Supplementary information

Efficient *O*-demethylation of lignin-derived aromatic compounds under moderate conditions

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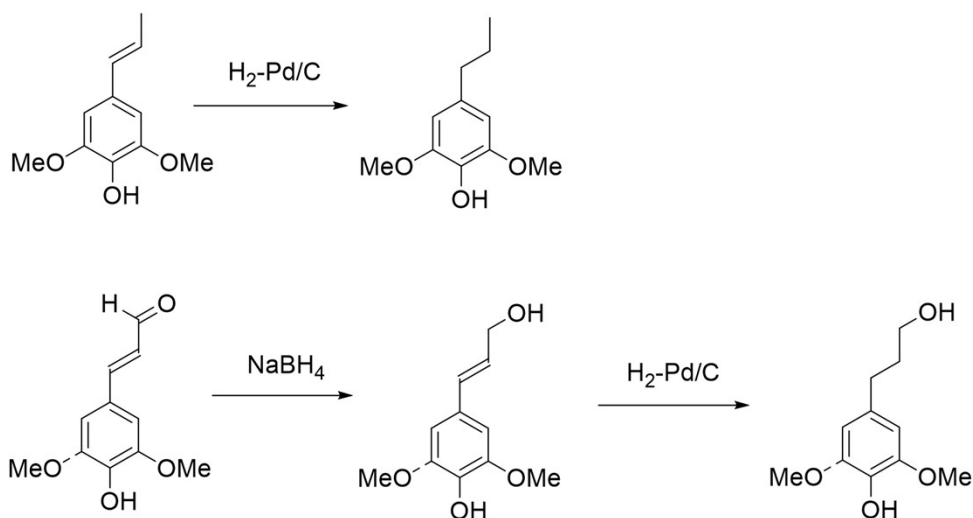*Corresponding author: xpan@wisc.edu

1. Synthesis of lignin compounds

Fig. S1 Preparation of 4-propylsyringol, 4-propanolguaiacol, and 4-propanolsyringol.

General procedure for the synthesis of 4-propylsyringol

4-Propylsyringol was synthesized from 4-propenylsyringol via double-bond saturating using H_2-Pd/C. The 4-propylsyringol was dissolved in MeOH in a round-bottom flask fitted with a magnetic stirrer. Pd/C (5 wt%) was then suspended in the solution. The gas in the solvent and flask was removed *in vacuo*, and the flask was then fitted with a hydrogen-filled balloon. The reaction suspension was stirred at room temperature for 2 h, then filtered through Celite. The reaction solvent was removed *in vacuo* and the crude product was redissolved in a small amount of EtOAc and then purified by flash-chromatography.[1]

General procedure for the synthesis of 4-propanolguaiacol and 4-propanolsyringol

4-Propanolguaiacol and 4-propanolsyringol were synthesized from coniferaldehyde and sinapaldehyde via $NaBH_4$ reduction followed by H_2-Pd/C double-bond saturation of coniferyl alcohol and sinapyl alcohol. $NaBH_4$ (5 eq.) was suspended in EtOH in a round-bottom flask and cooled in an ice-water bath. Aldehyde (1 eq. in EtOH) was added into the $NaBH_4$ suspension slowly through a dropping funnel. The reaction was gradually warmed to room temperature and

monitored by thin-layer chromatography (TLC) for 4 h. EtOAc was added, then DI-water and saturated NH₄Cl solution was added slowly using a dropping funnel. The aqueous layer was washed with EtOAc, and the combined organic layer was washed with brine, dried over MgSO₄, and evaporated in vacuo. The crude product was purified by flash chromatography. The procedure of double-bond saturation was as same as the above.[1]

2. Calculations of relative response factors (RRFs)

In our study, the RRFs of the compounds with commercial standards (pure reagent) were calculated and determined as follows:

$$RRF = \frac{m_0 \times A_{IS}}{m_{IS} \times A_0} \#(1)$$

where, m_0 and m_{IS} are the mass of the compound and internal standard, respectively; and A_0 and A_{IS} are the peak areas of the compound and internal standard, respectively.

