta,^[116]

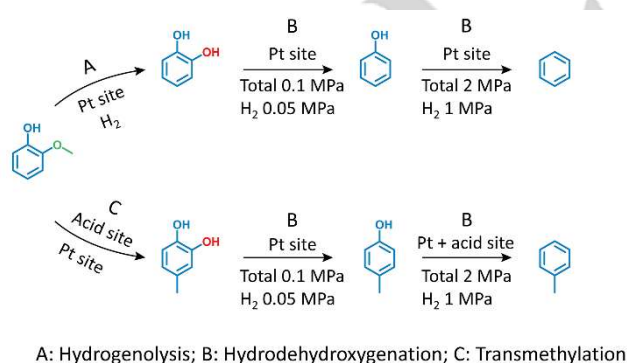
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transition metal phosphides,^[117] Mo₂N/C,^[118] Mo₂N/SBA-15,^[119] Mo₂N/Al₂O₃,^[119] and graphite encapsulated molybdenum carbides,^[120] also display potential for O-demethylating guaiacols. The resulting catechols are present as an intermediate of the reaction network and observed at low conversion (**Scheme 7**).



Scheme 7. The competing reaction pathways for the conversion of guaiacol over metallic supported catalysts e.g. Ru/ZSM-5 in the aqueous phase (under 2 bar H₂ and 6 bar N₂, at 240 °C). In the absence of Ru, route 3 is the dominant pathway.^[114]

In the presence of Ru/ZSM-5 as a catalyst, the selectivity shifts from catechol to phenol as the guaiacol concentration decreases.^[114] This might be attributed to the Ru hydrogenolysis activity promoted by the appearance of hydronium ions in presence of water, combined with the decreased amount of reactant at the catalyst surface that decreases the possibility of Me-OAr bond scission.^[114, 121] Non-acidic catalyst 1% Pt/C displayed a high selectivity (> 80% catechol at almost complete conversion) in the gas phase hydrogenolysis of guaiacol under atmospheric pressure (0.1 MPa; 1 : 1 N₂ and H₂) with a weight hourly space velocity (WHSV) of 33.3 h⁻¹ at 300 °C (**Scheme 8**; Entry 17, **Table 1**).^[122]



Scheme 8. Reaction network of guaiacol hydrodeoxygenation under H₂ (Gas-phase) over nonacidic (Up) and acidic catalysts (Bottom).^[122]

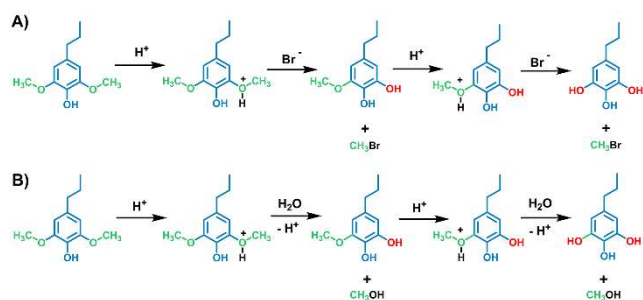
Other non-acidic catalysts (**Scheme 8**, up) such as 1% Pt/C-SBA-15, 1% Pt/Si-KIT-6, and 1% Pt/Si-ZSM-5 also exhibited high catechol selectivity at the high (65 h⁻¹) WHSV under atmospheric H₂ pressure (0.1 MPa), albeit at low (< 20%) guaiacol conversion. High contact times (11 h⁻¹) increased conversion at the expense of selectivity. For Pt/Si-ZSM-5 the catechol selectivity remained above 60%, but for Pt/C-SBA-15 and Pt/Si-KIT-6 phenol is

predominantly formed. The presence of acid sites (**Scheme 8**, bottom), as in 1% Pt/Nb-KIT-6, strongly accelerates transmethylation, explaining 4-methylcatechol and 4-methylphenol formation at low (0.1 MPa) H₂ pressure. Deep hydrogenolysis with formation of toluene happens at higher 2.5 MPa H₂ pressure. In contrast, Pd supported on (Lewis acidic) Al₂O₃, at 59 h⁻¹ WHSV and 300 °C in dilute H₂ atmosphere, yielded 70% catechol as the sole product (Entry 19, **Table 1**).^[117a] Further investigations can reveal the identity of the main active center, *i.e.* metallic Pd, Lewis acidic Al₂O₃, or activated H species (spill-over) at the surface. MoP(x)/γ-Al₂O₃ possessing strong acid sites, showed similarly high catechol selectivity.^[117c] Ranaware *et al.* reported a three-step complete conversion of vanillin to 4-methylcatechol (> 99% selectivity) using a non-noble metal-based bi-functional catalyst composed of ZnO/Co mixed phase supported on N-doped carbon nanotubes in water under 5.0 MPa of H₂ at 250 °C.^[123] In the first two steps, vanillin is converted via vanillic alcohol to 4-methylguaiacol, followed by ODM to 4-methylcatechol. An appropriate reaction temperature of 250 °C was crucial for the latter ODM, while avoiding formation of highly deoxygenated products (e.g. 4-methylphenol and 4-methylhexanone at 300 °C temperature).

Oxidation is another possible approach for the conversion of guaiacol (and eugenol) into catechols. Ozanne *et al.* reported a novel oxidative ODM for phenolic aryl methyl ethers over stabilized 2-iodoxybenzoic acid (SIBX) in THF at room temperature, followed by a reductive treatment with Na₂S₂O₄ to avoid degradation of the reactive *ortho*-quinone product, by which 89% yield of 4-propylcatechol was obtained (Entry 49, **Table 1**).^[124] The solid acid montmorillonite KSF in combination with H₂O₂ could afford excellent protocatechuic acid yield (75%) from vanillic acid via an oxidative demethylation.^[125] Additionally, the voltage-bias-assisted electrochemical ODM (with intermediate oxidation and reduction) of guaiacol into catechol over a multiwalled carbon nanotube (MWCNT) surface in neutral phosphate buffer solution has been reported.^[126]

4.2.2. ODM of Syringols

Syringols possess two chemically equivalent methoxy groups that can be O-demethylated to yield pyrogallols, with 3-methoxycatechols as intermediates from the first ODM step, as shown in **Scheme 9**. Syringols ODM is studied remarkably less compared to guaiacol. Similar reagents as for the ODM of guaiacols have been applied in syringols. Brønsted acids have been successfully applied in syringol ODM. *E.g.*, pyrogallol was obtained in 61% yield by heating syringol under reflux in aqueous 47 wt% HBr for 6.5 h.^[127] HBr was also used to transform dihydrosinapyl alcohol into 5-(3-hydroxypropyl)pyrogallol,^[128] but reaction conditions, yield, or selectivity were not reported. In a more recent study, Maes *et al.* reported a tandem catalytic O- and C-defunctionalization of an S-type phenolic, *i.e.* sinapic acid to pyrogallol, using catalytic HCl (50 mol%) in hot pressurized water (250 °C), achieving 59% of pyrogallol.^[44] FeCl₃ (20 mol%) has been shown to give a similar result under these conditions, via a presumed *in situ* generation of HCl, exemplified by converting dihydrosinapyl alcohol into pyrogallol in 45% yield.^[110] Furthermore, the same authors reported the twofold ODM of 4-propylsyringol (**Scheme 9B**), one of the major constituents in the lignin oil of hardwood RCF, on a 50 mmol (9.8 g) scale to give an 81 % yield of 5-propylpyrogallol, using catalytic HCl in hot water (250 °C, autogenic pressure; Entry 69, **Table 1**).^[39]



Scheme 9. Acid-catalyzed 4-propylsyringol ODM to 5-propylpyrogallols via 3-methoxy-5-propylcatechol. A) Reacting with aq. mineral hydrobromic acid (Brønsted acid) with bromide acting as nucleophile. B) General aq. Brønsted acid catalyzed ODM with water acting as nucleophile.

