An efficient demethylation of aromatic methyl ethers with HCl in water

Supporting information

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1 General considerations

Unless stated otherwise, all solvents and commercially available reagents were used as received. Heptane, used for flash chromatography, was distilled prior to use. Pine wood was bought from a local supplier (Aveve) and grinded to powder. Non-commercial starting materials were prepared as described below. Water was deionized using a EUROTEC L4 reverse osmosis plant. The used water had a conductivity of max. 0.5 µS·cm⁻¹. Nuclear Magnetic Resonance (NMR) spectra were recorded on a Bruker Avance III 400 (101 MHz for ¹³C) Fourier Transform NMR spectrometer at 300 K (unless stated otherwise), using the non or partly deuterated solvent as internal standard (¹H: δ 7.26 ppm and ¹³C{¹H}: δ 77.16 ppm for CDCl₃; ¹H: δ 2.50 ppm and ¹³C{¹H}: δ 39.52 ppm for DMSO-d₆). Chemical shifts (δ) are reported in ppm; coupling constants (J) are reported in Hz; splitting patterns are assigned s = singlet, d = doublet, t = triplet, q = quartet, quint = quint, sext = sextet, sept = septet, b = broad signal, m = multiplet or combinations thereof. ¹³C NMR spectra were recorded with complete proton decoupling. ¹H NMR Yields were determined by addition of a known amount of an internal standard and dissolving everything in a suitable deuterated solvent, followed by ¹H NMR analysis. Gas chromatography-mass spectrometry (GC-MS) samples were prepared by dissolving 0.1-5 mg of the compound in acetone or acetonitrile and further diluted to a concentration of 10^{-4} - 10^{-6} M. 3 µL of the samples were injected. The apparatus used was an Agilent Technologies 7890 A GC System coupled to an Agilent Technologies 5975 C inert MSD with triple-axis detector. As column an Optima 725820.30 30 m \times 250 μ m \times 0.25 μ m was selected. Carrier gas was helium. For enantiopurity determination using liquid-chromatographymass spectrometry (LC-MS), samples were prepared by dissolving 2-4 mg of the compound in hexane/EtOH (80:20) and further diluted to a concentration of 10 $^{\text{-3}}\text{-}10^{\text{-4}}$ M. From these samples 20 μL were injected and analyzed via a Kontron HPLC autosampler 465 equipped with a Kontron HPLC pump 522, Chiralpak column, Waters Photo Diode Array detector and Jasco X-LC 3195CD system. High resolution mass spectrometry (HRMS) samples were prepared by dissolving 0.1-5 mg of the compound in MeOH/H₂O-containing 0.1% formic acid and further diluted to a concentration of 10⁻⁵-10⁻⁶ M for positive ion mode and by dissolving 0.1-5 mg of the compound in MeCN/H₂O and further diluted to a concentration of 10⁻⁴-10⁻⁵ M for negative ion mode. 10 µL of each sample was injected using the CapLC system (Waters) and electrosprayed using a standard electrospray source. Samples were injected with an interval of 3 minutes. Positive and/or negative ion mode accurate mass spectra were acquired using a Q-TOF II instrument (Waters). The MS was calibrated prior to use with a 0.1% H₃PO₄ solution. The spectra were lock mass corrected using the known mass of the nearest H₃PO₄ cluster or nearest known background ion. In positive ion mode, analytes were detected as protonated molecule or as a sodium adduct. In negative ion mode, analytes were detected as deprotonated molecule. All measured masses are within a difference of 5 ppm compared to the calculated mass unless specified otherwise. Thin layer chromatography (TLC) was performed using an organic solvent as mobile phase and silica coated on an aluminum plate (Machery-Nagel Precoated TLC sheets Alugram[®] SIL G/UV₂₅₄) as stationary phase. Compounds were detected by irradiation with UV light (254 nm and 366 nm). Melting points (m.p.) (uncorrected) were measured on a Büchi Melting Point B-545 apparatus. Chromatographic purification of products was performed by using an automated flash chromatography BiotageTM or Combiflash® system eluting with a flow rate of 30 mL·min⁻¹, otherwise indicated, utilizing commercially available Grace[™] GraceResolv[™] Silica Flash Cartridges or Büchi Flash Pure Reversed Phase C18 Cartridges. Centrifugation was performed using an Eppendorf Centrifuge 5702 at 4000 rpm for 1 h, unless stated otherwise.

High pressure equipment 2

2.1 **Description of the reactors**

A Parr® 4625 Pressure Vessel (600 mL internal volume) and a Parr® 4596 Micro Stirred Reactor (25 mL internal volume) were used. The latter was connected to a Parr[®] 4848 control unit, which enables to control the heating and read the internal pressure.

Experiments in the Parr[®] 4625 Pressure Vessel (600 mL internal volume) were typically performed in 4 mL glass vials (Wheaton®) containing a magnetic stirring bar. The loaded vials were sealed with a plastic cap (Wheaton® 13-425 cap, phenolic) equipped with a septum (Wheaton® 13 mm septum, *PTFE/white rubber*), through which a syringe needle (*Sterican*[®] 0.55 \times 25 mm 24G \times 1) was sting, and placed in a home-made aluminum alloy plate (which can contain up to 7 vials), which was then placed in a glass beaker (Parr® glass liner 762HC3) (Figure S1(a)). The beaker was placed in the Parr® 4625 reactor (Figure S1(b)). The autoclave was sealed (Figure S1(b)), using a torque wrench set at 27 Nm, purged (10 bar, 3 times) and pressurized with the indicated gas (pressure was measured by a classical pressure gauge). Then, the autoclave was heated in an IHP® band heater under magnetic stirring (Figure S1(d)). When the reaction was stirred during the indicated time at the indicated temperature, the autoclave was cooled down to room temperature in air or in an ice bath and subsequently, the gas was released and the reactor was opened.

Large scale experiments were performed in the glass beaker from Figure S1(a) as reaction vessel, without using the metal insert. This beaker was placed in the Parr® 4625 Pressure Vessel (Figure S1(b)). The reactor was closed, pressurized and heated as described before.



(a) Figure S1. Set-up for screening: running multiple reactions at the same time.

(b)

(c)

(d)

- (a) Reactions are run in 4 mL glass vials, which are sealed with a cap and a septum. A syringe needle sting through the septum enables gas to enter the vial, which provides the reaction mixtures (inside the glass vials) of the same atmosphere as applied in the reactor (outside the glass vials).
- (b) The Parr[®] 4625 Pressure Vessel (600 mL internal volume).
- (c) The closed Parr® 4625 reactor equipped with a pressure gauge, gas inlet, gas outlet and rupture disk.
- (d) The complete set-up in which the reactor is placed in the heating mantle on a magnetic stirring plate. Heating is controlled by the heating mantle (IHP[®] ceramic band heater).

Experiments in the Parr® 4596 Micro Stirred Reactor (25 mL internal volume) were typically performed in 4 mL vials (*vide supra*), which were placed in a homemade stainless steel insert (Figure S2). Samples were prepared as described for the 600 mL reactor. The autoclave was managed similarly to the 600 mL reactor, with as difference that to seal the reactor no torque wrench was used but a normal wrench.

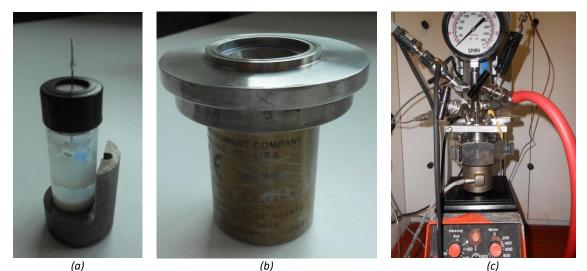


Figure S2. Set-up for running screening reactions.

(a) Reactions are run in 4 mL glass vials, which are sealed with a cap and a septum. A syringe needle sting through the septum enables gas to enter the vial, which provides the reaction mixtures (inside the glass vials) of the same atmosphere as applied in the reactor (outside the glass vials). The small gap next to the vial enables to measure the temperature of the insert.

- (b) The Parr® 4596 Micro Stirred Reactor vessel (25 mL internal volume).
- (c) The complete set-up in which the reactor is placed on a magnetic stirring plate. The Parr® 4596 Micro Stirred Reactor vessel is equipped with pressure gauge, gas inlet, gas outlet and rupture disk. A thermocouple is connected to the Parr® 4848 control unit in order to read the inside temperature (vide infra). This control unit itself is connected to the heating mantle, enabling regulation of heating rate.

2.2 Temperature control

The **Parr® 4596** reactor (25 mL internal volume) is connected to a **Parr® 4848 control unit** (Figure S3), which enables us to set the heating rate and regulate the temperature inside the reactor (for our specific set-up, i.e. a 4 mL glass vial in a home-made aluminum insert (see Figure S2(a)), the thermocouple fits in the small gap in the insert). This means that the temperature which is shown on the screen is the actual temperature of the reaction mixture, measured by a thermocouple connected to this control unit.

The IHP Ceramic ring heating mantle, which is used for heating of the **Parr® 4625 reactor** (600 mL internal volume) itself is connected to a similar control unit for heat regulation. In this case the temperature of the mantle is regulated rather than the temperature inside the reactor. Therefore, by placing a temperature sticker (*Thermax® Irreversible Temperature Recording Strips*) in the reactor (i.e. on the metal insert), it is possible to learn more about the heat transfer through the reactor wall and the actual temperature of the reaction mixture. It was found that to achieve a reaction temperature of 235 °C (Figure S4), it was necessary to heat the mantle to 260 °C. In this manuscript and SI, the temperature of the insert is always reported. For experiments in the Parr® 4625 reactor, this is the corrected temperature by using those stickers, while for the Parr® 4596 reactor, this is the temperature measured by the thermocouple.



Figure S3. A Parr® 4848 control unit. The left screen indicates the desired (green) and actual (red) temperature (in °C) inside the reactor. The middle screen indicates the desired (green) and actual (red) stirring rate (in rpm) of the mechanical overhead stirrer, which is not used in this project. The right screen indicates the actual (red) and maximal allowed (green) pressure (in bar) before the system stops working.



Figure S4. (a) A used temperature sticker, showing that the reaction media reached a temperature between 232 and 241 °C. (b) The heating system that was used for heating the Parr® 4625 reactor (IHP® Ceramic Ring Heating Mantle) (Figure S1(d)).

3 O-Dealkylation

3.1 General procedures

3.1.1 Screening experiments in the Parr® 4625 reactor

General procedure A

A 4 mL (or 20 mL if the reaction volume was higher than 3 mL) glass vial was charged with a magnetic stirring bar, the desired substrate (in the amount as reported), acidic catalyst and additional H₂O. The vial was closed using a black cap and septum and a needle was pierced through the septum. The vial was placed in the metal insert, together with other vials which could be run at the same time (when reaction time, atmosphere and temperature allowed it). The insert was placed in the glass beaker and the beaker was placed in the 600 mL reactor. The reactor was closed properly (in a criss-cross pattern, using a torque wrench which was set at 27 Nm, as requested by Parr®). The reactor was three times filled with 10 bar of the desired gas and released (while stirring magnetically), in order to flush. Subsequently, the reactor was filled with the desired gas (while stirring magnetically) to the desired pressure and the gas inlet line was closed and disconnected. The reactor was placed in the heating mantle and when the desired temperature was obtained (temperature heating mantle), counting of the reported reaction time started. After that time, the reactor was taken out of the heating mantle and cooled down to r.t., first in the air and when a safe temperature was reached (around 170 °C) further in an ice bath. Subsequently, the gas was released (while stirring magnetically), the reactor was opened and samples were taken out. To the crude sample were added an exact amount of internal standard and acetone (around 1-2 mL for 4 mL vials and around 10 mL for 20 mL vials) and the sample was stirred magnetically until homogenization. Subsequently, part of the solution was evaporated under reduced pressure. The residue was dissolved in a suitable deuterated solvent and measured with ¹H NMR spectroscopy. The yield for remaining substrate, formed product and other compounds was calculated versus the internal standard. Identity of the peaks on which the integration was performed was based on reference spectra in the same solvent. The experimental error on our data has been determined and the error related to the ^{1}H NMR yields was found to be +/- 5%.

3.1.2 Screening experiments in the Parr[®] 4596 reactor

General procedure B

A 4 mL glass vial was charged with a magnetic stirring bar, the desired substrate (in the amount as reported), acidic catalyst and additional H₂O. The vial was closed using a black cap and septum. A needle was pierced through the septum. The vial was placed in the metal insert, which was then placed in the 25 mL reactor. The reactor was closed properly (in a criss-cross pattern, as tight as possible). The reactor was three times filled with 10 bar of the desired gas and released (while stirring magnetically), in order to flush. Subsequently, the reactor was filled with the desired gas (while stirring magnetically) to the desired pressure and the gas inlet line was disconnected. The reactor was placed in the heating mantle, heating was started and when the desired temperature was obtained (temperature in the reactor), counting of the reported reaction time started. After that time, the reactor was taken out of the heating mantle and cooled down to r.t. in an ice bath. Subsequently, the gas was released (while stirring magnetically), the reactor was opened and samples were taken out. To the crude sample were added an exact amount of internal standard and acetone (around 1-2 mL) and the sample was stirred magnetically until homogenization. Subsequently, part of the solution was evaporated under reduced

pressure. The residue was dissolved in a suitable deuterated solvent and measured with ¹H NMR spectroscopy. The yield for remaining substrate, formed product and other compounds was calculated versus the internal standard. Identity of the peaks on which the integration was performed was based on reference spectra in the same solvent. The experimental error on our data has been determined and the error related to the ¹H NMR yields was found to be +/- 5%.

3.1.3 General procedure for experiments with isolation of the product

General procedure C

Reaction mixtures were prepared as described in General Procedure A or B and placed in the selected reactor. The reactor was closed, flushed, pressurized and heated as described. After the required reaction time, the reactor was cooled to r.t., depressurized and opened. The reaction mixture was transferred to a separatory funnel, NaCl (s) was added and the product was extracted with EtOAc. The combined organic layers were washed with brine and evaporated under reduced pressure.

General procedure D

Reaction mixtures were prepared as described in General Procedure A or B and placed in the selected reactor. The reactor was closed, flushed, pressurized and heated as described. After the required reaction time, the reactor was cooled to r.t., depressurized and opened. The reaction mixture was transferred to a separatory funnel, NaCl (s) was added and the product was extracted with EtOAc. The combined organic layers were treated with NaHCO₃ (aq., sat.). Subsequently, the aqueous layer was slowly neutralized with HCl (aq., 1 M) and extracted with EtOAc, after which the organic phase was evaporated under reduced pressure.

3.2 Reaction optimization

In preliminary research, we reported the *O*- and *C*-dealkylation of ferulic acid (**11**) to catechol (**2i**) in the presence of catalytic HCl in hot pressurized water. The formation of a benzylic alcohol upon Michael addition of H_2O to **11** was found to be crucial for the given conversion.¹ 4-Propylguaiacol (**1a**), not able to form a benzylic alcohol under the given conditions, only *O*-demethylated with the formation of 4-propylcatechol (**2a**) in 97% yield. However, these conditions were obtained through optimization of the *O*- and *C*-dealkylation of ferulic acid (**11**). Given the different nature of the side chain in 4-propylguaiacol (**1a**), it is expected that for selective *O*-demethylation of this compound, optimal conditions can be identified with improved Green Metrics also allowing scale-up.

We started from the initial reaction conditions (0.13 M, 50 mol% HCl, 250°C, initial N₂ pressure 50 bar, 3 h) reported for ferulic acid.¹ On 4-propylguaiacol (**1a**) these delivered 4-propylcatechol (**2a**) in 97% yield (Table S1, Entry 1). First, we looked if the substrate concentration could be increased, therefore leading to less solvent use, which will be beneficial for the green credentials of the reaction (see Section 4.3 of this SI). Gratifyingly, this was the case for concentrations up to 1.00 M (Table S1, Entries 1-6), since NMR yields for 4-propylcatechol (**2a**) higher than 90% were obtained in all cases. When pushing the substrate concentration further the yield decreased significantly from 92% at 1.0 M to 64% at 2.0 M (Entries 6-8). This is due to tar formation via unselective reactions clearly observed visually. At higher substrate concentration the crude product obtained after evaporation of volatiles became darker and more difficult to solidify, while the pure product is a(n) (off-) white solid. At 2.0 M, deposition of small black particles at the glass vial was also observed after 3 h. Interestingly, when the reaction time was reduced to 1 h at this concentration again 91% yield was obtained, pointing to an instability of reaction product (Entry 9). Despite the good result obtained in this reaction, it was decided to continue this optimization further at 1.00 M. This should prevent issues regarding solubility and subsequent decomposition of other organic molecules in the scheduled scope study.

	MeO HO 1a	Acic H ₂ O, te N ₂ (press.	mp.	HO	2a				
Entry	ELN code	Conc. 1a	la Acid Tem		Press.	ess. Time	NMR Yield (%) [a]		
Liitiy	ELIN COUE	(M) (mol%) (°		(°C)	(bar)	(h)	1a	2a	
1	MBAL-380, JBO-1658	0.13	HCI (50)	250	50	3	0	99 (97 ^[c])	
2	MBAL-405	0.20	HCI (50)	250	50	3	0	100	
3	MBAL-310	0.35	HCI (50)	250	50	3	0	98	
4	MBAL-406	0.50	HCI (50)	250	50	3	0	97	
5	MBAL-407	0.75	HCI (50)	250	50	3	0	93	
6	MBAL-408	1.00	HCI (50)	250	50	3	0	92	
7	MBAL-409	1.50	HCI (50)	250	50	3	0	84	
8	MBAL-410	2.00	HCI (50)	250	50	3	0	64 ^[b]	
9	JBO-643	2.00	HCI (50)	250	50	1	0	91 (91 ^[c])	

 Table S1. Optimization of the O-demethylation of 4-propylguaiacol (1a) to 4-propylcatechol (2a): substrate concentration.

Experiments were performed according to General Procedure B in 3 mL H₂O. ^[a] ¹H NMR Yield determined with dimethyl sulfone as internal standard. ^[b] Tar formation. ^[c] Yield of isolated product (General Procedure C).

Next to increasing substrate concentration, altering the amount of catalyst, i.e. HCl, was studied. Therefore, the amount of HCl present was varied from 100% to 10%. These loadings were performed at different substrate concentrations (i.e. 0.13, 0.35, 0.50, 0.75, 1.00 and 1.50 M) (Table S2). For all considered substrate concentrations, it was observed that no full conversion was obtained when using 10 mol% HCl (Entries 1, 5, 9, 13, 17 and 20). At 0.13 M **1a**, there was even no full conversion with 20 mol%, in contrast with all other substrate concentrations (Entry 2), while for 0.35, 0.50 and 0.75 M **1a**, no significant difference in yield was observed between 20 and 50 mol% HCl (Entries 6-7, 10-11, 14-15, 18-19 and 22-23), while increasing HCl loading to 100 mol% clearly had a deteriorating effect on the yield and the mass balance in combination with higher substrate concentrations (Entries 16, 20 and 24). This was even the case with 50 mol% at 1.00 and 1.50 M **1a** (Entries 19 and 23). From this Table S2, , it can be concluded that the best result was obtained when using 0.50 M **1a** and 20 mol% HCl (Entry 10). This loading is beneficial for the green credentials of the methodology when compared with the initial conditions reported (Table S1, Entry 1).

	MeO	\sim		Acid	но			
	но	 1a		O, temp. ress.), time	но	2a		
		Conc. 1a	Acid Temp.		Press. Time		NMR Yield (%) [a]	
Entry	ELN code	(M)	(mol%)	(°C)	(bar)	(h)	1a	2a
1	MBAL-412	0.13	HCI (10)	250	50	3	53	49
2	MBAL-379	0.13	HCI (20)	250	50	3	13	86
3	MBAL-380	0.13	HCI (50)	250	50	3	0	99
4	MBAL-413	0.13	HCI (100)	250	50	3	0	103
5	MBAL-308	0.35	HCI (10)	250	50	3	8	91
6	MBAL-309	0.35	HCI (20)	250	50	3	0	98
7	MBAL-310	0.35	HCI (50)	250	50	3	0	99
8	MBAL-414	0.35	HCI (100)	250	50	3	0	93
9	MBAL-415	0.50	HCI (10)	250	50	3	5	90
10	JBO-496, MBAL-441	0.50	HCI (20)	250	50	3	0	100 (97 ^[b])
11	MBAL-406	0.50	HCI (50)	250	50	3	0	97
12	MBAL-416	0.50	HCI (100)	250	50	3	0	97
13	MBAL-417	0.75	HCI (10)	250	50	3	2	98
14	MBAL-442	0.75	HCI (20)	250	50	3	0	98
15	MBAL-407	0.75	HCI (50)	250	50	3	0	93
16	MBAL-418	0.75	HCI (100)	250	50	3	0	84 ^[c]
17	MBAL-419	1.00	HCI (10)	250	50	3	3	97
18	MBAL-338, 382	1.00	HCI (20)	250	50	3	0	95
19	MBAL-409	1.00	HCI (50)	250	50	3	0	84 ^[c]
20	MBAL-420	1.00	HCI (100)	250	50	3	0	66 ^[c]
21	MBAL-421	1.50	HCI (10)	250	50	3	5	93
22	MBAL-422	1.50	HCI (20)	250	50	3	< 1	95
23	MBAL-409	1.50	HCI (50)	250	50	3	0	84 ^[c]
24	MBAL-423	1.50	HCI (100)	250	50	3	0	39 ^[c]

Table S2. Optimization of the O-demethylation of 4-propylguaiacol (1a) to 4-propylcatechol (2a): concentration and HCl loading.

Experiments were performed according to General Procedure B in 3 mL H₂O. ^[a] ¹H NMR Yield determined with dimethyl sulfone as internal standard. ^[b] Yield of the isolated product, obtained after evaporation and freeze-drying of the reaction mixture. ^[c] Tar formation.

Up to now, only HCl was considered as acidic catalyst. Since Chapter 2 showed that also other strong acids might be useful for this reaction,¹ an acid screening was subsequently performed, (Table S3). From a blank experiment revealved that addition of a suitable catalyst is required for this reaction (Entry 1), since no conversion was observed in neutral water. The optimal reaction conditions of Table S2 (Entry 10) were used as reference (Entry 3). Full conversion was not achieved using another Brønsted Acid (Entries 2-10). When analyzing the obtained results, we found a directly proportional relation between conversion and acid strength (Figure S5), where only triflic acid deviates (Entry 2). It was found that HCl could be successfully replaced by Lewis acid FeCl₃ leading to quantitative conversion (Entry 11), presumably by in situ HCl generation, while no reaction took place upon addition of CuCl2 (Entry 12). This route was not explored further, due to the more material intensive work-up when a metal is present in the reaction mixture.

	M	eO		cid	н		\checkmark		
	ł	HO 1a	H ₂ O, N ₂ (pres	temp. ss.), time	но	2a			
Fastaria	FIN and a	Conc. 1a	Acid	K [2]	Temp.	Press.	Time	NMR	Yield (%) ^[b]
Entry	ELN code	(M)	(mol%)	рК а ^[а]	(°C)	(bar)	(h)	1a	2a
1	JBO-799, MBAL-377	0.50	-	-	250	50	3	100	0
2	JBO-1476	0.50	TfOH (20)	-15	250	50	3	25	75
3	JBO-496, MBAL-441	0.50	HCI (20)	-8	250	50	3	0	100 (97 ^[c])
4	JBO-414, MBAL-311	0.50	H ₂ SO ₄ (20)	-3	250	50	3	6	94
5	JBO-435	0.50	MsOH (20)	-1.9	250	50	3	6	94
6	JBO-388	0.50	H ₃ PO ₄ (20)	2.15	250	50	3	70	30
7	JBO-452	0.50	4-NO ₂ PhCOOH (20)	3.41	250	50	3	89	11
8	JBO-451	0.50	PhCOOH (20)	4.20	250	50	3	97	3
9	JBO-372	0.50	HOAc (20)	4.76	250	50	3	100	0
10	JBO-371	0.50	H ₃ BO ₃ (20)	9.25	250	50	3	> 99	< 1 ^[d]
11	JBO-382	0.50	FeCl₃ (20)	N/A	250	50	3	0	100
12	JBO-381	0.50	CuCl ₂ (20)	N/A	250	50	3	> 99	< 1 ^[d]

 Table S3. Optimization of the O-demethylation of 4-propylguaiacol (1a) to 4-propylcatechol (2a): acid screening.

Experiments were performed according to General Procedure B in 3 mL H₂O. ^[a] pK_a of the used acid. For polyprotic acids, the pK_a of the first dissociation is mentioned. ^[b] ¹H NMR Yield determined with dimethyl sulfone as internal standard. ^[c] Yield of the isolated product, obtained after evaporation and freeze-drying of the reaction mixture. ^[d] Reaction product was observed via MS analysis of the crude mixture.

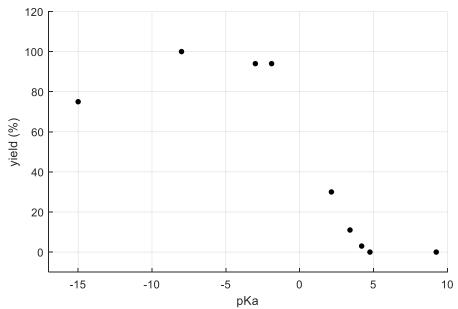


Figure S5. O-demethylation of propylguaiacol (1a) to propylcatechol (2a) as function of the pK_a of the used Brønsted Acid.

Considering of 20 mol% H₂SO₄ nearly delivered full conversion (Table S3, Entry 4), the effect of increasing the acid loading to 60 mol% and even a stoichiometric amount was investigated (Table S4).). Despite the increased acid loading, full conversion was not achieved as traces of substrate were still detected in the NMR analysis (Entries 3-5). Additionally, these new conditions revealed a loss of mass balance, in contrast with the result obtained by applying 100 mol% HCI (Entries 2 and 5). We found that when extending the reaction time to 6 h with 20 mol% H₂SO₄ gave full conversion and delivered the desired product in 97% yield (Entry 6). Also with the other H₂SO₄ loadings, full conversion of the starting material was observed after 6 h, though the desired product was obtained in significantly lower yield with lower mass balances (Entries 7-8), which was not the case when using HCI under the same conditions (Entries 8 and 9).

In a next stage, a temperature study was performed (Table S5). Increasing the temperature from 250 °C to 275 °C had no impact on the reaction outcome pointing to thermal stability of substrate and product (Entries 4 and 5). Lowering the temperature to 225 °C led to incomplete conversion (77%) (Entry 3). At 200 °C conversion decreased to only 3% (Entry 2). At 185 °C, substrate **1a** could be completely recovered (Entry 1). For comparison, applying Abu-Omar's conditions, based on 500 mol% HBr under reflux (Entry 6),² delivered a quantitative yield of **2a** after 20 h. When replacing this stronger acid by HCl, only 30% **2a** was obtained (Entry 7), leaving 56% **1a**.

An evaluation regarding the required reaction time was subsequently performed (Table S6). With reaction time, we mean the actual residence time of the reaction at the given temperature, not incorporating the time required for heating and cooling the set-up. We observed that already after 1 h more than 80% of the substrate was converted (Entry 1) and nearly quantitative conversion was achieved after 2 h (Entry 2). Therefore, a reaction time of 3 h was still considered to be optimal (Entry 3). By doubling the reaction time to 6 h 100% NMR and 95% isolated yield of the desired product was still achieved. This proves that this compound is relatively stable under the given reaction conditions

(Entry 4). 6 h at half the HCl loading still led to full conversion since only traces of the substrate remained (Entry 6). With this HCl loading 5% substrate remained after 3 h (Entry 5).

	HO HO 1	a	Ac H ₂ O, N ₂ (pres	temp.	но	2a		
Entry	ELN code	Conc. 1a	Acid	Temp.	Press.	Time	NMR	Yield (%) [a]
Entry	ELN COUE	(M)	(mol%)	(°C)	(bar)	(h)	1a	2a
1	JBO-496, MBAL-441	0.50	HCI (20)	250	50	3	0	100 (97 ^[b])
2	MBAL-416	0.50	HCI (100)	250	50	3	0	97
3	JBO-414, MBAL-463	0.50	H ₂ SO ₄ (20)	250	50	3	6	94
4	MBAL-464	0.50	H ₂ SO ₄ (60)	250	50	3	< 1	86
5	JBO-1421, MBAL-465	0.50	H ₂ SO ₄ (100)	250	50	3	< 1	89
6	MBAL-460	0.50	H ₂ SO ₄ (20)	250	50	6	0	97
7	MBAL-461	0.50	H ₂ SO ₄ (60)	250	50	6	0	81 ^[c]
8	MBAL-462	0.50	H ₂ SO ₄ (100)	250	50	6	0	26 ^[c]
9	MBAL550	0.50	HCI (100)	250	50	6	0	91

Table S4. Optimization of the O-demethylation of 4-propylguaiacol (1a) to 4-propylcatechol (2a): replacing HCl by H₂SO₄.

Experiments were performed according to General Procedure B in 3 mL H₂O. ^[a] ¹H NMR Yield determined with dimethyl sulfone as internal standard. ^[b] Yield of the isolated product, obtained after evaporation and freeze-drying of the reaction mixture. ^[c] Tar formation.

Table S5. Optimization of the O-demethylation of 4-propylguaiacol (1a) to 4-prop	ylcatechol (2a): screening of reaction
temperature.	

	MeO HO	H ₂ O	, temp. ss.), time	но_ но	2a	/		
Entry	ELN code	Conc. 1a	Acid	id Temp.	Press.	Time	NMR	Yield (%) [a]
Entry	ELN COUE	(M)	(mol%)	(°C)	(bar)	(h)	1a	2a
1	MBAL-439	0.50	HCI (20)	185	50	3	100	0
2	MBAL-444	0.50	HCI (20)	200	50	3	97	3
3	MBAL-357	0.50	HCI (20)	225	50	3	23	77
4	JBO-496, MBAL-441	0.50	HCI (20)	250	50	3	0	100 (97 ^[b])
5	MBAL-388	0.50	HCI (20)	275	50	3	0	100
6	BL-12	1.46 ^[c]	HBr (500)	115	1	20	0	99
7	JBO-598	2.40 ^[c]	HCI (500)	115	1	20	56	30

Experiments were performed according to General Procedure B in 3 mL H₂O. ^[a] ¹H NMR Yield determined with dimethyl sulfone as internal standard. ^[b] Yield of the isolated product, obtained after evaporation and freeze-drying of the reaction mixture. ^[c] The reported concentractions are obtained after dissolving substrate **1a** in the required amount of conc. HBr or HCl to deliver the reported acid loading.

	MeO	\sim		Acid			/	
	но	 1a), temp. ess.), time	HO 2a			
Factory of	ELN code	Conc. 1a	Acid	Temp.	Press.	Time	NMR	Yield (%) [a]
Entry	ELN CODE	(M)	(mol%)	(°C)	(bar)	(h)	1a	2a
1	MBAL-340	0.50	HCI (20)	250	50	1	17	83
2	MBAL-362	0.50	HCI (20)	250	50	2	4	96
3	JBO-496, MBAL-441	0.50	HCI (20)	250	50	3	0	100 (97 ^[b])
4	MBAL-449	0.50	HCI (20)	250	50	6	0	100
5	MBAL-415	0.50	HCI (10)	250	50	3	5	90
6	MBAL-466	0.50	HCI (10)	250	50	6	< 1	99

 Table S6. Optimization of the O-demethylation of 4-propylguaiacol (1a) to 4-propylcatechol (2a): screening of reaction time.

Experiments were performed according to General Procedure B in 3 mL H₂O. ^[a] ¹H NMR Yield determined with dimethyl sulfone as internal standard. ^[b] Yield of the isolated product, obtained after evaporation and freeze-drying of the reaction mixture.

In a final stage of this optimization, the influence of the addition of co-solvents was investigated, given the limited solubility of most organic molecules in water (Table S7). Both EtOH and MeOH were selected because of their miscibility with water and their classification as recommended solvent.³ In these experiments, a 100 mol% HCl loading was used since it delivered the same result as with 20 mol% when running the reaction in pure water (Entries 1-2), and in this way tackle a possible decrease in reaction rate because of the co-solvents. For both of the selected alcohols, an increase in reaction volume taken by this solvent had a negative impact on the yield for the desired product. For both, the decrease in yield is proportional to the amount of organic solvent added, leading to 0% of the desired product when running the reaction in pure alcohol (Entries 3-8 and 9-14). Furthermore, the increase in alcohol content negatively influenced the selectivity of the performed experiment. A noteworthy difference between EtOH and MeOH was observed, since when using the latter, a significant yield of the desired product **2a** with good mass balance is obtained even with 50% MeOH, opening opportunities for application of our methodology on (larger) less water soluble organic molecules.

Based on the results from this optimization, the conditions reported in Table S8 can be considered as "optimal" for the *O*-demethylation of 4-propylguaiacol (**1a**) to 4-propylcatechol (**2a**). With these conditions in hand, a substrate scope was performed.

		MeO		Acid	HO		\sim		
		HO 1a		Solvent, temp. N_2 (press.), time		HO ^{LI} 2a			
Entry	ELN code	Conc. 1a	Acid	Solvent	Temp.	Press.	Time	NMR Y	ield (%) ^[a]
Entry	ELIN COUP	(M)	(mol%)	Solvent	(°C)	(bar)	(h)	1a	2a
1	JBO-496 MBAL-441	0.50	HCI (20)	H ₂ O	250	50	3	0	100 (97 ^[b])
2	MBAL-416	0.50	HCI (100)	H ₂ O	250	50	3	0	97
3	MBAL-352	0.50	HCI (100)	H ₂ O / EtOH (90:10) ^[c]	250	50	3	< 1	78
4	MBAL-353	0.50	HCI (100)	H ₂ O / EtOH (75:25) ^[c]	250	50	3	3	69
5	MBAL-352	0.50	HCI (100)	H ₂ O / EtOH (50:50) ^[c]	250	50	3	11	65
6	MBAL-351	0.50	HCI (100)	H ₂ O / EtOH (25:75) ^[c]	250	50	3	48	30
7	MBAL-350	0.50	HCI (100)	H ₂ O / EtOH (10:90) ^[c]	250	50	3	97	6
8	MBAL-349 MBAL-368	0.50	HCI (100)	EtOH ^[c]	250	50	3	61	0
9	MBAL-367	0.50	HCI (100)	H ₂ O / MeOH (90:10)	250	50	3	4	85
10	MBAL-366	0.50	HCI (100)	H ₂ O / MeOH (75:25)	250	50	3	7	87
11	JBO-442 MBAL-365	0.50	HCI (100)	H ₂ O / MeOH (50:50)	250	50	3	19	72
12	MBAL-446	0.50	HCI (100)	H ₂ O / MeOH (25:75)	250	50	3	58	2
13	MBAL-447	0.50	HCI (100)	H ₂ O / MeOH (10:90)	250	50	3	38	0
14	MBAL-448	0.50	HCI (100)	MeOH ^[d]	250	50	3	16	0

 Table S7. Optimization of the O-demethylation of 4-propylguaiacol (1a) to 4-propylcatechol (2a): solvent screening.

Experiments were performed according to General Procedure B in 3 mL H₂O. ^[a] ¹H NMR Yield determined with dimethyl sulfone as internal standard. ^[b] Yield of the isolated product, obtained after evaporation and freeze-drying of the reaction mixture. ^[c] Commercial HCl in EtOH (1.25 M) was used, diluted with MeOH or EtOH or a mixture thereof. ^[d] Conc. HCl (aq.) was used, the amount of water present in the reaction medium is thus negligible.

Table S8. O-demethylation of 4-propylguaiacol (1a) to 4-propylcatechol (2a): optimal conditions.

	HO HO 1	a	Solven	t, temp. ss.), time	но	2a		
Entry	ELN code	Conc. 1a (M)	Acid (mol%)	Solvent	Temp. (°C)	Press. (bar)	Time (h)	Yield ^[a] (%)
1	JBO-496, MBAL-441	0.50	HCI (20)	H ₂ O	250	50	3	97
2	MBAL-560	0.50	HCI (20)	H₂O	275	50	3	92
3	MBAL-549	0.50	HCI (10)	H ₂ O	250	50	6	95
4	MBAL-551	0.50	H ₂ SO ₄ (20)	H₂O	250	50	6	97

Experiments were performed according to General Procedure C in 3 mL H₂O. Experiments were repeated 5 times and combined for work-up. ^[a] Yield of isolated product.

3.3 Reaction scope

3.3.1 Overview

In Table S9, an overview is given of all substrates mentioned in the Manuscript and their corresponding products. Each time, the conditions called "optimal" for the *O*-demethylation of 4-propylguaiacol (**1a**) were applied, as reported in Table S9, Entry 1: Substrate concentration: 0.50 M, HCl loading: 20 mol%, Reaction temperature: 250 °C, Reaction time: 3 h, Pressure at r.t.: 50 bar N₂). If required, a small optimization to improve conversion and yield was performed for every specific substrate, as shown underneath.

 Table S9. O-dealkylation of (substituted) anisols, guaiacols, dimethoxybenzenes, benzodioxoles, syringols.

			(R ¹ 0)		HCI		(HO)				
			Subst	rate	H ₂ O (3 mL), 250 °C N ₂ (50 bar), Time	Product					
		Conc	HCI	Time	Product 1		Product	2	Substr.		
ELN Code	Substrate	(M)	(mol%)	(h)	Structure	Yield (%) [a]	Structure	Yield (%) [a]	left (%) [a]		
JBO-510 MBAL-456	MeO、	0.50	20	3	HON	72	HO, A A	8	3		
MBAL-564	НО	0.50	20	6	HO	70	но	< 1	6		
MBAL-554	OMe	0.50	40	4	о́н	37	ОМе	0	4		
MBAL-500 MBAL-839	10	1b 2b 0.33 20 3	20	87 (74 ^[b, c])	1x	< 1	3				
MBAL-763	MeO	0.50	20	3	HO	87			7		
MBAL-775 MBAL-776	HO 1c	0.50	20	6	HO 2 c	90 (90 ^[b])			0		
MBAL-487 MBAL-494	HO HO 1d	0.50	20	3	HO HO 2d	99 (99 ^[b])			0		
MBAL-635	MeO	0.50	20	3	HO	92	HO HO	1a : 4 1v : 4	0		
MBAL-646 MBAL-660	MeO 1e	0.50	20	6	но 2а	96 (91 ^[b])	HO ↓ 1a (4- <i>n</i> Pr) 1v (5- <i>n</i> Pr)	0	0		
MBAL-726	EtO 0	0.50	20	3	HO	35			27		
MBAL-647 MBAL-659	Eto 1	0.50	20	6	HO 2a	97 (91 ^[b])			0		

^{[a] 1}H NMR Yield calculated with dimethyl sulfone as int. std. (General Procedure A); ^[b] Yield of isolated product (General Procedure C); ^[c] Additionally, recrystallization from toluene.

			(R ¹ 0)		HCI					
			Substrate		H ₂ O (3 mL), 250 °C N ₂ (50 bar), Time	$(HO) = \frac{1}{n} R^2$ Product				
	Cubatuata	Conc	HCI	Time	Product 1		Product	2	Substr.	
ELN Code	Substrate	(M)	(mol%)	(h)	Structure	Yield (%) [a]	Structure	Yield (%) ^[a]	left (%) ^[a]	
MBAL-451	0	0.50	20	3	0	93			3	
MBAL-614	МеО ОН	0.50	20	4	НООН	96		·	2	
MBAL-687 MBAL-699	HO [°] 1 g	0.50	20	6	т HO ² У 2е	90 (85 ^[d])			0	
MBAL-504	MeO,	0.50	20	3		87			4	
MBAL-688 MBAL-700	MeO 1h	0.50	20	6	HO Ze	91 (86 ^[d])			0	
MBAL-484		0.50	20	3		12		8	0	
MBAL-491	O	0.33	20	3	0	17	HO、	8	0	
MBAL-502	0.13 20	-	3	HOH	47	но	0	0		
MBAL-511	1i	0.13	20	1	HO 2f	61	2 i	0	0	
MBAL-543 MBAL-709		0.13	-	1		58 (62 ^[b])		0	0	

 Table S9 (continued).
 O-dealkylation of (substituted) anisols, guaiacols, dimethoxybenzenes, benzodioxoles, syringols.

^[a]¹H NMR Yield calculated with dimethyl sulfone as int. std. (General Procedure A); ^[b] Yield of isolated product (General Procedure C); ^[d] Yield of isolated product (General Procedure D).

			(R¹O) <u>, [²</u> , [∖ Subs	THE R	HCI H ₂ O (3 mL), 250 °C N ₂ (50 bar), Time	(HO)			
		Conc	HCI	Time	Product 1		Product	: 2	Substr.
ELN Code	Substrate	(M)	(mol%)	(h)	Structure	Yield (%) ^[a]	Structure	Yield (%) ^[a]	left (%) ^[a]
MBAL-695		0.13	20	3		14			31
MBAL-705		0.13	20	6		36			11
MBAL-710 (MBAL- 782)	N HCI	0.13	40	6	N HCI	57 (42 ^[b])			<1
MBAL-723	0	0.13	40	10	0	59			<1
MBAL-724		0.13	60	12		65			<1
MBAL-725	MeO OMe 1j	0.13	100	12	но он 2 g	60			<1
MBAL-505		0.50	20	3		34			<1
MBAL-627	0 //	0.50	20	6	O HO、 A	22			<1
MBAL-592	MeO	0.13	20	3	но	12			44
MBAL-628	MeO [×] 1k	0.13	20	6	2h	53			11
MBAL-639 MBAL-698		0.13	40	6		83 (79 ^[b])			<1
MBAL-428 SA-024	HO HO 1I	0.50	20	3	HO HO 2i	95 (97 ^[b])			0

 Table S9 (continued). O-dealkylation of (substituted) anisols, guaiacols, dimethoxybenzenes, benzodioxoles, syringols.

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 Anisola Signature

^[a] ¹H NMR Yield calculated with dimethyl sulfone as int. std. (General Procedure A); ^[b] Yield of isolated product (General Procedure C).

			(R ¹ 0) [HCI				
			(R'O), (. Subs	strate	H ₂ O (3 mL), 250 °C N ₂ (50 bar), Time	Product			
		Conc	HCI	Time	Product 1		Product	2	Substr.
ELN Code	Substrate	(M)	(mol%)	(h)	Structure	Yield (%) [a]	Structure	Yield (%) ^[a]	left (%) ^[a]
MBAL-453 MBAL-457	MeO	0.50	20	3	HO	97	MeO	2	0
MBAL-472	MeO 1m	0.50	20	4	HO 2i	86 (89 ^[b])	HO ² 1	<1	0
MBAL-480 MBAL-493	MeO EtO 1n	0.50	20	3	HO HO 2i	98 (98 ^[b])			0
MBAL-492 MBAL-497	MeO OMe 10	0.50	20	3	HO OH 2j	98 (98 ^[b])			
MBAL-452 JBO-325	MeO	0.50	20	3	HO	83	MeO	4	0
MBAL-503 MBAL-518	OMe 1p	0.33	20	3	он 2k	94 (92 ^[b])) ОН 1 w	0	0
SA-097		0.50	20	3		55			11
SA-101 SA-107	MeO 1q	0.50	100	3	HO 21	72 (62 ^[b])			< 1
MBAL-622	CI CI MeO	0.50	20	3	CI CI	63			25
MBAL-629 MBAL-640	™eO Cl 1r	0.50	20	6	CI 2m	99 (95 ^[b])			0

 Table S9 (continued).
 O-dealkylation of (substituted) anisols, guaiacols, dimethoxybenzenes, benzodioxoles, syringols.

^[a] ¹H NMR Yield calculated with dimethyl sulfone as int. std. (General Procedure A); ^[b] Yield of isolated product (General Procedure C).

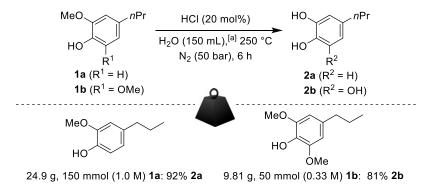
			(R ¹ O)	THR2	HCI → H ₂ O (3 mL), 250 °C N ₂ (50 bar), Time	$(HO)_{n} \stackrel{I}{\longrightarrow} R^{2}$ Product			
ELN Code	Substrate	Conc	HCI	Time	Product 1		Product 2		Substr.
ELIN CODE	Substrate	(M)	(mol%)	(h)	Structure	Yield (%) [a]	Structure	Yield (%) [a]	left (%) [a]
MBAL-526		0.50	20	3		92			3
MBAL-552 MBAL-613	MeO Is	0.50	20	4	HO 2n	88 (80 ^[b])			0
MBAL-625 MBAL-634	MeO It	0.50	20	3	HO 20	90 (94 ^[b])			0
MBAL-572		0.50	20	3	20	56		53	0
MBAL-573		0.13	20	3		71		70	0
MBAL-640		0.13	20	1		96	но	10	0
MBAL-631	1u	0.13	10	1	но́ 🗸 🗘 1 2р	97	2r	11	0
MBAL-665 ^[e] MBAL-668 ^[e]		0.13	20	3		100 (98 ^[b])		0	0

 Table S9 (continued).
 O-dealkylation of (substituted) anisols, guaiacols, dimethoxybenzenes, benzodioxoles, syringols.

^[a] ¹H NMR Yield calculated with dimethyl sulfone as int. std. (General Procedure A); ^[b] Yield of isolated product (General Procedure C); ^[e] Temperature = 200 °C.

3.3.2 Bench scale-up on two selected examples

The scalability of the developed *O*-demethylation protocol to multigram quantities was studied (Scheme S1) on 4-propylguaiacol (**1a**) and 4-propylsyringol (**1b**), which can be obtained from wood biorefinery, were selected for this study.⁴⁻⁷ The maximum scale was determined by the volume the reactor could be loaded with (150 mL) and the maximum applicable concentration for the selected substrate. Gratifyingly, *O*-demethylation of 9.81 grams **1b** at 0.33 M gave 6.69 grams **2b** (81%). With 4-propylguaiacol (**1a**) a higher concentration can be used and 24.9 grams **1a** at 1 M gave 21.1 grams **2a** (92%). These scale-up experiments can be performed without alterations of the reaction conditions at small scale, only the reaction time needed to be extended because of the larger volume to be heated.



Scheme S1. Bench scale-up examples. O-demethylation of 4-propylguaiacol (**1a**) and 4-propylsyringol (**1b**). ^[a] The volume of 150 mL was selected based on the employed 600 mL reactor with 375 mL glass insert (see Figure S1).

3.3.3 *O*-Demethylation of 4-propylguaiacol obtained from natural feedstock

The developed conditions were applied on two samples of 4-propylguaiacol (**1a**) obtained from natural feedstocks, i.e. eugenol (**3**) from *Eugenia* and lignin oil from pine wood. Methods for obtaining **1a** are described in Section 5.3.1 of this SI.

3.3.3.1 O-Demethylation of 4-propylguaiacol obtained from natural eugenol

Application of the optimal reaction conditions for the conversion of commercial 4-propylguaiacol (**1a**) into 4-propylcatechol on the same substrate **1a**, obtained upon hydrogenation of natural eugenol (**3**) from Merck (see Section 5.3.1.1), was insufficient as only 76% conversion **1a** was obtained after 3 h (Table S10, Entry 1). When doubling the reaction time to 6 h (Entry 2), **2a** was isolated with a yield of 96%, with work-up only involving extraction and filtration.

 Table S10.
 O-Demethylation of renewable 4-propylguaiacol (1a) obtained via hydrogenation of natural eugenol (3).

MeO HO :	- 3 tural	Pd/C (1 mol%) EtOH, r.t. H ₂ (2 bar), 16 h	MeO HO 1a, 97% (9	8% pure)	1.5 mmol 1a HCI (20 mol%) H ₂ O (3 mL), 250 °C N ₂ (50 bar), time	HO HO 2a
Entry	ELN Code	Scale 1a (mmol)	Conc. 1a (M)	Time (h)	No. of repetitions ^[a]	Yield 2a ^[b] (%)
1	MBAL-778	1.5	0.50	3	5	70 ^[c]
2	MBAL-781	1.5	0.50	6	4	96

Experiments were performed according to General Procedure C. ^[a] Samples were combined for work-up. ^[b] Yield of isolated product. ^[c] A mixture of 70% **2a** and 22% remaining **1a** was obtained.

3.3.3.2 O-Demethylation of 4-propylguaiacol obtained from lignin

Softwood-derived (*Pinus*) lignin oil (**1a**), obtained by Reductive Catalytic Fractionation (RCF) described in Section 5.3.1.2, was selected as second natural resource of 4-propylguaiacol (**1a**). Similarly to **1a** obtained by hydrogenation of natural eugenol (**3**), a reaction time of 6 h was required to obtain full conversion of the lignin oil (Table S11, Entries 1-2). The desired product **2a** could be successfully isolated with a yield of 77%, with the work-up involving only extraction and filtration (Entry 3).

 Table S11. O-Demethylation of 4-propylguaiacol (1a) obtained upon Reductive Catalytic Fractionation (RCF) of Pine wood.

Softwo (<i>Pinu</i> 150	(s)	C (15 g) M → 35 °C), 16 h	MeO HO t% 1a in 10.4 g lignin	N ₂ (50	HCI mL), 250 °C 0 bar), time	но	2a	\checkmark
Entry	ELN Code	Scale oil (mg)	Amount 1a in oil (mmol) ^[a]	Conc. 1a (M)	HCl (mmol)	Time (h)	Yie 1a	eld (%) ^[b] 2a
1	MBAL-797	352	1.35	0.50	0.30	3	19	70
2	MBAL-800	352	1.35	0.50	0.30	6	0	80
3	MBAL-813	390	1.50	0.50	0.30	6	0	79 (77 ^[c])

Experiments were performed according to General Procedure C. ^[a] Determined via ¹H NMR analysis using 1,3,5trimethoxybenzene or 2-MeTHF as int. std. ^{[b] 1}H NMR Yield determined with 1,3,5-trimethoxybenzene or 2-MeTHF as int. std. ^[c] Yield of isolated product.

4 Evaluation of the green credentials for the developed *O*-demethylation methodology

4.1 Introduction

In order to evaluate the *greenness* of the developed approach for the *O*-demethylation of 4propylguaiacol (**1a**) to 4-propylcatechol (**2a**), this reaction was evaluated using the CHEM21 Green Metrics Toolkit (Section 4.3).⁸ Assessment of the so-called *green metrics* is a relative concept. Therefore, the same analysis was performed for other methods, retrieved from literature, involving the same conversion. These methods are briefly described in Section 4.4. This way, we were able to compare our newly developed method with existing methods with respect to greenness.

For this paper, we specifically looked at green chemistry aspects when developing the *O*-demethylation method by reducing the amount of solvents used, and by carefully selecting the solvents used during reaction and work-up (no problematic or hazardous according to the CHEM21 Solvent Selection Guide)³ in order to maximize greenness. We are aware of the fact that literature procedures are often not written keeping aspects of green chemistry in mind. Moreover, exact amounts of solvents used for extraction as well as other auxiliary materials for purification (e.g. celite for filtration, amount of silicagel used for column chromatography) are simply not specified. In order to have a fair comparison, we therefore look into the *PMI Reactants, Reagents and Catalysts* (PMI RRC), which only takes into account reactants, reagents and catalysts and does not consider the used solvents and work-up methods. This parameter gives a good impression on the green potential of the used chemistry. Considering at discovery level small scales are applied, typically low concentrations are chosen for reactions. While there is in most cases no reason these reactions cannot be executed at a higher concentration, it will negatively influence the *PMI Reaction* (PMI Rxn) involving Reactants, Reagents, Catalysts and Solvent. PMI RRC, excluding reaction solvent, is therefore a fairer and safer way to look at the reaction than *PMI Reaction* (PMI Rxn) at the discovery stage.

4.2 The CHEM21 Green Metrics Toolkit

The CHEM21 Green Metrics Toolkit is split into four *passes* with increasing complexity.⁸ The two lowest levels, the so-called *zero pass* and *first pass*, are used for laboratory research (discovery phase), whereas the *second pass* and *third pass* are meant to be used at pilot and industrial scale. This toolkit consists of two major parts: *quantitative* and *qualitative* parameters. For assessing the first category, different calculations are performed after which the obtained values for different methods are compared, while for the latter different parameters are measured with a color code flag (green for *preferred*, yellow for *acceptable* and red for *undesirable*). A user friendly Microsoft Excel spreadsheet is available free of charge and was used in this paper for the assessment of the *greenness* of the different reactions.⁹

Before starting the analysis, the different chemicals used in the reaction need to be classified as either reactant, reagent, catalyst or solvent. The definitions for solvent and catalyst are obvious. A reactant is defined as a compound which contains at least one atom which is built in in the product, while a reagent is only consumed during the reaction without being incorporated in the product.

4.2.1 Quantitative parameters

For every evaluated reaction, the *yield* of the desired product is reported. This parameter can already give a first impression of how the reaction is behaving. When combined with *conversion*, a value for *selectivity* can be obtained. A reaction with high yield and high selectivity is desirable. These parameters are calculated using the following equations:

$$\begin{aligned} \text{Yield (\%)} &= \frac{\text{moles of product}}{\text{moles of limiting reactant}} \times 100\% \\ \text{Conversion (\%)} &= 100\% - \left(\frac{\text{mass of limiting reactant}}{\text{initial mass of limiting reactant}}\right) \times 100\% \\ \text{Selectivity (\%)} &= \frac{\text{Yield}}{\text{Conversion}} \times 100\% \end{aligned}$$

Next to the parameters presented above, *Atom Economy* (AE) and *Reaction Mass Efficiency* (RME) are often used by organic chemists to get a first view of the efficiency of the reaction. AE is measured by the number of the atoms in the reactants which appear in the final product and therefore, molecular weights are incorporated in the formula. An important remark about AE is that it does not incorporate used excesses of reactants and is a purely theoretical parameter of interest in the retrosynthesis phase. For this reason, RME is also defined incorporating the stoichiometry of the reaction. Important to mention is that both do not incorporate reagents or catalysts. The following formulas are used:

AE (%) =
$$\frac{MW_{product}}{\sum MW_{reactants}} \times 100\%$$
 RME (%) = $\frac{m_{product}}{\sum m_{reactants}} \times 100\%$

The most complete mass-based metric is the *Process Mass Intensity* (PMI), which takes into account all mass-based inputs: yield, stoichiometry, solvents, reagents and work-up. It is defined as "mass of all chemicals used in a reaction divided by the mass of the isolated product", therefore it is expressed on a mass/mass ($g \cdot g^{-1}$) basis:

$$PMI (g \cdot g^{-1}) = \frac{\sum \text{mass of all materials used in a process step}}{\text{mass of the isolated product}}$$
$$= \frac{m_{\text{reactants}} + m_{\text{reagents}} + m_{\text{catalysts}} + m_{\text{reaction solvent}} + m_{\text{work-up chemicals}} + m_{\text{work-up solvents}}}{m_{\text{product}}}$$

PMI is easier to follow if this parameter is split into three categories: *PMI Reactants, Reagents and Catalysts* (PMI RRC), which only takes into account reactants, reagents and catalysts; *PMI Reaction* (PMI Rxn), which additionally also contains reaction solvent; and *PMI Work-up* (PMI WU), in which only the work-up (both auxiliary materials for purification and solvents) of a certain reaction is considered. As already stated earlier, the latter sub category is of less relevance for discovery research.

$$PMI RRC (g \cdot g^{-1}) = \frac{m_{reactants} + m_{reagents} + m_{catalysts}}{m_{product}}$$

$$PMI Rxn (g \cdot g^{-1}) = \frac{m_{reactants} + m_{reagents} + m_{catalysts} + m_{reaction solvent}}{m_{product}}$$

$$PMI WU (g \cdot g^{-1}) = \frac{m_{work-up chemicals} + m_{work-up solvents}}{m_{product}}$$

Recently, a new quantitative metric was developed, when a co-product useful in another process is produced in the reaction and therefore not to be considered as waste.¹⁰ This is labelled Feedstock Intensity (FI) and is calculated similarly to PMI. The difference between PMI and PMI_{FI} is the mass of the produced co-product which is integrated in the denominator of the formula. When a step produces no useful co-product it is waste, PMI_{FI} is then equal to PMI.

$$PMI_{FI} (g \cdot g^{-1}) = \frac{\sum \text{mass of all materials used in a process step}}{\text{mass of the isolated products}}$$
$$= \frac{m_{\text{reactants}} + m_{\text{reagents}} + m_{\text{catalysts}} + m_{\text{reaction solvent}} + m_{\text{work-up chemical}} + m_{\text{work-up solvents}}}{m_{\text{product}} + m_{\text{co-product}}}$$

PMI_{FI} can also be split up in different categories:

$$PMI_{FI} RRC (g \cdot g^{-1}) = \frac{m_{reactants} + m_{reagents} + m_{catalysts}}{m_{product} + m_{co-product}}$$

$$PMI_{FI} Rxn (g \cdot g^{-1}) = \frac{m_{reactants} + m_{reagents} + m_{catalysts} + m_{reaction solvent}}{m_{product} + m_{co-product}}$$

$$PMI_{FI} WU (g \cdot g^{-1}) = \frac{m_{work-up chemicals} + m_{work-up solvents}}{m_{product} + m_{co-product}}$$

Similarly, formulas for AE and RME can also be adapted with inclusion of the formed useful co-product:

$$AE_{FI} (\%) = \frac{MW_{product} + MW_{co-product}}{\sum MW_{reactants}} \times 100\%$$
$$RME_{FI} (\%) = \frac{m_{product} + m_{co-product}}{\sum m_{reactants}} \times 100\%$$

A second quantitative parameter including the mass of all used materials, and therefore related to PMI, is the E-factor,¹¹ quantifying the amount of generated waste to produce a certain mass of the desired product:

$$E-factor (g \cdot g^{-1}) = \frac{mass of generated waste}{mass of the isolated product}$$
$$= \frac{m_{reactants} + m_{reagents} + m_{catalysts} + m_{reaction solvent} + m_{work-up chemical} + m_{work-up solvents} - m_{product}}{m_{product}}$$
$$= PMI (g \cdot g^{-1}) - 1$$

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4.2.2 Qualitative parameters

The second part of the CHEM21 Green Metrics Toolkit consists of a series of parameters for which the score is obtained by giving a colored flag. When for a certain item a green flag is scored, it means that the reaction is behaving well, while a red flag leads to the opposite conclusion. Intermediate scores are made visible by scoring a yellow flag which stands for "acceptable, but with some issues". Whenever possible further optimization should be considered in such case. In Table S12, a brief overview is given on how the flags are determined for each item (except solvents).

ltom	Green flag	Yellow flag	Red flag	
Item				
Catalyst / Enzyme use	Reaction uses a catalyst or enzyme or no additional reagent was used	Use of stoichiometric quantities of reagents	Use of reagents in excess	
Catalyst / Enzyme recovery	Recovery	No recovery	-	
Critical elements	Supply remaining for more than 500 years	Supply remaining for 50 to 500 years	Supply remaining for less than 50 years	
Energy (part 1)	Reaction temperature between 0 and 70 °C	Reaction run between -20 to 0 °C or 70 to 140 °C	Reaction run below -20 °C or above 140 °C	
Energy (part 2)	Reaction run 5 °C or more below the solvent's boiling point	-	Reaction run at reflux	
Batch / Flow	Flow	Batch	-	
Work-up	Quenching, Filtration, Centrifugation, Crystallization, Low temperature distillation / evaporation / sublimation	Solvent exchange, quenching into aqueous solvent	Chromatography, ion exchange, high temperature multiple recrystallization	
Health and Safety	-	H205, H220, H224, H241, H301, H311, H331, H341, H351, H361, H371, H373, H401, H412	H200, H201, H202, H203, H230, H240, H250, H300, H310, H330, H340, H350, H360, H370, H372, H400, H410, H411, H420	

Table S12. Brief overview of the different qualitative parameters to be considered in a green metrics analysis at First Pass.

For solvent use, one can make use of the open access CHEM21 Solvent Selection Guide.³ In Table S13, the most common solvents are listed together with the flag they score. When a solvent is not in this list, the Solvent Guide explains which properties of the solvent should be considered when classifying the solvent in a specific category. These parameters are physical properties (e.g. boiling and flash points, ignition temperature), peroxability, resistivity, H statements and REACH registration.

Green flag "Recommended"	water, methanol (MeOH), ethanol (EtOH), isopropanol (ⁱ PrOH), 1-butanol (ⁿ BuOH), <i>tert</i> - butanol (^t BuOH), ethylene glycol, acetone, methyl ethyl ketone (MEK), methyl isobutyl ketone (MIBK), ethyl acetate (EtOAc), isopropyl acetate (ⁱ PrOAc), <i>n</i> -butyl acetate (ⁿ BuOAc), anisole, isobutanol, isoamyl alcohol, isobutyl acetate, isoamyl acetate, glycol diacetate, <i>tert</i> - amyl methyl ether (TAME), dimethyl carbonate
Yellow flag "Problematic"	benzyl alcohol, cyclohexanone, methyl acetate, tetrahydrofuran (THF), 2-methyl tetrahydrofuran (2-MeTHF), heptane, cyclohexane, methylcyclohexane, toluene, xylene, chlorobenzene, acetonitrile, 1,3-dimethyl-3,4,5,6-tetrahydro-2(1 <i>H</i>)-pyrimidinone (DMPU), dimethyl sulfoxide (DMSO), formic acid, acetic acid, acetic anhydride, 1,3-propanediol, glycerol, diethyl succinate, cyclopentyl methyl ether (CPME), ethyl <i>tert</i> -butyl ether (ETBE), p-limonene, turpentine, <i>p</i> -cymene, ethylene carbonate, propylene carbonate, cyrene, ethyl lactate, lactic acid
Red flag "Hazardous"	di-isopropyl ether, methyl <i>tert</i> -butyl ether (MTBE), 1,4-dioxane, dimethoxyethane (DME), pentane, hexane, dichloromethane (DCM), <i>N</i> , <i>N</i> -dimethylformamide (DMF), <i>N</i> , <i>N</i> -dimethylacetamide (DMAc), <i>N</i> -methyl-2-pyrrolidone (NMP), sulfolane, methoxy-ethanol, pyridine, triethylamine, trimethylamine
Dark red flag "Highly hazardous"	diethyl ether (Et ₂ O), benzene, chloroform (CHCl ₃), carbon tetrachloride (CCl ₄), dichloroethane (DCE), nitromethane, hexamethylphosphoramide (HMPA), carbon disulfide (CS ₂)

4.3 Application of the CHEM21 Green Metrics Toolkit on the developed demethylation strategy

In the Manuscript, the Green Metrics analysis for Methods A1-3 has been reported. These methods describe the demethylation of 4-propylguaiacol [Method A1: 0.50 M **1a** and 20 mol% HCl (Table S14, Entry 2); Method A2: 1.0 M **1a** and 20 mol% HCl (Table S14, Entry 3); Method A3: 2.0 M **1a** and 50 mol% HCl (Table S14, Entry 4)] and guaiacol [Method A3: 2.0 M **1a** and 50 mol% HCl (Table S14, Entry 6)]. Furthermore, we also applied the Green Metrics Analysis for the demethylation of 4-propylguaiacol under the earlier reported conditions not specifically designed for this process [Method A4: 0.13 M **1a** and 50 mol% HCl (Table S14, Entry 1)],¹ and for demethylation of guaiacol under the conditions reported in the Scope Section of the Manuscript [Method A1: 0.50 M **1a** and 20 mol% HCl (Table S14, Entry 5)].

