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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 deprotection 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 hydrotreatment 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 amount of phenolic hydroxyl groups, which is desirable for adhesion[11,12] or polymer applications.[12,13]

Several strategies and methods have been developed to selectively cleave aryl ethers, which are the subject of comprehensive review articles from the field of organic chemistry.[14–16] In this context, the methylation of phenolic hydroxyl groups is a common strategy to protect this functional group, which then requires efficient demethylation procedures for subsequent deprotection. A common finding is that in particular aryl methyl ether bonds, which are present *e.g.* in guaiacol, anisole or eugenol, are highly stable.[17,18] This makes their cleavage inherently challenging, especially when other functional groups need to be preserved.

This literature review aims at providing a comprehensive overview over a broad range of demethylation methods for aryl methyl ethers. It is divided into three main sections representing different classes of demethylation approach, which will be assessed regarding their previous usage for different demethylation applications, their strengths and weaknesses as well as aspects of green chemistry. The first section comprises different methods originating mostly from the field of organic chemistry that are commonly used for the production of pharmaceuticals and fine chemicals as well as in the total syntheses of complex molecules. The use of stoichiometric amounts of reactants is characteristic, as is typically high selectivity. These methods are mostly harmful to the environment and use chemicals that are harmful to health, so there is an urgent need to find alternative, more environmentally friendly methods. In this context, new developments regarding AlI_3-based demethylation methods were reported in recent years. The second section includes comparatively simple, aqueous-phase methods based on either hydrolysis or acid-catalyzed demethylation. This includes studies under supercritical conditions as well as the utilization of different mineral acids and Lewis acids. The third section discusses demethylation under hydrotreatment conditions. Both non-catalytic as well as transition metal-catalyzed approaches are presented. Metal-catalyzed reactions are the most environmentally friendly of all, as they usually occur under milder reaction conditions and the catalyst can be easily recycled and reused. In terms of substrates, the first three sections of this review article are limited to the common lignin model compounds guaiacol, eugenol and similar functionalized guaiacols. Furthermore, biotechnological demethylation approaches[19–24] are not considered. Eventually, in the final section the application of different methods from all the previous categories to lignin samples is discussed. Here, the focus moves away from the model compound-based discussion and the issue of product selectivity to the broader aspect of lignin defunctionalization and modification by demethylation.

2. Stoichiometric approaches in organic solvents

In this section different, demethylation methods that have emerged from the field of organic chemistry are presented, with a focus on guaiacol and substituted 1-hydroxy-2-methoxybenzene compounds. Approaches discussed here have in common that they are conducted in organic solvents and require stoichiometric or excess amounts of reactants. The most common methods are based on Lewis acids (BBr_3, AlX_3), oxidizing agents (often iodine-containing) or nucleophiles. Almost all approaches presented show good to excellent product yield and high tolerance towards other functional groups. Among them, however, AlI_3-based approaches with acid scavengers (section 2.2.2.) and a method using 2-iodoxybenzoic acid as oxidizing agent followed by hydrolysis and mild reduction (section 2.5.1.) appear especially promising. Moreover, safety, health and environmental aspects are discussed qualitatively, primarily based on the classification of the chemicals used in each method using safety data sheet information.

2.1. Boron-based Lewis acids

2.1.1. Boron tribromide. Using the Lewis acid BBr_3 in organic solvents for the cleavage of ethers goes back to a study by Benton and Dillon.[25] Later, the method was also applied to aryl methyl ethers.[26] The main advantages of BBr_3 demethylation are that the reaction takes place under mild conditions (room temperature or below) and no corrosive Brønsted acids or bases are required. Furthermore, it is highly selective and tolerates several other functional groups like ester groups and double bonds.[15]

One recent example for a BBr_3 demethylation of a guaiacol derivative is that reported in ref. 27. 2-Bromo-6-methoxyphenol was dissolved in anhydrous dichloromethane and 1 equivalent of BBr_3 was added slowly at 0 °C. The mixture was stirred overnight at room temperature before 10% aqueous $NaHCO_3$ was added. After extraction and purification, a 98% yield of 3-bromobenzen-1,2-diol was obtained.[27]

In a study by Bovicelli *et al.*,[28] BBr_3 was used for the demethylation of homovanillyl alcohol (4-(2-hydroxyethyl)-2-methoxyphenol; (1)), which has a hydroxyethyl substituent (Fig. 1). The primary alcohol (as well as the phenol-OH) had to be acetylated prior to the demethylation to avoid undesired bromination. During the reaction with BBr_3, which was conducted in dichloromethane at −20 °C, both demethylation and deacetylation of the hydroxybenzene groups take place. With 1.5 eq. BBr_3, hydroxytyrosyl acetate (3) was obtained in yields of 80% after 2.5 hours of reaction.

In recent years, the mechanism of the ether cleavage reaction with BBr_3 has attracted research attention. Both a uni- and a bimolecular mechanism were discussed,[29,30] which is beyond the scope of this review article. DFT calculations showed that one 1 eq. of BBr_3 can demethylate 3 eq. of methyl aryl ethers.[30] In typical experimental procedures, however, excess amounts are used.

The BBr_3 method can be modified *e.g.* by using the $BBr_3{\cdot}S(CH_3)_2$ 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

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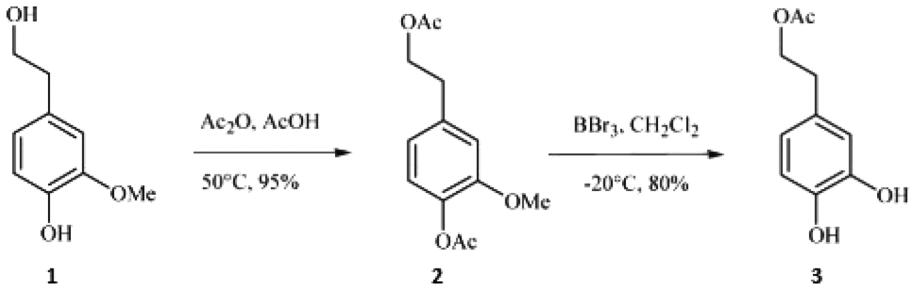

Fig. 1 Reaction sequence consisting of protection of the primary aliphatic alcohol by acetylation followed by aryl methyl cleavage with Lewis acid BBr_3.[28]

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.

