

Supporting info

Co(salen)-catalyzed Oxidation of Lignin Model Substrates: an Experimental Study on the Effect of Different Reaction Parameters in Batch and Continuous Flow

Jonas Mortier, Christian V. Stevens, Joseph J. Bozell, Thomas S.A. Heugebaert

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SYNTHESIS PROCEDURE CHEMICALS

Synthesis of N,N'-Bis(salicylidene)ethylenediaminocobalt(II) 1

6 grams of N,N'-Bis(salicylidene)ethylenediamine (22.36 mmol, 1 eq.), 1.79 grams of NaOH (44.72 mmol, 2 eq.) and 0.12 grams of NaOAc.3H₂O (0.89 mmol, 0.04 eq.) were dissolved in 300 ml of boiling water under nitrogen atmosphere after which 5.32 grams of CoCl₂.6H₂O (22.36 mmol, 1 eq.) dissolved in 20 ml of water was added to the solution dropwise via a dropping funnel. After stirring the reaction for 2 hours under nitrogen atmosphere, the reaction mixture is subjected to vacuum filtration and a brown paste is obtained as residue. The residue is washed with 3 x 250 ml of water and is dried under high vacuum, after which 6.44 grams of Co(salen) (89% yield) is obtained as a brown powder.

Synthesis of 4-(hydroxymethyl)-2,6-dimethoxyphenol 4

10 grams of syringaldehyde (54.89 mmol, 1 eq.) was added to 250 ml of methanol and was cooled to 0°C with an ice bath after which 3.11 grams of NaBH₄ (82.34 mmol, 1.5 eq.) was added to the solution in 10 portions over 10 minutes while stirring. Subsequently, the ice bath was removed and the reaction was allowed to stir for 1 hour after which 100 ml of a saturated NH₄Cl solution was added. After stirring for another 30 minutes, the methanol was removed under reduced pressure and the aqueous phase was extracted with 3 x 100 ml dichloromethane. The combined organic layers were washed with brine, dried with anhydrous MgSO₄ and the solvent was removed under reduced pressure. After recrystallization in ethyl acetate, 5.78 grams of syringyl alcohol (57% yield) was obtained as pure white crystals.

Other chemicals that are not mentioned above were commercially available.

Purchased at Sigma-Aldrich: Pyridine, vanillyl alcohol, N,N-Diisopropylethylamine, NaOAc·3H₂O, and NaBH₄.

Purchased at TCI Europe: 4-hydroxybenzyl alcohol and commercially available Co(salen) and syringaldehyde

Purchased at Fraunhofer: organosolv lignin:

Organosolv lignin (97.55 wt.% dry matter) originated from an organosolv pulping pilot from Fraunhofer-Gesellschaft, Germany. A detailed description of Fraunhofer's organosolv process is described by Schulze and co-workers.^[1]

REACTION PROCEDURES

Procedure and set-up for model substrate oxidation in continuous flow (example for a 50 ml 0.2 M solution of vanillyl alcohol with DIPEA and pyridine as base)

1542 mg (10 mmol, 1 eq.) of vanillyl alcohol **3** is added to a volumetric flask of 50 ml after which 325 mg of Co(salen)^a (1 mmol, 0.1 eq.), 129 mg of DIPEA (1 mmol, 0.1 eq.)^b and 79 mg of pyridine (1 mmol, 0.1 eq.)^b are added. The volumetric flask is filled until the mark with the corresponding solvent and after shaking the mixture very briefly to dissolve all components, the suction line of the pump is added to the flask after which the opening is shielded from air with parafilm. Both the dual-piston pump (Figure 1, **nr.1**) and mass flow controller (figure 1, **nr.2**) are activated simultaneously with a pre-determined flow rate^c. The reaction mixture and oxygen flow are mixed via a Y-piece (figure 1, **nr.3**) after which they continue through the reactor tubing (figure 1, **nr.4**: PTFE tubing 0,8 mm internal diameter) as a plug flow. At the end of the reactor, a back pressure regulator cartridge (figure 1, **nr.5**) is installed to maintain the desired pressure. After disposing the first 10 ml of reaction mixture reaching the end of the reactor to ensure equilibrium is reached^d, the remaining reaction mixture is collected.