From the results in Table S14 can be derived that, despite the high yield for Method A4 (Entry 1), a PMI of 52 g·g⁻¹ was obtained. The work-up of this Method did not require any material, as it consisted of removing volatiles via freeze-drying, and therefore its PMI is completely attributable to the reaction itself. The difference between PMI Rxn and PMI RRC, 50.6 g·g⁻¹, shows that the solvent use is the biggest material sink (more than 97% of the required input is attributed to the solvent). After the reaction optimization, Method A1 (Entry 2) revealed to be optimal , involving an increased substrate concentration and decreased HCl loading. Both modifications had a beneficial impact on the greenness of the reaction, since from the original PMI Rxn less than 30% was left (15 g·g⁻¹) and PMI RRC decreased

slightly to 1.3 g·g⁻¹, leading to a total PMI of 15 g·g⁻¹. By applying a further increase in substrate concentration to 1.0 M or 2.0 M (Methods A2-3, Entries 3-4), however with increased HCl loading (50 mol%) and decreased reaction time (1 h) for the latter, the desired product was obtained in good selectivity. Despite the decrease in yield to 91%, PMI decreased even further to 11 g·g⁻¹. In this case, work-up, based on extraction with EtOAc, was required in order to remove the formed impurities since freeze drying was not possible. Therefore, PMI WU is not equal to zero. Overall, PMI Rxn (including the reaction solvent, which is H₂O) could be reduced to 5.0 g·g⁻¹.

For the demethylation of guaiacol (1) to catechol (2i), similar conclusions could be drawn (Methods A1,3, Entries 5 and 6, respectively). Again, performing the reaction at a higher substrate concentration (2.0 M) and HCl loading (50 mol%) led to a 25% decrease in PMI. Because of the lower molecular weight of catechol (2i) compared to 4-propylcatechol (2a), PMI values are slightly higher in this case. For this specific conversion, the new conditions did not affect the yield. When looking at the qualitative metrics (Table S15), it can be seen that for this method mainly green flags are obtained. Only for energy consumption, a red flag is scored because of the high reaction temperature. One needs to realize that this is a very basic analysis of energy consumption, suitable for first pass green metrics, and does not reflect the final energy use, which is simply not possible at the discovery level as e.g. reaction times are not minimized, no heat recovery, etc. In development projects using this new method, a more indepth study should be performed. The required extraction in the work-up when working at higher substrate concentration (Methods A2-3), brings a yellow flag there, in contrast with the obtained green flag in the cases when freeze drying was sufficient to deliver pure reaction product.

Table S14. Quantitative metrics for the demethylation of (4-propyl)guaiacol (1a and 1l) to (4-propyl)catechol (2a and 2i) under acidic catalysis.

				(R = nPr) $I(R = H)$		Method A1 (HCl 20-50 m (0.13-2.00 M N ₂ (50 bar), t (97-91% y	ol%)), 250 °C time	A1,4	or A2,3		HO HO 2a (R = nPr) 2i (R = H)			
Entry	Method ^[a] [ELN Code]	Substrate	R	Time (h)	Conc. (M)	HCl (mol%)	Yield (%)	AE (%)	RME (%)	PMI (g∙g⁻¹)	PMI RRC ^[b] (g·g ⁻¹)	PMI Rxn ^[b] (g·g⁻¹)	PMI WU ^[b] (g·g ⁻¹)	E-factor (g·g ⁻¹)
1	A4 [JBO-1658]	1a	<i>n</i> Pr	3	0.13	50	97	83	80	52	1.4	52	0	51
2	A1 [JBO-496]	1a	<i>n</i> Pr	3	0.50	20	97	83	80	15	1.3	15	0	14
3	A2 [MBAL-766]	1a	<i>n</i> Pr	3	1.00	20	96	83	79	20	1.3	8.0	12	19
4	A3 [JBO-643]	1a	<i>n</i> Pr	1	2.00	50	91	83	75	11	1.5	5.0	6.4	10
5	A1 [SA-024]	11	н	3	0.50	20	96	77	75	20	1.4	20	0	19
6	A3 [MBAL-467]	11	Н	1	2.00	50	93	77	72	15	1.6	6.3	8.7	14

^[a] Experimental procedures are reported in Section 5.1 of this SI. The required N₂ gas to provide the pressurized atmosphere was not incorporated in the calculations since it is dependent on the volume of the reaction vessel and it would not affect the results significantly. ^[b] RRC: Reactants, Reagents, Catalysts. Rxn: Reaction. WU: Work-up.

Table S15. Qualitative Appraisal of Solvent Use, Inherent Hazards of Used Chemicals, Catalyst or Reagent Use, Energy and Work-up Methods for the demethylation of (4-propyl)guaiacol (1a and 1l) to (4-propyl)catechol (2a and 2i) under acidic catalysis.

Method [ELN Code] and Substrate	Solvent Rxn	Flag	Solvent WU	Flag	Critical elements ^[a]	Flag	Health and Safety ^[a, b]	Flag	Reagent use	Flag	Energy	Flag	Work-up	Flag
A4 [JBO-1658] (1a) A1 [JBO-496] (1a) A1 [SA-024] (1I)	H ₂ O		-		-		-		Catalyst		250 °C		Freeze drying	
A2 [MBAL-766] (1a) A3 [JBO-643] (1a) A3 [MBAL-467] (11)	H ₂ O		EtOAc		-		-		Catalyst		250 °C		Extraction	

^[a] When a yellow or red flag is not applicable, this column is left blank. ^[b] 4-propylguaiacol (**1a**), is toxic in contact with skin (H311). Also catechol (**2i**) has this property and has a long term toxicity issue (H341), which all lead to a yellow flag for "Health & Safety". However, these are the starting material or product for the different approaches and therefore not included.

4.4 Selection of reference O-demethylation methods for Green Metrics analysis

4.4.1 Literature reports for the synthesis of 4-propylcatechol from 4-propylguaiacol

In order to select suitable literature examples, a SciFinder[®] search was performed containing 4propylguaiacol (**1a**) as reactant and 4-propylcatechol (**2a**) as product. The methods reported in Table S16 were retrieved from this search. Methods B and F2 were repeated in our lab, since either no complete work-up was provided in literature (Method B) or the experiment was performed on a very small scale (Method F1). Full experimental procedures can be found in Sections 5.2.1 and 5.2.2.

		MeO	Reactants & Reagents	HO		
		но	Conditions	но		
Method	Scale (mmol)	1a Reactants & Reagents	Conditions	2a Work-up	Yield [a] (%)	Ref.
B [MBAL-810]	3.00	Nb ₂ O ₅ (25 mol%)	H ₂ O (0.30 M) 300 °C, 3 h N ₂ (65 bar)	Centrifugation Extraction with EtOAc	79	12
C1	100	HBr (4.9 equiv.)	H₂O (2.4 M) 115 °C, 19 h	NaCl for saturation Extraction with Et ₂ O	94	2
C2	200	HBr (5.0 equiv.)	H₂O (2.4 M) 115 °C, 16 h	Dilution with MTBE Washing with brine and NaHCO ₃	97	13
D	5.00	All₃ (1.1 equiv.) DMSO (1.1 equiv.)	MeCN (0.13 M) 80 °C, overnight	Quenching with HCl Extraction with EtOAc Washing with Na ₂ S ₂ O ₃	96	14
E	0.70	SIBX (2.1 equiv.) ^[c]	THF (0.05 M) r.t., 12 h	Dilution with H ₂ O Extraction with CH ₂ Cl ₂ Washing with aq. Solutions	89	15
F1	0.23	BBr ₃ (1.1 equiv.)	CH₂Cl₂ (0.35 M) -78 °C, 1 h	Quenching with H ₂ O Extraction with CH ₂ Cl ₂ Column chromatography	86	16
F2 [BL-10]	10.0	BBr ₃ (1.1 equiv.)	CH₂Cl₂ (0.67 M) -94 °C, 1 h	Quenching with H ₂ O NaCl (s) until saturation Extraction with CH ₂ Cl ₂	92	17
A3 [JBO-643]	10.0	HCl (0.2 equiv.)	H₂O (2.0 M) 250 °C, 3 h N₂ (50 bar)	Salting out with NaCl Extraction with EtOAc	91	-

 Table S16. Literature reports for the O-demethylation of 4-propylguaiacol (1a) to 4-propylcatechol (2a).

^[a] Yield of isolated product, unless stated otherwise. ^[b] 3% starting material was left. ^[c] SIBX: stabilized formulation of 2-iodoxobenzoic acid (IBX), i.e. a mixture of benzoic acid (22%), isophthalic acid (29%) and 2-iodoxobenzoic acid (49%).

4.4.2 Other classical *O*-demethylation procedures for Green Metrics analysis

Classical *O*-demethylating agents such as TMSI and AlCl₃ described for *O*-demethylation of guaiacol (**1**I) and analogues, are not reported on 4-propylguaiacol (**1**a). For these methods, we applied the reaction conditions as retrieved from literature for demethylation of guaiacol derivatives on **1a**. The amount of the reagents and/or the reaction temperature was increased if insufficient conversion of substrate **1a** was observed (optimization data and procedures are reported in Section 5.2 of this SI). 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. In Table S17, the different methods are summarized. Experimental procedures can be found in Sections 5.2.3-5.2.8.

O-demethylation with TMSI was reported on guaiacol.¹⁷ With 1.1 equiv. of this reagent no full conversion was obtained on 4-propylguaiacol (**1a**) (Method G1). 2.0 equiv. were required to achieve this (Method G2). Unfortunately, the crude mixture did not show sufficient purity of the reaction product, making an additional purification via column chromatography required. This step could also be replaced by filtration through a layer of silica (Method G3), though decreasing the yield from 89% to 74%.

The described *O*-demethylation of guaiacol (**1**) involving Al powder, I_2 and DMSO could be applied for demethylation of 4-propylguaiacol (**1a**),¹⁸ even without using DMSO (Method H), providing 4-propylcatechol (**2a**) with a yield of 86%.

Demethylation of 4-propylguaiacol (**1a**) with AlCl₃,^{19, 20} in combination with either NaI or Me₂S was achieved in 63% or 67% yield respectively (Methods I1 and I2), applying conditions reported for demethylation of veratrole or eugenol. However, in both cases full conversion was not observed, even with an excess of the reagents. Therefore, chromatographic separation of product **2a** and substrate **1a** was required, both leading to partial recovery of the starting material.

A pilot-scale demethylation of 4-methoxyphenylbutyric acid, involving an excess of molten Py·HCl,²¹ was successfully applied on **1a** providing 84% **2a** (Method J).

As last method, LiBr and HBr in excess, described for the demethylation of 4-methylguaiacol (1d),²² was employed on 1a, leading to 2a in 82% yield (Method K).

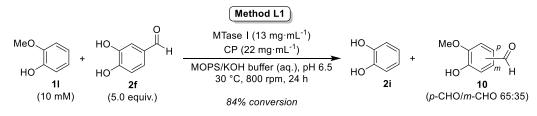
Table S17. O-Demethylation of 4-propylguaiacol (**1a**) to 4-propylcatechol (**2a**) by applying literature methodologies reported for the same reaction on related guaiacol derivatives.

		MeO		eactants & Reagents	\sim		
		НО	la la	Conditions HO			
Method [ELN Code]	Scale (mmol)	Reactants & Reagents	Conditions	Work-up	Yield [ª] (%)	Ref. ^[b]	Literature subtrate
G1 [BL-20]	10.0	TMSI (1.1 equiv.)	CHCl ₃ (1.0 M) r.t., 70 h	Quenching with MeOH Extraction with CHCl ₃ Washing with brine Column chromatography	54 ^[c]	17	MeO HO
G2 [BL-32]	10.0	TMSI (2.0 equiv.)	CHCl₃ (1.0 M) r.t., 70 h	Quenching with MeOH Extraction with CHCl₃ Washing with brine Column chromatography	74	17	MeO HO
G3 [BL-22]	10.0	TMSI (2.0 equiv.)	CHCl₃(1.0 M) r.t., 70 h	Quenching with MeOH Extraction with CHCl₃ Washing with brine Filtration over silica	89	17	MeO HO
Н [JBO-GM- 119]	10.0	Al (4.3 equiv.) I ₂ (1.7 equiv.)	MeCN (0.12 M) 80 °C, 18 h	Quenching with HCl Extraction with EtOAc Washing with aq. solutions Column chromatography	87	18	MeO HO
I1 [BL-47]	10.0	AlCl₃ (2.0 equiv.) Nal (2.0 equiv.)	EtOAc (1.0 M) 70 °C, 3 h	Quenching with Na ₂ S ₂ O ₃ (aq.) Extraction with EtOAc Column chromatography	63 ^[d]	19	MeO MeO
I2 [BL-44]	10.0	AlCl₃ (4.0 equiv.) Me₂S (4.0 equiv.)	CHCl₃ (1.0 M) 70 °C, 3 h	Quenching with Na ₂ S ₂ O ₃ (aq.) Extraction with CHCl ₃ Column chromatography	67 ^[e]	20	MeO HO
J [MBAL-642]	10.0	Py∙HCl (4.0 equiv.)	Neat 195 °C, 1 h	Quenching with HCl (aq.) Extraction with MTBE Washing with HCl	84	21	MeO OH
K [MBAL-795]	0.60	LiBr (117 equiv.) HBr (14.7 equiv.)	H₂O (0.15 M) reflux, 18 h	Diluting with brine Extraction with EtOAc Re-dissolving in MTBE Filtration over celite	82	22	MeO HO

^[a] Yield of isolated product. ^[b] The experimental procedure, reported in Section 5.2, was based on the given references. ^[c] The starting material **1a** was recovered for 26%. ^[d] The starting material **1a** was recovered for 2%.

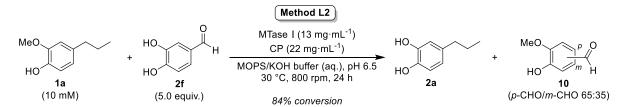
4.4.3 Synthesis of catechol from guaiacol via biocatalysis

The use of enzymes in organic synthesis is emerging. In 2018, Kroutil reported a biocatalytic method based on corrinoid-dependent methyl transferases acting as methyl transferring agent.²³ In the presence of methyl transferase (MTase I), corrinoid protein (CP) and the required buffer, guaiacol (**1**) was demethylated to catechol (**2i**), while at the same time methyl acceptor protocatechualdehyde (5. equiv.) was converted in a mixture of vanillin and isovanillin (**10**) (Scheme S2, Method L1). Unfortunately, the conversion for this specific reaction was only determined by means of HPLC-UV and the yield for the isolated products was not reported. Work-up involved addition of HPLC solvent (MeCN:H₂O) and removal of proteins via centrifugation. Considering multiple organic compounds are present in the crude mixture, purification via column chromatography may be expected for obtaining pure product **2i**, as the authors for example describe for the isolation of (iso)ferulic acid, obtained upon methylation of caffeic acid and simultaneous demethylation of syringol.²³



Scheme S2. Biocatalytic conversion of guaiacol (**1***I*) and protocatechualdehyde (**2***f*) in catechol (**2***i*) and vanillins **10** by MTase I and CP, as described by Kroutil.²³

As we did not have access to these enzymes, we could unfortunately not perform this experiment on 4-propylguaiacol (1a) directly. Therefore, a theoretical simulation was performed, assuming the reaction on 1a would occur with the same efficiency as reported on 1l (Method L2, Scheme S3). We recently disclosed that in this way a reliable quantitative metrics can be obtained when no data are available for a synthetic method on a specific substrate.²⁴



Scheme S3. Biocatalytic conversion of 4-propylguaiacol (**1a**) and protocatechualdehyde (**2f**) in 4-propylcatecholcatechol (**2a**) and vanillins **10** by MTase I and CP, simulated based on data described by Kroutil with **1I** and **2f**.²³

4.5 Comparison of the Green Metrics for classical versus new method

4.5.1 General remarks

For green metrics calculations, all experimental details (e.g. the exact amount of all chemicals involved) need to be gathered to obtain a meaningful analysis. Unfortunately, literature routes are often concise in description and some data are lacking in the experimental procedures with respect to work-up. Therefore, if not indicated in the experimental procedure, the following assumptions were made:

-	Solvent filtration / extraction:	5 mL for 1 mmol limiting reactant
-	Filtration over celite:	2 g for 1 mmol limiting reactant
-	Drying over MgSO ₄ / Na ₂ SO ₄ :	1 g for 1 mmol limiting reactant
-	Flash chromatography:	100 mL solvent (heptane / EtOAc 80:20)
		and 8 g SiO ₂ for 1 mmol limiting reactant

Often, the selected reactions were quenched with aq. solution(s). If this was the case, the quenching agent, delivering a proton to the product, was fully considered as reactant. If no quenching agent was used, H_2O itself was assumed to be the quenching agent. Then the theoretically required 1.0 equiv. was considered as reactant and the remaining amount was considered as work-up solvent.

A reagent amount higher than 1.0 equiv. is an excess, leading to a red flag. This definition should better be nuanced as a very small excess cannot be distinguished from a large excess applying the original qualitative metrics. Therefore, in this manuscript, the use of 1.0-1.5 equiv. of a certain reagent is given a yellow flag and amounts higher than 1.5 equiv. a red one. Consequently, considering reagent use, yellow flags will be obtained for the Methods D, F1, F2 and G1, while this would be a red flag when using the definition reported in the original metrics. Important to mention is that the use of reactants is not incorporated in this flag. Excess of reactants (as well as reagents) will always be reflected when looking at the quantitative metrics, i.e. PMI.

4.5.2 Demethylation of 4-propylguaiacol to 4-propylcatechol

In the manuscript, a comparison of *greenness* is described for the different methods allowing *O*-demethylation of 4-propylguaiacol (**1a**) to 4-propylcatechol (**2a**). Complete Excel sheets for all methods considered are reported in Section 7.⁹ For Method L2 (MTase), the results are based on simulated rather than experimental data, keeping all other parameters constant (*vide supra*, Section 4.4.3).

5 Experimental procedures

5.1 Products of O-demethylation

4-Propylbenzene-1,2-diol (2a) [JBO-296, JBO-496]

^{HO} _{HO} The reaction was performed using General Procedure C, using 2-methoxy-4propylphenol (**1a**, 166 mg, 1.0 mmol, 1.0 equiv.) as substrate and HCl (aq., 1 M, 0.2 mL, 0.2 mmol, 0.2 equiv.) and H₂O (1.8 mL) as reagents. The reaction mixture was heated to 250 °C and stirred for 3 h at this temperature, under a starting pressure of N₂ (50 bar). The experiment was repeated 5 times and samples were combined for work-up. In the work-up, NaCl (s, 2.00 g), EtOAc (10 mL) and brine (5.0 mL) were used. Pure 4-propylbenzene-1,2-diol (**2a**) was obtained in 97% yield (735 mg, 4.83 mmol). The obtained spectroscopic data are in accordance with literature.²

Off-white solid, m.p.: 58 °C (lit.: 58-59 °C),²⁵ R_f = 0.29 in heptanes/EtOAc (75:25). ¹H NMR (400 MHz, DMSO-d₆): δ 8.56 (bs, 2H), 6.61 (d, *J* = 7.9 Hz, 1H), 6.55 (d, *J* = 1.8 Hz, 1H), 6.40 (dd, *J* = 7.9, 1.8 Hz, 1H), 2.36 (t, *J* = 7.5 Hz, 2H), 1.50 (sext, *J* = 7.5 Hz, 2H), 0.85 (t, *J* = 7.5 Hz, 3H) ppm. ¹³C NMR (101 MHz, DMSO-d₆): δ 144.9 (C), 143.1 (C), 132.9 (C), 118.9 (CH), 115.7 (CH), 115.4 (CH), 36.7 (CH₂), 24.3 (CH₂), 13.6 (CH₃) ppm. HRMS (ESI) for C₉H₁₃O₂ [M+H]⁺ calcd. 153.0910, found 153.0916.

Remark [MBAL-766] - Reaction at substrate concentration of 1.0 M: This compound **2a** could also be synthesized using 2-methoxy-4-propylphenol (**1a**, 332 mg, 2.00 mmol, 1.0 equiv.) as substrate and HCl (aq., 1 M, 0.40 mL, 0.40 mmol, 0.2 equiv.) as reagent. Reaction time was 3 h, keeping other factors constant as in the previous example. The experiment was repeated 5 times and samples were combined for work-up, delivering the desired product **2a** in 96% yield (1.46 g, 9.59 mmol). This procedure was used for green metrics calculations further in this SI (Section 4.3).

Remark [JBO-643] - Reaction at substrate concentration of 2.0 M: This compound **2a** could also be synthesized using 2-methoxy-4-propylphenol (**1a**, 666 mg, 4.0 mmol, 1.0 equiv.) as substrate and HCl (aq., 1 M, 2.0 mL, 2.0 mmol, 0.5 equiv.) as reagent. The experiment was repeated 5 times and samples were combined for work-up. Reaction time was 1 h, keeping other factors constant as in the previous example, delivering the desired product **2a** in 91% yield (2.77 g, 18.2 mmol). This procedure was used for green metrics calculations further in this SI (Section 4.3).

Remark [JBO-1658] - Reaction at substrate concentration of 0.13 M: This compound **2a** could also be synthesized using 2-methoxy-4-propylphenol (**1a**, 66 mg, 0.40 mmol, 1.0 equiv.) as substrate and HCl (aq., 1 M, 0.2 mL, 0.20 mmol, 0.5 equiv.) as reagent. Reaction time was 3 h, keeping other factors constant as in the previous example. The experiment was repeated 5 times and samples were combined for work-up, delivering the desired product **2a** in 97% yield (295 mg, 1.95 mmol). This procedure was used for green metrics calculations further in this SI (Section 4.3).

Remark [MBAL-734] – Large scale synthesis of 2a (1.0 M): The glass insert (beaker shown in Figure S1(a), without metal insert containing vials) for the Parr[®] 4625 reactor, equipped with magnetic stirring bar, was loaded with 2-methoxy-4-propylphenol (**1a**, 24.93 g, 150 mmol, 1.0 equiv.), HCl (aq., 1 M, 30.0 mL, 30.0 mmol, 0.2 equiv.) and H₂O (120 mL). The beaker was placed in the Parr[®] 4625 reactor, which was then closed properly, flushed with N₂ (3 × 10 bar) and filled with N₂ gas (50 bar). The mixture in the reactor was heated to 250 °C and stirred for 6 h. Subsequently, the reactor was cooled to r.t., the pressure was released and the reactor was opened. The reaction mixture was transferred to a

separatory funnel, NaCl (s, 20 g) was added, the product was extracted with EtOAc (300 mL), and the aqueous layer was extracted with EtOAc (2×150 mL). The combined organic layers were washed with brine (150 mL), dried over MgSO₄, evaporated under reduced pressure and freeze-dried. Pure 4propylcatechol (2a) was obtained in 92% yield (21.06 g, 138 mmol).

5-Propylbenzene-1,2,3-triol (2b) [MBAL-839]

The reaction was performed using General procedure C, using 2,6-dimethoxy-4-HO propylphenol (1b, 196 mg, 1.0 mmol, 1.0 equiv.) as substrate and HCl (aq., 1 M, HO 0.2 mL, 0.2 mmol, 0.2 equiv.) and H₂O (2.8 mL) as reagents. The reaction mixture was heated to 250 $^{\circ}$ C and stirred for 6 h at this temperature, under a starting pressure of N₂ (50 bar). The experiment was repeated 8 times and samples were combined for work-up. In the work-up, NaCl (s, 2.00 g), EtOAc (10 mL) and brine (5.0 mL) were used. Subsequently, the crude mixture was recrystallized from toluene. Pure 5-propylbenzene-1,2,3-triol (2b) was obtained in 74% yield (376 mg, 2.24 mmol). There are no spectroscopic data available in literature.

Grey powder, m.p.: 75 °C (lit.: 78 °C), R_f = 0.37 in heptanes / EtOAc (50:50). ¹H NMR (400 MHz, DMSO-d₆): δ 8.51 (bs, 2H), 7.83 (bs, 1H), 6.08 (s, 2H), 2.29 (t, *J* = 7.4 Hz, 2H), 1.48 (sext, *J* = 7.4 Hz, 2H), 0.85 (t, J = 7.4 Hz, 3H) ppm. ¹³C NMR (101 MHz, DMSO-d₆): δ 145.9 (C), 132.2 (C), 130.7 (C), 107.0 (CH), 37.0 (CH₂), 24.1 (CH₂), 13.6 (CH₃) ppm.

Remark [MBAL-653] – Reaction at higher concentration 1b:

The reaction was performed using General procedure C, using 2,6-dimethoxy-4-propylphenol (1b, 294 mg, 1.5 mmol, 1.0 equiv.) as substrate and HCl (aq., 1 M, 0.3 mL, 0.3 mmol, 0.2 equiv.) and H₂O (2.7 mL) as reagents. The reaction mixture was heated to 250 °C and stirred for 6 h at this temperature, under a starting pressure of N_2 (50 bar). The experiment was repeated 3 times and samples were combined for work-up. In the work-up, NaCl (s, 2.00 g), EtOAc (10 mL) and brine (5.0 mL) were used. The product was purified by an automated reversed phase flash chromatography system using a H₂O/MeCN gradient (Cartridge: 12 g C18-SiO₂, flow rate: 20 mL·min⁻¹, eluent: 10% MeCN in H₂O, 30 min; 10% MeCN in H_2O to 40% MeCN in H_2O , 25 min; 40% MeCN in H_2O , 3 min; 40% MeCN in H_2O to 50% MeCN in H₂O, 7 min; 50% MeCN in H₂O, 3 min; 50% MeCN in H₂O to 60% MeCN in H₂O, 3 min; 60% MeCN in H₂O to 100% MeCN, 3 min; 100% MeCN, 10 min). Pure 4-methyl-5-propylbenzene-1,2,3triol (2q) was obtained in 22% yield (184 mg, 1.01 mmol). Furthermore, 5-propylbenzene-1,2,3-triol (2b) was obtained in 44% yield (332 mg, 1.97 mmol). There are no spectroscopic data available in literature.

4-Methyl-5-propyl-1,2,3-triol (2q) [MBAL-653]



Grey solid, m.p.: 114-117 °C, R_f = 0.54 in heptanes/EtOAc (50:50). ¹H NMR (400 MHz, DMSO-d₆): δ 8.52 (bs, 1H), 7.87 (bs, 2H), 6.09 (s, 1H), 2.34 (t, *J* = 7.4 Hz, 2H), 1.95 (s, 3H), 1.43 (sext, J = 7.4 Hz, 2H), 0.88 (t, J = 7.4 Hz, 3H) ppm. ¹³C NMR (101 MHz, DMSOd₆): δ 144.3 (C), 143.0 (C), 130.7 (C), 130.6 (C), 113.0 (C), 107.4 (CH), 34.8 (CH₂), 23.4 (CH₂), 13.9 (CH₃), 11.1 (CH₃) ppm.

Remark [MBAL-735] – Large scale synthesis of 2b: The glass insert (beaker shown in Figure S1(a), without metal insert containing vials) for the Parr® 4625 reactor, equipped with magnetic stirring bar, was loaded with 2,6-dimethoxy-4-propylphenol (1b, 9.81 g, 50.0 mmol, 1.0 equiv.), HCl (aq., 1 M, 10.0 mL, 10.0 mmol, 0.2 equiv.) and H_2O (140 mL). The beaker was placed in the Parr[®] 4625 reactor, which was then closed properly, flushed with N₂ (3×10 bar) and filled with N₂ gas (50 bar). The mixture in the reactor was heated to 250 °C and stirred for 6 h. Subsequently, the reactor was cooled to r.t., the pressure was released and the reactor was opened. The reaction mixture was transferred to a separatory funnel, NaCl (s, 20 g) was added, the product was extracted with EtOAc (200 mL), and the aqueous layer was extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with brine (150 mL), dried over MgSO₄, evaporated under reduced pressure and freeze-dried. The obtained purple solid was recrystallized from toluene. Pure 5-propylbenzene-1,2,3-triol (**2b**) was obtained in 80% yield (6.69 g, 39.8 mmol).

4-Methylbenzene-1,2-diol (2d) [MBAL-494]

 $\begin{array}{c} \text{HO} \\ \text{HO} \end{array} \label{eq:HO} The reaction was performed using General Procedure C, using 2-methoxy-4-methylphenol ($ **1d** $, 207 mg, 1.5 mmol, 1.0 equiv.) as substrate and HCl (aq., 1 M, 0.3 mL, 0.3 mmol, 0.2 equiv.) and H_2O (2.7 mL) as reagents. The reaction mixture was heated to 250 °C and stirred for 3 h at this temperature, under a starting pressure of N₂ (50 bar). The experiment was repeated 3 times and samples were combined for work-up. In the work-up, NaCl (s, 2.00 g), EtOAc (10 mL) and brine (5.0 mL) were used. Pure 4-methylbenzene-1,2-diol ($ **2d**) was obtained in 99% yield (551 mg, 4.43 mmol). The obtained spectroscopic data are in accordance with literature.²⁶

White solid, m.p.: 65 °C (lit.: 64 °C),²⁷ R_f = 0.57 in heptanes/EtOAc (50:50). ¹H NMR (400 MHz, DMSO-d₆): δ 8.56 (bs, 2H), 6.59 (d, *J* = 7.9 Hz, 1H), 6.54 (d, *J* = 2.0 Hz, 1H), 6.39 (dd, *J* = 7.9, 2.0 Hz, 1H), 2.12 (s, 3H) ppm. ¹³C NMR (101 MHz, DMSO-d₆): δ 144.9 (C), 142.8 (C), 127.8 (C), 119.4 (CH), 116.4 (CH), 115.4 (CH), 20.3 (CH₃) ppm.

4-Ethylbenzene-1,2-diol (2c) [MBAL-776]

^{HO}_{HO} The reaction was performed using General Procedure C, using 4-ethyl-2methoxyphenol (**1c**, 228 mg, 1.5 mmol, 1.0 equiv.) as substrate and HCl (aq., 1 M, 0.3 mL, 0.3 mmol, 0.2 equiv.) and H₂O (2.7 mL) as reagents. The reaction mixture was heated to 250 °C and stirred for 6 h at this temperature, under a starting pressure of N₂ (50 bar). The experiment was repeated 5 times and samples were combined for work-up. In the work-up, NaCl (s, 2.00 g), EtOAc (10 mL) and brine (5.0 mL) were used. Pure 4-ethylbenzene-1,2-diol (**2c**) was obtained in 90% yield (931 mg, 6.74 mmol). The obtained spectroscopic data are in accordance with literature.²⁸ Light brown oil, R_f = 0.60 in heptanes/EtOAc (50:50). ¹H NMR (400 MHz, DMSO-d₆): δ 8.58 (bs, 2H), 6.62 (d, *J* = 8.0 Hz, 1H), 6.57 (d, *J* = 2.2 Hz, 1H), 6.42 (dd, *J* = 7.9, 2.1 Hz, 1H), 2.42 (q, *J* = 7.6 Hz, 2H), 1.10 (t, *J* = 7.6 Hz, 3H) ppm. ¹³C NMR (101 MHz, DMSO-d₆): δ 145.0 (C), 143.0 (C), 134.6 (C), 118.2 (CH), 115.4 (CH), 115.1 (CH), 27.5 (CH₂), 15.9 (CH₃) ppm.

3-(3,4-Dihydroxyphenyl)propanoic acid (2e) [MBAL-699]

The reaction was performed using General procedure D, using 3-(4-hydroxy-3methoxyphenyl)propanoic acid (**1g**, 294 mg, 1.5 mmol, 1.0 equiv.) as substrate and HCl (aq., 1 M, 0.3 mL, 0.2 equiv.) and H₂O (2.7 mL) as reagents. The reaction mixture was heated to 250 °C and stirred for 6 h at this temperature, under a starting pressure of 50 bar N₂. After cooling down to r.t., the gas was released and the reactor was opened. The experiment was repeated 3 times and samples were combined for work-up. In the work-up, NaCl (s, 2.00 g), EtOAc (2 × 10 mL), brine (5.0 mL), NaHCO₃ (aq., sat., 10 mL) and HCl (aq., 1 M, 10 mL) and were used. Pure 3-(3,4-dihydroxyphenyl)propanoic acid (**2e**) was obtained in 85% yield (696 mg, 3.82 mmol). The spectroscopic data are in accordance with literature.²⁹

Grey solid, m.p.: 136 °C (lit.: 139 °C),³⁰ R_f = 0.21 in heptanes/EtOAc (50:50). ¹H NMR (400 MHz, DMSO-d₆): δ 11.97 (bs, 1H), 8.65 (bs, 2H), 6.61 (d, *J* = 8.0 Hz, 1H), 6.58 (d, *J* = 2.1 Hz, 1H), 6.44 (dd, *J* = 8.0, 2.1

Hz, 1H), 2.63 (t, J = 7.6 Hz, 2H), 2.42 (t, J = 7.6 Hz, 2H) ppm. ¹³C NMR (101 MHz, DMSO-d₆): δ 173.8 (C), 145.0 (C), 143.4 (C), 131.7 (C), 118.7 (CH), 115.6 (CH), 115.4 (CH), 35.7 (CH₂), 29.8 (CH₂) ppm. HRMS (ESI) for C₉H₁₁O₄ [M+H]⁺ calcd. 183.0652, found 183.0649.

Remark [MBAL-700]: This compound 2e could also be synthesized using using 3-(3,4dimethoxyphenyl)propanoic acid (1h, 315 mg, 1.5 mmol, 1.0 equiv.) as substrate and HCl (aq., 1 M, 0.3 mL, 0.3 mmol, 0.2 equiv.) as reagent. Keeping other factors constant as in the previous example delivered the desired product **2e** in 86% yield (705 mg, 3.87 mmol).

3,4-Dihydroxybenzaldehyde (2f) [MBAL-709]

The reaction was performed using General Procedure C, using 2H-1,3-benzodioxole-5carbaldehyde (1i, 60 mg, 0.40 mmol, 1.0 equiv.) as substrate and H₂O (3.0 mL) as HO reagent. The reaction mixture was heated to 250 °C and stirred for 1 h at this temperature, under a starting pressure of N_2 (50 bar). The experiment was repeated 5 times and samples were combined for work-up. Before work-up, all solids were removed by filtration. In the work-up, NaCl (s, 2.00 g), EtOAc (10 mL) and brine (5.0 mL) were used. Pure 3,4dihydroxybenzaldehyde (2f) was obtained in 62% yield (170 mg, 1.23 mmol). The spectroscopic data are in accordance with literature.³¹

Light grey solid, m.p.: 159 °C (lit.: 155 °C),³¹ R_f = 0.27 in heptanes/EtOAc (50:50). ¹H NMR (400 MHz, DMSO-d₆): δ 9.69 (s, 1H), 7.27-7.24 (m, 2H), 6.95-6.93 (m, 1H) ppm. ¹³C NMR (101 MHz, DMSO-d₆): δ 191.0 (CH), 152.2 (C), 145.9 (C), 128.8 (C), 124.3 (CH), 115.6 (CH), 114.5 (CH) ppm.

Benzene-1,2-diol (2i) [JBO-294, SA-024]

The reaction was performed using General Procedure C, using 2-methoxyphenol (11, 124 mg, 1.0 mmol, 1.0 equiv.) as substrate and HCl (aq., 1 M, 0.2 mL, 0.2 mmol, 0.2 equiv.) and H_2O HO (1.8 mL) as reagents. The reaction mixture was heated to 250 °C and stirred for 3 h at this temperature, under a starting pressure of N_2 (50 bar). The experiment was repeated 5 times and samples were combined for work-up. In the work-up, NaCl (s, 2.00 g), EtOAc (10 mL) and brine (5.0 mL) were used. Pure 4-propylbenzene-1,2-diol (2i) was obtained in 97% yield (535 mg, 4.86 mmol). The obtained spectroscopic data are in accordance with literature.³²

Grey solid, m.p.: 104 °C (lit.: 102-103 °C),³² R_f = 0.29 in heptanes/EtOAc (75:25). ¹H NMR (400 MHz, CDCl₃): δ 6.90-6.85 (m, 2H), 6.83-6.81 (m, 2H), 5.10 (s, 2H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ 143.7 (C), 121.5 (CH), 115.7 (CH) ppm. HRMS (ESI) for C₆H₇O₂ [M+H]⁺ calcd. 111.0446, found 111.0447.

Remark [MBAL-467]: This compound 2i could also be synthesized using using 2-methoxyphenol (1I, 496 mg, 4.0 mmol, 1.0 equiv.) as substrate and HCl (aq., 1 M, 2.0 mL, 2.0 mmol, 0.5 equiv.) as reagent. Keeping other factors constant as in the previous example, delivering the desired product 2i in 93% yield (410 mg, 3.73 mmol). This procedure was used for green metrics calculations further in this SI (Section 4.3).

Benzene-1,4-diol (2j) [MBAL-497]

HO

The reaction was performed using General Procedure C, using 1,4-dimethoxybenzene OH (10, 207 mg, 1.5 mmol, 1.0 equiv.) as substrate and HCl (aq., 1 M, 0.3 mL, 0.3 mmol, 0.2 equiv.) and H₂O (2.7 mL) as reagents. The reaction mixture was heated to 250 °C and stirred for 3 h at this temperature, under a starting pressure of N_2 (50 bar). The experiment was

repeated 3 times and samples were combined for work-up. In the work-up, NaCl (s, 2.00 g), EtOAc

(10 mL) and brine (5.0 mL) were used. Pure benzene-1,4-diol (**2j**) was obtained in 98% yield (488 mg, 4.43 mmol). The obtained spectroscopic data are in accordance with literature.^{1, 33}

White solid, m.p.: 169 °C (lit.: 169-171 °C),^{1, 33} $R_f = 0.61$ in heptanes/EtOAc (50:50). ¹H NMR (400 MHz, DMSO-d₆): δ 8.58 (s, 2H), 6.55 (s, 4H) ppm. ¹³C NMR (101 MHz, DMSO-d₆): δ 149.7 (C), 115.6 (CH) ppm.

Benzene-1,3-diol (2k) [JBO-325, MBAL-518]

The reaction was performed using General procedure C, using 1,3-dimethoxybenzene (**1p**, 138 mg, 1.0 mmol, 1.0 equiv.) as substrate and HCl (aq., 1 M, 0.2 mL, 0.2 equiv.) and H₂O (2.8 mL) as reagents. The reaction mixture was heated to 250 °C and stirred for 3 h at this temperature, under a starting pressure of N₂ (50 bar). The experiment was repeated 3 times and samples were combined for work-up. In the work-up, NaCl (s, 2.00 g), EtOAc (10 mL) and brine (5.0 mL) were used. Pure resorcinol (**2k**) was obtained in 92% yield (305 mg, 2.77 mmol). The spectroscopic data are in accordance with literature.³⁴

Brown solid, m.p.: 111 °C (lit.: 106-110 °C),³⁵ R_f = 0.10 in heptanes / EtOAc (75:25). ¹H NMR (400 MHz, DMSO-d₆): δ 9.12 (s, 2H), 6.90 (t, *J* = 7.8 Hz, 1H), 6.19-6.16 (m, 3H) ppm. ¹³C NMR (101 MHz, DMSO-d₆): δ 158.4 (C), 129.6 (CH), 106.2 (CH), 102.5 (CH) ppm. HRMS (ESI) for C₆H₇O₂ [M+H]⁺ calcd. 111.0441, found 111.0441.

Phenol (2I) [SA-107]

^{HO} The reaction was performed using General Procedure C, using anisole (**1q**, 108 mg, 1.0 mmol, 1.0 equiv.) as substrate and HCl (aq., 1 M, 1.0 mL, 1.0 mmol, 1.0 equiv.) and H₂O (1.0 mL) as reagents. The reaction mixture was heated to 250 °C and stirred for 3 h at this temperature, under a starting pressure of N₂ (50 bar). The experiment was repeated 5 times and samples were combined for work-up. In the work-up, NaCl (s, 2.00 g), MTBE (3×10 mL) and brine (5.0 mL) were used. Pure 4-propylbenzene-1,2-diol (**2l**) was obtained in 62% yield (290 mg, 3.10 mmol). The obtained spectroscopic data are in accordance with literature.³⁶

White solid, m.p.: 102 °C (lit.: 105 °C),³⁷ R_f = 0.619 in heptanes/EtOAc (50:50). ¹H NMR (400 MHz, CDCl₃): δ 7.26-7.21 (m, 2H), 6.95-6.91 (tt, *J* = 7.5, 1.0 Hz, 1H), 6.84-6.81 (m, 2H), 4.87 (s, 1H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ 156.6 (C), 129.8 (CH), 121.0 (CH), 115.5 (CH) ppm. EI (+) (m/z (%)): 94 (100), 66 (34), 65 (24).

2,4,6-Trichlorophenol (2m) [MBAL-640]

 $_{HO}^{Cl}$ $_{Cl}^{Cl}$ The reaction was performed using General Procedure C, using 1,3,5-trichloro-2methoxybenzene (**1r**, 317 mg, 1.5 mmol, 1.0 equiv.) as substrate and HCl (aq., 1 M, 0.3 mL, 0.3 mmol, 0.2 equiv.) and H₂O (2.7 mL) as reagents. The reaction mixture was heated to 250 °C and stirred for 6 h at this temperature, under a starting pressure of N₂ (50 bar). In the work-up, NaCl (s, 2.00 g), EtOAc (10 mL) and brine (5.0 mL) were used. Pure 2,4,6-trichlorophenol (**2m**) was obtained in 95% yield (283 mg, 1.43 mmol). The spectroscopic data are in accordance with literature.³⁸

Off-white solid, m.p.: 68 °C (lit.: 69-71 °C),³⁸ R_f = 0.77 in heptanes/EtOAc (50:50). ¹H NMR (400 MHz, CDCl₃): δ 7.28 (s, 2H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ 147.1 (C), 128.3 (CH), 125.5 (C), 121.8 (C) ppm.

1-(4-Hydroxyphenyl)propan-2-one (2n) [MBAL-613]

The reaction was performed using General Procedure C, using 1-(4methoxyphenyl)propan-2-one (**1s**, 246 mg, 1.5 mmol, 1.0 equiv.) as substrate and HCl (aq., 1 M, 0.3 mL, 0.3 mmol, 0.2 equiv.) and H₂O (2.7 mL) as reagents. The reaction mixture was heated to 250 °C and stirred for 4 h at this temperature, under a starting pressure of N₂ (50 bar). The experiment was repeated 3 times and samples were combined for work-up. In the work-up, NaCl (s, 2.00 g), EtOAc (10 mL) and brine (5.0 mL) were used. Pure 1-(4-hydroxyphenyl)propan-2-one (**2n**) was obtained in 80% yield (539 mg, 3.59 mmol). The spectroscopic data are in accordance with literature.³⁹ Pale colorless oil, R_f = 0.43 in heptanes/EtOAc (50:50). ¹H NMR (400 MHz, CDCl₃): δ 7.05 (dt, *J* = 8.4, 1.3 Hz, 2H), 6.79 (dt, *J* = 8.4, 1.3 Hz, 2H), 5.62 (bs, 1H), 3.63 (s, 2H), 2.15 (s, 3H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ 208.0 (C), 155.1 (C), 130.7 (CH), 126.2 (C), 115.9 (CH), 50.3 (CH₂), 29.3 (CH₃) ppm. EI (+) (m/z (%)): 150 (1), 107 (100), 77 (15).

4-(4-Hydroxyphenyl)butan-2-one (2o) [MBAL-634]

The reaction was performed using General Procedure C, using 4-(4methoxyphenyl)butan-2-one (**1t**, 267 mg, 1.5 mmol, 1.0 equiv.) as substrate and HCl (aq., 1 M, 0.3 mL, 0.3 mmol, 0.2 equiv.) and H₂O (2.7 mL) as reagents. The

reaction mixture was heated to 250 °C and stirred for 3 h at this temperature, under a starting pressure of N₂ (50 bar). The experiment was repeated 2 times and samples were combined for work-up. In the work-up, NaCl (s, 2.00 g), EtOAc (10 mL) and brine (5.0 mL) were used. Pure 4-(4-hydroxyphenyl)butan-2-one (**2o**) was obtained in 94% yield (460 mg, 2.80 mmol). The spectroscopic data are in accordance with literature.⁴⁰

Light brown solid, m.p.: 79 °C (lit.: 82-84 °C),⁴¹ R_f = 0.48 in heptanes/EtOAc (50:50). ¹H NMR (400 MHz, CDCl₃): δ 7.04 (dd, *J* = 8.5, 0.9 Hz, 2H), 6.75 (dd, *J* = 8.5, 0.9 Hz, 2H), 4.97 (s, 1H), 2.85-2.81 (m, 2H), 2.74-2.70 (m, 2H), 2.13 (s, 3H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ 208.7 (C), 154.1 (C), 133.2 (C), 129.6 (CH), 115.5 (CH), 45.6 (CH₂), 30.3 (CH₃), 29.1 (CH₂) ppm.

(2S)-2-(6-Hydroxynaphthalen-2-yl)propanoic acid (S-2p) [MBAL-668]

HO

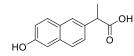
The reaction was performed using General Procedure C, using (2*S*)-2-(6-methoxynaphthalen-2-yl)propanoic acid (**1u**, 100% ee, 92 mg, 0.40 mmol, 1.0 equiv.) as substrate and HCl (aq., 1 M, 0.08 mL, 0.08 mmol, 0.2 equiv.) and

 H_2O (2.92 mL) as reagents. The reaction mixture was heated to 200 °C and stirred for 3 h at this temperature, under a starting pressure of N_2 (50 bar). The experiment was repeated 4 times and samples were combined for work-up. In the work-up, NaCl (s, 2.00 g), EtOAc (10 mL) and brine (5.0 mL) were used. Pure (2*S*)-2-(6-hydroxynaphthalen-2-yl)propanoic acid (*S*-2p) was obtained in 98% yield (340 mg, 1.58 mmol) with 84% ee. The spectroscopic data are in accordance with literature.⁴²

White solid, m.p.: 184 °C, $R_f = 0.23$ in heptanes/EtOAc (50:50). ¹H NMR (400 MHz, DMSO-d₆): δ 12.24 (bs, 1H), 9.67 (bs, 1H), 7.72 (d, J = 8.6 Hz, 1H), 7.64-7.62 (m, 2H), 7.32 (dd, J = 8.5, 1.8 Hz, 1H), 7.09-7.05 (m, 2H), 3.76 (q, J = 7.1 Hz, 1H), 1.42 (d, J = 7.1 Hz, 3H) ppm. ¹³C NMR (101 MHz, DMSO-d₆): δ 175.5 (C), 155.1 (C), 135.3 (C), 133.5 (C), 129.1 (CH), 127.6 (C), 126.1 (CH), 126.1 (CH), 125.5 (CH), 118.8 (CH), 108.4 (CH), 44.6 (CH), 18.4 (CH₃) ppm. HRMS (ESI) for C₁₃H₁₁O₃ [M-H]⁻ calcd. 215.0714, found 215.0723.

In order to proof enantiomeric purity of the obtained product *S***-2p**, its racemic counterparts was synthesized:

2-(6-Hydroxynaphthalen-2-yl)propanoic acid (rac-2p) [MBAL-742]: In a 50 mL roundbottomed flask,



equipped with magnetic stirring bar and reflux condenser, DL-naproxen (0.50 g, 2.17 mmol) was dissolved in HBr (aq., 48%, 14.19 g, 175 mmol, 81 equiv.) and heated under reflux for 2 h. Subsequently, the mixture was cooled to r.t. and

filtered. Solids were washed with ice cold water (10 mL) to afford racemic 2-(6-hydroxynaphthalen-2-yl)propanoic acid (*rac-2p*) in 81% yield (0.38 g, 1.75 mmol). The obtained spectroscopic data are in accordance with literature.⁴³

White solid, m.p.: 185 °C (lit.: 186-188 °C),⁴⁴ R_f = 0.23 in heptanes/EtOAc (50:50). ¹H NMR (400 MHz, DMSO-d₆): δ 12.22 (bs, 1H), 9.67 (bs, 1H), 7.72 (d, *J* = 8.6 Hz, 1H), 7.64-7.62 (m, 2H), 7.32 (dd, *J* = 8.6 Hz, 1.8 Hz, 1H), 7.09-7.05 (m, 2H), 3.76 (q, *J* = 7.1 Hz, 1H), 1.43 (d, *J* = 7.1 Hz, 3H) ppm. ¹³C NMR (101 MHz, DMSO-d₆): δ 175.5 (C), 155.1 (C), 135.3 (C), 133.5 (C), 129.1 (CH), 127.6 (C), 126.1 (CH), 126.1 (CH), 125.5 (CH), 118.7 (CH), 108.4 (CH), 44.5 (CH), 18.4 (CH₃) ppm.

Subsequently, the obtained carboxylic acids **2p** (both enantiomeric and racemic) were esterified to the corresponding methyl ester **12**, which was later on analyzed with chiral HPLC. The procedure and characterization for the racemic mixture are reported underneath.

Methyl 2-(6-hydroxynaphthalen-2-yl)propanoate (rac-12) [MBAL-815]

OMe

In a 50 mL roundbottomed flask, equipped with magnetic stirring bar and reflux condenser, 2-(6-hydroxynaphthalen-2-yl)propanoic acid (*rac-2p*, 0.20 g, 0.93 mmol) was dissolved in MeOH (12 mL) and 2 drops of conc. H₂SO₄ were

added. The reaction mixture was stirred for 4 h under reflux and subsequently cooled to r.t., diluted with CH_2Cl_2 (10 mL) and washed with $NaHCO_3$ (aq., sat., 10 mL). The organic phase was dried over Na_2SO_4 and evaporated under reduced pressure to afford pure racemic methyl 2-(6-hydroxynaphthalen-2-yl)propanoate (*rac*-12) in 95% yield (0.20 g, 0.88 mmol). The spectroscopic data are in accordance with literature.⁴⁴

White solid, m.p.: 90 °C (lit.: 90-92 °C),⁴⁴ R_f = 0.65 in heptanes/EtOAc (50:50). ¹H NMR (400 MHz, CDCl₃): δ 7.67-7.65 (m, 2H), 7.59 (d, *J* = 8.5 Hz, 1H), 7.37 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.09-7.06 (m, 2H), 5.87 (bs, 1H), 3.88 (q, *J* = 7.2 Hz, 1H), 3.70 (s, 3H), 1.59 (d, *J* = 7.2 Hz, 3H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ 175.8 (C), 153.8 (C), 135.5 (C), 133.9 (C), 129.7 (CH), 128.9 (C), 127.0 (CH), 126.4 (CH), 126.2 (CH), 118.3 (CH), 109.5 (CH), 52.3 (CH₃), 45.5 (CH), 18.6 (CH₃) ppm.

Methyl 2-(6-hydroxynaphthalen-2-yl)propanoate (S-12) [MBAL-814]

HO (S) OMe

In a 50 mL roundbottomed flask, equipped with magnetic stirring bar and reflux condenser, 2-(6-hydroxynaphthalen-2-yl)propanoic acid (*rac-2p*, 0.20 g, 0.93 mmol) was dissolved in MeOH (12 mL) and 2 drops of conc. H_2SO_4 were

added. The reaction mixture was stirred for 4 h under reflux and subsequently cooled to r.t., diluted with CH_2Cl_2 (10 mL) and washed with $NaHCO_3$ (aq., sat., 10 mL). The organic phase was dried over Na_2SO_4 and evaporated under reduced pressure to afford pure racemic methyl 2-(6-hydroxynaphthalen-2-yl)propanoate (**S-12**) in 84% yield (0.17 g, 0.78 mmol) with 84% ee. The spectroscopic data are in accordance with literature.⁴⁴

Result of the chiral HPLC analysis:

For the employed substrate **1u**, analysis of enantiopurity was performed on a Chiralpak IB column (4.6 mm × 150 mm, 5 μ m) using a Hexane/EtOH/TFA mixture (80:20:0.1%) at a flow rate of 1 mL·min⁻¹ at 235 nm (UV and CD analysis), showing enantiopurity of the used substrate (2*S*)-2-(6-methoxynaphthalen-2-yl)propanoic acid (*S*-1u), as shown in Figure S6.

Subsequently, enantiopurity of the esters *rac*-12 and *S*-12 was analyzed on a Chiralpak IA column (4.6 mm × 150 mm, 5 μ m) using a Hexane/*i*-PrOH mixture (95:5) at a flow rate of 1 mL·min⁻¹ at 235 nm (UV and CD analysis). The analysis revealed 84 ee% for *S*-12, as shown in Figure S7, while the same analysis of the racemic mixture is reported in Figure S8 as comparison. On the basis of analysis of *S*-12, enantiopurity of *S*-2p was determined.

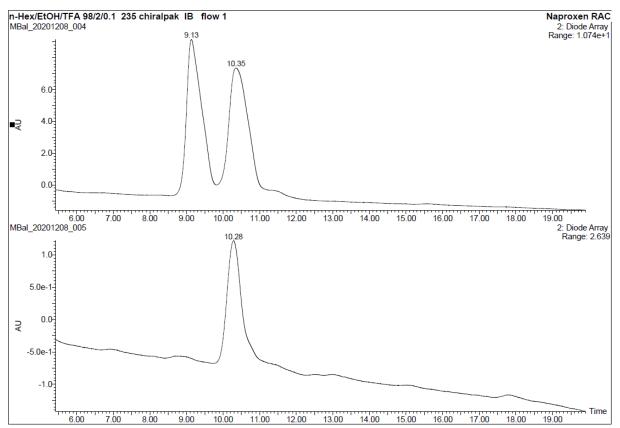


Figure S6. Determination of enantiomeric purity of (2S)-2-(6-methoxynaphthalen-2-yl)propanoic acid (**1u**). Chromatogram from PDA-detector between 200-400 nm. Top: DL-naproxen, Bottom: (2S)-2-(6-methoxynaphthalen-2-yl)propanoic acid (**1u**).

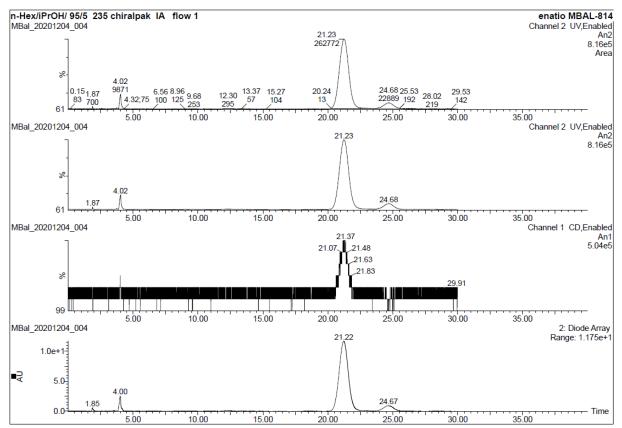


Figure S7. Determination of enantiomeric purity of *(S)-12*. Chromatograms 1 and 2: UV-trace at 235 nm, Chromatogram 3: CD-trace at 235 nm and Chromatogram 4: PDA-detector between 200-400 nm.

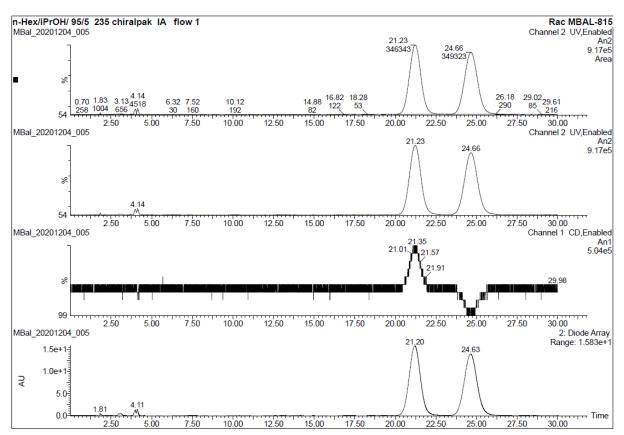


Figure S8. Determination of enantiomeric purity of *rac-12*. Chromatograms 1 and 2: UV-trace at 235 nm, Chromatogram 3: CD-trace at 235 nm and Chromatogram 4: PDA-detector between 200-400 nm.

6-Ethylnaphthalen-2-ol (2r) [MBAL-675]

The reaction was performed using General Procedure C, using (2*S*)-2-(6methoxynaphthalen-2-yl)propanoic acid (**1u**, 345 mg, 1.5 mmol, 1.0 equiv.) as substrate and HCl (aq., 1 M, 0.3 mL, 0.3 mmol, 0.2 equiv.) and H₂O (2.7 mL) as reagents. The reaction mixture was heated to 250 °C and stirred for 3 h at this temperature, under a starting pressure of N₂ (50 bar). The experiment was repeated 4 times and samples were combined for work-up. In the workup, NaCl (s, 2.00 g), EtOAc (10 mL) and brine (5.0 mL) were used. The product was purified by an automated flash chromatography system using a heptanes/EtOAc gradient (Cartridge: 12 g SiO₂, flow rate: 20 mL·min⁻¹, eluent: heptanes to 50% EtOAc in heptanes, 60 min). Pure 6-ethylnaphthalen-2-ol (**2r**) was obtained in 61% yield (631 mg, 3.66 mmol). Furthermore, pure (2*S*)-2-(6-hydroxynaphthalen-2-yl)propanoic acid (**2p**) was obtained in 2% yield (22 mg, 0.1 mmol). There are no spectroscopic data (in DMSO-d₆) available in literature.

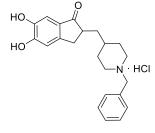
Grey solid, m.p.: 91 °C (lit.: 96-98 °C),⁴⁵ R_f = 0.65 in heptanes/EtOAc (50:50). ¹H NMR (400 MHz, DMSOd₆): δ 9.54 (bs, 1H), 7.67 (d, *J* = 8.7 Hz, 1H), 7.59 (d, *J* = 8.4 Hz, 1H), 7.54 (s, 1H), 7.26 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.07-7.07 (m, 1H), 7.04 (dd, *J* = 8.7, 2.4 Hz, 1H), 2.70 (q, *J* = 7.6 Hz, 2H), 1.24 (t, *J* = 7.6 Hz, 3H) ppm. ¹³C NMR (101 MHz, DMSO-d₆): δ 154.6 (C), 137.8 (C), 133.0 (C), 128.7 (CH), 127.9 (CH), 127.2 (CH), 126.0 (CH), 125.1 (CH), 118.5 (CH), 108.5 (CH), 28.1 (CH₂), 15.6 (CH₃) ppm. HRMS (ESI) for C₁₂H₁₁O [M-H]⁻ calcd. 171.0815, found 171.0814.

5,6-Dihydroxy-2,3-dihydro-1H-inden-1-one (2h) [MBAL-698]

The reaction was performed using General Procedure C, 5,6-dimethoxy-2,3-dihydro-1*H*inden-1-one (**1k**, 77 mg, 0.40 mmol, 1.0 equiv.) as substrate and HCl (aq., 1 M, 0.16 mL, 0.16 mmol, 0.4 equiv.) and H₂O (2.84 mL) as reagents. The reaction mixture was heated to 250 °C and stirred for 6 h at this temperature, under a starting pressure of N₂ (50 bar). The experiment was repeated 5 times and samples were combined for work-up. In the work-up, NaCl (s, 2.00 g), EtOAc (10 mL) and brine (5.0 mL) were used. The product was purified by an automated flash chromatography system using a heptanes/EtOAc gradient (Cartridge: 40 g SiO₂, flow rate: 20 mL·min⁻¹, eluent: heptanes to 15% EtOAc in heptanes, 10 min; 15% EtOAc in heptanes to 25% EtOAc in heptanes, 30 min; 25% EtOAc in heptanes, 15 min; 25% EtOAc in heptanes to 40% EtOAc in heptanes, 60 min; 40% EtOAc in heptanes, 55 min). Pure 5,6-dihydroxy-2,3-dihydro-1*H*-inden-1-one (**2h**) was obtained in 79% yield (260 mg, 1.58 mmol). The spectroscopic data are in accordance with literature.⁴⁶

Yellow solid, m.p.: 246 °C, $R_f = 0.14$ in heptanes/EtOAc (50:50). ¹H NMR (400 MHz, DMSO-d_6): δ 9.66 (bs, 2H), 6.92 (s, 1H), 6.83 (s, 1H), 2.90-2.87 (m, 2H), 2.49-2.47 (m, 2H) ppm. ¹³C NMR (101 MHz, DMSO-d_6): δ 204.2 (C), 153.0 (C), 148.7 (C), 145.6 (C), 128.4 (C), 111.8 (CH), 107.7 (CH), 36.1 (CH₂), 24.6 (CH₂) ppm. HRMS (ESI) for C₉H₇O₃ [M-H]⁻ calcd. 163.0401, found 163.0393.

2-[(1-Benzylpiperidin-4-yl)methyl]-5,6-dihydroxy-2,3-dihydro-1*H*-inden-1-one hydrochloride (2g) [MBAL-782]



The reaction was performed using General Procedure C, donepezil hydrochloride (**1j**, 166 mg, 0.40 mmol, 1.0 equiv.) as substrate and HCl (aq., 1 M, 0.16 mL, 0.16 mmol, 0.4 equiv.) and H₂O (2.84 mL) as reagents. The reaction mixture was heated to 250 °C and stirred for 6 h at this temperature, under a starting pressure of N₂ (50 bar). The experiment was repeated 3 times and samples were combined for work-up. In the work-up, the crude mixture was extracted with *n*BuOH (3 × 15 mL), after which the

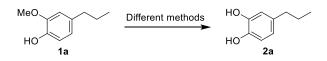
solvent was partially evaporated under reduced pressure and purified through a SiO₂ cartridge

(+/- 2 cm diameter, 10 cm length) using *n*BuOH as mobile phase. Subsequently, the solvent was evaporated and HCl (2 M in Et₂O, 5 mL) was added. Again, solvent was removed under reduced pressure. Pure 2-[(1-benzylpiperidin-4-yl)methyl]-5,6-dihydroxy-2,3-dihydro-1*H*-inden-1-one hydrochloride (**2g**) was obtained in 42% yield (195 mg, 0,50 mmol). There are no spectroscopic data available in literature.

Orange oil, $R_f = 0.04$ in EtOAc. ¹H NMR (400 MHz, DMSO-d₆): δ 11.14 (bs, 2H), 7.69-7.58 (m, 2H), 7.40-7.39 (m, 3H), 6.95 (s, 1H), 6.87 (s, 1H), 4.21 (d, J = 5.3 Hz, 2H), 3.24-3.20 (m, 2H), 3.10-3.04 (m, 1H), 2.90-2.81 (m, 2H), 2.50-2.46 (m, 1H), 1.87-1.83 (m, 2H), 1.75-1.71 (m, 2H), 1.63-1.56 (m, 4H), 1.19-1.18 (m, 1H) ppm. ¹³C NMR (101 MHz, DMSO-d₆): δ 206.2 (C), 153.6 (C), 147.2 (C), 146.0 (C), 131.7 (CH), 130.1 (C), 129.5 (CH), 128.8 (CH), 127.7 (C), 112.0 (CH), 108.3 (CH), 59.0 (CH₂), 51.5 (CH₂), 51.4 (CH₂), 44.6 (CH), 37.7 (CH₂), 32.4 (CH₂), 31.9 (CH), 29.3 (CH₂), 28.2 (CH₂) ppm. HRMS (ESI) for C₂₂H₂₇NO₃Cl [M+H]⁺ calcd. 352.1907, found 352.1911.

5.2 State of the art O-demethylations

The following methods were applied for the *O*-demethylation of 4-propylguaiaol (**1a**) to 4-propylcatechol (**2a**). These are based on methods published in literature for demethylation of similar guaiacol derived substrates. We repeated the method and if necessary, an optimization was performed to improve the conversion and yield. For those methods already reported for the demethylation of **1a** we refer to the corresponding reference. The data reported there were used in the Green Metrics (see Section 7).