The RRFs of the compounds without commercial standards including PS$_{int}$, PS, PGX, PCX, PSOH$_{int}$, PSX, PSX$_{int}$, and PPX were predicted using a model proposed by J. Y. de Saint Laumer *et al.* as follows:

$$RRF^{Pred} = 10^3 \times \frac{MW_0}{MW_{IS}} \times \left(\begin{array}{c} -61.3 + 88.8 \times n_C + 18.7 \times n_H - 41.3 \times n_O \\ + 6.4 \times n_N + 64.0 \times n_S - 20.2 \times n_F - 23.5 \times n_{Cl} \\ + 51.6 \times n_{Br} - 1.75 \times n_I + 39.9 \times n_{Si} \times 127 \times n_{Benz} \end{array} \right)^{-1} \#(2)$$

where, n_C, n_H, n_O, … are the number of carbon, hydrogen, oxygen, and other atoms in the compound; n_{Benz} is the number of benzene rings; and MW_0 and MW_{IS} are the molecular mass of the compound and the internal standard, respectively.

Since an FID is a burner, de Saint Laumer *et al.* [2–4] hypothesized that the RRFs would be correlated with the combustion enthalpies of compounds. Also, these combustion enthalpies were correlated

to the elemental composition of corresponding compounds. Therefore, the RRFs of the compounds can be predicted from their molecular formula. A database of 490 compounds indicated that the estimated RRFs had a mean accuracy of ±6%. The feasibility of this model in our study was confirmed by experimentally measuring the RRFs of PG and benzyl bromide, and then comparing them with the predicted RRF values. The measured RRFs of PG and benzyl bromide were 0.944 and 1.152, while the predicted RRFs were 0.931 and 1.220, respectively.

3. Brominated side-products

The brominated side-products were observed from GC-MS and the existence of bromine in ACLB was confirmed by the extraction of organic solvent. After adding the concentrated HCl to 61.7% LiBr, the colorless solution turned light yellow. After extraction by benzene, the organic phase was orange which indicates the existence of bromine, and the color of the aqueous phase became lighter.
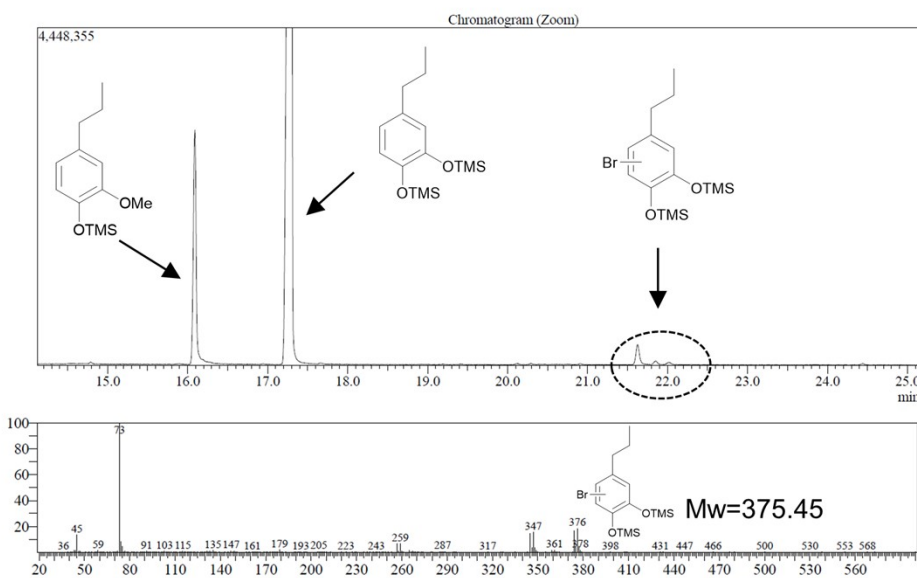