Starting product concentration for continuous flow reactions with:

- 4-hydroxybenzyl alcohol **2**: 0.2 M
- Vanillyl alcohol **3**: 0.2 M
- Syringyl alcohol **4**: 0.1 M (A reaction with 0.2 M resulted in reactor clogging with DMBQ, product solubility in DCM/MeOH (4/1) was experimentally determined to be around 0.13 M)

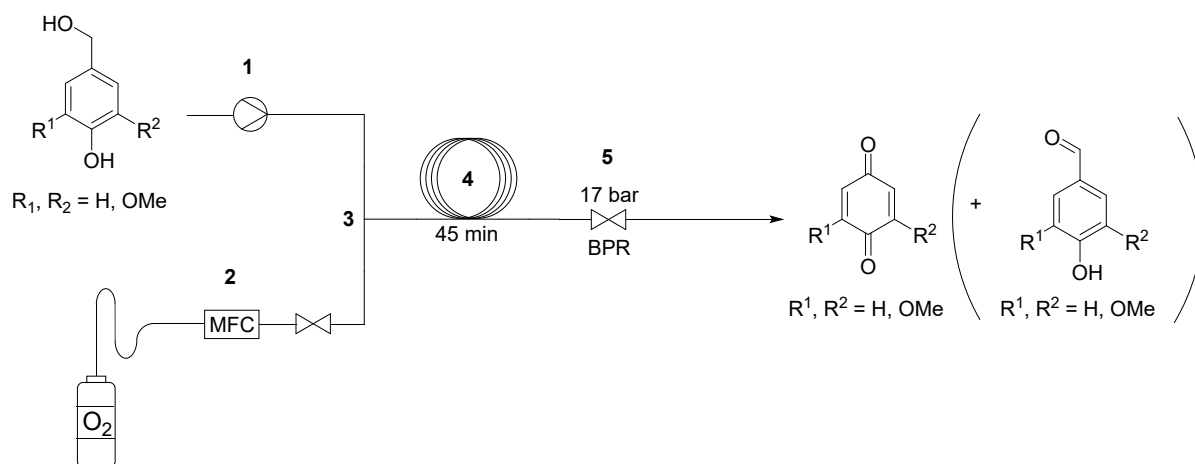


Figure 1. Graphical representation of continuous flow reactor

Procedure for model substrate oxidation in batch (example for a 25 ml 0.1 M solution of vanillyl alcohol with DIPEA and pyridine as base)

386 mg (2.5 mmol, 1 eq.) of vanillyl alcohol **3** is added to a volumetric flask of 25 ml after which 81 mg of Co(salen)^a (0.25 mmol, 0.1 eq.), 32 mg of DIPEA (0.25 mmol, 0.1 eq.)^b and 20 mg of pyridine (0.25 mmol, 0.1 eq.)^b are added. The volumetric flask is filled until the mark with the corresponding solvent and after shaking the mixture very briefly, it is added to the parr reactor. The reactor is sealed and flushed 3 times with O₂, after which the reactor is pressurized up to the desired O₂ pressure. The reaction is stirred for the appropriate amount of time after which a sample for analysis is taken.

Starting product concentration for batch reactions was 0.1 M for all model substrates.

Procedure for organosolv lignin oxidation in batch

380 mg of organosolv lignin was dissolved in 20 ml solvent in a flask and stirred for 15 minutes until everything was dissolved^e. The organosolv lignin mixture was brought in a volumetric flask of 25 ml whereafter 81 mg Co(salen)^a, 32 mg DIPEA and 20 mg pyridine were added. The flask was filled until the mark with the corresponding solvent whereafter the reaction was conducted as mentioned above.

^aPrior to weighing, Co(salen) is dried in an oven of 100 °C for 30 minutes because this is known to cause oxygen desorption of Co(salen).^[2] This is needed to make sure that 0.1 equivalents are weighed since partially oxygenated Co(salen) has a higher, but poorly defined, molar mass. It was also seen experimentally that deoxygenated Co(salen) was easier to dissolve.

^bbases were added on volumetric basis with a micropipette.

^cRatio of flow rate of reaction mixture (mL/min) with respect to oxygen (mL_N/min) can be used to calculate the exact amount of oxygen (eq.) to which the reaction mixture is exposed. The magnitude of both flow rates can be tuned to obtain the appropriate residence time.

^dDisposing the first 10 ml of reaction mixture was deemed to be sufficient because diffusion was very limited due to the reaction mixture/oxygen plug flow which made it impossible for components to diffuse and travel up-or downstream.

^eIn the case where methanol was used, not all organosolv lignin could be dissolved.

ANALYSIS PROCEDURES

Analysis procedure for oxidation of model substrates

Isolated yield calculation (only for table 1. Entries 1-4)

10 ml of reaction mixture is purified by normal phase (SiO₂) column chromatography (PE/EtOAc 7/3) after which methoxybenzoquinone **5** and vanillyl alcohol **3** (if no full conversion) are isolated. Since part of the reaction mixture is disposed to ensure equilibrium was reached in the collected sample, isolated yield calculation must be adapted to the amount of reaction mixture loaded on the silica column.

