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Selective demethylation reactions of biomass-derived aromatic ether polymers for bio-based lignin chemicals

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The selective demethylation of aryl methyl ethers is a reaction of high relevance both in the context of de-protection in organic syntheses as well as in the modification of lignin and lignin-derived chemicals. The resulting vicinal diol or triol configurations originating from guaiacyl or synapyl lignin moieties are particularly relevant for adhesive properties, while other positions are applicable for condensation polymerization. Throughout the years, a plethora of methods have been developed to efficiently cleave the particularly stable aryl methyl bond. This review provides, on the one hand, a comprehensive overview of conventional approaches associated with the field of organic chemistry, with a focus on recently developed methods with a focus on aspects of green chemistry. On the other hand, acid- and base-catalyzed as well as (hydro)thermal methods are discussed as well as the occurrence of demethylation reactions under metal-catalyzed hydro-treatment conditions, which, however, proved to be the most environmentally friendly principle. While the different chemical approaches are first presented for the conversion of selected model compounds, a subsequent section presents the application of these methods to lignin. The selective cleavage of aryl methyl ether moieties of lignin to increase the amount of phenolic hydroxyl groups has recently gained considerable attention, and research can benefit from the emerging knowledge gained from the new approaches on model compound demethylation. In sum, we provide a multi-faceted and critical overview of demethylation strategies to obtain phenol and catechol moieties from the renewable lignin and related compounds.

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1. Introduction and scope

Catechol (1,2-dihydroxybenzene) is an important chemical intermediate for the synthesis of pesticides, drugs and perfumes and serves as a polymerization inhibitor for polymer production. Catechol itself is used as a photographic developer, an analytical reagent and as an antioxidant.¹ Furthermore, catechol and its derivatives are well suited as adhesion promoters due to their strong and versatile interaction with surfaces.²

Despite being present as a common motif in nature, catechol and its derivatives are commercially produced together with hydroquinone by the direct hydroxylation of phenol with hydrogen peroxide in the presence of catalytic amounts of either acids or ferrocene-based catalysts.¹ Since phenol is most commonly produced by the oxidation of benzene-derived

cumene *via* the Hock process,³ the overall production of catechol and its derivatives heavily relies on the utilization of fossil resources.

A renewable alternative as a feedstock for phenolics as well as catechol and its derivatives is lignin. Being the underutilized fraction (between 1/6 and 1/3) of lignocellulosic biomass, lignin is a heterogeneous macromolecular compound consisting mainly of three monomer units. These are the guaiacyl, the syringyl and the *p*-hydroxyphenyl units. The most common one among them is the guaiacyl unit, making up 50 to 95% of lignin depending on its source.^{4–7} This structural unit consists of an aromatic moiety with one hydroxyl group and one methoxy group in the neighboring *ortho* position. Selectively demethylating the methoxy group results in the desired catechol motif. In the simplest case, catechol can in this way be derived from guaiacol. Similarly, 4-allyl(pyro)catechol can be obtained *via* the demethylation of eugenol, which is commercially available as the main component (≥50%) of clove oils.^{8,9} Therefore, *O*-demethylation is a crucial reaction to obtain catechol-based structures from renewable plant-based feedstock.¹⁰ Overall, demethylation of lignin is a means to increase

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The BBr_3 method can be modified *e.g.* by using the $\text{BBr}_3\text{S}(\text{CH}_3)_2$ complex or by using other boron trihalides as has been discussed in previous review articles.^{14,15} While the use of BBr_3 enables the successful demethylation of guaiacol-type compounds under mild conditions it has to be noted that BBr_3 is

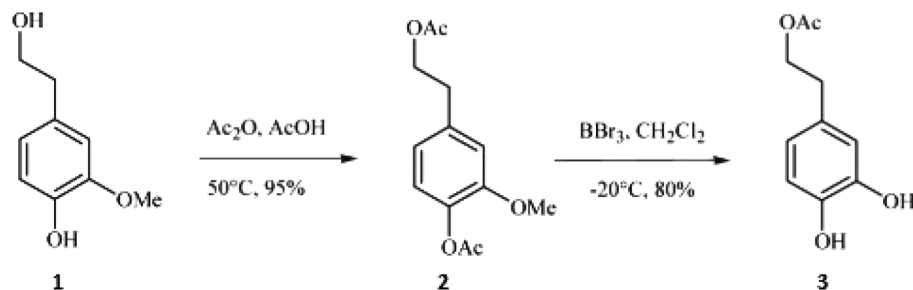


Fig. 1 Reaction sequence consisting of protection of the primary aliphatic alcohol by acetylation followed by aryl methyl cleavage with Lewis acid BBr_3 .²⁸

highly hazardous, it is toxic and it reacts violently with water and alcohols forming HBr , which also makes handling difficult.³¹ In addition, the reaction is currently tied to the use of DCM as solvent, which is considered a hazardous solvent.³² In sum, however, the BBr_3 -based approach, while highly efficient from a conventional perspective, is highly problematic from a green chemistry standpoint and should thus be avoided if suitable alternatives exist for the application in question.

2.1.1. Tris(pentafluorophenyl)boran. Torrens *et al.*³³ recently reported a new and robust demethylation method *via* the Piers–Rubinsztajn reaction relying on tris(pentafluorophenyl)boran (BCF) as a Lewis-acidic catalyst. As shown in Fig. 2, initially a complex between BCF and a silyl hydride (required in excess amounts, at least 1.1 eq.) is formed, which reacts with the methyl aryl ether. Hydride transfer to the methyl group results in eventual demethylation *via* the release of CH_4 and formation of a siloxane bond. The latter is cleaved in a subsequent step by acidic work-up, *e.g.* with HCl , to obtain the hydroxybenzene functionality.

Overall, the approach allows for the selective demethylation of differently substituted anisole derivatives in yields between 85 and 95% and it was shown that also complex guaiacol-type molecules could be demethylated selectively. It should be noted that both an allyl as well as a vinyl group could be tolerated without a significant decrease in selectivity when a polymerization inhibitor is added during the acidic work-up. Most importantly, BCF is stable in air and moisture and the reaction proceeds under ambient conditions in hexane, which makes it advantageous to *e.g.* the aforementioned BBr_3 -based methods.³³ While using BCF rather than BBr_3 presents a considerable advantage in terms of the health and safety aspects of the reaction, the use of hexane as solvent is highly problematic as the alkane is classified among the most harmful non-polar solvents using green chemistry metrics.³²

2.2. Aluminium halides

2.2.1. Aluminium chloride. Another group of Lewis acids that is commonly used to cleave aryl methyl ether bonds are aluminium halides. AlCl_3 was found to be suited for selective demethylation reactions in the presence of other functional groups such as aldehydes or ketones.³⁴ Node *et al.*³⁵ reported the successful combination of AlCl_3 or AlBr_3 with ethanethiol to selectively demethylate hydroxy-benzene-based compounds. Yields up to 98% were obtained. The use of thiols, however, was found to result in the addition of the thiol to aliphatic double bonds as well in thioacetal and thioketal formation when aldehyde or ketone functionalities were present.³⁵ More recently, it was shown that instead of *e.g.* ethanethiol also odorless sulfide can be used.³⁶

One recent example where the AlCl_3 approach was applied to a guaiacol derivative is a study by Arifin *et al.*³⁷ They selectively demethylated clove oil-derived eugenol to hydroxychavicol using 2.5 eq. AlCl_3 and excess dimethyl sulfide in dichloromethane at 0°C . After 24 hours reaction time the formed reaction intermediate was hydrolyzed by aqueous HCl to yield the demethylated product in yields around 30%. However, the authors argue that the reaction conditions chosen (0°C , nitrogen atmosphere) prevent side reactions like *e.g.* double bond isomerization.³⁷

In general, the use of AlCl_3 bears the hazard of working with a corrosive compound that reacts violently with water, as

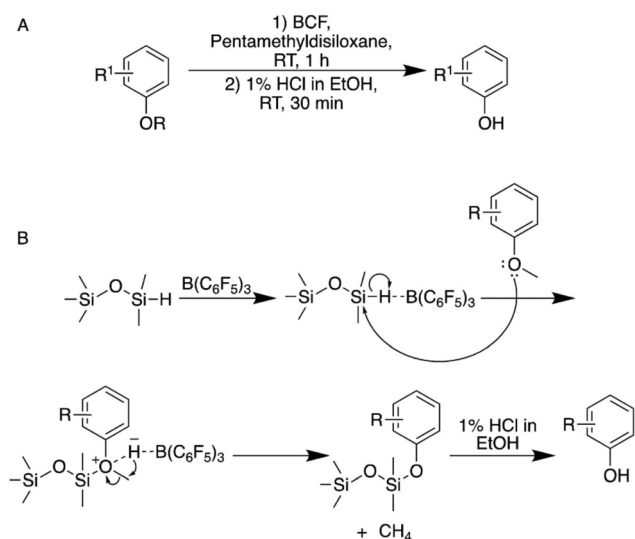


Fig. 2 (A) Two-step demethylation approach *via* the Piers–Rubinsztajn reaction using tris(pentafluorophenyl)boran (BCF). (B) Mechanism of the Piers–Rubinsztajn demethylation reaction.³³

applies to AlBr_3 and AlI_3 . Moreover, the use of thiols is particularly problematic since, *e.g.* in the case of ethanethiol, the flammability as well as ecotoxicity, causing risks of severe environmental impacts, must be highlighted. Other thiols such as dimethyl sulfide are less harmful but strongly odorous, and thus should be avoided as well if possible.

2.2.2. Aluminium iodide. Bhatt and Babu³⁸ first used AlI_3 to cleave aryl methyl ethers. AlI_3 is a stronger Lewis acid than the respective aluminium bromide or chloride, which allows for shorter reaction times. Furthermore, aromatic aliphatic esters were cleaved faster than aliphatic aliphatic esters when aluminium-based reagents were used, which is in contrast to the previously described use of boron-based reagents. 1,2-Dimethoxybenzene was cleaved into catechol (93% yield) with 1 eq. of freshly prepared AlI_3 in acetonitrile within 0.5 hours of reflux.

