Efficient demethylation of aromatic methyl ethers with HCl in water

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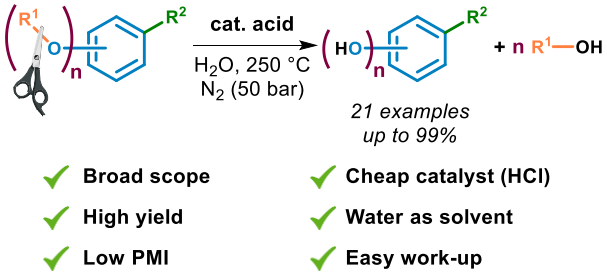
Abstract

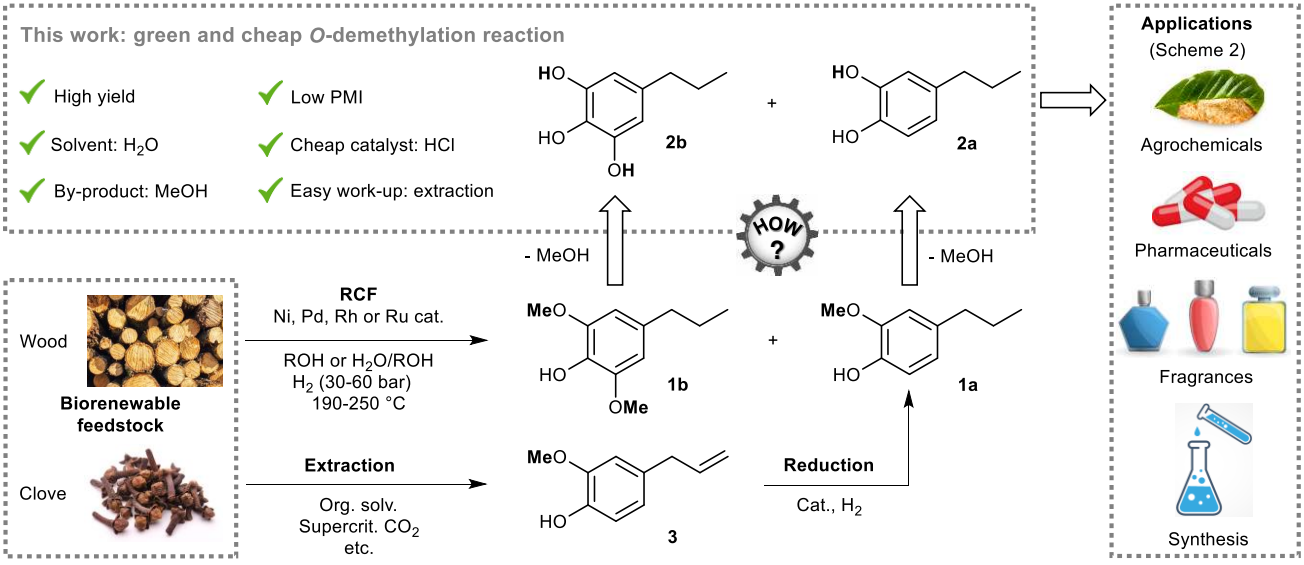
A green, efficient and cheap demethylation reaction of aromatic methyl ethers with mineral acid (HCl or H_2SO_4) as catalyst in high temperature pressurized water provided the corresponding aromatic alcohols (phenols, catechols, pyrogallols) in high yield. 4-Propylguaiacol was chosen as model, given the various applications of 4-propylcatechol reaction product. This demethylation reaction could be easily scaled and biorenewable 4-propylguaiacol from wood and clove oil could also be applied as a feedstock. Greenness of the developed method versus state-of-the-art demethylation reactions was assessed by performing a quantitative and qualitative Green Metrics analysis. Versatility of the method was shown on a variety of aromatic methyl ethers containing (biorenewable) substrates, yielding up to 99% of the corresponding aromatic alcohols, in most cases just requiring simple extraction as work-up.



Introduction

Following the transition of a fossil toward a more sustainable bio-based economy, the biorefinery concept, requiring the valorization of each component of a biorenewable feedstock, attracts a lot of interest.[1-3] The use of lignocellulose, world's most abundant organic material, has been extensively studied in this context and (hemi)cellulose derived products have already found some mature applications in industry.[4-6] However, studies toward the valorization of lignin, for other applications than energy generation, are not self-evident and immature.[7-10] This renewable polymeric structure, comprising 15-30% of the dry weight of woody biomass, contains electron-rich alkoxy-substituted arenes, and is therefore the largest source of biorenewable aromatic compounds on earth. It can be considered as a cross-linked polyphenolic, consisting of three main building blocks sinapyl (S), coniferyl

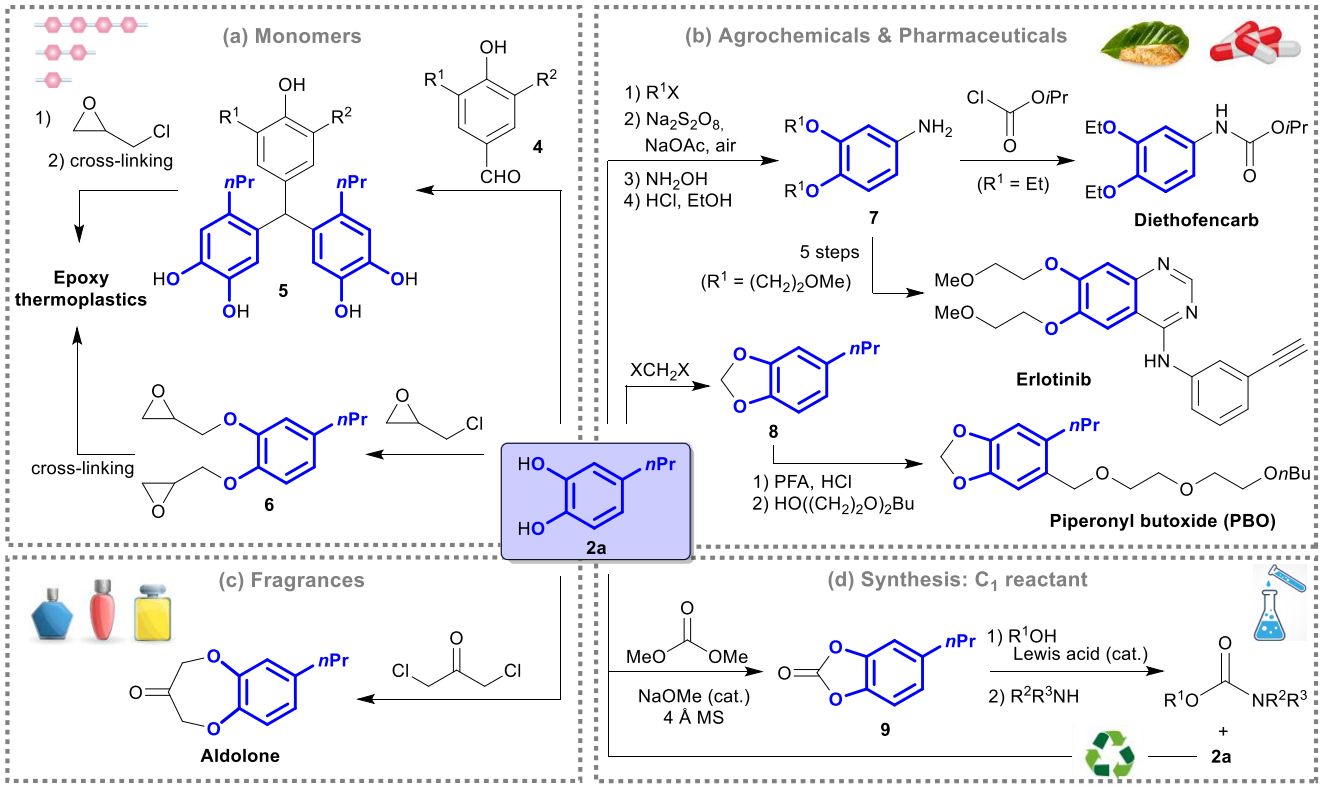
(G) and *para*-coumaryl (H) alcohols, called monolignols, among others, which are connected with specific *C-O* and *C-C* interlinkages. The relative occurrence of these monolignols and their interlinkages are mainly plant depending.[11-13] Lignin is an essential component of the plant cell wall, where it serves the plant rigidity, resistance to biotic and abiotic environmental stress and easy rotting.[14] Given its complex composition and structure, many different strategies toward its depolymerization have been reported, mainly producing variable mixtures of *para*-substituted guaiacol and syringol derivatives which are difficult to process further.[15-23] Therefore, lignin is currently used in existing biorefineries as energy feedstock. Though, because of its polyphenolic structure and its large abundance in Nature, lignin can be considered as renewable feedstock for the production of aromatic compounds, provided that conversion of its intricate and reactive structure to a handful of chemicals can be realized effectively and economically.[24-27] Recent advances in biorefinery technologies that are focusing on *in planta* lignin conversion, also called lignin-first approaches, have demonstrated high yields of phenolic monomers. For example, reductive catalytic fractionation (RCF) of birch wood, using Ru catalysis under a hydrogen pressure, delivers a mixture mainly consisting of 4-propylguaiacol (**1a**) and 4-propylsyringol (**1b**) in a 20:80 ratio with a total monomer yield up to 50% (carbon yield), representing more than 50 wt% of the original lignin content.[28-41] Treatment of pine sawdust under the same conditions gave a lignin oil consisting for more than 80% of **1a** in an amount corresponding to 12 wt% of the original lignin content. Alternatively, compound **1a** can be obtained upon reduction of eugenol (**3**), extracted from clove.[42-44] The aryl methyl ether functionalities are typically retained in these reductive depolymerizations of lignin and in the hydrogenation of eugenol (**3**). Therefore, an efficient, cheap and green *O*-demethylation method unlocking catechol and pyrogallol moieties from these compounds is highly looked for in order to allow further derivatization toward specific target compounds (Scheme 1).[45] The obtained products can serve as a new platform toward the production of aromatics chemicals, from which other useful end products and materials can be synthesized.[7, 10, 16, 46, 47]



Scheme 1. *O*-demethylation of biorenewable 4-propylguaiacol (**1a**) and 4-propylsyringol (**1b**).