5.2.1 Nb₂O₅

Procedure for Nb₂**O**₅ **synthesis:** Based on literature data, as published by Wang, Murayama and Ueda.^{12, 47} In a 100 mL autoclave with Teflon liner, Ammonium oxalate (0.35 g, 2.82 mmol, 1.0 equiv.) was mixed with deionized H₂O (25 mL) and a solution of niobium oxalate (9.6 g, 15.3 mmol, 5.4 equiv.) in H₂O (61.2 mL). Subsequently, the autoclave was sealed and kept in an oven at 180 °C during 24 h. After cooling to r.t., the contents of the autoclave were centrifuged (5500 rpm, < 8 min), washed with deionized HO (200 mL) and dried at 100 °C for 12 h. The obtained solid was calcined at 400 °C (heating rate of 5 °C·min⁻¹) for 4 h in static air.

Method B [MBAL-810]: Based on literature data, as published by Liu and Wang.¹² The Parr[®] 4596 reactor (25 mL internal volume) was charged with 2-methoxy-4-propylphenol (**1a**, 0.50 g, 3.01 mmol, 1.0 equiv.), Nb₂O₅ (0.20 g, 0.75 mmol, 0.25 equiv.) and H₂O (10.0 mL). The reactor was closed, flushed with N₂ gas (3×10 bar) and filled with N₂ gas (65 bar). Subsequently, stirring (mechanical overhead stirring, 400 rpm) was started and the reactor and its contents were heated to 300 °C. After the temperature reached the desired value, stirring was continued for 3 h at this temperature. Subsequently, the reactor and its contents were cooled to r.t. (using an ice bath), gas was released and the reactor was opened. The crude reaction mixture was extracted with EtOAc (1×15 mL, 2×5 mL). The combined organic fractions were centrifuged for 30 min at 4500 rpm. The organic solvent was subsequently evaporated under reduced pressure to afford a mixture of 4-propylbenzene-1,2-diol (**2a**, 79%, 0.36 g, 2.37 mmol), 2-methoxy-4-propylphenol (**1a**, 3%, 15 mg, 0.09 mmol) and catechol (**2i**, 5%,

19 mg, 0.17 mmol) as an orange oil. The obtained spectroscopic data are in accordance with those obtained using other demethylation procedures.

5.2.2 BBr₃

Based on literature data, as published by Eisenbraun.¹⁷ Further optimization was not required for the *O*-demethylation of 4-propylguaiacol (**1a**).

Method F2 [BL-10]: In a flame-dried and argon flushed 25 mL roundbottomed flask, equipped with magnetic stirring bar, 2-methoxy-4-propylphenol (**1a**, 1.66 g, 10.0 mmol, 1.0 equiv.) was dissolved in dry CH_2Cl_2 (15 mL). The obtained mixture was cooled to -94 °C and BBr₃ (1.06 mL, 11.0 mmol, 1.1 equiv.) was added dropwise. The cooling bath was removed and the reaction was allowed to reach r.t. The mixture was stirred for 1 h and subsequently, ice cold H_2O (15 mL) was added dropwise. The obtained suspension was stirred for 1 h. NaCl (s) was added until saturation and the crude mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic fractions were dried over MgSO₄, filtered and evaporated under reduced pressure. Pure 4-propylbenzene-1,2-diol (**2a**) was obtained in 92% yield (1.40 g, 9.20 mmol). The obtained spectroscopic data are in accordance with those obtained using other demethylation procedures.

5.2.3 TMSI

5.2.3.1 Optimization

Based on the procedure published by Eisenbraun,¹⁷ an optimization was initiated which is reported in Table S18. Combination of substrate **1a** and 1.1 equiv. TMSI led to 88% conversion toward the desired product after 48 h (Entry 1), which could not be improved when prolonging the reaction time to 72 h (Entry 2). Increasing TMSI loading to 2.0 equiv. led to nearly quantitative conversion (Entry 3). Replacing highly hazardous CHCl₃ by green alternative EtOAc delivered a complex mixture and a ¹H NMR spectrum not allowing to calculate the yield accurately (Entry 4). With these observations, three procedures were developed to obtain an isolated yield of product **2a**, as described below (Section 5.2.3.2).

HO 1a			TMSI	TMSI HO			
			Solvent, r.t. Ar (balloon), time HO 2a				
Entry	ELN code	TMSI (equiv.)	Solvent	Time (h)	NMR Yield (%) [a]		
					1a	2a	
1	BL-35	1.1	CHCl ₃	48	12	88	
2	BL-36	1.1	CHCl₃	72	10	90	
3	BL-37	2.0	CHCl₃	72	3	97	
4	BL-07	1.1	EtOAc	48	Complex mixture		

 Table S18.
 O-Demethylation of 4-propylguaiacol (1a) to 4-propylcatechol (2a) using TMSI.

Experiments were performed on a scale of 1.0 mmol **1a** and 1.0 mL solvent. ^[a] ¹H NMR Yield determined with 1,3,5-trimehoxybenzene as internal standard.

5.2.3.2 Procedures

Method G1 [BL-20]: In a flame-dried and argon-flushed 25 mL roundbottomed flask, equipped with magnetic stirring bar, septa and argon balloon, 2-methoxy-4-propylphenol (**1a**, 1.66 g, 10.0 mmol, 1.0 equiv.) and TMSI (1.57 mL, 11.0 mmol, 1.1 equiv.) were dissolved in dry CHCl₃ (10 mL) and the obtained reaction mixture was stirred for 70 h at r.t. Subsequently, MeOH (15 mL) and brine (30 mL) were added and the mixture was extracted with CHCl₃ (2 × 30 mL and 1 × 20 mL). The combined organic layers were dried over MgSO₄, filtered and evaporated under reduced pressure. The product was isolated using an automated flash chromatography system using a heptanes/EtOAc gradient (40 g SiO₂ cartridge, flow rate: 30 mL·min⁻¹, eluent: heptanes, 2 min; heptanes to 15% EtOAc in heptanes, 20 min; 15% EtOAc in heptanes; 15 min). Pure 4-propylphenol (**1a**) was recovered in 26% (0.43 g, 2.56 mmol). The obtained spectroscopic data are in accordance with those using other demethylation procedures.

Method G2 [BL-22]: In a flame-dried and argon-flushed 25 mL roundbottomed flask, equipped with magnetic stirring bar, septa and argon balloon, 2-methoxy-4-propylphenol (**1a**, 1.66 g, 10.0 mmol, 1.0 equiv.) and TMSI (2.85 mL, 20.0 mmol, 2.0 equiv.) were dissolved in dry CHCl₃ (10 mL) and the obtained reaction mixture was stirred for 70 h at r.t. Subsequently, MeOH (15 mL) and brine (30 mL) were added and the mixture was extracted with CHCl₃ (2 × 30 mL and 1 × 20 mL). The combined organic layers were dried over MgSO₄, filtered and evaporated under reduced pressure. The product was isolated using an automated flash chromatography system using a heptanes/EtOAc gradient (40 g SiO₂ cartridge, flow rate: 30 mL·min⁻¹, eluent: heptanes, 2 min; heptanes to 15% EtOAc in heptanes, 20 min; 15% EtOAc in heptanes; 15 min). Pure 4-propylbenzene-1,2-diol (**2a**) was obtained in 89% yield (1.35 g, 8.90 mmol). The obtained spectroscopic data are in accordance with those using other demethylation procedures.

Method G3 [BL-32]: In a flame-dried and argon-flushed 25 mL roundbottomed flask, equipped with magnetic stirring bar, septa and argon balloon, 2-methoxy-4-propylphenol (**1a**, 1.66 g, 10.0 mmol, 1.0 equiv.) and TMSI (2.85 mL, 20.0 mmol, 2.0 equiv.) were dissolved in dry CHCl₃ (10 mL) and the obtained reaction mixture was stirred for 70 h at r.t. Subsequently, MeOH (15 mL) and brine (30 mL) were added and the mixture was extracted with $CHCl_3$ (2 × 30 mL and 1 × 20 mL). The combined organic layers were dried over MgSO₄, filtered and evaporated under reduced pressure. The product was isolated by dissolving the crude material in MTBE (30 mL) and filtering it over a layer of silica. Volatiles were evaporated under reduced pressure. Pure 4-propylbenzene-1,2-diol (**2a**) was obtained in 74% yield (1.13 g, 7.41 mmol). The obtained spectroscopic data are in accordance with those using other demethylation procedures.

5.2.4 Al and I_2

5.2.4.1 Optimization

Based on the procedure published by Tian and Sang,¹⁸ an optimization was initiated which is reported in Table S19. By applying the literature conditions, no product **2a** was formed, even after 48 h, and substrate **1a** was recovered for 81% (Entry 1). Doubling the Al loading initiated conversion, delivering product **2a** in 62% (Entry 2). We observed that addition of DMSO was not required to convert substrate **1a**. Combination of 4.8 equiv. Al and 1.65 equiv. I₂ delivered desired product in quantitative NMR yield (Entry 3). With these observations, a procedure was developed to obtain an isolated yield of product **2a**, as described below (Section 5.2.4.2).

MeO HO 1a			AI, I _{2,}	DMSO	HO			
			MeCN, 80 °C Air, time		HO 2a			
Frature /	ELN code	Al ^[a] (equiv.)	l₂ (equiv.)	DMSO (equiv.)	Time (h)	NMR Yield (%) ^[b]		
Entry						1a	2a	
1	JBO-GM-99	2.2	1.65	2.5	48	81	0	
2	JBO-GM-98	4.4	1.65	2.5	18	38	62	
3	JBO-GM-105	4.8	1.65	0.0	18	0	> 99	

 Table S19.
 O-Demethylation of 4-propylguaiacol (1a) to 4-propylcatechol (2a) using Al, I_2 and DMSO.

Experiments were performed on a scale of 1.0 mmol **1a** and 6.0 mL MeCN. ^[a] Al powder was used. ^{[b] 1}H NMR Yield determined with 1,3,5-trimehoxybenzene or mesitylene as internal standard.

5.2.4.2 Procedure

Method H [JBO-GM-119]: In a 250 mL roundbottomed flask, equipped with reflux condenser and magnetic stirring bar, 2-methoxy-4-propylphenol (**1a**, 1.66 g, 10.0 mmol, 1.0 equiv.) was dissolved in MeCN (80 mL). Subsequently, Al powder (1.160 g, 43.0 mmol, 4.3 equiv.) was added to the solution and then I₂ (4.188 g, 16.5 mmol, 1.7 equiv.) was added in one portion. The obtained mixture was stirred for 18 h at 80 °C. After cooling to r.t., the mixture was quenched with HCl (aq., 2 M, 5 mL), and extracted with EtOAc (3 × 50 mL). The combined organic fractions were washed with Na₂S₂O₃ (aq., sat., 25 mL) and brine (25 mL), dried over MgSO₄, filtered and evaporated under reduced pressure. The crude mixture was purified with an automatic column chromatography system using a heptanes/EtOAc gradient (40 g SiO₂ cartridge, flow rate: 30 mL·min⁻¹, eluent: heptanes, 2 min; heptanes to 15% EtOAc in heptanes, 18 min). Pure 4-propylbenzene-1,2-diol (**2a**) was obtained in 86% yield (1.32 g, 8.66 mmol). The obtained spectroscopic data are in accordance with those using other demethylation procedures.

5.2.5 AlCl₃ and Nal

5.2.5.1 Optimization

Based on the procedure, published by Ghiaci,¹⁹ an optimization was initiated which is reported in Table S20. Solventless combination of substrate **1a**, 2.0 equiv. AlCl₃ and 2.0 equiv. Nal led to 66% conversion toward the desired product after 3 h at 70 °C (Entry 1). This solventless reaction showed some stirring issues, so we decided to add a solvent. CHCl₃ at reflux decreased the yield of **2a** to only 13% (Entry 2). Increasing the temperature to 70 °C in a closed system doubled the yield of **2a** to 26% (Entry 3). Replacing the highly hazardous CHCl₃ by the recommended EtOAc delivered the desired product in 71% yield (Entry 4), leaving 29% remaining substrate **1a**. With these observations, a procedure was developed to obtain an isolated yield of product **2a**, as described below (Section 5.2.5.2).

5.2.5.2 Procedure

Method I1 [BL-47]: A flame-dried and argon flushed 100 mL pressure tube, equipped with magnetic stirring bar and rubber septum, was charged with AlCl₃ (2.68 g, 20.0 mmol, 2.0 equiv.) and Nal (3.00 g, 20.0 mmol, 2.0 equiv.). Vacuum was applied and the tube was back-filled with argon. Subsequently, 2-methoxy-4-propylphenol (**1a**, 1.66 g 10.0 mmol, 1.0 equiv.) and dry EtOAc (10 mL) were added through

the septum. The septum was removed and the tube was closed. The reaction mixture was stirred for 3 h at 70 °C, cooled to r.t. and carefully quenched with $Na_2S_2O_3$ (aq., 5%, 10 mL). The obtained mixture was extracted with EtOAc (3 × 40 mL). The combined organic fractions were dried over MgSO₄, filtered and evaporated under reduced pressure. The product was isolated using an automated flash chromatography system using a heptanes/EtOAc gradient (40 g SiO₂ cartridge, flow rate: 30 mL·min⁻¹, eluent: heptanes, 2 min; heptanes to 15% EtOAc in heptanes, 30 min; 15% EtOAc in heptanes; 15 min). Pure 4-propylbenzene-1,2-diol (**2a**) was obtained in 63% yield (0.96 g, 6.30 mmol). Furthermore, 2-methoxy-4-propylphenol (**1a**) was recovered in 2% (36 mg, 0.22 mmol). The obtained spectroscopic data are in accordance with those using other demethylation procedures.

MeO HO XX			AlCl _{3,} Nal				
			Solvent, temp. Ar (balloon), 3 h		HOXX		
Entry	ELN code	AlCl₃ (equiv.)	Nal (equiv.)	Solvent	Temp. (°C)	NMR Yield (%) ^[a]	
Entry						1a	2a
1	BL-45	2.0	2.0	-	70	34	66
2	BL-19	2.0	2.0	CHCl₃	61	81	13
3	BL-23	2.0	2.0	CHCl₃	70	74	26
4	BL-16	2.0	2.0	EtOAc	70	29	71

Table S20. O-Demethylation of 4-propylguaiacol (1a) to 4-propylcatechol (2a) using AlCl₃ and Nal.

Experiments were performed on a scale of 1.0 mmol **1a** and 4.0 mL solvent (apart from Entry 1). ^[a] ¹H NMR Yield determined with 1,3,5-trimehoxybenzene as internal standard.

5.2.6 AICl₃ and Me₂S

5.2.6.1 Optimization

Based on the procedure, published by Arifin,²⁰ an optimization was initiated which is reported in Table S21. 64% Product **2a** was obtained by applying 2.0 equiv. of both AlCl₃ and Me₂S in CHCl₃ after 3 h at 70 °C in a closed vessel (Entry 1). This result could not be significantly improved by doubling reaction time (Entry 2), substrate concentration (Entry 3), Me₂S loading (Entry 4) or AlCl₃ and Me₂S loading (Entry 5). With these observations, a procedure was developed to obtain an isolated yield of product **2a**, as described below (Section 5.2.6.2).

5.2.6.2 Procedure

Method 12 [BL-44]: A flame-dried and argon flushed 100 mL pressure tube, equipped with magnetic stirring bar and rubber septum, was charged with AlCl₃ (5.34 g, 40.0 mmol, 4.0 equiv.). Vacuum was applied and the tube was back-filled with argon. Subsequently, 2-methoxy-4-propylphenol (**1a**, 1.66 g, 10.0 mmol, 1.0 equiv.), Me₂S (2.96 mL, 40.0 mmol, 4.0 equiv.) and dry CHCl₃ (10 mL) were added through the septum. The septum was removed and the tube was closed. The reaction mixture was stirred for 3 h at 70 °C, cooled to r.t. and carefully quenched with Na₂S₂O₃ (aq., 5%, 10 mL). The obtained mixture was extracted with CHCl₃ (3 × 40 mL). The combined organic fractions were dried over MgSO₄, filtered and evaporated under reduced pressure. The product was isolated using an automated flash chromatography system using a heptanes/EtOAc gradient (40 g SiO₂ cartridge, flow rate: 30 mL·min⁻¹, eluent: heptanes, 2 min; heptanes to 15% EtOAc in heptanes, 30 min; 15% EtOAc in

heptanes; 15 min). Pure 4-propylbenzene-1,2-diol (**2a**) was obtained in 67% yield (1.02 g, 6.70 mmol). 2-Methoxy-4-propylphenol (**1a**) was recovered in 20% (330 mg, 1.99 mmol). The obtained spectroscopic data are in accordance with those using other demethylation procedures.

	MeO			₃ , Me ₂ S	но	\sim	
HO la		CHCl _{3,} 70 °C Ar (balloon), time		HO 2a			
Fratrice	ELN code	Conc. 1a (M)	AlCl₃ (equiv.)	Me₂S (equiv.)	Time (h)	NMR Yield (%) [a]	
Entry						1a	2a
1	BL-25	0.25	2.0	2.0	3	36	64
2	BL-26	0.25	2.0	2.0	6	39	61
3	BL-28	0.50	2.0	2.0	6	39	61
4	BL-30	0.25	2.0	4.0	3	50	50
5	BL-34	0.25	4.0	4.0	3	32	68

Table S21. O-Demethylation of 4-propylguaiacol (1a) to 4-propylcatechol (2a) using AlCl₃ and Me₂S.

Experiments were performed on a scale of 1.0 mmol **1a** and solvent with volume to reach the given concentration. ^[a] ¹H NMR Yield determined with 1,3,5-trimehoxybenzene as internal standard.

5.2.7 Py·HCl

Based on literature data, as published by Schmid.²¹ Further optimization was not required for the *O*-demethylation of 4-propylguaiacol (**1a**).

Method J [MBAL-642]: A 50 mL two-necked roundbottom flask, equipped with magnetic stirring bar and reflux condenser, was charged with 2-methoxy-4-propylphenol (**1a**, 1.66 g, 10.0 mmol, 1 equiv.) and Py·HCl (4.62 g, 40.0 mmol, 4.0 equiv.). The obtained mixture was stirred for 1 h at 195 °C, after which it was allowed to cool to 90 °C. Subsequently, HCl (aq., 5 M, 2.5 mL, 12.5 mmol, 1.25 equiv.) and H₂O (2.33 mL) were added. Stirring was continued allowing the temperature of the mixture to reach 35 °C. Subsequently, to the crude mixture was added MTBE (5.2 mL). The organic layer was separated and the aqueous layer was extracted with MTBE (3×3.5 mL). The combined organic fractions were washed with HCl (aq., 5 M, 0.64 mL), dried over Na₂SO₄, filtered and evaporated under reduced pressure. Pure 4-propylbenzene-1,2-diol (**2a**) was obtained in 84% yield (1.28 g, 8.40 mmol). The obtained spectroscopic data are in accordance with those using other demethylation procedures.

5.2.8 LiBr and HBr

Based on literature data, as published by Pan.²¹ Further optimization was not required for the *O*-demethylation of 4-propylguaiacol (**1a**).

Method K [MBAL-795]: In a 50 mL roundbottomed flask, equipped with magnetic stirring bar and reflux condenser, LiBr (6.10 g, 70.2 mmol, 117 equiv.) was dissolved in H_2O (3.9 mL). When LiBr was completely dissolved, 2-methoxy-4-propylphenol (**1a**, 0.10 g, 0.60 mmol, 1.0 equiv.) and HBr (aq., 48%, 1.50 g, 8.84 mmol, 14.7 equiv.) were added. The mixture was stirred for 18 h under reflux, after which it was cooled to r.t. in ice water. The crude mixture was diluted with brine (10 mL), extracted with EtOAc (3 × 10 mL) and evaporated under reduced pressure. The crude product was re-dissolved in

MTBE (5 mL) and filtered over a plug of Celite. Volatiles were evaporated under reduced pressure, delivering 4-propylbenzene-1,2-diol (**2a**) in 82% yield (75 mg, 0.47 mmol). The obtained spectroscopic data are in accordance with those using other demethylation procedures.

5.2.9 Thiols

Based on literature data, as published by Magano.⁴⁸ The desired product **2a** was not formed and the substrate **1a** was recovered for 98%.

Procedure [MBAL-708]: An oven dried 100 mL roundbottomed flask, equipped with magnetic stirring bar, septa and N₂ balloon, was charged with 2-(diethylamino)ethane-1-thiol hydrochloride (4.07 g, 24.0 mmol, 2.4 equiv.) and DMF (20 mL). Subsequently, the flask and its contents were cooled in an ice bath and when the temperature was below 5 °C, NaOtBu (4.84 g, 50.4 mmol, 5.0 equiv.) was added. The obtained mixture was stirred for 5 min after which the cooling bath was removed and stirring was continued for 15 min, allowing the mixture to warm to r.t. Subsequently, 2-methoxy-4-propylphenol (1a, 1.66 g, 10.0 mmol, 1.0 equiv.) was added and the mixture was stirred for 5 h under reflux. The mixture was cooled to r.t., subsequently placed in an ice bath and HCl (aq., 1 M) dropwise added to decrease the pH to 1. Then H₂O (50 mL) was added. Subsequently, the obtained aqueous mixture was extracted with EtOAc (3×50 mL). The combined organic fractions were washed with H₂O (3×20 mL) and brine (20 mL), dried over MgSO₄, filtered and evaporated under reduced pressure. Pure 2-methoxy-4-propylphenol (1a) was obtained in 98% yield (1.64 g, 9.80 mmol). The obtained spectroscopic data are in accordance with those obtained from a commercial sample.

5.2.10 Mgl₂

Based on literature data, as published by Zhang and Yao.⁴⁹ The substrate **1a** was for 22% converted to the desired product **2a**, leaving the substrate **1a** in 78%, based on ¹H NMR analysis.

Procedure for MgI₂ synthesis [MBAL-758]: An oven dried 50 mL roundbottomed flask, equipped with magnetic stirring bar, septum and Ar balloon, was charged with Mg (powder, 165 mg, 6.80 mmol, 2.0 equiv.) and Et_2O (10 mL). I_2 (863 mg, 3.40 mmol, 1.0 equiv.) was added in portions. The mixture was stirred overnight in the dark under N₂ atmosphere. Subsequently, unreacted Mg was removed by filtration and the solvent was evaporated under reduced pressure, delivering MgI₂ as an orange solid (615 mg, 2.21 mmol, 65%).

Procedure [MBAL-764]: In a 50 mL roundbottomed flask, a solution of MgI₂ (284 mg, 1.02 mmol, 2.0 equiv.) in Et₂O (10 mL) was mixed with a solution of 2-methoxy-4-propylphenol (**1a**, 85 mg, 0.51 mmol, 1.0 equiv.) in CH₂Cl₂ (10 mL). The solvents were removed under reduced pressure and the residual solid was heated to 80 °C for 16 h. Subsequently, the reaction mixture was cooled to r.t. and H₂O (20 mL) and Na₂S₂O₃ (aq., sat., 20 mL) were added. The resulting mixture was poured into HCl (aq., 5%, 10 mL) and the obtained solution was extracted with EtOAc (2×15 mL). The combined organic layers were washed with NaHCO₃ (aq., sat., 20 mL) and brine (20 mL), dried over MgSO₄, filtered and evaporated under reduced pressure. The resulting crude material was analyzed with ¹H NMR spectroscopy, revealing that **1a** yielded 78% **2a**, while 22% **1a** remained, based on integration of the signals.

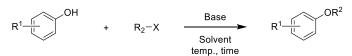
5.2.11 Cu₂O

Based on literature data, as published by Li and Xu.⁵⁰ The substrate **1a** was for 34% converted to the desired product **2a**, leaving the substrate **1a** in 60%, based on ¹H NMR analysis.

Procedure [JBO-1162]: In a Wheaton[®] 4 mL Vial, equipped with magnetic stirring bar, 2-methoxy-4propylphenol (**1a**, 166 mg, 1.00 mmol, 1.0 equiv.) was dissolved in MeOH (2.0 mL). Subsequently, Cu₂O (7.2 mg, 0.05 mmol, 5 mol%) and NaOMe (162 mg, 3.00 mmol, 3.0 equiv.) were added and the vial was placed in the Parr[®] 4596 reactor. The reactor was closed properly , flushed with N₂ (3 × 10 bar) and filled with N₂ (50 bar). The reactor was heated to 185 °C and the mixture was stirred for 12 h at this temperature. Subsequently, the reactor was cooled to r.t., depressurized and opened. The mixture was acidified to pH 4-5 using HCl (aq.) and extracted with MTBE (3 × 10 mL). The combined organic layers were dried over MgSO₄, filtered and evaporated under reduced pressure. The resulting crude material was analyzed with ¹H NMR spectroscopy with 1,3,5-trimethoxybenzene as internal standard, revealing that **1a** yielded 34% **2a**, while 60% **1a** remained.

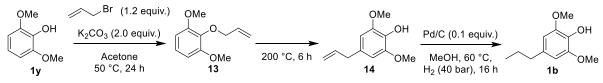
5.3 Synthesis of substrates

General procedure E

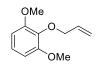


In a roudbottomed flask, equipped with a magnetic stirring bar and a reflux condenser, the appropriate substrate and base were mixed with acetone. The haloalkane (R²-X) was added and the obtained mixture was stirred for a certain time at a certain temperature. The mixture was filtered and the filtrate was concentrated under reduced pressure. The obtained residue was diluted with organic solvent and aq. solution. The layers were separated and the aqueous layer was extracted with organic solvent. The combined organic fractions were dried over MgSO₄ and concentrated under reduced pressure to afford the desired product.

Synthesis of 4-propylsyringol



Step 1: 1,3-Dimethoxy-2-[(prop-2-en-1-yl)oxy]benzene (13) [JBO-648]



This compound was obtained following General procedure E, 2,6-dimethoxyphenol (**1y**, 3.08 g, 20.0 mmol, 1.0 equiv.) and 3-bromoprop-1-ene (2.07 mL, 24 mmol, 1.2 equiv.) were used as reactants, K_2CO_3 (5.53 g, 40.0 mmol, 2.0 equiv.) as base and acetone (50 mL) as solvent. The work-up was performed using EtOAc (20 mL for

dilution and 3×20 mL for extraction) and NaOH (1 M, aq., 10 mL). Pure 1,3-dimethoxy-2-[(prop-2-en-1-yl)oxy]benzene (**13**) was obtained in 85% yield (3.28 g, 16.9 mmol). The obtained spectroscopic data are in accordance with literature.^{51, 52}

Yellow oil, $R_f = 0.45$ in heptanes/EtOAc (80:20). ¹H NMR (400 MHz, CDCl₃): δ 6.98 (t, J = 8.4 Hz, 1H), 6.58 (d, J = 8.4 Hz, 2H), 6.12 (ddt, J = 17.1, 10.5, 6.1 Hz, 1H), 5.31 (dd, J = 17.1, 1.3 Hz, 1H), 5.18 (d, J = 17.1, 1.3 Hz

10.5 Hz, 1H), 4.52 (dt, J = 6.1, 1.3 Hz, 2H), 3.85 (s, 6H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ 153.9 (C), 137.1 (C), 134.8 (CH), 123.8 (CH), 117.7 (CH₂), 105.5 (CH), 74.3 (CH₂), 56.3 (CH₃) ppm. HRMS (ESI) for C₁₁H₁₅O₃ [M+H]⁺ calcd. 195.1016, found 195.1007.

Step 2: 2,6-Dimethoxy-4-(prop-2-en-1-yl)phenol (14) [JBO-649, JBO-654]



A 4 mL glass vial, equipped with a magnetic stirring bar, was filled with 1,3dimethoxy-2-[(prop-2-en-1-yl)oxy]benzene (**13**, 1.00 g, 5.15 mmol). The vial was closed with a plastic cap and rubber septum and a needle was pierced through the septum. This vial was placed in the Parr[®] 4596 reactor (in the home made insert)

and the reactor was closed. Magnetic stirring was started and the reactor was heated to 200 °C during 6 h. Subsequently, the reactor was opened and cooled to r.t. The crude material was dissolved in MTBE (10 mL), mixed with SiO_2 (1.5 g) and evaporated under reduced pressure. The residue was poured onto a filter and washed with MTBE (10 mL). The filtrate was evaporated under reduced pressure to afford pure 2,6-dimethoxy-4-(prop-2-en-1-yl)phenol (14) in 83% yield (0.83 g, 4.25 mmol). The obtained spectroscopic data are in accordance with literature.⁵²

Colorless oil, $R_f = 0.37$ in heptanes/EtOAc (75:25). ¹H NMR (400 MHz, CDCl₃): δ 6.41 (s, 2H), 5.95 (ddt, J = 16.9, 10.1, 6.7 Hz, 1H), 5.37 (s, 1H), 5.11-5.06 (m, 2H), 3.87 (s, 6H), 3.32 (d, J = 6.7 Hz, 2H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ 147.2 (C), 137.7 (CH), 133.2 (C), 131.2 (C), 115.8 (CH₂), 105.4 (CH), 56.4 (CH₃), 40.5 (CH₂) ppm. HRMS (ESI) for C₁₁H₁₅O₃ [M+H]⁺ calcd. 195.1016, found 195.1006.

Step 3: 2,6-Dimethoxy-4-propylphenol (1b) [JBO-439, JBO-577]

^{MeO} HO HO OME The glass insert for the 600 mL Parr[®] reactor was loaded with a stirring bar, 4-allyl-2,6-dimethoxyphenol (**14**, 5.45 g, 28.1 mmol, 1.0 equiv.) and MeOH (100 mL). To this solution, Pd/C (10 m%, 300 mg, 0.3 mmol,1 mol%) was added under an argon flow. The beaker was placed in the Parr[®] 4625 reactor, which was then closed, flushed with of H₂ (g, 3×10 bar) and filled with H₂ gas (40 bar). The mixture in the reactor was heated to 60 °C and stirred for 16 h. Subsequently, the reactor was cooled to r.t., the pressure was released and the reactor was opened. The reaction mixture was filtered over celite (1 cm) and the filtrate was evaporated under reduced pressure to afford pure 2,6-dimethoxy-4-propylphenol (**1b**) in 83% yield (4.52 g, 23.3 mmol). The obtained spectroscopic data are in accordance with literature.⁵³

Yellow oil, $R_f = 0.29$ in heptanes/EtOAc (80:20). ¹H NMR (400 MHz, CDCl₃): δ 6.40 (s, 2H), 5.40 (s, 1H), 3.85 (s, 6H), 2.50 (t, J = 7.6 Hz, 2H), 1.61 (sext, J = 7.4 Hz, 2H), 0.93 (t, J = 7.3 Hz, 3H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ 146.9 (C), 133.8 (C), 132.8 (C), 105.1 (CH), 56.3 (CH₃), 38.3 (CH₂), 24.8 (CH₂), 13.8 (CH₃) ppm. HRMS (ESI) for C₁₁H₁₇O₃ [M+H]⁺ calcd. 197.1172, found 197.1163. HRMS (ESI) for C₁₁H₁₆O₃Na [M+Na]⁺ calcd. 219.0992, found 219.0991.

1,2-Dimethoxy-4-propylbenzene (1e) [MS-538, JBO-433]



EtO

EtO

A 100 mL pressure tube, equipped with magnetic stirring bar, was charged with K_2CO_3 (26 mg, 0.19 mmol, 0.01 equiv.), 2-methoxy-4-propylphenol (**1a**, 3.11 g, 18.8 mmol, 1.0 equiv.) and dimethyl carbonate (9.47 mL, 112 mmol, 6.0 equiv.).

The flask was sealed and the reaction mixture was heated at 200 °C for 24 h and cooled down to r.t. The content of the pressure tube was transferred with EtOAc (5 mL) and filtered through cotton wool into a roundbottomed flask, after which the precipitate was further washed with EtOAc (5 mL). The solvent was evaporated in order to afford **1e** in quantitative yield (3.39 g, 18.8 mmol). The obtained spectroscopic data are in accordance with literature.⁵⁴

Pale yellow oil, $R_f = 0.79$ in heptanes/EtOAc (50:50). ¹H NMR (400 MHz, CDCl₃): δ 6.79 (d, J = 8.6 Hz, 1H), 6.73-6.71 (m, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 2.54 (t, J = 7.5 Hz, 2H), 1.63 (sext, J = 7.5 Hz, 2H), 0.94 (t, J = 7.5 Hz, 3H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ 148.9 (C), 147.2 (C), 135.5 (C), 120.3 (CH), 112.0 (CH), 111.3 (CH), 56.0 (CH₃), 55.9 (CH₃), 37.7 (CH₂), 24.8 (CH₂), 13.9 (CH₃) ppm. HRMS (ESI) for C₁₁H₁₇O₂ [M+H]⁺ calcd. 181.1229, found 181.1229.

1,2-Diethoxy-4-propylbenzene (1f) [JBO-1375, JBO-1359, EB-558]

A 50 mL roundbottomed flask, equipped with magnetic stirring bar, was charged with 4-propylbenzene-1,2-diol (**2a**, 1.07 g, 7.00 mmol, 1.0 equiv.), K₂CO₃ (3.87 g, 28.0 mmol, 4.0 equiv.) and EtOH (10 mL). EtI (2.25 mL, 28.0 mmol, 4.0 equiv.) was

added and the reaction mixture was stirred for 24 h under reflux. The mixture was filtered and the filtrate evaporated under reduced pressure. The residue was dissolved in EtOAc (20 mL) and washed with an aqueous solution of NaOH (1 M, 10 mL). The organic layer was dried over MgSO₄, filtered and evaporated under reduced pressure in order to afford 1,2-diethoxy-4-propylbenzene (**1f**) in 99% yield (1.44 g, 6.92 mmol). The obtained spectroscopic data are in accordance with literature.⁵⁵

Brown liquid, $R_f = 0.89$ in heptanes/EtOAc (50:50). ¹H NMR (400 MHz, CDCl₃): δ 6.81 (d, J = 8.1 Hz, 1H), 6.73 (d, J = 2.1 Hz, 1H), 6.69 (dd, J = 8.1, 2.1 Hz, 1H), 4.09 (q, J = 7.0 Hz, 2H), 4.07 (q, J = 7.0 Hz, 2H), 2.52 (t, J = 7.4 Hz, 2H), 1.62 (sext, J = 7.4 Hz, 2H), 1.44 (t, J = 7.0 Hz, 3H), 1.43 (t, J = 7.0 Hz, 3H), 0.94 (t, J = 7.4 Hz, 3H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ 148.8 (C), 147.0 (C), 135.8 (C), 120.7 (CH), 114.5 (CH), 114.1 (CH), 64.9 (CH₂), 64.7 (CH₂), 37.8 (CH₂), 24.8 (CH₂), 15.1 (CH₃), 15.1 (CH₃), 13.9 (CH₃) ppm. HRMS (ESI) for C₁₃H₂₁O₂ [M+H]⁺ calcd. 209.1542, found 209.1544.

3-(4-Hydroxy-3-methoxyphenyl)propanoic acid (1g) [JBO-GM-126]

In a Parr[®] hydrogenation bottle (2*E*)-3-(4-hydroxy-3-methoxyphenyl)prop-2-MeO enoic acid (11, 5.00 g, 25.7 mmol, 1.0 equiv.) was dissolved in MeOH (50 mL). ОН Pd/C (10 m%, 0.50 g, 0.47 mmol, 2 mol%) was added under argon flow and the HO vessel was placed in a Parr[®] 3911 Hydrogenation Apparatus. The vessel was flushed with H₂ (3 × 4 bar) and filled with H₂ (4 bar). The vessel was shaken for 1 h at r.t.. Subsequently, the pressure was released and the crude mixture was filtered over Celite. The filter was rinsed with MeOH (50 mL) and the combined filtrates were evaporated under reduced pressure. The obtained residue was mixed with H₂O (33 mL) and NaOH (2.68 g, 6.70 mmol, 2.6 equiv.) was added. The mixture was stirred for 24 h under reflux. Subsequently, the mixture was cooled to r.t., neutralized with HCl (conc.) to neutral pH and extracted with MTBE (3 × 50 mL). The combined organic fractions were dried over MgSO₄, filtered and evaporated under reduced pressure to afford pure 3-(4-hydroxy-3-methoxyphenyl)propanoic acid (1g) in 94% yield (4.75 g, 24.2 mmol). The obtained spectroscopic data are in accordance with literature.56

Beige solid, m.p.: 91 °C (lit.: 91 °C),⁵⁷ R_f = 0.26 in heptanes/EtOAc (50:50). ¹H NMR (400 MHz, DMSO-d₆): δ 12.03 (bs, 1H), 8.64 (bs, 1H), 6.78 (d, *J* = 1.8 Hz, 1H), 6.66 (d, *J* = 8.0 Hz, 1H), 6.59 (dd, *J* = 8.0, 1.8 Hz, 1H), 3.74 (s, 3H), 2.71 (t, *J* = 7.7 Hz, 2H), 2.51-2.46 (m, 2H) ppm. ¹³C NMR (101 MHz, DMSO-d₆): δ 173.9 (C), 147.4 (C), 144.7 (C), 131.7 (C), 120.2 (CH), 115.3 (CH), 112.5 (CH), 55.5 (CH₃), 35.7 (CH₂), 30.0 (CH₂) ppm. HRMS (ESI) for C₁₀H₁₁O₄ [M-H]⁻ calcd. 195.0663, found 195.0667.

2H-1,3-Benzodioxole-5-carbaldehyde (1i) [MBAL-411]

In a 50 mL roundbottemed flask, equipped with magnetic stirring bar, (2H-1,3-benzodioxol-5-yl) methanol (**15**, 1.52 g, 10.0 mmol, 1.0 equiv.) was dissolved in CH₂Cl₂ (20 mL). MnO₂ (8.69 g, 100 mmol, 10 equiv.) was added and the mixture was stirred at r.t. for 20 h. Subsequently, the crude mixture was filtered through Celite and evaporated under reduced pressure. The crude material was purified by an automated flash chromatography system using a heptanes/EtOAc gradient (Cartridge: 40 g SiO₂, flow rate: 30 mL·min⁻¹, eluent: heptanes to 50% EtOAc in heptanes, 60 min). Pure 2*H*-1,3-benzodioxole-5-carbaldehyde (**1i**) was obtained in 85% yield (1.28 g, 8.54 mmol). The obtained spectroscopic data are in accordance with literature.⁵⁸

White solid, m.p.: 35 °C (lit.: 35-37 °C),⁵⁹ R_f = 0.73 in heptanes/EtOAc (50:50) ¹H NMR (400 MHz, CDCl₃): δ 9.81 (s, 1H), 7.41 (d, *J* = 7.9, 1.5 Hz, 1H), 7.33 (d, *J* = 1.5 Hz, 1H), 6.93 (d, *J* = 7.9 Hz, 1H), 6.07 (s, 2H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ 190.4 (CH), 153.3 (C), 148.9 (C), 132.1 (C), 128.8 (CH), 108.5 (CH), 107.1 (CH), 102.2 (CH₂) ppm. EI (+) (m/z (%)): 150 (80), 149 (100).

5,6-Dimethoxy-2,3-dihydro-1H-inden-1-one (1k) [MBAL-495]

In a 20 mL pressure tube 3-(3,4-dimethoxyphenyl)propanoic acid (**1h**, 1.00 g, 4.76 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (10 mL). The tube and its contents were cooled to 0 °C and TfOH (1.47 mL, 16.7 mmol, 3.5 equiv.) was slowly added to the mixture. The tube was sealed and heated to 80°C for 90 min under magnetic stirring. Subsequently, the mixture was cooled to r.t., poured into ice water (50 mL) and stirred for another 20 min. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic fractions were washed with H_2O (25 mL) and NaHCO₃ (aq., sat., 20 mL), dried over Na₂SO₄, and evaporated under reduced pressure to afford 5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-one (**1k**) in 96% yield (0.88 g, 4.57 mmol). The obtained spectroscopic data are in accordance with literature.⁶⁰

Pink solid, m.p.: 113 °C (lit.: 113-115 °C),⁶⁰ R_f = 0.40 in heptanes/EtOAc (50:50). ¹H NMR (400 MHz, CDCl₃): δ 7.17 (s, 1H), 6.88 (s, 1H), 3.96 (s, 3H), 3.90 (s, 3H), 3.06-3.03 (m, 2H), 2.68-2.65 (m, 2H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ 205.8 (C), 155.6 (C), 150.5 (C), 149.6 (C), 130.1 (C), 107.6 (CH), 104.4 (CH), 56.3 (CH₃), 56.2 (CH₃), 36.7 (CH₂), 25.7 (CH₂) ppm. HRMS (ESI) for C₁₁H₁₃O₃ [M+H]⁺ calcd. 193.0859, found 193.0860.

1-Ethoxy-2-methoxybenzene (1n) [SA-017, JBO-248]

MeO Eto This compound was obtained following General procedure E, using 2-methoxyphenol (**1**, 1.24 g, 10.0 mmol, 1.0 equiv.) and Etl (0.9 mL, 12.0 mmol, 1.2 equiv.) as reactants, K₂CO₃ (4.67 a, 12 mmol, 1.2 equiv.) as here and eastern (20 ml) as achieved.

(1.67 g, 12 mmol, 1.2 equiv.) as base and acetone (20 mL) as solvent. The mixture was stirred for 24 h under reflux. The work-up was performed using CH_2Cl_2 (3 × 30 mL) and NaOH (aq., 1 M, 10 mL). Pure 1-ethoxy-2-methoxybenzene (**1n**) was obtained in 86% yield (1.20 g, 7.88 mmol). The obtained spectroscopic data are in accordance with literature.⁶¹

Colorless oil, $R_f = 0.79$ in heptanes/EtOAc (50:50). ¹H NMR (400 MHz, CDCl₃): δ 6.94-6.88 (m, 4H), 4.11 (q, J = 7.0 Hz, 2H), 3.87 (s, 3H), 1.47 (t, J = 7.0 Hz, 3H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ 149.6 (C),

148.5 (C), 121.0 (CH), 120.9 (CH), 113.2 (CH), 111.9 (CH), 64.4 (CH₂), 56.0 (CH₃), 14.9 (CH₃) ppm. HRMS (ESI) for C₉H₁₃O₂ [M+H]⁺ calcd. 153.0916, found 153.0913.

5.3.1 Synthesis of 4-propylguaiacol from natural feedstocks

5.3.1.1 Hydrogenation of natural eugenol

Natural eugenol, obtained from *Eugenia* upon biological extraction and purification,⁶² had a purity of 97 wt%, which was determined via ¹H NMR spectroscopy using 1,3,5-trimethoxybenzene (1,3,5-TMB) as internal standard (Figure S9):

- Ratio between **3** and **1,3,5-TMB**: $ratio_{3/1,3,5-TMB} = \frac{154.26/1}{100.00/3} = 4.6278$
- The sample contains 16 mg **1,3,5-TMB**, corresponding to 0.0954 mmol
- Leading to $4.6278 \times 0.0954 = 0.4415 \text{ mmol } \mathbf{3} = 72.43 \text{ mg } \mathbf{3}$
- There is 72.43 mg **3** present in 75 mg natural eugenol, corresponding to $\frac{72.43}{75} \times 100\% = 97$ wt%

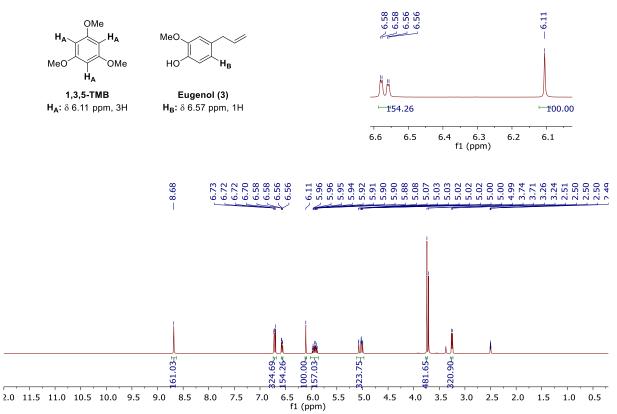
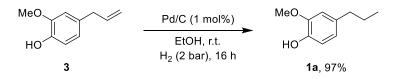
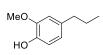


Figure S9. ¹H NMR Spectrum of natural eugenol (**3**), revealing 97% purity. Quantification is based on the integration of the assigned signals for H_A and H_B . Therefore, 75 mg natural feedstock and 16 mg 1,3,5-trimethoxybenzene were dissolved in DMSO-d₆.

Subsequently, hydrogenation was performed as follows:



2-Methoxy-4-propylphenol (1a) [MBAL-777]



In a Parr[®] hydrogenation bottle, 4-allyl-2-methoxyphenol (natural eugenol, **3**, 2.00 g, 12.2 mmol, 1.0 equiv.) was dissolved in EtOH (100 mL). Pd/C (10 wt% Pd, 0.13 g, 0.12 mmol, 1 mol%) was added under argon flow and the vessel was placed in a

Parr[®] 3911 Hydrogenation Apparatus. The vessel was flushed with H₂ (3 × 1 bar) and filled with H₂ (2 bar). The vessel was shaken for 16 h at r.t.. Subsequently, the pressure was released and the crude mixture was filtered over Celite. The filter was rinsed with acetone (25 mL), the combined filtrates were evaporated under reduced pressure to afford pure 2-methoxy-4-propylphenol (**1a**) in 97% yield (1.96 g, 11.8 mmol). The obtained spectroscopic data are in accordance with literature and commercial **1a**.⁶³

Colorless oil, $R_f = 0.76$ in heptanes/EtOAc (50:50). ¹H NMR (400 MHz, CDCl₃): δ 6.84 (d, J = 8.1 Hz, 1H), 6.70-6.67 (m, 2H), 5.48 (s, 1H), 3.88 (s, 3H), 2.53 (t, J = 7.4 Hz, 2H), 1.63 (sext, J = 7.4 Hz, 2H), 0.95 (t, J = 7.4 Hz, 3H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ 146.4 (C), 143.7 (C), 134.8 (C), 121.1 (CH), 114.2 (CH), 111.2 (CH), 56.0 (CH₃), 37.9 (CH₂), 25.0 (CH₂), 13.9 (CH₃) ppm.

5.3.1.2 Reductive catalytic fractionation of softwood lignin

In a Soxhlet set-up, pine wood particles (10 g) were extracted with a boiling mixture of toluene (250 mL) and EtOH (125 mL) during 3 h. This extraction was repeated 15 times and the remaining 'extracted pine wood' was combined and dried. A 2 L autoclave (Parr®) was loaded with the obtained extracted pine wood (150 g), Ru/C (5 wt% Ru, 15 g) and MeOH (800 mL). The autoclave was closed, pressurized with H₂ (30 bar), heated to 235 °C and kept under these conditions for 16 h under stirring (750 rpm). Subsequently, the autoclave and its contents were cooled to r.t., pressure was released and the reaction mixture was filtered and evaporated under reduced pressure. To the residue was added H_2O (220 mL) and the obtained mixture was extracted with EtOAc (200 mL and 2 × 175 mL). The combined organic fractions were evaporated under reduced pressure and to the residue was added heptane (140 mL). The obtained mixture was refluxed for 30 min and cooled to r.t. The solvent was decanted, fresh heptane (140 mL) was added to the residue and the obtained mixture was refluxed for 30 min. After cooling to r.t., the process of decantation and addition of heptane (140 mL) was repeated, followed by refluxing for 2 h and decantation. The three heptane fractions were combined, stored at 5 °C overnight and decanted. The decanted fraction was evaporated under reduced pressure, delivering a lignin oil, rich in 4-propylguaiacol (1a) (64 wt%, based on ¹H NMR analysis with 1,3,5trimethoxybenzene as int. std., vide infra), corresponding to 18.2% of the original lignin content of the wood.

In order to determine the lignin content of the used pine wood, the following procedure was followed, similarly to a previously published method:⁶⁴

Product yields in lignin depolymerisation literature are typically based on the amount of acid insoluble lignin, also called Klason lignin, in the lignocellulose sample. The determination of the Klason lignin

content of pine was based on a procedure from Lin & Dence.⁶⁵ Triplicate samples of pre-extracted pine wood (1 g each) were transferred to 50 mL beakers after which 15 mL of a 72 wt% H_2SO_4 solution was added. The mixture was left at room temperature for 2 h while being continuously stirred with a magnetic rod. Afterwards the content of each beaker was transferred to a round-bottom-flask which already contained 300 to 400 mL of water. The beakers were rinsed and additional water was added until a H_2SO_4 concentration of 3 wt% was reached. The diluted solution was boiled for 4 h under reflux conditions, to maintain a constant volume and acid concentration. After filtration of the hot solution, a brown lignin precipitate was retained. The precipitate was washed with hot water to remove any leftover acid and the obtained residue was dried at 80 °C overnight. The reported Klason lignin content of 24.6 wt% was determined relative to the oven dried substrate by averaging the measured weight of the residues.

Analysis of the obtained lignin oil:

Upon ¹H NMR Analysis using 1,3,5-trimethoxybenzene (1,3,5-TMB) as internal standard (Figure S10), we found that the obtained lignin oil contains 64 wt% 4-propylguaiacol (**1a**):

- Ratio between **1a** and **1,3,5-TMB**: $ratio_{1a/1,3,5-TMB} = \frac{\frac{84.85}{100.00/3}}{\frac{100.00}{3}} = 2.5455$
- The sample contains 15 mg 1,3,5-TMB, corresponding to 0.0911 mmol
- Leading to $2.5455 \times 0.0911 = 0.2321 \text{ mmol } 1a = 38.58 \text{ mg } 1a$
- There is 38.58 mg **1a** present in 60 mg lignin oil, corresponding to $\frac{38.58}{60} \times 100\% = 64$ wt%

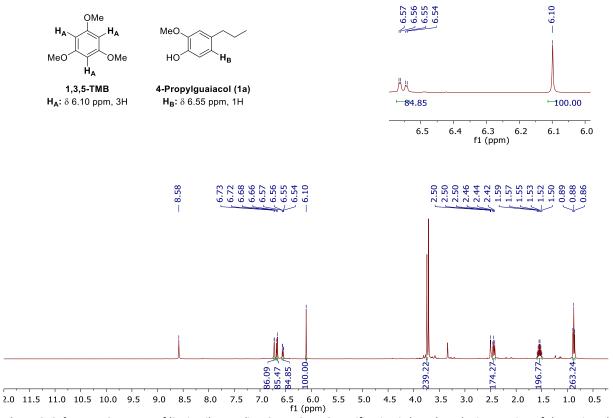


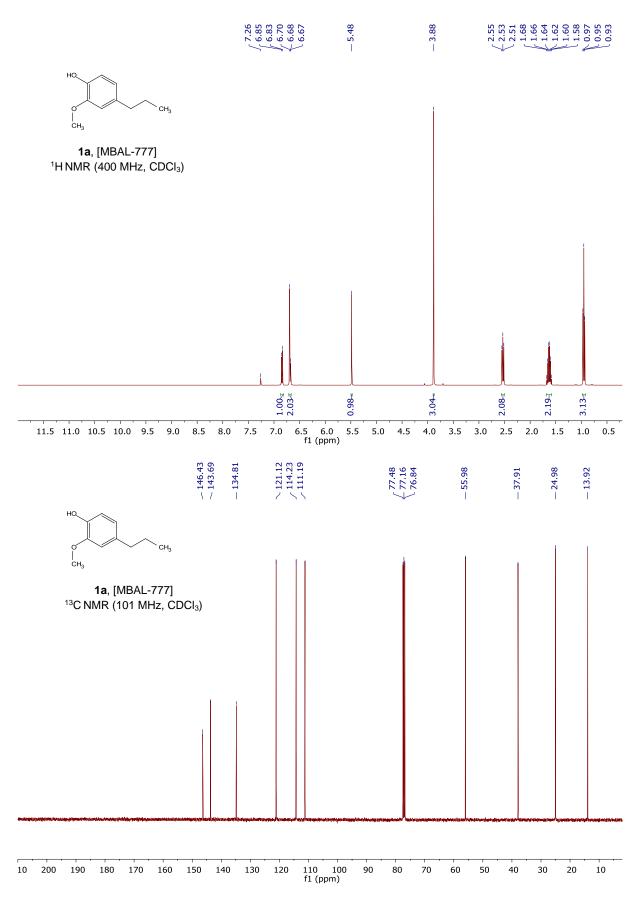
Figure S10. ¹H NMR Spectrum of lignin oil, revealing 64 wt% **1a**. Quantification is based on the integration of the assigned signals for H_A and H_B . Therefore, 60 mg oil and 15 mg 1,3,5-trimethoxybenzene were dissolved in DMSO-d₆.

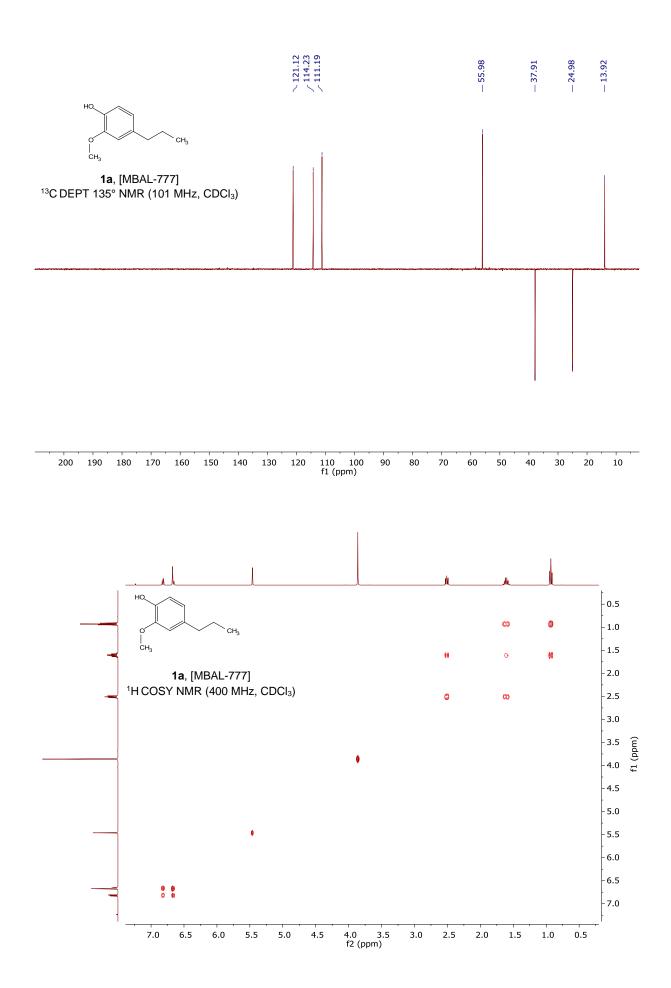
Analysis of the lignin oil using GC-MS showed that **1a** was present next to the following monomers as minor compounds:

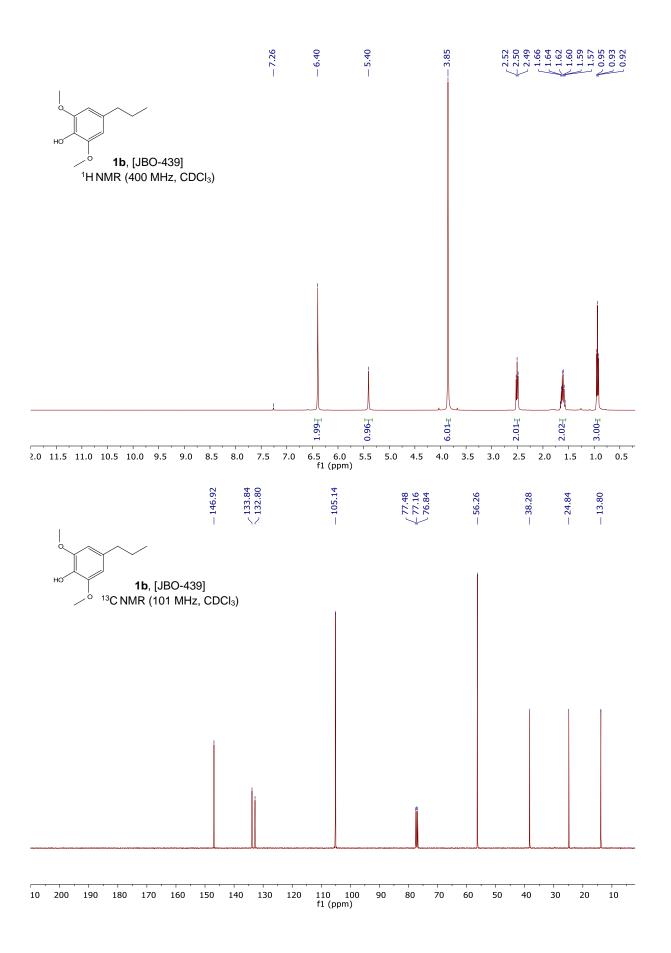
- 4-Ethylguaiacol (2 wt%)
- Isoeugenol (< 1 wt%)
- Methoxylpropanolguaiacol (< 1 wt%)
- Dihydroconiferylalcohol (< 1 wt%)

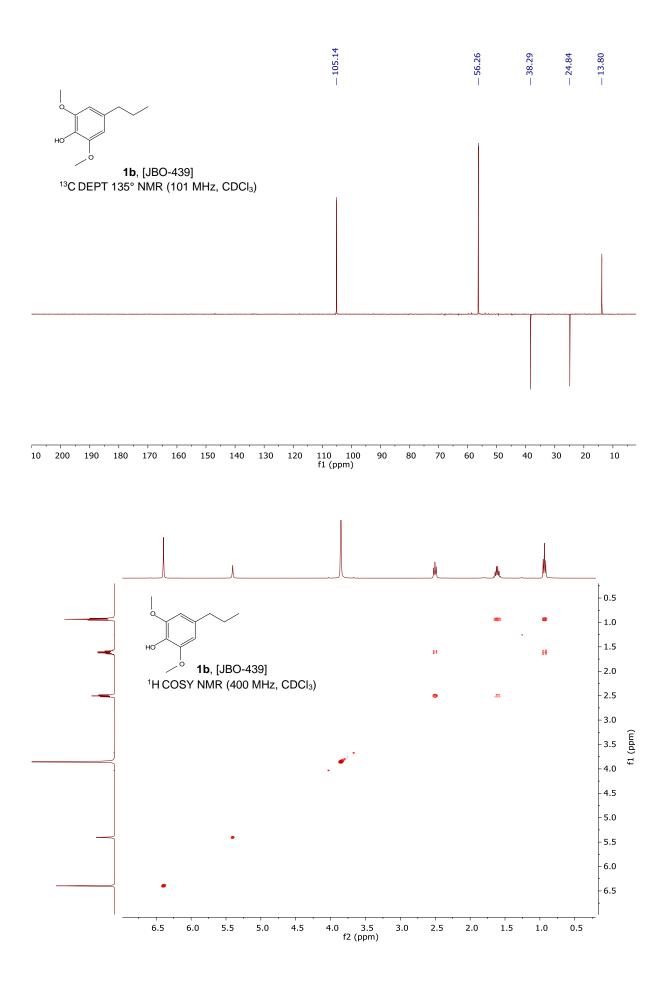
Also some unidentified dimers were present. All these compounds are minor based on the ¹H NMR Spectrum of the lignin oil presented in Figure S10.