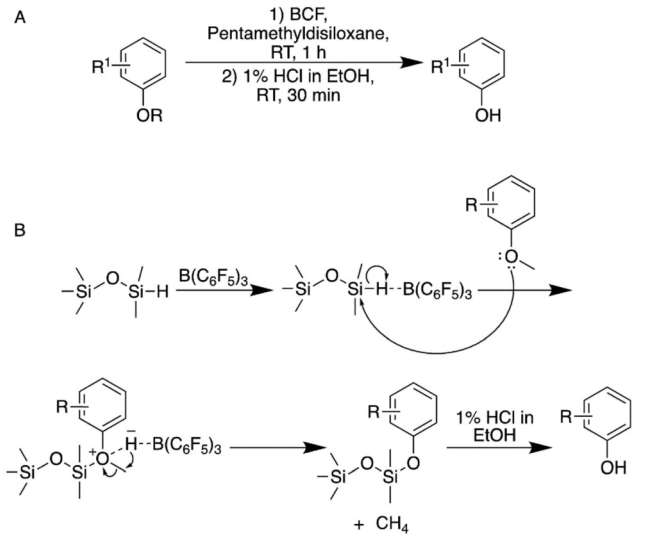

Fig. 2 (A) Two-step demethylation approach *via* the Piers–Rubinsztajn reaction using tris(pentafluorophenyl)boran (BCF). (B) Mechanism of the Piers–Rubinsztajn demethylation reaction.[33]

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 nonpolar 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

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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 Babu[38] 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-Dimethoxylbenzene 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 Al_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 hydroxychchavicol (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

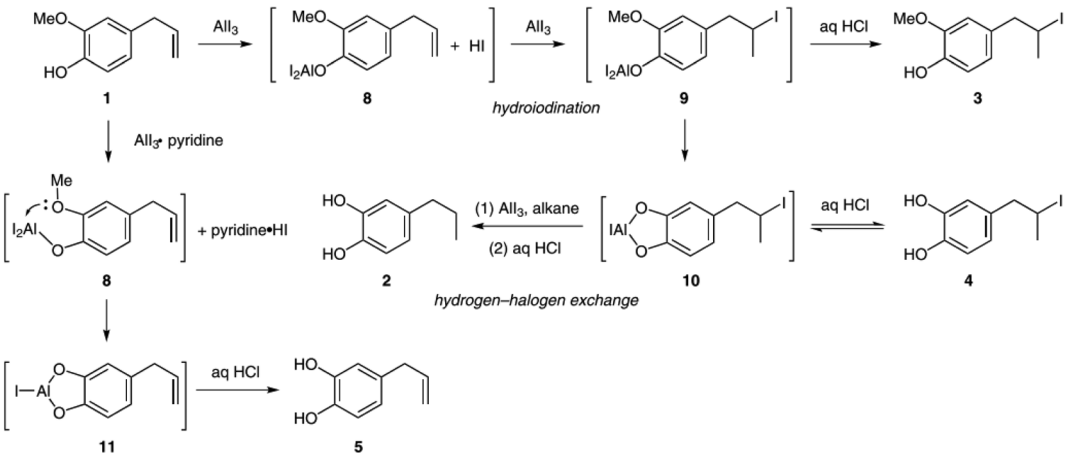

Fig. 3 Mechanistic explanation of hydrogenation observed during the demethylation of eugenol with AlI_3. The presence of the acid scavenger pyridine prevents the initial hydroiodination step, which results in the preservation of the allyl group.[41]

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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 the 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 study[53] 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-

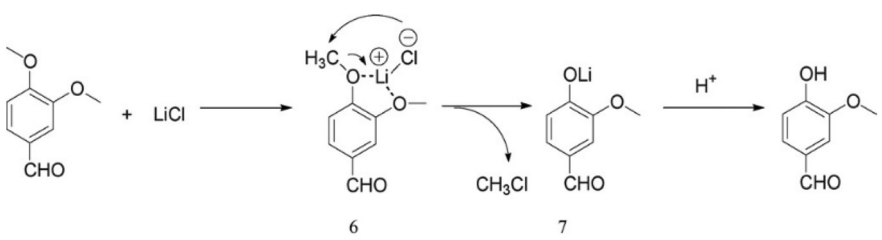

Fig. 4 Cleavage of aryl methyl ethers with LiCl; the reaction mechanism proposed by Fang *et al.*[47]

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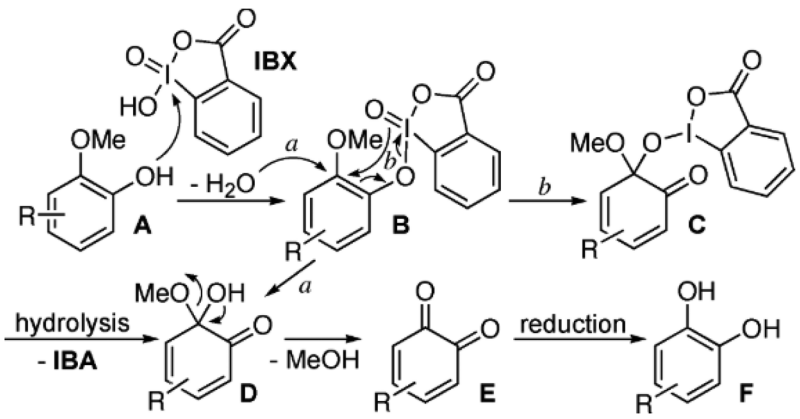

Fig. 5 Mechanism proposed by Ozanne *et al.*[52] explaining the oxidative demethylation with 2-iodoxybenzoic acid (IBX), including subsequent hydrolysis and reductive work-up.