Deffieux *et al.*³⁹ tried to apply the reaction to eugenol but found that the allyl group was hydrogenated during the demethylation reaction with AlI_3 . Instead of hydroxychavicol, an 81% yield of hydrogenated 1,2-dihydroxy-4-propylbenzene was obtained from eugenol after 0.5 hours with 2 eq. of AlI_3 (freshly prepared) under reflux in cyclohexane. Besides, 2 eq. of tetrabutylammonium iodide were added following a procedure by Andersson *et al.*⁴⁰

This study serves as a starting point for a series of studies published Sang and co-workers investigating the selective demethylation of eugenol and other guaiacol derivatives with AlI_3 .^{41–45} In their first article they investigated the mechanisms of allyl group hydrogenation.⁴¹ As shown in Fig. 3, they proposed that HI formed during the initial reaction of AlI_3 with the phenolic OH group added to the allyl group *via* hydroiodination. Subsequent hydrodeiodination *via* AlI_3 -catalyzed hydrogen–halogen exchange was regarded as the origin of the hydrogenated products.

Having identified HI as the origin of the side product formation, different acid scavengers were used to suppress the Hydroiodination side reaction during the demethylation of

eugenol with 1.1 eq. AlI_3 in acetonitrile. While the initial investigation was based on pyridine (4.5 eq.) as acid scavenger, resulting in a 99% hydroxychavicol yield,⁴¹ similar results were obtained with 0.6 eq. carbodiimide.⁴³ However, carbodiimide also allows for the complete demethylation of 1,2-dimethoxybenzene-type compounds whereas in the presence of pyridine no demethylation of such compounds is possible. In further articles inorganic bases and metal oxides (*e.g.* Na_2CO_3 , CaO , CuO and ZnO ; 1.5 eq.) were successfully used as acid scavengers,⁴² as well as dimethyl sulfoxide (1.1 eq.), which generally gave slightly lower hydroxychavicol yields (*ca.* 94%). Eventually, an up-scalable one-pot approach was developed, including the *in situ* formation of AlI_3 from the elements, which yielded 75% of hydroxychavicol (starting from 6 g of eugenol) after 18 hours at 80 °C in dichloromethane with dimethyl sulfoxide.⁴⁵ Besides allyl groups, aldehyde, ketone or carboxylic acid functionalities can be tolerated, while other alkyl ether bonds can be cleaved as well.⁴³

Among all approaches reported in this review the AlI_3 -based procedure using scavengers like pyridine or carbodiimide is the only one that gives an almost quantitative yield while tolerating the allyl group of eugenol as well as other functional groups. In combination with the comparatively accessible reactants, mild reaction conditions and its proven up-scaling it is probably the best-suited method for the demethylation of functionalized derivatives of guaiacol.

Considering additional factors, it needs to be highlighted that for the preparation of AlI_3 required for this reaction, typically Al powder is used, which is a flammable solid, as well as elemental iodine, which poses considerable threats to human health as well as environmental hazards. While the solvent acetonitrile is less harmful than many of the aforementioned organic solvents used in other approaches, it is still to be considered problematic.³² In terms of acid scavengers, especially pyridine (toxic, flammable, environmental hazards) and carbodiimides such as *N,N'*-dicyclohexylcarbodiimide (toxic, known allergen and sensitizer) are very harmful and, from safety and



Fig. 3 Mechanistic explanation of hydrogenation observed during the demethylation of eugenol with AlI_3 . The presence of the acid scavenger pyridine prevents the initial hydroiodination step, which results in the preservation of the allyl group.⁴¹



environmental standpoints, the solid alternatives are by far preferable despite their lower efficiency. Dimethyl sulfoxide is also a less harmful alternative; however it was also listed as a problematic compound based on green chemistry metrics.³² In general, the recently developed AlI_3 -based method can be considered an improvement over other Lewis acid-based approaches also from a green chemistry standpoint. However, it is by no means deserving of the label “green” and effort should be invested into adjusting the method taking into consideration health, safety and environmental factors as well.

2.3. Lithium chloride in dimethyl formamide

The use of LiCl in dimethyl formamide for aryl ether dealkylation was reported by Bernard *et al.*⁴⁶ The reaction was conducted with 3 eq. of LiCl in boiling dimethyl formamide for *ca.* 18 hours, after which aqueous work-up with NaOH solution and extraction was conducted. It was found that the demethylation reaction is benefited by electron-withdrawing substituents. On the other hand, the demethylation efficiency was limited for anisole as well as for dimethoxybenzenes. Moreover, when developing a more rapid microwave method, Fang *et al.*⁴⁷ showed that the reaction of 3,4-dimethoxybenzaldehyde with LiCl results in the cleavage of only one aryl methyl group. This indicates that the cleavage of the second methoxy group, *i.e.* the demethylation of the guaiacol motif, is considerably more demanding. Fang *et al.*⁴⁷ also suggested a reaction mechanism (Fig. 4), which is based on a nucleophilic attack by Li followed by the release of methyl chloride. Eventually, the phenolic hydroxyl group is formed upon hydrolysis.

Encouraged by recent results by Kraft and Eichenberger,⁴⁸ Alni *et al.*⁴⁹ attempted the demethylation of eugenol *via* the LiCl-dimethyl formamide method. They used 2 eq. of LiCl and conducted the reaction for 48 hours under reflux and in a flow of N_2 gas before aqueous work-up and extraction. After purification only an 18% yield of hydroxychavicol was obtained, which was explained by the sensitivity of the product towards oxygen.⁴⁹

It must be pointed out that due to the use of dimethyl formamide this method cannot be recommended from a work safety standpoint unless its replacement by other solvents is feasible.³² Dimethyl formamide is particularly problematic due to its inherent health risks, especially for being suspected of harming the unborn child. LiCl, on the other hand, poses the hazard of affecting the human central nervous system.

2.4. Iodocyclohexane in dimethyl formamide

Zuo *et al.*⁵⁰ discovered a demethylation method for aryl methyl ethers using iodocyclohexane in dimethyl formamide. When the reaction was *e.g.* conducted with guaiacol and 5 eq. of iodocyclohexane under reflux a 91% yield of catechol was obtained after 4 hours. Iodocyclohexane was considered to be a source for HI formed continuously during the reaction.

Compared with conventional HI-based methods^{14,51} the new approach is characterized by milder reaction conditions and a slow *in situ* generation of HI. Due to a lack of substrates subjected to the iodocyclohexane demethylation method there is no information available on how the reagent behaves towards other functional groups like double bonds, or hydroxyl or carboxyl groups. As discussed above, the use of dimethyl formamide is highly problematic in terms of health-related hazards and if possible other methods should be used or dimethyl formamide should be replaced by alternative solvents.

2.5. Iodine-based oxidizing agents

2.5.1. Stabilized 2-iodoxybenzoic acid. Selective demethylation of aryl methyl ethers is also possible *via* oxidative reactions. Ozanne *et al.*⁵² developed a stabilized derivative of the oxidation agent 2-iodoxybenzoic acid (IBX), which can be used for the demethylation of guaiacol and its derivatives. Their proposed reaction mechanism is shown in Fig. 5 and relies on stoichiometric amounts of the oxidizing agent. After addition of 2-iodoxybenzoic acid to the phenolic OH an intramolecular oxygen transfer is proposed. Hydrolysis yields an *ortho*-quinone intermediate, which can be reduced to the corresponding catechol derivative.⁵²

The demethylation of eugenol was performed with 2.1 eq. of stabilized 2-iodoxybenzoic acid in tetrahydrofuran. After 16 hours of reaction in the dark at room temperature the product was extracted, hydrolyzed with aqueous NaHCO_3 and reduced with 6 eq. of Na_2SO_4 . A 77% yield of hydroxychavicol was obtained.⁵²

In a later study⁵³ it was shown that besides an allyl group, substituents with hydroxyl groups may also be tolerated, *e.g.* in the case of demethylating homovanillyl alcohol into hydroxytyrosol. In the case of iso-vanillyl alcohol, however, the primary alcohol was reduced to an aldehyde. Moreover, when vanillyl alcohol was used as the substrate, no demethylation could be observed while the primary alcohol was converted into an aldehyde, thus yielding vanillin. The authors argue that the elec-



Fig. 4 Cleavage of aryl methyl ethers with LiCl; the reaction mechanism proposed by Fang *et al.*⁴⁷





Fig. 5 Mechanism proposed by Ozanne *et al.*⁵² explaining the oxidative demethylation with 2-iodoxybenzoic acid (IBX), including subsequent hydrolysis and reductive work-up.

tron-withdrawing aldehyde function in the *para* position is interfering with the reaction of the oxidizing agent with the phenolic OH group.⁵³

While stabilized 2-iodoxybenzoic acid has significant improvements compared with its unstabilized counterpart, which has explosive properties, it is still a strong oxidizing agent that needs to be handled cautiously and has to be deactivated before disposal.⁵⁴ Moreover, IBX poses considerably hazards to human health and is used typically in combination with tetrahydrofuran, which is also considered a problematic solvent primarily due to health concerns.³² Thus, while the demethylation reaction with IBX is highly selective and good yields can be obtained, this approach is also found particularly wanting in terms of health, safety and environmental aspects and required further improvements in that regard.

2.5.2. Sodium periodate. Another iodine-based oxidizing agent that has shown demethylation ability similar to 2-iodoxybenzoic acid is NaIO_4 . The approach goes back to works by Adler and co-workers.^{55,56} Deffieux *et al.*³⁹ applied the method to prepare hydroxytyrosol from its methylated precursor homovanillyl alcohol. To the reactant, which was dissolved in ethyl acetate, was added an aqueous solution of NaIO_4 (2 eq.). The reaction to form an *ortho*-quinone intermediate was observed immediately in the biphasic mixture. In parallel to the 2-iodoxybenzoic acid-based oxidation, the intermediate was reduced with aqueous Na_2SO_4 to yield the catechol product (78% yield).³⁹ So far, no systematic evaluation of NaIO_4 as a demethylating agent was published. Therefore, it remains unclear how suited the approach is for other guaiacol derivatives and whether it tolerates other functional groups such as aldehydes or double bonds. It must be highlighted that NaIO_4 poses several hazards. It is, most importantly, strongly oxidizing and has a severe impact on the environment if released. Thus, this method is inherently not a green demethylation approach.