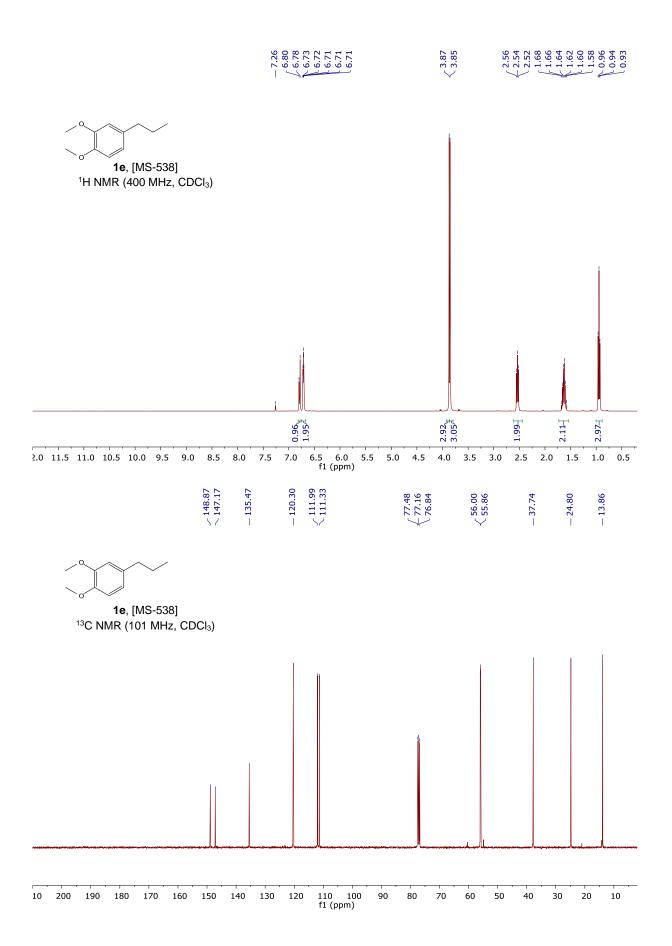
6 NMR spectra of compounds

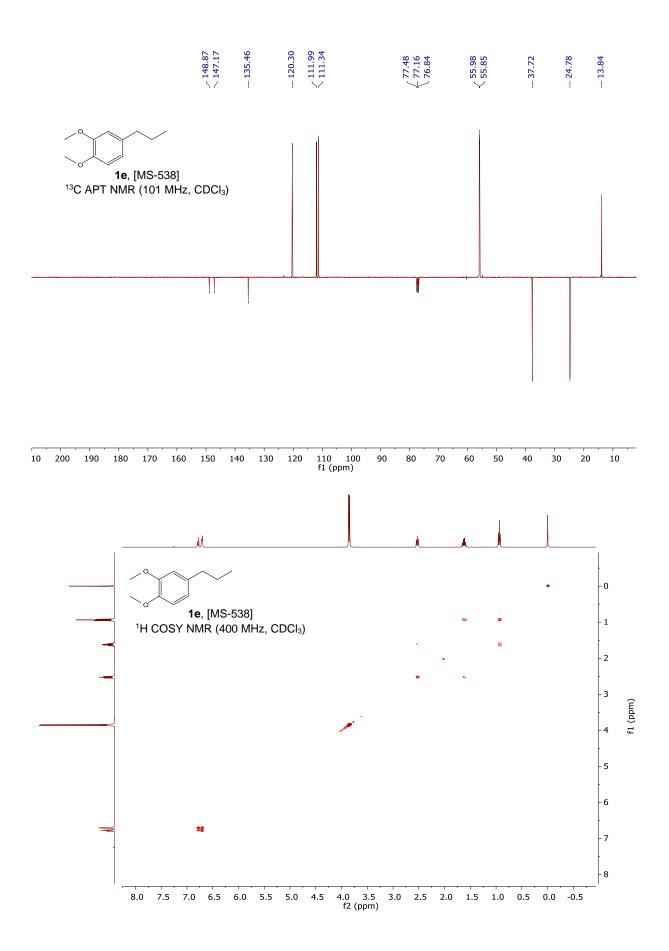


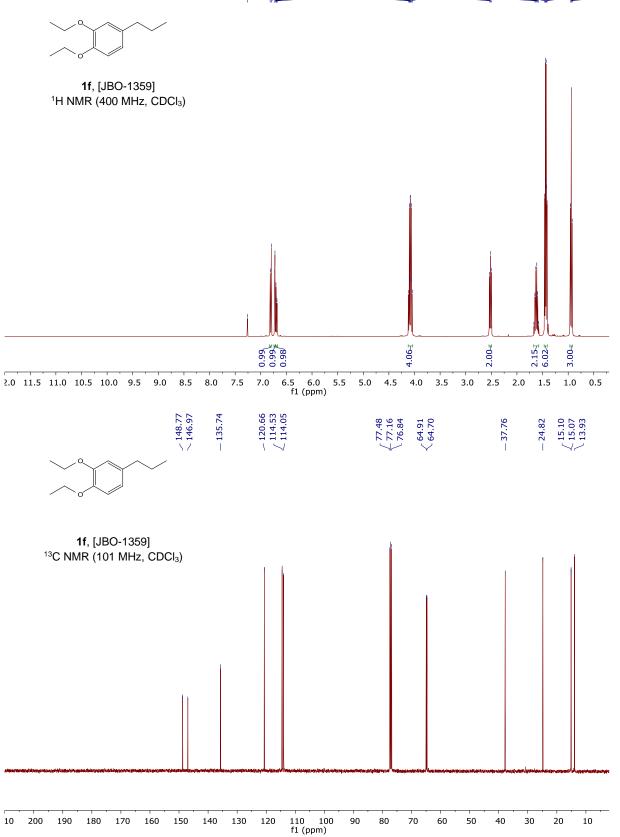


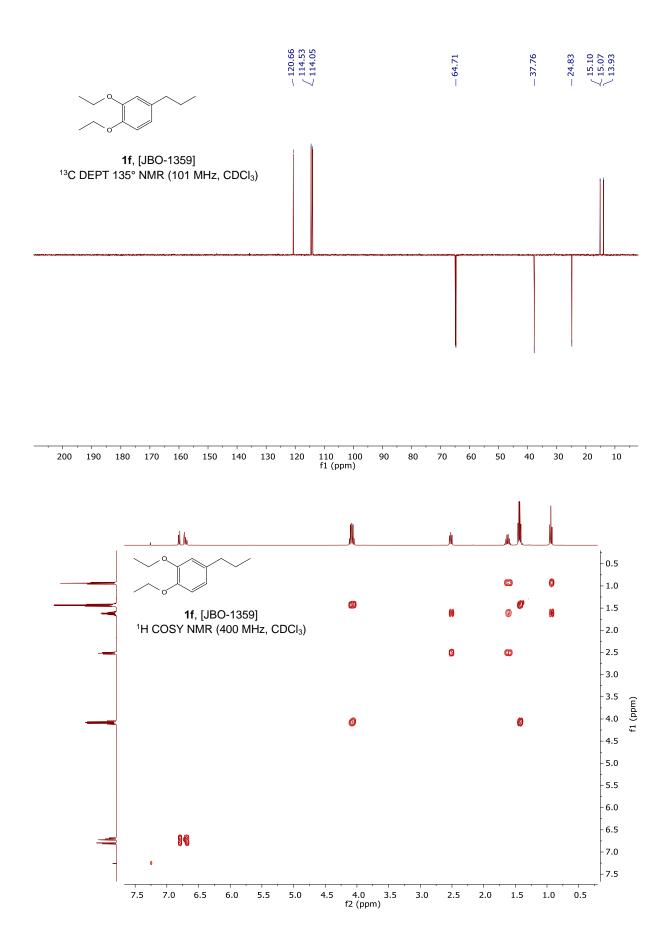


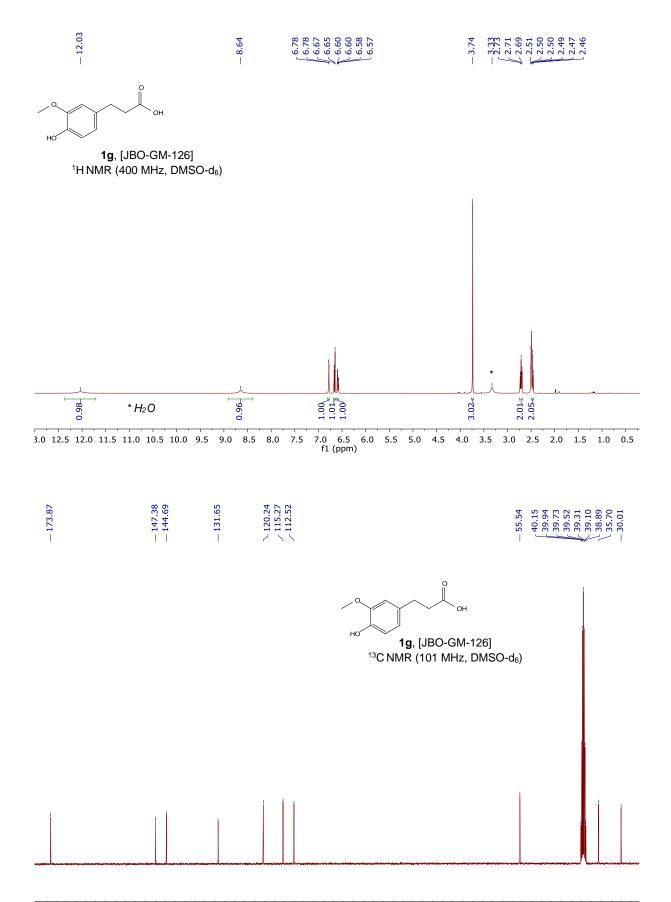




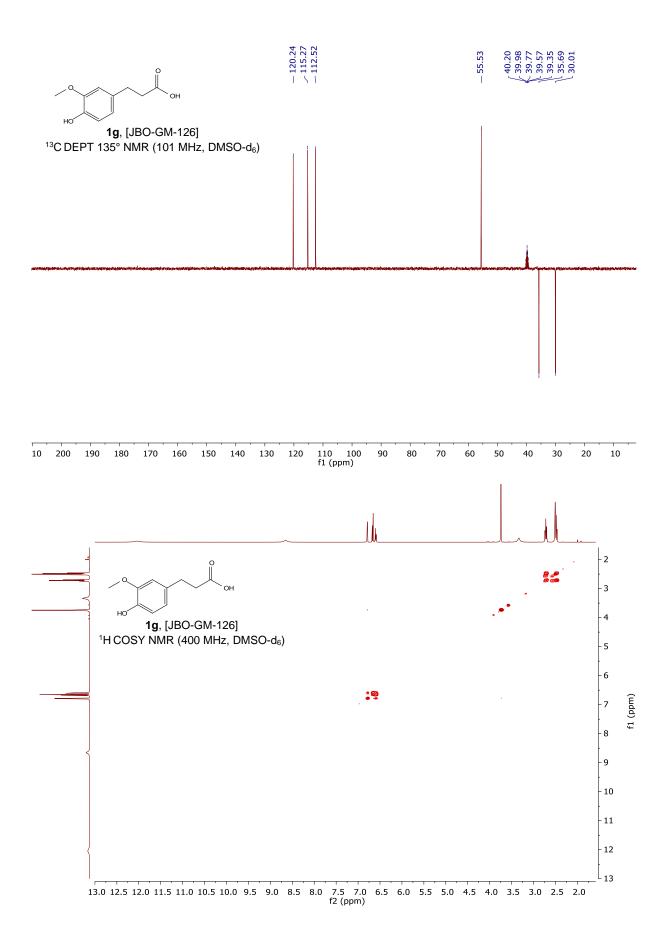


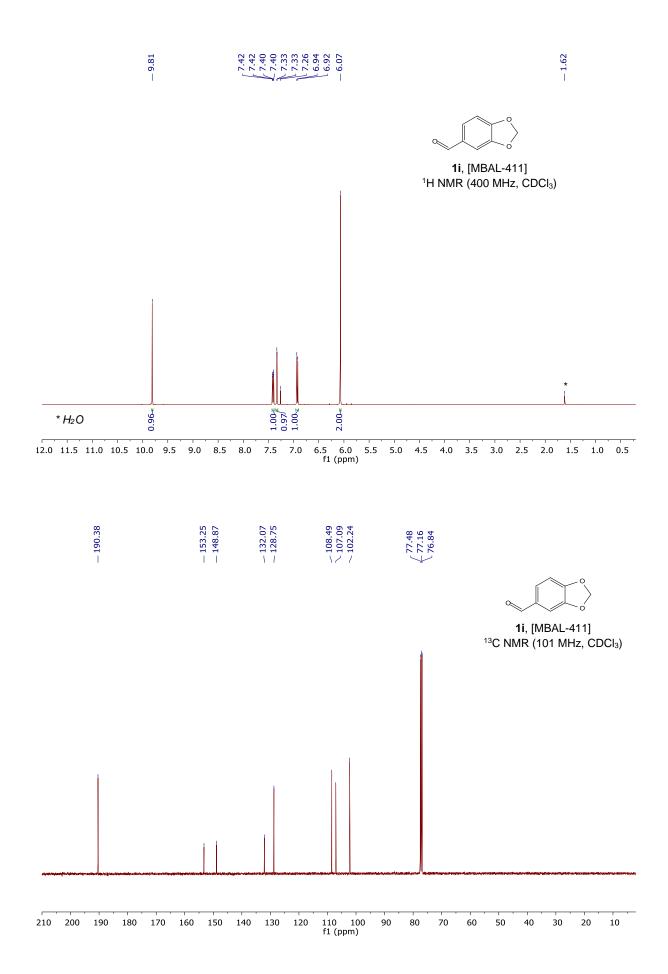


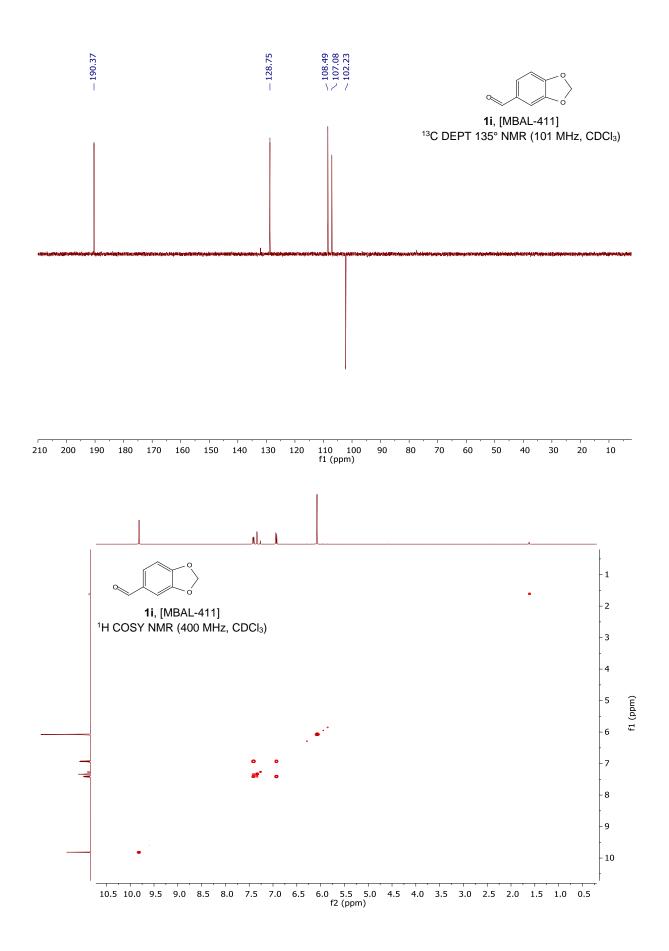


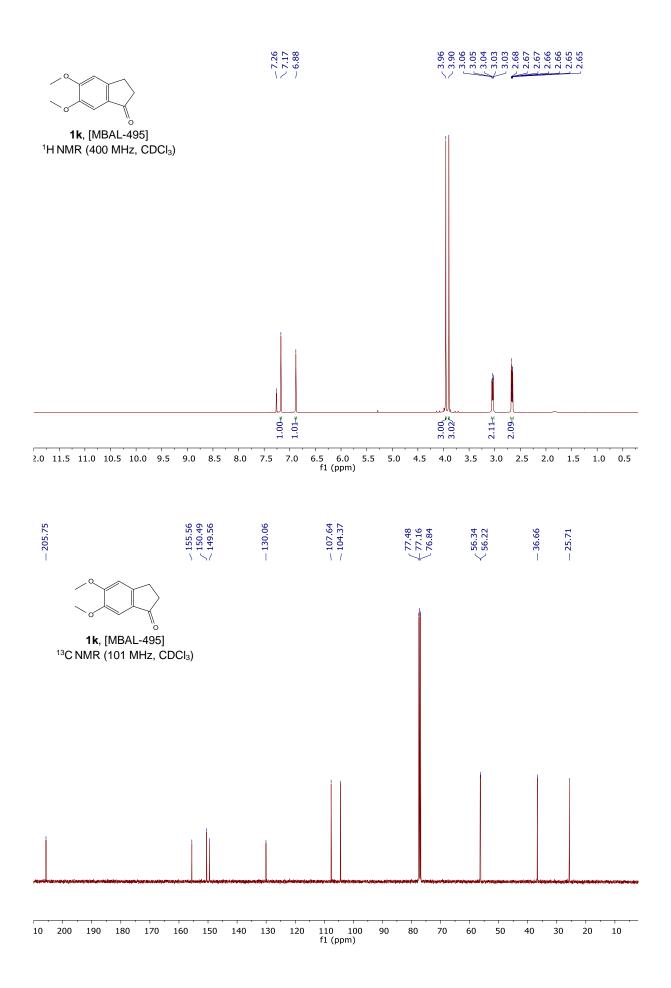


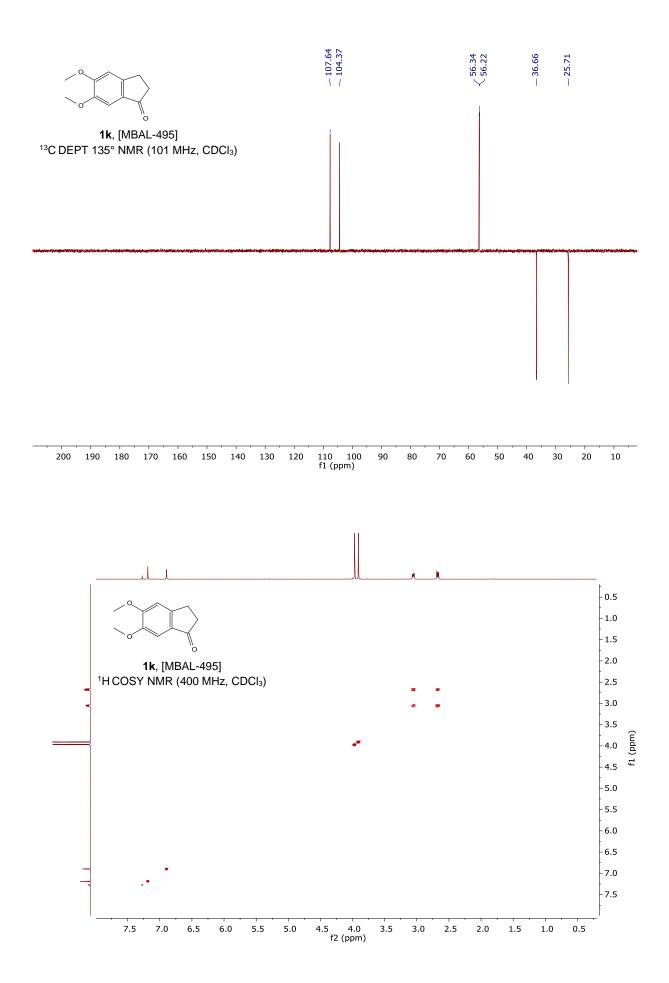
175 170 165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 f1 (ppm)

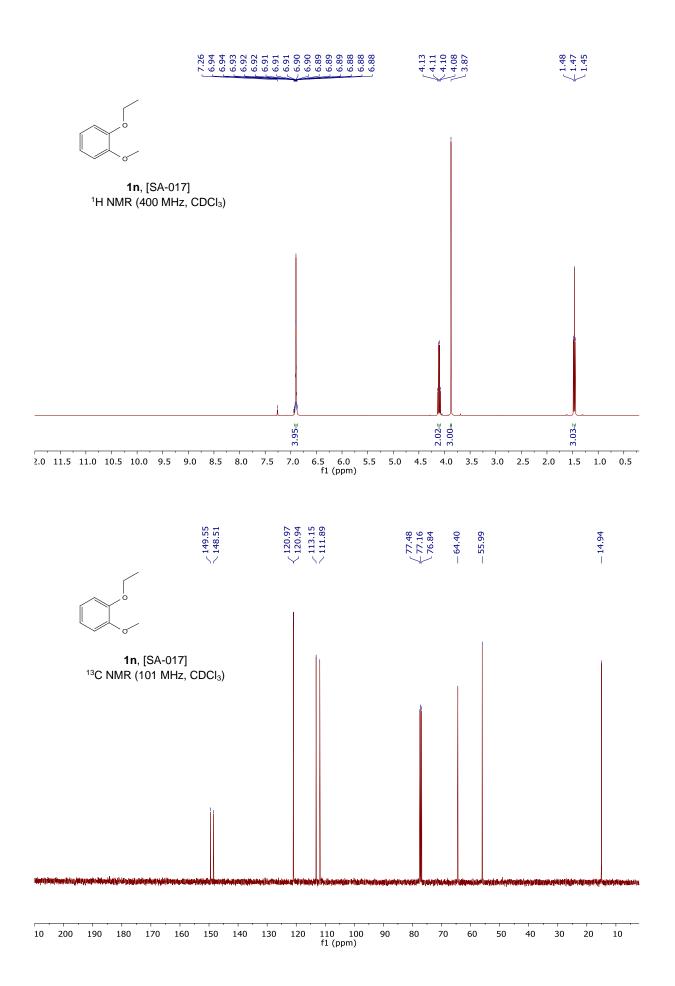


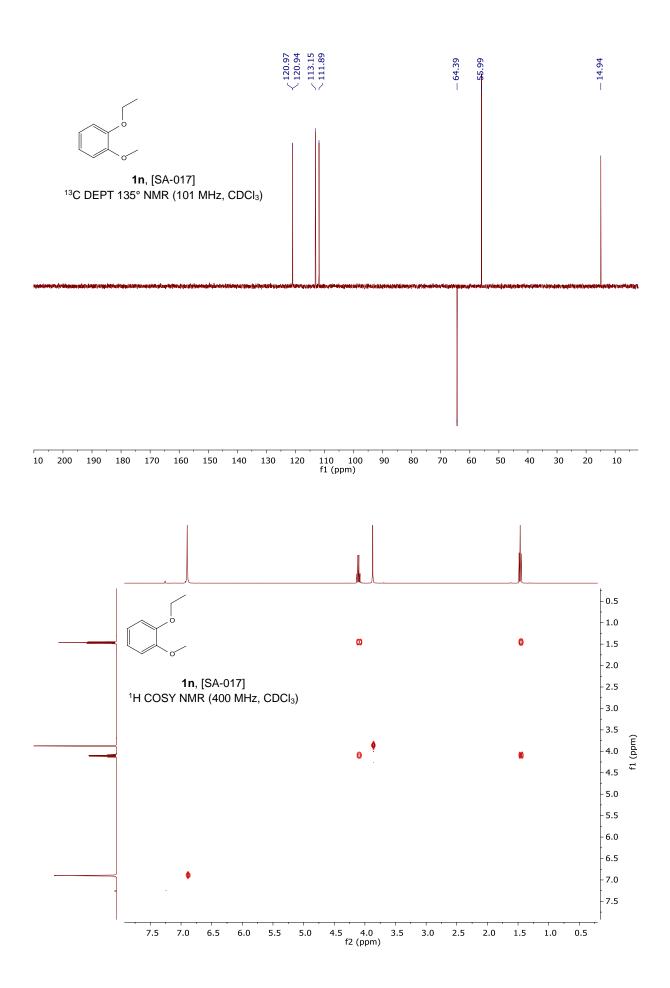


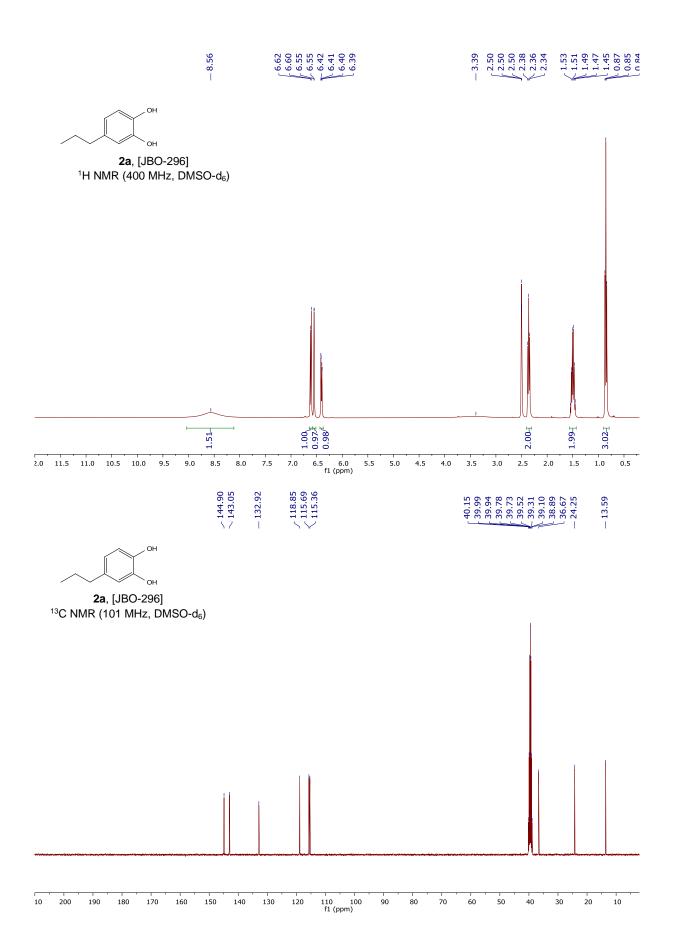


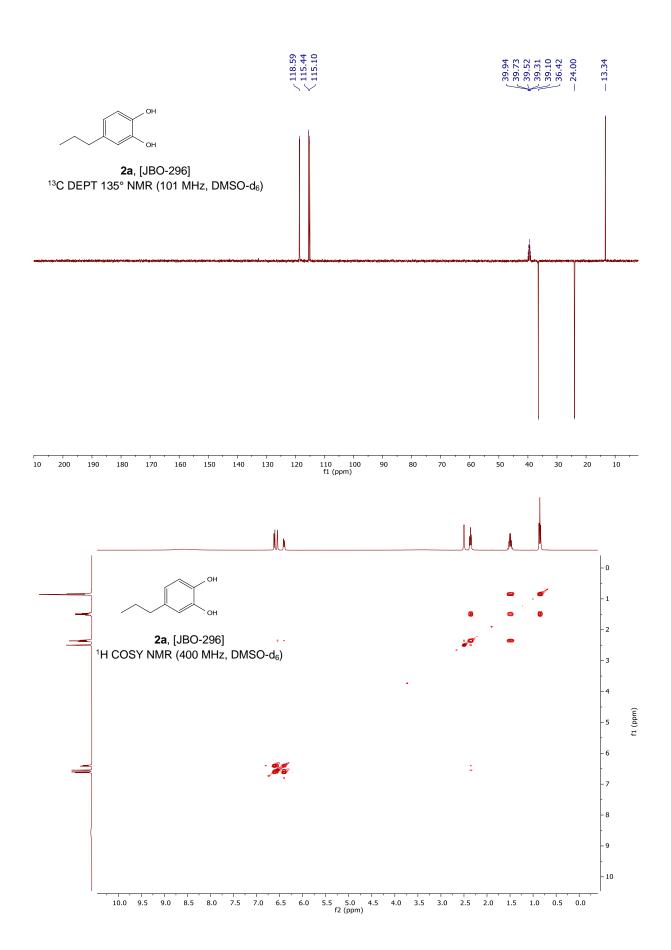


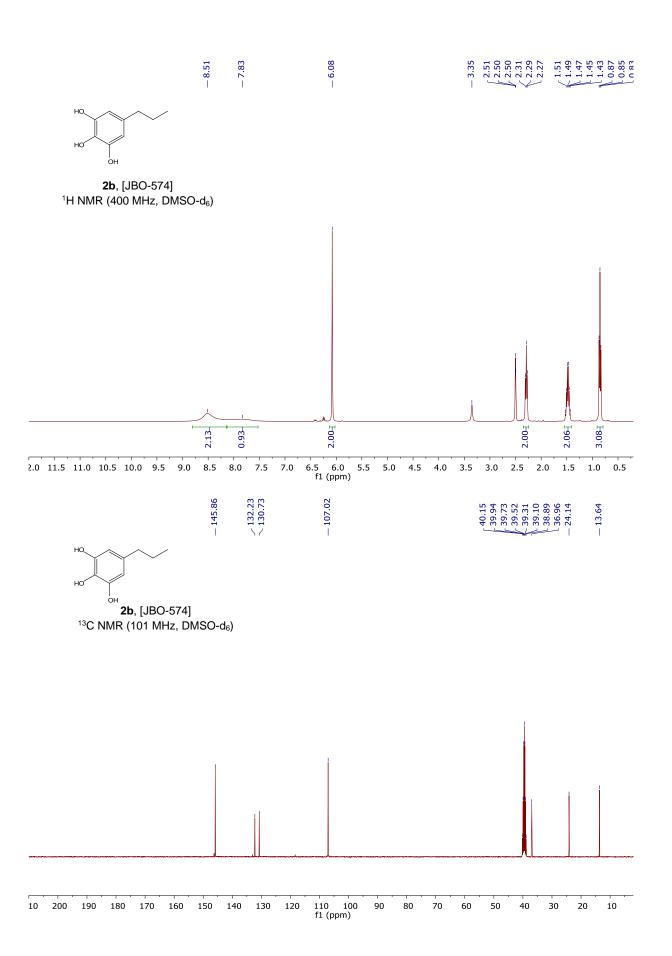


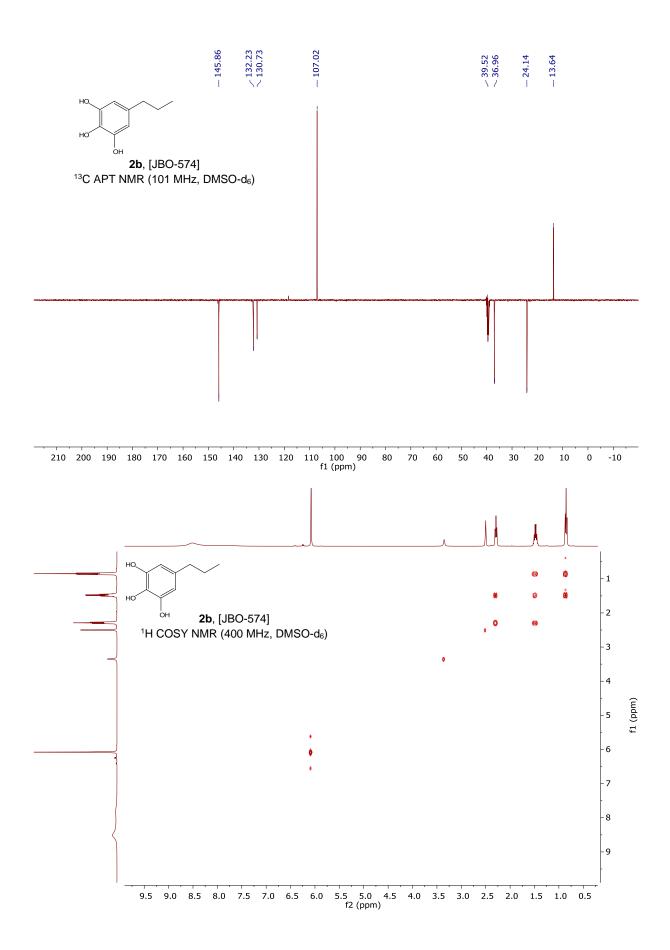












$$-8.58$$

$$-8.56$$

$$6.63$$

$$6.63$$

$$6.64$$

$$6.441$$

$$6.441$$

$$6.441$$

$$6.442$$

$$2.50$$

$$-3.34$$

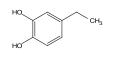
$$-2.51$$

$$1.122$$

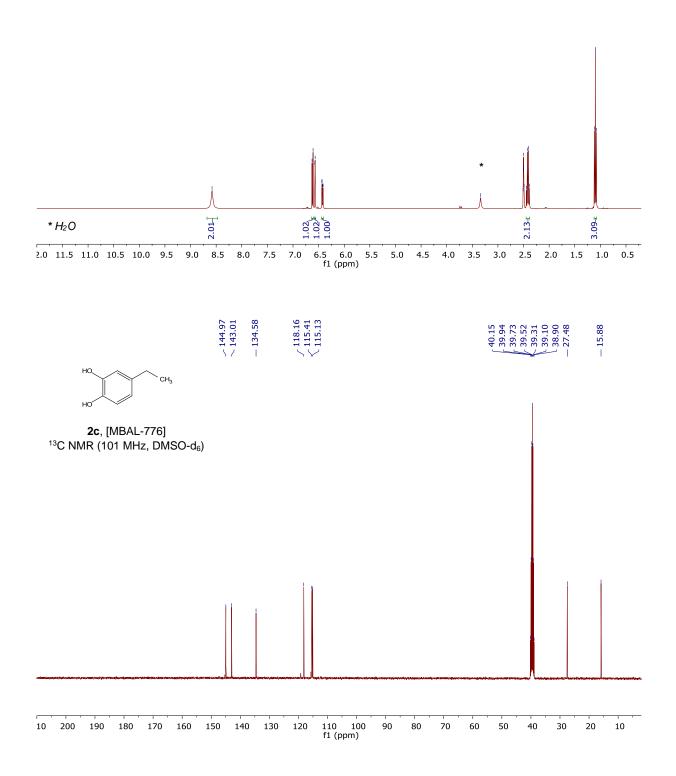
$$2.50$$

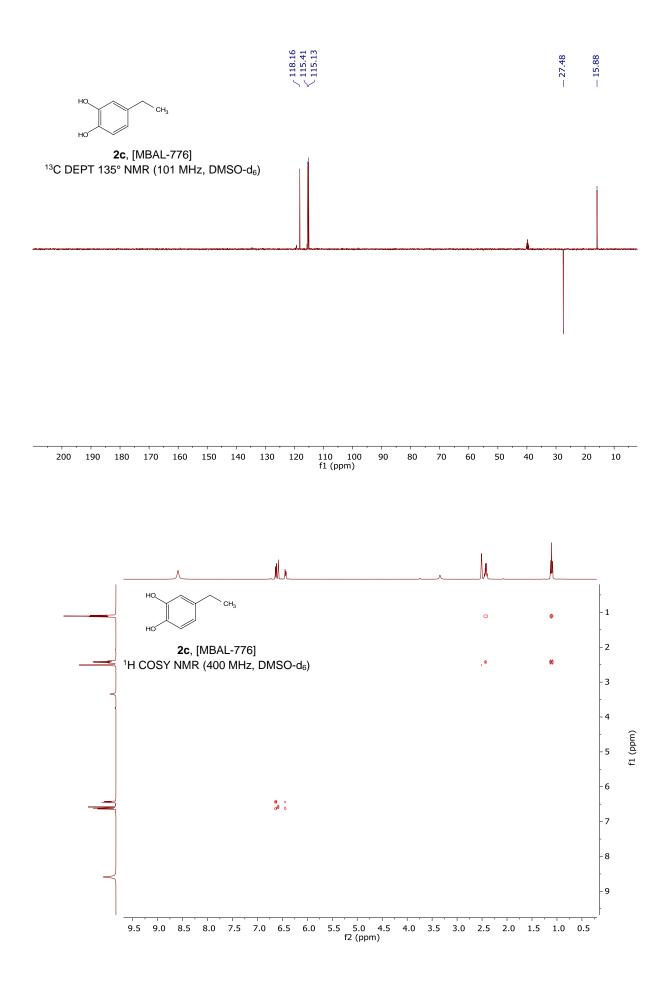
$$-2.533$$

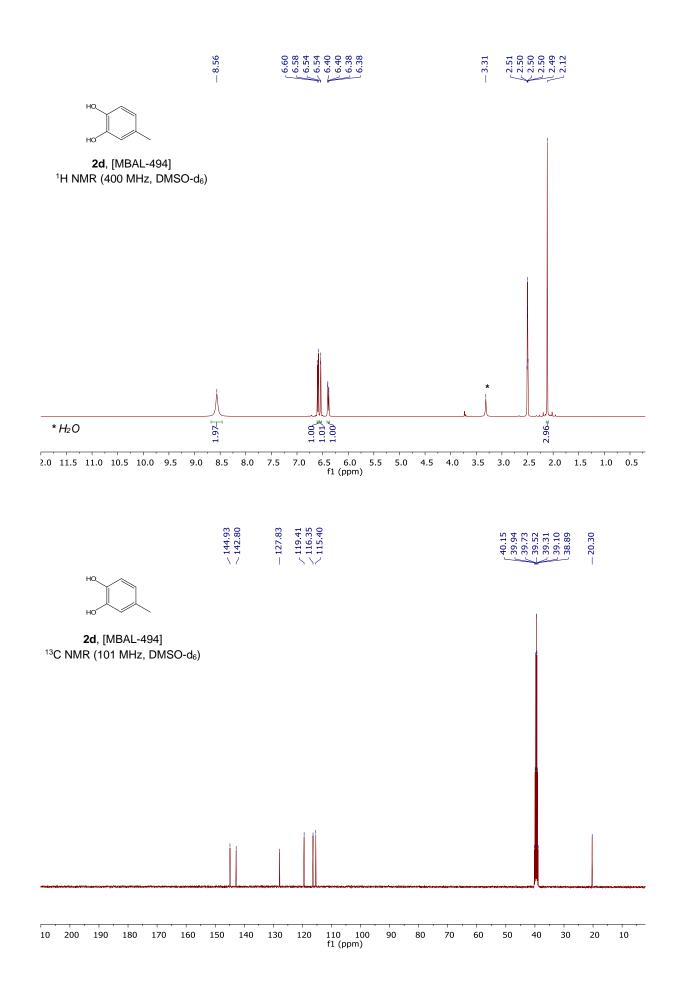
$$-1.112$$

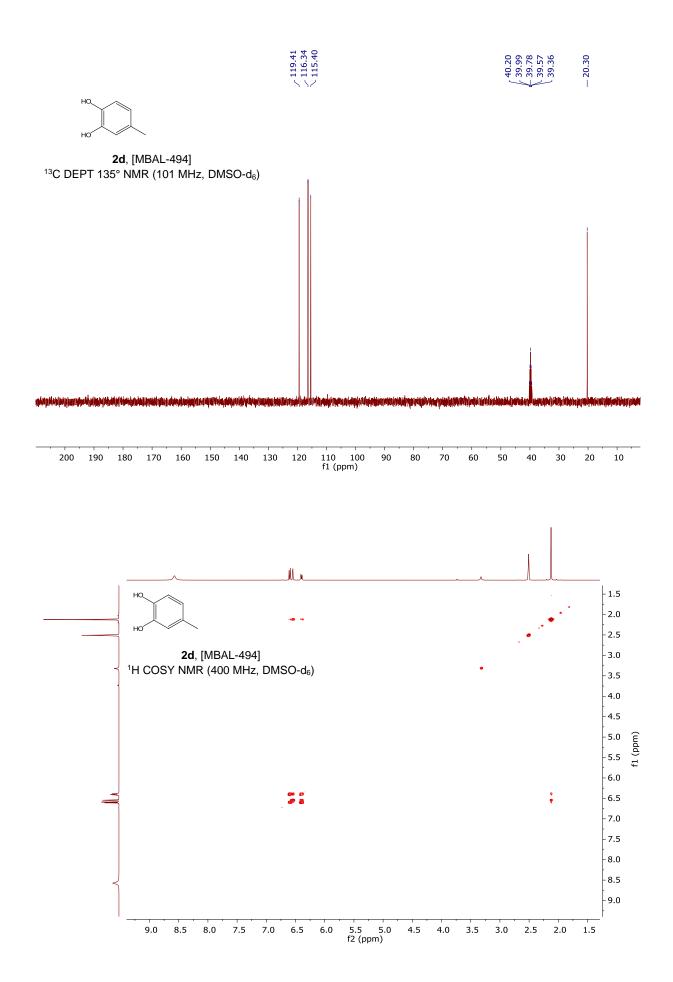


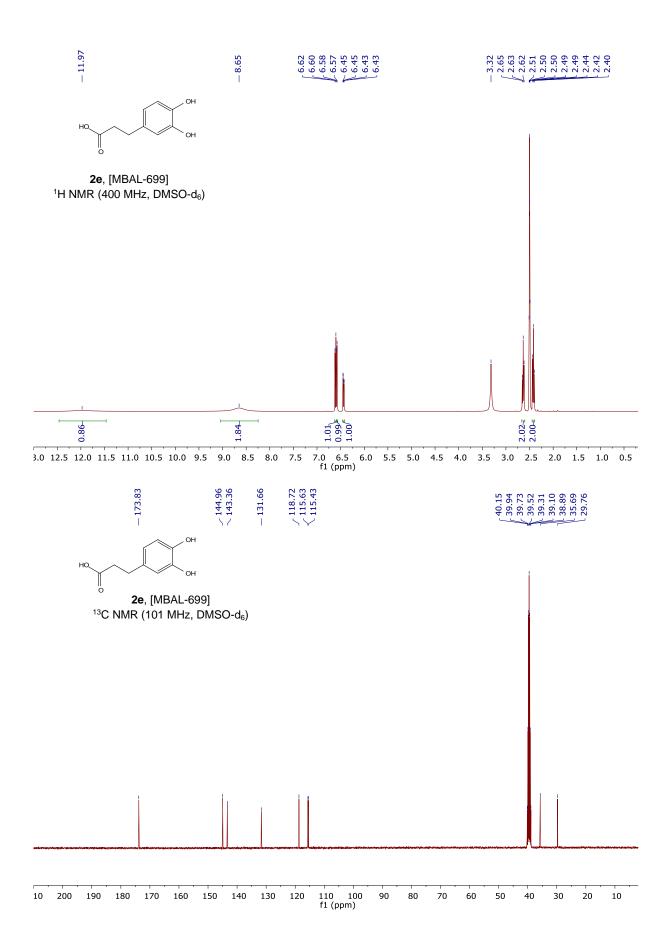
2c, [MBAL-776] ¹H NMR (400 MHz, DMSO-d₆)

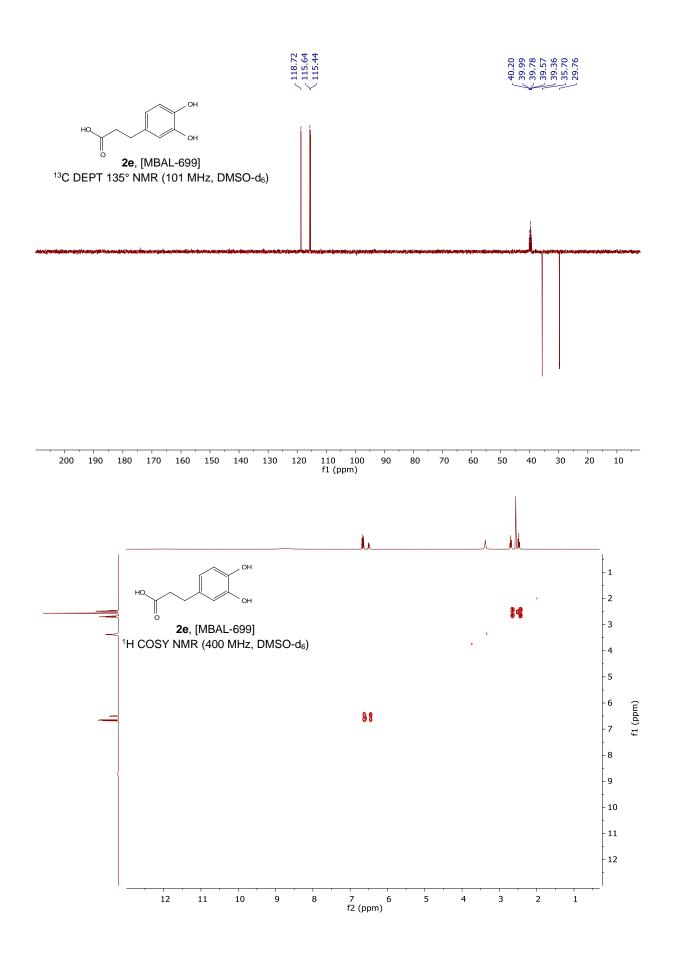


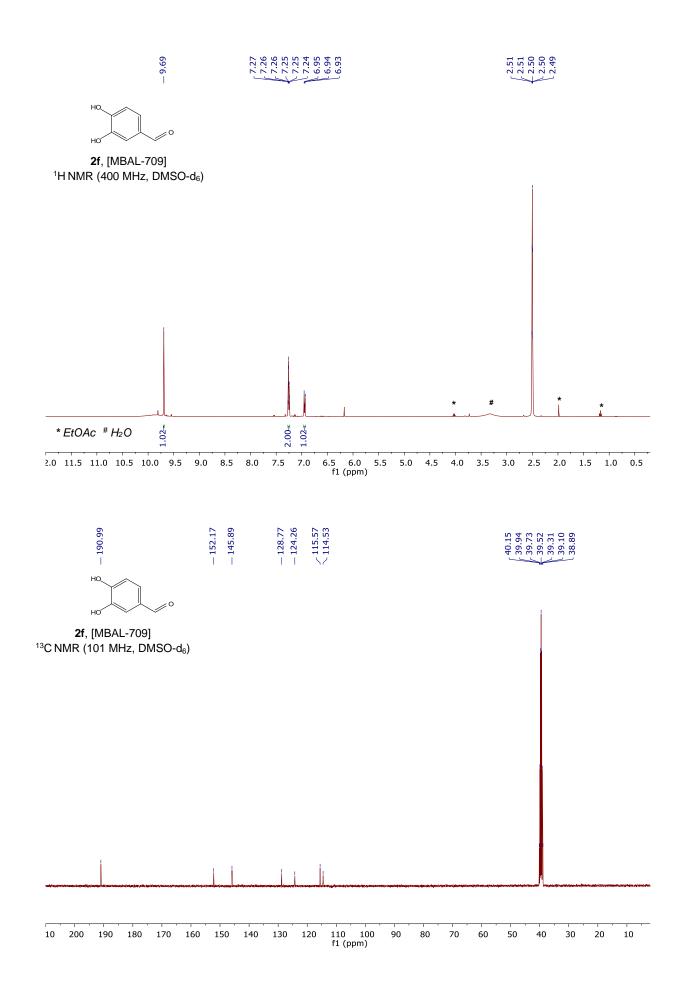


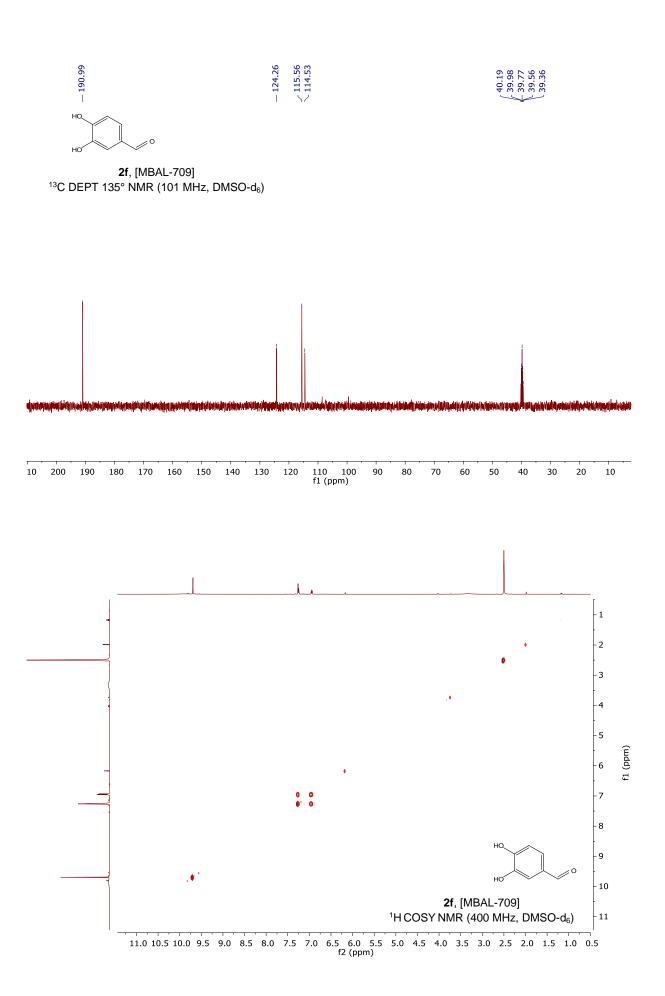




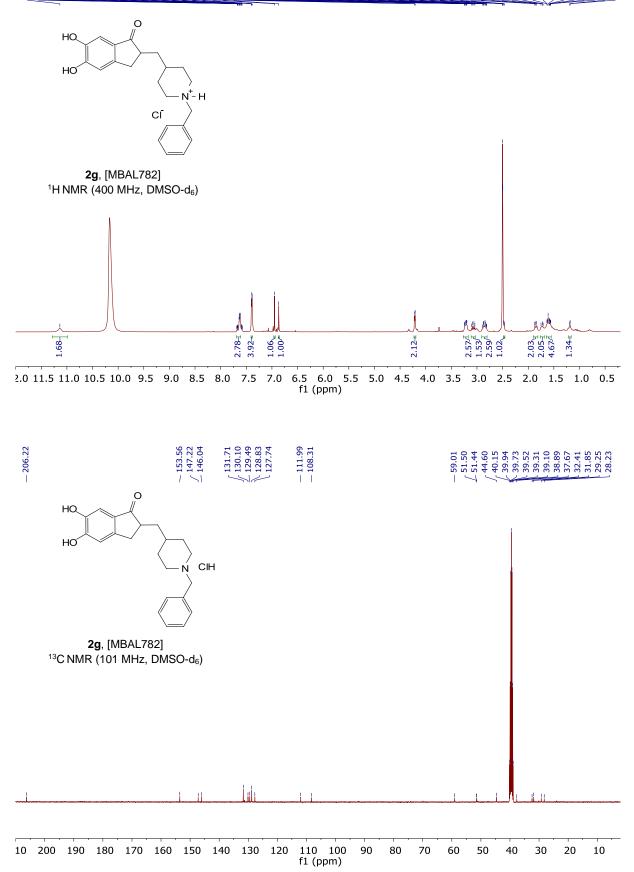


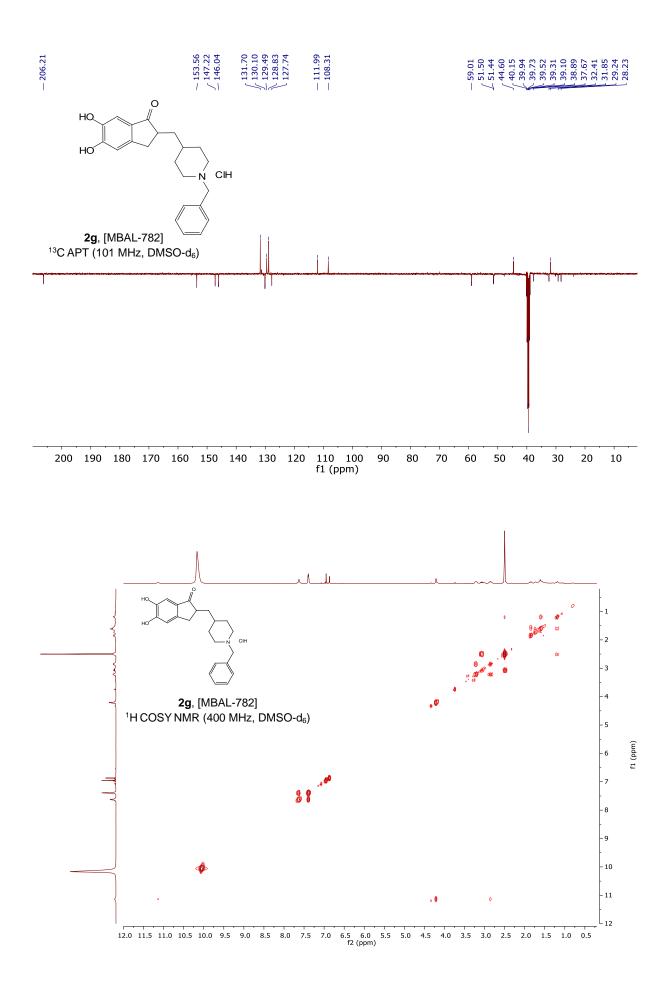


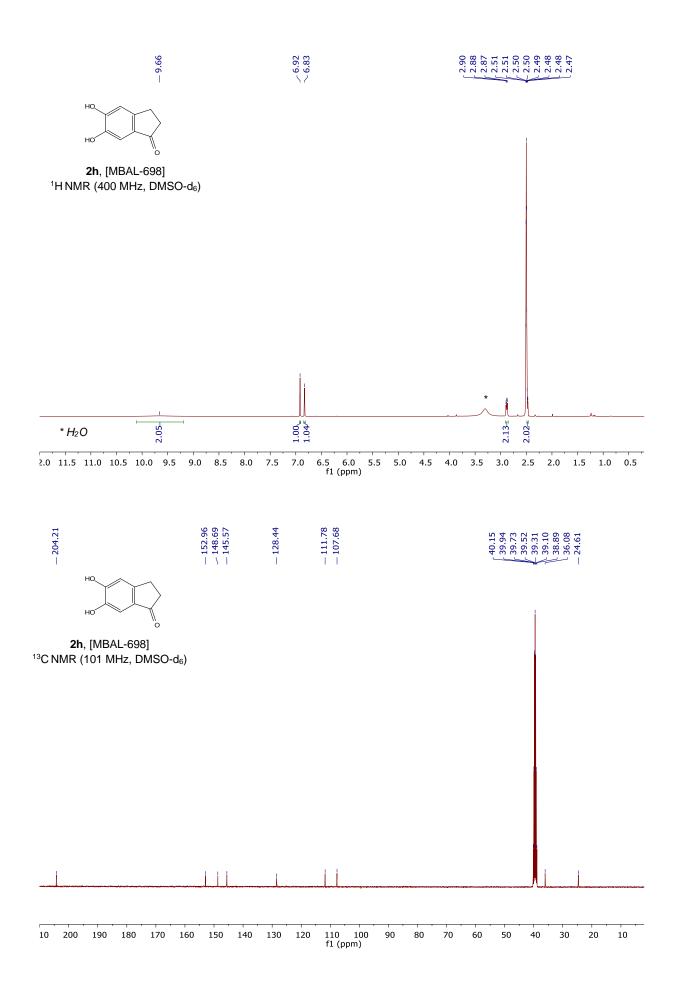


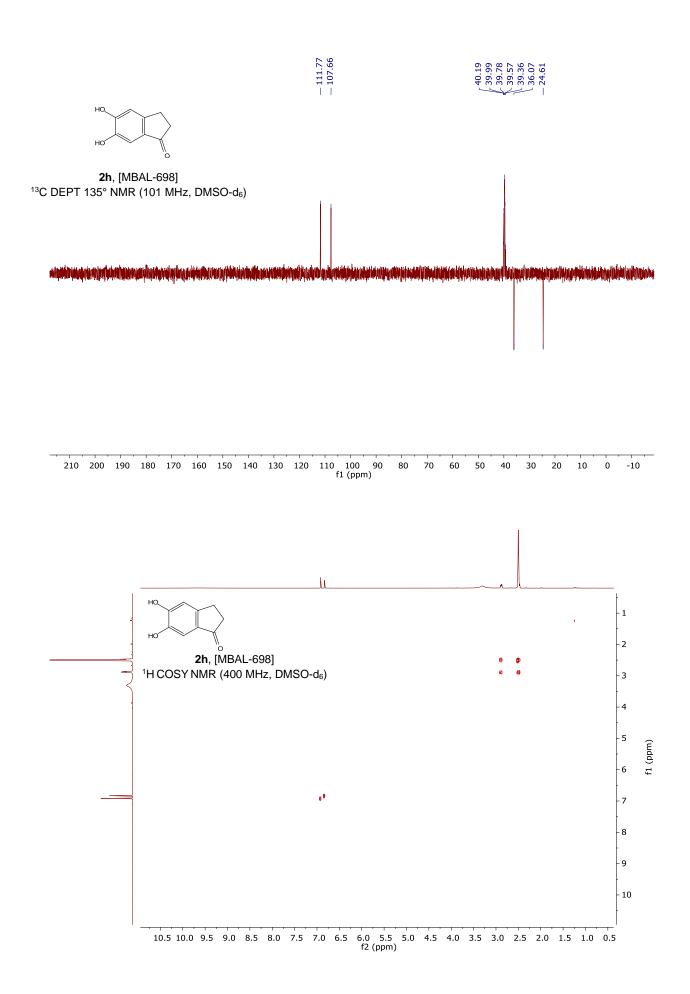


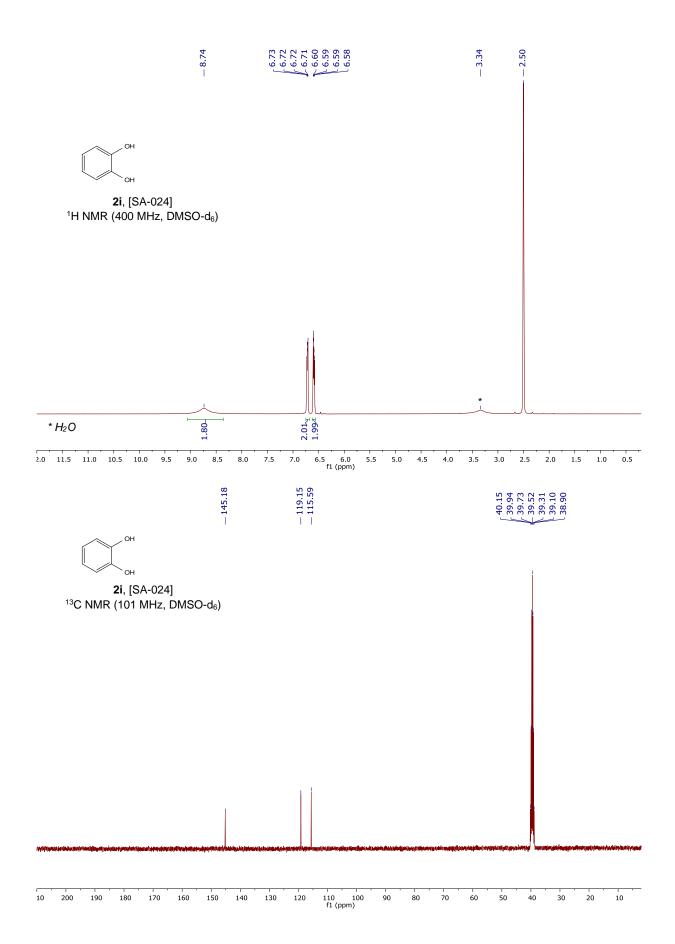
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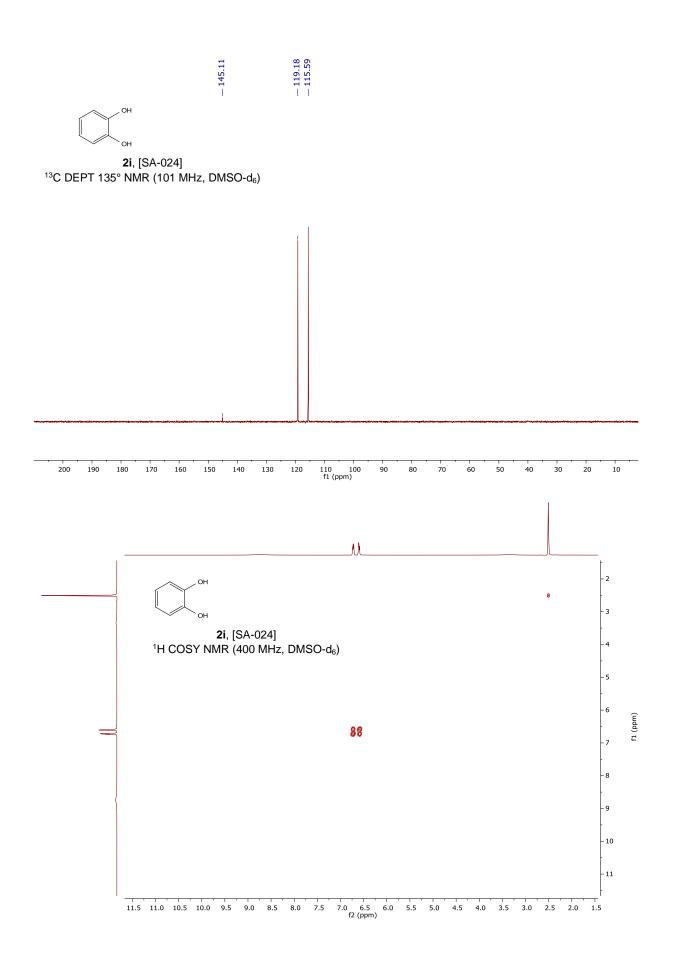