The previously discussed ACLB system has also been evaluated for syringols. Pan *et al.* reported a mixture of LiBr and HBr (53 and 6 wt%, respectively, in water) for syringol ODM, yielding 83% pyrogallol (Entry 62, **Table 1**).^[12] The reaction occurs in two steps through the 3-methoxycatechol intermediate (**Scheme 9A**). In the same study, 1,2,3-trimethoxybenzene was used as model S-type under similar conditions, yielding 87% pyrogallol. Note that, char formation was observed already under this relatively mild condition (100 °C) and extensive reaction times, indicating the high reactivity of pyrogallol.^[12] A different ACLB system, consisting of 61.7 wt% LiBr in 1.5 M aq. HCl transforms 4-propylsyringol into 5-propylpyrogallol in 98% yield, at 110 °C in 2 h.^[85] The estimated apparent activation energy of 4-propylsyringol ODM for the ACLB system (for 0.1 mmol 4-propylguaiaicol) is 74.5 kJ mol⁻¹. The lower value as compared to 4-propylguaiaicol (81.6 kJ mol⁻¹) may be attributed to the presence of an additional methoxy group, which increases the electron density on the benzene ring and promotes the protonation of the methoxy oxygen for the subsequent S_N2 substitution.^[85] Dihydrosinapyl alcohol is successfully O-demethylated under these conditions, but the aliphatic hydroxy group was concomitantly substituted by halides (Br and Cl).^[85] Additionally, syringic acid and syringaldehyde were fully converted, providing 97 and 36% yield of O-demethylated products, respectively, using the ACLB system. Various lignin-derivable syringols have been used for ODM using a Lewis acid. However, these reactions have not been used yet in this context, given they are all reported as part of multistep syntheses of bioactive compounds from petrochemical feedstock. BBr₃ in a chlorinated solvent has been used for ODM of sinapic acid, dihydrosinapyl alcohol, and methoxyeugenol,^[49, 129] showing 13, 43, and 68% fully O-demethylated product yield. In case of sinapic acid, 50 % yield of single O-demethylated product hydroxyvanillic acid was observed. For syringaldehyde ODM, AlCl₃ in combination with pyridine in a chlorinated solvent is typically used. The single O-demethylated product could be obtained in 95% yield (1 h, reflux),^[130] whereas full ODM yielded 64% gallic aldehyde (48 h, r.t.).^[131]

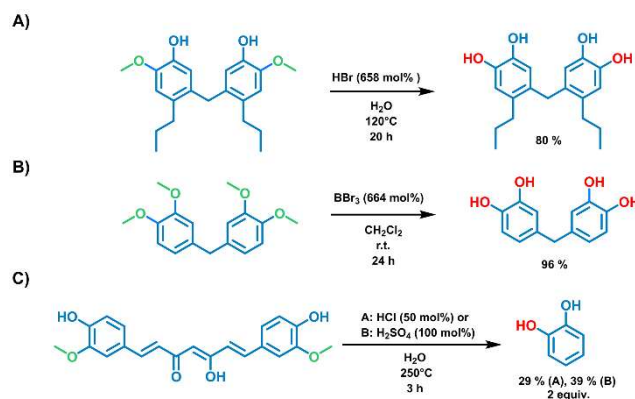
Abu Omar group reported the usage of Nb₂O₅ catalyst to O-demethylate the RCF-derived 4-propylsyringol.^[132] The reaction yielded 96% of 5-propylpyrogallol and 4% of the single demethylation product, 5-propyl-3-methoxycatechol, at 230 °C using water as a solvent under 10 bar of N₂ for 20 h. The ODM of 4-propylsyringol and dihydrosinapylalcohol with zeolite HBEA in hot pressurized water has also been reported by Maes.^[128] With 4-

propylsyringol, a 71% yield of 5-propylpyrogallol was obtained, with 12% of mono-demethylated intermediate at 83% conversion. A low 23% yield of 5-(3-hydroxypropyl)pyrogallol and some remaining mono-demethylated intermediate (16%) were obtained with dihydrosinapylalcohol, albeit at moderate conversion (39%) with good overall ODM selectivity.

Finally, transition metal based catalyst have been tested as well. Syringol is completely converted to pyrogallol with Ru-Co bimetallic catalyst, triphos, and Lil, under an atmosphere of CO₂ and H₂, with ethanol as by-product (Entry 64, **Table 1**).^[101] Pd(OAc)₂/[Na]⁺[7,8-bis(aminomethyl)-*nido*-dicarba-undecaborane (11)]⁻ catalyst yielded 61% pyrogallol from syringic acid, involving additional C-decarboxylation.^[102] Both catalysts were also reported for guaiacol (*vide supra*). Syringol conversion (89%) in the presence of vanadium powder in hot pressurized water (280 °C) yielded 43% pyrogallol and 40% 3-methoxycatechol at ~90% conversion.^[133]

4.2.3. ODM of Dimers and Oligomers

Given (well-characterized) lignin oligomers are not yet available (on the market), there is a lack of studies in literature focusing on their ODM. Nevertheless, a few studies have reported ODM of di-phenolic model compounds that can represent lignin dimers (Entry 77-80, **Table 1**). In this respect, Abu-Omar *et al.* prepared a G-type dimeric methylene bridged model compound from 4-propylguaiaicol, which was O-demethylated in 80 % yield using aqueous 48 wt% HBr at 120 °C (**Scheme 10A**).^[134] Similarly, in the report of Yan *et al.*, methylene bridged dimeric 4-methylguaiaicol (in CH₂Cl₂) has been O-demethylated by using Lewis acid BBr₃ (in CH₂Cl₂) at -78 °C for 1 h and subsequent reacting at room temperature with stirring overnight, yielding in 77% the fully O-demethylated product.^[136] This reaction system was also used by Göksu *et al.*, succeeding in the high yield ODM of methylene bridged veratrole (**Scheme 10B**).^[135] Moreover, Maes *et al.* used curcumin, a natural di-phenolic, for a tandem catalytic defunctionalization comprising of ODM and C-dealkylation to yield catechol using either HCl (50 mol%) or H₂SO₄ (100 mol%) (**Scheme 10C**) indicating the structure of the carbon linker is crucial to avoid cleavage.^[44] These O-demethylated dimeric compounds can be utilized for the production of lignin-based epoxy resins and polymers.



Scheme 10. ODM of dimeric model compounds. A) Methylene bridged 4-propylguaiaicol, from ref. [134]. B) ODM of methylene bridged veratrole, from ref. [135]. C) Curcumin with additional C-dealkylation, from ref. [44].

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4.3. ODM of Technical Lignin

Historically, the ODM reaction was applied in an analytic technique to determine the methoxy group content of (technical) lignins (**Scheme 11**), primarily by treating the lignin with aqueous HI, followed by quantification of CH₃I (*i.e.* the Zeisel–Vieböck–Schwappach method).^[137] An overview of ODM applied to technical lignins is summarized in **Table 2**. Almost exclusively non-catalytic reagent based systems have been applied on technical lignins.



Scheme 11. Graphical representation of ODM and functionalization in the valorization of technical lignin.

Brønsted acids have been mostly studied. Concentrated HI has for instance been used for ODM of alkaline lignin in DMF at 120 °C for 20 h.^[138] DMF is used as (co)-solvent in almost all ODM reactions of technical lignins to efficiently dissolve the polymer. The O-demethylated lignin finds application for heterogeneous Cu catalyst synthesis or as building block in lignin-based epoxy resin.^[138] During the ODM process, breaking of the major lignin interlinkage bonds (β -O-4, β -5, and β - β) forming higher molecular recalcitrant fragments occurs. Presence of such larger compounds is usually undesirable in polymer applications given precipitate formation and low quality thermomechanical performance in epoxy resins. Repolymerization can be partially avoided by adding phenol, that reacts with the lignin. Recently, Pan *et al.* used HI and HBr (both aq. 48 wt%) in DMF to improve the aromatic hydroxyl content of alkaline lignin for the synthesis of phenolic resins (Entry 2, **Table 2**).^[139] HI displayed a higher reactivity than that of HBr (increase in Ar-OH content from 0.52 to 0.67 mmol/g for HI vs. 0.64 mmol/g for HBr), due to the stronger nucleophilicity of iodide in water based solvents. The increase in aromatic hydroxyl groups leads to a faster curing time in the synthesis of lignin-based resins with a lower formaldehyde emission and a greater bonding strength. Aqueous 48 wt% HBr has also been used on various other lignin types in DMF, often combined with the phase-transfer catalyst tributylhexadecylphosphonium bromide (TBHDPB).^[140] The reaction is usually carried out in DMF at 110–120 °C for 20–24 h, but this can be decreased to 90 °C and 1.5 h by using microwave heating. Unfortunately, the increase in Ar-OH content is typically low, ranging from 15 to 33%. When adding phenol to the reaction mixture, the Ar-OH content of alkali lignin could be increased by a factor of 1.6 upon ODM, but this was mainly due to the incorporation of phenol.

The ACLB system (53 wt% LiBr, 6 wt% HBr in water) also showed effective cleavage of the ether bonds of technical lignin, including kraft lignin, corn stover lignin, and organosolv lignin,^[12] showing 69 to 82% of the aromatic methoxy groups were transformed into aromatic hydroxyl groups. The mild reaction conditions also resulted in less cleavage and recondensed lignin product. Use of ACLB has also been reported to produce O-demethylated lignins, specifically for adhesives and energy storage materials.^[141]

Finally, the effect of the acid concentration in an ACLB system of LiBr and aqueous HCl for ODM of kraft lignin has been investigated by Pan and Zhou *et al.*^[13c] They found that β -O-4 bond cleavage already occurs at mild conditions (< 0.5 M aq. HCl, 110 °C), whereas the cleavage of other bonds (β -5 and β - β) including ODM needs harsher conditions (*i.e.* higher acid concentration). Even though the harsher conditions cause lignin cleavage and repolymerization, the treatment using 60 wt% LiBr in 2.4 M aq. HCl at 110 °C for 2 h led to an 82% increase in Ar-OH content. The resulting lignin product displayed excellent antioxidant activity and Cr(VI) scavenging performance.