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 ethanethiolate) 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 iodide[18] 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

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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 methyltrioctylammonium 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 N_2 to H_2 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 H_2 atmosphere are beneficial. At optimum conditions (10 bar H_2, pH = 1.8, 280 °C) almost complete guaiacol conversion and an 89% yield of catechol were reported. The presence of H_2 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 N_2 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

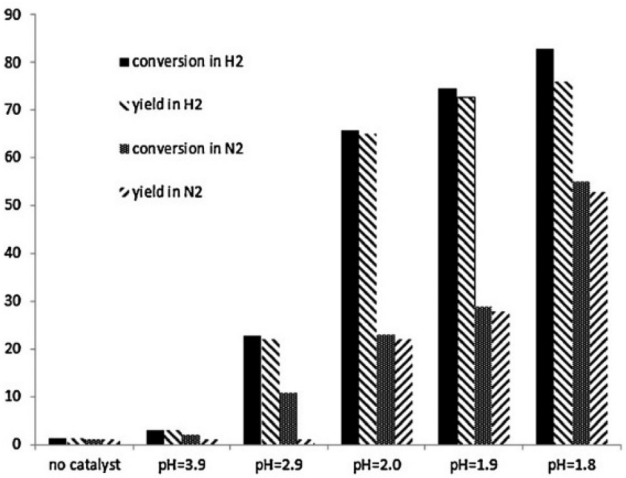

Fig. 6 Demethylation of guaiacol at 280 °C in aqueous HCl at different pH values. Both conversion of guaiacol and catechol yield after 3 hours are shown. Reactions were conducted either under a N_2 or H_2 atmosphere. Reproduced from ref. 72 with permission from Elsevier, copyright 2013.

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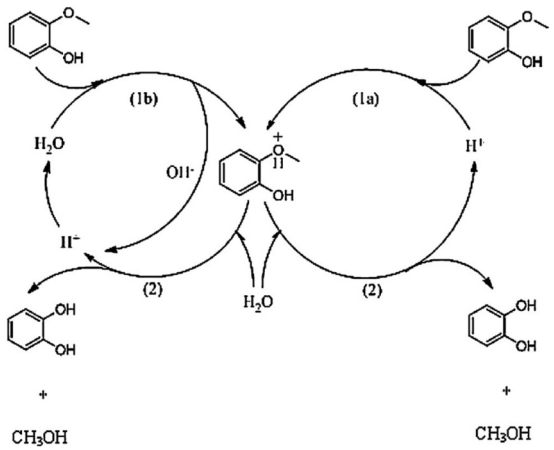

Fig. 7 Competing water-catalyzed (left) and acid-catalyzed (right) mechanism of guaiacol demethylation in aqueous HCl proposed by Yang *et al.*[72] The acid-catalyzed mechanism was suggested to dominate at a sufficiently low pH (<3.9).

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 vial 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 H_2SO_4, however requiring a higher concentration. H_3PO_4 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 H_2SO_4, while highly corrosive, are due to their elemental composition less toxic and less environmentally harmful. The discussed variation of the process under H_2 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: $In(OTf)_3$, $Sc(OTf)_3$, $InCl_3$ and $Yb(OTf)_3$.

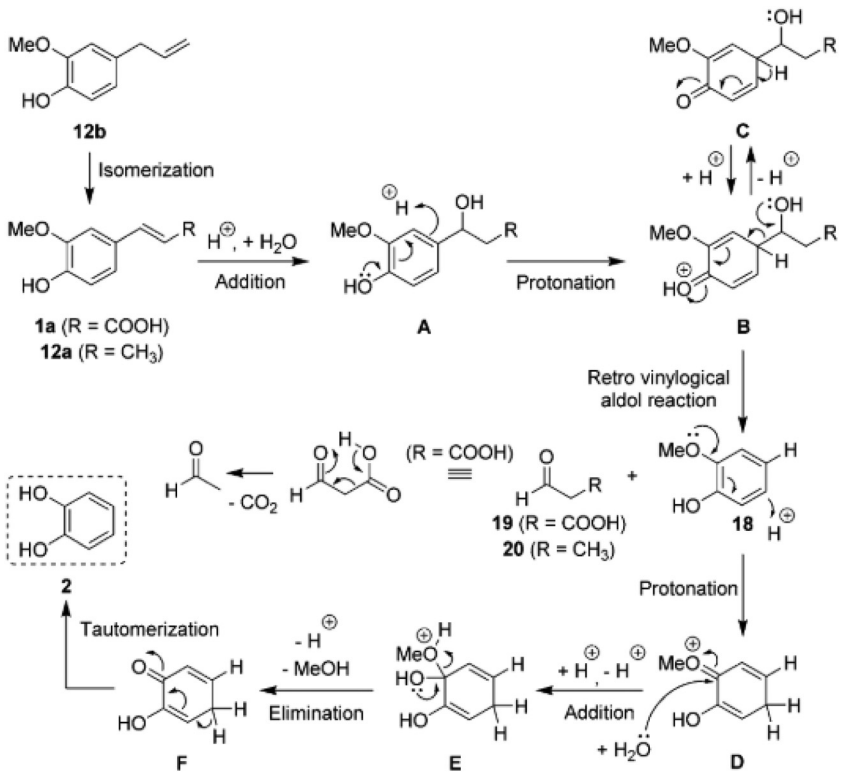

Fig. 8 Mechanistic view of a sequence of acid-catalyzed reactions proposed by Bomon *et al.*[73] for allyl- and vinyl-substituted guaiacol derivatives. For example, eugenol (12b) undergoes isomerization, dealkylation and demethylation resulting in the formation of catechol.

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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 In $(OTf)_3$ after 2.75 hours. A comparison with HCl-catalyzed demethylation showed that the activity was higher over In $(OTf)_3$.[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 $In(OTf)_3$ and $Sc(OTf)_3$ 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-