2.6. Thiols in combination with bases

Feutrill and Mirrington^{57,58} developed a demethylation method based on the nucleophile thioethoxide (alkali etha-

nethiolate) in dimethyl formamide. Focusing on the selective monodemethylation of 1,2-dimethoxybenzene to guaiacol, they also reported that about 25% of the identified product was catechol. This indicates that guaiacol was further demethylated under the following reaction conditions: 5 eq. thioethoxide (from ethanethiol and NaOH), reflux in dimethylformamide for 3 hours under a N_2 atmosphere, and aqueous work-up.⁵⁸

More recently, odorless thiols have been used for this reaction and different bases were investigated, *e.g.* *tert*-butoxides.^{59,60} However, no examples of guaiacol-type substrates were reported. As previously mentioned, thiols pose considerable health and environmental risks and, even more so does the solvent dimethyl formamide. Thus this type of demethylation cannot be recommended.

2.7. Other approaches

There are a variety of other methods for ether cleavage which are, however, not as commonly applied or as viable as the methods reviewed here. Many of these are included in previous review articles.^{14–16,51} These include demethylation using tetramethylsilyl iodide¹⁸ or pyridinium-based compounds.⁶¹ Furthermore, ionic liquids have been successfully used.^{62–64} Recently, Liu *et al.*⁶⁵ reported a Cu_2O -catalyzed demethylation procedure, which was conducted at 185 °C in methanol in the presence of sodium methanoate. A different catalytic approach was described by Duprat *et al.*,⁶⁶ which is an oxidative method based on an Fe^0 /acetic acid/ O_2 system. Moreover, ether cleavage is known to be feasible with alkali organometallic compounds or alkali metals.⁶⁷ Another classical approach, aqueous hydrolysis with Brønsted acids, will be discussed in the next section.

3. Aqueous hydrolysis, acids and bases

In this section different aqueous-phase approaches to selectively demethylate guaiacol and its derivatives into catechols



are reviewed. Like in the previous section, literature for guaiacol and its derivatives like *e.g.* eugenol was selected with a side focus on the fate of other functional groups during demethylation. The approaches discussed here include methods relying on either acids or bases as well as sub- and supercritical hydrothermal conditions. On the one hand, this means that the reagents required are comparatively simple and cheap. On the other hand, the reaction conditions are harsh and result in both enhanced corrosion and low selectivity for functionalized molecules. Moreover, this is associated with safety, health and environmental hazards.

One aspect that is rarely mentioned is the low solubility of guaiacol and especially its alkylated derivatives. This explains why the use of phase-transfer catalysts can strongly improve this reaction, as will be shown for aqueous HBr, and should certainly play a role for the processes conducted in sub- or supercritical water, where the solubility of nonpolar compounds is drastically increased.⁶⁸ On the other hand, in other cases a two-phase system may be present even at the reaction temperature unless the substrate is strongly diluted.

3.1. Mineral Brønsted acids

3.1.1. Hydrobromic acid. Aqueous HBr, which behaves similarly to HI, is a very common demethylation reagent. One comparatively recent example of a guaiacol derivative being demethylated with HBr was reported by Zhao and Abu-Omar.⁶⁹ They conducted the aryl methyl ether cleavage of 4-propylguaiacol in 48% aqueous HBr. After 19 hours of reaction at 115 °C and extraction a 4-propyl-dihydroxybenzene yield of 94% was obtained.

In other studies, acetic acid was added as a co-solvent. In a recent attempt, Alni *et al.*⁴⁹ exposed eugenol to a mixture (50 : 50 vol%) of acetic acid and aqueous HBr. Instead of the target compound hydroxychavicol only small amounts (*ca.* 1%) of what was identified as a dimer species could be obtained after 0.5 hours at 110 °C. The authors hypothesize that an allylic radical could be formed in the presence of oxygen that leads to dimerization.⁴⁹ In general, the allyl group appears not to be stable under these conditions and it might be speculated whether besides dimerization also the addition of HBr to the double bond takes place.

One significant improvement of the conventional HBr system is the addition of phase-transfer catalysts, which was reported by Landini *et al.*⁷⁰ Waghmode *et al.*⁷¹ used the quaternary ammonium salt methyltriethylammonium chloride, known as Aliquat 336, as the phase-transfer catalyst when studying the demethylation of aryl methyl ethers with HBr. The reaction was conducted with 48% aqueous HBr (4.5 eq.) and 10 wt% (based on substrate) of the phase-transfer catalyst at 105 °C. With guaiacol as substrate this approach yielded 78% of catechol after 6 hours.⁷¹ It is noteworthy that the reaction is considerably faster compared with approaches without phase-transfer catalysts.

Both HI and HBr are strong acids and their concentrated solutions are strongly corrosive and have severe detrimental health effects when in contact with skin, inhaled or ingested.

Moreover, HBr is known to be toxic to aquatic life, and thus it cannot be considered a green reagent. Of particularly high concern is especially the aforementioned phase-transfer catalyst Aliquat 366, which is toxic to reproduction and an environmental hazard. The use of this modified demethylation approach is particularly advised against.

3.1.2. Hydrochloric acid and sulfuric acid. Yang *et al.*⁷² systematically investigated the use of aqueous HCl for the demethylation of guaiacol into catechol. Their results showing the influence of pH, which was adjusted by the addition of HCl, as well as the effect of changing the gas phase from N₂ to H₂ are shown in Fig. 6. In all cases the reaction was conducted at 280 °C for 3 hours in a high-pressure batch reactor.

Both lower pH, *i.e.* higher acid concentration, and H₂ atmosphere are beneficial. At optimum conditions (10 bar H₂, pH = 1.8, 280 °C) almost complete guaiacol conversion and an 89% yield of catechol were reported. The presence of H₂ was suggested to open an additional reaction pathway resulting in the formation of methane besides the conventional hydrolysis product methanol. Furthermore, based on kinetic analysis the authors suggested a pH-dependent change in the reaction mechanism, shown in Fig. 7. It was proposed that below a certain pH threshold (*ca.* 3.9) a proton-catalyzed mechanism dominates while at higher pH water plays the role of a catalyst.⁷²

Very recently, Bomon *et al.*⁷³ investigated the demethylation of differently functionalized guaiacol derivatives under similar conditions. Experiments were conducted with aqueous HCl at 250 °C under a N₂ atmosphere for 3 hours. Their key finding was that, besides demethylation to yield a catechol derivative simultaneously, dealkylation was observed for certain substrates. This was the case for guaiacol derivatives with unsaturated alkyl chain substituents like *e.g.* 4-vinylguaiacol, eugenol

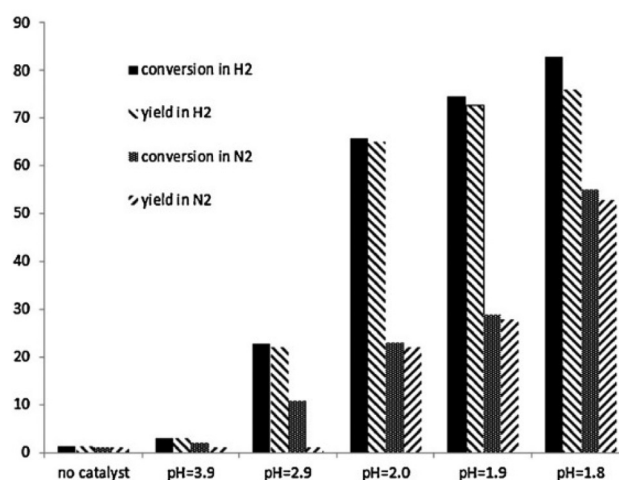


Fig. 6 Demethylation of guaiacol at 280 °C in aqueous HCl at different pH values. Both conversion of guaiacol and catechol yield after 3 hours are shown. Reactions were conducted either under a N₂ or H₂ atmosphere. Reproduced from ref. 72 with permission from Elsevier, copyright 2013.



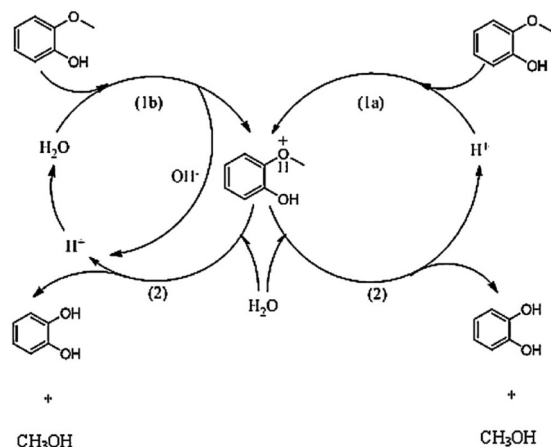


Fig. 7 Competing water-catalyzed (left) and acid-catalyzed (right) mechanism of guaiacol demethylation in aqueous HCl proposed by Yang *et al.*⁷² The acid-catalyzed mechanism was suggested to dominate at a sufficiently low pH (<3.9).

and isoeugenol, where the main product was unsubstituted catechol (yields of 40%, 71% and 62%, respectively). For the saturated analogue 4-propylguaiacol, however, only demethylation took place, yielding 4-propylcatechol in excellent yield (97%).⁷³

A mechanism was proposed (Fig. 8) to explain both acid-catalyzed reactions. The dealkylation was suggested to take

place *via* a retro vinylogical aldol reaction after addition of water to the double bond. The cleaved alkyl fragment was confirmed to give an aldehyde as a byproduct. The acid-catalyzed demethylation, which eventually produces methanol as a byproduct, was proposed to be initialized by arene protonation and proceed *via* a hemiacetal intermediate (E).⁷³ This is in contrast to the mechanism by Yang *et al.*⁷²

Besides HCl, Bomon *et al.*⁷³ tested several other acids and obtained similar results for H₂SO₄, however requiring a higher concentration. H₃PO₄ and triflic acid were significantly less active and acetic acid did not produce any catechol from ferulic acid. Overall, these results show that under acidic conditions double bonds are labile and prone to hydration and even dealkylation.