Iodocyclohexane in DMF with *in situ* generation of HI is also extensively used for ODM of various types of lignins (Entry 8, **Table 2**).^[142] The reported ODM efficiency is generally much higher than that of aqueous concentrated mineral acids in DMF, showing an up to a sevenfold Ar-OH content. Besides the usual applications of Ar-OH lignins products, *viz.* antioxidants, metal scavengers, adhesives, and hydrogels, iodocyclohexane treated lignins showed reactivity and selectivity improvements in pyrolysis and catalytic hydrogenolysis reactions.^[142d, 142f] Takano *et al.* compared dodecanethiol (DodecylSH), HI, and iodocyclohexane for the ODM of guaiacyl-type synthetic lignin.^[142h] With dodecanethiol in DMF and 28% NaOMe/MeOH, ODM was not efficient. For both aq. HI in DMF and iodocyclohexane in DMF, ODM proceeded smoothly. Remarkably, treatment with aqueous HI generated lower molecular weight (M_w) fragments when compared to the iodocyclohexane treatment.

Use of Lewis acids BBr₃ and AlCl₃ on technical lignins is reported to a lesser extent. The reaction is usually performed with TBHDPB as additive, at 115 °C for 4 to 24 h, in DMF or CH₂Cl₂. Ar-OH content increase from 34 to 81% were thus obtained with BBr₃ on various technical lignins.^[140a, 140b, 143] The O-demethylated was accompanied by significant depolymerization, observable by the lower M_w and β -O-4 content. Unlike BBr₃, AlCl₃ was able to O-demethylate alkaline poplar lignin with substantial twofold increase in Ar-OH, while retaining most of its macromolecular structure, including 75% preservation of the β -O-4 content.^[140a] Similar observations, *viz.* twofold Ar-OH increase and lignin structure conservation, were found for the AlCl₃-mediated ODM of organosolv lignins.^[144] Lehnen *et al.* have reported the use of the water tolerant Lewis acid In(OTf)₃ for ODM of organosolv lignin.^[145] Interestingly, this Lewis acid can be used catalytically (5 mol% compared to the ArOMe moieties) in aqueous (50 vol%) sulfolane. Microwave heating, which reduces the reaction time sixfold compared to conventional heating, was crucial in order to accelerate ODM, doubling the Ar-OH content.

There are reports demonstrating the successful use of ionic liquids for ODM. Han *et al.* reported an interesting strategy to produce acetic acid utilizing the methoxy groups of kraft lignin and organosolv lignin (over 80% conversion), thereby generating the O-demethylated lignin as by-product.^[25] Here, lignin is first O-demethylated with Lil and LiBF₄ in toluene, or Lil in BmimBF₄ or HmimBF₄, yielding CH₃I, which is subsequently carbonylated to acetic acid with RhCl₃ catalyst, CO, and H₂O, all in one-pot. Besides, the methyl groups can also be transferred to *N*-methylanilines, yielding *N,N*-dimethylanilines by Lil in HmimBF₄.^[146] The protocol did not depolymerize lignin while increasing catechyl units were obtained. The O-demethylated lignin was capable of catalyzing the CO₂/epoxide coupling reaction, yielding 93% of propylene carbonate at 60 °C for 8 h. Sun *et al.* reported ODM of technical lignins, *e.g.* enzymatic lignin,

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alkali lignin, and sodium lignosulfonate, with protic ionic liquids under mild and halogen-free conditions.^[147] For instance, the ArOMe content of enzyme-digested lignin was reduced by approximately 73% using [EOA][OAc], composed of a protonated ethanolamine cation and acetate anion.

Base conditions have also been applied though are rather rare. Wang *et al.* reported an approach using 1-dodecanethiol and sodium methoxide in DMF to increase the Ar-OH content of enzymatic hydrolysis lignin, achieving a rather low (19%) increase.^[148] Also, sodium sulfite (Na_2SO_3) in combination with NaOH in water has been used for ODM of alkali lignin under mild conditions, to enhance its applicability in phenolic resins.^[149a] The use of 15 wt% Na_2SO_3 and 10 wt% NaOH led to an increase in phenolic-OH content from 0.56 mmol/g to 0.82 mmol/g. Other technical lignins, including, organosolv lignin,^[149b] kraft lignin,^[150] sodium lignosulfonate,^[151] and corn straw lignin (treatments not described),^[152] have been reported as well. NaOH in aqueous urea also shows ODM activity and the Ar-OMe content of hardwood technical lignin, produced via alkali dissolution and acid precipitation, decreased from 0.32 to 0.18 mmol/g.^[153]

Electrochemical ODM under ambient pressure at 75 °C of sodium lignosulfonate (with 8.7 wt% Ar-OMe) in 85% aq. H_3PO_4 was reported to produce CH_3OH with 41.5% yield and 95% faradaic efficiency.^[154]

Despite the intense research on ODM of technical lignins in recent years, comparison between the different studies is elusive due to the large variety in technical lignins and the reaction conditions. But even with similar lignin substrates and conditions, comparison is difficult due to the variety of analysis techniques, *viz.* ^1H NMR, ^{31}P NMR, and UV VIS spectroscopy, as well as different reporting manners, *e.g.* the increase in Ar-OH content or the decrease in Ar-OMe content. In order to make better comparisons between the different ODM techniques it would be more beneficial to standardize both the analysis techniques and reporting of results. In this view, quantitative ^{31}P NMR spectroscopy is a promising technique for the analysis of hydroxyl groups in lignins upon phosphorylation, *e.g.* with 2-chloro-4,4,5,5-tetramethyl-1,3,2-dioxaphospholane reagent.^[155] Compared with traditional wet-chemical techniques, it offers unique advantages in measuring hydroxyl groups in a single spectrum with high signal resolution. The method provides complete quantitative information about the -OH groups and requires small sample amounts and short measurement time. Moreover, it can discriminate Ar-OH groups attached to syringyl, guaiacyl, and *p*-hydroxyphenyl units, as well as aliphatic OH groups instead of simply offering the total Ar-OH groups.

ODM reactions are also generally observed in depolymerization processes aiming to cleave the lignin interlinkage bonds (Entry 19-30, **Table 2**),^[156] where it is typically a minor and not desirable reaction. Depending on the conditions it can become a significant process which we illustrate for organosolv lignin. Catechol (1.5 wt% from lignin), 4-methylcatechol (0.8 wt% from lignin), and 4-ethylcatechol (0.5 wt% from lignin) were obtained in a CH_2Cl_2 -soluble fraction from hydrocracking with a NiW/silica-alumina catalyst.^[156h] When, bases such as NaOH, KOH, LiOH, and K_2CO_3 were used as the catalyst for the depolymerization catechol, and 4-methylcatechol were obtained as the main products (combined yield of 2.1 wt% from lignin).^[157] Finally, Barta *et al.* used a hydrotalcite-like Cu-doped porous metal oxide (PMO) catalyst with H_2 for C-lignin depolymerization, in which catechols are the preliminary products.^[156f] This is no ODM as C-lignin

consists of benzodioxane units but is still and O-dealkylation reaction.

4.4. Preliminary qualitative green metrics and cost analysis of ODM catalysts/reagents applied on lignin and derived oligomers and monomers

An overview of all commercial catalysts, reagents, and solvents used for the ODM of lignin and derived oligomers and monomers presented in this review is given in **Figure 7**. Based on their health, safety, and environment scores, they are categorized as recommended (**green**), problematic (**yellow**), hazardous (**red**), or highly hazardous (**dark red**).^[39, 158] Chemicals required for ODM that are labeled as problematic or worse are better to already avoid and substitute in the research and development (R&D) discovery phase, envisioning future applicability in chemical manufacturing. Therefore, the focus of (future) ODM strategies should be on using 'recommended' chemicals whenever possible. Moreover, the implementation of appropriate safety measures in ODM chemistry would require besides catalyst/reagents and solvents also the evaluation of the hazards of and necessary precautions in handling the intermediate products. The simplest ODM products catechol and pyrogallol, for example, possess health and environmental hazards and are therefore categorized as hazardous chemicals. However, *lignin-first* fractionation and subsequent ODM typically provides alkylated derivatives which can have different profiles. For instance catechol features acute toxicity, health hazards, and is irritant while 4-propylcatechol is irritant and hazardous to the aquatic environment. When working with these O-demethylated intermediates their hazards need to be evaluated, so the exposure of workers to these hazards can be minimized. The occupational asthma and other lung problems, as well as irritation of the eyes, nose, throat, and skin caused by prolonged exposure of workers to isocyanates serves as a representative example here. For most catechols and pyrogallols these hazards have been investigated. For O-demethylated oligomers and technical lignins, on the other hand, the related hazards are often unknown, so great care must be taken when using them.