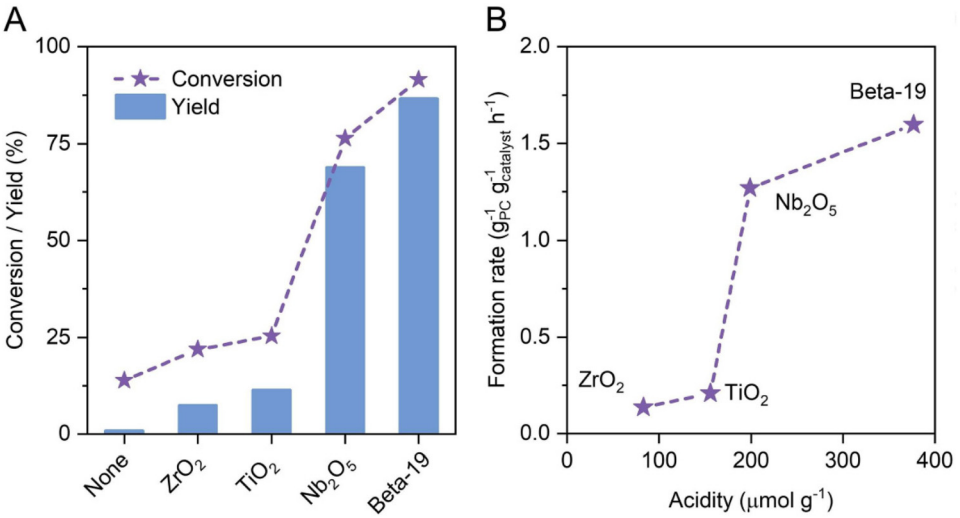

Fig. 9 Conversion of 4-propylguaiacol and yield of 4-propylcatechol over different solid acid catalysts after 2 h at 260 °C in water (A). Catalytic activity (given as the product formation rate) plotted against catalyst acidity (B). Reproduced from ref. 75 with permission from John Wiley and Sons, copyright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

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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, $CaCl_2$, $FeCl_3$) 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 catalyzed reaction is preferable, as it enables a sufficiently high reusability 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

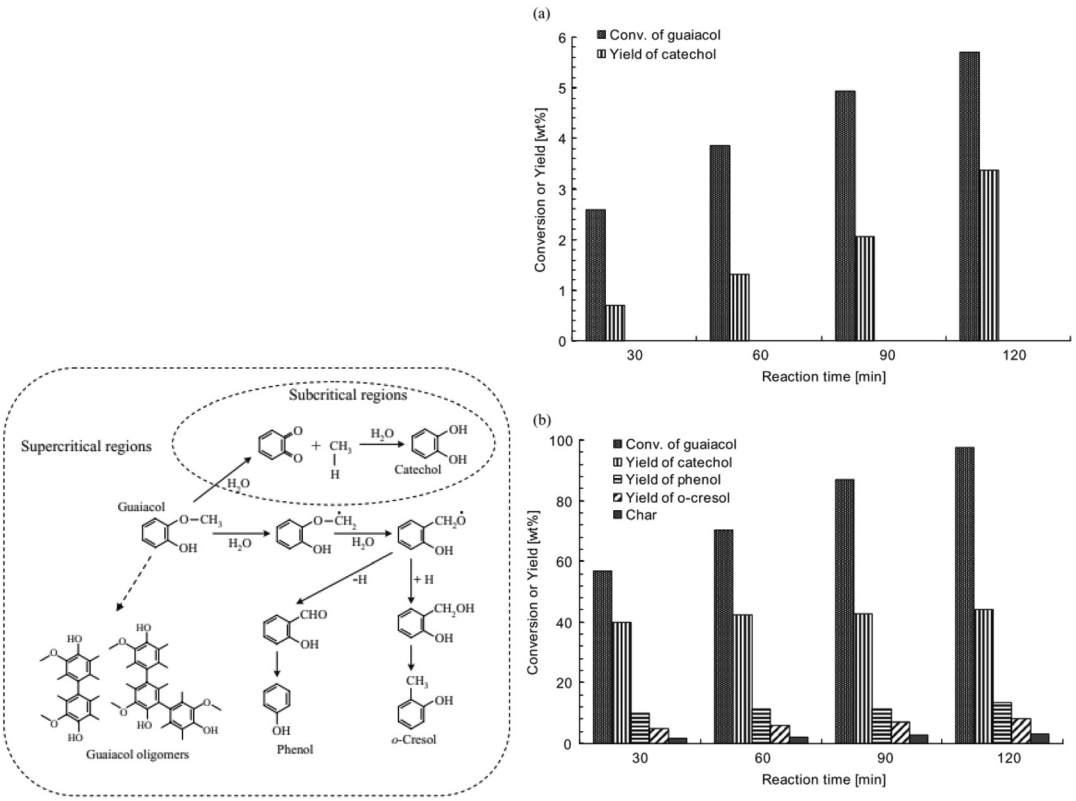

Fig. 10 Left: probable reaction pathways for guaiacol decomposition to achieve the desired products; Right: yields of guaiacol decomposition products in sub- and supercritical water as a function of reaction time, 400 °C and 400 bar.[82]

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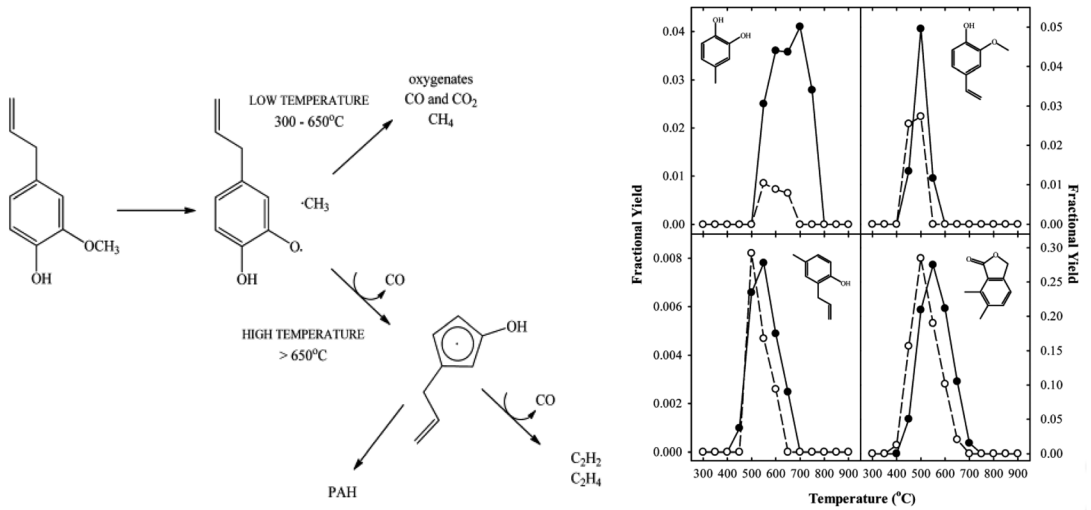