Compared with the aforementioned aqueous solutions of the acids HBr and HI used for demethylation, it is apparent that HCl and H₂SO₄, while highly corrosive, are due to their elemental composition less toxic and less environmentally harmful. The discussed variation of the process under H₂ pressure of up to 10 bar is not only less desirable from an economic but also from a safety-centered perspective due to the explosion hazard and should be omitted if the process is feasible under inert gas.

3.1.3. Water-tolerant Lewis acids. One study reports the use of water-tolerant Lewis acids for the demethylation of guaiacol.⁷⁴ Several such Lewis acids were tested, most of which are triflate salts: In(OTf)₃, Sc(OTf)₃, InCl₃ and Yb(OTf)₃.



Fig. 8 Mechanistic view of a sequence of acid-catalyzed reactions proposed by Bomon *et al.*⁷³ for allyl- and vinyl-substituted guaiacol derivatives. For example, eugenol (12b) undergoes isomerization, dealkylation and demethylation resulting in the formation of catechol.



Guaiacol hydrolysis was conducted with 5 mol% of the respective Lewis acid in water at 250 °C. The highest yield of catechol (65%) and guaiacol conversion (75%) was obtained over $\text{In}(\text{OTf})_3$ after 2.75 hours. A comparison with HCl-catalyzed demethylation showed that the activity was higher over $\text{In}(\text{OTf})_3$.⁷⁴ It should be noted that this approach was only applied only at a very small scale (<250 mg) and no guaiacol derivatives besides guaiacol itself were tested. It should be noted that due to the catalytic nature of the reaction, the use of water as solvent and the fact that $\text{In}(\text{OTf})_3$ and $\text{Sc}(\text{OTf})_3$ are not classified as hazardous chemicals, this approach can be considered comparatively “green”, especially in comparison with the aforementioned (organic) methods. In this context, proof that the catalyst can be recovered and reused is of crucial importance.

3.2. Solid Brønsted acid catalysts

Using solid Brønsted acid catalysts rather than mineral acids offers solutions to the corrosiveness and limited recyclability of the previously presented, homogeneously catalyzed approaches. Wu *et al.*⁷⁵ showed that in the heterogeneously catalyzed hydrolysis of 4-propylguaiacol over solid acids selective demethylation to 4-propylcatechol occurs (Fig. 9A) and selectivity comparable to mineral acids was observed. Probably due to its high density of acid sites (Fig. 9B), zeolite beta was found to be best suited among the different solid acids and 4-propylcatechol yields up to 90% were obtained at 275 °C. Moreover, the reusability of the zeolite catalyst was demonstrated but the catalyst lost *ca.* 60% of its initial activity over four recycling runs. Interestingly, silylation was shown to increase the stability of the catalyst, however at the cost of reduced catalytic activity. In addition, experiments showed lignin oil rich in 4-propylguaiacol could also be converted into 4-propylcatechol, achieving yields as high as 74%.⁷⁵ Overall,

the solid acid catalyst in an aqueous reaction environment is the best choice in terms of the environmental aspects of the process. The proven recyclability (even though it should be improved by developing more stable catalysts) in combination with the reasonably good product yields, the use of water as the solvent, the absence of any other additives and the low harm potential of the zeolite materials makes the process highly desirable. Nevertheless, the process will have to be shown to work on a significantly larger scale.

3.3. Aqueous bases

Aryl methyl ether hydrolysis is also feasible *via* a base-catalyzed pathway and can in certain cases be beneficial.⁷⁶ Yang *et al.*⁷² also reported a single demethylation experiment under basic conditions. Guaiacol was demethylated in aqueous NaOH (pH = 10.4) at 280 °C under a H_2 atmosphere, similar to their acid-catalyzed experiments discussed above. After 3 hours, it was confirmed that catechol was formed; however, no quantitative information was reported. Most importantly, significant amounts of “char” were found, indicating a strong contribution of undesired side reactions. Therefore, this approach was not pursued further.⁷²

3.4. Hydrolysis in sub- and supercritical water

At elevated temperature and pressure, guaiacol can be demethylated in water alone. The underlying effects that play a significant role are the higher solubility of nonpolar compounds as well as the drastically increased ion concentration due to the auto-dissociation of water under sub- and especially supercritical conditions.⁷⁷ In the 1980s the hydrolysis of guaiacol was investigated under supercritical conditions at 383 °C. Klein and co-workers^{78–80} investigated the decomposition of guaiacol without and with different amounts of water. Increasing contents of water were suggested to shift the domi-

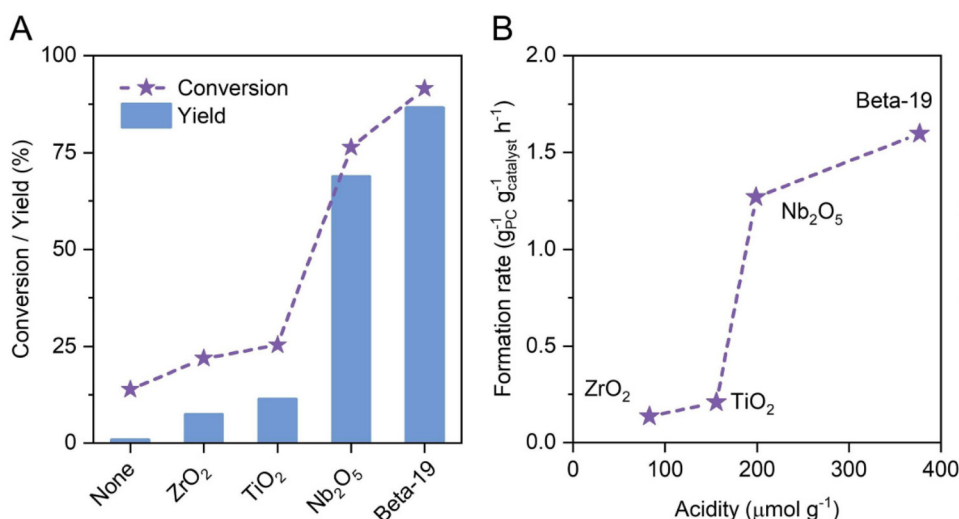


Fig. 9 Conversion of 4-propylguaiacol and yield of 4-propylcatechol over different solid acid catalysts after 2 h at 260 °C in water (A). Catalytic activity (given as the product formation rate) plotted against catalyst acidity (B). Reproduced from ref. 75 with permission from John Wiley and Sons, copyright 2022.



nating reaction mechanism from pyrolysis to hydrolysis, which results in the observed increasing selectivity for the hydrolysis products catechol and methanol with increasing density of water.^{78–80} Interestingly, at higher temperatures (400–500 °C) DiLeo *et al.*⁸¹ could not identify catechol or methanol.

More recently, Wahyudiono *et al.*⁸² revisited the reaction and compared the hydrolysis under super- and subcritical conditions (Fig. 10). In the subcritical regime at 250 °C and 80 bar, guaiacol conversion barely reached 6% after 2 hours while selectivity for catechol was *ca.* 70%. On the other hand, under supercritical conditions (400 °C, 400 bar) guaiacol conversion reached 55% and catechol yield 40% within 0.5 hours. After 2 hours the guaiacol was almost completely decomposed, however without a clear increase in product yield.⁸² In the super-critical aqueous system the addition of salts (NaCl, CaCl₂, FeCl₃) was found to promote the hydrolysis of guaiacol to catechol, probably by increasing the polarity of the solvent.⁸⁰

From a green chemistry perspective this approach appears very attractive based on the fact that only water, considered a highly recommended solvent, and no other compounds in catalytic or even stoichiometric reactions are required. Comparing the reaction conditions, however, with the solid Brønsted acid-catalyzed approach (section 3.2) it becomes apparent that the considerably milder reaction conditions and higher product yield indicate that the heterogeneously cata-

lyzed reaction is preferable, as it enables a sufficiently high re-usability of the catalyst.

3.5. Thermolysis

Thermochemical conversion of biomass includes fast pyrolysis, gasification, gasification, combustion and vapor phase cracking. The later was used for eugenol thermolysis in the temperature range 300–900 °C and residence times of 1–3 s in a non-isothermal laminar flow-reactor operated at atmospheric pressure. Temperatures above 650 °C led to aromatic hydrocarbons, while at lower temperature oxygenates were observed with a retained aromatic ring. Under pyrolytic conditions, free-radical reactions are the major pathways responsible for the decomposition and formation of species. In eugenol, it is expected that the methoxy C–O bond in eugenol is the weakest and the source of the initiation reaction, as presented in Fig. 11. Even though the diol was formed according to the below presented mechanism, the propyl chain was cracked into a methyl group. The yield of 3-methyl-1,2-benzenediol reached 4% at 750 °C and residence time 1 s. The yield of catechol at the same reaction conditions reached 2.5%.^{83,84}

The first and major step in the thermolysis of guaiacol in tetralin in the presence of hydrogen has been shown to be a monomolecular dissociation into phenoxy and methyl radicals with subsequent stabilization of the radicals by hydrogen abstraction from tetralin. The results show that hydrogen does