Fig. S2 GC-MS spectrum of the demethylation product from PG (Reaction conditions: 0.1 mmol PG, 2.5 mL 61.7% LiBr with 1.0 M HCl, 110 °C, and 2 h).
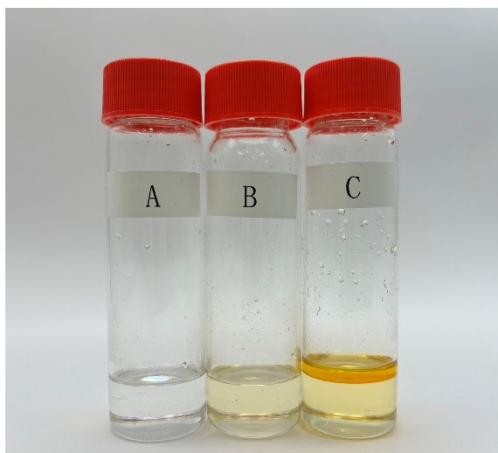
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Fig. S3 Observation of formation of bromine. (A) 61.7% LiBr solution (6.17 g LiBr and 3.83 g H$_2$O); (B) 61.7% LiBr solution with HCl (6.17 g LiBr, 3.27 g H$_2$O, and 0.89 g 37% HCl. The final HCl concentration is 1.5 M); (C) Bromine extracted into benzene (top layer).

4. Calculation of reaction rate constants

The rate constants for the demethylation of PG were examined by following the concentration of the reactant. As the concentration of Br$^-$ was much higher than the substrate (296 equiv.), the reaction can be considered a pseudo-first-order reaction. The equation for the concentration of PG is

$$[C] = [C_0]\exp\left(-kt\right) \#(3)$$

Where $[C_0]$ is the initial concentration of PG and the rate constant k was calculated using linear least squares fit of ln (C_0/C) versus t in Excel.
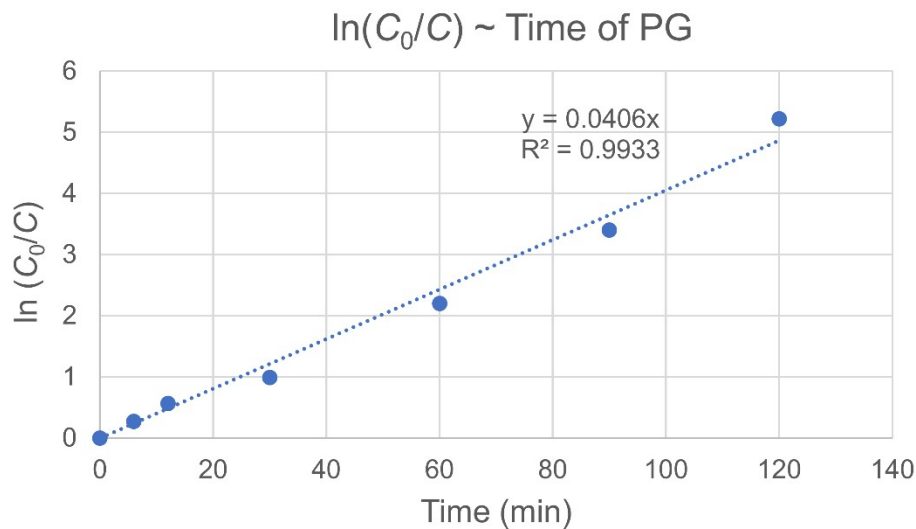
Fig. S4 Calculation for reaction constant for PG (Reaction conditions: 0.1 mmol 4-PG, 2.5 mL 61.7% LiBr with 1.5 M HCl, and 110 °C).

The rate constants for the demethylation of PS were examined by following the concentration of reactant and intermediate. The equation for the concentration of PS is as same as for PG to calculate k_1, and the equation for PS$_{int}$ is

$$[C] = [C_0]\frac{k_1}{k_1 - k_2}\{\exp\left(-k_1 t\right) - \exp\left(-k_2 t\right)\} \#(4)$$