Quantitative HPLC and ¹H-NMR yield calculation (for all other reactions)^a

A sample of the reaction mixture is diluted and analyzed by high performance liquid chromatography (HPLC). Yield is calculated with a calibration curve adjusting the result for the appropriate dilution factor. To minimize the error made by the apparatus, each sample was analyzed in triplicate and the average of these 3 runs is reported.

To analyze the reaction mixture via ¹H-NMR, a sample of the reaction mixture is taken and evaporated. Since non-oxygenated Co(salen) is paramagnetic and can demonstrate highly unpredictable magnetic behaviour, the sample is exposed to a stream of pure oxygen for 5 minutes to form what is believed the peroxo-bridged species, which is diamagnetic.^[3] Yield of a product visible on ¹H-NMR is calculated via integration with respect to a product with a previously established yield by quantitative HPLC.

^aInitially, isolated yield was calculated after column chromatography purification. But since product can be lost during column chromatography, it was decided to switch to direct quantitative HPLC analysis of the crude reaction mixture.

Analysis procedure for oxidation of organosolv lignin

If not all products were dissolved after reaction, dichloromethane is added until all products are dissolved and the extra solvent is taken into the dilution factor.

First, a sample of the reaction mixture is collected and diluted. Yield of 2,6-dimethoxybenzoquinone is determined via quantitative HPLC with a calibration curve adjusting the result for the appropriate dilution factor. A second sample which was collected from the reaction was filtered over a small silica column (SiO₂) with pure EtOAc to obtain the low weight aromatics which were analyzed via ¹H-NMR. Since yield (w%) of DMBQ is known, other yields can be estimated by integration of ¹H-NMR signals considering the different molecular masses. (**Table 7**)

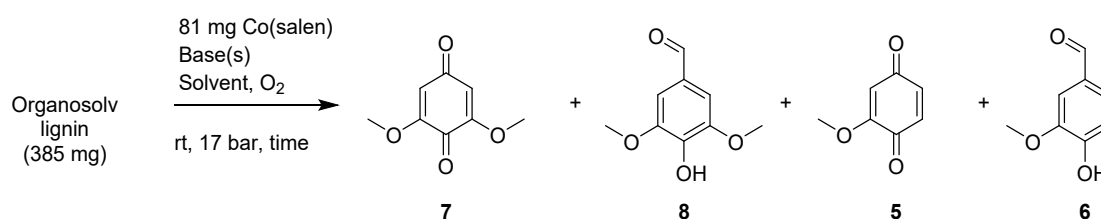


Table 7. Reaction of organosolv lignin towards low weight aromatics

Entry	Solvent	Base	Reaction time	Products
1	DCM/MeOH (4/1)	DIPEA (32 mg)+ Pyridine (20 mg)	22h	7 (3.4 w%) ^a 8 (1.1 w%) ^b 6 (0.8 w%) ^b
2	MeOH	DIPEA (32 mg) + Pyridine (20 mg)	18h	7 (1.1 w%) ^a 6 (0.3 w%) ^b 8 (0.2 w%) ^b 5 (0.2 w%) ^b
3	MeOH	Pyridine (20 mg)	18h	7 (0.9 w%) ^a 8 (0.5 w%) ^b 6 (0.4 w%) ^b
4	Aqueous NaOH (0.04 M)	/	17h	7 (traces) ^c 8 (traces) ^d 6 (traces) ^d

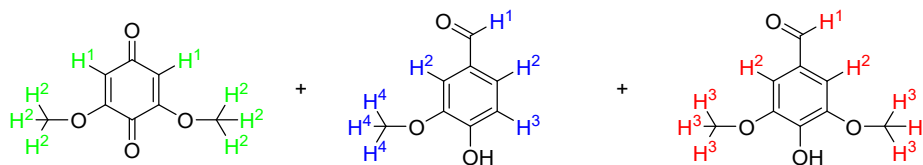
^aYield obtained via quantitative HPLC analysis of crude reaction mixture