In this paper, 4-propylguaiacol (**1a**), which can be derived from lignin[32, 34-36, 38, 40, 41] or eugenol[42, 43] (clove), is selected as model substrate for *O*-demethylation reaction development. After all, 4-

propylcatechol (**2a**), is known as a precursor for a variety of applications, as shown in Scheme 2. For example, it has been described in literature for the production of new bio-based epoxy thermoplastics (Scheme 2(a)), either *via* direct alkylation of the phenolic OH groups with epichlorohydrin, followed by cross-linking,[48, 49] or *via* similar functionalization of a triarylmethane core **5**, obtained through condensation of **2a** with renewable benzaldehydes **4**.[50] Recently, we have shown that this compound **2a** can be transformed into 3,4-dialkoxyanilines **7**, which serve as starting point for the synthesis of anti-cancer medicine Erlotinib and agrochemical Diethofencarb (Scheme 2(b)).[51, 52] Synthesis of 3,4-dialkoxyanilines **7** from **2a** involves *O*-alkylation followed by *C*-depropylation with concomitant amino group introduction.[53] Currently, insecticide synergist piperonyl butoxide (PBO) is made via reduction of safrole, a natural product from *Sassafras* plants.[54, 55] A cheaper route is starting from catechol, through benzodioxole formation and subsequent Friedel-Crafts propanoylation, followed by ketone reduction.[56] Though not described yet, the acetalization of catechol can also be applied on 4-propylcatechol giving direct access to dihydrosafrole (**8**) (Scheme 2(b)), which can be converted to PBO using paraformaldehyde (PFA), HCl and 2-(2-*n*-butoxyethoxy)ethan-1-ol.[54] Fragrance Aldolone can be synthesized from 4-propylcatechol (**2a**) via double alkylation with 1,3-dichloroacetone or other strategies involving double *O*-alkylation (Scheme 2(c)).[57] Finally, **2a** has also been used to produce a new shelf stable C_1 reactant with 100% renewable carbon, i.e. 4-propylcatechol carbonate **9** (Scheme 2(d)). This stable phosgene replacing C_1 reactant has been applied for carbamate synthesis, via consecutive reaction with alcohols and amines, allowing easy recycling of by-product **2a**.[58] **9** is synthesized from **2a** via transesterification with dimethyl carbonate, derived from CO_2, employing a reactive distillation.

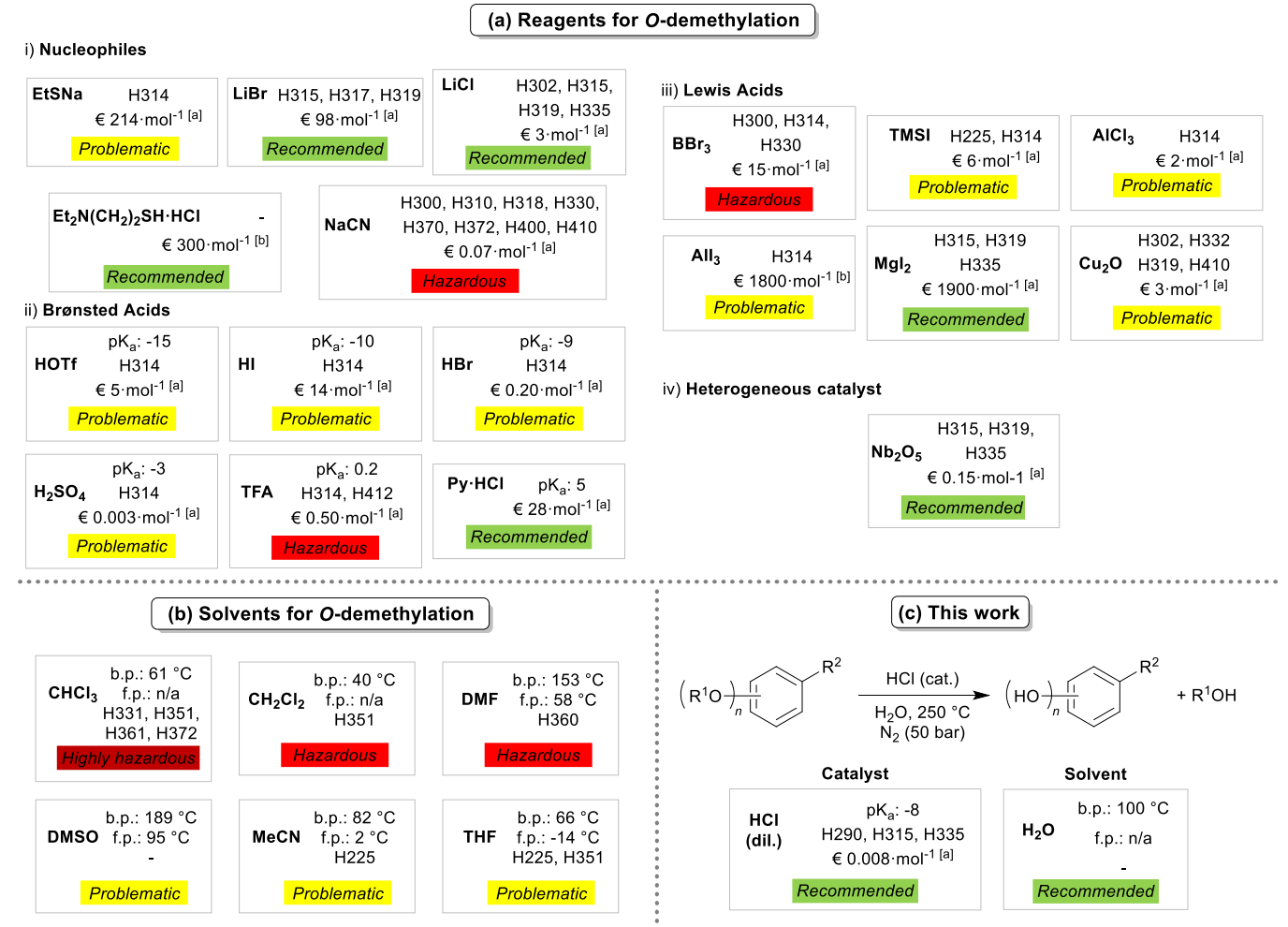


Scheme 2. Applications of 4-propylcatechol (2a): synthesis of (a) monomers for materials, (b) agrochemicals and pharmaceuticals, (c) fragrances, and (d) a new C_1 reactant.[48-53, 57, 58]