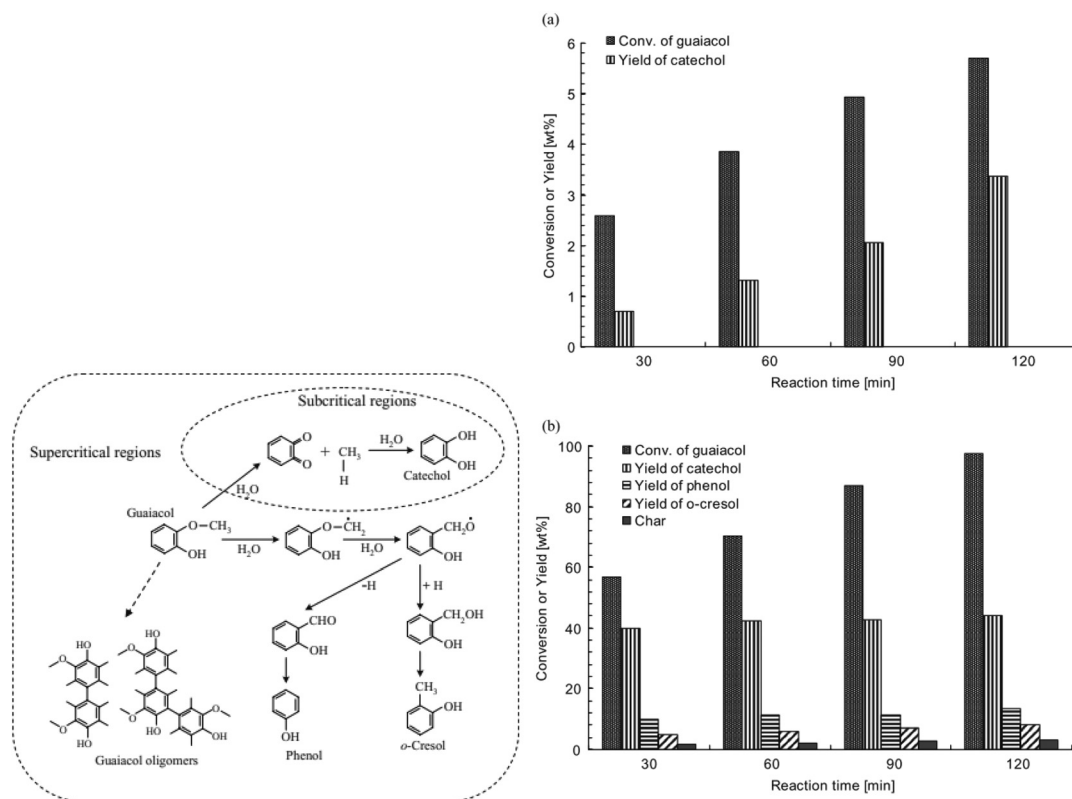


Fig. 10 Left: probable reaction pathways for guaiacol decomposition to achieve the desired products; Right: yields of guaiacol decomposition products in sub- and supercritical water as a function of reaction time, 400 °C and 400 bar.⁸²





Fig. 11 Left: general reaction scheme for the vapor-phase cracking of eugenol; right: fractional yields of 2,3-dihydrobenzofuran, 2-coumaranone, 3-methyl-1,2-benzenediol, and 4-(2-propenyl)-phenol (clockwise from top left) as functions of the temperature at (●) $\tau = 1$ s and (○) $\tau = 3$ s.⁸³

not participate in the reaction because no systematic difference is noted between nitrogen and hydrogen in the same solvent system.^{85,86} Afifi *et al.*⁸⁷ investigated the thermal treatment of guaiacol in tetralin in the absence of catalysts. The major reaction products identified were catechol, *o*-cresol and phenol and an oligomeric/polymeric material. At 375 °C the conversion of guaiacol reached 15% with around a 5% yield of catechol. With increasing conversion, the yield of catechol decreased. An increased initial concentration of guaiacol in tetralin yielded a smaller amount of catechol.⁸⁷

Supercritical water gasification (SCWG) of guaiacol was performed between 400 °C and 700 °C in the presence or absence of Ni wire as a heterogeneous catalyst. At 400–500 °C, guaiacol was completely converted in SCWG, but not all of it was gasified. Phenol and *o*-cresol were decomposition products and larger amounts of char also formed. The SCWG of phenol at 600–700 °C did not produce any char. The major liquid-phase decomposition product was benzene, which was in yields up to about 5% at 600 °C and 12% at 700 °C. Up to 99% of the carbon was gasified when using three Ni wires, and the major products were hydrogen and carbon dioxide in yields close to equilibrium.⁸¹ Overall, the non-catalytic thermolysis processes are far too unselective to be considered viable alternatives for the demethylation of methyl aryl ethers.

4. Hydrotreatment

The scope of the published literature is mostly focused on the total (hydro)deoxygenation (HDO) of the oxygenated lignin-based aromatics (eugenol, vanillin, guaiacol) rather than selective conversion into targeting value-added compounds. Especially 1,2-dihydroxy compounds are rarely mentioned in the existing literature. However, general conclusions can be

outlined from the screened reaction conditions, used supported metals and mechanistic studies.

Among the metals, noble (Pt, Pd, Ru) and transition metals (Ni, Mo, Co, Ir, Ce, Cu) as well as their bimetallic combinations were screened in numerous studies using eugenol or guaiacol as a reactant. Almost in all research studies high H₂ pressure was used (10–60 bar), resulting in deoxygenated aromatic and aliphatic (due to the ring saturation) compounds. The selected metals were usually supported on neutral or acidic supports (C, SiO₂, TiO₂, MgO, Al₂O₃, ZrO₂, CaCO₃, HZSM, *etc.*). The choice of the metal and support is important for the selective conversion of compounds in particular chemical reactions, such as hydrogenation, deoxygenation, demethylation, decarboxylation, ring opening, *etc.*

It cannot be overstated that the selective demethylation of methyl aryl ether groups during metal-catalyzed hydrotreatment appears to be very challenging and, in particular, hydrogenation reactions are occurring in general more facily. However, the reaction does occur and due to the lack of studies investigating this particular pathway it is difficult to estimate the true potential of this reaction. Nevertheless, it is certain that the demethylation pathway will probably be more prevalent under conditions less favorable to hydrogenation and with purposefully designed catalysts. As it stands, the low yields of demethylated products are currently the main impediment for this type of process and also problematic from a sustainability point of view.

While the use of solid and potentially reusable catalysts is promising regarding the green chemistry metrics of this process, the use of H₂ gas at elevated pressure presents a severe harm potential that also may limit the applicability in industry. Significantly lowering the required H₂ pressure would therefore be highly desirable. An additional hazard arises from the use of organic solvents, typically, which are considered hazardous solvents,³² which are used in some

cases rather than the more desirable solvent water. Lastly, for the development of suitable solid catalysts the focus should also be placed on the health, safety and environmental impact of the components of the catalyst. The use of Ni should *e.g.* be avoided due to its carcinogenicity, while elements such as Ru, Mo or Pt are considered most “green” by Bystrzanowska *et al.*⁸⁸

4.1. Noble metals (supported Pt, Pd, Ru)

Noble metals showed high activity for HDO and especially for hydrogenation (ring saturation) under high hydrogen pressure and at high reaction temperatures (>300 °C). In the presence of Pt catalyst significant hydrogenation of the propenyl chain took place besides HDO and deallylation when eugenol was used as a reactant. In the absence of H₂, Al₂O₃ catalyzed similar reactions (isomerization and deallylation) to zeolites.⁷⁴ Pd/C in a combination with HZSM-5 zeolite was used for aqueous phase HDO of eugenol under 20 bar of H₂. The introduction of acidic active sites increased the dehydration of 4-propyl-1,2-cyclohexanediol, while Pd was responsible for the hydrogenation of the aromatic ring; the proposed reaction pathway is presented in Fig. 12. However, the hydrogenation is more pronounced.⁸⁹ Carbon- and HZSM-5-supported Pd catalysts were tested for aqueous-phase HDO of methoxy-substituted lignin monomers (such as guaiacol and 2,6-dimethoxyphenol) under 20 bar H₂. Again, hydrogenation was the dominant reaction, resulting in aromatic ring saturation, which proceeded even before the HDO of oxygen-containing functional groups.⁹⁰

The hydrothermal conversion of eugenol over a Pt/C catalyst at temperatures between 250 °C and 300 °C in a water/ethanol mixture in the absence of gaseous H₂ was investigated using various catalysts. Under these conditions, the C=C double bond of the propenyl chain is hydrogenated, but the hydroxyl and methoxy groups of eugenol do not react.⁹¹

Pt was found to catalyze the demethylation of guaiacol to catechol, while acid sites on the support (HBeta and SiO₂)

were responsible for transalkylation and dehydroxylation reactions into monohydroxyl phenolic compounds.⁹² Besides silica-supported Pt, Rh was also tested for the HDO of *p*-methyl guaiacol in a fixed bed reactor at a temperature of 300 °C with a hydrogen pressure of 4 bar. Silica-supported Rh improved the selectivity towards 4-methyl-catechol in comparison with the respective Pt catalyst.⁹³ Zhang *et al.*⁹⁴ studied the aqueous-phase HDO of eugenol over Pd/C combined with HZSM-5 zeolite catalysts in the presence of 50 bar H₂ at the reaction temperature of 240 °C. The results showed that hydrogenation is the dominant reaction; firstly the alkyl chain was saturated and next the aromatic ring.⁹⁴

An interesting approach was used by González-Borja *et al.*,⁹⁵ where inconel monoliths were impregnated with Pt and Sn and tested for the HDO of anisole and guaiacol under atmospheric pressure of H₂/N₂ (17 : 83 vol%) at 400 °C in a quartz tube. Guaiacol was vaporized in the gas mixture before entering the reactor. The results showed that guaiacol first produces catechol, followed by deoxygenation to phenol and finally to benzene. The decomposition of the methoxy group results in catechol or phenol from guaiacol and anisole, respectively. Thermodynamically, this CO bond is weaker than the CO bond connecting the methoxyl to the aromatic ring and weaker than the CO bond of the hydroxyl group. Therefore, producing catechol from guaiacol is more favorable than directly producing anisole or phenol. However, only traces of catechol were observed in the product mixture from guaiacol, which suggests that catechol is rapidly converted to phenol, perhaps even before it desorbs from the metal surface.⁹⁵

MgO-supported Pt catalyzed the conversion of guaiacol into phenol, catechol and cyclopentanone. However, the dominant pathway was through a complete cleavage of the methoxy group, while a slightly higher yield of catechol was observed when Pt/Al₂O₃ was used as a catalyst. In the absence of acidic sites, catechol is expected to be formed over Pt/MgO, primarily