^bYield obtained via ¹H-NMR integration

^cNot detected via HPLC analysis, traces seen on ¹H-NMR

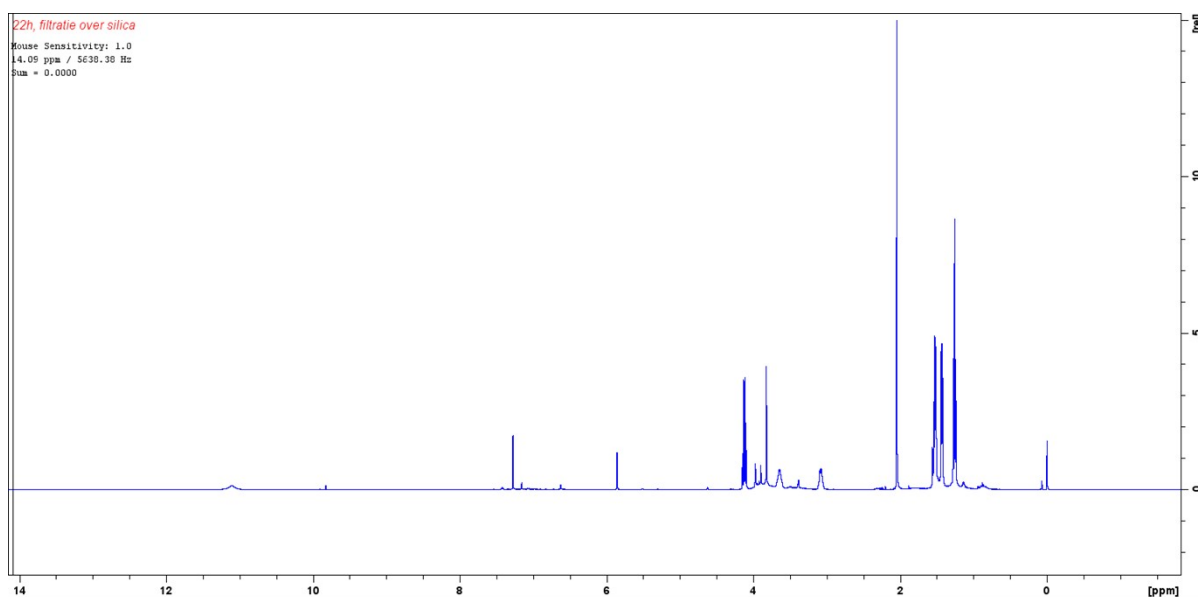
^dDetected via ¹H-NMR analysis

For **entry 1**, following low weight aromatics were identified^a:

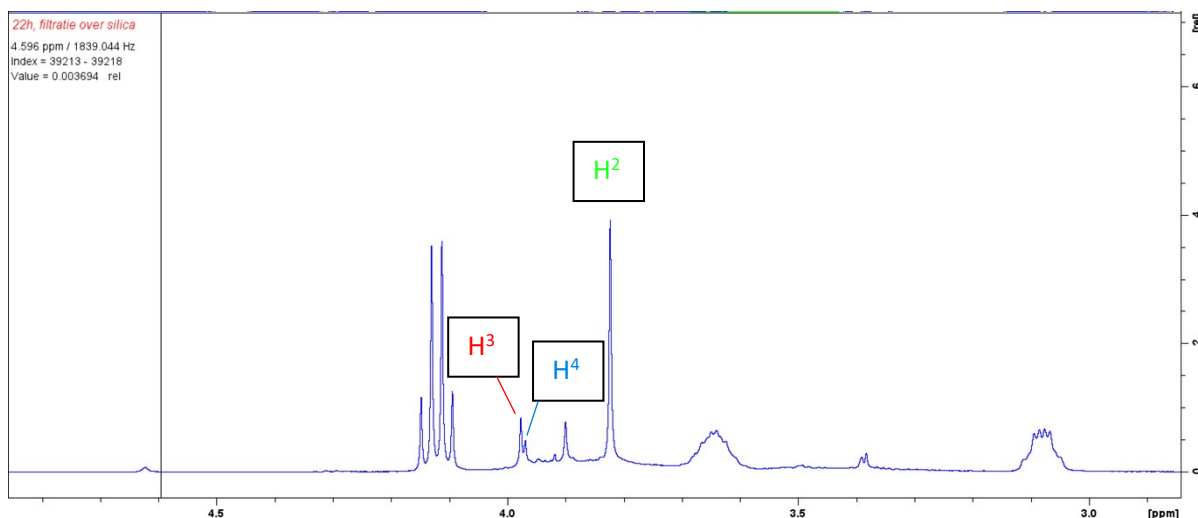


^asignals match with ¹H-NMR signals of isolated products and literature

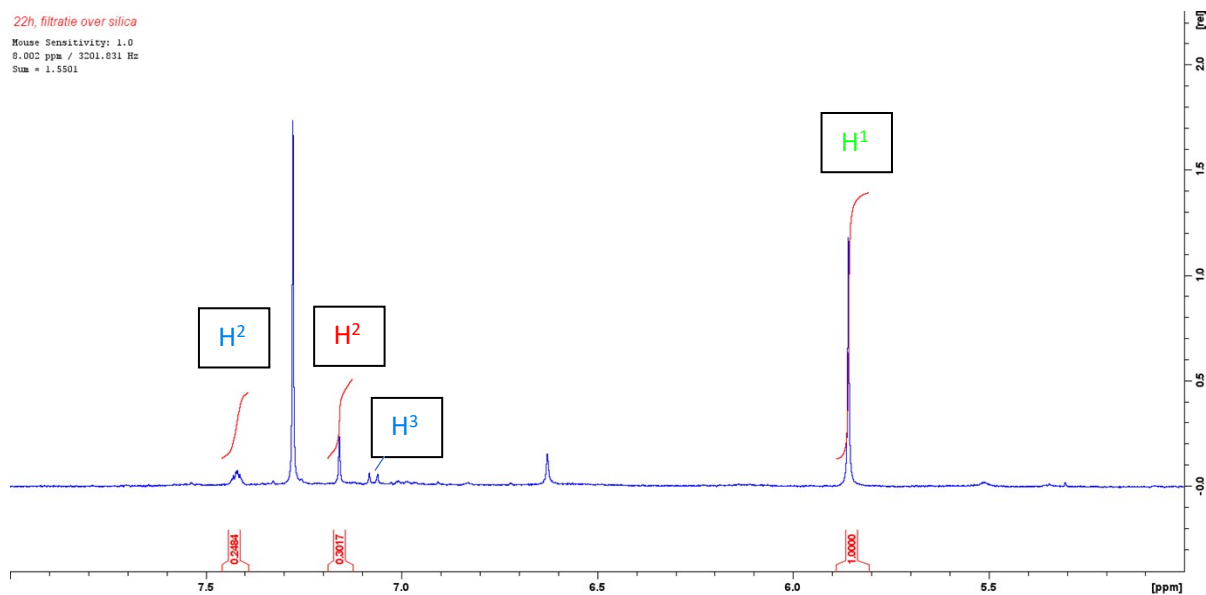
¹H-NMR of reaction mixture filtered over silica (SiO₂):