Also byproducts of the ODM reaction need to be considered. For instance when Lewis acids or concentrated Brønsted acids based on halogen are used, the corresponding methyl halides (*i.e.* CH_3I , CH_3Br , and CH_3Cl) are formed. These byproducts are 'problematic' or even 'highly hazardous' (CH_3Cl) (**Table S3**). However, these are reactive and depending on the reaction conditions applied these can potentially be transformed further into less harmful compounds. Mineral acids are used in water and reaction of MeX with water generates MeOH. MeOH is also considered a toxic compound with label 'hazardous' by the default ranking of the CHEM21 solvent selection guide.^[158] However, upon discussion amongst companies it received the status 'recommended' (**Table S3**).

Since ultimately the goal is to integrate a developed ODM technique into a commercial biorefinery, this step should moreover be economically viable considering the price the final target product can have. In **Figure 7** therefore the price per mole for each catalyst and reagent is given to provide an idea about its applicability on large scale in an economic setting. Checking whether a catalyst/reagent is traded on large scale or is only a research chemical typically rationalizes these data. The number

A. Homogeneous catalyzed or mediated reaction systems			
A1. Lewis acid-based systems		A2. Brønsted acid-based systems	
<i>Lewis acids</i>		<i>Brønsted acids</i>	
AlCl₃ 133 g·mol ⁻¹ - 1.1 eq € 2·mol ⁻¹ [a] Problematic	AlI₃ 408 g·mol ⁻¹ - 1.1 eq € 2400·mol ⁻¹ [b] Problematic	BBr₃ 251 g·mol ⁻¹ - 1.1 eq € 15·mol ⁻¹ [a] Hazardous	BBr₃-Me₂S 313 g·mol ⁻¹ - 1.8 eq € 1240·mol ⁻¹ [c] Problematic
BF₃-Me₂S 130 g·mol ⁻¹ - 6 eq € 330·mol ⁻¹ [b] Problematic	BCl₃ 117 g·mol ⁻¹ - 1.1 eq € 62·mol ⁻¹ [a] Hazardous	B(C₆F₅)₃ 512 g·mol ⁻¹ - 0.002 eq € 25450·mol ⁻¹ [b] Problematic	In(OTf)₃ 562 g·mol ⁻¹ - 0.05 eq € 7950·mol ⁻¹ [b] Problematic
SiCl₄ 170 g·mol ⁻¹ - 1.1 eq € 0.24·mol ⁻¹ [a] Recommended	TMSI 200 g·mol ⁻¹ - 1.1 eq € 6·mol ⁻¹ [a] Problematic	<i>Additional reagents</i>	
		CaO 56 g·mol ⁻¹ - 1.5 eq € 0.026·mol ⁻¹ [a] Problematic	DIC 126 g·mol ⁻¹ - 0.6 eq € 5.75·mol ⁻¹ [a] Hazardous
DMF + DMA 73 g·mol ⁻¹ - 1.5 eq € 0.037·mol ⁻¹ [a] Hazardous	DMSO 78 g·mol ⁻¹ - 1.1 eq € 0.068·mol ⁻¹ [a] Recommended	Et₃SiH 116 g·mol ⁻¹ - 2.3 eq € 1.66·mol ⁻¹ [a] Hazardous	<i>Additional reagents</i>
Pyridine 79 g·mol ⁻¹ - 4 eq € 0.16·mol ⁻¹ [a] Problematic	KI 166 g·mol ⁻¹ - 3 eq € 8.34·mol ⁻¹ [a] Problematic	NaI 150 g·mol ⁻¹ - 2 eq € 13.24·mol ⁻¹ [a] Problematic	LiBr 87 g·mol ⁻¹ - 87 eq € 98·mol ⁻¹ [a] Recommended
			TBHDPB 508 g·mol ⁻¹ - 0.01 eq € 775·mol ⁻¹ [b] Recommended
			<i>Solvents</i>
			H₂O Recommended
			Aliquat-336 404 g·mol ⁻¹ - 0.03 eq € 2580·mol ⁻¹ [b] Problematic
			H₂ 2 g·mol ⁻¹ - excess € 0.004·mol ⁻¹ [d] Problematic
A3. Other reaction systems			
<i>Reagents</i>			
[Bmim]Cl 174 g·mol ⁻¹ - 2.9 eq € 296·mol ⁻¹ [a] Problematic	CH₃-ReO₃ 249 g·mol ⁻¹ - 0.05 eq € 66420·mol ⁻¹ [b] Recommended	[Bpyr]Br 171 g·mol ⁻¹ - 1 eq € 877·mol ⁻¹ [b] Problematic	
Iodocyclohexane 201 g·mol ⁻¹ - 5 eq € 54·mol ⁻¹ [a] Recommended	LiCl 42 g·mol ⁻¹ - 12 eq € 0.76·mol ⁻¹ [a] Recommended	LiI 134 g·mol ⁻¹ - 0.6 eq € 16.7·mol ⁻¹ [a] Recommended	
SIBX 280 g·mol ⁻¹ - 2.1 eq € 6750·mol ⁻¹ [b] Problematic	Al 27 g·mol ⁻¹ - 2.5 eq € 1.19·mol ⁻¹ [a] Problematic	I₂ 254 g·mol ⁻¹ - 1.5 eq € 4·mol ⁻¹ [a] Problematic	
Na₂SO₃ 126 g·mol ⁻¹ - 0.57 eq € 1.4·mol ⁻¹ [a] Problematic	NaOH 40 g·mol ⁻¹ - 1.3 eq € 0.016·mol ⁻¹ [a] Problematic	<i>Solvents</i>	
DodecylSH 202 g·mol ⁻¹ - 1.5 eq € 5.65·mol ⁻¹ [b] Hazardous	NaOMe 54 g·mol ⁻¹ - 2.5 eq € 0.068·mol ⁻¹ [a] Problematic	DMF Hazardous	DMI Problematic
NaOH 40 g·mol ⁻¹ - 13.7 eq € 0.016·mol ⁻¹ [a] Problematic	Urea 60 g·mol ⁻¹ - 15.6 eq € 0.023·mol ⁻¹ [a] Recommended	MeCN Problematic	THF Problematic
LiBF₄ 94 g·mol ⁻¹ - 1.4 eq € 460·mol ⁻¹ [b] Problematic		H₂O Recommended	[Bmim]BF₄ Problematic
B. Heterogeneous catalyzed reaction systems			
<i>Catalysts</i>		<i>Solvents</i>	
Nb₂O₅ € 0.034·g ⁻¹ [a] Recommended	Vanadium € 27·g ⁻¹ [b] Recommended	H₂O Recommended	
HBEA € 0.014·g ⁻¹ [a] Recommended			
Montmorillonite KSF € 0.018·g ⁻¹ [a] Recommended	H₂O₂ € 0.036·mol ⁻¹ [a] Problematic		

Figure 7. Schematic overview of commercial catalysts/reagents and solvents used for the ODM of lignin and derived oligomers and monomers.^[39] More info on the colour code labelling (recommended, problematic, hazardous, highly hazardous) can be found in the supporting information Tables S1-S3. [a] Bulk Chemicals: prices for import/export based on data found on Zauba.com in October 2023. [b] Research chemicals: prices based on data from Merck (largest batch available) retrieved in October 2023. [c] Similar procedure as [b], but data from Thermo Fischer Scientific. [d] H₂ price obtained from CRU H₂ cost model.

of equivalents applied indicates whether a reagent or catalyst is used to demethylate monomers. HI, Na₂SO₃ + NaOH, and DodecylSH + NaOMe have only been reported for the ODM of

lignin. For these reagents, the amount of equivalents is therefore determined relative to the amount of methoxy groups present in the lignin.

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As waste is critical in a chemical process affecting cost and sustainability the molecular weight of these reagents/catalysts has been included in **Figure 7** as well. After all, while catalysts can be recycled, reagents typically cannot.

As discussed in **Section 3**, a wide variety of Lewis acids, with and without additives, has been used for ODM. Unfortunately, the majority of these reagents are categorized as problematic or hazardous due to their corrosive and/or toxic characteristics (**Figure 7**, A1). Only one Lewis acid, *i.e.* SiCl_4 , is recommended, however, it is used in combination with rather expensive and problematic NaI in a 1:1 mixture of hazardous DCM and problematic MeCN , making the reaction system unsustainable. Another disadvantage of Lewis acids is that all of them, except for $\text{B}(\text{C}_6\text{F}_5)_3$ and $\text{In}(\text{OTf})_3$, are used in (super)stoichiometric amounts creating large amounts of waste. In this view, the use of catalytic, but still problematic $\text{In}(\text{OTf})_3$, might be more acceptable, as it is used in water, a highly desired solvent in the context of green chemistry. Highly concentrated aqueous Brønsted acids are often used for ODM reactions (**Figure 7**, A2), but are deemed problematic due to their corrosive nature. Dilute aqueous Brønsted acids, on the other hand, are not problematic and can even be used catalytically. Its corrosiveness at higher temperatures can be compensated by corrosive resistant equipment albeit with increasing CapEx. Additionally, the very low price of these acids (with the exception of HI) makes them very desirable for industrial applications. Other commercial reaction systems comprise ionic liquids, nucleophiles, iodocyclohexane, and SIBX (**Figure 7**, A3). These systems are unsuited for future industrial applications as they use expensive reagents, which are often not recommended, in problematic or hazardous solvents (or are solvent themselves, *i.e.* ionic liquids). Finally, the commercial heterogeneous catalysts are all categorized as recommended (**Figure 7**, B) and thus suited for future large scale processes.