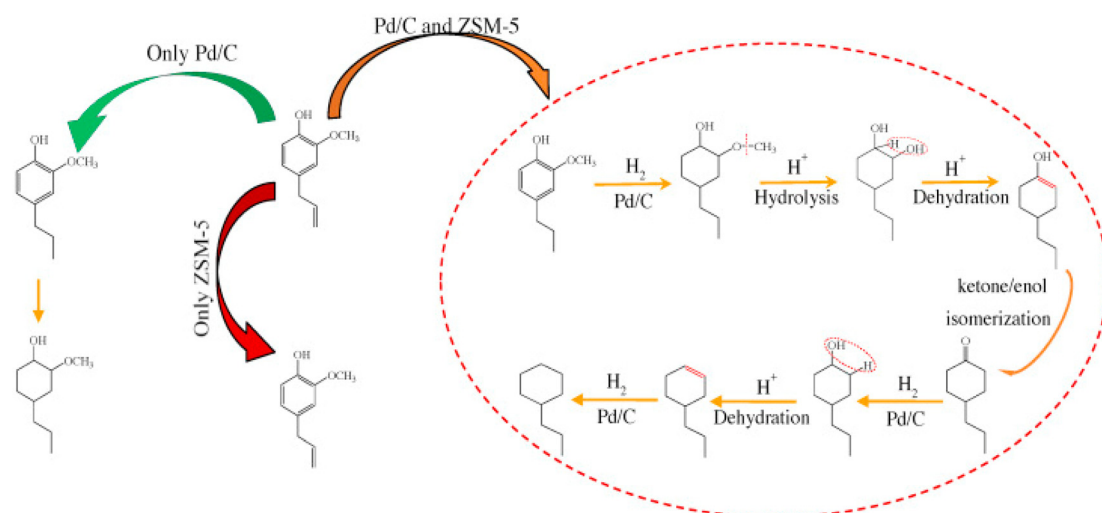
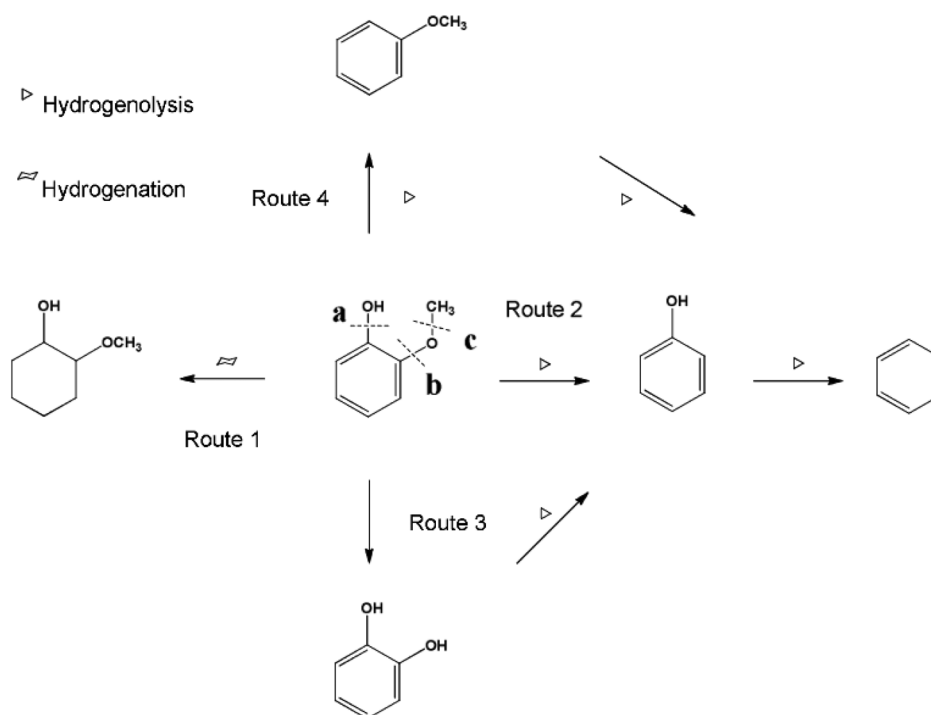


Fig. 12 Reaction pathways of eugenol to cyclohexanes over Pd/C and HZSM-5 in the aqueous phase.⁸⁹



Ru also showed very high activity towards the complete HDO of guaiacol even at low temperatures, while selective demethoxylation from aqueous guaiacol proceeded over Ru catalysts.¹⁰⁰ The addition of MgO to the reaction media suppressed the unselective C–O dissociation.¹⁰¹ Similar behavior was observed with magnetically separable Ru/C catalyst, where 70% of the oxygen was removed from eugenol.¹⁰² CaCO₃-supported Ru even surpassed the HDO activity compared with ZrO₂- or MgO-supported Ru catalysts. The aromatic

Alumina-supported Ru was tested in a H₂-free reaction system for the HDO of guaiacol, using a hydrogen donor



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Fig. 14 Reaction network of guaiacol HDO over Ni-based catalysts. 1: demethylation, 2: demethoxylation, 3: dehydroxylation, 4: hydrogenation, 5: transalkylation, 6: ring opening. Reproduced from ref. 124 with permission from Elsevier, copyright 2018.

With a commercial $\text{Pd}/\text{Al}_2\text{O}_3$ the only formed product was catechol at 70% conversion; reaction conditions: contact time 0.339 min and space velocity 59 h^{-1} at 300°C with a hydrogen : guaiacol ratio of 33.¹²⁹

Peters *et al.*¹³⁰ studied guaiacol HDO over Ni-based and Fe-based catalysts. Separately zeolites were also used as catalysts. The reaction was performed in gaseous phase in a fixed-bed reactor at $300\text{--}500^\circ\text{C}$ in the presence of hydrogen. Catechol was proposed as an intermediate even though it was not detected in the liquid phase; however, a significant concentration of methane (1–8%) was detected in the gaseous phase, which proved the formation of catechol from guaiacol.¹³⁰

Molybdenum nitrides on commercial activated carbon were used for the HDO of guaiacol in decalin as solvent at 300°C under 50 bar of H_2 , which was filled into the reactor at the plateau temperature. The highest yield of catechol was obtained over unsupported Mo_2N catalyst. After 4 h of reaction and 4% conversion, the yield of catechol and phenol was 3% and 1%, respectively. HDO was more prominent over supported catalyst, resulting in higher yields of phenol.¹³¹ Moreover pre-sulphided MoS_2 supported on activated carbon converted guaiacol into catechol with a yield of 10% at 300°C under 50 bar of H_2 in a batch regime in decalin as solvent.¹³²

The influence of the presence of H_2S in the reaction feed was studied for the HDO of guaiacol, catalyzed with pre-sulphided CoMo catalyst at 270°C . The increased H_2S concentration significantly improved the catechol formation but at the same time did not affect the guaiacol conversion.¹³³

Jimenez *et al.*¹³⁴ tested carbon-supported molybdenum catalysts for the HDO of guaiacol in aqueous and organic (dodecane) environments in the presence of hydrogen. The results showed relatively high selectivity towards catechol

when reaction was performed in dodecane at 300°C under an initial 40 bar of H_2 and even better results in a water environment. However, guaiacol conversion was significantly better in the organic environment, reaching up to 91% with 24% selectivity towards catechol (with 20% Ac/CNT catalyst).¹³⁴

Copper has a low tendency to hydrogenation, preventing over-reduction and thus improving the selectivity. Copper-doped PMO (Cu-PMO) was used for the HDO of eugenol in the temperature range between 22°C and 180°C under 40 bar of hydrogen, performed from 3–18 hours. Even though the most thermodynamically favorable product is predicted to be catechol (based on DFT calculations) in the experiments it was not detected.¹³⁵

Rhenium oxide (Re_2O_7) converted guaiacol into phenol and alkyl phenols at $280\text{--}320^\circ\text{C}$ in ethanol as a (hydrogen donor) solvent under an inert gaseous atmosphere.¹³⁶ Bimetallic RuRe catalyst supported on carbon showed considerably higher activity for HDO; after 4 hours of treatment at 240°C under 20 bar of H_2 almost all the guaiacol was converted into cyclohexane.¹³⁷ When water was added to the reaction mixture using a $\text{ReS}_2/\text{SiO}_2$ catalyst the conversion of guaiacol was significantly lower. Moreover, the preferential adsorption of water on the acidic active sites inhibited the demethylation reaction pathway, resulting in less catechol.¹³⁸

Many studies used supported bimetallic NiMo, CoMo or NiCo catalyst for the HDO of lignin-based monomers.^{139,140} Blanco *et al.*¹⁴¹ studied the HDO of guaiacol in the liquid phase at 300°C under 50 bar of hydrogen, where nickel-cobalt bimetallic catalysts supported on high surface area graphite with different Ni/Co ratios were tested. The highest activity was reached with Ni/Co = 2 : 1, but the results showed that Ni was more active in the hydrogenation, favoring cyclohexanol pro-

Jongerius *et al.*¹⁴⁶ focused in their study on the HDO of different aromatic monomers (*o*-cresol, *p*-cresol, anisole,

Pre-reduced NiCu/MCM-41 and NiCu/Ti-MCM-41 catalysts were synthesized and tested for the HDO of guaiacol at 260 °C under 40–100 bar of H₂. As expected, high hydrogen pressure led the reaction towards partially or totally deoxygenated products, among which no catechol was detected, but it was supposed to be one of the possible intermediates.¹¹⁶

Natural lignin does not consist of any structural unit that contains the catechol motif with both free hydroxyl groups. However, guaiacyl units are abundant and selective demethylation of these aryl methyl groups is a pathway that leads to the formation of 1,2-dihydroxybenzene structures. In a more general context, demethylation can be viewed as a method to increase the content of phenolic hydroxyl groups, which is desirable for adhesion¹¹ as well as polymer applications.¹⁴⁷ Some of the demethylation approaches reviewed above for guaiacol and its derivatives have been successfully applied to lignin. These specific methods will be discussed after a brief overview of catechol formation during more general lignin depolymerization approaches.