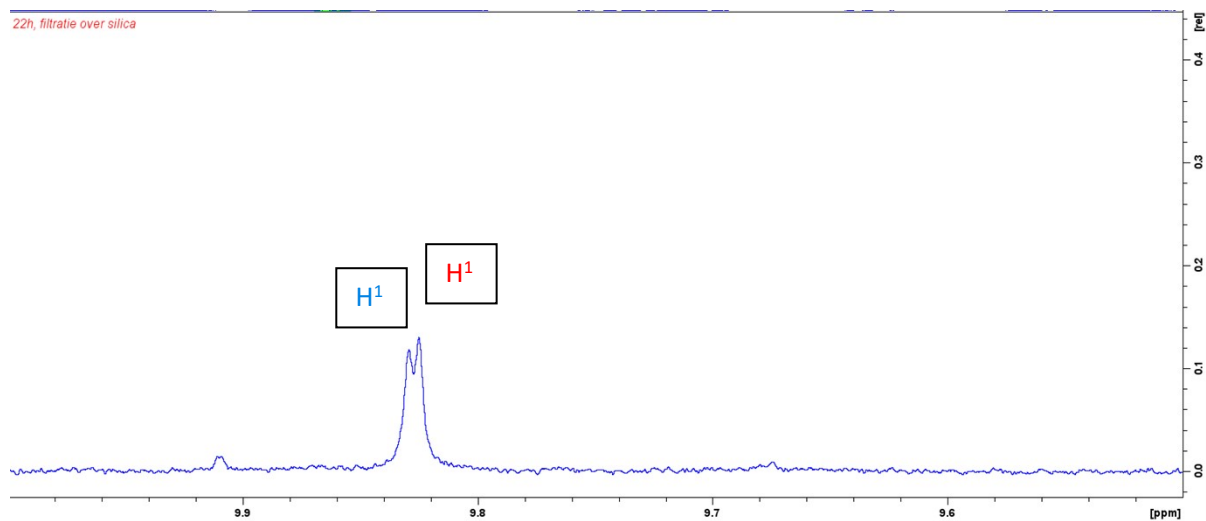
Region 3-5 ppm



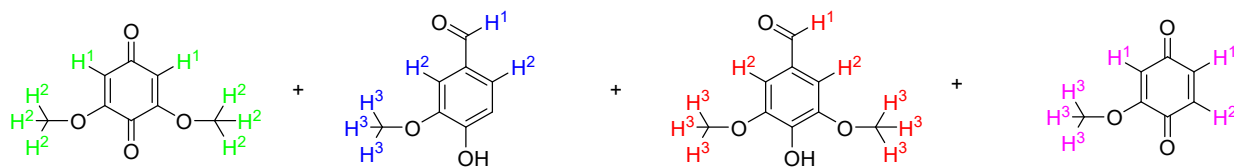
Region 5-8 ppm



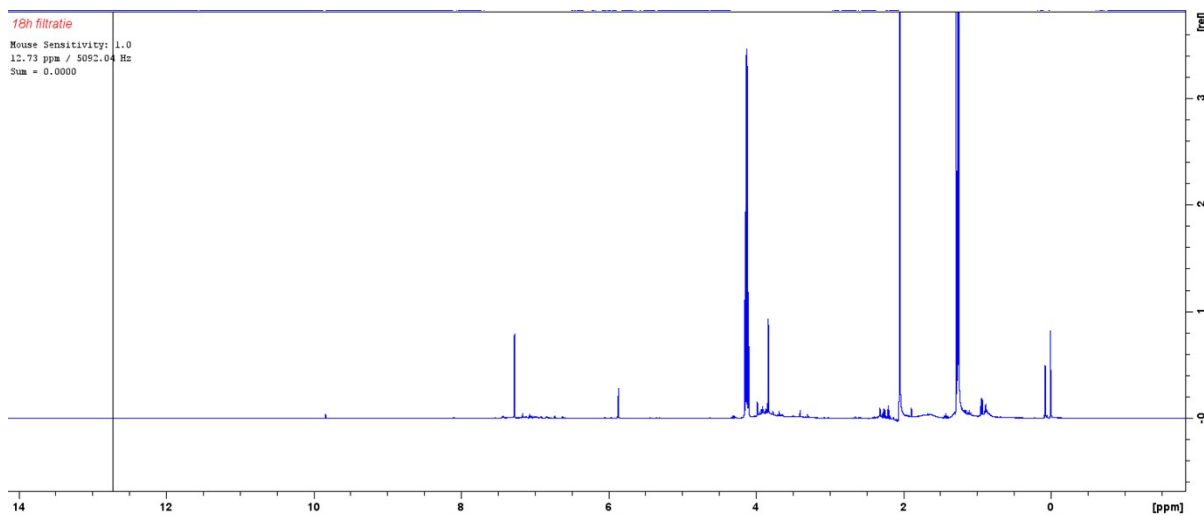
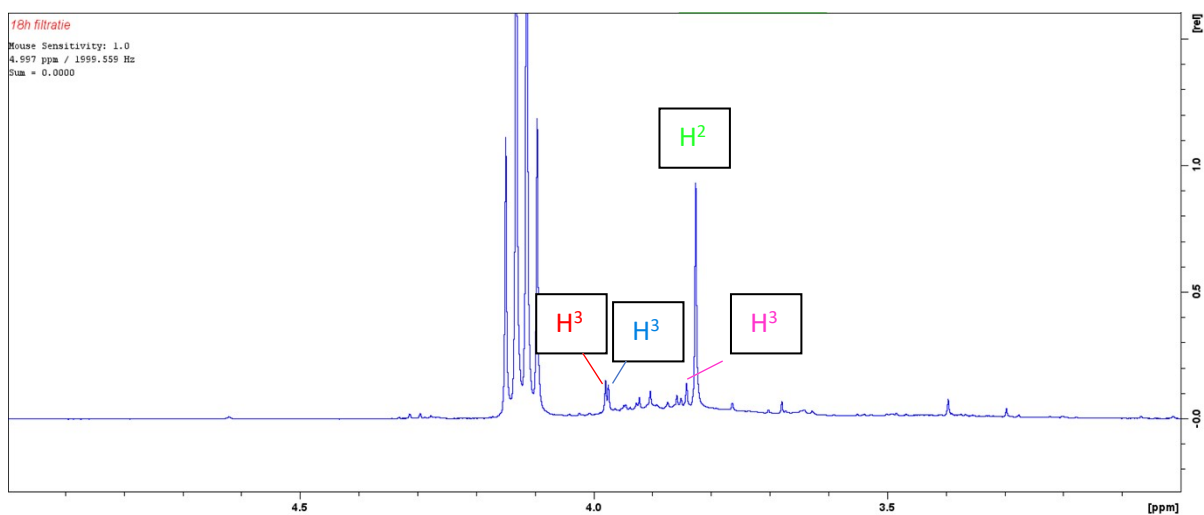
Region 9.5-10 ppm