Fig. 11 Left: general reaction scheme for the vapor-phase cracking of eugenol; right: fractional yields of 2,3-dihydrobenzofuran, 2-coumaranone, 3-methyl-1,2-benzenediol, and 4-(2-propenyl)-phenol (clockwise from top left) as functions of the temperature at (●) τ = 1 s and (○) τ = 3 s.[83]

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 H_2 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, SiO_2, TiO_2, MgO, Al_2O_3, ZrO_2, $CaCO_3$, 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 facilely. 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 H_2 gas at elevated pressure presents a severe harm potential that also may limit the applicability in industry. Significantly lowering the required H_2 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

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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 H_2, Al_2O_3 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 H_2. 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 H_2. 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 H_2 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 SiO_2) 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 H_2 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 H_2/N_2 (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/Al_2O_3 was used as a catalyst. In the absence of acidic sites, catechol is expected to be formed over Pt/MgO, primarily

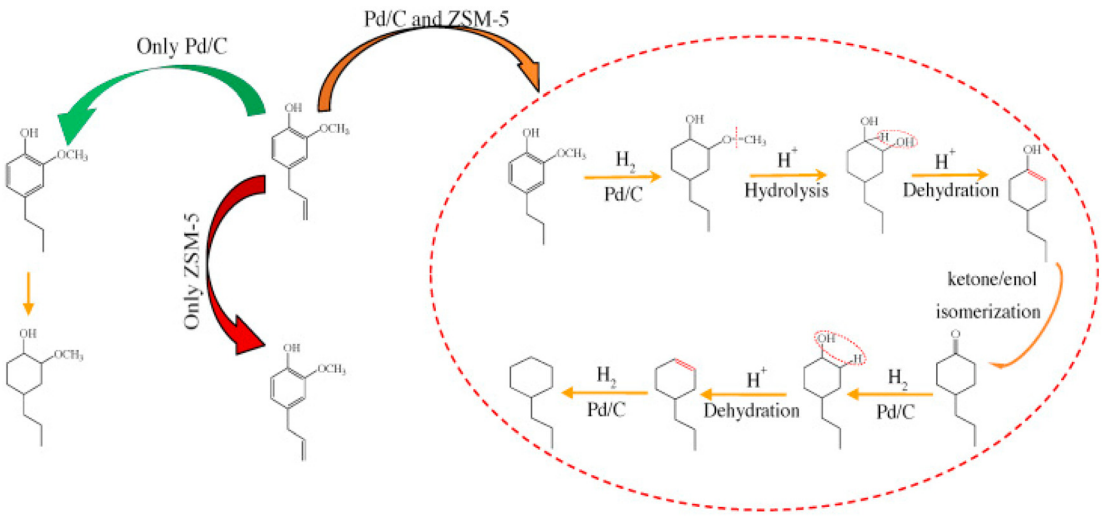

Fig. 12 Reaction pathways of eugenol to cyclohexanes over Pd/C and HZSM-5 in the aqueous phase.[89]

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by hydrogenolysis on the Pt, with methane as a co-product.[96] Guaiacol was hydrotreated in the presence of Pt/HZSM-5 catalysts with different crystallite sizes. The reactions were performed in dodecane at 250 °C with 40 bar of hydrogen; within 120 min the guaiacol conversion reached near 100% in all cases, but no catechol was formed, except in minor concentrations (0.25 wt%) in the presence of Pt/NS-2 catalyst.[97] When using a flow reactor with Pt/γ-Al_2O_3 catalyst, and HDO performed at 300 °C in the presence of H_2 (1.4 bar), the major products from guaiacol conversion were phenol, catechol and 3-methylcatechol. The study by Runnebaum *et al.* showed that the higher reaction temperature did not influence the formation of catechol, while the higher H_2 pressure decreased the catechol selectivity.[98]

When alumina-supported Pt catalyst was doped with different loadings of Nb_2O_5 the HDO activity increased and yielded more deoxygenated products. However, at a low hydrogen concentration (H_2 : guaiacol = 1 mol/mol) the selectivity towards catechol was very high (80%), but the conversion remained low (15%). These experiments were performed in a continuous flow reactor.[99]

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] $CaCO_3$-supported Ru even surpassed the HDO activity compared with ZrO_2- or MgO-supported Ru catalysts. The aromatic ring was saturated and complete deoxygenation was reached.[103] Ru/HZSM-5 was used for the HDO of guaiacol in an aqueous environment at moderate reaction conditions (240 °C with 2 bar H_2). The reaction pathway with guaiacol is presented in Fig. 13. In the presence of H_2 Ru-catalyzed guaiacol conversion in aqueous phase proceeds along 4 different pathways: (1) hydrogenation to 2-methoxy-1-cyclohexanol, (2) hydrogenolysis of the C–O bond at position b to phenol and methanol with further deoxygenation to benzene, (3) hydrogenolysis of C–O bond at position c to catechol and (4) hydrogenolysis of C–O bond at position a to produce anisole. The results showed that the C–O bond cleavage at position b (to form phenol) was the primary and major step, with a selectivity of 85% at 120 min. The highest yield of catechol (40%) was reached in a solvent-free system at 240 °C with 2 bar of H_2 and 6 bar of N_2 in a batch system. A slightly lower yield of catechol (35%) was obtained in a fixed bed reactor under similar reaction conditions.[104] When carbon black-supported Ru–MnO_x/C catalyst was used, guaiacol was demethoxylated and then hydrogenated, forming cyclohexanol and methanol under relatively mild reaction conditions (160 °C and 15 bar H_2). A lower H_2 pressure and higher reaction temperature were advantageous to demethoxylation. The addition of MnO_x species slowed down the reaction rate of total hydrogenation of the aromatic ring, which increased the relative rate of the elimination of methoxy groups to that of total hydrogenation before the elimination.[105]

Alumina-supported Ru was tested in a H_2-free reaction system for the HDO of guaiacol, using a hydrogen donor