Significant progress has been made in evaluating lignin's structural features by nuclear magnetic resonance (NMR) methodologies. A variety of lignin functional groups and structural insights have been identified by quantitative ^{31}P NMR and semiquantitative two-dimensional heteronuclear (2D ^1H - ^{13}C HSQC) NMR spectroscopy (Fig. 16).¹⁴⁸⁻¹⁵⁰ The technique of phosphorylation followed by ^{31}P NMR spectroscopy extends straightforward advantages in measuring lignin hydroxyl (OH) groups at high single-spectrum resolution. Meng *et al.* published a well-defined protocol to ensure the scientific accuracy and uniform application of this methodology.¹⁴⁹ With an appropriate phosphorus reagent, different lignin OH groups, which also depend on the biomass source, can be quantified by ^{31}P NMR. Among the aliphatic, phenolic and carboxylic OH groups, the content of phenolic OH is the key lignin structural feature that affects its chemical properties and reactivity.^{151,152}

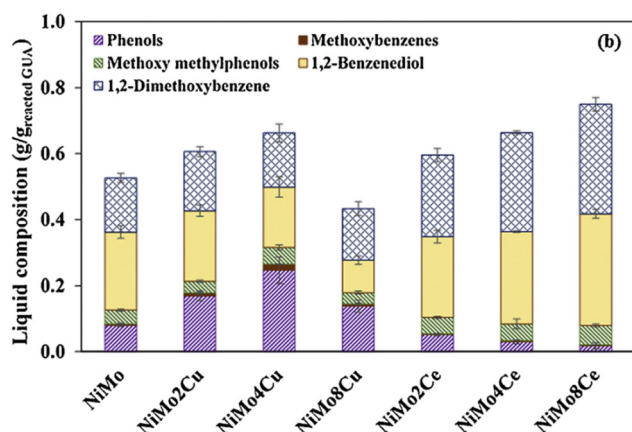


Fig. 15 Effect of the promoter type and content on the liquid compositions obtained from the HDO of GUA (condition: catalyst concentration = 15 wt% based on the GUA content at 10 bar H₂ pressure and 300 °C for 1 h).¹⁴⁴

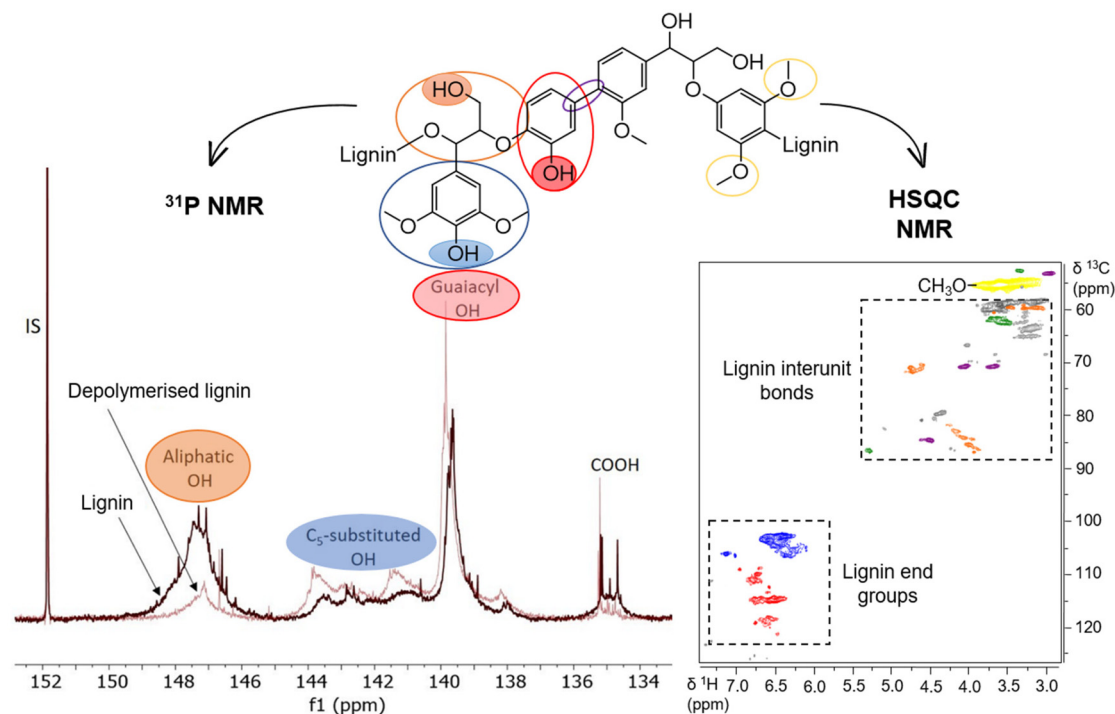


Fig. 16 Representative quantitative ^{31}P NMR spectrum (colored filled ellipses: hydroxyl groups) and semi-quantitative 2D HSQC NMR spectrum (colored ellipses: lignin structural units) of lignin samples.

Critically, one-dimensional NMR spectroscopy (*i.e.*, ^1H and ^{13}C NMR) can be employed to quantify the phenolic hydroxyl and methoxyl groups in lignin, but is usually associated with severe signal overlap and an inability to measure the aliphatic OH group content. On the other hand, the use of 2D HSQC NMR has brought advances in the determination of lignin sub-units (aliphatic and aromatic regions, methoxyl groups, *etc.*) and lignin carbohydrate complexes. The principles, applications and comparisons of the extremely useful NMR methods for lignin characterization have been summarized in critical reviews.^{153,154} However, the use of only one NMR technique provides limited opportunities for the structural prediction of the efficient demethylation of lignin.

Lignin undergoes various structural modifications and rearrangements with each type of treatment (*i.e.*, depolymerization, hydrogenation, demethylation, *etc.*).¹⁵⁵ This means that the characterization of demethylated lignin cannot be limited to a single NMR method. ^{31}P NMR provides the content of hydroxyl groups, while C_5 -substituted and guaiacyl phenolic OH groups overlap with either hydroxyl or methoxyl groups in the C_3 or C_5 position. Crestini *et al.* studied different lignin and tannin samples by the ^{31}P NMR method; these have methoxyl and hydroxyl substituted functional groups, respectively.¹⁵⁶ The results showed that the signals of guaiacyl and syringyl phenolic OH still overlapped in lignin and tannin even with differently substituted functional groups.¹⁴⁹ Therefore, the higher content of phenolic OH groups does not necessarily reflect the demethylation of lignin after treatment, as previously reported.^{157–159} To detect the demethylation of

lignin, HSQC or the molecular weight of lignin had to be performed and determined, respectively. The change in molecular weight of lignin with altered phenolic OH groups content indicates the cleavage of lignin into smaller lignin-based molecules and rearrangements rather than demethylation. On the other hand, the constant molecular weight of lignin and demethylated lignin samples suggests that efficient demethylation occurred. The HSQC method was used to determine the number of methoxyl groups per 100 C_9 units by integrating the signals in the aromatic and methoxyl regions. Efficient demethylation of lignin is therefore evidenced by the reduced number of methoxyl groups per 100 C_9 units or the reduced ratio of methoxyl groups to total aromatic units.^{150,160}

5.2. Demethylation in the context of lignin depolymerization

In general, lignin depolymerization strategies, in particular ones that target phenolic compounds, are conducted under reaction conditions which also allow for aryl methyl ether cleavage. A review article by Schutyser *et al.*¹⁶¹ gives a good summary of the literature on acid- and base-catalyzed depolymerization and clearly highlights the formation of catechol and its derivatives. They conclude that catechol mainly appears at high reaction temperatures and typically towards the end of the reaction time;¹⁶¹ a similar behavior is observed during lignin pyrolysis.¹⁶² This is indicative of the previously mentioned comparatively high stability of the aryl methyl ether bond. Hydrothermal treatment (sub- or supercritical conditions) of lignin often gives catechol as the main product.^{163–168} A general problem of these methods relying on



harsh reaction conditions is that myriad products are formed and yields for selected molecules are typically low. On the other hand, if these issues could be resolved by substantially improved reaction efficiencies as well as milder reaction conditions, the combination of lignin depolymerization and demethylation would be highly promising. From the viewpoint of green chemistry, the aqueous-phase demethylation approaches appear especially preferable when compared with the organic chemistry-based methods presented in section 5.3. Similarly, catalytic depolymerization and demethylation *via* hydrotreatment offers the advantage of combining several reaction steps in one pot, thus avoiding additional intermediate separation and purification steps. As highlighted in section 3 and 4, however, neither approach represents an ideal case of a green process; in particular the use hydrogen gas, which presents an explosion hazard, is problematic. It should also be noted that this limits the chances of implementing these processes in industry. Nevertheless, improvements have been reported using catalytic processes, and further developing more suitable catalysts could be a pathway to not only increase the sustainability but also the applicability of these approaches. Some relevant examples are shown in the following paragraph.

It is noteworthy that in certain studies it was still possible to obtain unusually high catechol yields. They report reductive catalytic depolymerization approaches performed under conditions similar to the hydrotreatment methods reviewed in section 4. Onwudili and Williams¹⁶⁹ found that the presence of formic acid during the catalytic depolymerization of lignin over Pd/C strongly enhanced the demethylation pathway under hydrothermal conditions. The highest catechol yield, *ca.* 18 wt% based on lignin, was obtained without the Pd catalyst but with formic acid after 6 hours at 265 °C and 65 bar.¹⁶⁹ In other studies, not catechol but substituted C9 catechol derivatives could be obtained as primary products. Probably the highest yield of any catechol derivative from lignin was reported by Barta *et al.*,¹⁷⁰ who conducted the demethylation of candlenut shell-derived organosolv lignin over a Cu-based catalyst. After 20 hours at 140 °C a total yield of 64% (four different C9 catechol species) was obtained. After purification, a 43% yield of 4-(3-hydroxypropyl)-catechol could be obtained.¹⁷⁰ Another very interesting study was published recently that reported propylcatechol and propenylcatechol as the main products. The approach is based on the reductive catalytic fractionation of C-lignin over a Ni catalyst, which was conducted in a flow setup.¹⁷¹

5.3. Selective lignin demethylation

Besides the examples in the previous subsection that more or less deliberately make use of demethylation as one of the key reactions during depolymerization, a number of studies are reported that focus on demethylation reaction specifically. Furthermore, overviews of different lignin demethylation and defunctionalization methods were included in several recent review articles.^{11,172,173} It should be noted that in most cases reactions were carried out under inert gas to prevent side reactions.