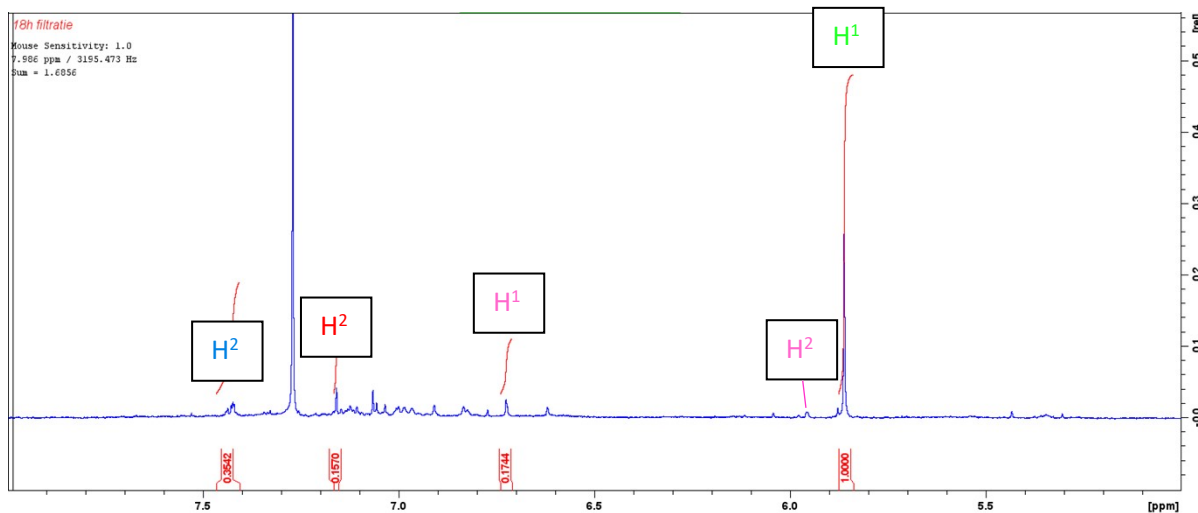
For **entry 2**, following low weight aromatics were identified^a:



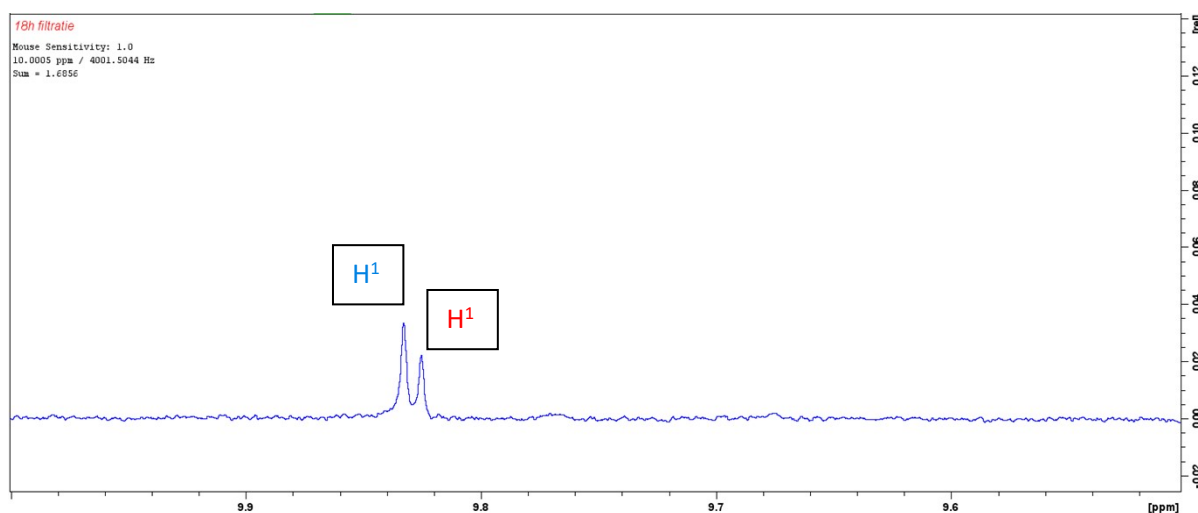
^asignals match with ¹H-NMR signals of isolated products and literature