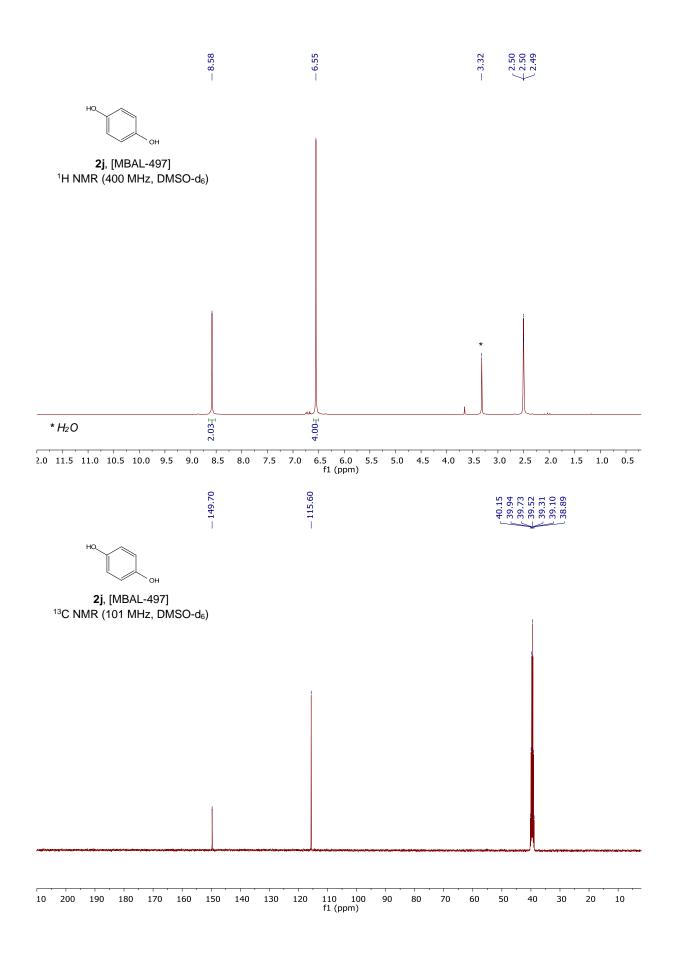


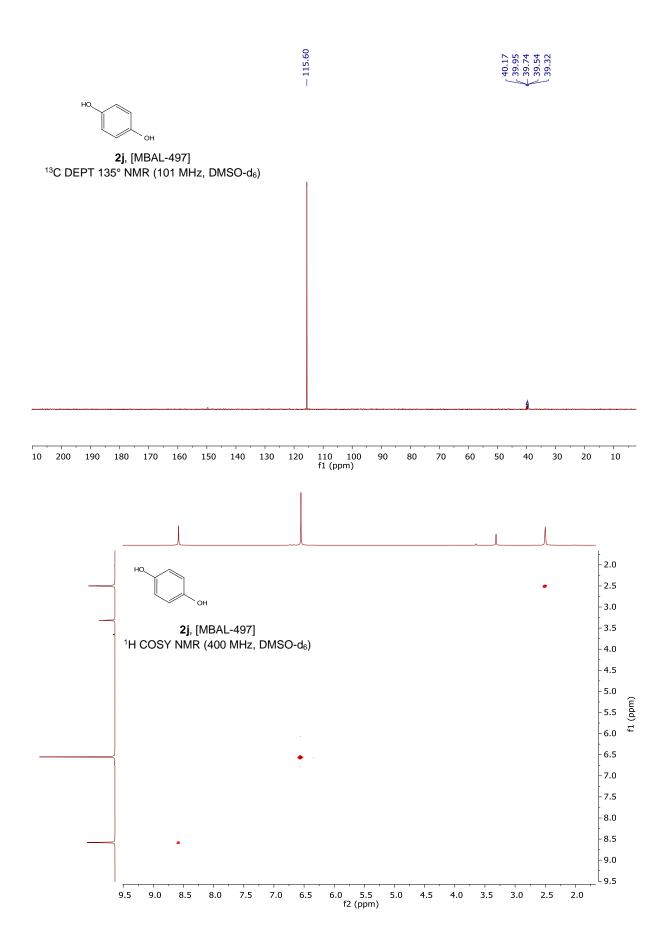


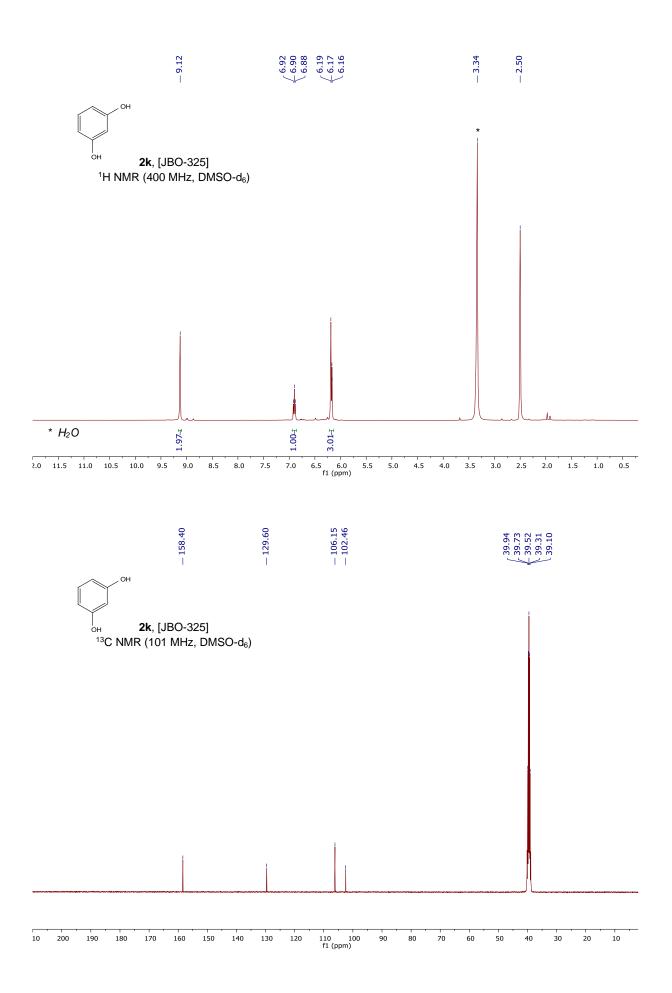


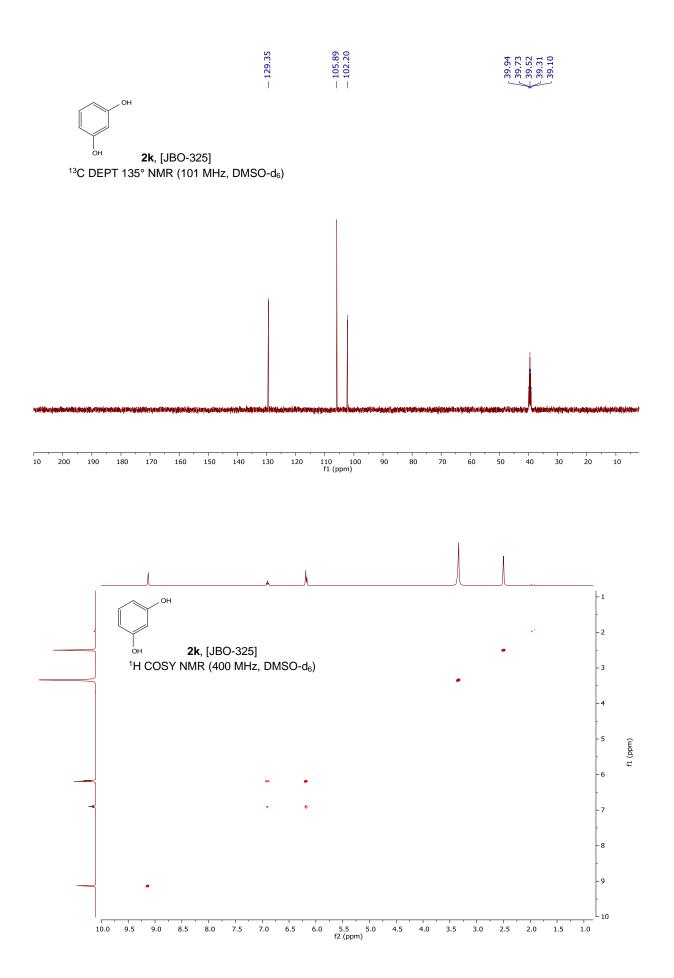






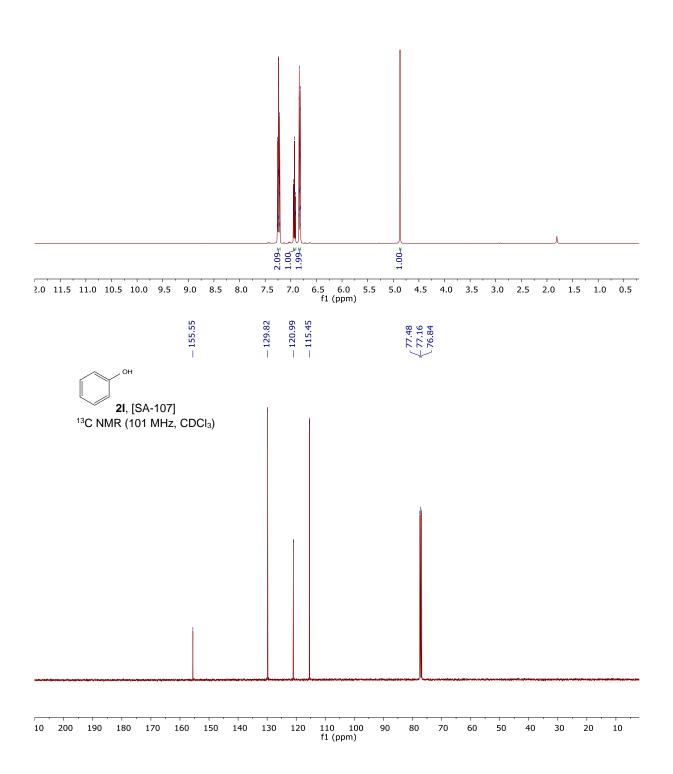


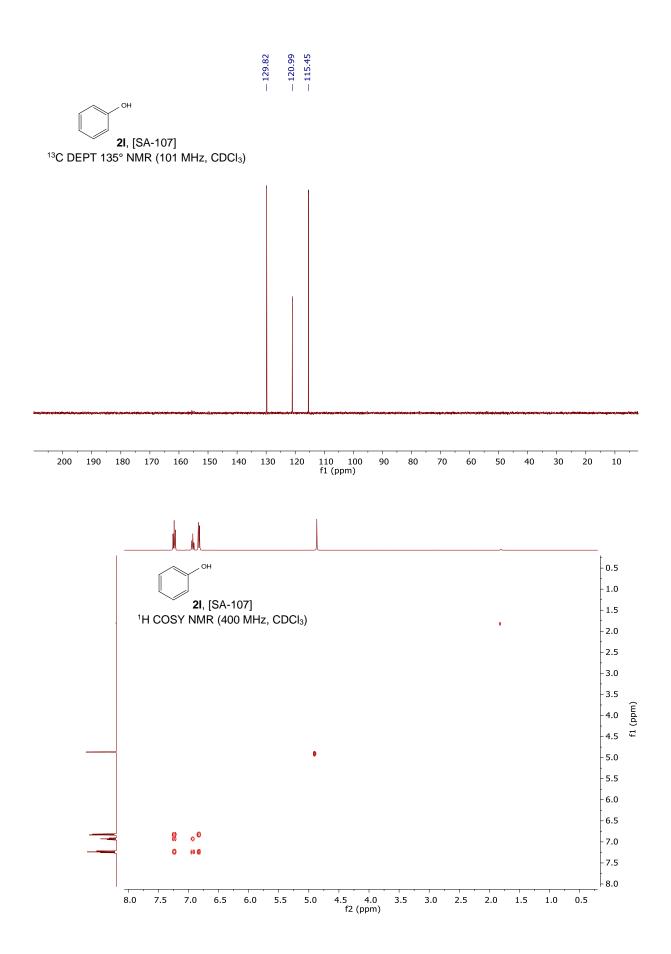


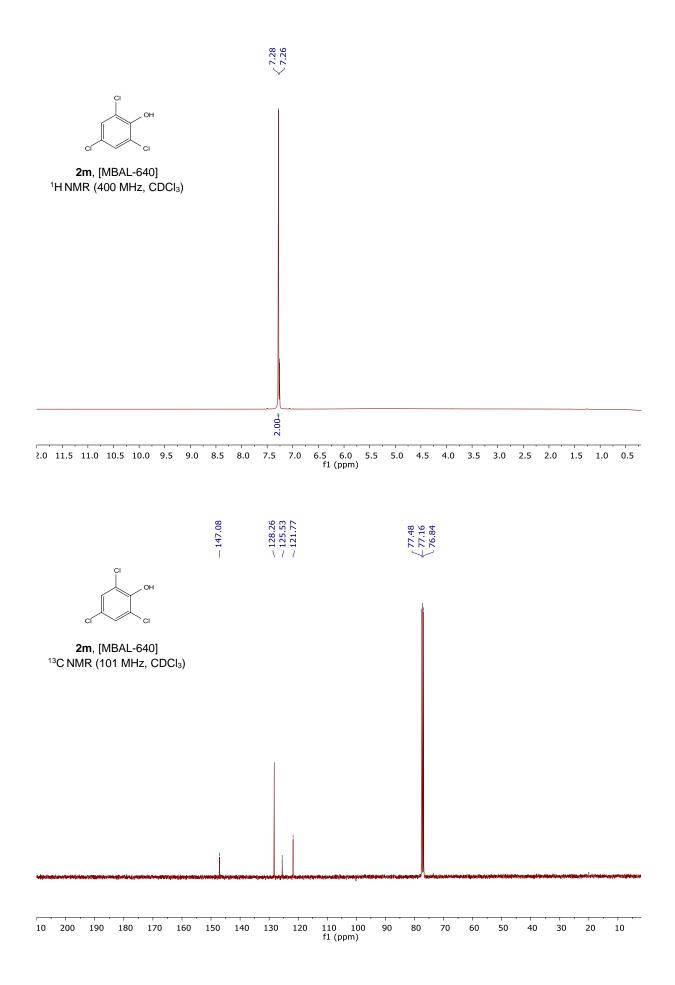


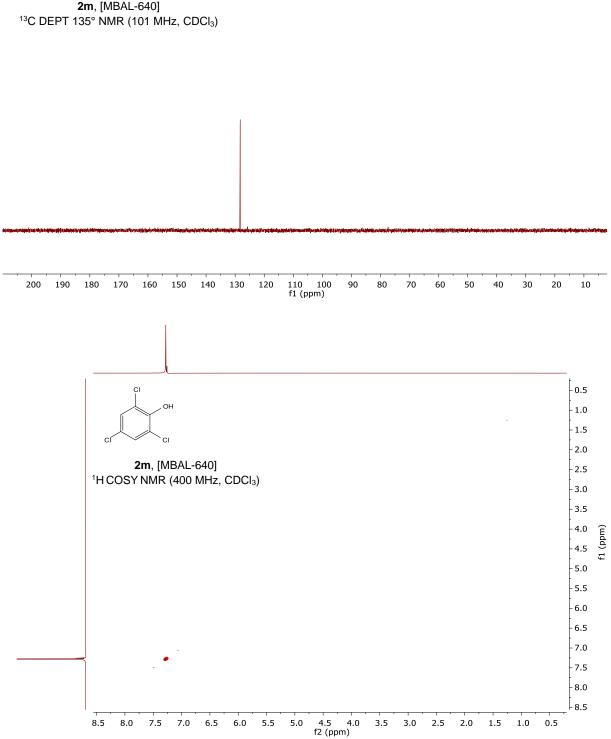


2I, [SA-107] ¹H NMR (400 MHz, CDCl₃)



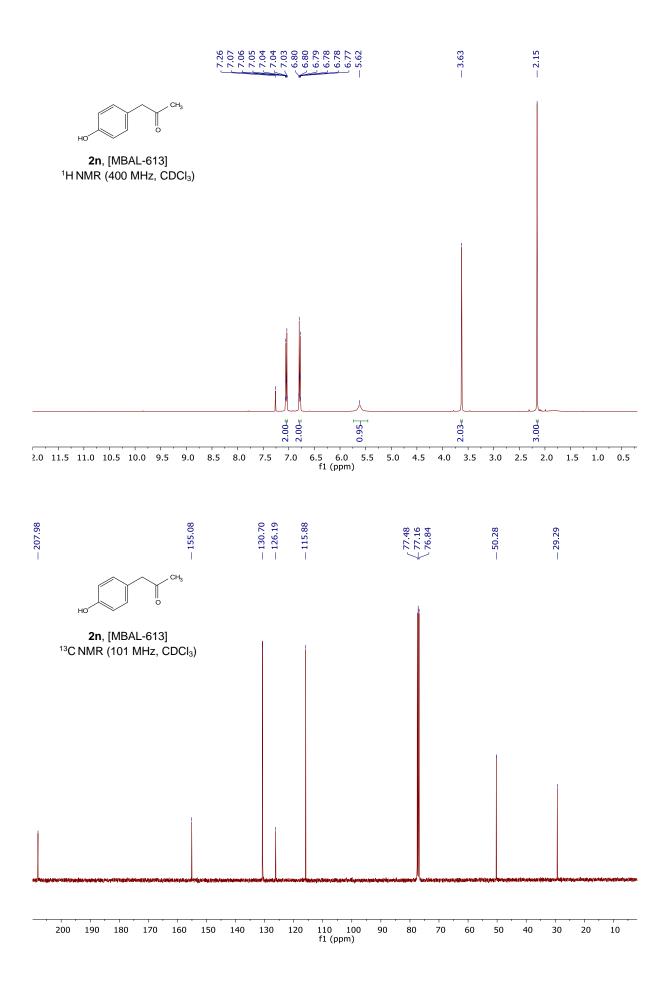


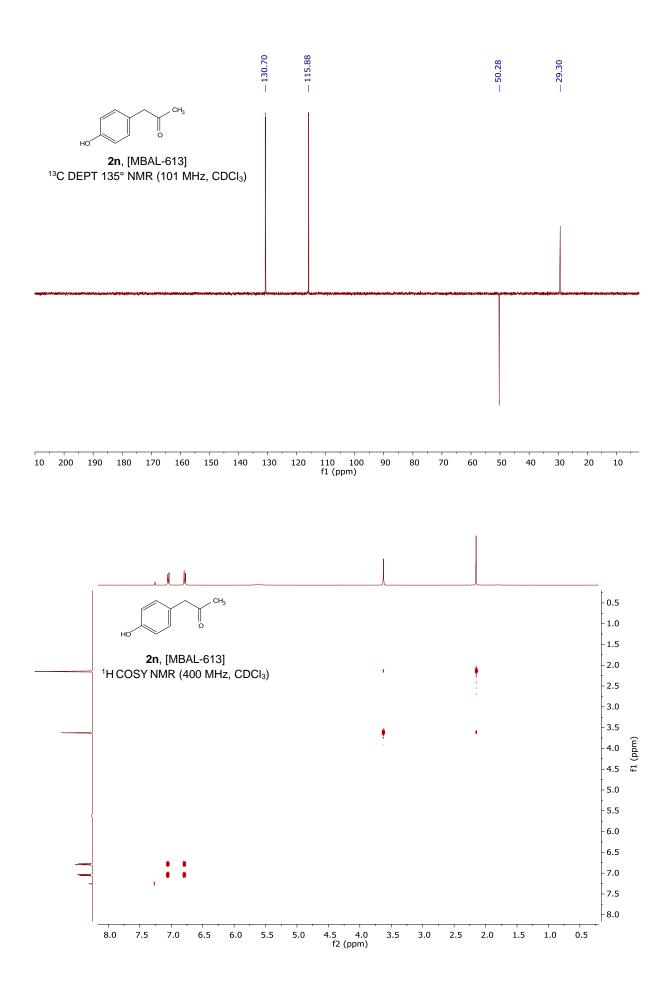


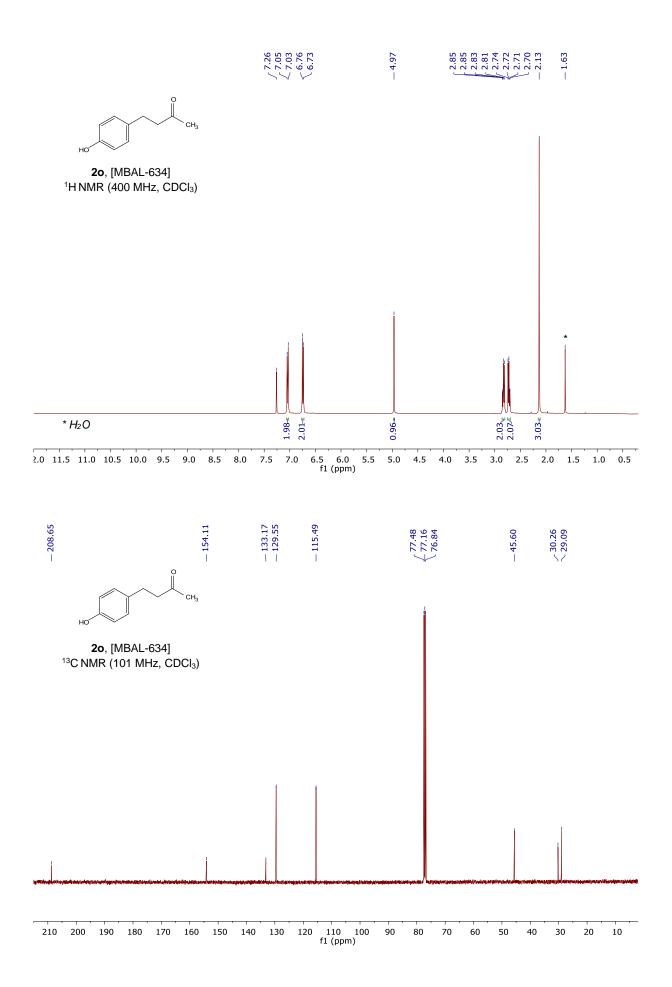


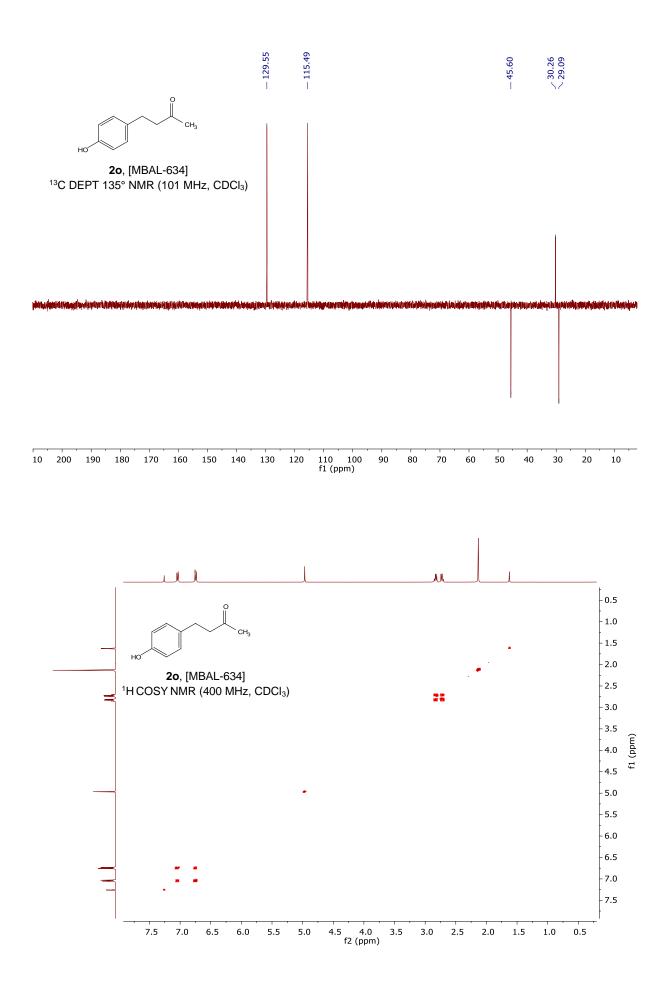
2m, [MBAL-640]

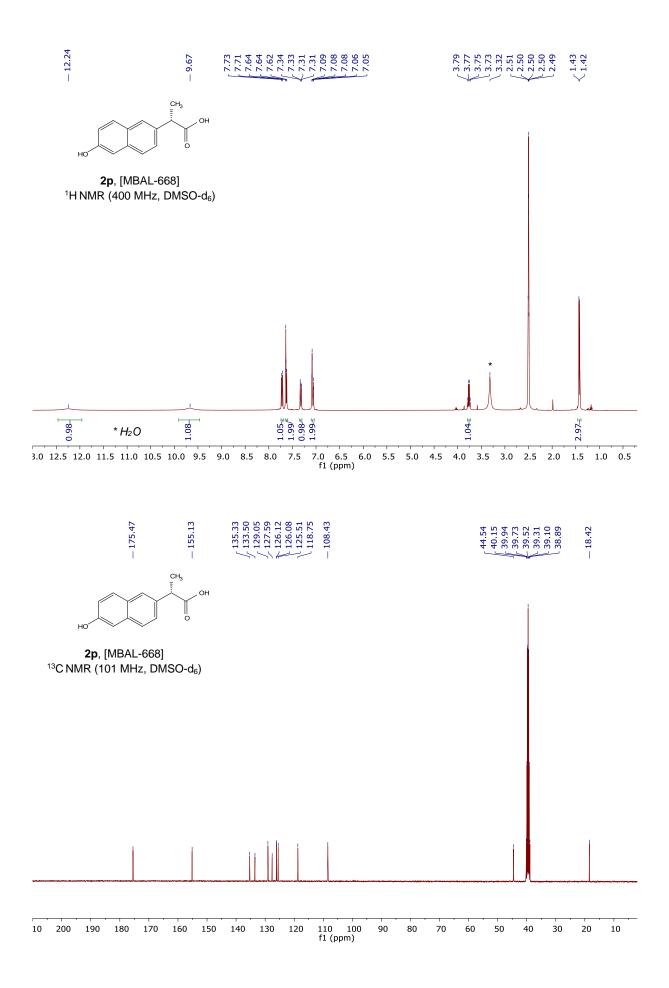
- 128.26

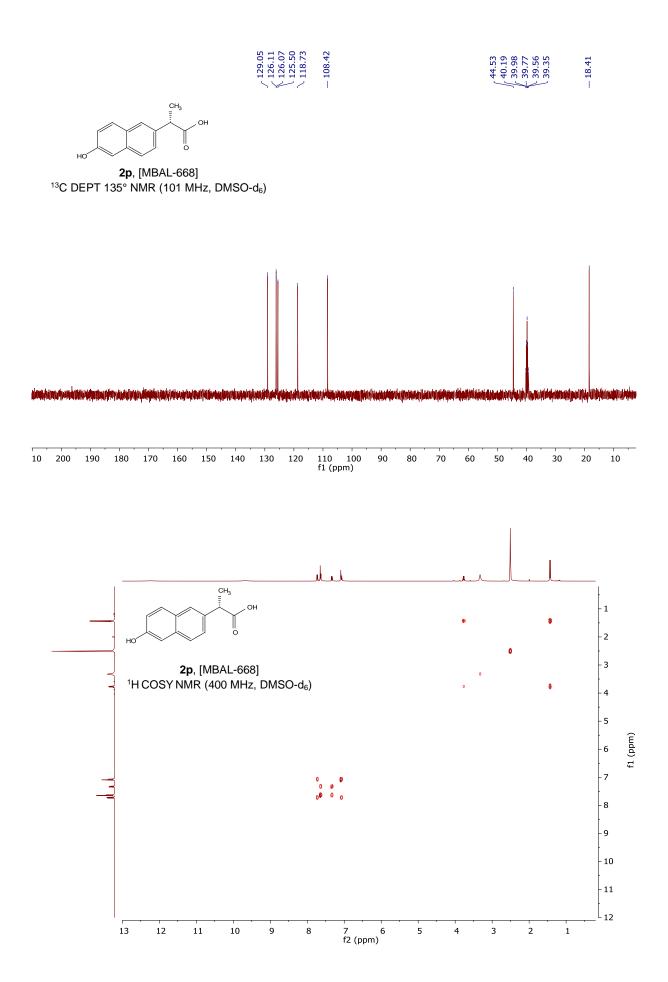


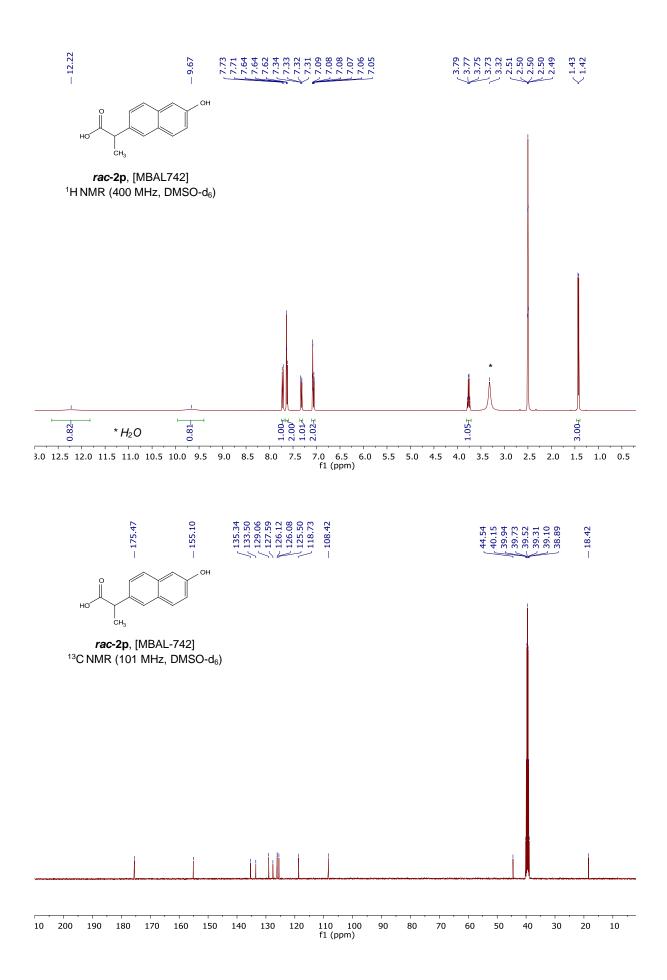


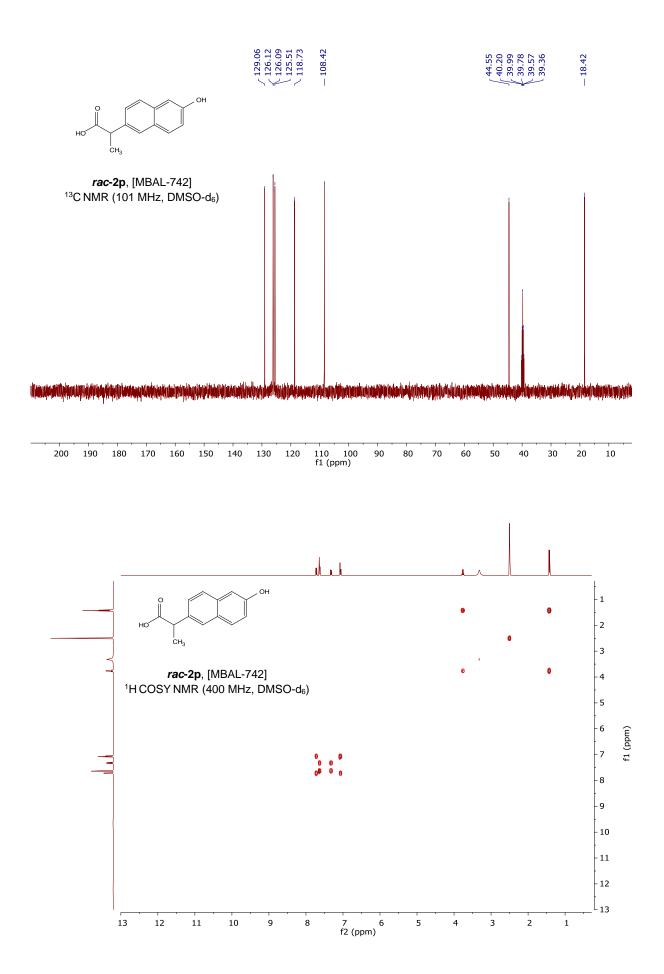


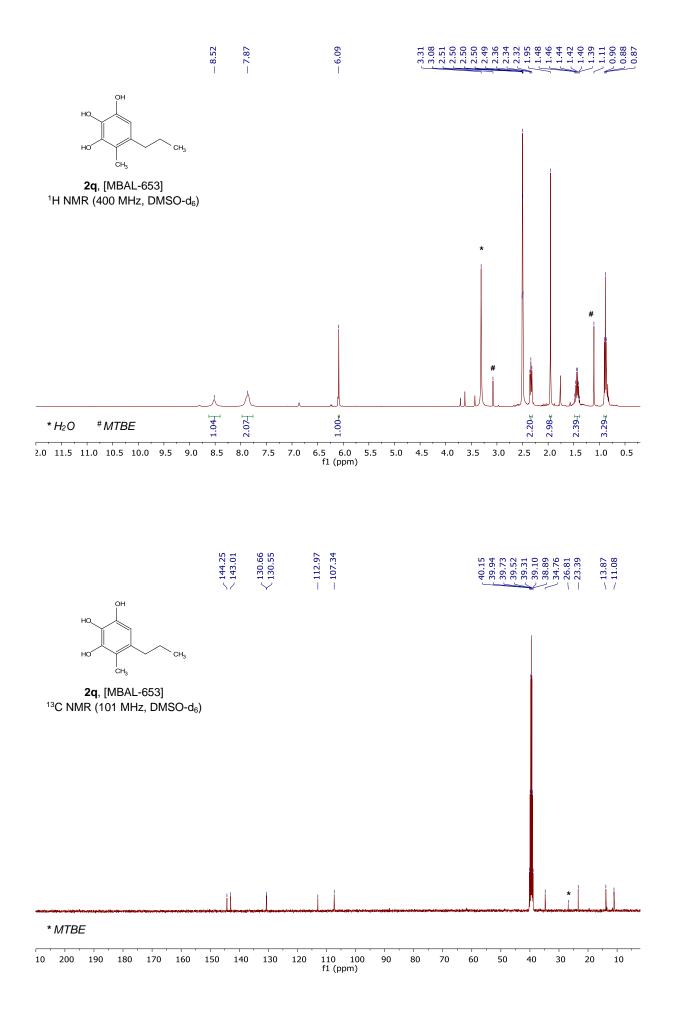


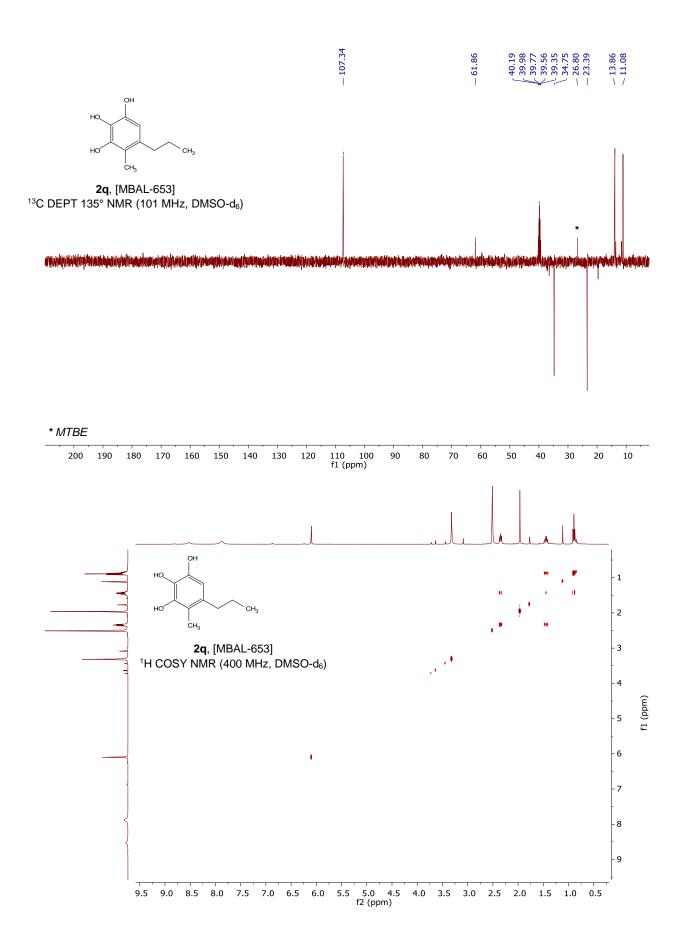




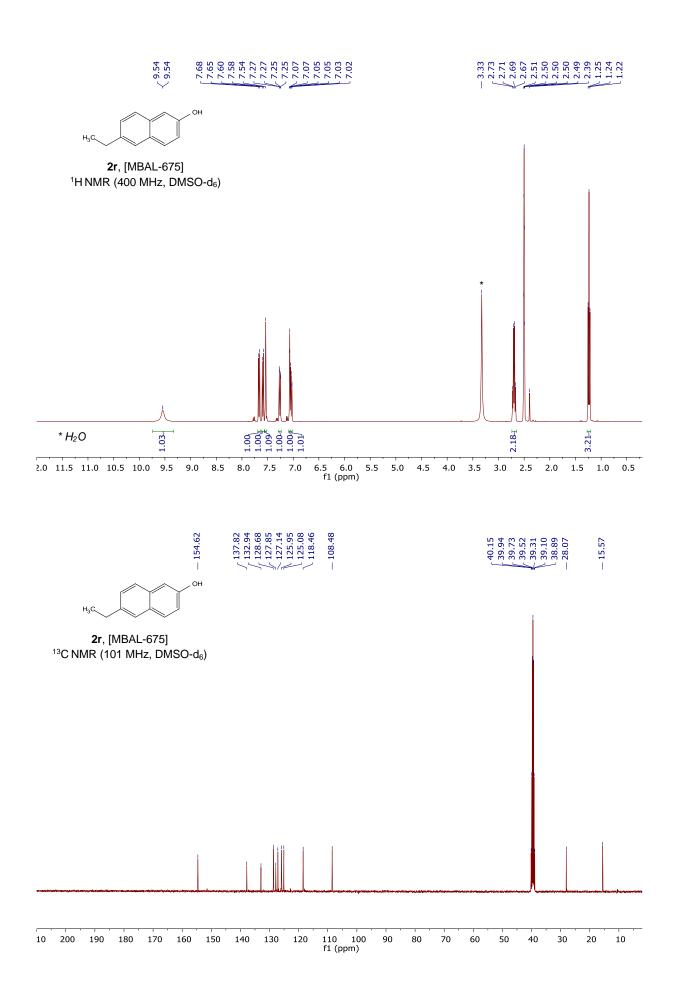


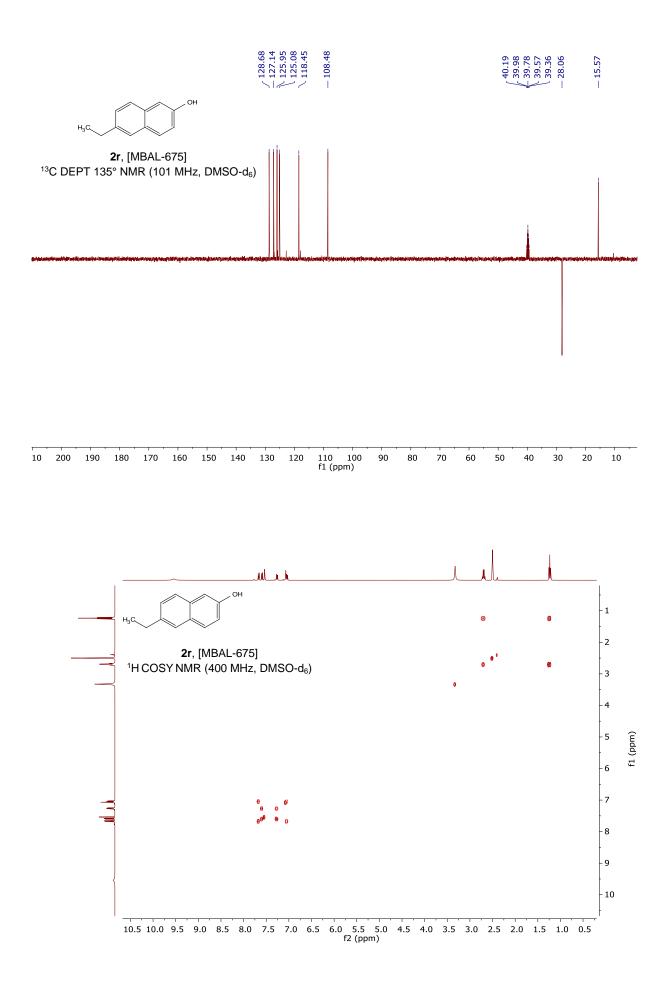


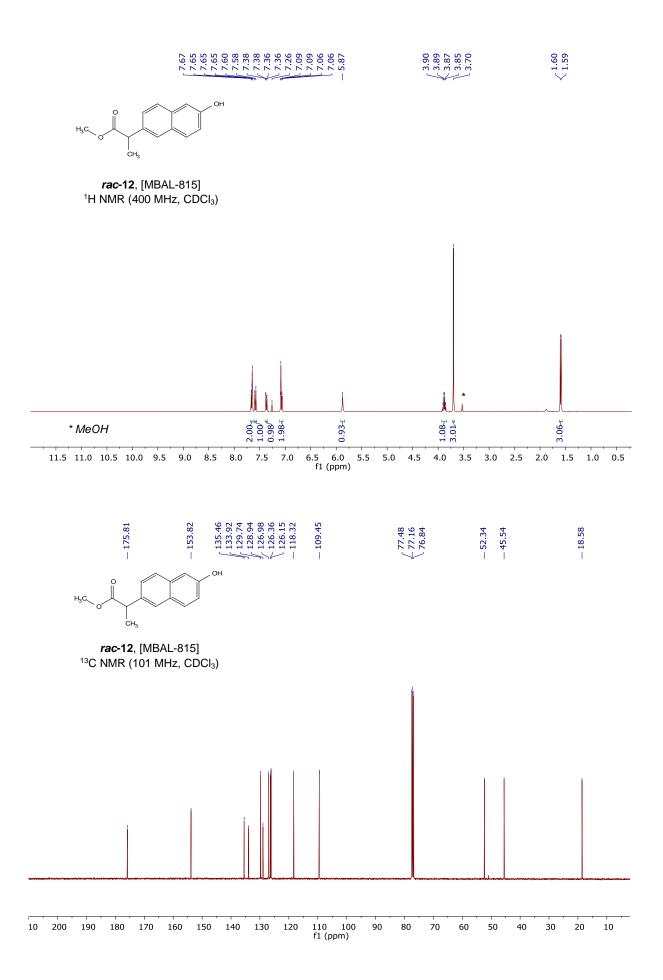


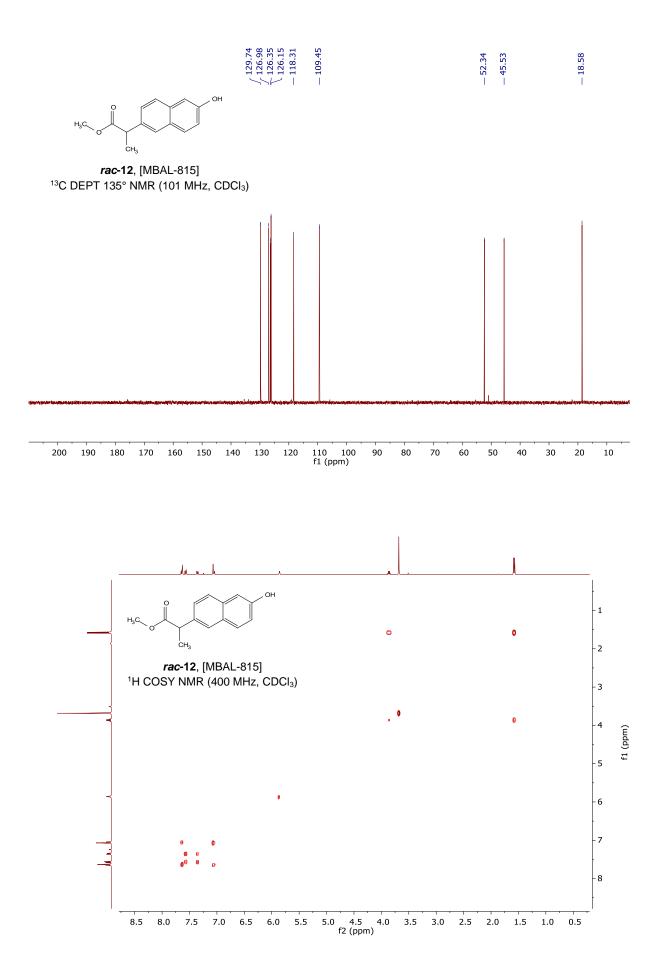


S113

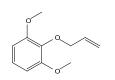




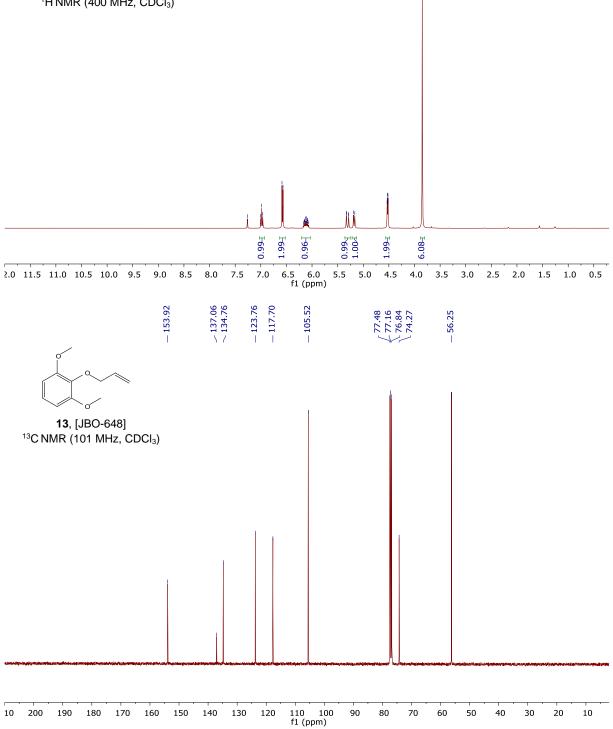


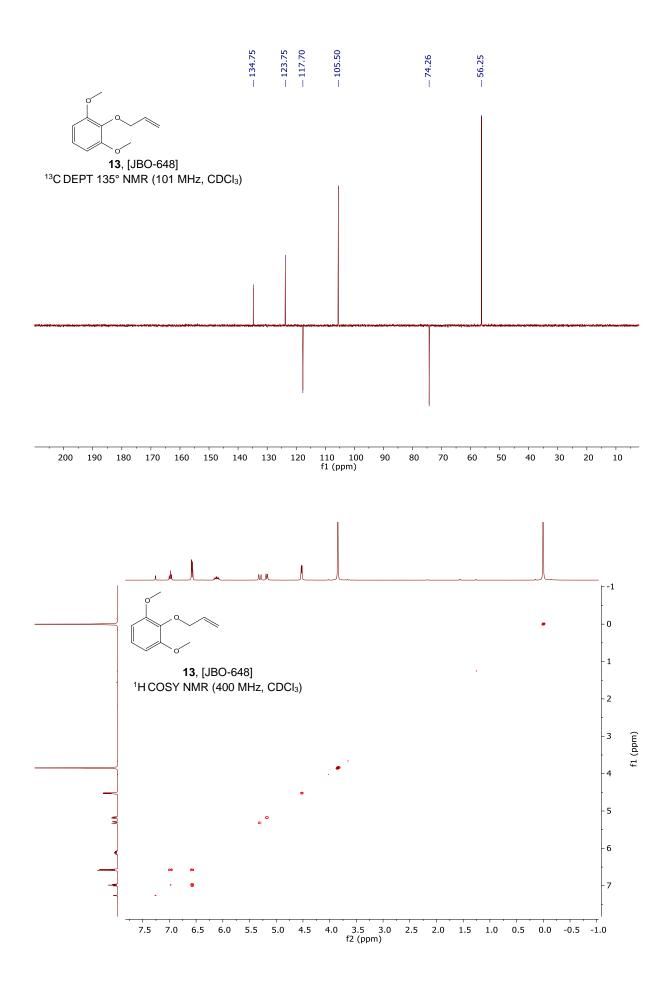


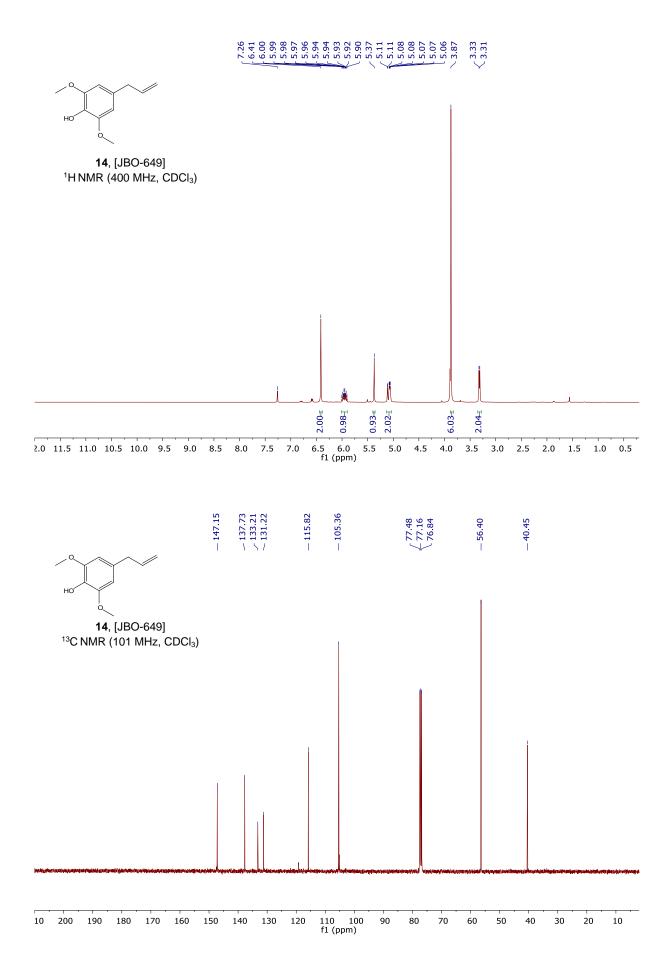
7.26 6.699 6.659 6.657 6.617 6.617 6.617 6.617 6.617 6.613 6.617 6.613 6.613 6.613 6.613 6.613 6.613 6.6146 6.6146 6.6146 6.6

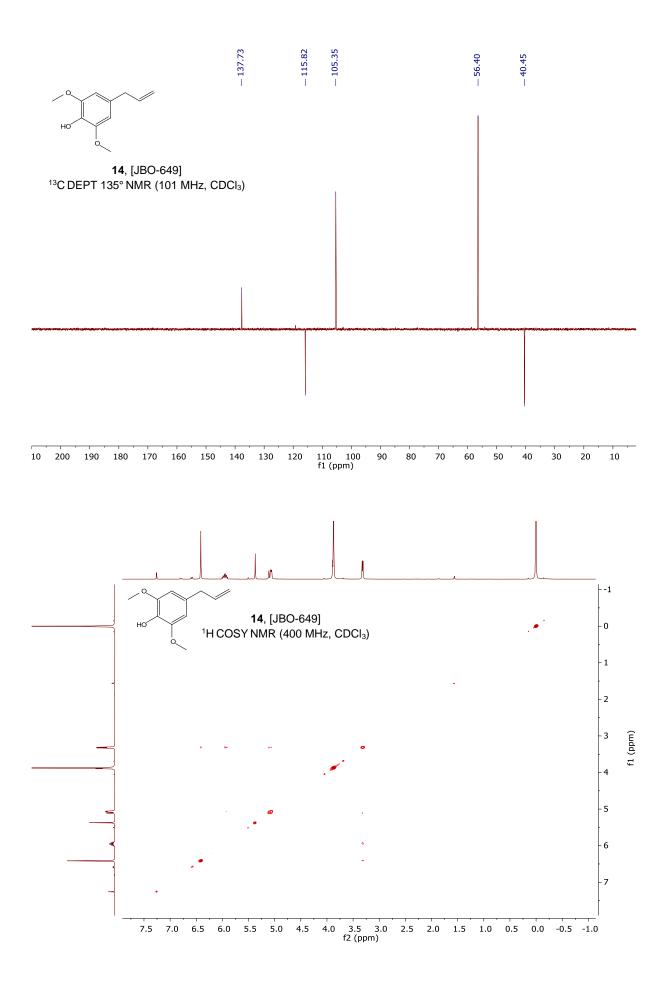


13, [JBO-648] ¹H NMR (400 MHz, CDCl₃)





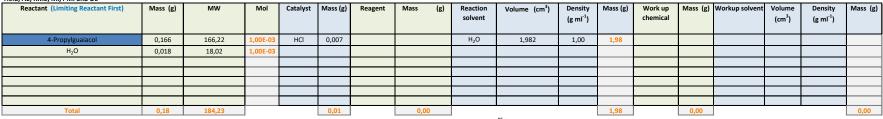


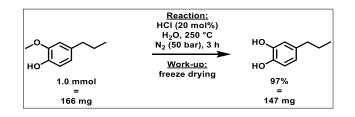


7 Copies of the Excel Sheets used for Green Metrics calculations

• Method A1 on 4-propylguaiacol (1a): [JBO-496]

Yield, AE, RME, MI/PMI and OE





Conversion	100,00
	82,61
PMI total	14,79
PMI Reaction	14,79
PMI Workup	0,00
PMI Workup	
chemical	0,00
PMI workup	
solvents	0,00
PMI RRC	1,30
PMI FI Total	12,21
PMI FI React	12,21
PMI FI Workup	0,00
PMI FI RRC	1,08
AE FI	100,00
RME FI	96,59
E factor	13,79
E factor FI	11,21

	Mass	MW	Mol
Product	0,147	152,19	9,66E-04
	mass		
Unreacted limiting			
reactant	0,00		
	Mass	MW	Mol
Co-Product	0,031	32,04	9,66E-04
	excluding	including	
	co-products	co-	
Generated waste	2,027	1,996	

Experimental [JBO-496]

96.6

96,6 100,0

96,6

The reaction was performed using General Procedure C, using 2-methoxy-4-propylphenol (166 mg, 1.00 mmol, 1.0 equiv.) as substrate and HCl (aq., 1 M, 0.2 mL, 0.20 mmol, 0.2 equiv.) and H₂O (1.8 mL) as regents. The reaction mixture was heated to 250 °C and stirred for 3 h at this temperature, under a starting pressure of N₂ (50 bar). The experiment wa repeated 5 times and samples were freeze-dried to remove all volatiles. The residue was pure product.

Solvents (First Pass)		List solvents below
Preferred solvents	water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane	H ₂ O
Problematic solvents: (acceptable only if substitution does not offer advantages)	DMSO, cyclohexanone, DMPU, AcOH, Ac2O, Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene, MTBE, cyclohexane , chlorobenzene, formic acid, pyridine, Me-THF	
Hazardous solvents: These solvents have significant health and/or safety concerns.	dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane	
Highly hazardous solvents: The solvents which are agreed not to be used, even in screening	$Et_2O,$ Benzene, $CCl_4,$ chloroform, DCE, nitromethane, $CS_2,$ HMPA	

Catalyst/enzyme (First Pass)							
Catalyst or enzyme used, or reaction takes place without any catalyst/reagents.	Green Flag	х					
Use of stoichiometric quantities of reagents	Amber Flag						
Use of reagents in excess	Red Flag						

		Tick
Facile recovery of catalyst/enzyme	Green Flag	
catalyst/enzyme not recovered	Amber Flag	

Supply remaining	Flag colour	Note element		H 1.00794			until de known	pletion reserve												He
5-50 years	Red Flag			Juli B			(based on c								5 B	°c	7 N	* 0	° F	10 Ne
50-500 years	Amber Flag			6.941 9.012 11 12) years)0 years							10.811 13	12.0107	14.00674 15	15.9994	18.99840 17	20.1793
+500 years	Green Flag	х		Na M 22.58977 24.30			100-5	00 years							AI 26.98153	Si 28.0855	P 39.97376	S 32.056	CI 35.4527	Ar 39.948
1500 years	Greennag	~		¹⁹ K C				Cr	Mn	Fe	27 Co	Ni	Cu	Zn	Ga	Ge	aa As	Se	³⁵ Br	³⁶ Kr
				39.0983 40.07 57 38 Rb S	78 44.95 39	591 47.86 40 Z	41	42 Mo	43 Tc	55.845 44 Ru	45 Rh	58.6934 46 Pd	63.546	45.39 45 Cd	49 In	50 Sn	51 Sb	78.96 52 Te	79.504 53	83.80 54 Xe
				KD 5 85.4678 87.62 55 56	88.90 57				(98)	101.07	KN 102.9055	Pd 106.42	Ag 107.8682	112.411 80	10 114.818	5n 111.700	50 121.760	127.60 84	126.9044	131.2
				Cs B 132.9654 137.3	a La		f Ta	w	Re	Os	Ir	Pt	Au	Hg	т	Pb	Bi	Po (2091)	At (210)	RI (222)
				132.9654 137.3 87 88 Fr R	89	104	105 f Db	106 Sg	107 Bh	108 Hs	109 Mt	110 Ds	111 Rq	112 Uub	113 Uut	114 Uuq	115 Uup	116 LV	117 Uus	118 Uu
				(223) 226.0				3g (263)	(262)	(265)	(266)	(271)	(272)	(285)	(284)	(289)	(288)	(292)	ous	
							58	59			<u>a</u> (8	64	65	66	67	68	69	70	71
					Lantha	nides *	Ce 140.9077	Pr 144.24	Nd (145)	150.36	151.964	Eu 157.25	Gd 158.9253	Tb 158.9253	Dy 162.50	Ho 164.9303	Er 167.26	Tm 168.9342	Yb 173.04	LL 174.90
					Acti	nides ‡	50 Th	91 Pa	υ	Np	Pu	Am	Cm	Bk	Cf	90 Es	100 Fm	101 Md	102 No	103 Lr
r (First Pass)			Tick				232.0381	231.0289	238.0289	(237)	[244] (243)	(247)	(247)	(251)	(252)	(257)	(258) Tic	(259)	(262)
Reaction run between 0 to	0.70°C		TICK			Г		_												
		Green Flag						Rea	action	run at	reflux	(r.	Red Fl	ag		X		
Reaction run between -20 to 0 o	r 70 to 140°C	Amber Flag							0											
						Re	eaction	n run 5		more ng poi		the s	olven	nt Gr	een F	lag	ag			
Reaction run below -20 or ab	ove 140°C	Red Flag	Х																	
flow			Tick	_		14	/ork Up	•										Lis	+	
now	Gr	een Flag	TTER			Г		<u>,</u>	que	nchin	g							213		
	An	nber Flag								ration							_			
						centrifugation Green Flag														
						- L	ow ten	npera				apora	ation	crystallisation Sublimation						
						1		-		10 °C a	at atm			<i>.</i>						
								matio	n (< 14 inge, c	uench		osphe	eric	-	nber I	Flag				
							sublii olvent	matio	n (< 14 inge, c sc	uench lvent	ning in	osphe to aq	eric ueous	-	nber I	Flag				

Health & safety				List substances and H-codes	List substances and H-codes	List substances and H-codes
	Red Flag	Amber Flag	Green Flag			
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber			
			flagged H codes present			
Explosive thermal runaway	H230, H240, H250	H241	then green flag			
Тохіс	H300, H310, H330	Н301, Н311, Н331,			4-Propylguaiacol: H311	H2O HCI
Long Term toxicity	H340, H350, H360, H370, H372	H341, H351, H361, H371, H373				
Environmental implications	H400, H410, H411, H420	H401, H412				

high temperature multiple recrystallisation

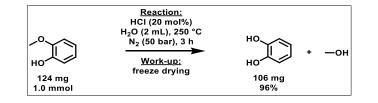
Use of chemicals of environmental concern		List substances of very high concern
Chemical identified as Substances of Very High Concern by ChemSec which are utilised	Red Flag	

Red Flag

• Method A1 on guaiacol (11): [SA-024]

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction	Volume (cm ³)	Density	Mass (g)	Work up	Mass (g)	Workup solvent	Volume	Density	Mass (g)
								solvent		(g ml ⁻¹)		chemical			(cm ³)	(g ml ⁻¹)	
																	1
Guaiacol	0,124	124,14	1,00E-03	HCI	0,007			H ₂ O	1,982	1,00	1,98						
H ₂ O	0,018	18,02	1,00E-03														
Total	0,14	142,16			0,01		0,00				1,98		0,00				0,00



		Flag
Yield		
Conversion	100,00	
Selectivity		
AE	77,46	
RME		OE
PMI total	20,11	
PMI Reaction	20,11	
PMI Workup	0,00	
PMI Workup		
chemical	0,00	
PMI workup		
solvents	0,00	
PMI RRC	1,41	
PMI FI Total	15,58	
PMI FI Reaction	15,58	
PMI FI Workup	0,00	
PMI FI RRC	1,09	
AE FI	100,00	
RME FI	96,26	
E factor	19,11	
E factor FI	14,58	

	Mass	MW	Mol
Product	0,106	110,11	9,63E-04
	mass		
Unreacted limiting			
reactant	0,00		
	Mass	MW	Mol
Co-Product	0,031	32,04	9,63E-04
		including	
	excluding	co-	
	co-products	products	
Generated waste	2,025	1,995	

Experimental [SA-024]

96,3 100,0 96,3

The reaction was performed using General Procedure C, using 2-methoxyphenol (124 mg, 1.00 mmol, 1.0 equiv.) as substrate and HCI (aq., 1 M, 0.2 mL, 0.20 mmol, 0.2 equiv.) and H₂O (1.8 mL) as reagents. The reaction mixture was heated to 250 °C and stirred for 3 h at this temperature, under a starting pressure of N₂ (50 bar). The experiment was repeated 5 times and samples were freeze-dried to remove all volatiles. The residue was pure product.

Solvents (First Pass)		List solvents belov
Preferred solvents	water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane	H ₂ O
Problematic solvents: (acceptable only if substitution does not offer advantages)	DMSO, cyclohexanone, DMPU, AcOH, Ac2O, Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene, MTBE, cyclohexane , chlorobenzene, formic acid, pyridine, Me-THF	
Hazardous solvents: These solvents have significant health and/or safety concerns.	dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane	
Highly hazardous solvents: The solvents which are agreed not to be used, even in screening	$Et_2O, Benzene, CCl_4, chloroform, DCE, nitromethane, CS_2, HMPA$	

Catalyst/enzyme (First Pass)		Tick
Catalyst or enzyme used, or reaction takes place without any catalyst/reagents.	Green Flag	х
Use of stoichiometric quantities of reagents	Amber Flag	
Use of reagents in excess	Red Flag	

		Tick
Facile recovery of catalyst/enzyme	Green Flag	
catalyst/enzyme not recovered	Amber Flag	
· · · · · · · · · · · · · · · · · · ·		

Supply remaining	Flag colour	Note element		H 1.00754			until deg known													H
5-50 years	Red Flag			3 4			(based on ci	urrent rate ction)	e of						5 B	°c	7	8	2	10
50-500 years	Amber Flag				Be 112182			years D years							10.811	12.0107	N 14.00674	0 15.9994	F 18.59840	Ne 20.175
					Mg			0 years							AI	Si	P	S	CI 35.4527	Ar
+500 years	Green Flag	Х		19 20	Ca S	c 22	23 V	24 Cr	25 Mn	26 Fe	27 Co	28 Ni	29 Cu	so Zn	n Ga	32 Ge	aa As	34 Se	35 Br	36 Kr
				39.0983 40. 37 18	078 44.95 39	47.86	41	51.9961 42	54 93804 43	55.845 44	58.93320 45	58.6934 46	63.546 47	05.39 44				78.96 52	79.904 53	83.80 54
				85.4678 87.	Sr 1 62 88.90	/ Z i 385 91.22	r Nb 92.90638	Mo 95.94	Tc (98)	Ru 101.07	Rh 102.9055	Pd 106.42	Ag 107.8682	Cd 112411	In 114.818	Sn 118.760	Sb 121.760	Te 127.60	126.9044	Xe 131.29
					Ba La		Ta	w	²⁵ Re	⁷⁶ Os	" Ir	Pt	Au	80 Hg	TI	*2 Pb	so Bi	84 Po	At	Rn
				87 88	7.327 138.5	104	180.9479 105 f Db	183.84	186.207 107 Bh	190.23	102.217	195.078	196,9665	200.59	204.3833	270.2	115	(209) 116	(210)	(222) 118 Uuc
					Ra Ac		(260)	Sg (263)	(262)	Hs (265)	Mt (266)	Ds (271)	Rq (272)	Uub (285)	Uut (284)	Uuq (289)	Uup (288)	Lv (292)	Uus	
							58	59	60 0	a (2	6	64	65	66	67	68	69	70	71
					Lantha	anides *	Ce 140.9077	Pr 144.24	Nd (145) 1	Pm 50.36 1	Sm 151.964	Eu 157.25	Gd 158.9253	Tb 158.9253	Dy 162.50	Ho 164.9303	Er 167.26	Tm 168.9342	Yb 173.04	Lu 174.96
					Acti	nides ‡	50 Th 232.0381	Pa 221.0289	ັບ	Np	Pu 244)	Am [243]	26 Cm (247)	97 Bk (247)	26 Cf (251)	99 Es (252)	100 Fm (257)	101 Md (258)	102 No (259)	103 Lr (262)
Energy (First Pass)			Tic	k			252,0381	231.0289		ord 1	244)	[263]	(247)	(247)	(234)	(252)	lesit	Tic		(202)
Reaction run between 0 to 70°C		Green Flag	The	×		Γ		Rea	ction	run at	reflu	×			Red Fl	ag		х		
						⊢														
Reaction run between -20 to 0 or 70 to	140°C	Amber Flag				Re	eaction	run 5	°C or i	nore	below	the s	olver	nt c		1				
Reaction run below -20 or above 14	0°C	Red Flag	x						boilir	ng poi	nt			G	reen F	-lag				
						L														
Batch/flow			Tic	k		w	ork Up											Lis	t	
FlowBatch		een Flag Iber Flag								nchin; ration										
									centri	fugati	on			G	reen F	lag		vapor		
							ow ten		crysta ure di			anor	ation			.0	S	ublim	ation	
							sublir	natior	n (< 14	0 °C a	t atm	osphe	eric							
						S	olvent	exchai		uench Ivent	ing in	to aq	ueous	s Ar	nber I	Flag				
							ch		tograp	hy/io		nange								
									igh te iple re			on			Red Fl	ag				
						L		····arti												
											_	_	_	_	_	_	_			
Health & safety											List	subst	tance	s and	H-coc	les	Lis	t subs	tance	s an

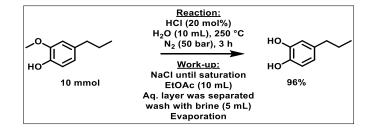
lealth & safety				List substances and H-codes	List substances and H-codes	List substances and H-codes
	Red Flag	Amber Flag	Green Flag			
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber			
			flagged H codes present			
Explosive thermal runaway	H230, H240, H250	H241	then green flag			
Toxic	H300, H310, H330	Н301, Н311, Н331,			4-Propylguaiacol: H311	H2O HCI
Long Term toxicity	H340, H350, H360, H370, H372	H341, H351, H361, H371, H373				
Environmental implications	H400, H410, H411, H420	H401, H412				
Use of chemicals o	f environmental concern		y high concern			

Use of chemicals of environmental concern		List substances of very
Chemical identified as Substances of Very High Concern by ChemSec which are utilised	Red Flag	

• Method A2 on 4-propylguaiacol (1a): [MBAL-766]

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction	Volume (cm ³)	Density	Mass (g)	Work up	Mass (g)	Workup solvent	Volume	Density	Mass (g)
									solvent		(g ml ⁻¹)		chemical			(cm³)	(g ml ⁻¹)	
4-Propylguaiacol	0,332	166,22	2,00E-03	HCI	0,015				H ₂ O	1,964	1,00	1,96	NaCl	0,40	EtOAc	2,00	0,90	1,79
H ₂ O	0,036	18,02	2,00E-03										NaCl	0,36	H ₂ O	1,00	1,00	1,00
								_										
Total	0,37	184,23			0,01		0,00					1,96		0,76	1			2,79



	Flag	
Yield	95,97 🔵	
Conversion	100,00 🔵	
Selectivity	95,97 🔵	
AE	82,61	
RME	79,27 OE	
PMI total	20,20	
PMI Reaction	8,03	
PMI Workup	12,17	
PMI Workup		
chemical	2,60	
PMI workup		
solvents	9,57	
PMI RRC	1,31	
PMI FI Total	16,69	
PMI FI React	6,64	
PMI FI Workup	10,05	
PMI FI RRC	1,08	
AE FI	100,00	
RME FI	95,96	
E factor	19,20	
E factor FI	15,69	

	Mass	MW	Mol
Product	0,292	152,19	1,92E-03
	mass		
Unreacted limiting			
reactant	0,00		
	Mass	MW	Mol
Co-Product	0,061	32,04	1,92E-03
	excluding	including	
	co-products	co-	
Generated waste	5,609	5,547	

Experimental [MBAL-766]

96,0 100,0

96,0

The reaction was performed using General Procedure C, using 2-methoxy-4-propylphenol (332 mg, 2.00 mmol, 1.0 equiv.) as substrate and HCl (aq., 1 M, 0.4 mL, 0.40 mmol, 0.2 equiv.) and H₂O (1.6 mL) as reagents as reagent. The reaction mixture was heated to 250 °C and stirred for 3 h at this temperature, under a starting pressure of N₂ (50 bar). The experiment was performed 5 times and samples were combined for work-up. In the work-up, NaCl (s, 2.00 g), EtOAc (10 mL) and brine (5.0 mL) were used. The residue was pure product.