Provided sufficient stability, these catalysts can also be easily separated after the reaction or used in flow processes (provided solubility is no issue), greatly facilitating downstream processing and reducing waste. Out of all ODM systems, these show the greatest potential for utilization in large scale industrial settings, meeting both greenness and economic requirements. Such preliminary qualitative analyses give a good first indication of the suitability for future large-scale applications considering both greenness and economics. However, in the next phase other more qualitative (*e.g.* energy use, separation, process integration & development) as well as quantitative parameters (*e.g.* yield, selectivity, reaction mass efficiency, process mass intensity, productivity, mass balances) need to be considered.^[159] Also, the use of the C1 by-product generated in the C-O bond cleavage reaction in other chemical processes will be crucial for the final economic viability. While these preliminary data by no means aim to replace Technoeconomic Assessment (TEA) and Lifecycle Assessment (LCA) they are embracing greenness and economics early on in the discovery process, thereby avoiding the development of new but inherently unsuitable methods.

5. Conclusion and Perspectives

In addition to the already existing classical biorefineries for extraction of lignin providing technical lignins, a large number of methoxyphenols (sometimes in remarkably high yields), have demonstrated to be accessible from lignocellulose biomass via

lignin-first technologies, simultaneously extracting (hemi)cellulose and depolymerizing lignin. This review emphasizes the significance of the ODM reaction as a potential tool to selectively de-functionalize technical lignin and lignin derived depolymerized compounds, towards more valuable product and applications. Particularly, ODM enables the transformation of lignin derived methoxyphenols into catechols and pyrogallols, which due to their high content of nearby Ar-OH groups possess distinct chemical and physical properties that offer diverse applications. ODM products have two major application areas upon further transformation: 1) molecules for commodity, fine & specialty chemicals, and 2) macromolecules for functional materials. The significant potential of the ODM components has yet to be fully realized. The expansion of their utilization will catalyze the development of better ODM processes. Several catalytic and non-catalytic reagents have been reported for the ODM reactions, including three major classical types: Brønsted acids, Lewis acids, and nucleophilic reagents. To date, homogeneous reaction systems are still holding a principal role in ODM. Among them, protic acids such as HCl , HBr , HI , and H_2SO_4 in water or water/DMF are common. Brønsted acids such as HCl need a higher reaction temperature. Iodocyclohexane provides HI *in situ*. Also inorganic Lewis acids such as AlCl_3 , and BBr_3 , and organic Lewis acids such as $\text{B}(\text{C}_6\text{F}_5)_3$ and TMSI , show high reactivity for the ODM. Though catalytic amounts of Brønsted acid are in principle sufficient, often excesses are used to avoid long reaction times. Lewis acid can produce the nucleophile *in situ* or be combined with external nucleophile. The combination of mineral acids with LiBr , the so-called ACLB system, is very popular as milder reaction conditions can be applied. Though catalytic in nature the loadings are typically high. Moreover, the stability, reusability, and process safety of these systems are to be defined, and their susceptibility to corrosion diminishes their prospects when compared to heterogeneous catalysts. Heterogeneous catalysts are still minor in this field but are progressively gaining attention, especially solid acid catalysts. Brønsted acids are generally more effective than Lewis acids for ODM reactions when it comes to solid acid catalysts. Heterogeneous Lewis acid catalysts, such as $\gamma\text{-Al}_2\text{O}_3$, ZrO_2 , and TiO_2 , exhibit low reactivity, while layered Nb_2O_5 with both Brønsted and Lewis acid sites proves to be a viable candidate. Similarly, zeolites showed excellent performance in the ODM process in high temperature water. Unfortunately, their hydrothermal stability under such aggressive conditions ($> 200^\circ\text{C}$) is a major foreseeable obstacle in industry. Hence, it is essential to adopt appropriate methodologies to comprehend the factors governing the hydrothermal stability of zeolites. Accordingly, potential measures to enhance zeolite efficacy should be implemented. Metal-supported catalysts also exhibited reactivity in the cleavage of the aryl methyl ether bonds with H_2 , though in the overall reaction network of the aimed hydrodeoxygenation reaction. Here, selective ODM often competes with other reactions such as hydrogenation, hydrocracking, and polymerization, resulting in undesirable by-products. Controlling reaction pathways is difficult, and a particular role of catalysis can be anticipated here, so future research in this area should focus on expanding the portfolio of innovative heterogeneous catalysts for ODM. The catalysts need to be designed to target specific functional groups to promote the desired reactions while minimizing the side reactions. While more effective and selective alternatives need to be sought, a deeper

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understanding of the mechanisms and kinetics of catalytic ODM of lignin derivatives with existing catalysts needs to be established. One example is the high proton activity in zeolites for ODM. Understanding the kinetics of ODM is essential for new catalyst design and process optimization, as (re)activity and selectivity can vary significantly depending on the substrate and reaction conditions chosen. Furthermore, maintaining appropriate temperature and pressure conditions for ODM can be challenging, as different compounds may require different conditions for an optimal conversion. Notably, researchers have so far focused almost exclusively on the guaiacol model compounds and macromolecular technical lignin, while less attention has been paid to syringols and no studies report on the now-available *lignin-first* dimers and oligomers in ODM. Syringols are definitely more challenging than guaiacols considering these are even more electron rich, particularly requiring caution when Lewis/Brønsted acid activation is used considering side reactions, such as self-polymerization. While extending the ODM process to these more unconventional dimer/oligomer compound mixtures is challenging, *e.g.* analytically, it also offers numerous untapped opportunities to valorize real woody biomass-derived feed. These feedstocks are chemically complex and contain a wide range of oxygen-containing functional groups with different reactivities. Achieving selectivity in removing specific functional groups while preserving others is without doubt challenging. Therefore, researchers are encouraged to explore the potential of these starting materials and pay attention to the selection of suitable analytics, perhaps by embracing new analysis developments.

From a mechanistic perspective, the specific role of acidic sites and the effect of the solvent in heterogeneous catalysts, as well as the exact reaction mechanism when present in a confined environment, are not well understood for the ODM reaction which is in sharp contrast to the homogeneous systems which are well understood. One promising aspect in this context is the role of water: subcritical and supercritical water in combination with zeolite have been reported to play an active role in several other reactions, *e.g.* dehydration, warranting further studies for ODM. Both in homogeneous and heterogeneous catalyzed systems water is clearly a preferred (co)-solvent. Moreover, most studies focus only on the main product, while the released "CH₃" group is not considered. However, for an atom efficient process, ODM should be coupled with other reactions to capture and upgrade the released "CH₃" group, *e.g.* carbonylation with CO or a transmethylation reaction. The formation of methanol reported in some studies is interesting as C1 by-product valorization. The aqueous solution obtained when using water as solvent may however require distillation to separate methanol. Furthermore, ODM is often only studied with methoxyphenols, which contain a fairly stable alkyl moiety, while other potentially interesting functionalities in lignin-derived compounds, such as unsaturated (*i.e.* allyl) or heteroatom-containing functional groups (*i.e.* alcohol, aldehyde, and carboxyl group), are not well considered in ODM yet. The work on technical lignin already shows that repolymerization appears in ODM, which may in some cases be undesirable. Utilizing these methoxy unlocked chemical moieties has the potential to unveil novel synthetic pathways for value-added products. It's thus worth noting that they may also exhibit a higher susceptibility to undergo side reactions, including polymerization or alkylation. In this respect, ODM products can be integrated into a more complex framework of multi-step reactions

involving the more functional-rich lignin-derived compounds as substrates.

Certainly, addressing the challenges and exploring the potential prospects are essential steps in advancing ODM as a sustainable and economically viable technology for renewable fuel and chemicals production. ODM stands out as a valuable process for converting technical lignin derived from biomass into specialty chemicals with a wide range of applications. Its integration into the *lignin-first* biorefinery concept holds promise for efficiently utilizing various biomass components to create valuable products (commodity, fine & specialty chemicals). By selectively removing ArO-Me groups (on aryl methyl ethers) from lignin molecules while preserving other desirable properties, this process significantly contributes to the development of sustainable and environmentally friendly alternatives to petrochemicals.