Despite the vast literature on cleavage of aromatic methyl ethers, most of them are not applicable to large scale synthesis as they employ (super)stoichiometric reagents in undesired solvents.[59, 60] The most commonly used solvents for this type of reactions are reported in Figure 1(b), together with their classification in the CHEM21 Solvent Selection Guide,[61] showing that none of these are classified as 'recommended'. This ranking system is based on safety (flash point, auto ignition temperature, H2xx), health (H3xx) and environmental (boiling point, REACH registration, H4xx) criteria of the solvents. Classical reagents for the cleavage of aryl methyl ethers can be classified in different categories, according to their function in this reaction, i.e. nucleophile, Brønsted acid, Lewis acid or heterogeneous catalyst (Figure 1(a)). As a first category (i), demethylation can be performed using nucleophilic reagents, with alkanethiols as most important representatives. These can be employed as the alkanethiolates or -thiols, where in the latter case a (super)stoichiometric base will be added to generate the thiolate *in situ*. For example, sodium ethanethiolate (EtSNa) is suitable to demethylate electron rich anisole derivatives.[62] However, the formed ethyl methyl sulfide by-product generates an unpleasant odour, which can be circumvented by using a less volatile thiol reagent, such as DodSH,[63] or 2-(diethylamino)ethanethiol,[64] both in combination with base. 2-(Diethylamino)ethanethiol is interesting as both the methyl thioether by-product as well as the excess thiol reactant can be easily removed by aqueous acid extraction. Unfortunately, it was only applied on substrates bearing electron withdrawing groups on the anisole.[64] Apart from thiol reagents, sodium cyanide was used for demethylation of a variety of anisole derivatives substituted with different functional groups, though not including electron donating ones.[65] Given the specific safety aspects related to this chemical require the use of specific equipment and handlings, its use is not desired. Also LiBr and LiCl are known to behave as demethylating agents.[66, 67] In a second category (ii), Brønsted acids are used for demethylation. Here, a strong acid is required to protonate the ether functionality, after which a weak nucleophile from the environment (i.e. conjugated base of acid) performs the actual cleavage. The use of strong inorganic acids aq. HBr,[49, 68] and aq. HI[69] is common. Chemically, HI is a very suitable Brønsted acid as it has one of the lowest pK_A of all mineral acids. It is either used as such,[69] or generated *in situ* from iodocyclohexane in refluxing DMF, the latter successfully demethylating guaiacol with 91% yield.[70] Strong organic acids, such as HOTf and TFA, have also been applied.[71, 72] In addition, also salts based on the combination of a strong acid and a weak base have been described for demethylation, as exemplified by pyridinium chloride (Py·HCl). This has been used for solventless demethylation of 4-methoxyphenylbutyric acid at elevated temperature, even on pilot scale.[73] In this case, pyridine's nitrogen atom acts as nucleophile in an S_N2 reaction after the substrate has been activated by the present HCl. Substrates unsuited for use in (strong) Brønsted acidic conditions can be activated with a Lewis acid (iii), after which the actual cleavage can occur with the aid of a weak nucleophile. Often a second reagent is added for this purpose. BBr_3 and TMSI, both in halogenated solvent, are widely used as sole reagents,[74-76] while $AlCl_3$ is typically employed in the presence of a second reagent, e.g. NaI or Me_2S.[77-79] Also the combination of cat. Cu_2O and an excess of NaOMe has been described.[80] Most of these Lewis acids react violently with water and therefore dry conditions and an inert atmosphere are required. Most of these classical reagents are classified as 'hazardous' or 'problematic' based on the CHEM21 Metrics (Figure 1, top) with the exception of 2-(diethylamino)ethanethiol and Py·HCl. However, these two reagents feature a high molecular weight and thereby generate more waste, negatively influencing the most important quantitative metrics, i.e. Process Mass Intensity (PMI) (*vide infra*). In addition, all reagents in Figure 1 are used in (super)stoichiometric amount and even then incomplete conversion of substrate is not uncommon. Moreover, column chromatography is often used to isolate the target compound. Finally, layered

Nb_2O_5, a heterogeneous catalyst (iv), has been used for *O*-demethylation in hot pressurized water.[81] The method has only been shown on 4-propylguaiacol (**1a**) and no work-up and isolated yield (GC analysis) has been reported.

Developing a general method to demethylate aryl methyl ethers to unlock phenol, catechol and pyrogallol moieties from the corresponding methyl ethers using a catalytic amount of a recommended reagent in a preferred solvent producing a low amount of non-harmful waste (avoiding resource intensive column chromatography) is of huge interest in the context of green chemistry. HCl is a suitable candidate, since it is cheap, recommended by the CHEM21 Metrics and features a low molecular weight (Figure 1(c)). The combination of HCl and water, the most sustainable solvent, looks very attractive. The expected by-product methanol is easy to remove and an important bulk chemical.[82] However, HCl is not strong enough to effectively protonate anisole derivatives, in contrast to the more expensive and problematic HBr and HI.



[a] Bulk chemicals: prices for import/export based on data found on Zauba.com retrieved in October 2020. [b] Research chemicals: prices based on data from Merck (largest batch available) retrieved in October 2020.

Figure 1. An overview of commonly used demethylating agents (a). Generally, they are used in one of the solvents mentioned in part (b). For these reagents and solvents, their classification as '(highly) hazardous', 'problematic' or 'recommended' is based on the CHEM21 (solvent) guide.[61, 83] Specifications of the new method are summarized in part (c).

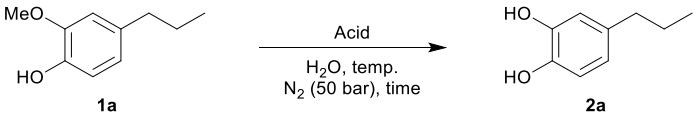
Recently, we reported on the transformation of ferulic acid into catechol employing acid (HCl or H_2SO_4) in hot pressurized water.[84] This transformation comprises two consecutive defunctionalizations of the substrate, i.e. *C*-*C* (de-2-carboxyvinylation) and *C*-*O* (demethylation) bond cleavage, occurring in one step. The acid, its concentration and the reaction temperature proved crucial to achieve high selectivity and yield, avoiding tar formation. We wondered whether these reaction conditions could be further optimized to provide a general protocol for the *O*-demethylation of anisole derivatives, with 4-propylguaiacol (**1a**) as model substrate.

Results and discussion

Reaction optimization

Application of the reactions conditions developed for ferulic acid defunctionalization [0.13 M in H_2O, 50 mol% HCl, 250 °C, 50 bar N_2, 3 h] on 4-propylguaiacol (**1a**) yielded 97% 4-propylcatechol (**2a**) (Table 1, Entry 1).[84] The low substrate concentration (0.13 M) and relatively high catalyst loading (50 mol%) are drawbacks for scaling. Gratifyingly, raising the substrate concentration to 0.50 M or 1.0 M did not significantly affect the yield (Entries 2-3). However, at 2.0 M, a 33% decrease in yield, caused by unselective side reactions giving tar, was observed (Entry 4). Interestingly, this could be overcome by decreasing the reaction time to 1 h, leading to a yield of 91% (Entry 5). HCl loading could be decreased to 20 mol% at 0.5 M, still achieving quantitative conversion to the desired product **2a** (Entry 6), which was still possible with double substrate concentration (Entry 8). Even the use of 10 mol% HCl led to 95% conversion and 90% yield (Entry 9), which could be pushed further to essentially full conversion by prolonging the reaction time (Entry 10). For comparison, we showed that subcritical water, without addition of acidic catalyst, is not able to *O*-demethylate **1a** (Entry 7). Conversion of substrate **1a** diminished with decreasing reaction temperature, since at 225 °C, 77% **2a** (Entry 11) and at 200 °C, only 3% **2a** were observed (Entry 12), in both cases leaving the remaining substrate unaffected, while at 185 °C, substrate **1a** could even be fully recovered (Entry 13). It was found that HCl could be successfully replaced by Lewis acid $FeCl_3$ leading to quantitative conversion of **1a** into **2a** (Entry 14), presumably by *in situ* HCl generation. Also the use of H_2SO_4 (Entry 15) led to the desired product **2a** in 94% yield. Full conversion with this acid could be achieved by increasing the reaction time (Entry 16) or increasing acid loading to stoichiometric quantity (Entry 17), though in the latter case with slightly reduced mass balance (90%). Weaker acid H_3PO_4 (Entry 18) led to partial (30%) and HOAc to no conversion (Entry 19). A full optimization of this reaction can be found in the SI (Section 3).

Table 1. Selected optimization data for the *O*-demethylation of 4-propylguaiacol (**1a**) into 4-propylcatechol (**2a**).



1a **2a**

Entry	Conc. 1a (M)	Acid (mol%)	pK_a	Temp. (°C)	Time (h)	NMR Yield (%) [a]	
						1a	2a
1	0.13	HCl (50)	-7.0	250	3	0	97
2	0.50	HCl (50)	-7.0	250	3	0	97
3	1.00	HCl (50)	-7.0	250	3	0	92
4	2.00	HCl (50)	-7.0	250	3	0	64 [b]
5	2.00	HCl (50)	-7.0	250	1	0	91 (91[c])
6	0.50	HCl (20)	-7.0	250	3	0	100 (97[c])
7	0.50	-	-7.0	250	3	100	0
8	1.00	HCl (20)	-7.0	250	3	0	95 (96[c])
9	0.50	HCl (10)	-7.0	250	3	5	90
10	0.50	HCl (10)	-7.0	250	6	< 1	99 (95[c])
11	0.50	HCl (20)	-7.0	225	3	23	77
12	0.50	HCl (20)	-7.0	200	3	97	3
13	0.50	HCl (20)	-7.0	185	3	100	0
14	0.50	$FeCl_3$ (20)	n/a	250	3	0	100
15	0.50	H_2SO_4 (20)	-3.0	250	3	6	94
16	0.50	H_2SO_4 (20)	-3.0	250	6	0	97 (97[c])
17	0.50	H_2SO_4 (100)	-3.0	250	3	< 1	89
18	0.50	H_3PO_4 (20)	2.2	250	3	70	30
19	0.50	HOAc (20)	4.8	250	3	100	0

Reaction conditions: amount (0.4-6.0 mmol) **1a** in H_2O (3.0 mL) to achieve the given concentration. [a] ^1H NMR Yield determined with dimethyl sulfone as internal standard. [b] Low mass balance due to tar formation. [c] Yield of the isolated product.