Several studies were published using aqueous HBr or HI for aryl methyl ether cleavage of lignin samples. Wang *et al.*¹⁴⁷ used aqueous HBr and HI for the demethylation of alkali lignin at 130 °C. They obtained increases in the content of phenolic hydroxyl groups of 20–30%. The demethylation efficiency was slightly higher with HI compared with HBr.¹⁴⁷ Aqueous HBr was also used in a study by Gao *et al.*¹⁷⁴ in combination with microwave irradiation. After 2 hours at 90 °C the phenolic hydroxyl content of the lignin sample doubled, which made it suitable for polymer applications.¹⁷⁴ Variations of this method were reported recently relying on acidic concentrated lithium bromide, *i.e.* HBr/LiBr, with a reported increase in phenolic OH of up to nearly 100%.^{175,176}

Chai *et al.*¹⁷⁷ applied different acid-based approaches discussed earlier to demethylate lignin. In particular, they used either HBr, BBr₃ or AlCl₃ as the demethylating agent at 115 °C in dimethyl formamide. BBr₃ and AlCl₃ proved to be considerably more active for demethylation than HBr, which was found to primarily result in depolymerization of the alkaline lignin. The phenol hydroxyl content could be increased by 80 (BBr₃) and 172% (AlCl₃) after 4 h. While using BBr₃ also led to significant depolymerization, selectivity for demethylation was much higher with AlCl₃, so that 75% of β-O-4 linkages could be retained. Moreover, it was shown that especially the reaction time is a crucial parameter of the demethylation reaction.

Song *et al.*¹⁵⁹ applied the approach using iodocyclopropane in dimethyl formamide, which was described in section 2.4, to lignin. After 3 hours at 145 °C the phenolic hydroxyl group content more than tripled while at the same time the amount of methoxy groups decreased by 80%.¹⁵⁹ Moreover, the thiolate-based demethylation method (section 2.6) can be used for lignin as well. The hydroxyl group content increased and methoxy group content decreased by *ca.* 30–40% when Kraft lignin was subjected to dodecanethiol and sodium methoxide in dimethyl formamide at 130 °C for 1 hour.¹⁷⁸

A highly interesting study was conducted by Sawamura *et al.*,¹⁷⁹ who compared three different methods, namely thiol-based, iodocyclohexane-based and HI-based demethylation, each under typical reaction conditions. In all cases not only demethylation but also cleavage of other linkages was observed. The iodine-containing reagents showed higher degrees of demethylation than the thiol, and in the case of iodocyclohexane recondensation of fragments was observed, which led to the conclusion that demethylation with iodocyclohexane is most promising.¹⁷⁹

In a later study, Kim *et al.*¹⁸⁰ applied Sawamura's approach to milled wood lignin and used iodocyclohexane in dimethyl formamide as demethylation agent at 100 °C. After 24 h the content of phenolic OH increased from 1.02 to 2.98 mmol g⁻¹, indicating a high degree of demethylation, which was confirmed by 2D NMR, even though also a contribution from other aryl-ether bond cleavages is likely. Interestingly, in the study a subsequent depolymerization step by catalytic hydrogenolysis over Ru/C at 300 °C was conducted with the demethylated lignin. This allowed for a high selectivity of catechol-type compounds in the oil fraction (up to 80%). However, the



higher content of phenolic OH resulted in a *ca.* 30% increase in char formation, indicating a tendency towards undesired condensation reactions.

Relying on the acid- and base-catalyzed aryl methyl ether cleavage reactions, Zhao *et al.*¹⁸¹ investigated the use of protic ionic liquids formed from organic amine bases and organic or mineral acids as reactive solvents for lignin demethylation. In particular, the combination of monoethanolamine and acetic acid resulted in a highly active demethylation agent, which selectively removed 73% of the aromatic methoxy groups after treatment at 90 °C for 2 h. The authors also showed the reusability of the ionic liquid and emphasize the benign reaction conditions.¹⁸¹

Finally, Podschun *et al.*¹⁵⁷ used indium triflate as a Lewis acid for the aqueous-phase demethylation of organosolv lignin. The content of phenolic hydroxyl groups was found to more than double within 3 hours of reaction at 275 °C.¹⁵⁷

In view of the discussion of safety, health and environmental factors presented in the previous sections, it may suffice to summarize here that many of the presented lignin demethylation reactions, while highly efficient, cannot be recommended and should be either considerably improved following green chemistry guidelines or avoided in favor of other suitable methods. Among the successfully applied methods for lignin demethylation, the approach using catalytic amounts of non-harmful Lewis acids in combination with water as the solvents reported by Podschun *et al.*¹⁵⁷ stands out as a reaction coming closest to the case of a “green” reaction.

6. Conclusions

Cleavage of aryl methyl ethers is a reaction not only relevant for syntheses of organic molecules used as pharmaceuticals and pesticides, where phenolic hydroxyl groups often have to be initially protected by methylation. Demethylation has also gained attention in the context of lignin utilization where it is a crucial method to convert guaiacyl units into catechol motifs. Increasing the amount of phenolic hydroxyl groups in this way is a valuable means to tune the lignin properties for adhesion and polymer applications, which will be a crucial step towards the utilization of lignin-based resources and replacing conventional fossil feedstocks. With a focus on the lignin model compounds guaiacol and eugenol, different types of demethylation strategy were reviewed.

The toolbox of organic chemistry offers a variety of different methods for selective aryl methyl ether cleavage. Here, in particular two comparatively recently modified approaches offer high selectivity while requiring comparatively mild reaction conditions. Stabilized 2-iodoxybenzoic acid can be used in an oxidative demethylation approach followed by a reductive work up. This method tolerates *e.g.* substituents with primary hydroxyl groups to a high degree. The second strategy is a variation of the long-known aluminium halide-based method. By applying acid scavengers like carbodiimide, pyridine or dimethyl sulfoxide the AlI₃-mediated demethylation tolerates

e.g. allyl substituents, which are labile *e.g.* under acidic demethylation conditions. Interestingly, these highly selective approaches have not been applied to lignin samples. Other organic chemistry-derived reagents like *e.g.* thiol in combination with base or iodocyclohexane, on the other hand, have recently been successfully applied to lignin as well. It should be pointed out, however, that none of these demethylation methods can be considered “green”. On the contrary, in some cases highly hazardous reactants, *e.g.* BBr₃ or IBX, or solvents, *e.g.* dimethyl formamide or linear alkanes, are required. Thus, none of the reactions can be recommended without reservation.

Acid-catalyzed demethylation in an aqueous medium is a very popular demethylation approach during organic syntheses as well as for lignin modification since no elaborate reagents are needed. Unfortunately, it requires high temperatures and strong mineral acids, which can lead to severe corrosion and the environmental, health and safety hazards associated with it. Furthermore, demethylation under these conditions often suffers from the occurrence of side reactions. On the other hand, in certain cases this means that demethylation can be combined with dealkylation (as one example with eugenol showed) or accompany general lignin depolymerization. Similar selectivity challenges, often resulting in the formation of tar-like side products, also accompany base-catalyzed as well as sub- and supercritical water-based demethylation strategies when applied to pure chemicals like guaiacol. On the other hand, examples of lignin depolymerization show that these latter methods often yield catechol and its derivatives in high yields. For further development, the arguably most promising studies report the use of recyclable solid catalysts in aqueous solution. Considering safety, health and environmental aspects, these reactions are closest to a “green” demethylation procedure among the presented methods.

Finally, the heterogeneously catalyzed hydrotreatment of guaiacol and eugenol typically includes demethylation as one of the earliest reaction steps. In the case of eugenol, over most catalysts the allyl functionality is almost immediately hydrogenated followed by demethylation or demethoxylation. Here, the difficulty is to achieve sufficient selectivity for the demethylated product since competing demethoxylation as well as subsequent dehydroxylation can occur. While most hydrotreatment studies target highly deoxygenated and hydrogenated products up to cyclohexanes, the recent research focus has shifted more towards phenolic products. Catechol and its derivatives, however, have so far not been directly targeted by this approach, which is also evident from the reaction conditions in most studies, which are too harsh to effectively suppress the aforementioned side and follow-up reactions. Hydrotreatment is also relevant from the viewpoint of reductive catalytic lignin depolymerization, where in certain cases surprisingly large amounts of catechol could be obtained. While the true potential of the hydrotreatment approach is currently difficult to assess and remains to be unlocked by purposeful catalyst and process development, it must be pointed out that the industrial applicability will strongly depend on ways to



mitigate the explosion hazard associated with hydrogen gas. Nevertheless, in terms of waste production and material balance the catalytic approaches are preferable from an environmental point of view and should not be disregarded *per se*.

In the overall picture, aryl methyl ether cleavage is a highly important reaction that draws attention from two opposite poles: on the one hand, fine chemical synthesis relies on highly selective demethylation methods while, on the other hand, lignin depolymerization and (de)functionalization more or less deliberately makes use of demethylation. Therefore, it is probably not too far-fetched to expect that selective lignin demethylation could greatly benefit from applying promising demethylation methods from a more organic chemistry background also to lignin. As described in section 5.2., a limited number of studies already pioneered this approach. In turn, the efficient conversion of lignin biomass into catechol and its derivatives has the potential to offer this renewable feedstock for a wide range of applications.

Conflicts of interest

There are no conflicts to declare.

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