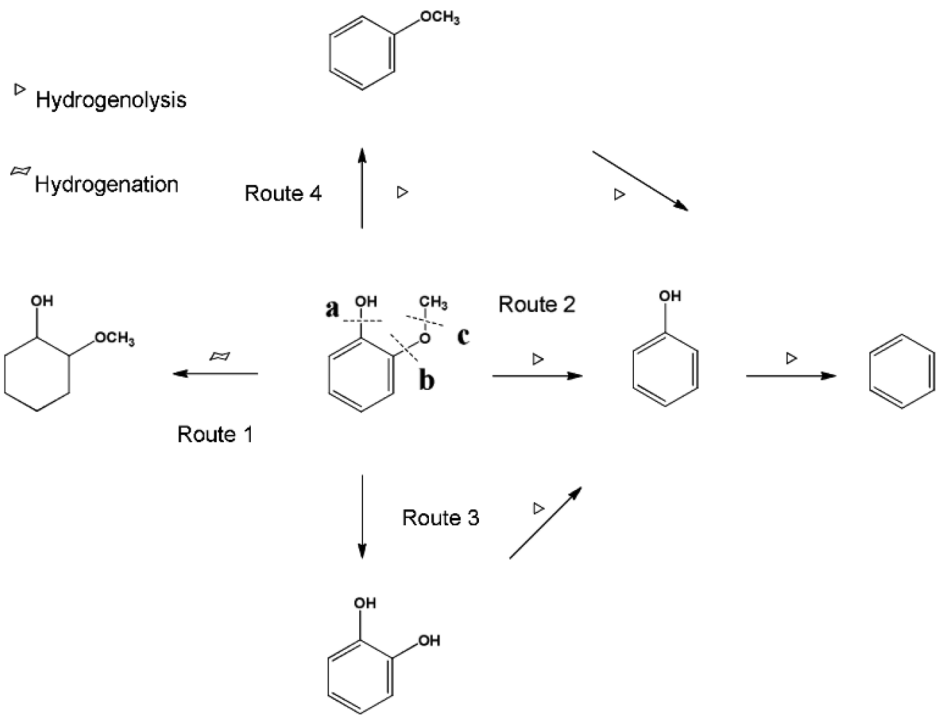

Fig. 13 The plausible reaction pathways for guaiacol conversion with metal/acid bifunctional catalysts in the aqueous phase. Reproduced from ref. 104 with permission from the Royal Society of Chemistry, copyright 2016.

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solvent (iso-propyl alcohol). In the catalytic transfer hydrogenation firstly 2-metoxycyclohexanol was formed from guaiacol, which was further hydrodeoxygenated to cyclohexanol. Without the external source of hydrogen, there was a sufficient amount of *in situ*-formed hydrogen to saturate the aromatic ring first, even before the further hydrodeoxygenation of oxygen-containing functional groups (–OH, –O–CH_3).[106]

Lee *et al.*[107] tested different supported noble metals (Pt, Rh, Pd, Ru on Al_2O_3, SiO_2–Al_2O_3 and NAC) for the HDO of guaiacol in *n*-decane under 40 bar of H_2 at 250 °C. All the tested metals were highly active for HDO to the final completely or partially deoxygenated products (cyclohexane, cyclohexanol, cyclohexanone and 2-metoxycyclohexanol). Among the products catechol was not detected, and thus rather the demethylation demethoxylation proceeded under the selected reaction conditions.[107]

A combination of supported noble and transition metals was screened for guaiacol, eugenol and isoeugenol HDO in hexadecane or dodecane as solvents under high hydrogen pressure (30 to 50 bar) at elevated temperatures (200–350 °C). As expected, hydrogenation of the aromatic ring and propenyl chain was the dominant reaction, and no diol was found among the formed products.[108–115] The comparison between transition metal catalysts (sulfided CoMo and NiMo) and noble metals (Rh, PtRh and PdRh) supported on ZrO_2 showed that the latter (Rh) has higher HDO activity than CoMo or NiMo. However, the addition of Pt and Pd had no positive effect. The temperature and H_2 pressure were supposed to be too high to allow the formation of catechol.[116]

Afifi *et al.*[87] investigated the effect of homogeneous catalysis, Fe and Ru ($FeCl_3$, $RuCl_3$), on the conversion of guaiacol in tetralin as the hydrogen donor solvent to catechol. In the absence of catalyst and at low ratios of guaiacol to tetralin, the primary product is catechol; however, the yield of a secondary product phenol is increased with both Fe and Ru. The yield of catechol reached up to 55% with $FeCl_3$ at 400 °C in the presence of hydrogen in addition to the hydrogen donor solvent (tetralin).[87]

4.2. Transition metals (supported Ni, Mo, Co, Re, Cu)

Transition metals offer a larger potential for the selective demethylation of eugenol or guaiacol, since they have lower hydrogenation activity. Moreover, supported Ni, Mo and Co are widely used in the chemical industry for hydrodeoxygenation and hydrodesulphurization reactions where oxygen and sulphur species are removed, respectively.

A series of cobalt-based catalysts with different supports were prepared and used to catalyze lignin-derived phenols to cyclohexanols. Among the catalysts, TiO_2-supported Co showed the highest HDO activity under 10 bar of hydrogen at 200 °C. In the first step, a complete –O-CH_3 group was removed, followed by saturation of the aromatic ring. All the Co-based catalysts selected in the study by Liu *et al.*[117] showed high activity to cleave the C_{aryl}–OCH_3 bond before the hydrogenation of the aromatic ring. Similar deoxygenation activity was obtained with an activated carbon-supported α-molybdenum carbide catalyst (α-MoC_{1-x}/AC). The reaction was performed in supercritical ethanol at 340 °C. 87% conversion of guaiacol was reached with 85% selectivity for phenol and alkylphenols. The solvent selection (methanol, isopropanol, tetralin, *n*-hexane, water, ethanol) showed the best performance between 280 and 340 °C, where the reaction took place *via* demethylation followed by deoxygenation and transalkylation. Catechol, which was not detected in the products with organic solvents, was formed with a selectivity of 94% in water.[118]