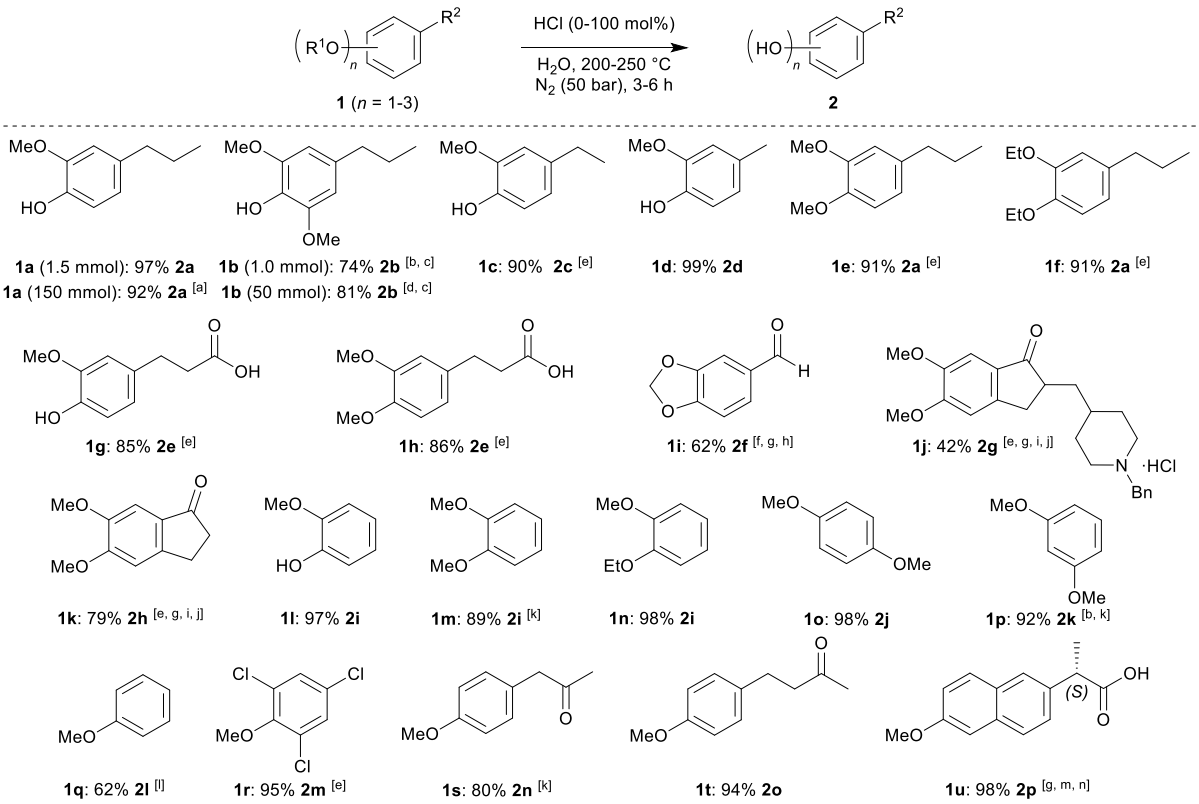
Substrate scope

The developed *O*-demethylation of 4-propylguaiacol (**1a**) could be applied on a variety of different substrates (Scheme 3). 4-Propylsyringol (**1b**), next to 4-propylguaiacol (**1a**) a major product obtained in lignin biorefinery,[34, 35, 38, 40, 41] gave 74% of 5-propylpyrogallol (**2b**). However, a lower substrate concentration was required to suppress side product formation (4-methyl-5-propylpyrogallol, see SI). Next, 4-propylveratrole (**1e**), containing two methoxy groups, and its *O*-ethylated counterpart (**1f**) delivered 4-propylcatechol (**2a**) in 91% yield, proving that our methodology also enables cleavage of aryl ethyl ethers, albeit with doubling of the reaction time. Several modifications in the alkyl side chain were allowed without affecting the pursued reactivity. For example, 4-ethylguaiacol (**1c**), also obtained from lignin biorefinery,[85-88] delivered the expected 4-ethylcatechol (**2c**) in 90% yield. Similar observations could be made for 4-methylguaiacol (**1d**) and dihydroferulic acid (**1g**), leading to their corresponding *O*-demethylated counterparts (**2d**-**2e**) in 99% and 85% yield, respectively. Also in the latter case, the presence of a second methoxy functionality, i.e. *O*-methyl-dihydroferulic acid, did not significantly affect the product yield (86% **2e**). From piperonal (**1i**), featuring a methylene acetal of catechol, protocatechuic aldehyde (**2f**) was produced in 62% yield, even without addition of an acidic catalyst. Next, our attention switched to *C*-unsubstituted molecules delivering dihydroxybenzenes. Guaiacol (**1l**), veratrole (**1m**) and *O*-ethyl guaiacol (**1n**) delivered catechol (**2i**) in high (89-98%) yield.

Two isomers of veratrole, *p*- (**1o**) and *m*- (**1p**) dimethoxybenzene, delivered hydroquinone (**2j**) and resorcinol (**2k**) with a yield of 98% and 82%, respectively. Anisole (**1q**), the smallest molecule used in this study, formed phenol (**2l**) in 62%, a decrease in yield probably due to the applied work-up because of azeotrope formation of phenol and water and required extraction with organic solvent,[89, 90] allowing for product loss, which was not observed during *O*-demethylation of 2,4,6-trichloroanisole (**1r**), known for causing cork taint in wine,[91] delivering 2,4,6-trichlorophenol (**2m**), possessing agrochemical activity,[91] in 95% yield. Other substituted anisoles, 4-methoxyphenylacetone (**1s**) (found in anise oil as oxidation product of the major oil constituents)[92] and 4-(4-methoxyphenyl)butan-2-one (**1t**), delivered products **2n** and **2o** in 80% and 94% yield, respectively. The latter product **2o** is raspberry ketone and can be found in several fruits, e.g. cranberry and blackberry, and is widely used in perfume industry, cosmetics or as food additive.[93] Finally, *O*-demethylation of APIs was tested. Nonsteroidal anti-inflammatory drug naproxen (**1u**) could be *O*-demethylated quantitatively.[94] The temperature had to be lowered to 200 °C to avoid benzylic decarboxylaton. Interestingly, donepezil hydrochloride (**1j**), a cholinesterase inhibitor used for treatment of Alzheimer's disease,[95] and 5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-one (**1k**), a known precursor in its synthesis,[96] could both be demethylated successfully in 42% and 79% yield, respectively, leaving the 2,3-dihydro-1*H*-inden-1-one core and, in case of **1j**, the *N*-benzyl moiety unaffected. Interestingly, **1k** can also be obtained from lignin-derived dihydroconiferyl alcohol with dihydroferulic acid (**1g**) as intermediate in its synthesis.[97] To conclude this part, the efficiency of our method at larger bench scale was evaluated, as exemplified with two substrates, i.e. 4-propylguaiacol (**1a**) and 4-propylsyringol (**1b**) These aryl methyl ethers could be *O*-demethylated with the same yield on a scale of 150 and 50 mmol, respectively. A more detailed description can be found in the SI (Section 3.3.2).

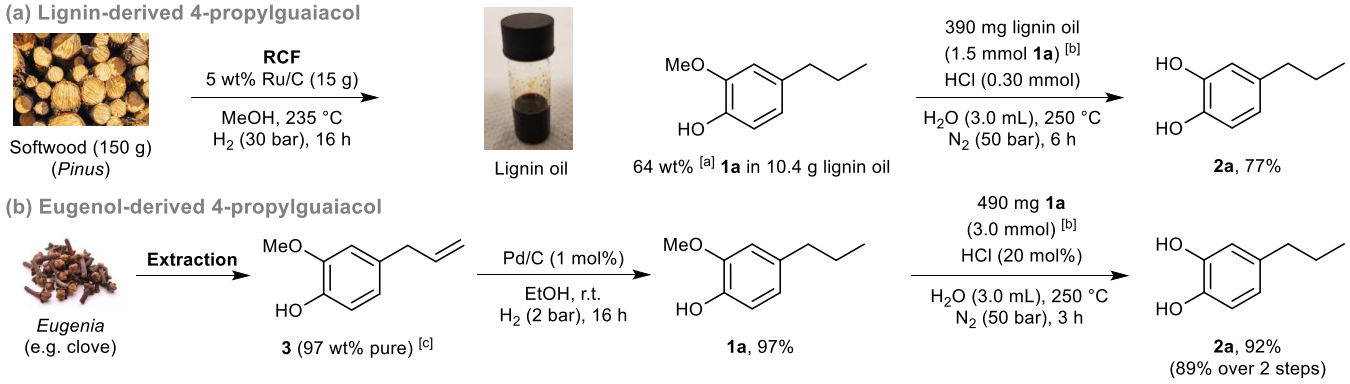
Lignin oil and clove oil

Finally, two natural sources of 4-propylguaiacol (**1a**) were selected and used in this newly developed *O*-demethylation strategy. As first example, softwood (*Pinus*) was treated under reductive conditions,[45] delivering a lignin oil consisting of 64 wt% **1a**, corresponding to 18 wt% of the original lignin content. Subsequent HCl-catalyzed *O*-demethylation of this lignin oil delivered 4-propylcatechol (**2a**) with a yield of 77% for this step, corresponding to 14 wt% of the original lignin content (Scheme 4(a)). Secondly, eugenol (**3**), obtained from *Eugenia*,[98] was easily reduced to the desired substrate **1a** with the aid of H_2 and cat. Pd/C.[44] Subsequently, *O*-demethylation of **1a** delivered 4-propylcatechol (**2a**) with a total yield of 89% over 2 steps (Scheme 4(b)). Important to mention is that all steps involved are extraction and filtration based and do not involve column chromatography.