Where $[C_0]$ is the initial concentration of the reactant PS. After the k_1 was calculated, the k_2 was then calculated by non-linear least-squares curve fitting using Excel Solver.
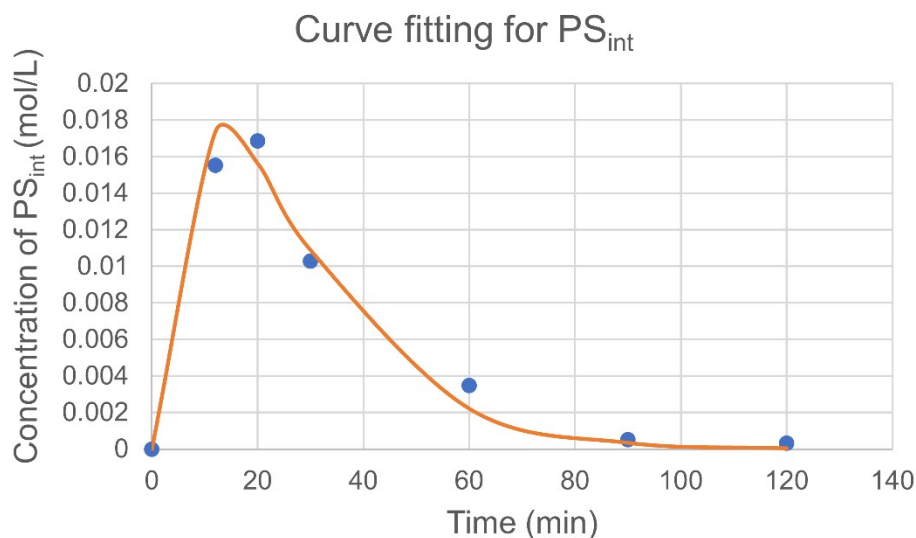
Fig. S5 Calculation for reaction constant for PS (Reaction conditions: 0.1 mmol PS, 2.5 mL 61.7% LiBr with 1.5 M HCl, and 110 °C).

5. Recent studies on the demethylation of aryl methyl ethers

Table S1. Demethylation methods of guaiacol derivatives and anisole retrieved from literature.

Substrate	Reagent and solvent	Hazard ranking[a]	Price[b]	Reaction condition	Yield (%)	Reference
4-PG	LiBr (296 equiv.)	Recommended	0.2 $/g	110 °C, 2 h	96	This work
	HCl (37.5 equiv.)	Recommended	0.02 $/g			
	H_2O (0.07 M)	Recommended	–			
4-PG	HCl (20–50 mol%)	Recommended	0.02 $/g	250 °C, N_2	91–97	(5)
	H_2O (0.50–2.00 M)	Recommended	–	(50 bar), 3 h		
4-PG	Nb_2O_5 (25 mol%)	Recommended	1.1 $/g	300 °C, N_2	84	(6)
	H_2O (0.30 M)	Recommended	–	(65 bar), 3 h		
4-PG	aq. 48% HBr (5 equiv.)	Problematic	0.08 $/g	115 °C, 20 h	97	(7)
4-PG	AlI_3 (1.1 equiv.)	Problematic	5.5 $/g	80 °C, 18 h	96	(8)
	DMSO (1.1 equiv.)	Problematic	0.2 $/g			

	MeCN (0.13 M)	Problematic	0.1 $/g			
Creosol	Al (2.6 equiv.)	Problematic	0.2 $/g	80 °C, 18 h	96	(9)
	I_2 (1.65 equiv.)	Problematic	0.3 $/g			
	MeCN (0.13 M)	Problematic	0.1 $/g			
Anisole	BCF (1 mol%)	Recommended	51.6 $/g	r.t., 1 h	87	(10)
	PMDS (1.1 equiv.)	Recommended	97.1 $/g			
Anisole	MgI_2 (1.5 equiv.)	Recommended	11.2 $/g	50 °C, 4 h	92	(11)
	[BMIM]BF_4 (0.5 M)	Problematic	1.3 $/g			
Vanillin	[BMIM]Br (12 equiv.)	Problematic	2.7 $/g	110 °C, microwave for 10 s	61	(12)
Anisole	LiI (2 equiv.)	Recommended	4.9 $/g	CO (5 MPa), 120 °C, 12 h	91[c]	(13)
	HMimBF$_4$ (7 equiv.)	Problematic	20.4 $/g			
	$RhCl_3$ (0.05 equiv.)	Hazardous	828.0 $/g			
	H_2O (15 equiv.)	Recommended	–			

[a] Hazard ranking for reagents and solvents is based on CHEM21 solvent selection guide.[14] [b] Prices based on data from Sigma-Aldrich (largest batch available) retrieved in February 2023. [c] Only the conversion was reported.

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