The transition from laboratory-scale batch reactions to continuous industrial-scale processes might reveal scale-up challenges, making it difficult to maintain the same level of selectivity and performance on a larger scale. Therefore, it is essential to conduct investigations in laboratory-scale flow systems to gain a better insight into the challenges faced when performing ODM reactions in flow, particularly when dealing with technical lignins featuring limited solubility. Furthermore, conducting LCA and TEA studies for ODM reactions, building further on the preliminary CHEM21 and cost assessments, will be crucial to provide a holistic evaluation of the environmental and economic aspects of the current ODM technology and the necessary improvements required.

Ultimately, bringing ODM products to chemical industry is still very challenging and would require advancing various aspects: 1) wood plant resource and pre-treatment selection, 2) biorefinery engineering considerations for (hemi)cellulose extraction of lignocellulose (and for additional lignin depolymerization with *lignin-first*), 3) more efficient ODM reaction conditions, involving catalyst development, 4) scale-up engineering considerations (*e.g.* continuous production), 5) environmental (LCA) and economic (TEA) considerations, as well as 6) specific new and out-performing applications versus classical products/materials by further modification of the ODM products.

In conclusion, while ODM offers significant promise in terms of sustainability and reducing our dependence on fossil feedstock, it does face new challenges that must be addressed before its full potential can be realized, but the future looks promising.

Acknowledgements

B.S. and B.U.W.M. acknowledge The Flemish Interuniversity Council (VLIR) through the iBOF project Next-BIOREF (iBOF/21/105, project 42433) and FWO through EoS project BIOFACT (G0H0918N) for funding. B.S. received financial support through KULeuven C2 project GORILLA (C2M/23/025). X.W. thanks the Chinese Scholarship Council (No. 201806890016) for financial support. B.U.W.M. acknowledges UA Antwerp for funding via BOF GOA project 36083.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

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- [131] a) H.-B. Zou, L. Zhang, L.-X. Yang, L.-Q. Yang, Y. Zhao, Y.-P. Yu, J. Stöckigt, *Nat. Prod. Res.* **2011**, *25*, 203-221; b) X. Wang, J. Xu, Q. Li, CN201610543119A, **2016**.
- [132] B. Liu, M. Sanchez, J. Truong, P. C. Ford, M. M. Abu-Omar, *Green Chem.* **2022**, *24*, 4958-4968.
- [133] P. Yu, X. Xie, P. Tan, W. Zhang, Z. Wang, C. Zhang, H. Liu, *Front. Chem.* **2020**, *8*, 2296-2646.
- [134] S. Zhao, M. M. Abu-Omar, *ACS Sustainable Chem. Eng.* **2016**, *4*, 6082-6089.
- [135] J. Miao, Z. Wang, X.-d. Ji, J.-l. Yan, *Acta Polym. Sin.* **2019**, *50*, 261-270.
- [136] H. T. Balayđın, İ. Gülçin, A. Menzek, S. Gökso, E. Şahin, *J. Enzyme Inhib. Med. Chem.* **2010**, *25*, 685-695.
- [137] a) I. Sumerskii, T. Zweckmair, H. Hettegger, G. Zinoviyev, M. Bacher, T. Rosenau, A. Potthast, *RSC Adv.* **2017**, *7*, 22974-22982; b) H. Li, X.-S. Chai, M. Liu, Y. Deng, *J. Agric. Food Chem.* **2012**, *60*, 5307-5310; c) F. Vieböck, A. Schwappach, *Ber. Dtsch. Chem. Ges.* **1930**, *63*, 2818-2823.
- [138] a) B. Mo, Z. Li, J. Peng, C. Chen, *Int. J. Biol. Macromol.* **2023**, *239*, 124263; b) X. Zhen, H. Li, Z. Xu, Q. Wang, J. Xu, S. Zhu, Z. Wang, Z. Yuan, *Ind. Crops Prod.* **2021**, *173*, 114135.
- [139] H. Wang, T. L. Eberhardt, C. Wang, S. Gao, H. Pan, *Polymers* **2019**, *11*, 1771.
- [140] a) L. Chai, B. Du, S. Yan, W. Li, X. Chen, R. Sun, *Int. J. Biol. Macromol.* **2022**, *222*, 2571-2580; b) S. Yan, L. Chai, W. Li, L.-P. Xiao, X. Chen, R.-C. Sun, *Colloids Surf., A* **2022**, *643*, 128815; c) M. Li, J. Shan, Y. Hu, C. Gao, H. Long, T. Shen, Z. Tan, W. Zhuang, D. Liu, C. Zhu, H. Ying, *J. Appl. Polym. Sci.* **2022**, *139*, 52019; d) C.-A. Xu, Z. Qu, M. Lu, H. Meng, B. Chen, E. Jiao, E. Zhang, K. Wu, J. Shi, *J. Colloid Interface Sci.* **2021**, *602*, 394-405; e) S. Liu, C. Liu, Z. Bai, W. Zhang, L. Tong, X. Liu, *J. Appl. Polym. Sci.* **2021**, *138*, 50522; f) S. Zhao, M. M. Abu-Omar, *ACS Sustainable Chem. Eng.* **2017**, *5*, 5059-5066; g) H. Chung, N. R. Washburn, *ACS Appl. Mater. Interfaces* **2012**, *4*, 2840-2846.
- [141] a) S. Zhang, X. Zhao, P. Chen, G. Sun, Y. Li, Y. Han, X. Wang, J. Li, *New J. Chem.* **2023**, *47*, 6721-6729; b) M. Sun, X. Wang, S. Ni, L. Jiao, H. Bian, H. Dai, *Ind. Crops Prod.* **2022**, *187*, 115441.
- [142] a) G. Zhu, D. Ye, X. Chen, Y. Wu, Z. Yang, Y. Mai, B. Liao, J. Chen, *Int. J. Biol. Macromol.* **2023**, *237*, 124030; b) T. Kobayashi, Y. Tobimatsu, H. Kamitakahara, T. Takano, *J. Wood Sci.* **2022**, *68*, 51; c) Y. Qian, Y. Zhou, M. Lu, X. Guo, D. Yang, H. Lou, X. Qiu, C. F. Guo, *Small Methods* **2021**, *5*, 2001311; d) H. Ma, T. Li, S. Wu, X. Zhang, *Fuel* **2021**, *286*, 119394; e) Y. Song, Z. Wang, X. Zhang, R. Zhang, J. Li, *J. Renewable Mater.* **2021**, *9*, 943-957; f) K. H. Kim, K. Jeong, J. Zhuang, H. J. Jeong, C. S. Kim, B. Koo, C. G. Yoo, *Ind. Crops Prod.* **2021**, *159*, 113095; g) Y. Wang, J. Wu, R. Shen, Y. Li, G. Ma, S. Qi, W. Wu, Y. Jin, B. Jiang, *J. Bioresour. Bioprod.* **2023**, *8*, 306-317; h) K. Sawamura, Y. Tobimatsu, H. Kamitakahara, T. Takano, *ACS Sustainable Chem. Eng.* **2017**, *5*, 5424-5431; i) Y. Wu, J. Gao, J.-H. Li, B.-K. Chen, *Int. J. Biol. Macromol.* **2023**, *253*, 127289.
- [143] a) X. Zhao, L. Shi, B. Tian, S. Li, S. Liu, J. Li, S. Liu, T. D. James, Z. Chen, *J. Mater. Chem. A* **2023**, *11*, 12308-12314; b) X. Li, J. He, Y. Zhang, *J. Org. Chem.* **2018**, *83*, 11019-11027.
- [144] a) B. Du, W. Li, H. Zhu, J. Xu, Q. Wang, X. Shou, X. Wang, J. Zhou, *Int. J. Biol. Macromol.* **2023**, *239*, 124268; b) B. Du, L. Chai, Y. Wang, X. Wang, X. Chen, J. Zhou, R.-C. Sun, *J. Mol. Liq.* **2023**, *382*, 121935.
- [145] J. Podschun, B. Saake, R. Lehnen, *React. Funct. Polym.* **2017**, *119*, 82-86.
- [146] Q. Mei, X. Shen, H. Liu, H. Liu, J. Xiang, B. Han, *Chem. Sci.* **2019**, *10*, 1082-1088.
- [147] W. Zhao, C. Wei, Y. Cui, J. Ye, B. He, X. Liu, J. Sun, *Chem. Eng. J.* **2022**, *443*, 136486.
- [148] F. Wang, J. Kuai, H. Pan, N. Wang, X. Zhu, *Wood Sci. Technol.* **2018**, *52*, 1343-1357.
- [149] a) J. Li, J. Zhang, S. Zhang, Q. Gao, J. Li, W. Zhang, *Polymers* **2017**, *9*, 428; b) Y. Han, Z. Ma, X. Wang, Y. Sheng, Y. Liu, *Sustainable Chem. Pharm.* **2023**, *36*, 101312.
- [150] Q. Liu, Y. Xu, F. Kong, H. Ren, H. Zhai, *Wood Sci. Technol.* **2022**, *56*, 1527-1549.
- [151] A. Zhang, X. Wu, X. Ouyang, H. Lou, D. Yang, Y. Qian, X. Qiu, *ACS Sustainable Chem. Eng.* **2022**, *10*, 9381-9388.
- [152] K. Zhang, Y. Liu, Z. Guo, J. Wang, Y. Liu, J. Zhao, P. Huo, *Ind. Crops Prod.* **2022**, *177*, 114452.
- [153] Y. Chen, J. Shen, W. Wang, L. Lin, R. Lv, S. Zhang, J. Ma, *Int. J. Biol. Macromol.* **2023**, *242*, 124462.
- [154] T. Hibino, K. Kobayashi, D. Zhou, S. Chen, A. Zinchenko, S. Teranishi, A. Miyawaki, Y. Sawada, *Appl. Catal., B* **2024**, *341*, 123328.
- [155] X. Meng, C. Crestini, H. Ben, N. Hao, Y. Pu, A. J. Ragauskas, D. S. Argyropoulos, *Nat. Protoc.* **2019**, *14*, 2627-2647.
- [156] a) S. Jeenpadiphat, I. Mongkolpichayarak, D. N. Tungasmita, *J. Anal. Appl. Pyrolysis* **2016**, *121*, 318-328; b) T. Yoshikawa, S. Shinohara, T. Yagi, N. Ryumon, Y. Nakasaka, T. Tago, T. Masuda, *Appl. Catal., B* **2014**, *146*, 289-297; c) M. Otromke, P. S. Shuttleworth, J. Sauer, R. J. White, *Bioresour. Technol. Rep.* **2019**, *5*, 251-260; d) H. Pińkowska, P. Wolak, A. Ziocińska, *Chem. Eng. J.* **2012**, *187*, 410-414; e) M. Sasaki, M. Goto, *Chem. Eng. Process.* **2008**, *47*, 1609-1619; f) K. Barta, G. R. Warner, E. S. Beach, P. T. Anastas, *Green Chem.* **2014**, *16*, 191-196; g) R. W. Thring, E. Chornet, R. P. Overend, *Can. J. Chem. Eng.* **1993**, *71*, 107-115; h) R. W. Thring, J. Breau, *Fuel* **1996**, *75*, 795-800.
- [157] a) A. Toledano, L. Serrano, J. Labidi, *J. Chem. Technol. Biotechnol.* **2012**, *87*, 1593-1599; b) X. Erdocia, R. Prado, M. A. Corcuera, J. Labidi, *Biomass Bioenergy* **2014**, *66*, 379-386; c) A. Toledano, L. Serrano, J. Labidi, *Chem. Eng. J.* **2012**, *193*, 396-403.
- [158] D. Prat, A. Wells, J. Hayler, H. Sneddon, C. R. McElroy, S. Abou-Shehadeh, P. J. Dunn, *Green Chem.* **2016**, *18*, 288-296.
- [159] a) C. R. McElroy, A. Constantinou, L. C. Jones, L. Summerton, J. H. Clark, *Green Chem.* **2015**, *17*, 3111-3121; b) E. R. Monteith, P. Mampuy, L. Summerton, J. H. Clark, B. U. W. Maes, C. R. McElroy, *Green Chem.* **2020**, *22*, 123-135.
- [160] M. Asmadi, H. Kawamoto, S. Saka, *J. Anal. Appl. Pyrolysis* **2011**, *92*, 88-98.
- [161] R. Beauchet, F. Monteil-Rivera, J. Lavoie, *Bioresour. Technol.* **2012**, *121*, 328-334.