Yield of isolated products. Reactions were typically performed in 3 mL H_2O. General conditions: Substrate concentration = 0.50 M, 20 mol% HCl, Temperature = 250 °C, Time = 3 h. [a] 150 mmol **1a**, Substrate concentration = 1.0 M, Time = 6 h; [b] Substrate concentration = 0.33 M; [c] Purified via recrystallization from toluene; [d] 50 mmol **1a**, Substrate concentration = 0.33 M, Time = 6 h; [e] Time = 6 h; [f] 0 mol% HCl; [g] Substrate concentration = 0.13 M; [h] Time = 1 h; [i] 40 mol% HCl; [j] Purified via column chromatography; [k] Time = 4 h; [l] 100 mol% HCl; [m] Temperature = 200 °C; [n] 84% ee.

Scheme 3. *O*-demethylation of (substituted) anisols, guaiacols, dimethoxybenzenes, benzodioxoles, syringols.



[a] Determined via ^{1}H NMR Analysis with dimethyl sulfone as int. std. [b] The experiment was performed 2 times and samples were combined for work-up. [c] Eugenol (**3**), obtained from *Eugenia* through biological extraction and purification, was bought from Merck.[98]

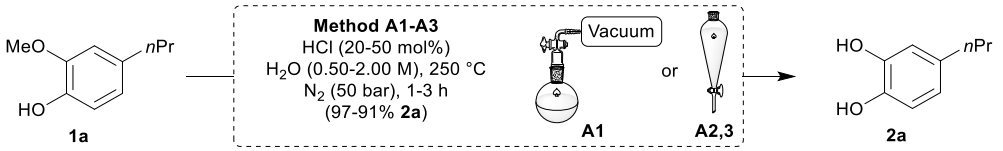
Scheme 4. *O*-Demethylation of 4-propylguaiacol (**1a**) obtained from a natural resource: (a) *Pinus,*[45] and (b) *Eugenia*.[98]

Green Metrics toolbox

In order to evaluate the *greenness* of the developed *O*-demethylation method, the optimal conditions for the conversion of 4-propylguaiacol (**1a**) into 4-propylcatechol (**2a**) were analyzed using the *first pass* CHEM21 Green Metrics Toolkit, comprising quantitative and qualitative aspects, developed for discovery research.[83, 99, 100] The same analysis has been performed for classical *O*-demethylation methods as well. To achieve this, the conditions reported on **1a** have been taken directly from literature (Scheme 5) and if not reported on **1a**, but on similar substrates, we have applied it on **1a** to access the required data (**Scheme 6**). A detailed overview of these selected classical methods, including the scale the experiment was performed on and the applied work-up, can be found in the SI (Section 4.4). The following quantitative parameters were calculated for each considered method: Yield, AE (Atom Economy), RME (Reaction Mass Efficiency), PMI Tot (Total Process Mass Intensity), PMI RRC (Reactants, Reagents, Catalysts), PMI Rxn (Reaction: RRC + reaction solvent), and PMI WU (Work-up, i.e. considering the mass of all chemicals and solvents used in the work-up). Next to the assessment of these mass-based metrics, qualitative aspects, i.e. solvent type, use of critical elements, health and safety aspects of all chemicals involved, energy and reagent consumption and the applied work-up method, were also evaluated. In order to clearly analyze these aspects, a flag system is applied. In this regard, a green, yellow or red 'flag' is assigned to each of the assessed criteria, where green denotes 'preferred', yellow is 'acceptable with some issues' and red is 'undesirable'.

Selection of reaction conditions for the new *O*-demethylation reaction. The newly developed method was quantitatively evaluated under three different conditions, i.e. respectively low and high substrate concentration and HCl loading [Method A1: 0.50 M **1a** and 20 mol% HCl (Table 1, Entry 6); Method A2: 1.00 M **1a** and 20 mol% HCl (Table 1, Entry 7); Method A3: 2.00 M **1a** and 50 mol% HCl (Table 1, Entry 5)]. As water acts both as reactant and solvent in the reaction,[84] 1.0 equiv. of H_2O was considered as reactant and the remaining amount as solvent in the calculations. When comparing A1 and A3 it can be seen that by increasing substrate concentration and catalyst loading, a slightly lower yield (97% vs. 91%) and RME (80% vs. 75%) were obtained (Table 2). However, when looking at the PMI, this most complete mass-based metric has a beneficial impact on the *greenness* of the reaction since both PMI Tot (15 $g \cdot g^{-1}$ vs. 11 $g \cdot g^{-1}$) and PMI Rxn (15 $g \cdot g^{-1}$ vs. 4.9 $g \cdot g^{-1}$) could be decreased. Logically, the higher catalyst loading slightly increased the PMI RRC value (1.3 $g \cdot g^{-1}$ vs. 1.5 $g \cdot g^{-1}$). The only drawback of the more concentrated conditions is the need for an extractive work-up, while in Method A1 pure reaction product could be obtained with simple freeze drying. This difference reveals when looking at PMI WU (0 $g \cdot g^{-1}$ vs. 6.4 $g \cdot g^{-1}$). For most quantitative metrics, Method A2 brings an intermediate result, despite for PMI Tot and PMI WU, which can be attributed to the extractive work-up with the same amount of organic solvent as Method A3. The lower PMI Tot makes Method A3 still the *greenest* and therefore, these conditions will be used for comparison with classical methods (*vide infra*).

Table 2. Quantitative metrics for the *O*-demethylation of 4-propylguaiacol (**1a**) to 4-propylcatechol (**2a**) using cat. HCl in hot pressurized water.



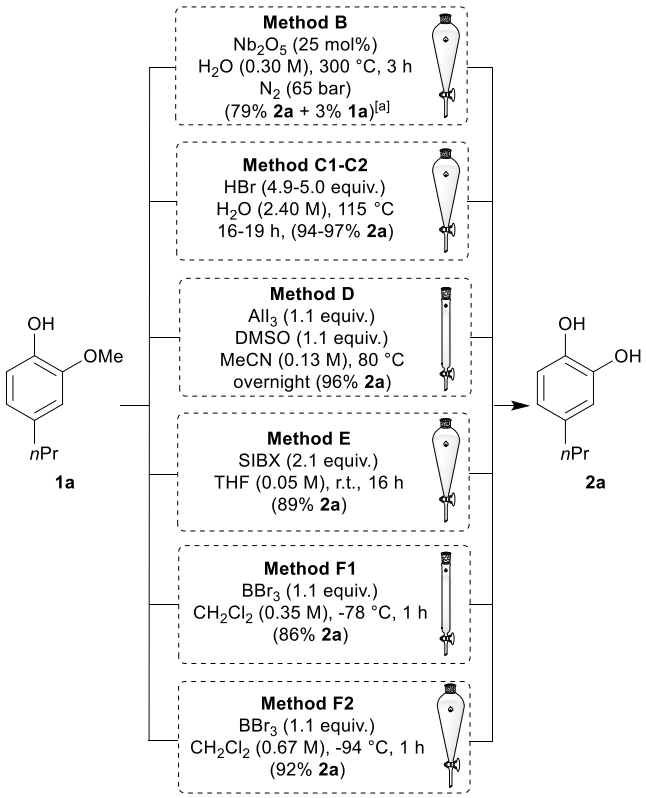
Entry	Method	Conc. 1a (M)	HCl (mol%)	Time (h)	Yield (%)	AE (%)	RME (%)	PMI (g·g^{-1})			
								Tot [a]	RRC [a]	Rxn [a]	WU [a]
1	**A1**	0.50	20	3	97	83	80	15	1.3	15	0 [b]
2	**A2**	1.00	20	3	96	83	79	20	1.3	8.0	12 [b]
3	**A3**	2.00	50	1	91	83	75	11	1.5	4.9	6.4 [b]

Results from Table 1 (Entries 5-6); the applied work-up method (freeze drying or extraction) is shown graphically. [a] Tot: Total; RRC: Reactants, Reagents, Catalysts; Rxn: Reaction; WU: Work-up. [b] In the first example, freeze drying was sufficient to obtain pure **2a** (leading to a green flag in qualitative metrics analysis), while in the second and third example extraction was required with 10 mL EtOAc (yellow flag).