Solvents (First Pass)		List solvents below
Preferred solvents	water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane	H ₂ O, EtOAc
Problematic solvents: (acceptable only if substitution does not offer advantages)	DMSO, cyclohexanone, DMPU, AcOH, Ac2O, Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene, MTBE, cyclohexane , chlorobenzene, formic acid, pyridine, Me-THF	
Hazardous solvents: These solvents have significant health and/or safety concerns.	dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane	
Highly hazardous solvents: The solvents which are agreed not to be used, even in screening	Et_2O , Benzene, CCl_4 , chloroform, DCE, nitromethane, CS_2 , HMPA	

Catalyst/enzyme (First	Pass)		Tick	1			Tick
Catalyst or enzyme use	ed, or reaction takes place without any catalyst/reagents.	Green Flag	Х		Facile recovery of catalyst/enzyme	Green Flag	
Use	of stoichiometric quantities of reagents	Amber Flag			catalyst/enzyme not recovered	Amber Flag	
	Use of reagents in excess	Red Flag					

Supply remaining	Flag colour	Note element	н				until dep known													H
5-50 years	Red Flag		1.00794	4			ased on cu extra	rrent rate							5	6	7	8	9	10
50-500 years	Amber Flag		Li 6.941	Be 9.012182			5-50	years							B 10.811	C 12.0107	N 14.00674	O 15.9994	F 18.99840	20.
50-500 years	Amber Flag		¹¹ Na	12 Mg			50-10 100-50								D Al	³⁴ Si	15 P	16 S	17 Cl	18
+500 years	Green Flag	x	22.98977 19	24.3050 20	21	22	23	24	25	26	27	28	29	30	26.98153	28.0855	39.97376 13	32.066 34	35.4527 35	39.
			K 39.0983	Ca 40.078	Sc	Ti 47,857	V	Cr	Mn	Fe 55.845	Co	Ni 58.6934	Cu	Zn	Ga	Ge	As	Se	Br 79.904	83.
			37	38	39	40	41	42	43	44	45	45	47	48		50		52	53	54
			Rb 85.4678	Sr 87.62	¥ 88.9085	Zr 91.224	Nb 92.90638	Mo 95.94	Tc (98)	Ru 101.07	Rh 102.9055	Pd 106.42	Ag 107.8682	Cd	In 114.818	Sn 118.760	Sb 121.760	Te 127.60	126.9044	13
			SS Cs	56 Ba	57 La *	72 Hf	73 Ta	w	25 Re	76 Os	" Ir	78 Pt	Au	ao Hg	а П	82 Pb	as Bi	PO	as At	84
			132.9054 87	137.327	138.9055	178.49	180.9479	183.84	186.207 107	190.23 108	192.217	195.078 110	196.9665	200.59	204.3833	270.2	208,9804	(209) 116	(210)	(2
			Fr (223)	Ra 226.025	Ac \$	Rf (257)	Db	Sg (263)	Bh (262)	Hs (265)	Mt (266)	Ds (271)	Rq (272)	Uub	Uut	Uuq	Uup (288)	Lv (292)	Uus	l
																				_
				La	anthanio	les *	S8 Ce		∾ Nd	⁶¹ Pm	ୟ Sm	63 Eu	⊶ Gd	65 Tb	⁶⁶ Dy	ਕ Ho	68 Er	•• Tm	70 Yb	71
						-		144.24 (145)	150.36 93	151.964 94	157.25 95	158.9253 96	158.9253 97	162.50 58	164.9303 99	167.26 100	168.9342 101	173.04 102	17
					Actinid		Th 232.0381	Pa	U	Np	Pu (244)	Am	Cm	Bk	Cf (251)	Es	Fm	Md	No (259)	(26
nergy (First Pass)		Г	 Fick	T							11.14	(***)	(c)	(a)	(1.1.1)	1000	1	1000	Tick	-
Reaction run between 0 to 7	0°C	Green Flag							Reac	tion r	un at r	eflux			R	ed Fla	g		Х	
			 																	-
Reaction run between -20 to 0 or 7	'0 to 140°C	Amber Flag					Reac	tion ru	un 5°(Corm	ore b	elow	the sc	olvent	_					
Reaction run below -20 or abov	a 140°C	Red Flag	x						I	boilin	g poin	t			Gre	een Fl	ag			
	e 140 C	Red Hug	<u>^</u>																	
atch/flow		г	 Fick	_			Wor	lin									Г		List	
ow	Gr	een Flag	 Tex					(OP		quen	ching								LISC	-
atch	An	nber Flag					filtration centrifugation Gree													
												een Fl	ag		aporat					
							1.000	tomn			lisatio tillatic			tion/				Sublimation	tio	
											0°C at		-							
											enchi									
							1				ont	-	÷		Am	ber Fl	ag	E)	tracti	.on

Health & safety				List substances and H-codes	List substances and H-codes	List substances and H-codes
	Red Flag	Amber Flag	Green Flag			
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber			
			flagged H codes present			
Explosive thermal runaway	H230, H240, H250	H241	then green flag			H2O
Тохіс	H300, H310, H330	H301, H311, H331,			4-Propylguaiacol: H311	HCI NaCI
Long Term toxicity	H340, H350, H360, H370, H372	H341, H351, H361, H371, H373				EtOAc
Environmental implications	H400, H410, H411, H420	H401, H412				

solvent chromatography/ion exchange

high temperature multiple recrystallisation

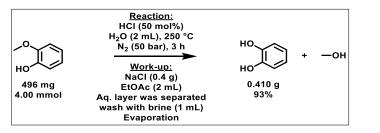
Use of chemicals of environmental concern		List substances of very high concern
Chemical identified as Substances of Very High Concern by ChemSec which are utilised	Red Flag	

Red Flag

• Method A2 on guaiacol (11): [MBAL-467]

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm ³)	Density (g ml ⁻¹)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm ³)	Density (g ml ⁻¹)	Mass (g)
Guaiacol	0,496	124,14	4,00E-03	HCI	0,073			H ₂ O	1,928	1,00	1,93	NaCl	0,40	EtOAc	2,00	0,90	1,79
H ₂ O	0,072	18,02	4,00E-03									NaCl	0,36	H ₂ O	1,00	1,00	1,00
Total	0,57	142,16			0,07		0,00				1,93		0,76				2,79



Conversion	100,00
	77,46
PMI total	14,93
PMI Reaction	6,27
PMI Workup	8,67
PMI Workup	
chemical	1,85
PMI workup	
solvents	6,81
PMI RRC	1,56
PMI FI Total	11,57
PMI FI Reaction	4,85
PMI FI Workup	6,71
PMI FI RRC	1,21
AE FI	100,00
RME FI	93,19
E factor	13,93
E factor FI	10,57

	Mass	MW	Mol
Product	0,410	110,11	3,72E-03
	mass		
Unreacted limiting			
reactant	0,00		
	Mass	MW	Mol
Co-Product	0,119	32,04	3,72E-03
		including	
	excluding	co-	
	co-products	products	
Generated waste	5,713	5,594	

Experimental [MBAL467]

The reaction was performed using General Procedure C, using 2-methoxyphenol (496 mg, 4.00 mmol, 1.0 equiv.) as substrate and HCl (aq., 1 M, 2.0 mL, 2.00 mmol, 0.5 equiv.) as reagent. The reaction mixture was heated to 250 °C and stirred for 3 h at this temperature, under a starting pressure of N₂ (50 bar). The experiment was performed 5 times and samples were combined for work-up. In the work-up, NaCl (s, 2.00 g), EtOAc (10 mL) and brine (5.0 mL) were used. The residue was pure product.

Solvents (First Pass)		List solvents below
Preferred solvents	water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane	H₂O EtOAc
Problematic solvents: (acceptable only if substitution does not offer advantages)	DMSO, cyclohexanone, DMPU, AcOH, Ac2O, Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene, MTBE, cyclohexane , chlorobenzene, formic acid, pyridine, Me-THF	
Hazardous solvents: These solvents have significant health and/or safety concerns.	dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane	
Highly hazardous solvents: The solvents which are agreed not to be used, even in screening	Et ₂ O, Benzene, CCl ₄ , chloroform, DCE, nitromethane, CS ₂ , HMPA	

Catalyst/enzyme (First Pass)								
Catalyst or enzyme used, or reaction takes place without any catalyst/reagents.	Green Flag	х						
Use of stoichiometric quantities of reagents	Amber Flag							
Use of reagents in excess	Red Flag							

		Tick
Facile recovery of catalyst/enzyme	Green Flag	
catalyst/enzyme not recovered	Amber Flag	

Supply remaining	Flag colour	Note element		H 00794			intil dep known r	letion of the serves												H
5-50 years	Red Flag		3	4			ised on cu extrac	rrent rate							5	6	7	8	9	10
50-500 years	Amber Flag		6	Li Be 941 9.01218	2			/ears							B 10.811	C 12.0107	N 14.00674	0 15.9994	F 18.99840	20.1
So Soo years	Amber Hug			Na Mg			100-50								AI	¹⁴ Si	P	¹⁶ S	ั่วเ	18
+500 years	Green Flag	х	2		21	22	23	24	25	26	27	28	29	30	26.98153	28.0855	39.97376 33	32.066 34	35.4527 35	39.9 36
			2	K Ca	Sc 44.95591	Ti 47.867	V 50.9415	Cr 51.9961	Mn 54.93804	Fe 55.845	Co 58.93320	Ni 58.6934	Cu 63.546	Zn 65.39	Ga 09.723	Ge 77.61	As 74.92160	Se 78.96	Br 79.504	83.8
				Rb Sr	Ϋ́	Zr	Nb	Mo	Тс	Ru	Rh	Pd	Ag	Cd	in .	Sn	Sb	Te	° I	54 X
			8		88.9085 57	91.224	92.90638	95.94	(98) 75	101.07		106.42 78	107.8682	80	81	82	83	127.60 84	85	131.2 86
			1	Cs Ba 12.9054 137.327	La * 138.9055	Hf 178.49	Ta 180.9479	W 181.84	Re 186.207	Os 190.23	192,217	Pt 195.078	Au 196.9665	Hg 200.59	TI 2013103	Pb 270.2	Bi 208.5604	Po (209)	At (210)	R(
			8	Fr Ra	89 Ac ‡	104 Rf	105 Db	106 Sg	107 Bh	108 Hs	109 Mt	110 Ds	111 Rq	112 Uub	113 Uut	114 Uuq	115 Uup	116 LV	Uus	118 Uu
			0	23] 226.025	(227)	(257)	(260)	(263)	(262)	(265)	(266)	(271)	(272)	(285)	(284)	(289)	(288)	(292)		
					anthanic		Ce	Pr	Nd (Pm	୍ଦ Sm	ទ Eu	⊶ Gd	65 Tb	бору Бу	67 Ho	ea Er	∞ Tm	70 Yb	n L
					anthanic	1				Pm 150.36		EU 157.25	158.9253	158.9253	162.50 18	164.9303	EF 167.26	168.9342 101	173.04 102	174.9 103
					Actinid	es‡	Th	Pa	ŰU	Np	Pu	Am	Cm	Bk	Cf	Es	Fm	Md	No	Lr
				_		2	132.0381 2	31.0289	238.0289	237)	(244)	(243)	(247)	(247)	(251)	(252)	(257)	(258)	(259)	(262)
nergy (First Pass) Reaction run between 0 to 70	°c		Tick															Tic		
Reaction full between 0 to 7		Green Flag						Rea	ction	run at	reflu	x		1	Red Fl	ag		Х		
Reaction run between -20 to 0 or 70	0 to 140°C	Amber Flag				Reaction run 5°C or more below the solvent														
				boiling point							lag									
Reaction run below -20 or above	140°C	Red Flag	Х																	
atch/flow			Tick	_		Mo	rk Up											Lis	•	
low	Gr	een Flag	TICK				ik op		que	nchin	g							-		
	An	nber Flag	filtration																	
atch						centrifugation Green Flag								lag			ation			
atch										crystallisation Crystallisation Low temperature distillation/evaporation/					reenr		Sublimation			
atch															reen r		3		acion	
atch								perat	ure di	stillat	ion/e				reenr		3		acion.	
atch							sublin	perat natior	ure di n (< 14	stillat 0 °C a	ion/e at atm	Iosphe	eric	/						
atch							sublin	perat natior	ure di <u>1 (< 14</u> nge, q	stillat 0 °C a	ion/e <u>at atm</u> ning ir	Iosphe	eric	/	nber I			Extra		
atch							<u>sublin</u> vent e	perat natior exchar	ure di <u>1 (< 14</u> nge, q	stillat 0 °C a uench lvent hy/io	ion/e <u>at atm</u> ning in n excl	iosphe ito aq	eric ueous	/ ^S Ar		Flag				

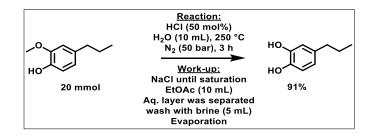
alth & safety				List substances and H-codes	List substances and H-codes	List substances and H-codes
·	Red Flag	Amber Flag	Green Flag			
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber			
			flagged H codes present			
Explosive thermal runaway	H230, H240, H250	H241	then green flag			H2O
Τοχίς	H300, H310, H330	Н301, Н311, Н331,			4-Propylguaiacol: H311	HCI NaCl
Long Term toxicity	H340, H350, H360, H370, H372	H341, H351, H361, H371, H373				EtOAc
Environmental implications	H400, H410, H411, H420	H401, H412				
Use of chemicals o	f environmental concern		List substances of ver	y high concern		

Chemical identified as Substances of Very High Concern by ChemSec which are utilised	Red Flag

• Method A3: [JBO-643]

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction	Volume (cm ³)	Density	Mass (g)	Work up	Mass (g)	Workup solvent	Volume	Density	Mass (g)
								solvent		(g ml ⁻¹)		chemical			(cm³)	(g ml ⁻¹)	
4-Propylguaiacol	0,665	166,22	4,00E-03	HCI	0,073			H ₂ O	1,928	1,00	1,93	NaCl	0,40	EtOAc	2,00	0,90	1,79
H ₂ O	0,072	18,02	4,00E-03									NaCl	0,36	H ₂ O	1,00	1,00	1,00
Total	0,74	184,23			0,07		0,00				1,93		0,76				2,79



		Flag
Yield	91,00	
Conversion	100,00	
Selectivity		
AE	82,61	
RME	75,18	OE
PMI total	11,36	
PMI Reaction	4,94	
PMI Workup	6,42	
PMI Workup		
chemical	1,37	
PMI workup		
solvents	5,04	
PMI RRC	1,46	
PMI FI Total	9,38	
PMI FI React	4,08	
PMI FI Workup	5,30	
PMI FI RRC	1,21	
AE FI	100,00	
RME FI	91,00	
E factor		
E factor FI	8,38	

	Mass	MW	Mol
Product	0,554	152,19	3,64E-03
	mass		
Unreacted limiting		I	
reactant	0,00		
	Mass	MW	Mol
Co-Product	0,117	32,04	3,64E-03
	excluding	including	
	co-products	co-	
Generated waste	5,738	5,621	

Experimental [JBO-643]

91,0

91,0 100,0 91,0

The reaction was performed using General Procedure C, using 2-methoxy-4-propylphenol (666 mg, 4.00 mmol, 1.0 equiv.) as substrate and HCl (aq., 1 M, 2.0 mL, 2.00 mmol, 0.5 equiv.) as reagent. The reaction mixture was heated to 250 °C and stirred for 3 h at this temperature, under a starting pressure of N₂ (50 bar). The experiment was performed 5 times and samples were combined for work-up. In the work-up, NaCl (s, 2.00 g), EtOAc (10 mL) and brine (5.0 mL) were used. The residue was pure product.

Solvents (First Pass)		List solvents below
Preferred solvents	water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane	H ₂ O, EtOAc
Problematic solvents: (acceptable only if substitution does not offer advantages)	DMSO, cyclohexanone, DMPU, AcOH, Ac2O, Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene, MTBE, cyclohexane , chlorobenzene, formic acid, pyridine, Me-THF	
Hazardous solvents: These solvents have significant health and/or safety concerns.	dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane	
Highly hazardous solvents: The solvents which are agreed not to be used, even in screening	Et_2O , Benzene, CCl_4 , chloroform, DCE, nitromethane, CS_2 , HMPA	

Catalyst/enzyme (First Pass)		Tick	
Catalyst or enzyme used, or reaction takes place without any catalyst/reagents.	Green Flag	х	
Use of stoichiometric quantities of reagents	Amber Flag		
Use of reagents in excess	Red Flag		

		Tick
Facile recovery of catalyst/enzyme	Green Flag	
catalyst/enzyme not recovered	Amber Flag	

Supply remaining	Flag colour	Note element		H 1.00794				depletion wn rese												He
5-50 years	Red Flag			1.00794 3 Li	4 Be		(based	on current extraction]	t rate of						з В	° c	7 N	* 0	° F	10 10
50-500 years	Amber Flag			6.941	9.012182 12			5-50 years 0-100 yea							10.811 13	12.0107	14.00674	15.9994	18.59840 17	20.175
				Na 22.58977	Mg			0-500 yea							AI 26.98153	Si 28.0855	P 39.97376	S 32.066	CI 35.4527	Ar 39.948
+500 years	Green Flag	x		19 K	20 Ca	21 Sc	22 23 Ti	V 24	25 Cr	An Fe	27 Co	28 Ni	29 Cu	se Zn	и Ga	32 Ge	33 As	зя Se	35 Br	36 Kr
				39.0983 37	40.078	44.95591 39			9961 54	3804 55.845	58.93320	58.6934 46	63.546 47	65.39 48				78.96 52	79.504 53	83.80 54
				Rb 85.4678	Sr 87.62	Y 88.9085			No	Tc Ru	Rh	Pd 105.42	Ag	Cd	In	Sn 118.760	Sb 121.700	Te 127.60	1 126.9044	Xe
				SS Cs	56 Ba	57 La *	72 73 Hf	Ta 74	25 W	Re Os	77 Ir	78 Pt	79 Au	80 Hg	an Ti	≈ Pb	er Bi	84 Po	as At	⁸⁶ Rn
				132.9054 87	137.327 88	138.9055 89	178.49 18 104 10	5 106	184 180 i 107	207 190.23 108	192.217 109	195.078 110	196.9665 111	200.59 112	204.3833 113	270.2 114	208.9804 115	(209) 116	(210)	[222] 118
				Fr (223)	Ra 226.025	Ac \$		Db 9		Bh Hs (265)	Mt (266)	Ds (271)	Rq (272)	Uub (285)	Uut (284)	Uuq (289)	Uup (288)	LV (292)	Uus	Uu
										-	0	0		6		67	68	-		
					Lar	nthanid	es * Ce	Pr	Nd	Pm	Sm	Eu 157.25	Gd	Tb	Dy	Ho 164,9303	Er	Tm	Yb	Lu 174.96
						Actinide	s ‡ Th	91	92 U	93 Np	94 Pu	55 Am	96 Cm	97 Bk	58 Cf	99 Es	100 Fm	101 Md	102 No	103 Lr
																			140	
					,	Actinide	232.03			(237)	(244)	(243)	(247)	(247)	(251)	(252)	(257)	(258)	(259)	(262)
			Ті	ick		Actinide				n (237)			(247)	(247)	(251)	(252)	(257)	(258) Tic		
i nergy (First Pass) Reaction run between 0 to 70 [°]	c	Green Flag	Ті	ick	,	Actimide		81 231.028	238.02	on run a	(244)	(243)	(247)		Red Fl		[257]		k	
	-	Green Flag Amber Flag	Ti	ick	,	Actimide	232.03	81 231.028	eactio		t reflu	(243)		ŗ			(257)	Tic	k	
Reaction run between 0 to 70° Reaction run between -20 to 0 or 70 t	o 140°C	Amber Flag	Ti	ick		Actinue	232.03	81 231.028	eaction 5°C	or more	t reflu	(243)		F		ag	(257)	Tic	k	
	o 140°C	-		ick X	,	Actinue	232.03	81 231.028	eaction 5°C		t reflu	(243)		F	Red Fl	ag	[257]	Tic	k	
Reaction run between 0 to 70° Reaction run between -20 to 0 or 70 t Reaction run below -20 or above 1	o 140°C	Amber Flag	;	x		Actimue	Reacti	R on rur	eaction 5°C	or more	t reflu	(243)		F	Red Fl	ag	(257)	Tic	k	
Reaction run between 0 to 70 ^o Reaction run between -20 to 0 or 70 t Reaction run below -20 or above 1 Reacth/flow Iow	o 140°C 40°C Gr	Amber Flag Red Flag reen Flag	;			Actimue	232.03	R on rur	eaction n 5°C o bo	or more piling po	t reflu below	(243)		F	Red Fl	ag	(257)	Tic	k	
Reaction run between 0 to 70 ^o Reaction run between -20 to 0 or 70 t Reaction run below -20 or above 1 Batch/flow	o 140°C 40°C Gr	Amber Flag Red Flag	;	x			Reacti	R on rur	eaction n 5°C o bo	or more biling po uenchin filtratio	t reflu below bint	(243)		F	Red Fl	ag		Tic X Lis	t.	
Reaction run between 0 to 70 ^o Reaction run between -20 to 0 or 70 t Reaction run below -20 or above 1 Batch/flow	o 140°C 40°C Gr	Amber Flag Red Flag reen Flag	;	x			Reacti	R on rur	eaction n 5°C o bo cer	or more biling po juenchin filtratio ntrifuga	e below bint	(243)		f It Gr	Red Fl	ag	E	Tic X Lis	k	
Reaction run between 0 to 70 ^o Reaction run between -20 to 0 or 70 t Reaction run below -20 or above 1 Reacth/flow Iow	o 140°C 40°C Gr	Amber Flag Red Flag reen Flag	;	x			Reacti Work	R on rur Up	e reaction Reaction boot cer cry rature	pr more piling po guenchin filtratio ntrifuga rstallisa e distilla	t reflue below bint n tion tion tion/e	v the s	solver	fit Gr	Red Fl	ag	E	Tic X Lis	t ration	
Reaction run between 0 to 70° Reaction run between -20 to 0 or 70 t	o 140°C 40°C Gr	Amber Flag Red Flag reen Flag	;	x		Actinue	Reacti Work	R R On rur Up	ee action the section the section the section the section (<	pr more piling po puenchin filtratio ntrifuga rstallisa e distilla 140 °C	t reflu below below int n tion tion/e at atn	vapor nosph	ation,	F It Gr Gr	Red Fl reen F	ag Flag	E [,] S	Tic X Lis vapor ublim	k it ation	
Reaction run between 0 to 70 ^o Reaction run between -20 to 0 or 70 t Reaction run below -20 or above 1 Reacth/flow low	o 140°C 40°C Gr	Amber Flag Red Flag reen Flag	;	x	,	Actinue	Reacti Work	R R On rur Up	ee action the section the section the section the section (<	pr more piling po guenchin filtratio ntrifuga rstallisa e distilla	t reflu t below int tion tion tion/e at atm hing in	vapor nosph	ation,	F It Gr Gr	Red Fl	ag Flag	E [,] S	Tic X Lis	k it ation	
Reaction run between 0 to 70 ^o Reaction run between -20 to 0 or 70 t Reaction run below -20 or above 1 Batch/flow	o 140°C 40°C Gr	Amber Flag Red Flag reen Flag	;	x		Actinue	Reacti Work	R on rur Up emper blimat nt excl	Reaction n 5°C (bo cer cry rature hange	pr more piling po guenchin filtratio ntrifuga estallisa e distilla <u>140 °C</u> c, quenc	t reflu t below int below int n tion tion tion hing in t	vapor nosphito aq hange	ation, eric_ueous	Fit Gr Gr /	Red Fl reen F	ag Flag	E [,] S	Tic X Lis vapor ublim	k it ation	

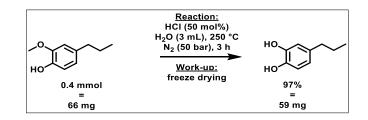
ealth & safety				List substances and H-codes	List substances and H-codes	List substances and H-codes
	Red Flag	Amber Flag	Green Flag			
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber			
			flagged H codes present			
Explosive thermal runaway	H230, H240, H250	H241	then green flag			H ₂ O
Τοχίς	Н300, Н310, Н330	Н301, Н311, Н331,			4-Propylguaiacol: H311	HCI NaCl
Long Term toxicity	H340, H350, H360, H370, H372	H341, H351, H361, H371, H373				EtOAc
Environmental implications	H400, H410, H411, H420	H401, H412				
Use of chemicals of	environmental concern		List substances of ver	y high concern		

Chemical identified as Substances of Very High Concern by ChemSec which are utilised Red Flag

• Method A4: [JBO-1658]

Yield, AE, RME, MI/PMI and OE

						_			2						1		1
Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction	Volume (cm ³)	Density	Mass (g)	Work up	Mass (g)	Workup solvent	Volume (cm ³)	Density	Mass (g)
								solvent		(g ml ⁻¹)		chemical				(g ml ⁻¹)	
4-Propylguaiacol	0,066	166,22	4,00E-04	HCI	0,007			H ₂ O	2,993	1,00	2,99						
H ₂ O	0,007	18,02	4,00E-04														
Total	0,07	184,23			0,01		0,00				2,99		0,00				0,00



	Flag	
	96,92 🔵	96,9
Conversion	100,00	100,0
	96,92 🔵	96,9
AE	82,61	
RME	80,06 OE	
PMI total	52,10	
PMI Reaction	52,10	
PMI Workup	0,00	
PMI Workup		
chemical	0,00	
PMI workup		
solvents	0,00	
PMI RRC	1,37	
PMI FI Total	43,04	
PMI FI Reaction	43,04	
PMI FI Workup	0,00	
PMI FI RRC	1,13	
AE FI	100,00	
RME FI	96,92	_
	51,10	Expe
E factor FI	42,04	The

	Mass	MW	Mol
Product	0,059	152,19	3,88E-04
	mass		
Unreacted limiting			
reactant	0,00		
	Mass	MW	Mol
Co-Product	0,012	32,04	3,88E-04
	excluding	including	
	co-products	co-products	
Generated waste	3,015	3,002	

Experimental [JBO-1658]
The reaction was perform.

The reaction was performed using General Procedure C, using 2-methoxy-4-propylphenol (66 mg, 0.40 mmol, 1.0 equiv.) as substrate and HCl (aq., 1 M, 0.2 mL, 0.20 mmol, 0.5 equiv.) and H₂O (2.8 mL) as reagents. The reaction mixture was heated to 250 °C and stirred for 3 h at this temperature, under a starting pressure of N₂ (50 bar). The experiment was repeated 5 times and samples were freeze-dried to remove all volatiles. The residue was pure product.

Solvents (First Pass)		List solvents below
Preferred solvents	water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane	H ₂ O
Problematic solvents: (acceptable only if substitution does not offer advantages)	DMSO, cyclohexanone, DMPU, AcOH, Ac2O, Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene, MTBE, cyclohexane , chlorobenzene, formic acid, pyridine, Me-THF	
Hazardous solvents: These solvents have significant health and/or safety concerns.	dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane	
Highly hazardous solvents: The solvents which are agreed not to be used, even in screening	$Et_2O, Benzene, CCl_4, chloroform, DCE, nitromethane, CS_2, HMPA$	

Catalyst/enzyme (First Pass)		Tick
Catalyst or enzyme used, or reaction takes place without any catalyst/reagents.	Green	х
······,·······························	Flag	
Use of stoichiometric quantities of reagents	Amber	
	Flag	
Use of reagents in excess	Red Flag	

		Tick
Facile recovery of catalyst/enzyme	Green Flag	
catalyst/enzyme not recovered	Amber Flag	

Supply remaining	Flag colour	Note element		1.00	H				letion o eserves												He 4.00260
5-50 years	Red Flag			3	4		(bi	ised on cu extra	rrent rate ction)	of						5 B	с	7 N	8 0	° F	10 Ne
50-500 years	Amber Flag			6.94				5-50 ⁻								10.811	12.0107	14.00674	15.9994	18.99840	20.179
50 500 (cars	7.110011108			Ň	la <mark>Mg</mark>			100-50								AI	Si	P	S	ci	Ar
+500 years	Green Flag	х		22.9	20	21	22	23	24	25	26	27	28	29	30	26.98153 31	28.0855 32	39.97376 33	32.066 34	35.4527 35	39.948 36
			'	39.0			Ti 47.867	V 50.9415	Cr 51.9961	Mn 54.93804	Fe 55.845	Co 58.93320	Ni 58.6934	Cu 63.546	Zn 65.39	Ga 09.723	Ge 72.61	As 74.92160	Se 78.95	Br 79.904	Kr 83.80
				37 R	ab Sr	³⁰ y	40 Zr	41 Nb	42 Mo	43 Tc	44 Ru	45 Rh	46 Pd	47 Ag	" Cd	eo In	so Sn	SI Sb	ः Te	8	54 Xe
				85.4		88.9085	91.224	92.90638	95.94	(98)	101.07		106.42	107,8682	112.411	114.818	118,760	121.760	127.60	126.9044	131.29
				c	Cs Ba	La *	Hf	Та	w	Re	Os	Ir	Pt	Au	Hg	TI	Pb	Bi	Ро	At	Rn
				132.9	88	89	104	180.9479 105	181.84	186.207	100.23	102.217	195.078	196,9665	200.59	113	270.2 114	115	(209) 116	(210) 117	(222) 118
				(223)			Rf (257)	Db (260)	Sg (263)	Bh (262)	Hs (265)	Mt (266)	Ds (271)	Rq (272)	Uub (285)	Uut (284)	Uuq (289)	Uup (288)	Lv (292)	Uus	Uuc
											61	0	6	4	65	16	6	68	10		71
						Lanthani		Ce		Nd	Pm	Sm	Eu	Gd	ть	Dy	Но	Er	Tm	Yb	Lu
								40.9077 1	44.24 (150.36	151.964	157.25	158.9253	158.9253	162.50	164,9303	167.26	168.9342	173.04	174.967
								10 1	91 1	e	93	94 1	95	96	97	58	99	100	101	102	103
						Actinic	des ‡	Th	_	2 I U 38.0299	Np	94 Pu			97 Bk (247)	58 Cf (251)				102 No (259)	
nerzy (First Pass)				ick		Actinic	des ‡	Th	Pa	e	Np	94 Pu	95 Am	96 Cm	Bk	Cf	99 Es	100 Fm	101 Md	No (259)	103 Lr
nergy (First Pass) Reaction run between 0 to	70°C	Green Flag	Ti	ick	-	Actinic	des ‡	Th	11 1 Pa 131.0289 2	2 (U 38.0289	93 Np (237)	94 Pu	95 Am (243)	96 Cm	Bk (247)	Cf (251)	99 Es (252)	100 Fm	101 Md (258) Tic	No (259) k	103 Lr
	70°C	Green Flag	Ti	ick		Actinic	des ‡	Th	11 1 Pa 131.0289 2	2 (U 38.0289	93 Np (237)	94 Pu (244)	95 Am (243)	96 Cm	Bk (247)	Cf	99 Es (252)	100 Fm	101 Md (258)	No (259) k	103 Lr
		Green Flag Amber Flag	Ti	ick		Actinic	des ‡	10 1 Th 1322.0381 2	Pa Pa Pa Read	ction	⁹³ Np 2237) run at	Pu Pu (244)	55 Am (243)	26 Cm (247)	Bk (247)	Cf (251)	99 Es (252)	100 Fm	101 Md (258) Tic	No (259) k	103 Lr
Reaction run between 0 to	70 to 140°C	Amber Flag				Actinio	des ‡	10 1 Th 1322.0381 2	Pa Pa Pa Read	ction	run at	Pu Pu (244) t reflu: below	55 Am (243)	96 Cm	Bk (247)	Cf (251)	99 Es (252)	100 Fm	101 Md (258) Tic	No (259) k	103 Lr
Reaction run between 0 to	70 to 140°C	Ŭ		ick X		Actinio	des ‡	10 1 Th 1322.0381 2	Pa Pa Pa Read	ction	⁹³ Np 2237) run at	Pu Pu (244) t reflu: below	55 Am (243)	26 Cm (247)	Bk (247)	cf (251)	99 Es (252)	100 Fm	101 Md (258) Tic	No (259) k	103 Lr
Reaction run between 0 to Reaction run between -20 to 0 or Reaction run below -20 or abo	70 to 140°C	Amber Flag		x		Actinic	des‡	nth 1222.03881	Read	ction	run at	Pu Pu (244) t reflu: below	55 Am (243)	26 Cm (247)	Bk (247)	cf (251)	99 Es (252)	100 Fm	101 Md (258) Tic	No (259) k	103 Lr
Reaction run between 0 to	70 to 140°C ve 140°C	Amber Flag				Actinic	des‡	10 1 Th 1322.0381 2	Read	ction r boilir	run at	Pu Pu (244)	55 Am (243)	26 Cm (247)	Bk (247)	cf (251)	99 Es (252)	100 Fm	101 Md (258) Tic	No (259) k	103 Lr
Reaction run between 0 to Reaction run between -20 to 0 or Reaction run below -20 or abo atch/flow	70 to 140°C ve 140°C	Amber Flag Red Flag		x		Actinic	des‡	nth 1222.03881	Read	ction r boilir que filt	run at more ng poi	Pu Pu t reflu: below int	55 Am (243)	26 Cm (247)	Bk (247)	cf (251)	99 Es (252)	100 Fm (257)	Tic X	No [259] k	103 Lr
Reaction run between 0 to Reaction run between -20 to 0 or Reaction run below -20 or abo atch/flow ow	70 to 140°C ve 140°C	Amber Flag Red Flag reen Flag		x		Actinic	des‡	nth 1222.03881	Read	ction de la construction de la c	run at more ng poi	Pu Pu t reflu: below int	55 Am (243)	26 Cm (247)	Bk (247)	cf (251)	es (232)	100 Fm (257)	Tic X Lis	k t ation	103 Lr
Reaction run between 0 to Reaction run between -20 to 0 or Reaction run below -20 or abo atch/flow ow	70 to 140°C ve 140°C	Amber Flag Red Flag reen Flag		x		Actinic	des #	rtion	Pa Pa Rear run 5 ⁴	ction n boilir que filti crysta	nchin ratior ratior	Pu Pu t reflu: below int g ion ion	95 Am (243) X	90 Cm (247)	Bk (247) G	Cf (251) Red Fl	es (232)	100 Fm (257)	Tic X	k t ation	103 Lr
Reaction run between 0 to Reaction run between -20 to 0 or Reaction run below -20 or abo atch/flow ow	70 to 140°C ve 140°C	Amber Flag Red Flag reen Flag		x		Actinic	des ‡	viction rk Up	Read	du d	nchin ratior stillat	⁹⁴ Pu Pu t reflu: below int g 1 ion ion ion	Am Am (243) x v the :	90 Cm (ρ47) solver	Bk (247) G	Cf (251) Red Fl	es (232)	100 Fm (257)	Tic X Lis	k t ation	103 Lr
Reaction run between 0 to Reaction run between -20 to 0 or Reaction run below -20 or abo atch/flow ow	70 to 140°C ve 140°C	Amber Flag Red Flag reen Flag		x		Actinic	des ‡	v tem sublin	Read	ction of control of co	nchin ratior ifugat stillat 0°C a	Pu P	Am Am (243) x v the : vapor nosph	90 Cm (ρ47) solver	Bk (247)	Cf (251) Red Fl	es Es (253) Flag	100 Fm (257)	Tic X Lis	k t ation	103 Lr

ealth & safety				List substances and H-codes	List substances and H-codes	List substances and H-codes
·····,	Red Flag	Amber Flag	Green Flag			
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber			
			flagged H codes present			
Explosive thermal runaway	H230, H240, H250	H241	then green flag			
Τοχίς	H300, H310, H330	Н301, Н311, Н331,			4-Propylguaiacol: H311	H₂O HCl
Long Term toxicity	H340, H350, H360, H370, H372	H341, H351, H361, H371, H373				
Environmental implications	H400, H410, H411, H420	H401, H412				

chromatography/ion exchange

high temperature multiple recrystallisation

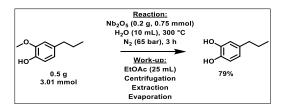
Use of chemicals of environmental concern		List substances of very high concern
Chemical identified as Substances of Very High Concern by ChemSec which are utilised	Red Flag	

Red Flag

• Method B: Nb₂O₅.¹²

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction	Volume (cm ³)	Density	Mass (g)	Work up	Mass (g)	Workup solvent	Volume	Density	Mass (g)
								solvent		(g ml⁻¹)		chemical			(cm³)	(g ml ⁻¹)	
4-Propylguaiacol	0,50	166,22	3,0E-03	Nb ₂ O ₅	0,20			H ₂ O	9,95	1,00	9,95			EtOAc	25,00	0,90	22,55
H ₂ O	0,05	18,02	3,0E-03														
Total	0,55	184,24			0,20		0,00				9,95		0,00				22,55
									Flag								



	i lag	
Yield	78,64 🔴	78,6
Conversion	97,00 🔵	97,0
Selectivity	81,07 🔴	81,1
AE	82,61	
RME	64,96 OE	
PMI total	92,36	
PMI Reaction	29,72	
PMI Workup	62,64	
PMI Workup		
chemical	0,00	
PMI workup		
solvents	62,64	
PMI RRC	2,09	
E factor	91,36	Expe

		Mass	MW	Mol
	Product	0,360	152,19	2,37E-03
		mass		
l	Unreacted limiting			
	reactant	0,02		

Experimental [MBAL-810]

78.6

Solvents (First Pass)		List solvents below
Preferred solvents	water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane	H ₂ O, EtOAc
Problematic solvents: (acceptable only if substitution does not offer advantages)	DMSO, cyclohexanone, DMPU, AcOH, Ac2O, Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene, MTBE, cyclohexane , chlorobenzene, formic acid, pyridine, Me-THF	
Hazardous solvents: These solvents have significant health and/or safety concerns.	dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane	
Highly hazardous solvents: The solvents which are agreed not to be used, even in screening	Et_2O , Benzene, CCl_4 , chloroform, DCE, nitromethane, CS_2 , HMPA	

Catalyst/enzyme (First Pass)		Tick
Catalyst or enzyme used, or reaction takes place without any catalyst/reagents.	Green	х
catalyst of enzyme used, of reaction takes place without any catalyst/reagents.	Flag	^
Use of stoichiometric quantities of reagents	Amber	
ose of scolenometric quantities of reagents	Flag	
Use of reagents in excess	Red Flag	

		Tick
Facile recovery of catalyst/enzyme	Green Flag	
catalyst/enzyme not recovered	Amber Flag	х

The Parr[®] 4596 reactor (25 mL internal volume) was charged with 2-methoxy-4propylphenol (0.50 g, 3.01 mmol), Nb₂O₅ (0.20 g, 0.75 mmol) and H₂O (10 mL). The reactor was closed properly, flushed with N₂ gas (3 × 10 bar) and filled with N₂ gas (65 bar). Subsequently, stirring (mechanical overhead stirring, 400 rpm) was started and the reactor and its contents were heated to 300 °C. After the temperature reached it desired value, stirring was continued for 3 h at this temperature. Subsequently the reactor was opened. The crude reaction mixture was extracted with EtOAc (1 x 15 mL, 2 x 5 mL). The combined organic fractions were centrifuged for 30 min at 4500 rpm. The organic solvent was subsequently evaporated under reduced pressure to afford a mixture of 4-propylcatechol (79%, 0.36 g, 2.37 mmol), catechol (6%, 19 mg, 0.17 mmol) and 2-methoxy-4-propylphenol (3%, 15 mg, 0.09 mmol) as an orange oil.

Generated waste

Supply remaining	Flag colour	Note element		H 1.00794				intil dep known i	letion o												He
5-50 years	Red Flag			3	4			ised on cu extra	rrent rate							5	6	7	8	2	10
50-500 years	Amber Flag	Nb		Li 6.941	80012182			5-50 50-100) years							B 10.811	C 12.0107 14	N 14.00674	0 15.9994	F 18.59840	Ne 20.1797 18
+500 years	Green Flag			Na 22.9897 19	Mg 24.3050 20	21	22	23	24	25	26	27	28	29	30	AI 26.98153 21	Si 28.0855	P 39.97376 33	S 32.066 34	Cl 35.4527 35	Ar 39.948 36
			•	K 39.0983	Ca 40.078	Sc 44.95591	Ti 47.867	V 50.9415	Cr 51.9961	Mn 54.93804	Fe 55.845	Co 58.93320	Ni 58.6934	Cu 63.546	Zn 65.39	Ga 09.323	Ge 72.61	As 74.92160	Se 78.95	Br 79.504	Kr 83.80
				37 Rb	Sr Sr	30 Y	40 Zr	41 Nb	42 Mo	43 Tc	Ru	Rh	46 Pd	47 Ag	دة Cd	in In	so Sn	ST Sb	se Te	я Т	54 Xe
				85.4678 55	87.52 56	88.9085 57	91.224 72	92.90638 73	95.94 74	(98) 75	101.07		106.42 78	107.8682	112.411 80	114.818 81	118.760 82	121.760 83	127.60 84	126.9044 85	131.29 86
				Cs 132.905	Ba 4 137.327	La *	Hf	Ta 180.9479	W	Re 186.207	Os	lr 192.217	Pt 195.078	Au 196.9665	Hg 200.59	TI 2013133	Pb 270.2	Bi 208.9804	Po (209)	At (210)	Rn
				87 Fr	⁸⁸ Ra	89 Ac ‡	104 Rf	105 Db	106 Sg	107 Bh	108 Hs	109 Mt	110 Ds	111 Rq	112 Uub	113 Uut	114 Uuq	115 Uup	116 LV	117 Uus	118 Uuo
				(223)	226.025	(227)	(257)	(260)	(263)	(262)	(265)	(266)	(271)	(272)	(285)	(284)	(289)	(288)	(292)		
								8 1	19	10	61	Q	6	64	65	66	67	68	69	70	71
					La	inthanio	des *	Ce :	Pr (Nd 145) :	Pm 150.36	Sm 151.964	Eu 157.25	Gd 158.9253	Tb 158.9253	Dy 162.50	Ho 164.9303	Er 167.26	Tm 168.9342	Yb 173.04	Lu 174.967
						Actinid	es‡	Th	Pa	U U	Np	94 Pu	95 Am	96 Cm	97 Bk	⁵⁸ Cf	99 Es	100 Fm	101 Md	102 No	103 Lr
							4	32.0381	131.0289	38.0289	(2.17)	(244)	(243)	(247)	(247)	(251)	(252)	(257)	(258)	(259)	(262)
nergy (First Pass)			Ti	ck			_												Tic	k	
Reaction run between 0 to 70°0	2	Green Flag							Rea	ction	run at	t reflu	іх		1	Red Fl	ag		Х		
Reaction run between -20 to 0 or 70 t	o 140°C	Amber Flag					Rea	ction	run 5'	°C or i	more	belov	v the s	solven	t _						
Reaction run below -20 or above 1	40°C	Red Flag	>	K							ng poi				G	reen F	lag				
Batch/flow			Ti	ck	• 1			rk Up											Lis		
Flow	Gr	een Flag		CK				кор		que	nchin	g							LIS	<u>.</u>	
Batch	Am	nber Flag	>	ĸ							ratior										
										centri	-				G	reen F	lag	Ce	ntrifu	gatio	n
							LOV	<i>w</i> tem		crysta ure di			vapor	ation/	,						
								sublin	natior	ı (< 14	l0 °C a	at atm	nosphe	eric							
							sol	vent e	exchar				nto aq	ueous	Ar	nber I	Flag		Extrac	tion	
							\vdash	ch	romat		lvent hy/io		hange								
							1		h	igh te	mper	ature	-			Red Fl	ag				
									multi	ple re	crysta	allisat	ion								
												List	t subs	tance	s and	H-coc	les	List	t subs	tance	es and
lealth & safety		od Elog		Amb	or Elec			<u> </u>	reen F	lag	_										
Highly explosive		ed Flag 01, H202, H203	H2		er Flag 220, H			If no r			er										
							flag	ged I		es pre	sent										

Chemical identified as Substances of Very High Concern by ChemSec which are utilised

Health & safety				List substances and H-codes	List substances and H-codes	List substances and H-codes
	Red Flag	Amber Flag	Green Flag			
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber			
			flagged H codes present			
Explosive thermal runaway	H230, H240, H250	H241	then green flag			
Τοχίς	H300, H310, H330	Н301, Н311, Н331,			4-Propylguaiacol: H311	H ₂ O EtOAc Nb ₂ O ₅
Long Term toxicity	H340, H350, H360, H370, H372	H341, H351, H361, H371, H373				2.5
Environmental implications	H400, H410, H411, H420	H401, H412				
Use of chemicals of e	environmental concern		List substances of ver	y high concern		

Red Flag

S1	35	

• Method C1: HBr.²

Yield, AE, RME, MI/PMI and OE

	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm ³)	Density (g ml ⁻¹)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm ³)	Density (g ml ⁻¹)	Mass
4-propylguaiacol	16,60	166,22	0,100			H ₂ O	1,80	H ₂ O	41,36	1,00	41,36	NaCl	15,54	Et ₂ O	299,61	0,71	213,
HBr	39,84	80,91	0,49									MgSO ₄	99,87				
Total	56,44	247,13			0,00		1,80				41,36		115,41				213
HO HO 100 mmol	HBr (aq. 115° Wo saturate Extracte M	eaction , 48%, 83 g) °C, 19 h ork-up d with NaCl ed with Et ₂ O gSO ₄ poration	→	H0 H0 949	%		Yield Conversion Selectivity AE RME PMI total PMI Reaction PMI Workup PMI Workup chemical PMI workup solvents PMI RRC	94,00 100,00 94,00 61,58 25,31 30,02 6,97 23,05 8,08 14,97 4,08	00,0 94,0 0E)		Prod Unreacted react	l limiting ant	Mass 14,287 mass 0,00 Mass 414,574	MW 152,19	Mol 0,09	9
							E factor		Fv	nerimenta	l. conied f	from Abu-O	mar et al	Biomacromo	lecules 20	15 16 202	5
ants (Eirst Dass)									Ex					, Biomacroma To Make			
ents (First Pass) Preferred solvents		water, EtOH, nBuOH ethylene gly		cOnBu, PhON ≥, MEK, MIBK			List solve		([hy	2.1. o - DHEO). D	Demeth DHE (16. ic acid. '	ylation 6 g, 0.1 m The reacti	of DHE nol) was		e Propy g of 48 gnetically	v lcatecho % aqueous 7 stirred a	l s t
ents (First Pass) Preferred solvents blematic solvents: (acceptable only if subst not offer advantages)	titution does	ethylene gly DMSO, cyclohexad THF, heptane, Me-c	none, DMPL	e, MEK, MIBK J, AcOH, Ac20	, AcOEt, sul O, Acetoniti ene, MTBE,	folane rile, AcOMe, cyclohexane,	List solve	nts below	([h 1 an di 0	2.1. o - DHEO). Dydrobrom 15 °C for nd extract ried over btained D	Demeth DHE (16. ic acid. ' 19 h, co red three MgSO ₄ DHE o-de	ylation 6 6 g, 0.1 m The reaction oled to am times with and concernethylate	of DHE nol) was ion mixtu bient ter th diethy entrated d produc	To Make added to 83 ure was ma mperature, s d ether. The using rotar ct (DHEO)	e Propy g of 48 gnetically aturated e organic y evapor (yield =	Vicatecho % aqueous y stirred a with NaCl c layer was ation. The 94%) was	l s t s s s s
Preferred solvents blematic solvents: (acceptable only if subst not offer advantages)		ethylene gly DMSO, cyclohexar THF, heptane, Me-c chlorob dioxane, pentane,	none, DMPU cyclohexane enzene, form	e, MEK, MIBK J, AcOH, Ac20 , toluene, xyl mic acid, pyri	, AcOEt, sul O, Acetoniti ene, MTBE, dine, Me-Th DME, DCM,	folane rile, AcOMe, cyclohexane, HF	List solve	nts below	([h 1 an di 0	2.1. o - DHEO). Dydrobrom 15 °C for nd extract ried over btained D	Demeth DHE (16. ic acid. ' 19 h, co red three MgSO ₄ DHE o-de	ylation 6 6 g, 0.1 m The reaction oled to am times with and concernethylate	of DHE nol) was ion mixtu bient ter th diethy entrated d produc	To Make added to 83 ure was may mperature, sa d ether. The using rotar	e Propy g of 48 gnetically aturated e organic y evapor (yield =	Vicatecho % aqueous y stirred a with NaCl a layer was ation. The 94%) was	l s t s s s s
Preferred solvents lematic solvents: (acceptable only if subst not offer advantages) ardous solvents: These solvents have signi and/or safety concerns.	ficant health	ethylene gly DMSO, cyclohexar THF, heptane, Me-c chlorob dioxane, pentane,	none, DMPl cyclohexane enzene, for TEA, diisop NMP, metho	e, MEK, MIBK J, AcOH, Ac20 , toluene, xyl mic acid, pyri ropyl ether, xyyethanol, h	, AcOEt, sul O, Acetoniti ene, MTBE, dine, Me-TI DME, DCM, exane	folane rile, AcOMe, cyclohexane, IF DMF, DMA,	List solve	nts below	([h 1 an di 0	2.1. o - DHEO). Dydrobrom 15 °C for nd extract ried over btained D	Demeth DHE (16. ic acid. ' 19 h, co red three MgSO ₄ DHE o-de	ylation 6 6 g, 0.1 m The reaction oled to am times with and concernethylate	of DHE nol) was ion mixtu bient ter th diethy entrated d produc	To Make added to 83 ure was ma mperature, s d ether. The using rotar ct (DHEO)	e Propy g of 48 gnetically aturated e organic y evapor (yield =	Vicatecho % aqueous y stirred a with NaCl a layer was ation. The 94%) was	l s t s s s
Preferred solvents plematic solvents: (acceptable only if subst not offer advantages) ardous solvents: These solvents have signi and/or safety concerns. hly hazardous solvents: The solvents which not to be used, even in screening	ficant health	ethylene gly DMSO, cyclohexau THF, heptane, Me-c chlorob dioxane, pentane,	col, acetone none, DMPL cyclohexane enzene, for TEA, dilsop MMP, metho Cl ₄ , chlorofo	e, MEK, MIBK J, AcOH, Ac20 , toluene, xyl mic acid, pyri ropyl ether, xyyethanol, h	, AcOEt, sul O, Acetoniti ene, MTBE, dine, Me-TI DME, DCM, exane	folane rile, AcOMe, cyclohexane, IF DMF, DMA,	List solve	nts below	([h 1 an di 0	2.1. o - DHEO). Dydrobrom 15 °C for nd extract ried over btained D	Demeth DHE (16. ic acid. ' 19 h, co red three MgSO ₄ DHE o-de	ylation 6 6 g, 0.1 m The reaction oled to am times with and concernethylate	of DHE nol) was ion mixtu bient ter th diethy entrated d produc	To Make added to 83 ure was ma mperature, s d ether. The using rotar ct (DHEO)	e Propy g of 48 gnetically aturated e organic y evapor (yield =	Vicatecho % aqueous y stirred a with NaCl a layer was ation. The 94%) was	l s t s s s s
Preferred solvents blematic solvents: (acceptable only if substinct offer advantages) ardous solvents: These solvents have signiand/or safety concerns. hly hazardous solvents: The solvents which	ficant health h are agreed	ethylene gly DMSO, cyclohexa THF, heptane, Me-c chlorob dioxane, pentane, Et ₂ O, Benzene, C	col, acetone cyclohexane enzene, for TEA, diisop NMP, methe Cl ₄ , chlorofo Green Flag	e, MEK, MIBK J, AcOH, Ac2u , toluene, xyl mic acid, pyri ropyl ether, oxyethanol, h orm, DCE, nitr	, AcOEt, sul O, Acetoniti ene, MTBE, dine, Me-TI DME, DCM, exane	folane rile, AcOMe, cyclohexane, HF DMF, DMA, CS ₂ , HMPA	List solve	0 0 ,0	([h 1 an di 0	2.1. O- DHEO). D ydrobrom 15 °C for nd extract ried over btained D sed as a d	Demeth DHE (16. ic acid. ' 19 h, co red three MgSO ₄ DHE o-de	ylation 6 6 g, 0.1 m The reaction oled to am times with and concernethylate	of DHE nol) was ion mixtu bient ter th diethy entrated d produc	To Make added to 83 ure was ma mperature, s d ether. The using rotar ct (DHEO)	e Propy g of 48 gnetically aturated e organic y evapor (yield =	Vicatecho % aqueous y stirred a with NaCl a layer was ation. The 94%) was	l s t s s s
Preferred solvents plematic solvents: (acceptable only if subst not offer advantages) ardous solvents: These solvents have signi and/or safety concerns. hly hazardous solvents: The solvents which not to be used, even in screening lyst/enzyme (First Pass)	ficant health h are agreed ce without an	ethylene gly DMSO, cyclohexa THF, heptane, Me-c chlorob dioxane, pentane, Et ₂ O, Benzene, C y catalyst/reagents.	col, acetone none, DMPU yclohexane enzene, forr TEA, diisop NMP, metho Cl ₄ , chlorofo Green	e, MEK, MIBK J, AcOH, Ac2u , toluene, xyl mic acid, pyri ropyl ether, oxyethanol, h orm, DCE, nitr	, AcOEt, sul O, Acetoniti ene, MTBE, dine, Me-TI DME, DCM, exane	folane rile, AcOMe, cyclohexane, IF DMF, DMA, CS ₂ , HMPA Facile r	List solve	0 0 0 0 t/enzyme	([hy 1 dı ol u:	2.1. O- DHEO). D ydrobrom 15 °C for nd extract ried over btained D sed as a d	Demeth DHE (16. ic acid. ' 19 h, co red three MgSO ₄ DHE o-de	ylation 6 6 g, 0.1 m The reaction oled to am times with and concernethylate	of DHE nol) was ion mixtu bient ter th diethy entrated d produc	To Make added to 83 ure was ma mperature, s d ether. The using rotar ct (DHEO)	e Propy g of 48 gnetically aturated e organic y evapor (yield =	Vicatecho % aqueous y stirred a with NaCl a layer was ation. The 94%) was	l s t s s s

Supply remaining	Flag colour	Note element		1.00	H 2794				pletion o reserve												H
5-50 years	Red Flag			3	4		(b		urrent rate action)	of						5 B	°c	2 N	8 0	° F	10 N
50-500 years	Amber Flag			6.94 11	11 9.01218 12			50-10	years 0 years							30.813 13	12.0107	14.00674	15.9994 16	18.99840 17	20.17
+500 years	Green Flag	х		22.90 19	18977 24.3050	21	22	100-50	0 years	25	26	77	28	29	32	Al 26.98153	28.0855	P 39.97376	S 32.056	Cl 35.4527 25	A 39.94
·	, j			39.07	к Са	Sc	Ti 47.857	V	Cr 51.9961	Mn	Fe 55.845	Co	Ni	Cu	Zn	Ga	Ge	As	Se 78.96	Br 79,504	K 83.80
				37	Rb Sr	39 ¥	40 Zr	41 Nb	42 Mo	43 Tc	44 Ru	45 Rh	46 Pd	47 Ag	44 Cd	49 In	50 Sn	51 51 5b	52 Te	53	54 X
				85.0	6578 87.62	88.9085 57	91.224	92.50638	95.94	(98)	101.07	102.9055	106.42	107.8682	112.411	114.818	118.760 82	121.760	127.60	126.9044	131.
				c	Cs Ba	La *		Та	w	Re	Os	lr.	Pt	Au	Hg	TI	Pb	Bi	Ро	At	R
				132.	88	89	104	105 Db	106	186.207 107 Bh	108	109 109 Mt	110 Ds	111	112 Uub	113	114	115	(209)	(210)	118
				(223		Ac 1 (227)	(257)	(260)	Sg (263)	(262)	Hs (265)	(266)	(271)	Rq (272)	(285)	Uut (284)	Uuq (289)	Uup (288)	Lv (292)	Uus	U
								58	59	60	61	ର	63	64	65	66	67	68	69	70	71
					1	anthan	ides *	Ce	Pr 144.24	Nd (145) :	Pm	Sm 151.964	Eu 157.25	Gd 158.9253	Tb 158.9253	Dy 162.50	Ho 164.9303	Er 167.26	Tm 168.9342	Yb 173.04	L1 174.9
						Actini		⁵⁰ Th	91 Pa	° I	⁹³ Np	94 Pu	ss Am	⁹⁶ Cm	97 Bk	58 Cf	20 Es	100 Fm	101 Md	102 No	103 L
							L	232.0381	231.0289	238.0289	(237)	(244)	(243)	(247)	(247)	(251)	(252)	(257)	(258)	(259)	(262)
			Т	lick	_		_												Tic	ck	
nergy (First Pass) Reaction run between 0 to 70°C	:	Green Flag	Ť	Tick			Γ		Rea	ction	run a	t reflu	ix			Red F	lag		Tio X		
		Green Flag Amber Flag		rick X			Rea	iction	Rea					solver	.+		<u> </u>				
Reaction run between 0 to 70°C	o 140°C			-			Rea	action			more	below		solver	.+	Red F reen I	<u> </u>				
Reaction run between 0 to 70°C Reaction run between -20 to 0 or 70 to	o 140°C	Amber Flag		-				action ork Up	run 5	°C or i	more	below		solver	.+		<u> </u>				
Reaction run between 0 to 70°C Reaction run between -20 to 0 or 70 to Reaction run below -20 or above 14 Reaction run below -20 or above 14 Reacth/flow	o 140°C 40°C Gr	Amber Flag Red Flag reen Flag	T	X					run 5	°C or i boilii	more ng po nchir	below int		solver	.+		<u> </u>		X		
Reaction run between 0 to 70°C Reaction run between -20 to 0 or 70 to Reaction run below -20 or above 14 Reaction run below -20 or above 14	o 140°C 40°C Gr	Amber Flag Red Flag	T	x					run 5	°C or i boilii que filt	more ng po nchir ratior	below int ng		solver	^{nt} G	reen l	Flag		X Lis	st	
Reaction run between 0 to 70°C Reaction run between -20 to 0 or 70 to Reaction run below -20 or above 14 Reaction run below -20 or above 14 Reacth/flow	o 140°C 40°C Gr	Amber Flag Red Flag reen Flag	T	X					run 5	°C or i boilii	more ng po nchir ratior ifugat	below int ng n		solver	^{nt} G		Flag		X	st	
Reaction run between 0 to 70°C Reaction run between -20 to 0 or 70 to Reaction run below -20 or above 14 Reaction run below -20 or above 14 Reacth/flow	o 140°C 40°C Gr	Amber Flag Red Flag reen Flag	T	X			Wo	w tem	run 5	°C or i boilin que filt centri crysta ure di	nore ng po nchir ratior ifugat allisat	below int ng tion tion	v the	ration,	nt G	reen l	Flag		X Lis	st	
Reaction run between 0 to 70°C Reaction run between -20 to 0 or 70 to Reaction run below -20 or above 14 Reaction run below -20 or above 14 Reacth/flow	o 140°C 40°C Gr	Amber Flag Red Flag reen Flag	T	X			Lo	w tem	run 5	°C or r boilin que filt centri crysta cure di cure di cure di	more ng po nchin ratior ifugat allisat stillat	below int ng tion tion/e at atm	v the	ration, eric	G G	reen l	Flag		Lis Filtra	st	
Reaction run between 0 to 70°C Reaction run between -20 to 0 or 70 to Reaction run below -20 or above 14 atch/flow	o 140°C 40°C Gr	Amber Flag Red Flag reen Flag	T	X			Lo	w tem	run 5	°C or i boilin que filt centri crysta cure di <u>n (< 14</u> nge, q	more ng po nchin ratior ifugat allisat stillat	below int n tion tion/e at atm hing in	v the	ration, eric	G G	reen l	Flag		X Lis	st	

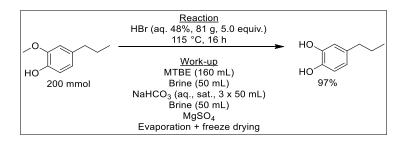
Health & safety				List substances and H-codes	List substances and H-codes	List substances and H-codes
	Red Flag	Amber Flag	Green Flag			
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present		Et ₂ O: H224	
Explosive thermal runaway	H230, H240, H250	H241	then green flag			
Τοχίς	H300, H310, H330	H301, H311, H331,			4-propylguaiacol: H311 HBr: H331	H ₂ O NaCl
Long Term toxicity	H340, H350, H360, H370, H372	H341, H351, H361, H371, H373				
Environmental implications	H400, H410, H411, H420	H401, H412				

_	Use of chemicals of environmental concern	List substances of very high concern	
	Chemical identified as Substances of Very High Concern by ChemSec which are utilised	Red Flag	

• Method C2: HBr.¹³

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction	Volume (cm ³)	Density	Mass (g)	-	Mass (g)	Workup solvent	Volume	Density	Mass (g)
								solvent		(g ml ⁻¹)		chemical			(cm³)	(g ml ⁻¹)	
4-propylguaiacol	33,24	166,22	0,200			H ₂ O	3,600	H ₂ O	84,15	1,00	84,15	NaCl	18,00	MTBE	160,00	0,74	118,40
HBr	81,00	80,91	1,001									NaHCO ₃	15,00	H ₂ O (brine)	50,00	1,00	50,00
												NaCl	18,00	H ₂ O (NaHCO ₃)	150,00	1,00	150,00
														H ₂ O (brine)	50,00	1,00	50,00
	ļ																
Total	114,24	247,13			0,00		3,60				84,15		51,00				368,40



	Flag
Yield	97,25 🔵
Conversion	100,00 🔵
	97,25 🔵
AE	61,58
RME	25,91 OE
PMI total	20,99
PMI Reaction	6,82
PMI Workup	14,17
PMI Workup	
chemical	1,72
PMI workup	
solvents	12,45
PMI RRC	3,98
E factor	19.99

97,2

100,0

97,2

Mass MW Product 29,60 152,19	Mol
Broduct 20.60 152.10	
29,00 152,19	0,19
mass	
Unreacted limiting reactant 0,00	

	Mass
Generated waste	591,793

Solvents (First Pass)		List solvents below
Preferred solvents	water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane	H ₂ O
Problematic solvents: (acceptable only if substitution does not offer advantages)	DMSO, cyclohexanone, DMPU, AcOH, Ac2O, Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene, MTBE, cyclohexane , chlorobenzene, formic acid, pyridine, Me-THF	МТВЕ
Hazardous solvents: These solvents have significant health and/or safety concerns.	dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane	
Highly hazardous solvents: The solvents which are agreed not to be used, even in screening	Et_2O , Benzene, CCI_4 , chloroform, DCE, nitromethane, CS_2 , HMPA	

Experimental: copied from Maes et al., ChemSusChem 2019, 12, 3103.