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Table 1. The ODM of lignin-derived chemicals (majorly from *lignin-first* technologies).

Entry	Substrate	Product	Reagent/Catalyst	Solvent	Conditions			Conv. /%	Yiel. /%	Ref.
					T/°C	P/bar	Time/h			
1			20 mol% HCl	Water	250	N ₂ , 50 ^a	3	100	97	[39]
2			HCl (pH = 1.8)	Water	280	H ₂ , 10	3	99	89	[83]
3			48% HBr	Water	Reactive distillation	–	7	–	87	[78]
4			320 mol% H ₃ PO ₄ (85 wt%)	Water	–	–	–	–	90	[80]
5			47% HBr; Aliquat-336	Water	105	–	6	–	78	[84]
6			61.7% LiBr and 1.5 M HCl	Water	110	–	2	100	94	[85]
7			Iodocyclohexane	DMF	Reflux	–	4	–	91	[82]
8			BBr ₃	CH ₂ Cl ₂	-78	–	1	–	100	[86]
9			Iodotrimethylsilane	Chloroform	r.t.	–	48	67	67	[86]
10			AlCl ₃ NaI	CH ₃ CN	80	–	18	–	93	[87a]
11			AlI ₃ Dimethyl sulfoxide	CH ₃ CN	80	–	18	–	92	[93]
12			[RuCl ₂ (CO) ₃] ₂ Co ₂ (CO) ₈ Triphos and Lil	1,3-Dimethyl-2-imidazolidinone	190	CO ₂ , 30 H ₂ , 50	10	100	~99	[101]
13			Al ₂ O ₃	Toluene	300	H ₂ , 65	3	~45	~28	[108b]
14			α-MoC _{1-x} /AC	Water	340	N ₂ , 1	4	36	34	[109]
15			In(OTf) ₃	Water	250	–	2.75	~74	~67	[100]
16			HZSM-5	Benzene	350	H ₂ , 50	2	54	31	[11b]
17			Pt/C	–	300	H ₂ , 1	–	~95	> 80	[122]
18			Pt/Si-ZSM-5	–	300	H ₂ , 1	–	~85	> 50	[122]
19			Pd/Al ₂ O ₃	–	300	H ₂ /N ₂	–	70	~70	[117a]
20			Pd(OAc) ₂ /[Na] ⁺ [7,8-bis(aminomethyl)- <i>nido</i> -dicarbaundecaborane (11)	Water; DMA	240	H ₂	4	99	94	[102]

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21	MoP(5)/ γ -Al ₂ O ₃	Decalin	300	H ₂ , 50	4	~85	~35	[117c]
22	Al; I ₂	CH ₃ CN	80	–	18	–	97	[95]
23	Al; I ₂	CH ₃ CN	80	–	18	–	96	[95]
24	20 mol% HCl	Water	250	N ₂ , 50 ^a	3	100	99	[39]
25	AlI ₃ Dimethyl sulfoxide	CH ₃ CN	80	–	18	–	96	[93]
26	Ti _{0.07} - S/AC	Water	300	–	1	–	49	[108d]
27	Nb ₂ O ₅	Water	300	–	1	69	21	[108d]
28	TiO ₂	Water	300	–	1	73	26	[108d]
29	53 wt% LiBr with 6 wt% HBr	Water	100 (reflux)	–	4	100	83	[12]
30	61.7% LiBr and 1.5 M HCl	Water	110	–	1	96	92	[85]
31	Pd(OAc) ₂ /[Na] ⁺ [7,8- bis(aminomethyl)- <i>nido</i> -dicarba- undecaborane (11)	Water; DMA	240	H ₂	4	100	90	[102]
32	ZnO/Co@N-CNTs	Water	250	H ₂ , 50	6	100	> 99	[123]
33	AlCl ₃ ; NaI	CH ₃ CN	80	–	18	–	83	[87a]
34	AlI ₃ Dimethyl sulfoxide	CH ₃ CN	80	–	2	–	91	[93]
35	Al; I ₂	CH ₃ CN	80	–	18	–	75	[95]
36	61.7% LiBr and 1.5 M HCl	Water	110	–	1	98	50	[85]
37	AlI ₃ Dimethyl sulfoxide	CH ₃ CN	80	–	18	–	91	[93]
38	AlCl ₃ ; NaI CaO	CH ₃ CN	80	–	18	–	94	[87a]

39	20 mol% HCl	Water	250	N ₂ , 50 ^a	6	100	90	[39]
40	20 mol% HCl	Water	250	N ₂ , 50 ^a	3 or 6	100	97	[39]
41	20 mol% FeCl ₃	Water	250	N ₂ , 50 ^a	3	100	100	[39]
42	20 mol% H ₂ SO ₄	Water	250	N ₂ , 50 ^a	6	100	97	[39]
43	20 mol% H ₃ PO ₄	Water	250	N ₂ , 50 ^a	3	30	30	[39]
44	TiO ₂	Water	260	N ₂ , 1	2	18	11	[30a]
45	ZrO ₂	Water	260	N ₂ , 1	2	14	7	[30a]
46	Nb ₂ O ₅	Water	300	N ₂ , 65	2	~95	92	[108a]
47	Au/ZrO ₂	Water	300	H ₂ , 65	8	~96	~90	[108a]
48	Beta zeolite	Water	275	N ₂ , 1	2	~97	90	[30a]
49	1. Stabilized 2-iodoxybenzoic acid 2. Na ₂ S ₂ O ₄ (aq.) work-up	THF	r.t.	–	12	–	89	[124]
50	50 mol% HCl or 100 mol% H ₂ SO ₄	Water	250	N ₂ , 50 ^a	3	–	62 or 50	[44]
51	All ₃ ; 1,3-Diisopropylcarbodiimide	CH ₃ CN	80	–	18	–	94	[91]
52	All ₃ Dimethyl sulfoxide	CH ₃ CN	80	–	18	–	43	[93]
53	AlCl ₃ NaI 1,3-Diisopropylcarbodiimide	CH ₃ CN	35	–	2	–	99	[87a]
54	1. Stabilized 2-iodoxybenzoic acid 2. aq Na ₂ S ₂ O ₄ work-up	THF	r.t.	–	16	–	77	[124]
55	AlI ₂ Dimethyl sulfoxide	CH ₃ CN	25	–	18	–	89	[95]