Selection of classical state-of-the-art methods. Six reported methods describing the *O*-demethylation of 4-propylguaiacol (**1a**) are summarized in Scheme 5. One method involves a heterogeneous catalyst.[101] As part of a study regarding the hydrodeoxygenation of lignin, a layered Nb_2O_5 (25 mol%) catalyst allowed *O*-demethylation of **1a** in hot pressurized water (N_2 pressure).[81] Unfortunately, demethylation as a separate step was not the main topic of this study and the yield of **2a** was therefore only quantified by GC-FID. We repeated this experiment leading to a mixture of product **2a** (79%), substrate **1a** (3%) and catechol (**2i**, 5%) (Method B) and decided not to purify this mixture further because of its negative impact on the Green Metrics analysis. The next two methods (C1-2) make use of Brønsted acid HBr (aq.) in excess under reflux,[49, 58] with the applied work-up method as only difference. Stoichiometric aluminium oxide iodide, *in situ* generated from AlI_3 and DMSO, was also found to serve as a good demethylating agent, yielding 4-propylcatechol (**2a**) in nearly quantitative yield (Method D).[102] Stabilized IBX (SIBX) in excess was reported to *O*-demethylate substrate **1a** selectively in 89% yield (Method E).[103] Demethylation based on BBr_3, followed by an aqueous quenching step, was found in a patent by Ghosh (Method F1).[75] Because of the low substrate concentration and small scale applied in this last method, we reproduced this example by increasing scale and substrate concentration without the need for chromatographic purification, yielding 92% of **2a** (Method F2).

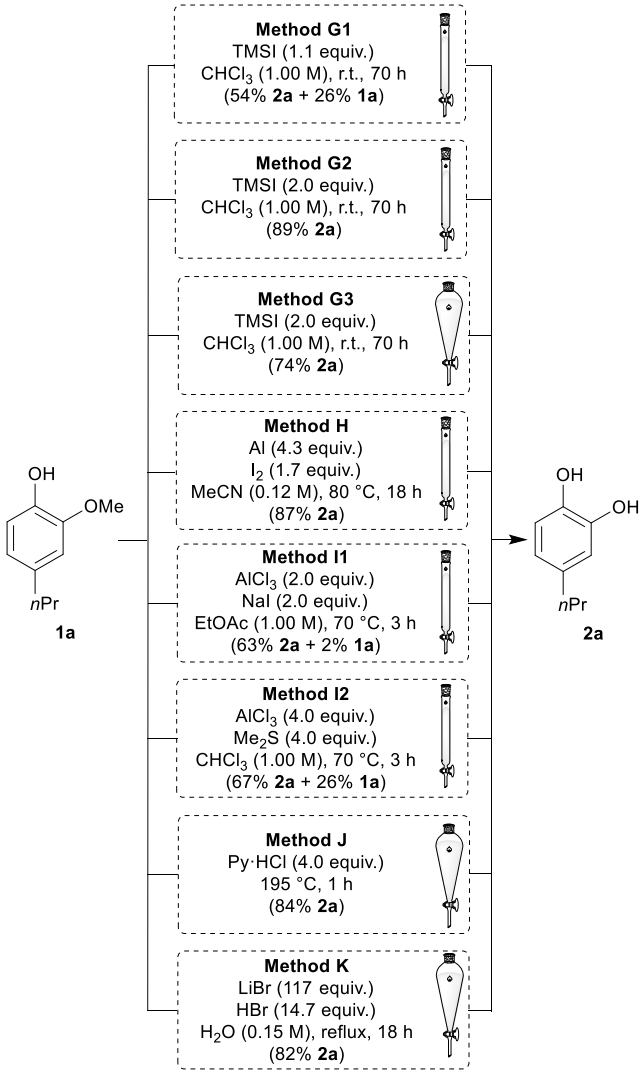
In literature, multiple other classical demethylation methods have been applied on guaiacol or anisole derivatives different from 4-propylguaiacol (**1a**), and six of these methods were selected and applied on the standard substrate **1a**. The results are summarized in Scheme 6 and a detailed description is reported in the SI (Section 4.4.2). For these methods, we performed the reactions with the conditions as retrieved from literature on similar substrates and we only increased the amounts of reagents and reaction temperatures if insufficient conversion of substrate **1a** was observed. Also, work-up was performed as originally described and material intensive column chromatography was only considered if *greener* purification methods did not deliver the desired product **2a** with sufficient purity. Stoichiometric trimethyl silyl iodide (TMSI, 1.1 equiv.) demethylated guaiacol with 67% conversion after 48 h,[76] a rate that could not be improved for 4-propylguaiacol. Even after prolonging the reaction time to 70 h, 54% **2a** and 26% substrate **1a** recovery was achieved (Method G1). Increasing the amount

of demethylating agent pushed the substrate to full conversion, leading to 4-propylcatechol **2a** in 74-89% yield, depending on the applied work-up (Methods G2 and G3). The described *O*-demethylation of guaiacol (**1l**) involving Al powder, I_2 and DMSO could be applied on our main substrate of interest **1a**,[104] even in the absence of DMSO (Method H), providing 4-propylcatechol (**2a**) with a yield of 87%. By applying a method based on $AlCl_3$ and NaI, delivering quantitative double demethylation of veratrole,[79] desired **2a** was only obtained in 63% yield (with 2% remaining substrate **1a**) (Method I1). Similarly, a combination of $AlCl_3$ and dimethyl sulfide,[78] led to 67% **2a** and 26% remaining substrate (Method I2), even with a large excess of the used reagents. A pilot-scale demethylation of 4-methoxyphenylbutyric acid involving an excess of molten Py·HCl,[73] was successfully applied on **1a** in 84% yield (Method J). As last method, LiBr and HBr in excess, described for demethylation of 4-methylguaiacol (**1d**),[66] was employed on **1a**, leading to **2a** in 82% yield (Method K). Finally, three chemical methods describing high-yielding demethylation of substituted anisoles mainly bearing electron withdrawing groups on the arene were evaluated.[64, 74, 80] As described in Scheme 7, translating these procedures to demethylation of electron rich 4-propylguaiacol (**1a**) did not provide good results. For example, MgI_2 and the combination of Cu_2O and NaOMe only partially converted **1a** to **2a**, and combination of 2-diethylaminoethanethiol and NaO*t*Bu even did not form 4-propylcatechol (**2a**), enabling quantitative recovery of substrate **1a**.



For all methods, the applied work-up method (extraction or column chromatography) is shown graphically. [a] For Method C, 5% catechol (**2i**) was also obtained.

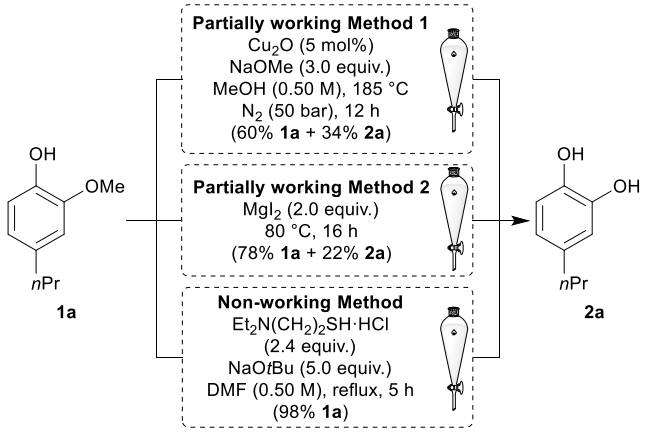
Scheme 5. *O*-Demethylation of 4-propylguaiacol (**1a**) to 4-propylcatechol (**2a**) as retrieved from literature.[49, 58, 75, 81, 102, 103, 107]



For all methods, the applied work-up method (extraction or column chromatography) is shown graphically.

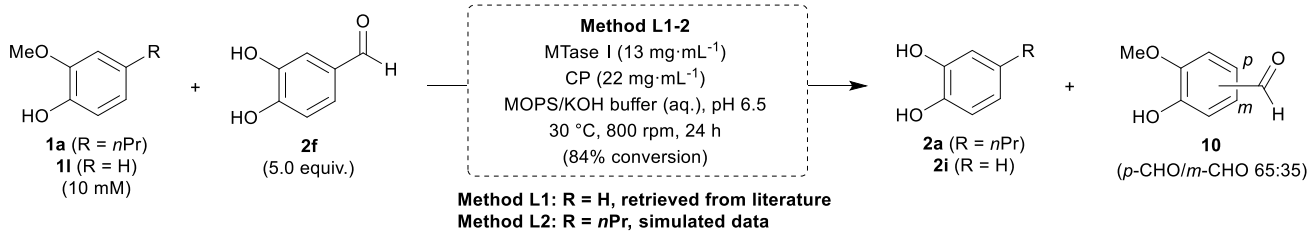
Scheme 6. *O*-Demethylation of 4-propylguaiacol (**1a**) to 4-propylcatechol (**2a**), applying methods retrieved from literature for other guaiacol derivatives.[73, 76, 78, 79, 104]

Besides chemical, also biocatalytic routes are possible for *O*-demethylation. In 2018, an enzymatic method, based on corrinoid-dependent methyl transferases acting as methyl transferring agent, was reported.[105] In the presence of the respective methyl transferase (MTase I), corrinoid protein (CP) and the required buffer, guaiacol (**1l**) was demethylated to catechol (**2i**) with a conversion of 84%, while at the same time methyl acceptor protocatechualdehyde (**2f**, 5.0 equiv.) was converted into a mixture of vanillins (Scheme 8, Method L1). This experiment could not be evaluated on 4-propylguaiacol (**1a**) as we did not have access to these enzymes. Therefore, a theoretical simulation was performed, assuming the reaction would occur with the same efficiency (Method L2, Scheme 8). This procedure was recently disclosed as a reliable metrics analysis when no data are available for a synthetic method on a specific substrate.[106]



For all methods, the applied work-up method (extraction) is shown graphically

Scheme 7. Attempted methods for *O*-Demethylation of 4-propylguaiacol (**1a**) to 4-propylcatechol (**2a**), applying methods retrieved from literature for anisole derivatives.[64, 74, 80]



Scheme 8. Method L1: Biocatalytic conversion of guaiacols (**1a**,**l**) and protocatechualdehyde (**2f**) in catechols (**2a,i**) and vanillins **10** by MTase I and CP.[105] Method L2: simulated data for demethylation of 4-propylguaiacol (**1a**), based on the data from Method L1 employing guaiacol (**1l**).