A 250 mL roundbottom flask, equipped with magnetic stirring bar and reflux condenser, was charged with 2-methoxy-4-propylphenol (1) (32.2 g, 200.0 mmol, 1 equiv) and 48% aq. HBr (31.0 g, 1000.0 mmol, 5 equiv). The obtained mixture was stirred for 16 h at 115 °C. After oH cooling down to room temperature, it was diluted with 160 ml MTBE (2-methoxy-2methylpropane), washed with 50 ml brine, 3x50 ml saturated NaHCO₃ solution, and again with 50 ml brine. The organic layer was collected and dried over MgSO₄, filtered and concentrated under reduced pressure. Subsequently, the residue was freeze dried in order to remove the last traces of solvent and to obtain pure 4-propylcatechol (2) as an offwhite solid (29.6 g, 97%). The obtained spectroscopic data (NMR in CDCl₃) of the product are in accordance with literature.^[5]

Catalyst/enzyme (First Pass)						
Catalyst or enzyme used, or reaction takes place without any catalyst/reagents.	Green					
catalyst of enzyme used, of reaction takes place without any catalyst/reagents.	Flag					
Use of stoichiometric quantities of reagents	Amber	v				
ose of storemometrie quantities of reagents	Flag	~				
Use of reagents in excess	Red Flag					

		Tick
Facile recovery of catalyst/enzyme	Green Flag	
catalyst/enzyme not recovered	Amber Flag	

Supply remaining	Flag colour	Note element			H 0794				pletion o reserve												H 4.002
5-50 years	Red Flag			3	4		(b	ased on co extra	urrent rate action)	of						5 B	°c	7	8 0	° F	10 N
50-500 years	Amber Flag			6.9 11					years 0 years							10.811 13	12.0107	N 14.00674 15	15.9994	18.99840	20.17
+500 years	Green Flag	х		22	Na Mi 58977 24.305	,		100-50	00 years	_						Al 26.98153	Si 28.0855	P 39.97376	S 32.066	Cl 35.4527	A 39.94
+500 years	Green nag	^			к Са		22 Ti	23 V	Cr	25 Mn	²⁶ Fe	Co	28 Ni	29 Cu	» Zn	Ga	Ge	an As	Se	as Br	³⁶
				37		39	47.857	50.9415 41	51.9961 42	54.93804 43	55.845 44	58.93320 45	58.6934 46	63.546 47	65.39 48				78.96 52	79.504 53	83.80 54
				85	Rb Sr .6578 87.62	¥ 88.908	2r 91.224	Nb 92.90638	Mo 95.94	Tc (98)	Ru 101.07	Rh 102.9055	Pd 106.42	Ag 107.8682	Cd	114.010	Sn 118.760	Sb 121.760	Te 127.60	126.9044	X 131.3
					Cs Ba			Ta	w	Re	⁷⁰ Os	" Ir	Pt	Au	Hg	TI	^{≈2} Pb	Bi	Po	At	R
				87	2.9054 137.32	89	104	180.947 105	183.84	186.207 107	190.23 108	192.217 109	195.078 110	196.9665 111	200.59	204.3833	270.2	208,5804	(209)	(210)	[222] 118
				(22	Fr Ra 3) 226.03		Rf (257)	Db (260)	Sg (263)	Bh (262)	Hs (265)	Mt (266)	Ds (271)	Rq (272)	Uub (285)	Uut (284)	Uuq (289)	Uup (288)	LV (292)	Uus	Uu
								58	59	60	61	62	6	64	65	66	67	68	69	70	71
						Lantha	nides *	Ce	Pr	Nd (145)	Pm	Sm	Eu	Gd	Tb 158.9253	Dy	Ho	Er 167.26	Tm	Yb	174.9
						Actin	ides ‡	_	91 Pa	° u	93 Np	94 Pu	so Am	⁹⁶ Cm	97 Bk	58 Cf	90 Es	100 Fm	101 Md	102 No	103 L
								232.0381	231.0289	238.0289	(237)	(244)	(243)	(247)	(247)	(251)	(252)	(257)	(258)	(259)	(262)
nergy (First Pass)			Т	Tick			_												Tic	ck	
Reaction run between 0 to 70°C		Green Flag																			
		Green nag							Rea	ction	run a	t reflu	х		I	Red F	lag		Х		
Reaction run between -20 to 0 or 70 to	140°C	Amber Flag		x			Rea	iction	Rea					solver	.+				×		
Reaction run between -20 to 0 or 70 to Reaction run below -20 or above 14		5		x			Rea	iction			more	belov		solver	.+	Red F			×		
Reaction run below -20 or above 14		Amber Flag		X					run 5	°C or	more	belov		solver	.+				Lis		
Reaction run below -20 or above 14 atch/flow	0°C Gr	Amber Flag Red Flag een Flag	Т	Tick				oction	run 5	°C or boilin	more ng po	belov int		solver	.+						
	0°C Gr	Amber Flag Red Flag	Т						run 5	°C or boiling	more ng po enchir ratio	belov int ng		solver	^{it} Gi	reen l	Flag		Lis	st	
Reaction run below -20 or above 14 atch/flow	0°C Gr	Amber Flag Red Flag een Flag	Т	Tick					run 5	°C or boilin	more ng po enchir ratioi	belov int ng n		solver	^{it} Gi		Flag		Lis		
Reaction run below -20 or above 14 atch/flow	0°C Gr	Amber Flag Red Flag een Flag	Т	Tick			Wo	rk Up w ten	run 5	°C or boili que filt centr crysta ure di	more ng po enchir ration ifugat allisat	belov int ng tion tion/e	v the :	ation,	Gi	reen l	Flag		Lis	st	
Reaction run below -20 or above 14 atch/flow ow	0°C Gr	Amber Flag Red Flag een Flag	Т	Tick			Wc Lo	w ten	run 5	°C or i boilin que filt centr crysta cure di n (< 14	more ng po enchir ration ifugat allisat istillat	belov int ng tion tion/e at atm	v the : vapor	ation, eric	Gi Gi	reen l	Flag	F	Lis Evapor reeze	st ration dryinį	
Reaction run below -20 or above 14 atch/flow ow	0°C Gr	Amber Flag Red Flag een Flag	Т	Tick			Wc Lo	w ten	run 5	°C or film boilin que filt centr crysta crysta ure di <u>n (< 14</u> nge, q	more ng po enchir ration ifugat allisat istillat	belov int ng tion tion/e at atm hing ir	v the : vapor	ation, eric	Gi Gi	reen l	Flag	F	Lis	st ration dryinį	
Reaction run below -20 or above 14 atch/flow low	0°C Gr	Amber Flag Red Flag een Flag	Т	Tick			Wc Lo	w ten sublir	run 5 pperat matior exchai	°C or f boilin que filt centr crysta ure di n (< 14 nge, q sc tograp	more ng po ifugat allisat istilla istilla uenc <u>lvent</u>	belov int n tion tion/e at atm hing in	v the : vapor nosph	ation, eric ueou:	GI GI GI GI	reen l	Flag Flag Flag	F	Lis Evapor reeze	st ration dryinį	

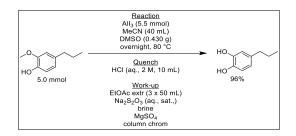
Health & safety				List substances and H-codes	List substances and H-codes	List substances and H-codes
	Red Flag	Amber Flag	Green Flag			
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present			
Explosive thermal runaway	H230, H240, H250	H241	then green flag			H₂O
Toxic	H300, H310, H330	H301, H311, H331,			4-Propylguaiacol: H311 HBr: H331	MTBE NaCl
Long Term toxicity	H340, H350, H360, H370, H372	H341, H351, H361, H371, H373				NaHCO ₃
Environmental implications	H400, H410, H411, H420	H401, H412				

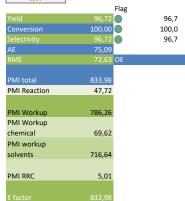
Use of chemicals of environmental concern		List substances of very high concern
Chemical identified as Substances of Very High Concern by ChemSec which are utilised	Red Flag	

• Method D: All₃ + DMSO.¹⁴

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction	Volume (cm ³)	Density	Mass (g)	Work up	Mass (g)	Workup solvent	Volume	Density	Mass (g)
								solvent		(g ml ⁻¹)		chemical			(cm³)	(g ml ⁻¹)	
4-propylguaiacol	0,83	166,22	0,005			All ₃	2,24	MeCN	40,00	0,79	31,44	HCI	0,55	H ₂ O	10,00	1,00	10,00
HCI	0,18	36,46	0,005			DMSO	0,43					$Na_2S_2O_3$	2,09	EtOAc	150,00	0,90	134,55
												NaCl	3,60	H ₂ O (Na ₂ S ₂ O ₃)	10,00	1,00	10,00
												MgSO ₄	5,00	H ₂ O (NaCl)	10,00	1,00	10,00
												SiO ₂	40,00	Heptane	400,00	0,68	273,20
														EtOAc	100,00	0,90	89,70
Total	1,01	202,68			0,00		2,67				31,44		51,24				527,45





	Mass	MW	Mol	
Product	0,736	152,19	0,00	
	mass			
Inreacted limiting	0.00			

	Mass	
Generated waste	613,076	ĺ

Experimental: copied from Tian *et al.*, *Synthesis* **2019**, *51*, 704. Cleavage of Catechol Monoalkyl Ethers by Aluminum Triiodide– Dimethyl Sulfoxide; General Procedure

To a suspension of All₃ (5.5 mmol, 1.1 equiv) in MeCN was added anhyd DMSO (0.430 g, 5.5 mmol, 1.1 equiv). After stirring for 0.5 h at 80 °C, the selected substrate (5 mmol) was added in one portion. The mixture was stirred overnight (18 h) at that temperature before quenching with aq 2 M HCl (10 mL). After extraction with EtOAc (3 × 50 mL), the organic phases were combined, washed with sat. aq Na₅2₀₃ and brine, and dried (MgSO₄). The solvents were removed on a rotary evaporator, and the residue was purified by column chromatography to give the relevant catechol or phenol.

4-Propylcatechol (7d)

[CAS Reg. No. 2525-02-2]

Yield: 0.736 g (96%); off-white solid; mp 57.5–58.5 °C (Lit.⁴⁴ mp 59–60 °C); R_f = 0.27 (PE/EtOAc 3:1).

¹H NMR (400 MHz, CDCl₃): δ = 6.76 (d, *J* = 8.0 Hz, 1 H), 6.69 (d, *J* = 1.6 Hz, 1 H), 6.60 (dd, *J*₁ = 8.0 Hz, *I*₂ = 1.6 Hz, 1 H), 5.42 (br s, 2 H), 2.45 (t, *J* = 7.6 Hz, 2 H), 1.56 (h, *J* = 7.6 Hz, 2 H), 0.90 (t, *J* = 7.6 Hz, 3 H). ¹³C NMR (100 MHz, CDCl₃): δ = 143.19, 141.12, 136.20, 121.01, 115.67, 115.34, 37.34, 24.70, 13.81.

Solvents (First Pass)		List solvents below
Preferred solvents	water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane	H ₂ O EtOAc
Problematic solvents: (acceptable only if substitution does not offer advantages)	DMSO, cyclohexanone, DMPU, AcOH, Ac2O, Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene, MTBE, cyclohexane , chlorobenzene, formic acid, pyridine, Me-THF	DMSO MeCN Heptane
Hazardous solvents: These solvents have significant health and/or safety concerns.	dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane	
Highly hazardous solvents: The solvents which are agreed not to be used, even in screening	Et_2O , Benzene, CCl_4 , chloroform, DCE, nitromethane, CS_2 , HMPA	

Catalyst/enzyme (First Pass)		Tick
Catalyst or enzyme used, or reaction takes place without any catalyst/reagents.	Green	
catalyst of enzyme used, of reaction takes place without any catalyst/reagents.	Flag	
Use of stoichiometric quantities of reagents	Amber	х
ose of stolchiometric quantities of reagents	Flag	^
Use of reagents in excess	Red Flag	

		Tick
Facile recovery of catalyst/enzyme	Green Flag	
catalyst/enzyme not recovered	Amber Flag	

itical elements Supply remaining	Flag colour	Note element		H 1.00794			know	epletion reserve	s											_
5-50 years	Red Flag		1	° Li	4 Be		ext	current rat raction)	of						5 B	°c	2 N	°	°F	
50-500 years	Amber Flag	I, Al, S		6.941 11 Na	9.012182 12 Mg		50-1	0 years 00 years 600 years							10.811 13 Al	12.0107 14 Si	14.00674 15 P	15.9994 16 S	18.59840 17 CI	
+500 years	Green Flag			22.58977 19 K	24.3050 20 22 Ca	Sc 22	i 23	24 Cr	25 Mn	26 Fe	27 Co	28 Ni	29 Cu	» Zn	26.98153 31 Ga	28.0855 32 Ge	392.97376 33 As	32.066 34 Se	35.4527 35 Br	-
			-	39.0983 37 Rb	40.078 44	4.95591 47.8 19 40 Y	41	42	54.93834 43	55.845 44	58.93320 45	46	63.546 47	65.39 48 Cd		72.61 50 Sn	74.92160 51	78.96 52	79.504 53	
				RD 85.4678 55	Sr	Y 2 8.9085 91.2 67 72			Tc (98) 75	Ru 101.07	Rh 102.9055 77	Pd 106.42	Ag 107.8682 79	Cd 112411 80	In 114.015	5n 118.760	Sb 121.760	Te 127.60 84	226.9044 85	-
				Cs 132.9054		La* 1	If Ta	W 181.84	Re 186.207	Os	I r 192.217	Pt 195.078	Au 196.9665	Hg 200.59	TI 204.3133	Pb 270.2	Bi 208.5854	Po (209)	At (210)	
				87 Fr	Ra	19 104 Ac‡ H	f Db		107 Bh	108 Hs	109 Mt	110 Ds	111 Rq	112 Uub		114 Uuq		116 LV	Uus	Ī
				(223)	226.025 (2	227) (257	(260)	(263)	(262)	(265)	(266)	(271)	(272)	(285)	(284)	(289)	(288)	(292)	1	
					Lant	thanides '	58 Ce	59 Pr 144.24	60 Nd (145)	61 6 Pm 150.36	Sm	Eu	Gd	65 Tb	66 Dy	67 Ho	Er	oo Tm	Yb	
																		168,9342		
					Ac	ctinides ‡	³⁰ Th	91 Pa	92 U	_	ы 94 Ри	95 Am	∞ Cm	97 Bk	58 Cf	99 Es	167.26 100 Fm	168.9342 101 Md	173.04 102 NO	
					Ac	ctinides ‡	90	91	92	⁹³ 1 Np		157.25 95 Am (243)	96	97	58	99				
			Tick		Ac	ctinides ‡	³⁰ Th	91 Pa	92	⁹³ 1 Np	Pu		∞ Cm	97 Bk	58 Cf	99 Es	Fm	Md (258)	No	_
nergy (First Pass) Reaction run between 0 to 7)°C	Green Flag	Tick		Ac	ctinides ‡	90 Th 232.0381	91 Pa	92 U 238.0289	93 1 Np (237) (Pu		96 Cm (247)	97 Bk	58 Cf (251)	99 Es	Fm (257)	Md (258)	No	-
		Green Flag Amber Flag	Tick X		F	eactior	so Th 232.0381 Read	91 Pa 231.0289	u u matr	<mark>Νρ</mark> ματη	Pu [244]	[243]	96 Cm (247) Re	97 Bk (247) ed Fla	56 Cf (251)	99 Es	Fm (257)	Md (258)	No	
Reaction run between 0 to 7) to 140°C				F		so Th 232.0381 Read	91 Pa 231.0289	un at r	⁹³ Np (227) reflux elow t	Pu [244]	[243]	96 Cm (247) Re	97 Bk (247)	56 Cf (251)	99 Es	Fm (257)	Md (258)	No	
Reaction run between 0 to 7 Reaction run between -20 to 0 or 7 Reaction run below -20 or above	0 to 140°C 140°C	Amber Flag Red Flag			Re		Read	Pa Pa 231.0289	un at r	⁹³ Np (227) reflux elow t	Pu [244]	[243]	96 Cm (247) Re	97 Bk (247) ed Fla	56 Cf (251)	99 Es	Fm (257)	Md (258)	No	_
Reaction run between -20 to 0 or 7 Reaction run below -20 or above Batch/flow Iow	0 to 140°C 140°C Gr	Amber Flag Red Flag reen Flag	X		Re	eactior	Read	Pa Pa 221.0289	un at r ore b g poin	⁹³ Np (227) reflux elow t	Pu [244]	[243]	96 Cm (247) Re	97 Bk (247) ed Fla	56 Cf (251)	99 Es	Fm ₍₂₅₇₎	Md (258)	No	
Reaction run between 0 to 7 Reaction run between -20 to 0 or 7 Reaction run below -20 or above atch/flow	0 to 140°C 140°C Gr	Amber Flag Red Flag	×		Re	eactior /ork Up	Rear run 5	Pa Pa 2112000 C or m boiling quen filtr: centrif crystal	un at r oore b g poin ching ation ugatio lisatio tillatic	n n n n n/eva	Pu (244)	blvent	⁹⁶ Cm (247) Re Gre	97 Bk (247) ed Fla	ag	22 Es (252)	Fm ₍₂₅₇₎	Md (258)	No	
Reaction run between 0 to 7 Reaction run between -20 to 0 or 7 Reaction run below -20 or above atch/flow	0 to 140°C 140°C Gr	Amber Flag Red Flag reen Flag	X		Re	eactior /ork Up	Read run 5 ⁴	Pa Pa 2122200 C or m boiling filtra ccentrif crystal ure dis (< 140 pge, qu	un at r oore b g poin ching ation ugatio lisatio tillatic	n n n n/eva atmos	Pu put	pai)	⁹⁶ Cm (μη) Gre	ed Fla	est of the second secon	99 Es (757)	Fm psyl Tick List	<u>Md</u> (254)	No	

a & safety				List substances and H-codes	List substances and H-codes	List substances and H-code
-	Red Flag	Amber Flag	Green Flag			
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber			
			flagged H codes present			
Explosive thermal runaway	H230, H240, H250	H241	then green flag			All ₃
Toxic	H300, H310, H330	H301, H311, H331,				CH ₃ CN
					4-propylguaiacol: H311	DMSO
						HCI
Long Term toxicity	H340, H350, H360, H370, H372	H341, H351, H361,				Na ₂ S ₂ O ₃
		H371, H373				
Environmental implications	H400, H410, H411, H420	H401, H412		Heptane: H410		

Use of chemicals of environmental concern		List substances of very high concern
Chemical identified as Substances of Very High Concern by ChemSec which are utilised	Red Flag	

Method E: SIBX.¹⁵

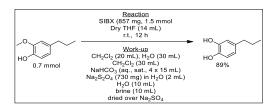
Yield, AE, RME, MI/PMI and OE

Solvents (First Pass)

Preferred solvents

Use of reagents in excess

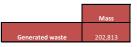
Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm ³)	Density (g ml ⁻¹)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm ³)	Density (g ml ⁻¹)	Mass (g)
4-propylguaiacol	0,116	166,22	7,00E-04			SIBX	0,857	THF	14,00	0,89	12,40	NaHCO ₃	6,00	CH ₂ Cl ₂	50,00	1,33	66,50
												$Na_2S_2O_4$	0,73	H ₂ O	30,00	1,00	30,00
												NaCl	3,60	H ₂ O (NaHCO ₃)	60,00	1,00	60,00
												Na ₂ SO ₄	0,70	H ₂ O (Na ₂ S ₂ O ₄)	2,00	1,00	2,00
														H ₂ O	10,00	1,00	10,00
														H ₂ O (brine)	10,00	1,00	10,00
Total	0,12	166,22			0,00		0,86		51a -		12,40		11,03				178,50



	0,86			
			Flag	
				89,0
		100,00		100,0
				89,0
	AE	91,56		
			OE	
	PMI total	2140,05		
	PMI Reaction	141,09		
	PMI Workup	1998,96		
	PMI Workup			
	chemical	116,33		
	PMI workup			
	solvents	1882,63		
	PMI RRC	10,27		
	E factor			
	List solvent	s below		
OH,				

но

	Mass	MW	Mol
Product	0,095	152,19	6,23E-04
	mass		
Unreacted limiting			
reactant	0,00		



Experimental: copied from Quideau et al., Org. Lett. 2003, 5, 2903.

Procedure D. To a stirred suspension of SIBX (857 mg, 1.5 mmol) in dry THF (14 mL, *ca.* 0.05 M) was added 2-methoxyphenol (0.7 mmol). After stirring in the dark at room temperature for 16 h, the white suspension was filtered out from the resulting red solution. The filter cake was washed with CH₂Cl₂ (20 mL) and the combined filtrate and washings were poured into water (30 mL). After separation, the aqueous layer was further extracted with CH₂Cl₂ (30 mL). The combined organic layers were washed with saturated aqueous NaHCO₃ (4 × 15 mL) and treated with an aqueous solution (2 mL) of Na₂S₂O₄ (730 mg, 4.2 mmol) for 10 min with vigorous stirring under nitrogen in the dark. The resulting yellow solution was washed with water (10 mL), brine (10 mL), dried over Na₂SO₄, filtered and evaporated to dryness.

4-Propyl-benzene-1,2-diol (36). Oxidation of 2-methoxy-4-propylphenol (**35**) was performed according to the procedure D. The reaction was run for 12 h, after which time it was processed as indicated to furnish **36** as a viscous orange solid (89%): IR (NaCl) 3364 cm⁻¹; ¹H NMR (CDCl₃, 250 MHz) δ 0.91 (t, *J* = 7.3 Hz, 3H), 1.50-1.65 (m, 2H), 2.46 (t, *J* = 7.3 Hz, 2H), 5.43 (s, 2H), 6.70 (m, 3H); ¹³C NMR (CDCl₃, 75.5 MHz) δ 143.3, 141.2, 136.0, 120.8, 115.6, 115.2, 37.3, 24.6, 13.7; EIMS *m/z* (rel intensity) 152 (M⁺, 26), 123 (100), 77 (12).

	etriviene giv	coi, acetoine	, IVIER, IVIIBR	, ACOLI, SU	liolarie	1120
Problematic solvents: (acceptable only if substitution does not offer advantages)	DMSO, cyclohexar THF, heptane, Me-c chlorobe	THF				
Hazardous solvents: These solvents have significant health and/or safety concerns.	dioxane, pentane,		ropyl ether, oxyethanol, h		, DMF, DMA,	CH ₂ Cl ₂
Highly hazardous solvents: The solvents which are agreed not to be used, even in screening	Et ₂ O, Benzene, Co	Cl ₄ , chlorofo	orm, DCE, nitr	omethane,	CS₂, HMPA	
Catalyst/enzyme (First Pass)			Tick			
Catalyst or enzyme used, or reaction takes place without any	<pre>/ catalyst/reagents.</pre>	Green Flag			Facile re	ecovery of catalyst/enzyme
Use of stoichiometric quantities of reagent	s	Amber Flag			cataly	st/enzyme not recovered

water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, Bn

ne glycol acetone MEK MIRK AcOEt sulfola

Tick

Green Flag

Amber Flag

Supply remaining	Flag colour	Note element		H 20754			pletion of reserve											ŀ
5-50 years	Red Flag		3	4		(based on a	current rate raction)						5	6	7	8	9	10
50-500 years	Amber Flag	I, S		Li Be 9.012182 12		5-50	0 years 00 years						B 10.811 13	C 12.0107 14	N 14.00674 15	0 15.9994	F 18.59840 17	20.1 18
+500 years	Green Flag			Na Mg 58977 24.3050 20	21 2		00 years	25	6 27	28	29	50	Al 26.98153 31	Si 28.0855 32	P 39.97376 23	S 32.066 34	Cl 35.4527 35	39.9 36
				K Ca	Sc 44,00001 4	Ti V	Cr	Mn	Fe (Ni Ci	J Zn	Ga	Ge	As	Se 78.95	Br 79.904	83.86
			37	Rb Sr	30 4	Zr Nb	42 Mo	43 Tc	e e Ru F	Rh ⁴⁶	Pd A	t Cd	40 In	so Sn	51 Sb	⁵² Te	53	54 X
				4678 87.62	88.9085 9	1.224 92.9063	95.94	(98)		2.9055 10	6.42 107.8	112.411	114.818	118,760	121.760	127.60	126.9044	131.3
				Cs Ba	La *	Hf Ta	w	Re	Os	lr	Pt A	Hg	TI	Pb	Bi	Po	At	R
			87	2.9054 137.327		78.49 180.943 14 105	106		90.23 192 08 109			200.59	204.3833	270.2	208.9804	(209) 116	(210) 117	(222) 118
				Fr Ra 226.025	Ac \$	Rf Db (260)	Sg (263)	Bh (262) (Hs /		Ds Re (272)	1 Uub (285)	Uut (284)	Uuq (289)	Uup (288)	LV (292)	Uus	U
				L	anthanide		Pr		m Sn			ть	Dy	Но	Er	Tm	Yb	L
						140.9077 50	144.24 91	(145) 150 92 93	36 151.96 94	64 157.3 95	5 158.925 96	3 158.9253 97	162.50 58	164.9303 99	167.26 100	168.9342 101	173.04 102	174.9 103
					Actinides	Th 232.0381	Pa 231.0289	U N	1p Pu (244)	J A		Bk (247)	Cf (251)	Es (252)	Fm (257)	Md (258)	No (259)	L (262)
																		-
nergy (First Pass)			Tick	_												Tid	-k	
Energy (First Pass) Reaction run between 0 to 70°C			Tick		1											Tie	ck	
e nergy (First Pass) Reaction run between 0 to 70°C	:	Green Flag	Tick				Rea	ction ru	in at re	flux			Red F	lag		Tie	ck	
		Green Flag Amber Flag				Reactior					he solv			Ū		Tie	ck	
Reaction run between 0 to 70°C	o 140°C	¥				Reactior			ore bel	low t	he solv		Red F	Ū		Tie	;k	
Reaction run between 0 to 70°C Reaction run between -20 to 0 or 70 to Reaction run below -20 or above 14	o 140°C	Amber Flag					n run 5	°C or m	ore bel	low t	he solv			Ū		Li		
Reaction run between 0 to 70°C Reaction run between -20 to 0 or 70 to	o 140°C 10°C Gr	Amber Flag Red Flag	x			Reactior Work U	n run 5	°C or m	ore bel point	low t	he solv			Ū				
Reaction run between 0 to 70°C Reaction run between -20 to 0 or 70 to Reaction run below -20 or above 14 Batch/flow	o 140°C 10°C Gr	Amber Flag Red Flag	x				n run 5 p	°C or m boiling quen filtra	ore bel point ching tion	low t	he solv			Ū				
Reaction run between 0 to 70°C Reaction run between -20 to 0 or 70 to Reaction run below -20 or above 14 Batch/flow Flow	o 140°C 10°C Gr	Amber Flag Red Flag	X				n run 5	°C or m boiling quen filtra centrifu	ore bel point ching tion	low th	he solv	ent G		Flag			st	
Reaction run between 0 to 70°C Reaction run between -20 to 0 or 70 to Reaction run below -20 or above 14 Batch/flow Flow	o 140°C 10°C Gr	Amber Flag Red Flag	X			Work Uj	n run 5	°C or m boiling quen filtra centrifu crystall	ore bel point ching tion ugation isation	low th		G G	ireen l	Flag		Lis	st	
Reaction run between 0 to 70°C Reaction run between -20 to 0 or 70 to Reaction run below -20 or above 14 Batch/flow Flow	o 140°C 10°C Gr	Amber Flag Red Flag	X			Work Uj	p n run 5	°C or m boiling quen filtra centrifu crystall	ore bel point ching tion igation isation	low the	poratio	G G	ireen l	Flag		Lis	st	
Reaction run between 0 to 70°C Reaction run between -20 to 0 or 70 to Reaction run below -20 or above 14 Batch/flow Flow	o 140°C 10°C Gr	Amber Flag Red Flag	X			Work Uj	p mperat	°C or m boiling quen filtra centrifu crystall cure dist n (< 140	ore bel point ching tion igation isation illatior <u>°C at a</u> enching	low the	poratio	ent G n/	ireen l	Flag		Lis	st	

	Red Flag	Amber Flag	Green Flag		
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber		IBX
			flagged H codes present		Benzoic acid
Explosive thermal runaway	H230, H240, H250	H241	then green flag		Isophthalic acid
Toxic	H300, H310, H330	H301, H311, H331,			THF
				4-propylguaiacol: H311	NaHCO ₃
Long Term toxicity	H340, H350, H360, H370, H372	H341, H351, H361,			Na ₂ S ₂ O ₈
		H371, H373		CH ₂ Cl ₂ : H315	NaCl
Environmental implications	H400, H410, H411, H420	H401, H412			Na ₂ SO ₄

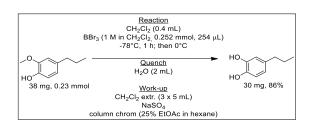
Use of chemicals of environmental concern		List substances of very high conc
Chemical identified as Substances of Very High Concern by ChemSec which are utilised	Red Flag	

ern

• Method F1: BBr₃.¹⁶

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm ³)	Density	Mass (g)	Work up chemical	Mass (g)	Workup solvent		Density	Mass (g)
								solvent		(g ml ⁻⁺)		chemical			(cm³)	(g ml ⁻¹)	
4-propylguaiacol	0,0380	166,22	2,286E-04			BBr ₃	0,063	CH ₂ Cl ₂	0,40	1,33	0,53	Na_2SO_4	0,23	H ₂ O	2,00	1,00	2,00
H ₂ O	0,0041	18,02	2,286E-04					CH ₂ Cl ₂	0,25	1,33	0,34	SiO ₂	2,29	CH ₂ Cl ₂	15,00	1,33	19,95
														Hexane	17,15	0,66	11,23
														EtOAc	5,72	0,90	5,16
																<u> </u>	
Total	0,04	184,23		-	0,00		0,06		-	-	0,87		2,51				38,33



	Flag
	86,22 🔴
Conversion	100,00 🔵
	86,22 🔴
AE	82,61
	71,23 OE
PMI total	1394,06
PMI Reaction	32,50
PMI Workup	1361,56
PMI Workup	
chemical	83,83
PMI workup	
solvents	1277,73
PMI RRC	3,51
E factor	1393,06

86,2 100,0 86,2

Solvents (First Pass)		List solvents below
Preferred solvents	water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane	H ₂ O EtOAc
Problematic solvents: (acceptable only if substitution does not offer advantages)	DMSO, cyclohexanone, DMPU, AcOH, Ac2O, Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene, MTBE, cyclohexane , chlorobenzene, formic acid, pyridine, Me-THF	
Hazardous solvents: These solvents have significant health and/or safety concerns.	dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane	Hexane CH ₂ Cl ₂
Highly hazardous solvents: The solvents which are agreed not to be used, even in screening	Et_2O , Benzene, CCl_4 , chloroform, DCE, nitromethane, CS_2 , HMPA	

Catalyst/enzyme (First Pass)								
Catalyst or enzyme used, or reaction takes place without any catalyst/reagents.	Green							
Catalyst of enzyme used, of reaction takes place without any catalyst/reagents.	Flag							
Use of stoichiometric quantities of reagents	Amber	х						
Ose of stolchiometric quantities of reagents	Flag	^						
Use of reagents in excess	Red Flag							

		Tick
Facile recovery of catalyst/enzyme	Green Flag	
catalyst/enzyme not recovered	Amber Flag	

	Mass	MW	Mol
Product	0,030	152,19	1,971E-04
	mass		
Unreacted limiting			
reactant	0,00		
		-	

	Mass	
Generated waste	41,792	

Experimental: copied from Ghosh et al., WO9937294A2, 1999.

To 38 mg (0.23 mmole) of 2-methoxy-4-propylphenol in 0.4 ml of CH_2Cl_2 at -78°C and under argon was added 254 µl (0.252 mmole) of a 1M BBr₃ solution in CH_2Cl_2 . The reaction mixture was stirred at -78°C for one hour and then warmed to 0°C. The reaction was quenched by addition of 2 ml of water. The mixture was extracted three times with 5 ml of CH_2Cl_2 dried over anhydrous Na_2SO_4 and concentrated by rotary evaporation. The crude product was flash chromatographed over silica gel using 25% ethyl acetate in hexane to furnish 30 mg of 2-hydroxy-4-propylphenol, Structure (I-6), in 86% yield.

Supply remaining	Flag colour	Note element		H 1.00794					etion o eserves												He
5-50 years	Red Flag			3 Li	4 Be		(based		rent rate							s B	°c	7 N	* 0	° F	10 N
50-500 years	Amber Flag			6.941 11	9.012182 12		50	5-50 ye 0-100 y	years							10.811 13	12.0107 14	14.00674 15	15.9994 16	18.59840 17	20.175
+500 years	Green Flag	х		Na 22.98977 19	Mg 24.3050 20	21	12 23	10-500	years 24	25	26	27	28	29	30	Al 26.98153 31	Si 28.0855	P 39.97376 31	S 32.066 34	Cl 35.4527 35	Ar 39.948 36
				K 39.0983	Ca 40.078	Sc 44.95091	Ti	V	Cr 51.9961	Mn 54.93804	Fe 55.845	Co 58.93320	Ni 58.6934	Cu 63.546	Zn 65.39	Ga 69.723	Ge 72.61	As 74.92160	Se 78.96	Br 79.504	Kr 83.80
				37 Rb	an Sr	30 Y	0 41 Zr	Nb	42 Mo	43 Tc	44 Ru	65 Rh	ec Pd	ہ۔ Ag	" Cd	in In	so Sn	ST Sb	52 Te	53 	54 Xe
				85.4678 55	87.62 56	88.9085 57	1.224 92 73	.90638	95.94 74	(98)			106.42 28	107.8682	112.411 80	114.818	118.760 82	121.760	127.60 84	126.9044 85	131.29 86
				Cs 132.9054	Ba 137.327	La *	H	Та	w	Re	Os	Ir	Pt	Au	Hg	TI	Pb	Bi	Po	At (210)	Rn (222)
				87 Fr	88	89	104 107 Rf	5 Db	106	107 Bh	108 Hs	109 Mt	110 Ds	111	112 Uub	113 Uut	114 Uuq	115	116	117 Uus	118 Uu
				(223)	Ra 226.025	Ac \$	RT (20	(0)	Sg (263)	(262)	(265)	(266)	(271)	Rq (272)	(285)	(284)	(289)	Uup (288)	Lv (292)	ous	
							58	59	6	0 6	1	62	6	64	65	66	67	68	60	70	71
					La	nthanide	s* Ce		Pr (1		Pm	Sm	Eu 157.25	Gd	Tb	Dy	Ho	Er 167.26	Tm	Yb	Lu 174.96
						Actinide	50	91	Pa	u s	Np	94 Pu	95 Am	96 Cm	97 Bk	58 Cf	99 Es	100 Fm	101 Md	102 No	103 Lr
						Actinue	232.03		1.0289 2	38.0289 0	137)	(244)		(247)	(247)	(251)	(252)	(257)	(258)	(259)	(262)
Energy (First Pass)			Tick												Tic	:k					
Reaction run between 0 to 70°C		Green Flag	Reaction run at reflux Red Flag																		
Reaction run between -20 to 0 or 70 to	o 140°C	Amber Flag					Reacti	ion r	un 5º	°C or n	nore	helow	/ the s	olven	t						
	200	De d Else		Reaction run 5°C or more below the solvent Green Flag								х									
Reaction run below -20 or above 14	iu c	Red Flag	Х																		
Batch/flow			Tio	-k			Work	lln									1		Lis	+	_
Flow	Gr	een Flag	- 11				quenching														
Batch	Am	iber Flag	Х	(ation										
										centri					G	reen F	lag	(Quenc	ching	
							Low t	emr		crysta			vanor	ation	,						
										(< 14											
							solve			nge, qu	uench	ning ir			5 Ar	nber f	Flag		Extrac	tion	
											vent				~	inder i	lug	Extraction			
								chro		ograpi igh ter			nange			Red Fl	ag	Co	lumn	chron	n
								r		ple red			ion				-6				
Health & safety												List	subst	ance	s and	H-cod	les	List	t subs	tance	s an
וכמונוו ע זמופנץ	R	ed Flag		Ambe	r Flag			Gre	een F	lag									_		
				05. H2																	

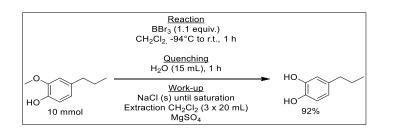
ealth & safety				List substances and H-codes	List substances and H-codes	List substances and H-codes
	Red Flag	Amber Flag	Green Flag			
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber			
			flagged H codes present			
Explosive thermal runaway	H230, H240, H250	H241	then green flag			H ₂ O
Τοχίς	H300, H310, H330	Н301, Н311, Н331,		BBr ₃ : H300, H330	4-propylguaiacol: H311	Na ₂ SO ₄ SiO ₂
Long Term toxicity	H340, H350, H360, H370, H372	H341, H351, H361, H371, H373			CH ₂ Cl ₂ : H351	EtOAc
Environmental implications	H400, H410, H411, H420	H401, H412		Hexane: H410		

Use of chemicals of environmental concern		List substances of very high concern
Chemical identified as Substances of Very High Concern by ChemSec which are utilised	Red Flag	

• Method F2: BBr₃ [BL-10]

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction	Volume (cm ³)	Density	Mass (g)	Work up	Mass (g)	Workup solvent		Density	Mass (g)
								solvent		(g ml ⁻¹)		chemical			(cm3)	(g ml ⁻¹)	
4-propylguaiacol	1,66	166,22	0,0100			BBr ₃	2,80	CH ₂ Cl ₂	15,00	1,33	19,88	NaCl	5,40	CH ₂ Cl ₂	60,00	1,33	79,80
H ₂ O	0,18	18,02	0,0100									$MgSO_4$	10,00	H ₂ O	14,82	1,00	14,82
Total	1,84	184,24			0,00		2,80	1			19,88		15,40				94,62



2,80	
	Flag
	92,07 🔵
Conversion	100,00 🔵
	92,07 🔵
AE	82,61
	76,05 <mark>OE</mark>
PMI total	96,03
PMI Reaction	17,50
PMI Workup	78,53
PMI Workup	
chemical	10,99
PMI workup	
solvents	67,54
PMI RRC	3,31
E factor	95.03

	Mass	MW	Mol
Product	1,40	152,19	0,0092
	mass		
Unreacted limiting			
reactant	0,00		

	Mass
Generated waste	133,137

Experimental	[BL-10]:
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92,1 100,0

92,1

Solvents (First Pass)		List solvents below
Preferred solvents	water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane	H ₂ O
Problematic solvents: (acceptable only if substitution does not offer advantages)	DMSO, cyclohexanone, DMPU, AcOH, Ac2O, Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene, MTBE, cyclohexane , chlorobenzene, formic acid, pyridine, Me-THF	
Hazardous solvents: These solvents have significant health and/or safety concerns.	dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane	CH ₂ Cl ₂
Highly hazardous solvents: The solvents which are agreed not to be used, even in screening	Et_2O , Benzene, CCI_4 , chloroform, DCE, nitromethane, CS_2 , HMPA	

Catalyst/enzyme (First Pass)		Tick
Catalyst or enzyme used, or reaction takes place without any catalyst/reagents.	Green	
catalyst of enzyme used, of reaction takes place without any catalyst/reagents.	Flag	
Use of stoichiometric quantities of reagents	Amber	v
ose of scoleniometric qualitities of reagents	Flag	~
Use of reagents in excess	Red Flag	

		Tick
Facile recovery of catalyst/enzyme	Green Flag	
catalyst/enzyme not recovered	Amber Flag	

In a flame-dried and argon flushed 25 mL roundbottomed flask, equipped with magnetic stirring bar, 2-methoxy-4-propylphenol (1.66 g, 10.0 mmol, 1.0 equiv.) was dissolved in dry CH₂Cl₂ (15 mL). The obtained mixture was cooled to -94 °C and subsequently, BBr₃ (1.06 mL, 11.0 mmol, 1.1 equiv.) was added dropwise. The cooling bath was removed and the reaction was allowed to reach r.t. The mixture was stirred for 1 h and subsequently, ice cold H₂O (15 mL) was added dropwise. The obtained suspension was stirred for 1 h and NaCl (s) was added until saturation and the product was extracted with CH₂Cl₂ (3 × 20 mL). The combined organic fractions were dried over MgSO₄, filtered and evaporated under reduced pressure. Pure 4-propylbenzene-1,2-diol was obtained with a yield of 92% (1.40 g,

Supply remaining	Flag colour	Note element			H 2794				pletion												H
5-50 years	Red Flag			3	4			(based on a								5	6	7	8	2	10
50-500 years	Amber Flag	в		6.94) years 00 years							B 10.811	C 12.0107	N 14.00674	0 15.9994	F 18.59840	20.1
So soo years	Amber Hug				Na M				00 years 00 years							AI	¹⁴ Si	15 P	¹⁶ S	¹⁷ CI	18 A
+500 years	Green Flag	Br, Cl		19		21	22	23	24	25	26	27	28	29	30	26.98153	28.0855	39.97376 33	32.066 34	35.4527 35	39.94 36
			-	39.0	K C		C T		Cr 51.9961	Mn 54.93804	Fe 55.845	Co 58.93320	Ni 58.6934	Cu 63.546	Zn 65.39	Ga 69.723	Ge 72.61	As 74.92160	Se 78.96	Br 79.504	K 83.80
				37 F	ар Краз	39	40 Z	41 Nb	42 Mo	43 Tc	Ru	45 Rh	46 Pd	47 Ag	44 Cd	40 In	so Sn	SI Sb	52 Te	53	54 X
					1678 87.62	88.9	91.22		8 95.94	(98)	101.07		106.42	107.8682	112.411	114.818	118.760	121.760	127.60 84	126.9044 85	131.2
				(Cs B	a La		f Ta	w	Re	Os	lr.	Pt	Au	Hg	т	Pb	Bi	Ро	At	R
				87	9054 137.3	89	104	180.943	9 183.84 106	186.207 107	190.23	192.217	195.078 110	196.9665	200.59	204.3833	270.2	208.9804	(209) 116	(210) 117	(222) 118
				(22)	Fr R 1) 226.0			f Db (260)	Sg (263)	Bh (262)	Hs (265)	Mt (266)	Ds (271)	Rq (272)	Uub (285)	Uut (284)	Uuq (289)	Uup (288)	LV (292)	Uus	U
								_													
						Lanth	anides *	SH Ce	50 Pr	∞ Nd	Pm	⁶² Sm	Eu	Gd Gd	Tb	⁶⁶ Dy	67 Ho	Er	Tm	Yb	n Lu
								140.9077 50	144.24 91	(145)	150.36 93	151.964 94	157.25 95	158.9253 96	158.9253 97	162.50 58	164.9303 99	167.26 100	168.9342	173.04 102	174.9 103
						Acti	nides ‡	Th	Pa	U	Np	Pu	Am	Cm	Bk	Cf (251)	Es (252)	Fm (257)	Md (258)	No	L
					-			232.0381	231.0289	7360785	(111)	(244)	[243]	(247)	(247)	(251)	(252)	(157)		(259)	(262)
nergy (First Pass)		T	ick			Ē												Ti	ck		
Reaction run between 0 to 70 ^c	C	Green Flag							Rea	oction	run a	t reflu	IX			Red F	120				
																neu i	ag				
Reaction run between -20 to 0 or 70	to 140°C	Amber Flag					R	eaction	n run 5					solver							
Reaction run between -20 to 0 or 70 Reaction run below -20 or above :		Amber Flag Red Flag		x			R	eactior	n run 5	°C or		belov		solver		reen I			>	(
Reaction run below -20 or above :										°C or	more	belov		solver							
Reaction run below -20 or above :	140°C	Red Flag		X				eactior /ork U		°C or boili	more ng po	belov int		solver) Li:		
Reaction run below -20 or above : Batch/flow 'low	140°C Gr		Т							°C or boili que	more	belov int		solver							
	140°C Gr	Red Flag een Flag	Т	lick						^o C or boili que filt centr	more ng po enchir ratioi	belov int Ig 1		solver	G	reen l	Flag		Li	st ching,	
Reaction run below -20 or above : latch/flow low	140°C Gr	Red Flag een Flag	Т	lick				ork Uj	0	^o C or boili que filt centr cryst	more ng po enchir ration ifugat	belov int Ig 1 ion	v the s		G G		Flag	(Li	st ching,	
Reaction run below -20 or above : latch/flow low	140°C Gr	Red Flag een Flag	Т	lick				York Uj	p npera	^o ^o C or boili que filt centr cryst ture d	more ng po enchir ration ifugat allisat	belov int ig ion ion tion/e	v the s	ation	G G	reen l	Flag	(Li	st ching,	
Reaction run below -20 or above : latch/flow low	140°C Gr	Red Flag een Flag	Т	lick			N	York Uj	p npera matio	^o C or boili que filt centr cryst ture d n (< 14	more ng po enchir ration ifugat allisat istillat	belov int int ion tion/e at atm	v the s	ation	G G	reen l	Flag Flag		Li: Quent Filtra	st ching, ation	
Reaction run below -20 or above : latch/flow low	140°C Gr	Red Flag een Flag	Т	lick			N	ow ter subli	npera matio excha	que filt centr cryst ture d n (< 14 nge, c	more ng po enchir ration ifugat allisat istillai 40 °C uuenc	belov int int ion tion/e at atm hing in	v the s vapor <u>nosph</u> nto aq	ation eric ueou	G G	reen l	Flag Flag		Li	st ching, ation	
Reaction run below -20 or above : atch/flow low	140°C Gr	Red Flag een Flag	Т	lick			N	ow ter subli	npera matio excha	que filt centr cryst ture d n (< 14 nge, c	more ng po ifugal allisat istilla istilla uenc ilvent	belov int g ion ion cion/e at atm hing ir	v the s	ation eric ueou	nt G G /	reen l	Flag Flag Flag		Li: Quent Filtra	st ching, ation	

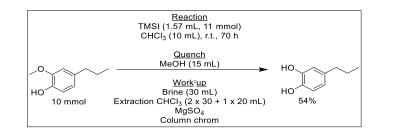
	Red Flag	Amber Flag	Green Flag			
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber			
			flagged H codes present			
Explosive thermal runaway	H230, H240, H250	H241	then green flag			
Toxic	H300, H310, H330	Н301, Н311, Н331,		BBr ₃ : H300, H330	4-propylguaiacol: H311	NaCl H ₂ O
Long Term toxicity	H340, H350, H360, H370, H372	H341, H351, H361, H371, H373			CH ₂ Cl ₂ : H351, H373	
Environmental implications	H400, H410, H411, H420	H401, H412				

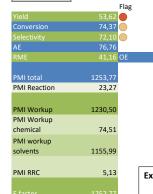
Use of chemicals of environmental concern		List substances of very high cor
Chemical identified as Substances of Very High Concern by ChemSec which are utilised	Red Flag	

• Method G1: TMSI [BL-20]

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction	Volume (cm ³)	Density	Mass (g)	Work up	Mass (g)	Workup solvent	Volume	Density	Mass (g)
								solvent		(g ml ⁻¹)		chemical			(cm³)	(g ml ⁻¹)	
4-propylguaiacol	1,66	166,22	0,0100			TMSI	2,21	CHCl ₃	10,00	1,48	14,80	NaCl	10,80	CHCl ₃	80,00	1,48	118,40
MeOH	0,32	32,04	0,0100									MgSO ₄	10,00	MeOH	14,60	0,79	11,55
												SiO ₂	40,00	EtOAc	112,50	0,90	101,25
														heptane	997,50	0,68	682,09
														H ₂ O	30,00	1,00	30,00
Total	1,98	198,26			0,00		2,21				14,80		60,80				943,29





	Mass	MW	Mol
Product	0,82	152,19	0,0054
	mass		
Unreacted limiting			
reactant	0,43		

Experimental [BL-20]:

53,6 74,4

72,1

53,6

Solvents (First Pass)		List solvents below
Preferred solvents	water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane	H ₂ O, MeOH, EtOAc
Problematic solvents: (acceptable only if substitution does not offer advantages)	DMSO, cyclohexanone, DMPU, AcOH, Ac2O, Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene, MTBE, cyclohexane , chlorobenzene, formic acid, pyridine, Me-THF	Heptane
Hazardous solvents: These solvents have significant health and/or safety concerns.	dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane	
Highly hazardous solvents: The solvents which are agreed not to be used, even in screening	Et_2O , Benzene, CCl_4 , chloroform, DCE, nitromethane, CS_2 , HMPA	CHCl₃

In a flame-dried and argon-flushed 25 mL roundbottomed flask, equipped with magnetic stirring bar, septa and argon balloon, 2-methoxy-4-propylphenol (1.66 g, 10.0 mmol, 1.0 equiv.) and TMSI (1.57 mL, 11.0 mmol, 1.1 equiv.) were dissolved in dry CHCl₃ (10 mL) and the obtained reaction mixture was stirred for 70 h at r.t. Subsequently, MeOH (15 mL) and brine (30 mL) were added and the mixture was extracted with CHCl₃ (2 × 30 mL and 1 × 20 mL). The combined organic layers were dried over MgSO₄, filtered and evaporated under reduced pressure. The product was isolated using an automated flash chromatography system using a heptanes/EtOAc gradient (40 g SiO₂ cartridge, flow rate: 30 mL·min⁻¹, eluent: heptanes, 2 min; heptanes to 15% EtOAc in heptanes, 20 min; 15% EtOAc in heptanes; 15 min). Pure 4-propylbenzene-1,2-diol was obtained in 54% yield (0.82 g, 5.36 mmol). Furthermore, 2-methoxy-4-propylphenol was recovered for 26% (0.43 g, 2.56 mmol). The obtained spectroscopic data are in accordance with those reported before.

Generated waste

	Tick
Green	
Flag	
Amber	х
Flag	~
Red Flag	
	Flag Amber Flag

		Tick
Facile recovery of catalyst/enzyme	Green Flag	
catalyst/enzyme not recovered	Amber Flag	

Supply remaining	Flag colour	Note element		H 1.00794		k	nown	letion of the serve	s											4.00
5-50 years	Red Flag			Li B	le l	(ba	sed on cu extrac	rrent rate	e of						s B	°c	7 N	* 0	° F	10
50-500 years	Amber Flag	I.		6.941 9.013 11 12	2182		5-50 50-100	years							10.811 13	12.0107	14.00674 15	15.9994 16	18.95840 17	20.1
+500 years	Green Flag	Cl, Na		Na N 22.58977 24.30 19 20	ng 050 21	22	23	24	25	26	27	28	29	30	Al 26.98153	Si 28.0855 33	P 39.97376 33	S 32.066 34	CI 35.4527 35	39.5 36
				K C		Ti 47.867	V 50.9415	Cr 51.9961	Mn 54.93804	Fe 55.845	Co 58.93320	Ni 58.6934	Cu 63.546	Zn 65.39	Ga 69.723	Ge 72.61	As 74.92160	Se 78.96	Br 79.904	83.80
				s7 31 Rb S	ir Y	40 Zr	41 Nb	42 Mo	43 Tc	Ru	45 Rh	46 Pd	40 Ag	Cd	40 In	so Sn	st Sb	52 Te	53 	54 Xe
				85.4678 87.6. \$5 56	2 88.9085 57	91.224	92.90638 73	95.94 24	(58) 75	101.07 76		106.42 78	107.8682	80	81	118.760 82	121.760	127.60 84	126.9044 85	131.25 86
				Cs B 132.9054 137.3 87 88		Hf 178.49	Ta 180.9479	W 111.14	Re 186.207	Os 199.21	192.217 199.2	Pt 195.078	Au 196.9665	Hg 200.59	TI 201.3133	Pb 270.2	Bi 208, 9804	Po (209)	At (210)	Rr (222)
				Fr R	ta Ac‡	Rf	105 Db	Sg	107 Bh	108 Hs	Mt	110 Ds	n Rq	112 Uub	113 Uut	¹¹⁴ Uuq	115 Uup	116 LV	Uus	118 Uu
				(223) 226.0	025 (227)	(257)	(260)	(263)	(262)	(265)	(266)	(271)	(272)	(285)	(284)	(289)	(288)	(292)		
					Lanthani	les *	Ce	Pr	Nd	61 Pm	⁶² Sm	ea Eu	Gd Gd	es Tb	۵۰ Dy	୍ମ Ho	68 Er	∽ Tm	20 Yb	71 Lu
						9	D 5	144.24	(145) 92	150.36 93	151.964 94	157.25 95	158.9253 96	158.9253 97	162.50 98	164.9303 99	167.26 100	168.9342 101	173.04 102	174.96 103
					Actinid		Th 32.0381 2	Pa 31.0289	U 238.0289	Np (237)	Pu (244)	Am (243)	Cm (247)	Bk (247)	Cf (251)	Es (252)	Fm (257)	Md (258)	No (259)	Lr (262)
nergy (First Pass)			Tick															т	ick	
Reaction run between 0 to 70°C	:	Green Flag	х					Rea	iction	run a	t reflu	х			Red Fl	ag				
Reaction run between -20 to 0 or 70 to	o 140°C	Amber Flag				Roo	ction	run E	°C or	moro	holou	v tho	colvor	. +						
Reaction run below -20 or above 14	40°C	Red Flag				Nea	ction	iuns		ng po		w the s	Solvei	G	reen f	lag			х	
Batch/flow			Tick			Wo	rk Up												ist	
Flow		een Flag								enchin	•							-		
Batch	Am	nber Flag	Х						filt centr	ration										
									crysta	-				G	reen F	lag		Filtr	ation	
									ure d					/						
									n (< 14 nge, q					s .						-
									so	lvent	-			A	mber I	Flag		Extra	action	
							ch		tograp iigh te				2		Red Fl	ag	Ch	iroma	togra	oby
									iple re										u	
										I										_
Health & safety											List	t subs	tance	s and	H-coo	les	Li	ist sul	ostano	es a
		ed Flag		mber F				reen F												

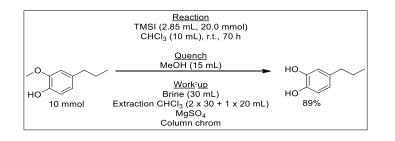
alth & safety				List substances and H-codes	List substances and H-codes	List substances and H-codes
•	Red Flag	Amber Flag	Green Flag			
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber			
			flagged H codes present			
Explosive thermal runaway	H230, H240, H250	H241	then green flag			TMSI
Τοχίς	Н300, Н310, Н330	Н301, Н311, Н331,			4-propylguaiacol: H311	EtOAc NaCl
Long Term toxicity	H340, H350, H360, H370, H372	H341, H351, H361,		CHCl ₃ : H372		H ₂ O
-		H371, H373		MeOH: H370		
Environmental implications	H400, H410, H411, H420	H401, H412		Heptane: H410		

Use of chemicals of environmental concern		List substances of very high concern
Chemical identified as Substances of Very High Concern by ChemSec which are utilised	Red Flag	

• Method G2: TMSI [BL-22]

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction	Volume (cm ³)	Density	Mass (g)	Work up	Mass (g)	Workup solvent	Volume	Density	Mass (g)
								solvent		(g ml⁻¹)		chemical			(cm³)	(g ml ⁻¹)	
4-propylguaiacol	1,66	166,22	0,0100			TMSI	4,01	CHCl ₃	10,00	1,48	14,80	NaCl	10,80	CHCl ₃	80,00	1,48	118,40
MeOH	0,32	32,04	0,0100									MgSO ₄	10,00	MeOH	14,60	0,79	11,55
												SiO ₂	40,00	EtOAc	112,50	0,90	101,25
														heptane	997,50	0,68	682,09
														H ₂ O	30,00	1,00	30,00
Total	1,98	198,26			0,00		4,01				14,80		60,80				943,29





	Mass	MW	Mol
Product	1,35	152,19	0,0089
	mass		
Unreacted limiting reactant	0,00		

	Mass
Generated waste	1023,526

Solvents (First Pass)		List solvents below
Preferred solvents	water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane	H ₂ O, MeOH, EtOAc
Problematic solvents: (acceptable only if substitution does not offer advantages)	DMSO, cyclohexanone, DMPU, AcOH, Ac2O, Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene, MTBE, cyclohexane , chlorobenzene, formic acid, pyridine, Me-THF	Heptane
Hazardous solvents: These solvents have significant health and/or safety concerns.	dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane	
Highly hazardous solvents: The solvents which are agreed not to be used, even in screening	Et_2O , Benzene, CCl_4 , chloroform, DCE, nitromethane, CS_2 , HMPA	CHCl ₃

Experimental [BL-22]:

89,0

100,0

89,0

In a flame-dried and argon-flushed 25 mL roundbottomed flask, equipped with magnetic stirring bar, septa and argon balloon, 2-methoxy-4-propylphenol (1.66 g, 10.0 mmol, 1.0 equiv.) and TMSI (2.85 mL, 20.0 mmol, 2.0 equiv.) were dissolved in dry $CHCl_3$ (10 mL) and the obtained reaction mixture was stirred for 70 h at r.t. Subsequently, MeOH (15 mL) and brine (30 mL) were added and the mixture was extracted with $CHCl_3$ (2 x 30 mL and 1 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The product was isolated using an automated flash chromatography system using a heptanes / EtOAc gradient (40 g SiO₂ cartridge, flow rate: 30 mL/min, eluent: heptanes, 2 min; heptanes to 15% EtOAc in heptanes, 20 min; 15% EtOAc in heptanes; 15 min). Pure 4-propylbenzene-1,2-diol was obtained in 89% yield (1.35 g, 8.9 mmol).

Catalyst/enzyme (First Pass)							
Catalyst or enzyme used, or reaction takes place without any catalyst/reagents.	Green						
catalyst of enzyme used, of reaction takes place without any catalyst/reagents.	Flag						
Use of stoichiometric quantities of reagents	Amber						
	Flag						
Use of reagents in excess	Red Flag	х					

		Tick
Facile recovery of catalyst/enzyme	Green Flag	
catalyst/enzyme not recovered	Amber Flag	

Supply remaining	Flag colour	Note element		H 20794				etion o eserves												H
5-50 years	Red Flag		3	Li Be		(base	d on curr extracti	rent rate	of						s B	° c	7 N	* 0	° F	10
50-500 years	Amber Flag	I.	6. 13	9,01218	2		5-50 ye 50-100 y	years							10.811 13	12.0107	14.00674 15	15.9994 16	18.99840	20.12
+500 years	Green Flag	Cl, Na			21	22	23	24	25	26	27	28	29	30	Al 26.98153 31	Si 28.0855 32	P 39.97376 33	S 32.066 34	CI 35.4527 35	A 39.54
	, 		35	K Ca	Sc 44.95591	Ti 47,867	V 50.9415	Cr 51.9961	Mn 54.93804	Fe 55.845	Co 58.93320	Ni 58.6934	Cu 63.546	2n 55.39	Ga 69.323	Ge 72.61	As 74.92160	Se 78.96	Br 79.904	Ki 83.80
				Rb Sr	Y	Zr 91.724	Nb	Mo	TC	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	53 126 9044	Xe
			55		57 La *	n Hf	73 Ta	24 W	75 Re	⁷⁶ Os	n Ir	78 Pt	77 Au	80 Hg	" TI	az Pb	au Bi	84 Po	as At	85 Rr
			87		89		180.9479 105	183.84 106		190.23 108	192.217 109	195.078 110	196.9665 111	200.59 112	204.3411 113	270.2 114	208.0804	(209) 116	(210) 117	(222) 118
				Fr Ra 23) 226.025		Rf (257)	Db (260)	Sg (263)	Bh (262)	Hs (265)	Mt (266)	Ds (271)	Rq (272)	Uub (285)	Uut (284)	Uuq (289)	Uup (288)	Lv (292)	Uus	Uud
						58	59	6	0 61	6	2 1	8	4	65	66	ଗ	68	69	70	71
				'	Lanthanid	es * C		Pr 4.24 (1		Pm 1	Sm 51.964 1	Eu 157.25 1	Gd 58.9253	Tb 158.9253	Dy 162.50	Ho 164.9303	Er 167.26	Tm 168.9342	Yb 173.04	Lu 174.96
					Actinide			Pa 1.0289	2 93 U (23 38.0289 (23				6 Cm (47)	97 Bk (247)	98 Cf (251)	99 Es (252)	100 Fm (257)	101 Md (258)	102 No (259)	103 Lr (262)
nergy (First Pass)			Tick															Т	ïck	
Reaction run between 0 to 70°C		Green Flag	х					Read	ction r	un at	reflux	ĸ		1	Red Fl	lag				
Reaction run between -20 to 0 or 70 to	o 140°C	Amber Flag				React	tion r	un 5°	°C or m	ore b	pelow	the s	olven	t _						
Reaction run below -20 or above 14	10°C	Red Flag							boilin	g poii	nt			G	reen F	-lag	X			
Batch/flow			Tick	-		Work	k Up											L	.ist	_
low		een Flag							quen		-									
3atch	Am	iber Flag	X						filtra centrif	ation ugati										
									crystal	lisati	on				reen F	-lag		Filti	ration	
									ure dis (< 140					1						
									nge, qu	ench				Ar	nber	Flag		Extr	action	
						1			solv	vent										
							chro	omat	ograph	ny/ior	n exch	nange								
								hi	igh ten	npera	ture	-			Red Fl	lag	Cł	roma	atogra	bhy
								hi		npera	ture	-			Red Fl	ag	Cł	nroma	atogra	bhy

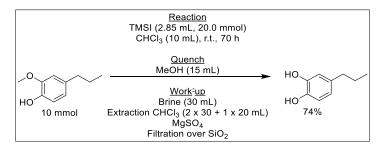
lealth & safety				List substances and H-codes	List substances and H-codes	List substances and H-codes
•	Red Flag	Amber Flag	Green Flag			
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber			
			flagged H codes present			
Explosive thermal runaway	H230, H240, H250	H241	then green flag			TMSI
Toxic	H300, H310, H330	Н301, Н311, Н331,			4-propylguaiacol: H311	EtOAc NaCl
Long Term toxicity	H340, H350, H360, H370, H372	H341, H351, H361,		CHCl ₃ : H372		H ₂ O
		H371, H373		MeOH: H370		
Environmental implications	H400, H410, H411, H420	H401, H412		Heptane: H410		

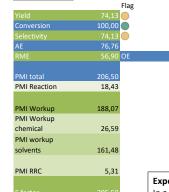
Use of chemicals of environmental concern		List substances of very high concern
Chemical identified as Substances of Very High Concern by ChemSec which are utilised	Red Flag	

• Method G3: TMSI [BL-32]

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction	Volume (cm ³)	Density	Mass (g)		Mass (g)	Workup solvent		Density	Mass (g)
								solvent		(g ml⁻¹)		chemical			(cm3)	(g ml ⁻¹)	
4-propylguaiacol	1,66	166,22	0,0100			TMSI	4,01	CHCl ₃	10,00	1,48	14,80	MgSO ₄	10,00	MeOH	14,60	0,79	11,55
MeOH	0,32	32,04	0,0100									SiO ₂	20,00	H ₂ O	30,00	1,00	30,00
														CHCl ₃	80,00	1,48	118,40
														MTBE	30,00	0,74	22,20
Total	1,98	198,26			0,00		4,01				14,80		30,00				182,15





	Mass	MW	Mol
Product	1,13	152,19	0,0074
	mass		
Unreacted limiting			
reactant	0.00		

	Mass
Generated waste	231,809

Experimental [BL-32]:

74,1

100,0 74,1

Solvents (First Pass)		List solvents below
Preferred solvents	water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane	H ₂ O, MeOH
Problematic solvents: (acceptable only if substitution does not offer advantages)	DMSO, cyclohexanone, DMPU, AcOH, Ac2O, Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene, MTBE, cyclohexane , chlorobenzene, formic acid, pyridine, Me-THF	
Hazardous solvents: These solvents have significant health and/or safety concerns.	dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane	
Highly hazardous solvents: The solvents which are agreed not to be used, even in screening	Et_2O , Benzene, CCl_4 , chloroform, DCE, nitromethane, CS_2 , HMPA	CHCl ₃

In a flame-dried and argon-flushed 25 mL roundbottomed flask, equipped with magnetic stirring bar, septa and argon balloon, 2-methoxy-4-propylphenol (1.66 g, 10.0 mmol, 1.0 equiv.) and TMSI (2.85 mL, 20.0 mmol, 2.0 equiv.) were dissolved in dry CHCl₃ (10 mL) and the obtained reaction mixture was stirred for 70 h at r.t. Subsequently, MeOH (15 mL) and brine (30 mL) were added and the mixture was extracted with CHCl₃ (2 x 30 mL and 1 x 20 mL). The combined organic layers were dried over MgSO₄, filtered and evaporated under reduced pressure. The product was isolated by dissolving the crude material in MTBE (30 mL) and filtering it over a layer of silica. Volatiles were evaporated under reduced pressure and pure product was obtained in 74% yield (1.13 g, 7.4 mmol).