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56	50 mol% HCl or 100 mol% H ₂ SO ₄	Water	250	N ₂ , 50 ^a	3	–	56 or 71	[44]
57	50 mol% HCl or 100 mol% H ₂ SO ₄	Water	250	N ₂ , 50 ^a	3	–	65 or 16	[44]
58	20 mol% HCl	Water	250	N ₂ , 50 ^a	6	100	85	[39]
59	50 mol% HCl	Water	250	N ₂ , 50 ^a	3	100	70	[44]
60	None	None	600	N ₂	80s	100	1.5	[160]
61	47 wt% HBr	Water	Reflux	–	6.5	–	61	[127]
62	53 wt% LiBr with 6 wt% HBr	Water	Reflux	–	2	100	82	[12]
63	Vanadium powder	Methanol; water	280	N ₂	48	89	43	[133]
64	[RuCl ₂ (CO) ₃] ₂ Co ₂ (CO) ₈ Triphos and Lil	1,3- Dimethyl-2- imidazolidinon e	190	CO ₂ , 30 H ₂ , 50	10	100	~99	[101]
65	61.7% LiBr and 1.5 M HCl	Water	110	–	1	100	97	[85]
66	Pd(OAc) ₂ /[Na] ⁺ [7,8- bis(aminomethyl)- nido-dicarb- undecaborane (11)	Water; DMA	240	H ₂	4	98	61	[102]
67	61.7% LiBr and 1.5 M HCl	Water	110	–	1	100	36	[85]
68	61.7% LiBr and 1.5 M HCl	Water	110	–	1	100	32	[85]
69	20 mol% HCl	Water	250	N ₂ , 50 ^a	6	100	81	[39]
70	61.7% LiBr	Water	110	–	1.5	100	98	[85]

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		and 1.5 M HCl							
71		Nb ₂ O ₅	Water	230	N ₂ , 10	20	96	92	[132]
72		HBr	Water	–	–	–	–	–	[128]
73		BBr ₃	CH ₂ Cl ₂	r.t.	–	0.5	–	68	[49]
74		50 mol% HCl	Water	250	N ₂ , 50 ^a	3	–	59	[44]
75		20 mol% FeCl ₃	Water	250	N ₂ , 50 ^a	3	–	45	[110]
76		BBr ₃	CH ₂ Cl ₂	0	–	1	–	13	[129a]
77		50 mol% HCl or 100 mol% H ₂ SO ₄	Water	250	N ₂ , 50 ^a	3	–	29 or 39	[44]
78		48 wt% HBr	Water	120 (reflux)	–	20	–	80	[134]
79		BBr ₃	CH ₂ Cl ₂	r.t.	N ₂	Overnig ht	–	86	[135]
80		BBr ₃	CH ₂ Cl ₂	r.t.	–	24	–	96	[136]

a) Autogenic pressure is sufficient when the reaction is performed on a larger scale using the reactor as the reaction vessel, rather than small glass vials.

Table 2. An overview of ODM applied to the utilization of technical lignin.

Entry	Substrate	Product	Reagent/Catalyst	Solvent	Conditions			Conv. /%	Yield. /%	Ref.
					T/°C	P/bar	Time/h			
1	Softwood lignin	Demethylated lignin	HBr/TBHDPB	DMF	115	–	20	–	–	[140g]
2	Alkali lignin	Demethylated lignin	HBr or HI	DMF	130	–	12	–	–	[139]
3	Organosolv lignin	Demethylated lignin	HBr	DMF	120	–	20	–	–	[140f]
4	Alkaline lignin	Demethylated lignin	HI	DMF	120	–	20	–	–	[138]
5	Lignosulfonate	Demethylated lignin	Pt/C	85% H ₃ PO ₄	75	He	–	–	–	[154]

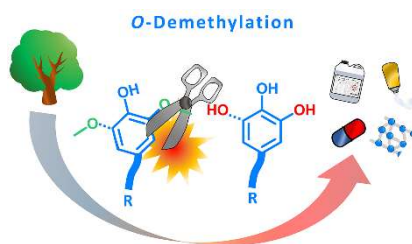
REVIEW

6	Hardwood kraft lignin, corn stover lignin, ethanol lodgepole pine lignin, ethanol poplar lignin	Demethylated lignin	ACLB; 53 wt% LiBr, 6 wt% HBr,	Water	100	4				[12]
7	Alkaline lignin	Demethylated lignin	BBr ₃	DMF	115	N ₂ atm	–	–	–	[140a, 140b]
8	Softwood milled wood lignin, enzymatic lignin, alkaline lignin, organosolv lignin	Demethylated lignin	Iodocyclohexane	DMF	100	–	24	–	–	[142]
9	Alkaline poplar lignin	Demethylated lignin	Tributylhexadecyl phosphonium bromide, AlCl ₃	DMF	115	–	20	–	–	[60, 140a]
10	Kraft lignin	Demethylated lignin	LiI and LiBF ₄	Toluene	140	–	12	–	–	[25]
11	Organosolv lignin	Demethylated lignin	In(OTf) ₃	Water and Sulfolane	275	N ₂	3	–	–	[145]
12	Kraft lignin	Demethylated lignin	LiI	[Hmim] BF ₄	120	–	13	–	–	[146]
13	Alkali lignin	Demethylated lignin	NaOH, urea	Water	r.t.	–	16	–	–	[153]
14	Alkali lignin, corn straw lignin, organosolv lignin, sodium lignosulfonate	Demethylated lignin	Na ₂ SO ₃ , NaOH	Water	80-180	–	0.5-2	–	–	[149-152]
15	Enzymatic lignin, alkali lignin, lignosulfonate	Demethylated lignin	Protic ionic liquids	–	70-130	–	0.5-6	–	–	[147]
16	Hardwood kraft lignin	Demethylated lignin	60% LiBr aqueous solution with 0.10 – 2.4 M HCl concentration	Water	110	–	2	–	–	[13c]
17	Artificial lignin	Demethylated lignin	Iodocyclohexane	DMF	Reflux	–	1-12	–	–	[142b]
18	Enzymatic lignin	Demethylated lignin	1-Dodecanethiol and NaOH	DMF	80	N ₂ atm.	2.5	–	–	[148]
19	Organosolv lignin	Catechol, methylcatechol, and 4-ethylcatechol	4- Ni-W/silica-alumina	Tetraline	410	–	1	~50	21.9	[156b]
20	Acid-depolymerized lignin	Catechols, phenols	Alkyl ZrO ₂ -Al ₂ O ₃ -FeO _x	Water-n-butanol (4:1, v/v)	300	150	2	–	–	[156b]

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21	Organosolv lignin	Phenol, guaiacol, Catechol, catechol	cresol, 4-methyl	NaOH, LiOH, Ca(OH) ₂	KOH, K ₂ CO ₃	Water	300	900	0.7	20	6-20	[157a]
22	Organosolv lignin	Catechol 3-methylcatechol 4-methylcatechol 4-ethylcatechol cresols phenols	4-	NaOH		Water	300	90	1.3	12-18	19-27	[157b]
23	Organosolv lignin	Catechol and methylcatechol	4-	NaOH		Water	310	105	0.5	18-20	12-30	[157c]
24	Kraft lignin	Catechol and methylcatechol	4-	NaOH		Water	300	180	0.13-0.4	8-13	7-30	[156c]
25	Kraft lignin	Pyrocatechol		NaOH		Water	270-315	130	–	–	~2.5	[161]
26	Organosolv lignin	Catechol and methyl derivative	and their ethyl	No		Tetralin	370-430	–	0.25-1	20-70	–	[156g]
27	Organosolv lignin	Catechol		Cu-PMO		Methanol	180	40	20	92	49	[156f]
28	Alkali lignin	Catechol		No		Water	390	–	0	~50	11.1	[156d]
29	Alkali lignin	Catechol		No		Water	350-400	–	0.1-4	90-95	25-30	[156e]
30	Alkali lignin	Benzenediol derivatives		Al-MCM-41		Water	300	–	0.5	–	–	[156a]

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O-Demethylation (ODM) is a strategic tool to unlock lignin applications for drop-in and new commodity, fine & specialty chemicals.

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