Quantitative aspects. From the data reported in Scheme 5-Scheme 6 and Table 3, it can be seen that Methods B (Nb_2O_5), I1 and I2 ($AlCl_3$, either in combination with Me_2S or NaI) were the only procedures not capable of driving the reaction to full conversion. All other demethylating agents were able to do so and delivered the desired product **2a** with a yield of at least 82%. Generally, high values for AE were obtained in almost all cases, since only the methods using HBr (Methods C1 and C2), HBr with LiBr (Method K) and Py·HCl (Method J) scored less than 75%. In these cases, a large excess of reactants (4.0-117 equiv.) also resulted in a low RME value (9% to 40%), while the other demethylating agents feature an RME ranging from 41% to 84%. Based on these metrics (yield, AE, RME), our newly developed approach A3, as well as classical approaches B, D, E, and F2 perform the best.

However, also PMI, the most complete mass-based metric, including all used chemicals for synthesis and work-up, needs to be considered. Interestingly, for aq. HCl (Method A3), the lowest PMI Tot as well as subvalue for all categories was obtained when comparing with all literature procedures. The method relying on Py·HCl (Method J) uses the least waste generating reaction conditions of all classical procedures. It has the same PMI Rxn as achieved for Method A3. When excluding the amount of solvent used (PMI RRC), differences between the methods become smaller and the method based on Nb_2O_5 (Method B) scores here second best with a slightly higher value than A3. It is worth mentioning that in Method J molten Py·HCl is used without any solvent, leading to a value for PMI RRC equal to

PMI Rxn, which explains the low PMI Tot. In this regard, the second- and third-best demethylating agents are HBr (Methods C1 and C2) and BBr_3 (Methods F1 and F2). For Method F1, the effect of working under high dilution becomes clear when looking at the difference between PMI Rxn and PMI RRC, which could be halved by repeating the method with a higher substrate concentration (Method F2). Obviously, the mass efficient work-up in Method C2, based on extraction with a relatively small amount of organic solvent, leads to low PMI WU and therefore to the lowest PMI Tot of all classical methods. However, these values are still higher than those for Method A3. Column chromatography is inherently a material consuming nature, leading to (very) high PMI WU (Methods D, F1, G1, G2, H, I1 and I2). Noteworthy, in Table 3 is shown that when extractions are not performed mass-efficiently, they can actually lead to higher values for PMI WU than methods relying on chromatography (Method E vs. D, F1, G1, G2, H, I1 and I2).

Table 3. Quantitative metrics for the *O*-demethylation of 4-propylguaiacol (**1a**) to 4-propylcatechol (**2a**).

Method	Yield (%)	AE (%)	RME (%)	PMI ($g \cdot g^{-1}$) [a]			
				Tot	RRC	Rxn	WU
A3	91	83	75	11	1.5	4.9	6.4
B	79	83	65	92	2.1	30	63
C1	94	62	25	30	4.1	7.0	23
C2	97	62	26	21	4.0	6.8	14
D	97	75	73	834 (287) [b]	5.0	48	786 (239) [b]
E	89	92	81	2140	10	141	1999
F1	86	83	71	1394 (772) [b]	3.5	33	1362 (739) [b]
F2	92	83	76	96	3.3	18	79
G1	54 [c]	77	41	1254 (319) [b]	5.1	23	1231 (296) [b]
G2	89	77	68	757 (193) [b]	4.4	15	742 (178) [b]
G3	74	77	57	207	5.3	18	188
H	87	75	65	896 (225) [b]	5.6	53	842 (172) [b]
I1	63 [d]	83	52	1289 (151) [b]	7.8	17	1272 (133) [b]
I2	67 [e]	83	55	1232 (219) [b]	9.5	24	1208 (195) [b]
J	84	47	40	27	4.9	4.9	22
K	82	62	9	762	92	155	608

Conditions of the methods can be found in Schemes 6-7. [a] Tot: Total; RRC: Reactants, Reagents, Catalysts; Rxn: Reaction; WU: Work-up. [b] The values between brackets are obtained when column chromatography is omitted from work-up. [c] 26% **1a** was recovered. [d] 2% **1a** was recovered. [e] 20% **1a** was recovered.

Although the use of water as solvent is a specifically attractive feature in enzymatic reactions (e.g. Method L), several chemicals, e.g. buffer, need to be added for the reaction to proceed effectively. Also the diluted reaction conditions of 10 mM (PMI RRC comprises only 8.4% of PMI Rxn) and mass-intensive work-up (PMI WU comprises 86% of PMI Tot) have their impact on the mass based metrics. These factors lead to very high total (6890 $g \cdot g^{-1}$) and partial PMI values (Table 4). When considering demethylation of guaiacol (**1l**) via biocatalysis, PMI Tot increases with 38% (Method L1), which was also observed when applying our new approach (experimentally) on this substrate **1l** (Table 4, Method A3). Though this biocatalytic methyl transfer is conceptually a very interesting study, besides the high PMI Tot another problem rises. Two reactants deliver one product and two isomeric co-products (**2a**, **2i**, **10**) rather than pure 4-propylcatechol (**2a**). This will require separation which will even further increase PMI WU, making it less interesting from a preparative point of view. If we consider these co-products as valorizable products and not as waste,[99] by adding the mass of the generated co-product

in the denominator of the PMI formula, a PMI_{FI} (FI = Feedstock Intensity) value is obtained. Similarly, AE_{FI} and RME_{FI} can be defined (see SI, Section 4.5.3), which are also reported in Table 4. PMI_{FI} is in a sense actually moving from PMI towards the E-factor where for the latter any input which isn't waste, i.e. useful co-product, is not included in the numerator.[108] PMI decreased with a factor 2 for all categories when the co-products formed are considered useful and not as waste, but these values remain nevertheless significantly higher than the PMIs reported for the chemical methods, revealing these co-products are not the main cause of the poor performance with respect to PMI of the biocatalysis. Obviously, an ideal AE_{FI} is obtained when co-products are not waste. Although RME doubles (RME_{FI}), the applied excess of one of the reactants is pronounced, still leading to a low value (30%). Also for our chemical demethylation strategy (cat. HCl, Methods A), a valuable molecule is produced as by-product during the reaction, i.e. stoichiometric methanol. Although we did not develop a method for isolation of this volatile alcohol from the water, it is interesting to know its contribution to the mass based metrics. The PMI_{FI} value decreased the earlier obtained PMI further with around 15% when methanol is not considered as waste. Also AE_{FI} and RME_{FI} increased to (almost) ideal numbers.

Qualitative aspects. The qualitative parameters of the Toolkit were studied for each method and the results are summarized in Table 5. First we looked into solvent use. Here it can be seen that our newly developed Method A3 (HCl) and Method B (Nb_2O_5) are the only methods scoring a green flag for both reaction solvent and work-up solvent, in both cases H_2O and EtOAc, respectively. Methods C1-2 (HBr), I1 ($AlCl_3$ + NaI) and L2 (MTase I) also received a green flag for reaction solvent, while a yellow or (dark) red flag was obtained for work-up. Method J, relying on molten Py·HCl, is performed 'neat' and therefore a green flag is scored for reaction solvent. A red flag was obtained for the work-up solvent in this method, due to the use of MTBE, which is also applied in Method K. Potentially, those work-up solvents can be altered for greener alternatives when additional research is performed, making these methods potentially more acceptable from a separation point of view. In contrast, the other methods rely on halogenated and ether solvents during reaction (e.g. $CHCl_3$, CH_2Cl_2, Et_2O) and therefore bring significant issues from a Health & Safety point of view. In these cases, solvents are often crucial for the efficiency of the reaction and can therefore not be simply substituted by greener alternatives.