ZrO_2-supported Ni and Ir both showed a high activity towards the hydrodeoxygenation of isoeugenol, guaiacol and vanillin under high H_2 pressure (30 bar). Ni metal was active in hydrogenation of the phenyl ring, but at the same time exhibited lower HDO activity; however, no diol products were detected.[119] Supported Ni catalysts showed high activity for the hydrogenation and hydrogenolysis of eugenol, but again no diol products were detected.[120–123] Surprisingly the catechol was obtained in a catalytic hydrotreating over nickel catalyst supported on red mud with a selectivity of 5.3% at 300 °C and with 50% conversion. The selectivity decreases with increased temperature and hydrogen pressure. With commercial Ni/SiO_2–Al_2O_3 catalyst the obtained catechol selectivity reached 8.1% (Fig. 14).[124]

When performing the HDO of guaiacol over nickel phosphide (Ni_2P) supported on ZSM-5 zeolite in acetic acid as solvent, surprisingly the obtained selectivity of catechol reached 30%. While the H_2 pressure did not have an influence in the range of 10–30 bar, the increased reaction temperature (from 260 to 300 °C) significantly improved the catechol yield. Interestingly, the possibility of using carboxylic acids as a source of hydrogen, for the deoxygenation of guaiacol, is a potentially attractive route for the upgrading of bio-oils.[125] Ni_2P supported on SiO_2 revealed that direct demethoxylation and dehydroxylation are major reaction pathways in guaiacol HDO, producing phenol and anisole as intermediates. Demethylation of guaiacol is of minor importance because only small amounts of catechol form even at very low contact times.[126] Wu *et al.*[127] tested different silica-supported Ni/P ratios (1–3) for the HDO of guaiacol, performed in a fixed-bed reactor at 300 °C with a continuous flow composed of an 80% H_2/N_2 stream at atmospheric pressure. The most favorable ratio of Ni/P for the formation of catechol was 2. The major influence was shown to be the weight hourly space velocity (WHSV); the highest WHSV gave the highest catechol yield. The highest yield of catechol (27.1%) was reached with Ni/P = 2 at 10.68 h^{-1} WHSV.[127] Moreover, alumina and zirconia were tested as supports of Ni_2P catalysts under the same reaction conditions. The catechol yield significantly increased. At 5.34 h^{-1} WHSV reached 67.7% over a ZrO_2-supported catalyst, while a SiO_2-supported catalyst yielded 46.7% of catechol at 2.67 h^{-1} WHSV. However, the high selectivity towards catechol was connected to the low conversion of guaiacol.[128] HDO activity of the transition metal phosphides was tested on guaiacol as a model compound. At a lower contact time using Co_2P/SiO_2 and WP/SiO_2 catalysts there was 99% and 88% of catechol formed (at 35 and 12% conversion, respectively), respectively.

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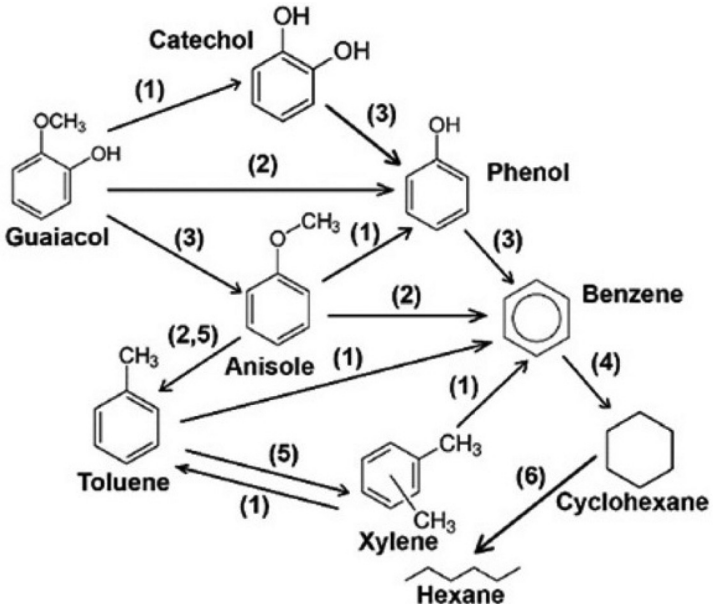

Fig. 14 Reaction network of guaiacol HDO over Ni-based catalysts. 1: demethylation, 2: demethoxylation, 3: dehydroxylation, 4: hydrogenation, 5: transalkylation, 6: ring opening. Reproduced from ref. 124 with permission from Elsevier, copyright 2018.

With a commercial Pd/Al_2O_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 300–500 °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 280–320 °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 ReS_2/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-

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duction from phenol, while this was inhibited on the Co-containing catalysts. However, the major products were phenol and cyclohexanol.[141] The demethylation of guaiacol was studied in the presence of alumina-supported NiMo and CoMo catalysts. It was found that selective demethylation occurs for a large part on the Lewis acid–base sites of the alumina support. The addition of hydrogen sulphide or water does not inhibit the demethylation, while the reaction is inhibited by the addition of a strong base as ammonia. The alumina support alone had a non-negligible activity for the conversion of guaiacol but only catechol was produced in low quantity. At 50% of guaiacol conversion, the ratio between phenol and catechol was 0.4 and 0.15 when no H_2S is added using CoMo and NiMo catalysts, respectively. The addition of H_2S decreased the obtained phenol/catechol ratio.[142] $NiMo/Al_2O_3$ was found to be highly active and selective for the HDO of guaiacol in a fixed bed reactor at 300 °C and 71 bar of H_2, leading to the hydrogenation of the aromatic ring, followed by demethylation and dihydroxylation to the final cyclohexane. Pt/TiO_2 was more stable than alumina-supported catalysts (Ni and Pt). However, no catechol formation was detected, probably due to the excessive amount of hydrogen, used at high pressure.[143] Doping the NiMo catalyst with Cu enhanced the reducibility of the NiMo catalyst, while the addition of Ce at an appropriate quantity induced a higher dispersion of active metals and made it difficult to reduce the catalyst. The addition of Ce could effectively inhibit coke formation during the HDO. 1,2-Benzenediol (catechol) was one of the major products formed in the HDO of guaiacol over all the tested catalysts (NiMo, $NiMo_4Cu$, $NiMo_4Ce$, $NiMo_8Ce$); the product distribution can be seen in Fig. 15.[144] However, Na-doped CoMo catalysts supported on alumina (γ-Al_2O_3) showed decreased activity for the HDO of guaiacol compared with undoped catalyst on supports with different Al/Si ratios.[145]