Catalyst/enzyme (First Pass)		Tick
Catalyst or enzyme used, or reaction takes place without any catalyst/reagents.	Green	
catalyst of enzyme used, of reaction takes place without any catalyst/reagents.	Flag	
Use of stoichiometric quantities of reagents	Amber	
	Flag	
Use of reagents in excess	Red Flag	x

			Tick
Facile recove	ery of catalyst/enzyme	Green Flag	
catalyst/er	zyme not recovered	Amber Flag	

Supply remaining	Flag colour	Note element		н				ntil dep known r	letion o												He
5-50 years	Red Flag			3	4		(b	ised on cu extrac	rrent rate	e of						5	6	7	8	9	10
50-500 years	Amber Flag	I.		6.941	Be 9.012182 12			5-50 50-100								B 10.811 13	C 12.0107	N 14.00574 15	0 15.9994	F 18.99840 17	Ne 20.1797 18
+500 years	Green Flag	Si, Na, Cl		Na 22.5897 19	20	21	22	23	24	25	26	27	28	29	30	Al 26.58153 31	Si 28.0855 32	P 39.97376 33	S 32.066 34	Cl 35.4527 35	Ar 39.948 36
			I	K 39.0983 37	Ca 40.078	Sc 44.95591	Ti 47.867	V 50.9415	Cr 51.9961	Mn 54.93804	Fe 55.845	Co 58.93320	Ni 58.6934	Cu 63.546	Zn 65.39	Ga 69.323	Ge 72.61	As 24.92160	Se 78.96	Br 79.904	Kr 83.80
				Rb 85.4678	Sr at sa	Y 88.9085	Zr 91.224	Nb 92.90638	Mo 95.94	Tc (58)	Ru 101.07	Rh 102.9055	Pd 105.42	Ag 107.8682	Cd	in 	Sn 118.700	Sb 121.700	Te 127.60	126.9044	Xe 131.29
				55 Cs	56 Ba	57 La*	Hf	73 Ta	W	75 Re	os Os	" Ir	Pt	Au	80 Hg	TI	82 Pb	Bi	84 Po	85 At (210)	85 Rn (222)
				87 Fr (223)	⁸⁸ Ra	89 Ac ‡	104 Rf	105 Db	106 Sg	107 Bh (262)	108 Hs	109 Mt	110 Ds (271)	nn Rq	112 Uub	113 Uut	114 Uuq	115 Uup	116 Lv	117 Uus	118 Uuo
				(223)	216.025	(227)	(257)	(260)	9	(262)	(265)	(206)	(2/1) 63	(272)	(285)	(284)	(289)	(288)	(292)	70	71
					La	inthani	des *	Ce 1	Pr 44.24	Nd (145)	Pm 150.36	Sm 151.964	Eu 157.25	Gd 158.9253	Tb 158.9253	Dy 162.50	Ho 164,9303	Er 167.26	Tm 168.9342	Yb 173.04	Lu 174.967
						Actinid		0 9 Th 132.0381 2	1 Pa 31.0289	92 U 238.0289	93 Np (237)	94 Pu (244)	95 Am (243)	96 Cm (247)	97 Bk (247)	98 Cf (251)	99 Es (252)	100 Fm (257)	101 Md (258)	102 No (259)	103 Lr (262)
nergy (First Pass)			1	lick			_												т	ick	
Reaction run between 0 to	70°C	Green Flag		x					Rea	ction	run a	t reflu	IX			Red Fl	lag				
Reaction run between -20 to 0 or	70 to 140°C	Amber Flag					Rea	ction	run 5	°C or	more	belov	v the	solven	t						
Reaction run below -20 or abo	ove 140°C	Red Flag									ng po				Gi	reen F	lag			х	
Batch/flow			1	lick	1		Wo	rk Up											L	ist	
low		een Flag									nchin	-									
Jatch	An	nber Flag		Х	J						ratior										
										centr cryst					G	reen F	lag		filtr	ation	
								w tem	nerat				vano	ation/	,						
								sublin	-				-								
										nge, q	uencl	hing ii		lneona	Ar	nber l	Flag	so	lvent	excha	nge
							\vdash	ch	omat	sc tograp	lvent hy/ic		hange	5							
										igh te iple re					ł	Red Fl	lag	С	olumi	n chro	m.
												Lis	t subs	tance	sand	H-cor	los		ist sul	ostano	os an
lealth & safety		ad Flag		Anak		_		<u> </u>		Tien	_				Jana					Jotania	
Highly explosive		ed Flag 01, H202, H203	μ		er Flag 220, H			lf no r	een l		er -										
THE THE EXPLOSIVE						~~~		ged I													
Explosive thermal runaway		H240, H250			241			ther	gree	n flag											
Toxic	H300,	H310, H330	н	301, H	311, H	331,													4-pr	opylgı	uaiaco
Long Term toxicity	H340, H350,	H360, H370, H372	н		351, H							CI	HCl ₃ : I	1372;	MeOF	н: Н37	70				
				H37	1, H373	5															

Use of chemicals of environmental concern		List substances of very high concern
Chemical identified as Substances of Very High Concern by ChemSec which are utilised	Red Flag	

H401, H412

H400, H410, H411, H420

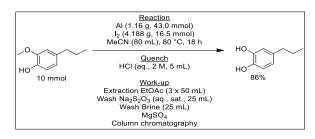
Environmental implications

List substances and H-codes

TMSI NaCl H₂O • Method H: Al + I₂ [JBO-GM-119]

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm ³)	Density (g ml ⁻¹)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density (g ml ⁻¹)	Mass (g)
4-n -propylguaiacol	1,66	166,22	0,010			Al	1,16	CH ₃ CN	80,00	0,79	62,88	NaCl	9,00	H ₂ O	55,00	1,00	55,00
HCI	0,36	36,46	0,010			I ₂	4,19					$Na_2S_2O_3$	17,53	EtOAc	150,00	0,90	134,55
												MgSO ₄	9,99	heptane	1074,00	0,68	730,32
												SiO ₂	40,00	EtOAc	126,00	0,90	113,02
Total	2,02	202,68			0,00		5,35				62,88		76,51				1032,89
									Flag								



		ilag	
			86,7
Conversion	100,0		100,0
			86,7
	75,1		
		OE	
PMI total	895,5		
PMI Reaction	53,3		
PMI Workup	842,18		
PMI Workup			
chemical	58,08		
PMI workup			
solvents	784,10		
PMI RRC	5,60		
	894,51		Experim

	Mass	MW	Mol
Product	1,32	152,19	0,0087
	mass		
Unreacted limiting			
reactant	0,00		

	Mass	
Generated waste	1178,341	

Solvents (First Pass)		List solvents below
Preferred solvents	water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane	H ₂ O, EtOAc
Problematic solvents: (acceptable only if substitution does not offer advantages)	DMSO, cyclohexanone, DMPU, AcOH, Ac2O, Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene, MTBE, cyclohexane , chlorobenzene, formic acid, pyridine, Me-THF	CH ₃ CN, heptane
Hazardous solvents: These solvents have significant health and/or safety concerns.	dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane	
Highly hazardous solvents: The solvents which are agreed not to be used, even in screening	Et_2O , Benzene, CCl_4 , chloroform, DCE, nitromethane, CS_2 , HMPA	

xperimental	[JBO-GM-119]:
-------------	---------------

Tick

86.7

In a 250 mL roundbottomed flask, equipped with reflux condenser and magnetic stirring bar, 2-methoxy-4-propylphenol (1.66 g, 10.0 mmol, 1.0 equiv.) was dissolved in acetonitrile (80 mL). Subsequently, aluminium powder (1.160 g, 43.0 mmol, 4.3 equiv.) was added to the solution and then I_2 (4.188 g, 16.5 mmol, 1.7 equiv.) was added in one portion. The obtained mixture was stirred for 18 hr at 80 °C. After cooling to r.t., the mixture was quenched with HCl (aq., 2 M, 5 mL), and extracted with EtOAc (3 x 50 mL). The combined organic fractions were washed with $Na_2S_2O_3$ (aq., sat., 25 mL), brine (25 mL), dried over MgSO₄, filtered and evaporated under reduced pressure. The crude mixture was purified with an automatic column chromatography system (column: 40 g SiO₂ cartridge; flow rate: 30 mL/min; eluent: heptanes, 2 min; heptanes to 15% EtOAc in

Catalyst/enzyme (First Pass)		Tick
Catalyst or enzyme used, or reaction takes place	Green Flag	
Use of stoichiometric quantities of reagents	Amber Flag	
Use of reagents in excess	Red Flag	x

Supply remaining	Flag colour	Note element	1 H 1.00794			u I	Remaini Intil dep known I	etion of the serve	of s											2 H 4.002
5-50 years	Red Flag		, Li	4 Be		(bi	ised on cu extra	ction)	e of						з В	° c	7 N	° 0	°F	10 Ne
50-500 years	Amber Flag	Al, I, S	6.941 11 Na	9.0121#2 12 Mg			50-100	years Dyears Oyears							10.811 13 Al	12.0107 14 Si	14.00674 15 P	15.9994 16 S	18.99840 17 Cl	20.1793 18 Ar
+500 years	Green Flag	Na, Cl,	22.98977 19 K	24.3050 20 Ca	23 Sc	22 Ti	23 V	24 Cr	25 Mn	26 Fe	27 Co	28 Ni	29 Cu	» Zn	26.98153 31 Ga	28.0855 32 Ge	39.97376 33 As	32.066 34 Se	35.4527 35 Br	39.948 26 Kr
	•		39.0983 37	40.078	44.95591 39	47,867	50.9415 41	51.9961	43	55.845	58.93320 45	58.6934 46	63.546 47	65.39 48				78.96 52	79.904 53	83.80 54
			Rb 85.4678 55	5r 87.62	¥ 88.9085 57	Zr 91.224	Nb 92.90538	Mo 95.94	Tc (98)	Ru 101.07	Rh 102.5055	Pd 106.42	Ag 107.8682	Cd 112.411	In 114.818	5n 118.700	Sb 121.760	Te 127.60 84	126.9044	Xe 131.29
			Cs	Ba 137.327	La *	Hf	Ta 180.9479	W	Re 186.207	Os	lr 192.217	Pt 195.078	Au	Hg	T1	Pb	Bi 208.9804	Po (209)	At (210)	Rn (222)
			87 Fr	88 Ra	89 Ac ‡	104 Rf	105 Db	106 Sg	107 Bh	108 Hs	109 Mt	110 Ds	111 Rq	112 Uub	113 Uut	114 Uuq	115 Uup	116 LV	117 Uus	118 Uud
			(223)	226.025	(227)	(257)	(260)	(263)	(262)	(265)	(266)	(271)	(272)	(285)	(284)	(289)	(288)	(292)		
				Li	anthanic		68 5 Ce	9 Pr	60 Nd (145)	61 Pm 150.35	62 Sm 151.964	63 Eu	64 Gd 158,9253	65 Tb	66 Dy 162.50	67 Ho 164,9303	68 Er 167.26	69 Tm 168,9342	70 Yb 173.04	71 Lu 174.967
					Actinid			91 Pa	92 U		94 Pu	55 Am	96 Cm	97 Bk	98 Cf	99 Es	100 Fm	101 Md	102 No	1/4.96/ 103 Lr
					-	1	232.0381	231.0289	238.0289	(237)	(244)	(243)	(247)	(247)	(251)	(252)	(257)	(258)	(259)	(262)
nergy (First Pass) Reaction run betwee	n 0 to 70°C		Tick				Г						_							ick
		Green Flag							Re	eactio	n run a	at ref	lux			Red	Flag			X
Reaction run between	-20 to 0 or 70	Amber Flag	х																	
to 140°C								Rea	iction	run 5	°C or r	more	belov	/ the		_				
to 140°C Reaction run below - 140°C	20 or above	Red Flag						Rea			°C or r boilir			/ the		Greer	n Flag			
Reaction run below - 140°C	20 or above	Red Flag	Tick					Rea	S					v the		Greer	n Flag			ist
Reaction run below - 140°C Batch/flow	Gree	n Flag							S	olvent	boilir Jenchi	ng poi		v the		Greer	n Flag		U	ist
Reaction run below - 140°C Batch/flow	Gree		Tick X					/ork L	s Ip	qu qu fi cen crys	uenchi iltratic trifuga stallisa	ing on ation	int			Greer			Quer	
Reaction run below - 140°C atch/flow low	Gree	n Flag		_			L	ork U	s Ip mper	qu qu fi cen crys ature on (< 2	uenchi ltratic trifuga stallisa distilla 140 °C	ing on ation ation/ Cat at	/evap	oratio	n/				Quer	nchin
Reaction run below - 140°C atch/flow low	Gree	n Flag					L	ork U	s Ip mper	qu fi cen crys ature on (< con	uenchi iltratic trifuga stallisa distilla	ing on ation ation ation/ Cat at ching	/evap	oratio	n/		n Flag		Quer	nchin atior

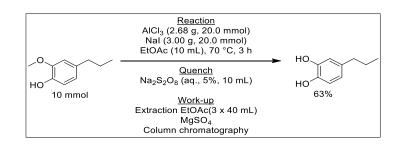
Health & safety				List substances and H-codes	List substances and H-codes	List substances and H-codes
	Red Flag	Amber Flag	Green Flag			
Highly explosive	H200, H201, H202, H203	H205, H220, H224				
Explosive thermal runaway	H230, H240, H250	H241	If no red or amber	Al: H250		NaCl $Na_2S_2O_3$
Toxic	H300, H310, H330	H301, H311, H331,	flagged H codes present		4-propylguaiacol: H311	CH₃CN
Long Term toxicity	H340, H350, H360, H370, H372	H341, H351, H361, H371, H373	then green flag	I ₂ : H372		EtOAc HCI
Environmental implications	H400, H410, H411, H420	H401, H412		I ₂ : H400 heptane: H410		

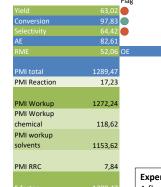
Use of chemicals of environmental concern		List substances of very high concern
Chemical identified as Substances of Very High Concern by ChemSec which are utilised	Red Flag	

• Method I1: AlCl₃ + Nal [BL-47]

Yield, AE, RME, MI/PMI and OE

field, AE, Rivie, Wil/ Fivil and OE	I ()								3.					h., , , , ,			1
Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction	Volume (cm ³)	Density	Mass (g)	Work up	Mass (g)	Workup solvent	Volume	Density	Mass (g)
								solvent		(g ml ⁻¹)		chemical			(cm ³)	(g ml ⁻¹)	
										,					v , v	(0)	
4-propylguaiacol	1,66	166,22	0,0100			AICI ₃	2,68	EtOAc	10,00	0,90	9,00	$Na_2S_2O_3$	63,76	EtOAc (extr)	120,00	0,90	108,00
water	0,18	18,02	0,0100			Nal	3,00					MgSO ₄	10,00	EtOAc (column)	135,00	0,90	121,50
												silica	40,00	heptane	1275,00	0,68	867,00
														H ₂ O	9,82	1,00	9,82
Total	1,84	184,24			0,00		5,68				9,00		113,76				1106,32
									Flee								





I	Mass	MW	Mol
Product	0,96	152,19	0,0063
	mass		
Unreacted limiting reactant	0,036		
		•	

Experimental: [BL-47]

63,0 97,8 64,4

Solvents (First Pass)		List solvents below
Preferred solvents	water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane	H ₂ O, EtOAc
Problematic solvents: (acceptable only if substitution does not offer advantages)	DMSO, cyclohexanone, DMPU, AcOH, Ac2O, Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene, MTBE, cyclohexane , chlorobenzene, formic acid, pyridine, Me-THF	Heptane
Hazardous solvents: These solvents have significant health and/or safety concerns.	dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane	
Highly hazardous solvents: The solvents which are agreed not to be used, even in screening	Et_2O , Benzene, CCI_4 , chloroform, DCE, nitromethane, CS_2 , HMPA	

A flame-dried and argon flushed 100 mL pressure tube, equipped with magnetic stirring bar and rubber septum, was charged with AlCl₃ (2.68 g, 20.0 mmol, 2.0 equiv.) and Nal (3.00 g, 20.0 mmol, 2.0 equiv.). Vacuum was applied and the tube was back-filled with argon. Subsequently, 2-methoxy-4-propylphenol (1.60 mL, 10.0 mmol, 1.0 equiv.) and dry EtOAc (10 mL) were added through the septum. The septum was removed and the tube was closed properly. The reaction mixture was stirred for 3 h at 70 °C, cooled to r.t. and carefully quenched with Na₂S₂O₃ (aq., 5%, 10 mL). The obtained mixture was extracted with EtOAc (3 x 40 mL). The combined organic fractions were dried over MgSO₄, filtered and evaporated under reduced pressure. The product was isolated using an automated flash chromatography system using a heptanes / EtOAc in heptanes, 30 min; 15% EtOAc in heptanes; 15 min). Pure 4-propylbenzene-1,2-diol was obtained in 63% yield (0.96 g, 6.3 mmol). 2-Methoxy-4-propylphenol was recovered for 2% (36 mg, 0,2 mmol).

Generated wast

Catalyst/enzyme (First Pass)		Tick
Catalyst or enzyme used, or reaction takes place without any catalyst/reagents.	Green	
Catalyst of enzyme used, of reaction takes place without any catalyst/reagents.	Flag	
Use of stoichiometric quantities of reagents	Amber	
	Flag	
Use of reagents in excess	Red Flag	x

		Tick
Facile recovery of catalyst/enzyme	Green Flag	
catalyst/enzyme not recovered	Amber Flag	

Supply remaining	Flag colour	Note element	1	H 1.00794				ıntil dep known r													H
5-50 years	Red Flag			3	4			ased on cu extrac	rrent rate							5	6	7	8	9	10
				Li 6.941	Be 9.012182			5-50 y	years							B 30.811	C	N 14.00674	0 15.9994	F 18.95840	No 20.17
50-500 years	Amber Flag	Al, I		11 Na	12 Mg			50-100								13 Al	14 Si	15 P	16 S	17 CI	18 A
+500 years		Cl, Na		22.58977	24.3050			100-500	0 years							AI 26.98153	31 28.0855	P 39.97376	32.066	35.4527	39.94
+500 years	Green Flag	CI, Na		19 K	20 Ca	21 Sc	22 Ti	23 V	24 Cr	25 Mn	26 Fe	27 Co	28 Ni	29 Cu	30 Zn	an Ga	32 Ge	AS	зя Se	as Br	36 K
				39.0983	40.078	44.95591	47,867	50.9415	51.9961	54.93804	55.845	58.93320	58.6934	63.546	65.39				78.96	79.904	83.80
				37 Rb	38 Sr	30 Y	40 Zr	A1 Nb	Mo	43 Tc	Ru	AS Rh	46 Pd	Ag	"Cd	in In	so Sn	S1 Sb	s₂ Te	8 	54 X
				85.4678 55	87.62	88.9085 57	91.224	92.90638	95.94	(98)	101.07		105.42	107.8682	112.411	114.818	118,760	121.760	127.60 84	126.9044 85	131.2
				Cs	Ba	La *	Hf	Та	Ŵ	Re	Os	lr.	Pt	Au	Hg	TI	Pb	Bi	Po	At	R
				132.9054	137.327	138.9055	178.49	180.9479 105	183.84 106	186.207 107	190.23 108	192.217 109	195.078 110	196.9665	200.59	204.3833	270.2 114	208.9804	(209)	(210) 117	(222) 118
				Fr	Ra	Ac‡	Rf	Db	Sg	Bh	Hs	Mt	Ds	Rq	Uub	Uut	Uuq	Uup	Lv	Uus	Uu
				(223)	226.025	(227)	(257)	(260)	(263)	(262)	(265)	(266)	(271)	(272)	(285)	(284)	(289)	(288)	(292)		
								58 5	0	60	61	62	63	64	65	66	67	68	69	70	71
					La	nthanic		Ce	Pr	Nd	Pm	Sm	Eu	Gd	Tb	Dy	Ho	Er	Tm	Yb	LL 174.9
							1	90 9		92 92		94	95 95	96	97	58	99	100	101	102	103
						Actinid		Th 232.0381 2	Pa 31.0289	U	Np	Pu (244)	Am (243)	Cm (247)	Bk (247)	Cf (251)	Es (252)	Fm (257)	Md (258)	No (259)	Lr (262)
												(1 - 1)	1	(e.r.)	(a.c.)	(1 - 1)	(111)	(e.s.)			(cort)
ergy (First Pass)	-		Tic	:K			_												11	ck	
Reaction run between 0 to 70°	C	Green Flag							Rea	ction	run at	reflu	x		F	Red Fla	ag			ĸ	
Reaction run between -20 to 0 or 70 t	o 140°C	Amber Flag	x																		
	.0 1 10 0	, and crimes	^					React	ion ru	ın 5°C	or m	ore be	elow t	the	Gr	een F	lag				
Reaction run below -20 or above 1	40°C	Red Flag							sol	vent l	oiling	point	t		0.		.u.р				
			Tic																		
tch/flow w	Gr	een Flag	IIC	к			^{wo}	rk Up		auc	nchin	~								st	
ich		iber Flag	Х								ration	•									
			<u> </u>				1				ifugat										
							1				allisati				Gr	een F	lag		filtra	ation	
							Lov	w tem					vapor	ation	/						
								sublim	nation	ı (< 14	IO °C a	at atm	osphe	eric							
							sol	vent e	xchar	nge, q	uench	ning ir	ito aq	ueous	5 An	nber F	laσ		Extra	ction	
											lvent										

& safety						
	Red Flag	Amber Flag	Green Flag			
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber			
			flagged H codes present			
Explosive thermal runaway	H230, H240, H250	H241	then green flag			AICI
Toxic	H300, H310, H330	H301, H311, H331,				EtOAc
					4-propylguaiacol: H311	H ₂ O
Long Term toxicity	H340, H350, H360, H370, H372	H341, H351, H361,				$Na_2S_2O_3$
		H371, H373				
Environmental implications	H400, H410, H411, H420	H401, H412		Heptane: H410; Nal: H400		
				neptane: h410; Nai: h400		

chromatography/ion exchange

high temperature multiple recrystallisation

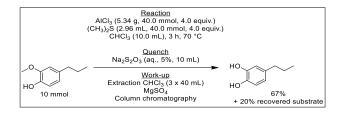
Use of chemicals of environmental concern		List substances of very high concern
Chemical identified as Substances of Very High Concern by ChemSec which are utilised	Red Flag	

Red Flag

• Method I2: AlCl₃ + Me₂S [BL-44]

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm ³)	Density (g ml ⁻¹)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm ³)	Density (g ml ⁻¹)	Mass (g)
										·- ·							
4-propylguaiacol	1,66	166,22	0,0100			AICI ₃	5,34	CHCl ₃	10,00	1,48	14,80	$Na_2S_2O_3$	0,50	CHCl ₃	120,00	1,48	177,60
H ₂ O	0,18	18,02	0,0100			(CH ₃) ₂ S	2,49					MgSO ₄	10,00	EtOAc	135,00	0,90	121,50
												SiO ₂	40,00	heptane	1275,00	0,68	867,00
														H ₂ O	9,82	1,00	9,82
Total	1,84	184,24			0,00		7,83				14,80		50,50				1175,92



.,	
	Flag
	66,70 🔴
Conversion	80,14 🔴
	83,22 🔴
AE	82,61
RME	55,10 OE
PMI total	1232,40
PMI Reaction	24,11
PMI Workup	1208,29
PMI Workup	
chemical	49,75
PMI workup	
solvents	1158,54
PMI RRC	9,53
	E
	1231,40 A

	Mass	MW	Mol
Product	1,02	152,19	0,0067
	mass		
Unreacted limiting reactant	0,33		
_		_	

	Mass
Generated waste	1249,872

Experimental: [BL-44]

66,7 80,1

83,2

olvents (First Pass)		List solvents below
Preferred solvents	water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane	H ₂ O, EtOAc
Problematic solvents: (acceptable only if substitution does not offer advantages)	DMSO, cyclohexanone, DMPU, AcOH, Ac2O, Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene, MTBE, cyclohexane , chlorobenzene, formic acid, pyridine, Me-THF	Heptane
Hazardous solvents: These solvents have significant health and/or safety concerns.	dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane	
Highly hazardous solvents: The solvents which are agreed not to be used, even in screening	Et_2O , Benzene, CCl_4 , chloroform, DCE, nitromethane, CS_2 , HMPA	CHCl ₃

A flame-dried and argon flushed 100 mL pressure tube, equipped with magnetic stirring bar and rubber septum, was charged with AlCl₃ (5.34 g, 40.0 mmol, 4.0 equiv.). Vacuum was applied and the tube was back-filled with argon. Subsequently, 2-methoxy-4-propylphenol (1.66 g, 10.0 mmol, 1.0 equiv.), $(CH_3)_2S$ (2.96 mL, 40.0 mmol, 4.0 equiv.) and dry CHCl₃ (10 mL) were added through the septum. The septum was removed and the tube was closed properly. The reaction mixture was stirred for 3 h at 70 °C, cooled to r.t. and carefully quenched with Na₂S₂O₃ (aq., 5%, 10 mL). The obtained mixture was extracted with CHCl₃ (3 x 40 mL). The combined organic fractions were dried over MgSO₄, filtered and evaporated under reduced pressure. The product was isolated using an automated flash chromatography system using a heptanes / EtOAc gradient (40 g SiO₂ cartridge, flow rate: 30 mL/min, eluent: heptanes, 2 mir; heptanes to 15% EtOAc in heptanes, 30 mir; 15% EtOAc in heptanes; 15 min). Pure 4propylbenzene-1,2-diol was obtained in 67% yield (1.02 g, 6.7 mmol). 2-Methoxy-4propylphenol was recovered for 20% (330 mg, 2.0 mmol).

Catalyst/enzyme (First Pass)		Tick
Catalyst or enzyme used, or reaction takes place without any catalyst/reagents.	Green	
Catalyst of enzyme used, of reaction takes place without any catalyst/reagents.	Flag	
Use of stoichiometric quantities of reagents	Amber	
	Flag	
Use of reagents in excess	Red Flag	x

		Tick
Facile recovery of catalyst/enzyme	Green Flag	
catalyst/enzyme not recovered	Amber Flag	

Supply remaining	Flag colour	Note element	1.007	1			depleti wn rese												He 4.00260
5-50 years	Red Flag		2	4		(based	on curren extraction	t rate of						s B	° c	7 N	* 0	°F	10 Ne
50-500 years	Amber Flag	AI, S	6.941	9,012182		50	i-50 year)-100 yea	irs						10.811 13 Al	12.0107 14 Si	14.00574 15	15.9994 16 S	18.99840 17 CI	20.1797
+500 years	Green Flag	Cl, Na	N 22.58 19	24,3050	21 Sc	12 23	0-500 ye	25	26 An Fe	27 Co	28 Ni	29	30	AI 26.98153 31 Ga	51 28.0855 32 Ge	P 39.97376	32.066 34 Se	35.4527 35	Ar 39.948
			39.05			17.867 50		9961 54.5	An Fe 1804 55.845	58.93320	58.6934	Cu 63.546	2n 65.39	Ga 09.723	72.61	As 24.92160	78.96	Br 79.904	Kr 83.80
			R 85.45		Y	Zr	Nb		Tc Ru	Rh	Pd	Åg	Cd	In	Sn	Sb	Те	1	Xe
			55 C	56	57 La *	1.224 92 2 73 Hf	74 Ta	94 (98) 75 W F	Re Os	77 102.9655	78 Pt	79 Au	80 Hg	TI	R2 Pb	*1 Bi	84 Po	#5 At	85 Rn
			132.5		138.9055	28.49 18 04 10	0.9479 18	186	207 190.23 108	192.217	195.078	196.9665	200.59 112	201.2113	270.2	208.9804	(209)	(210)	(222)
			F (223)		Ac #		Db		Sh Hs	Mt (256)	Ds	Rq (272)	Uub	Uut (284)	Uuq	Uup	Lv (292)	Uus	Uud
			(23)	228.025	(11)	<i>DI</i>] [2	0) [120	5) (25)	1 [203]	(200)	(271)	1010	(285)	(204)	(285)	(200)	(04)		
				Li	anthanide					sa Sm	ea Eu	Gd	ть	⁶⁶ Dy	୍ମ Ho	Er	∞ Tm	P0 Yb	71 Lu
						140.90 90	91	92	150.36 93	151.964 94	157.25 95		158.9253 97	162.50 58	164.9303 99	167.26 100	168.9342 101	173.04 102	174.967 103
					Actinide	232.03			Np (237)	Pu (244)	Am (243)	Cm (247)	Bk (247)	Cf (251)	Es (252)	Fm (257)	Md (258)	No (259)	Lr (262)
ergy (First Pass)			Tick														T	ïck	
Reaction run between 0 to 70°C	2	Green Flag					F	Reactio	on run a	ıt reflu	іх			Red Fl	ag			x	
						Reaction run 5°C or more below the solvent													
Reaction run between -20 to 0 or 70 to	o 140°C	Amber Flag	х			Reacti	on ru	n 5°C (or more	belov	v the s	olven	t _						
Reaction run between -20 to 0 or 70 to Reaction run below -20 or above 14		Amber Flag Red Flag	x			Reacti	on rui		or more oiling po		v the s	olven	t Gi	reen F	lag				
			X			Reacti Work					v the s	olven	t Gi	reen F	lag			.ist	
Reaction run below -20 or above 14 tch/flow W	40°C Gr	Red Flag een Flag	Tick					bo	piling po	ng	v the s	olven	t Gi	reen F	lag		-	ist	
Reaction run below -20 or above 14	40°C Gr	Red Flag						bc q	piling po Juenchi filtratio	ng	v the s	olven	G						
Reaction run below -20 or above 14 tch/flow W	40°C Gr	Red Flag een Flag	Tick			Work	Up	cer cry	uenchi filtratio ntrifuga	ng n tion			Gi	reen F reen F				<u>ist</u>	
Reaction run below -20 or above 14 tch/flow W	40°C Gr	Red Flag een Flag	Tick			Work Low t	Up empe	d cer cry rature	uenchi filtratio ntrifuga stallisa e distilla	ng n tion tion/e	vapor	ation/	Gi						
Reaction run below -20 or above 14 tch/flow W	40°C Gr	Red Flag een Flag	Tick			Work Low t	Up empe	cer cry rature	uenchi filtratio ntrifuga	ng n tion tion/e at atn	vapor	ation/	GI	reen F	lag		Filt	ration	
Reaction run below -20 or above 14 c ch/flow w	40°C Gr	Red Flag een Flag	Tick			Work Low t sul	Up empe olimat nt exc	cer cry rature ion (<	uenchi filtratio ntrifuga e distilla 140 °C	ng n tion tion/e at atn ching in	vapor nosphi nto aq	ation/ eric ueous	GI		lag		Filt		

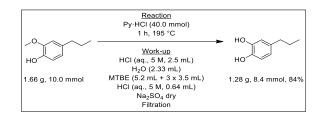
Health & safety				List substances and H-codes	List substances and H-codes	List substances and H-codes
	Red Flag	Amber Flag	Green Flag			
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber			
			flagged H codes present			
Explosive thermal runaway	H230, H240, H250	H241	then green flag			AICI ₃
Тохіс	H300, H310, H330	H301, H311, H331,			4-propylguaiacol: H311	(CH₃)₂S EtOAc H₂O
Long Term toxicity	H340, H350, H360, H370, H372	H341, H351, H361, H371, H373		CHCl ₃ : H372		Na ₂ S ₂ O ₃
Environmental implications	H400, H410, H411, H420	H401, H412		Heptane: H410		

_	Use of chemicals of environmental concern		List substances of very high concern
	Chemical identified as Substances of Very High Concern by ChemSec which are utilised	Red Flag	

• Method J: Py·HCl [MBAL-642]

Yield, AE, RME, MI/PMI and OE

			Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction	Volume (cm ³)	Density	Mass (g)	Work up	Mass (g)	Workup solvent	Volume	Density	Mass (g
								solvent		(g ml ⁻¹)		chemical			(cm³)	(g ml ⁻¹)	
4-propylguaiacol	1,66	166,22	0,010			Py·HCl	3,066					Na ₂ SO ₄	9,99	MTBE	15,70	0,74	11,62
Py·HCl	1,55	155,56	0,010									HCI	0,57	H ₂ O	2,33	1,00	2,33
														H ₂ O (HCI)	3,14	1,00	3,14
																	0,00
Total	3,21	321,78			0,00		3,07	l	Flag		0,00		10,56				17,09



		гіа
Yield	84,21	
Conversion	100,00	
	84,21	
AE	47,30	
	39,83	OE
PMI total	26,51	
PMI Reaction	4,91	
PMI Workup	21,60	
PMI Workup		
chemical	8,25	
PMI workup		
solvents	13,35	
PMI RRC	4,91	
	25,51	

 Mass
 MW
 Mol

 Product
 1,28
 152,19
 0,0084

 mass
 mass
 Unreacted limiting reactant
 0,000

Mass
32,654

Solvents (First Pass)		List solvents below
Preferred solvents	water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane	H ₂ O
Problematic solvents: (acceptable only if substitution does not offer advantages)	DMSO, cyclohexanone, DMPU, AcOH, Ac2O, Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene, MTBE, cyclohexane , chlorobenzene, formic acid, pyridine, Me-THF	
Hazardous solvents: These solvents have significant health and/or safety concerns.	dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane	MTBE
Highly hazardous solvents: The solvents which are agreed not to be used, even in screening	Et_2O , Benzene, CCI_4 , chloroform, DCE, nitromethane, CS_2 , HMPA	

Experimental [MBAL-462]:

84,2

A 50 mL two-necked roundbottom flask, equipped with magnetic stirring bar and reflux condenser, was charged with 2methoxy-4-propylphenol (xx, 1.66 g, 10.0 mmol, 1 equiv.) and Py-HCI (4.62 g, 40.0 mmol, 4.0 equiv.). The obtained mixture was stirred for 1 h at 195 °C, after which it was allowed to cool to 90 °C. Subsequently, HCI (aq., 5 M, 2.5 mL, 12.5 mmol, 1.25 equiv.) and H₂O (2.33 mL) were added. Stirring was continued allowing the temperature of the mixture to reach 35 °C. Subsequently, to the crude mixture was added MTBE (5.2 mL). The organic layer was separated and the aqueous layer was extracted with MTBE (3 × 3.5 mL). The combined organix fractions were washed with HCI (aq., 5 M, 0.64 mL), dried over Na₂SO₄, filtered and evaporated under reduced pressure. Pure 4-propylbenzene-1,2-diol (xx) was obtained in 84% yield (1.28 g, 8.40 mmol).

Catalyst/enzyme (First Pass)						
Catalyst or enzyme used, or reaction takes place without any catalyst/reagents.	Green					
catalyst of enzyme used, of reaction taxes place without any catalyst/reagents.	Flag					
Use of stoichiometric quantities of reagents	Amber					
use of stolenometric quantities of reagents	Flag					
Use of reagents in excess	Red Flag	х				

		Tick
Facile recovery of catalyst/enzyme	Green Flag	
catalyst/enzyme not recovered	Amber Flag	

Supply remaining	Flag colour	Note element		H 1.00794					letion of the serves of the se												He 4,002
5-50 years	Red Flag			3 Li	4 Be		(ba	sed on cu extrac	rrent rate tion)	of						5 B	°c	7 N	* 0	°F	10 Ne
50-500 years	Amber Flag			6.941 11	9.012182 12			5-50 50-100	years							10.811	12.0107	14.00674 15	15.9994 16	18.59840 17	20.17
+500 years	Green Flag	х		Na 22.98977 19	Mg 24.3050 20	21	22	100-50	0 years	25	26	27	28	29		Al 26.98153	Si 28.0855	P 39.97376	S 32.066 24	Cl 35.4527	Ar 39.948
	Ŭ		I	K 39.0983	Ca 40.078	Sc 44.95591	Ti 47.867	V 50.9415	Cr 51.9961	Mn 54.93804	Fe 55.845	Co 58.93320	Ni 58.6934	Cu 63.546	Zn 05.39	Ga 09.723	Ge	As 74.92160	Se 78.96	Br 79.904	Kr 83.80
				37 Rb 85.4678	31 Sr	30 Y	40 Zr 91,224	41 Nb	42 Mo	43 Tc (98)	Ru	Rh	46 Pd	Ag	Cd	e. In	so Sn	ST Sb	S2 Te	53	54 Xe
				55 Cs	56 Ba	57 La *	72 Hf	73 Ta	24 W	75 Re	75 Os	77 Ir	78 Pt	77 Au	80 Hg	si Ti	ez Pb	83 Bi	81 Po	as At	as Rn
				132.9054 87 Fr (223)	137.327 88 Ra 226.025	138.9055 89 Ac ‡ (227)	178.49 104 Rf (257)	180.9479 105 Db (260)	105 106 Sg (263)	186.207 307 Bh (262)	190.2) 108 Hs (265)	192.217 109 Mt (266)	193.078 110 DS (271)	196.9665 111 Rq (272)	200.59 112 Uub (285)	204.3833 113 Uut (254)	270.2 114 Uuq (289)	208.9804 115 Uup (288)	(209) 116 LV (292)	(210) 117 Uus	(222) 118 Uu
					La	inthani		Ce 40.9077 1	0 Pr 44.24	0 Nd 145)	61 Pm 150.36	62 Sm 151.964	63 Eu 157,25	64 Gd 158.9253	65 Tb 158.9253	66 Dy 162.50	67 Ho 164.9303	68 Er 167.26	69 Tm 168.9342	70 Yb 173.04	71 Lu 174.96
						Actinid	es‡	Th	Pa 31.0289	U 138.0289	93 Np (237)	94 Pu (244)	95 Am (243)	96 Cm (247)	Bk	98 Cf (251)	99 Es (252)	100 Fm (257)	101 Md (258)	102 No (259)	103 Lr (262)
nergy (First Pass)			Tic	:k															Tic	k	
Reaction run between 0 to 70°C		Green Flag							Rea	ction	run a	t reflu	x			Red Fl	ag				
Reaction run between -20 to 0 or 70 to	o 140°C	Amber Flag					Rea	ction	run 5'	°C or	more	belov	, the s	solver	nt -						
Reaction run below -20 or above 14	ł0°C	Red Flag	х	[ng po				Gi	reen F	-lag				
atch/flow			Tic	:k			Wo	rk Up											Lis	t	
low	Gr	een Flag	quenching																		
atch	Am	ber Flag	Х	(1			filt	ratior	۱		Evano		vanor	ation				
										crysta	ifugat allisat	ion	Green Flag Filtra		Filtra	tion					
												tion/e at atm			′						

Health & safety				List substances and H-codes	List substances and H-codes	List substances and H-codes
	Red Flag	Amber Flag	Green Flag			
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber			
			flagged H codes present			
Explosive thermal runaway	H230, H240, H250	H241	then green flag			
Τοχίς	H300, H310, H330	Н301, Н311, Н331,			4-Propylguaiacol: H311	H ₂ O MTBE Py·HCl
Long Term toxicity	H340, H350, H360, H370, H372	H341, H351, H361,				, y no.
		H371, H373				
Environmental implications	H400, H410, H411, H420	H401, H412				

solvent exchange, quenching into aqueous

solvent chromatography/ion exchange

high temperature multiple recrystallisation Amber Flag

Red Flag

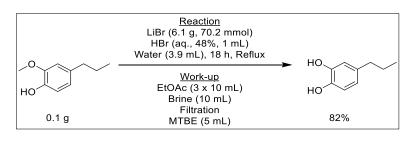
Extraction

Use of chemicals of environmental concern		List substances of very high concern
Chemical identified as Substances of Very High Concern by ChemSec which are utilised	Red Flag	

• Method K: LiBr and HBr [MBAL-795]

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction	Volume (cm ³)	Density	Mass (g)	Work up	Mass (g)	Workup solvent	Volume	Density	Mass (g)
								solvent		(g ml ⁻¹)		chemical			(cm³)	(g ml ⁻¹)	
4-propylguaiacol	0,10	166,22	6,016E-04			H ₂ O	0,011	H ₂ O (HBr)	0,78	1,00	0,78	NaCl	3,60	EtOAc	30,00	0,90	27,06
HBr	0,72	80,91	8,899E-03			LiBr	6,10	H ₂ O	3,89	1,00	3,89	Celite	1,20	H ₂ O (brine)	10,00	1,00	10,00
														MTBE	5,00	0,74	3,70
																	0,00
Total	0,82	247,13			0,00		6,11		-		4,67		4,80				40,76





	Mass	MW	Mol
Product	0,075	152,19	4,93E-04
	mass		
Unreacted limiting			
reactant	0,00		

	Mass
Generated waste	57,090

Solvents (First Pass)		List solvents below
Preferred solvents	water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane	H ₂ O, EtOAc
Problematic solvents: (acceptable only if substitution does not offer advantages)	DMSO, cyclohexanone, DMPU, AcOH, Ac2O, Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene, MTBE, cyclohexane , chlorobenzene, formic acid, pyridine, Me-THF	
Hazardous solvents: These solvents have significant health and/or safety concerns.	dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane	МТВЕ
Highly hazardous solvents: The solvents which are agreed not to be used, even in screening	Et ₂ O, Benzene, CCl ₄ , chloroform, DCE, nitromethane, CS ₂ , HMPA	

Experimental [MBAL-795]:

81,9 100,0

81,9

In a 50 mL roundbottomed flask, equipped with magnetic stirring bar and reflux condenser, LiBr (6.10 g, 70.2 mmol, 117 equiv.) was dissolved in H₂O (3.9 mL). When LiBr was completely dissolved, 2-methoxy-4-propylphenol (0.10 g, 0.60 mmol, 1.0 equiv.) and HBr (aq., 48%, 1.50 g, 8.84 mmol, 14.7 equiv.) were added. The mixture was stirred for 18 h under reflux, after which it was cooled to r.t. in ice water. The crude mixture was diluted with brine (10 mL), extracted with EtOAc (3 × 10 mL) and evaporated under reduced pressure. The crude product was redissolved in MTBE (5 mL) and filtered over a plug of Celite. Volatiles were evaporated under reduced pressure, delivering 4-propylbenzene-1,2-diol in 82% yield (75 mg, 0.47 mmol). The obtained spectroscopic data are in accordance with those reported before.

Catalyst/enzyme (First Pass)		Tick
Catalyst or enzyme used, or reaction takes place without any catalyst/reagents.	Green	
Catalyst of enzyme used, of reaction takes place without any catalyst/reagents.	Flag	
Use of stoichiometric quantities of reagents	Amber	
ose of stoichiometric quantities of reagents	Flag	
Use of reagents in excess	Red Flag	x

		Tick
Facile recovery of catalyst/enzyme	Green Flag	
catalyst/enzyme not recovered	Amber Flag	

Catalyst/enzyme (First Pass)		Tick
talyst or enzyme used, or reaction takes place without any catalyst/reager Use of stoichiometric quantities of reagents	Green	
catalyst of enzyme used, of reaction takes place without any catalyst/reagents.	Flag	
Use of steichiometric quantities of reagents	Amber	
	Flag	
Use of reagents in excess	Red Flag	х

		Tick
Facile recovery of catalyst/enzyme	Green Flag	
catalyst/enzyme not recovered	Amber Flag	

ritical elements			- I	н				em ntil
Supply remaining	Flag colour	Note element		1.00794				no
5-50 years	Red Flag			3	4		(ba	sed
5 50 (cuis	incu i iug			Li	Be			
50-500 years	Amber Flag	Li		6.941	9.012182			
SU-SUU years	Alliber Flag	LI		11	12			50
				Na	Mg			10
+500 years	Green Flag			22.58977	24.3050			_
+500 years	Greening			19	20	21	22	23
				ĸ	Ca	Sc	Ti	
				39.0983	40.078	44.95591	47.867	50
				37		39	-40	41

H .00794				until de known	pletion reserve	of											2
u	4 Be		(1	ext	urrent rat action)	e of						5 B	° c	2 N	* 0	° F	10
941	9.012182) years							10.811	12.0107	14.00674	15.9994	18.59840	20.5
1	12				00 years							13	54	15	16	17	18
Na	Mg			100-5	00 years							AI	Si	Р	S	CI	Ŀ
2.58977	24.3050	21	22	23	24		25	27	28	29	10	26.98153	28.0855	39.97376	32.066	35.4527	39.
ĸ	Ca	Sc	ті	v	⁷ Cr	Mr		Co	Ni	Cu	70	Ga	Ge	Ås.	Se	Br	1
R (1983	43.028	5C 44.95591	42.867	50.941	51,9961	MIN		58.93320		63.546	20	69.723	72.61	74.92360	78.96	79.504	
9.0983 g	40.078	44.95591	47,867	41	42	43	55.845	58.9332	46	63.546	48				78.96	79.504	82
Rb	Sr	ν.	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Те	Ĩ.	Ľ
5.4678	87.62	88.9085	21.224	92,906		(28)	101.07	102,9951	106.42	107 8683		114.010	115,760	121.750	127.60	126.5044	
5	56	57	11	73	24	25	75		24	77	80	81	82	83	84	85	8
Cs	Ba	La *	Hf	Та	w	Re	Os	10	Pt	Au	Hg	т	Pb	Bi	Po	At	L
32.9054	137.327	138.9055	178.49	180.94		186.20	190.21				200.59	201.3111	270.2	208.9804	(209)	(210)	0
g.	88	89	104	105	106	107	108	109	110	111	112	113	114	115	116	117	11
Fr	Ra	Ac ‡	Rf	Db	Sg	Bh	Hs	Mt	Ds	Rq	Uub	Uut	Uuq	Uup	Lv	Uus	L.
223)	226.025	(227)	(257)	(260)	(263)	(262)	(265)	(266)	(271)	(272)	(285)	(284)	(289)	(288)	(292)		L
				58	59	60	61	62	63	64	65	66	67	68	69	70	71
	La.	nthanic	105 ¥	Ce	Pr	Nd	Pm	Sm	Eu	Gd	Tb	Dy	Ho	Er	Tm	Yb	
		manne	~	140.9077	144.24	(145)	159.36	151,994	157.25	158,9253	158,9253	162.50	164,9303	167.26	168.9342	173.04	17
				90	91	92	93	94	95	96	97	98	99	100	101	102	10
		Actinid	es‡	Th	Ра	U	Np	Pu	Am	Cm	Bk	Cf	Es	Fm	Md	No	
				232.0381	231.0289		(227)	(244)	(243)	(247)	(247)	(251)	(252)	(257)	(258)	(259)	0

nergy (First Pass)					
Reaction run between 0 to 70°C	Green Flag				
Reaction run between $\ -20$ to 0 or 70 to 140°C	Amber Flag	x			
Reaction run below -20 or above $140^{\circ}C$	Red Flag				

Batch/flow		Tick
Flow	Green Flag	
Batch	Amber Flag	Х

		TICK
Reaction run at reflux	Red Flag	x
Reaction run 5°C or more below the solvent boiling point	Green Flag	

Work Up	List	
quenching		
filtration		
centrifugation	Green Flag	Evaporation
crystallisation		Filtration
Low temperature distillation/evaporation/		
sublimation (< 140 °C at atmospheric		
solvent exchange, quenching into aqueous	Amber Flag	Extraction
solvent	Amber Hug	Extraction
chromatography/ion exchange		
high temperature	Red Flag	
multiple recrystallisation		

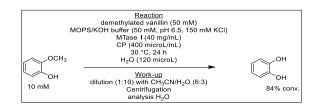
Health & safety				List substances and H-codes	List substances and H-codes	List substances and H-codes
	Red Flag	Amber Flag	Green Flag			
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber			
			flagged H codes present			
Explosive thermal runaway	H230, H240, H250	H241	then green flag			H ₂ O
Toxic	Н300, Н310, Н330	H301, H311, H331,			4-Propylguaiacol: H311 HBr: H331	MTBE NaCl EtOAc
Long Term toxicity	H340, H350, H360, H370, H372	H341, H351, H361, H371, H373				LiBr
Environmental implications	H400, H410, H411, H420	H401, H412				
Use of chemicals of a	nvironmental concern		List substances of ver	v high concern		

Use of chemicals of environmental concern		List substances of very r
Chemical identified as Substances of Very High Concern by ChemSec which are utilised	Red Flag	

• Method L1: MTase I.²³

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm ³)	Density (g ml ⁻¹)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm³)	Density (g ml ⁻¹)	Mass (g)
Guaiacol	1,49E-04	124,14	1,20E-06	MTase I	4,80E-03	MOPS	1,256E-03	H ₂ O	0,12	1,00	0,12			CH ₃ CN	0,72	0,79	0,57
Demethylated vanillin	8,29E-04	138,12	6,00E-06	CP	2,64E-03	KCI	1,342E-03							H ₂ O	0,36	1,00	0,36
Total	0,00	262,26			0,01		0,00				0,12		0,00				0,93



NP - 1.1	04.00
Yield	84,00
Conversion	84,00
Selectivity	100,00
AE	41,99
	11,35
PMI total	9522,67
PMI Reaction	1180,41
PMI Workup	8342,26
PMI Workup	
chemical	0,00
PMI workup	
solvents	8342,26
PMI RRC	99,24
PMI FI total	3998,15
PMI FI Reaction	495,60
PMI FI Workup	3502,55
PMI FI RRC	41,67
AE FI	100,00
RME FI	27,04
E factor	9521,67
E factor FI	3997,15

	Mass	MW	Mol
Product	1,11E-04	110,11	1,01E-06
	mass		
Unreacted limiting reactant	2,38E-05		
	Mass	MW	Mol
Co Product	1,53E-04	152,15	1,01E-06
	excluding co-products	including co- products	
Generated waste	1,057	1,057	

Experimental: copied from Kroutil et al. Nature Communications. 2018, 1:82, DOI 10.1038/s42004-018-0083-2.

Representative biotransformation procedure. Analytical biotransformation reactions were carried out on 120 μ L scale as follows: MTase I (10–20 mU, 40 mg mL $^{-1}$ CFE or 13 mg mL $^{-1}$ pure enzyme, respectively) was dissolved in holo-CP solution (400 μ L mL $^{-1}$, containing 67 mg mL $^{-1}$ CFE or 22 mg mL $^{-1}$ pure enzyme, respectively). Then appropriate amounts of substrate (10–50 mM final concentration) and co-substrate (10–50 mM final concentration) and co-substrate (10–50 mM KCl) were added and the reaction samples were shaken at 30 °C and 800 rpm. See Supplementary Note 2 for details with respect to the use of an O₂-scavenger system during initial experiments. After 24 h an aliquot of the reaction was withdrawn and diluted (1:10) with MeCN (6 parts) and deionized water (3 parts). Precipitated protein was removed by centrifugation (14,000 rpm, 15 min) and the clear supernatant was filtered and directly analyzed by reversed-phase HLPC.

Solvents (First Pass)		List solvents below
Preferred solvents	water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane	H ₂ O
Problematic solvents: (acceptable only if substitution does not offer advantages)	DMSO, cyclohexanone, DMPU, AcOH, Ac2O, Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene, MTBE, cyclohexane, chlorobenzene, formic acid, pyridine, Me-THF	CH₃CN
Hazardous solvents: These solvents have significant health and/or safety concerns.	dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane	
Highly hazardous solvents: The solvents which are agreed not to be used, even in screening	Et ₂ O, Benzene, CCl ₄ , chloroform, DCE, nitromethane, CS ₂ , HMPA	

Catalyst/enzyme (First Pass)		Tick
Catalyst or enzyme used, or reaction takes place without any catalyst/reagents.	Green Flag	х
Use of stoichiometric quantities of reagents	Amber Flag	
Use of reagents in excess	Red Flag	

		Tick
Facile recovery of catalyst/enzyme	Green Flag	
catalyst/enzyme not recovered	Amber Flag	x

Supply remaining	Flag colour	Note element	1	H 1.00794				until dep known													He
5-50 years	Red Flag			3 Li	4 Be		0	based on cu extra	rrent rate							s B	°c	7 N	* 0	° F	10 Ne
50-500 years	Amber Flag	S		6.941 11	9,012182			5-50 50-100								10.811 13	12.0107	14.00674	15.9994	18.95840	20.1797
				Na	Mg			100-50								AI	Si	P	s	ci	Ar
+500 years	Green Flag			22.58977	24.3050	21	22	23	24	25	26	27	28	29	30	26.98153	28.0855	39.97376	32.066	35.4527 35	39.948 36
			•	K 39.0983	Ca 40.078	Sc 44.95591	Ti 47.867		Cr 51.9961	Mn 54.93804	Fe 55.845	Co 58.93320	Ni 58.6934	Cu 63.546	Zn 65.39	Ga 69.723	Ge 72.61	As 74.92160	Se 78.96	Br 79.904	Kr 83.80
				Rb	Sr	39 Y	Zr		Mo	43 Tc	Ru	Rh	Pd	Ag	Cd	 In	so Sn	Sb	se Te	53	54 Xe
				85.4678 55	87.63 56	88.9085 57	91.224 72	73	95.94 74	(98) 75	101.07		106.42 78	107.8682	112.411 80	81	118.760 82	121.760 83	127.60 84	126.9044 85	131.29 86
				Cs 132.9054	Ba 137.327	La * 138.9055	Hf 178.49	180.9479	W	Re 186.207	Os 190.23	lr 192.217	Pt 195.078	Au 196.9665	Hg 200.59	TI 201.313	Pb 270.2	Bi 208.9804	Po (209)	At (210)	Rn (222)
				87 Fr	⁸⁸ Ra	Ac‡	104 Rf		106 Sg	307 Bh	108 Hs	109 Mt	110 Ds	111 Rq	Uub	113 Uut	¹¹⁴ Uuq	115 Uup	116 LV	Uus	118 Uuo
				(223)	226.025	(227)	(257)	(260)	(263)	(262)	(265)	(266)	(271)	(272)	(285)	(284)	(289)	(288)	(292)		
						anthani		58 5 Ce	Pr	∞ Nd	61 Pm	Ω Sm	63 Eu	64 Gd	5 Tb	66 Dy	e7 Ho	68 Er	∞ Tm	≫ Yb	71 Lu
						antriani	ues	140.9077			150.36		157.25	158.9253	158.9253 97	162.50 98	164.9303	167.26 100	168.9342	173.04 102	174.967 103
						Actinic	ies‡	Th	Pa	U	Np	Pu	Am	Cm	Bk	Cf (251)	Es	Fm	Md	No (259)	Lr (262)
ergy (First Pass)				ick				111.001	31.0005		(11)	4449	[243]	(147)	(101)	(174)	lesel	(13)		Tick	(eas)
Reaction run between 0 to 70°C	:	Green Flag		X			Г	Reaction run at reflux Red Flag										IICK			
		Green Flag		^			L	Reaction run at reflux Red							Flag						
Reaction run between -20 to 0 or 70 to	o 140°C	Amber Flag																			
							ľ	Reaction run 5°C or more below the solvent boiling point										х			
Reaction run below -20 or above 14	40°C	Red Flag						Sound Point													
atch/flow				ick	-			Work l	la.											List	
ow	Gr	een Flag		ICK			r	WORK	р	a	uench	ning								LIST	
itch		Amber Flag									filtrati										
										cer	ntrifug	ation				C					
										cry	stallis	ation				Gree	n Flag				
								Low te	mper	ature	distil	lation	/evap	oratio	on/						
														pheric							
							Ī	solven	t exch	nange	, quei	nching	; into	aqueo	ous	Ambe	er Flag	,			
											solve	nt					1 1 1 1 2	`			

	Red Flag	Amber Flag	Green Flag		
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber		
			flagged H codes present		
Explosive thermal runaway	H230, H240, H250	H241	then green flag		MeCN
Тохіс	H300, H310, H330	H301, H311, H331,			KCI
					MOPS MTase I
Long Term toxicity	H340, H350, H360, H370, H372	H341, H351, H361,			CP
		H371, H373			
Environmental implications	H400, H410, H411, H420	H401, H412			

solvent chromatography/ion exchange

high temperature multiple recrystallisation

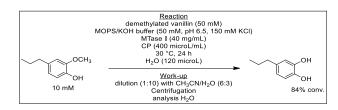
Use of chemicals of environmental concern		List substance
Chemical identified as Substances of Very High Concern by ChemSec which are utilised	Red Flag	

Red Flag

• Method L2: MTase I.²³ Simulated data.

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm ³)	Density (g ml ⁻¹)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm³)	Density (g ml ⁻¹)	Mass (g)
4-propylguaiacol	1,99E-04	166,22	1,20E-06	MTase I	4,80E-03	MOPS	1,256E-03	H ₂ O	0,12	1,00	0,12			CH ₃ CN	0,72	0,79	0,57
Demethylated vanillin	8,29E-04	138,12	6,00E-06	CP	2,64E-03	KCI	1,342E-03							H ₂ O	0,36	1,00	0,36
Total	0,00	304,34			0,01		0,00				0,12		0,00]			0,93



Yield	84,00
Conversion	84,00
Selectivity	
AE	50,01
RME	
PMI total	6890,05
PMI Reaction	854,36
PMI Workup	6035,69
PMI Workup	
chemical	0,00
PMI workup	
solvents	6035,69
PMI RRC	72,13
PMI FI total	3445,51
PMI FI Reaction	427,24
PMI FI Workup	3018,27
PMI FI RRC	36,07
AE FI	100,00
RME FI	29,84
E factor	6889,05
E factor FI	3444,51

	Mass	MW	Mol
Product	1,53E-04	152,19	1,01E-06
	mass		
Unreacted limiting reactant	3,19E-05		
	Mass	MW	Mol
Co Product	1,53E-04	152,15	1,01E-06
	excluding co-products	including co- products	
Generated waste	1,057	1,057	

Experimental: copied from Kroutil *et al*. Nature Communications. **2018**, *1:82*, DOI 10.1038/s42004-018-0083-2.

Representative biotransformation procedure. Analytical biotransformation reactions were carried out on 120 μ L scale as follows: MTase I (10–20 mU, 40 mg mL $^{-1}$ CFE or 13 mg mL $^{-1}$ pure enzyme, respectively) was dissolved in *holo*-CP solution (400 μ L mL $^{-1}$, containing 67 mg mL $^{-1}$ CFE or 22 mg mL $^{-1}$ pure enzyme, respectively). Then appropriate amounts of substrate (10–50 mM final concretation) and co-substrate (10–50 mM final concretation) and co-substrate (10–50 mM KCl) were added and the reaction samples were shaken at 30 °C and 800 rpm. See Supplementary Note 2 for details with respect to the use of an O₂-scavenger system during initial experiments. After 24 h an aliquot of the reaction was withdrawn and diluted (1:10) with MeCN (6 parts) and deionized water (3 parts). Precipitated protein was removed by centrifugation (14,000 rpm, 15 min) and the clear supernatant was filtered and directly analyzed by reversed-phase HLPC.

Solvents (First Pass)		List solvents below
Preferred solvents	water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane	H ₂ O
Problematic solvents: (acceptable only if substitution does not offer advantages)	DMSO, cyclohexanone, DMPU, AcOH, Ac2O, Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene, MTBE, cyclohexane, chlorobenzene, formic acid, pyridine, Me-THF	CH₃CN
Hazardous solvents: These solvents have significant health and/or safety concerns.	dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane	
Highly hazardous solvents: The solvents which are agreed not to be used, even in screening	Et_2O , Benzene, CCl ₄ , chloroform, DCE, nitromethane, CS ₂ , HMPA	

Catalyst/enzyme (First Pass)		Tick
Catalyst or enzyme used, or reaction takes place without any catalyst/reagents.	Green Flag	x
Use of stoichiometric quantities of reagents	Amber Flag	
Use of reagents in excess	Red Flag	

		Tick
Facile recovery of catalyst/enzyme	Green Flag	
catalyst/enzyme not recovered	Amber Flag	х

Supply remaining	Flag colour	Note element		H 1.00794				until dep known													H
5-50 years	Red Flag			3 Li	4 Be			based on cu								5 B	° c	7 N	* 0	° F	10 10
50-500 years	Amber Flag	S		6.941 11	9,012182			50-100	years D years					10.811 13	12.0107	14.00674	15.9994 16	18.95840	20.175		
+500 years	Green Flag			Na 22.58977 19	Mg 24.3050 20	21	22	23	0 years	25	26	27	28	29	30	Al 26.98153	Si 28.0855	P 39.97376 33	S 32.066 34	Cl 35.4527 35	Ar 39.948 36
			·	K 39.0983	Ca 40.078	Sc 44.95591	Ti 47.867	V 50.9415	Cr 51.9961	Mn 54.93804	Fe 55.845	Co 58.93320	Ni 58.6934	Cu 63.546	Zn 65.29	Ga 69.723	Ge 72.61	As 74.92160	Se 78.96	Br 79.904	Kr 83.80
				37 Rb 85,4678	38 Sr	30 Y	40 Zr	Nb	42 Mo	43 Tc (98)	Ru	Rh	46 Pd	Ag	Cd	en .	so Sn	St Sb	52 Te 127.60	53 125-9044	54 Xe 131.29
				ss Cs	56 Ba	57 La *	72 Hf	73 Ta	⁷⁴ w	75 Re	76 Os	n n Ir	78 Pt	79 Au	80 Hg	*1 TI	82 Pb	83 Bi	84 Po	as At	85 Rn
				132.9054 87	137.327 88	138.9055 89	178.49 104	180.9479 105	183.84 106	186.207 107	190.23 108	192.217 109	195.078 110	196.9665 111	200.59 112	204.3833 113	270.2 114	208.9804 115	(209) 116	(210) 117	(222) 118
				Fr (223)	Ra 226.025	Ac ‡	Rf (257)	Db (260)	Sg (263)	Bh (262)	Hs (265)	Mt (266)	Ds (271)	Rq (272)	Uub (285)	Uut (284)	Uuq (289)	Uup (288)	Lv (292)	Uus	Uud
							[58				62	63	ы	65	66	67	68	69	20	71
					La	anthani	des *		Pr 544.24	Nd (145)			Eu 157.25 95	Gd 158.9253	Tb 158.9253	Dy 162.50 98	Ho 164,9303 99	Er 167.26	Tm 168.9342	Yb 173.04	Lu 174.967
						Actinic	es‡	Th	Pa 231.0289	U 738.0799	Np	Pu	Am (243)	Cm	Bk	Cf	Es	Fm	Md (258)	No (259)	Lr (262)
ergy (First Pass)				ick						_	_									Tick	
Reaction run between 0 to 70	°C	Green Flag		х				Reaction run at reflux Red Flag													
Reaction run between -20 to 0 or 70	to 140°C	Amber Flag					,	Reaction run 5°C or more below the solvent													
Reaction run below -20 or above	140°C	Red Flag					ľ	boiling point Green Flag								x					
tch/flow			т	ick	-			Work l	Jn									_		List	
DW	Gr	een Flag					Ē			q	uench	ning								2.51	
tch	An	Amber Flag									filtrati										
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								Low te													
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											, 9900		,	-9000		Ambe	or Flac	7			

Chemical identified as Substances of Very High Concern by ChemSec which are utilised

h & safety					
	Red Flag	Amber Flag	Green Flag		
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber		
			flagged H codes present		
Explosive thermal runaway	H230, H240, H250	H241	then green flag		MeCN
Toxic	H300, H310, H330	H301, H311, H331,			KCI
					MOPS
					MTase I
Long Term toxicity	H340, H350, H360, H370, H372	H341, H351, H361,			СР
		H371, H373			
Environmental implications	H400, H410, H411, H420	H401, H412			

Red Flag

solvent chromatography/ion exchange

high temperature multiple recrystallisation

C1	67
21	07

Red Flag

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