Concerning critical elements use, none of the considered methods scores a red flag, which would mean that an element is used of which the remaining supply is estimated less than 100 years. Method B, based on Nb_2O_5, scores a yellow flag for the involvement of Nb, which has a predicted reserve of 100-500 years. Also Li, I, Al, S and/or B lead on the same basis to a yellow flag (Methods D, E, F, G, H, I, J and L). Next, Health & Safety aspects were evaluated. The combination of H_2O and HCl (Method A3) or Nb_2O_5 (Method B), followed by a simple work-up based on extraction with EtOAc, or the use of Py·HCl is clearly beneficial, since all other methods contain at least one chemical with an H phrase leading to a yellow or red flag. Method H is clearly the worst, since three chemicals leading to a red flag are involved (Al, I_2 and heptane). It is important to emphasise that the substrate of our route, i.e. 4-propylguaiacol (**1a**), is toxic in contact with skin (H311) and it therefore always generates a yellow flag. However, since this is the substrate for all methods considered, it is obviously not incorporated in Table 5. Concerning additional reagent use the new method scores very well as only a catalyst is required. Apart from Methods B (0.3 equiv. Nb_2O_5), C1-2 (4.9-5.0 equiv. HBr) and L2 (enzyme) none of the literature methods score a green flag in this category. For Methods C1-2, we should mention that HBr is already considered as a reactant (since it cannot be used catalytically and delivers a proton in the reaction equation) and therefore not included in this category, which only looks at additional

reagents and catalysts. The effect of the excess of reactant in these methods (C1-2) has already been reflected in the poor AE and RME values. Comparing the applied work-up techniques, either extraction or column chromatography is used. The methods based on extraction, including the new method (A3), are the best leading to a yellow flag. For those classical methods relying on column chromatography in order to obtain pure product **2a**, a red flag is scored, since this mass-intensive purification is clearly not sustainable, which was already revealed in the quantitative metrics. Finally, in the category energy consumption, a red flag is obtained for our HCl catalyzed demethylation due to the elevated temperature, while a few examples from the classical methods could be performed at room temperature leading to a green flag. However, one needs to realize that this is a very basic first analysis of energy consumption and does not reflect the final process energy consumption, which is simply not yet possible at the discovery level as reaction times are not minimized and heat recovery, typically applied in bulk chemicals synthesis, not considered yet. In development projects using this new method, a more in-depth study should be performed in this respect applying *second* and *third pass* CHEM21 metrics.

Table 4. Quantitative metrics for the *O*-demethylation of 4-propylguaiacol (**1a**) into 4-propylcatechol (**2a**) and guaiacol (**1l**) into catechol (**2i**), excluding or including formation of by-products, respectively.

Method	Substrate	Yield (%)	Excluding co-products [a]						Including co-products [a]					
			AE (%)	RME (%)	PMI ($g \cdot g^{-1}$) [b]				AE_{FI} (%)	RME_{FI} (%)	PMI_{FI} ($g \cdot g^{-1}$) [b]			
					Tot	RRC	Rxn	WU			Tot	RRC	Rxn	WU
A3	**1a**	91	83	75	11	1.5	4.9	6.4	100	91	9.4	1.2	4.1	5.3
L2	**1a**	84	50	15	6890	72	854	6036	100	30	3445	36	427	3018
A3	**1l**	93	77	72	15	1.6	6.3	8.7	100	93	11	1.2	4.9	6.2
L1	**1l**	84	42	11	9523	99	1180	8342	100	27	3998	42	496	3503

[a] Co-products: vanillins **10** for Methods L, MeOH for Methods A. [b] Tot: Total; RRC: Reactants, Reagents, Catalysts; Rxn: Reaction; WU: Work-up.

Table 5. Qualitative Appraisal of Solvent Use, Inherent Hazards of Used Chemicals, Catalyst or Reagent Use, Energy and Work-up Methods for the Different Approaches for the *O*-demethylation of 4-propylguaiacol (**1a**) to 4-propylcatechol (**2a**).

Method	Solvent Rxn [a]	Flag	Solvent WU [a]	Flag	Critical elements [b]	Flag	Health and Safety [b, c]	Flag	Reagent use	Flag	Energy	Flag	Work-up	Flag
A3	H_2O		EtOAc		-		-		Catalyst [d]		250 °C		Extraction	
B	H_2O		EtOAc		Nb		-		Catalyst		300 °C		Extraction	
C1	H_2O		Et_2O		-		Et_2O: H224 HBr: H331		- [d]		115 °C		Extraction	
C2	H_2O		MTBE		-		HBr: H331		- [d]		115 °C		Extraction	
D	DMSO, MeCN		Heptane		I, Al, S		Heptane: H410		Stoichiometric		Reflux		Chrom.	
E	THF		CH_2Cl_2		I, S		CH_2Cl_2: H315		Excess		r.t.		Extraction	
F1	CH_2Cl_2		CH_2Cl_2, hexane		B		BBr_3: H300, H330 Hexane: H410		Stoichiometric		-78 °C		Chrom.	
F2	CH_2Cl_2		CH_2Cl_2		B		BBr_3: H300, H330		Stoichiometric		-94 °C		Extraction	
G1	$CHCl_3$		$CHCl_3$		I		$CHCl_3$: H372 MeOH: H370		Stoichiometric		r.t.		Chrom.	
G2	$CHCl_3$		$CHCl_3$		I		$CHCl_3$: H372 MeOH: H370		Excess		r.t.		Chrom.	
G3	$CHCl_3$		$CHCl_3$		I		$CHCl_3$: H372 MeOH: H370		Excess		r.t.		Extraction	
H	MeCN		Heptane		Al, I, S		Al: H250 I_2: H372, H400 Heptane: H410		Excess		Reflux		Chrom.	
I1	EtOAc		Heptane		Al, I		NaI: H400 Heptane: H410		Excess		Reflux		Chrom.	
I2	$CHCl_3$		Heptane		Al, S		$CHCl_3$: H372 Heptane: H410		Excess		Reflux		Chrom.	
J	-		MTBE		-		-		Excess		195 °C		Extraction	
K	H_2O		MTBE		Li		HBr: H331		Excess		Reflux		Extraction	
L2	H_2O		MeCN		S, Co		-		Enzyme		30 °C		Chrom. [e]	

[a] Rxn: reaction; WU: work-up. Solvents are classified according to the most recent CHEM21 Solvent Selection Guide.[61] [b] When a yellow or red flag is not applicable, this column is left blank. [c] The substrate, 4-propylguaiacol (**1a**), is toxic in contact with skin (H311), which leads to a yellow flag for 'Health & Safety'. However, it is the substrate for all approaches and therefore not included. H224: Extremely flammable liquid and vapour; H250: Catches fire spontaneously if exposed to air; H300: Fatal if swallowed; H315: Causes skin irritation; H330: Fatal if inhaled; H331: Toxic if inhaled; H370: Causes damage to organs; H372: Causes damage to organs through prolonged or repeated exposure; H400: Very toxic to aquatic life; H410: Very toxic to aquatic life with long lasting effects. [d] H_2O, the reaction solvent, is involved in the mechanism and therefore, 1.0 equiv. was considered as reactant in the calculations. This was neglected for the qualitative analysis in this Table. [e] The mixture is only analyzed with HPLC, no work-up for obtaining pure product(s) was performed. Column chromatography will be required to get target compound **2a** pure.

Conclusion

In conclusion, we have developed an efficient green method for the cleavage of methyl aryl ethers catalyzed by HCl, a cheap Brønsted acid, in hot pressurized water under nitrogen atmosphere. Both acid and solvent are recommended with respect to green chemistry. The versatility of our method was demonstrated by cleaving various aryl methyl ether substrates, in most cases only requiring simple extraction for the purification. Biorenewables such as 4-propylguaiacol and 4-propylsyringol obtained via wood biorefinery can also be used. Application on multigram quantities is possible under the reaction conditions applied on small scale. Further scaling will be evaluated in future research (pilot-scale testing). A full *first pass* Green Metrics Analysis of our new synthetic method revealed that in comparison with classical *O*-demethylation methods our new approach scored best for most parameters considered, both quantitatively (PMI) and qualitatively (Solvent, Critical elements, Health and Safety, Reagent use).

Author contributions

B.U.W.M. conceived the idea and designed the experiments together with J.B.. J.B. (optimization), M.B. (optimization and scope) and T.K.A. (revision) carried out the experimental work regarding *O*-dealkylation of alkyl aryl ethers and synthesis of the required starting materials when not commercially available. X.W. synthesized the Nb_2O_5 catalyst and B.W. delivered lignin oil via reductive catalytic fractionation of pine. B.U.W.M. was guiding the scientists in Antwerp and B.S. in Leuven. J.B. performed the Green Metrics assessment. F.L. accomplished the HRMS analyses. The manuscript text was initially composed by J.B., which B.U.W.M. reworked. Subsequently, all authors commented and gave input on the final version. B.U.W.M. and S.S. identified and worked out the application potential of the synthetic methodology. S.S. assisted B.U.W.M. in the grant applications to secure funding for this work.

Conflicts of interest

There are no conflicts to declare.

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