Jongerius *et al.*[146] focused in their study on the HDO of different aromatic monomers (*o*-cresol, *p*-cresol, anisole, 4-methylanisole, catechol, guaiacol, 4-methylguaiacol, 1,3-dimethoxybenzene, syringol, and vanillin) and dimers (mimicking the β-O-4 bond) using $CoMo/Al_2O_3$ catalyst under 50 bar H_2 pressure, performing the reaction in dodecane at 300 °C. The proposed reaction network showed that HDO, demethylation and hydrogenation took place simultaneously. When guaiacol was used as a reactant, 11% of catechol was formed, but the major product was phenol, proposed to be formed in a demethoxylation reaction. Similarly, 4-methylcatechol was formed in 13% yield from 4-methylguaiachol, with the highest yield of methylphenol (42%) as a demethoxylation product. However, converting a dimer with a β-O-4 bond resulted in many monomeric products, but only 1% of catechol was formed among the diol products.[146]

Pre-reduced NiCu/MCM-41 and NiCu/Ti-MCM-41 catalyst were synthesized and tested for the HDO of guaiacol at 260 °C under 40–100 bar of H_2. 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]

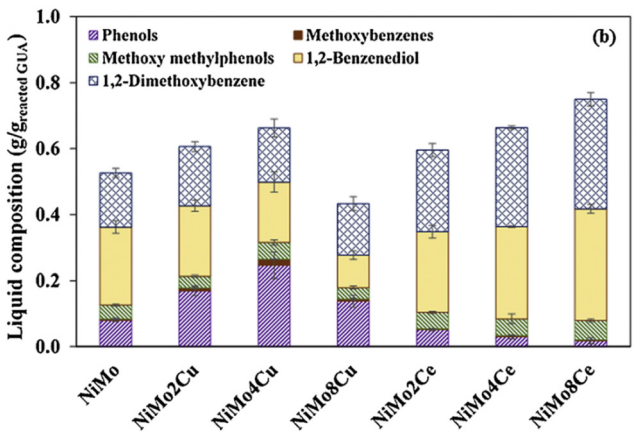

Fig. 15 Effect of the promoter type and content on the liquid compositions obtained from the HDO of GUA (condition: catalyst concentration = 15 wt% based on the GUA content at 10 bar H_2 pressure and 300 °C for 1 h.)[144]

5. Demethylation of lignin

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 adhesion[11] 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.

5.1. Lignin functional groups analysis by NMR spectroscopy

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 ^{1}H–^{13}C HSQC) NMR spectroscopy (Fig. 16).[148–150] The technique of phosphitylation 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]

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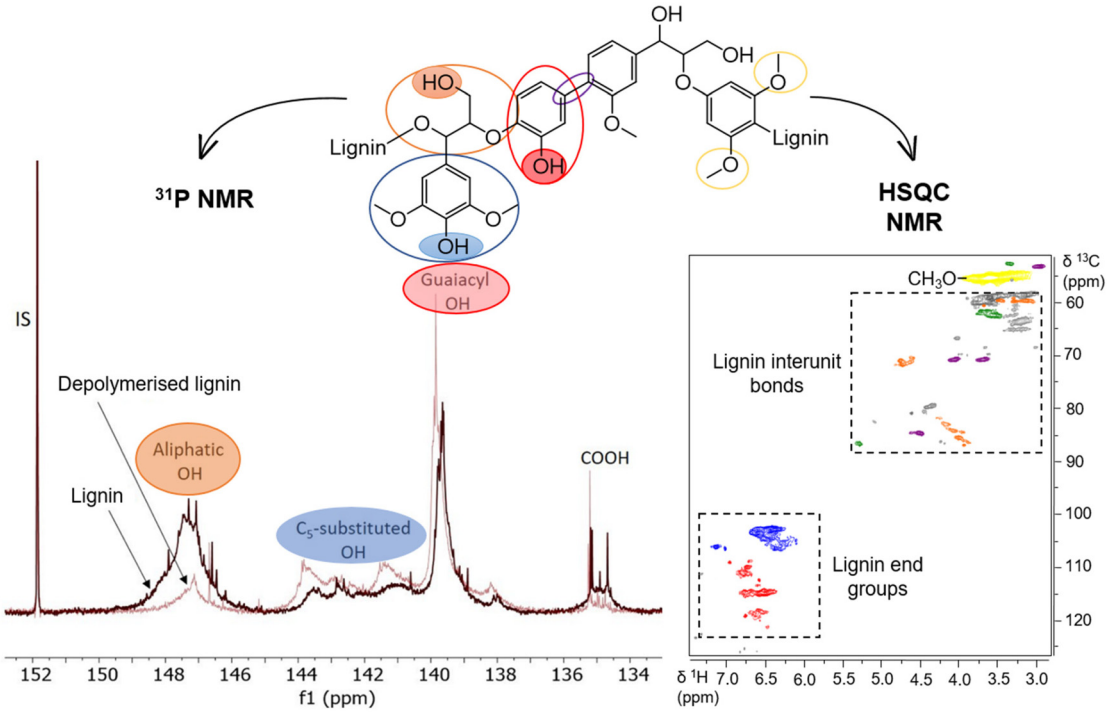

Fig. 16 Representative quantitative ^{31}P NMR spectrum (colored filled ellipses: hydroxyl groups) and semi-quantitative 2D HSQC NMR spectrum (colored ellipses: lignin structural units) of lignin samples.

Critically, one-dimensional NMR spectroscopy (*i.e.*, ^{1}H 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 subunits (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 C9 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 C9 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

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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 obtained unusually high catechol yields. They report reductive catalytic depolymerization approaches performed under conditions similar to the hydrotreatment methods reviewed in section 4. Onwudili and Williams[169] 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, BBr_3 or $AlCl_3$ as the demethylating agent at 115 °C in dimethyl formamide. BBr_3 and $AlCl_3$ 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 (BBr_3) and 172% ($AlCl_3$) after 4 h. While using BBr_3 also led to significant depolymerization, selectivity for demethylation was much higher with $AlCl_3$, 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

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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 AlI_3-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.* BBr_3 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

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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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