^1H -NMR of reaction mixture filtered over silica (SiO_2):**Region 3-5 ppm**

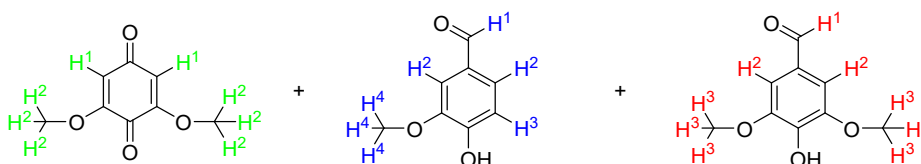
Region 5-8 ppm



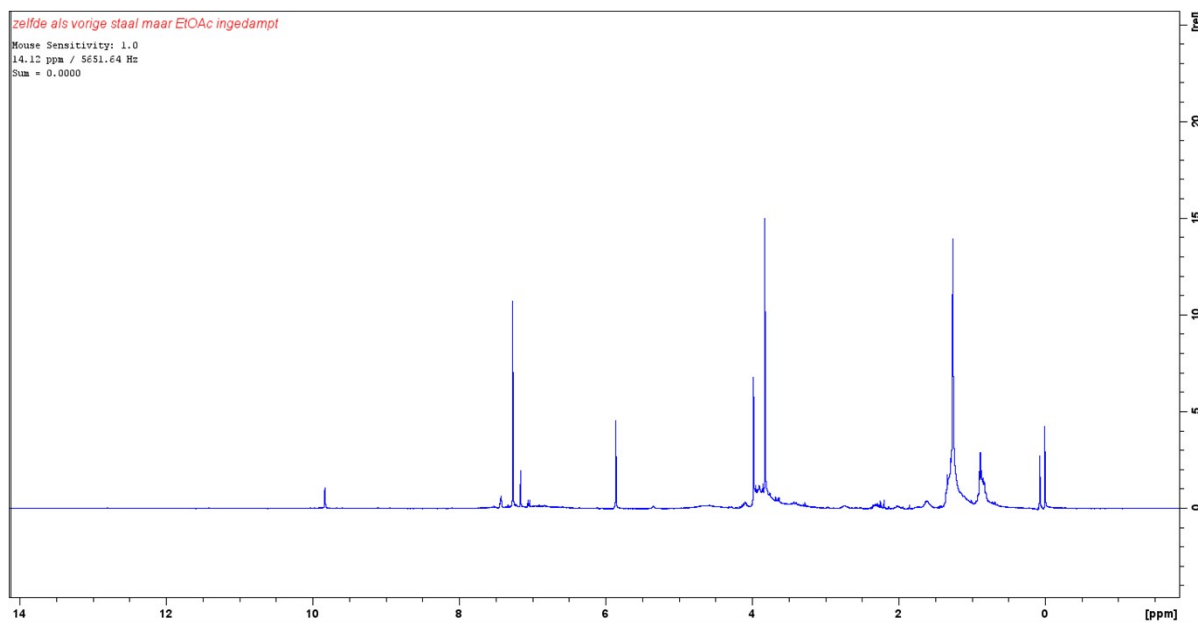
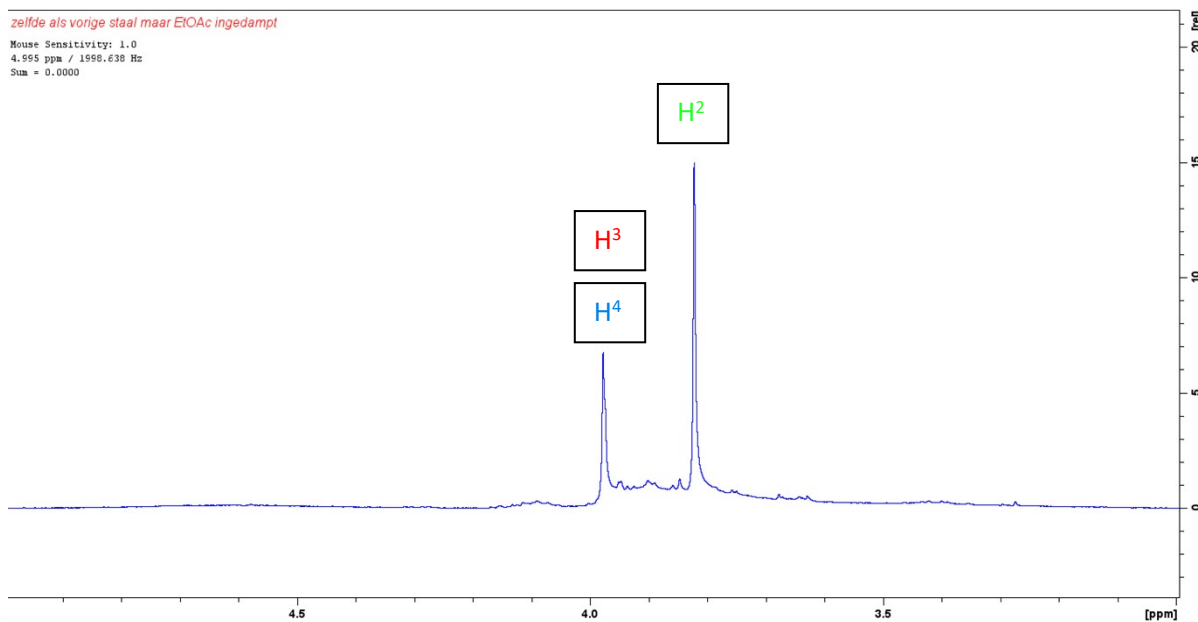
Region 9.5-10 ppm

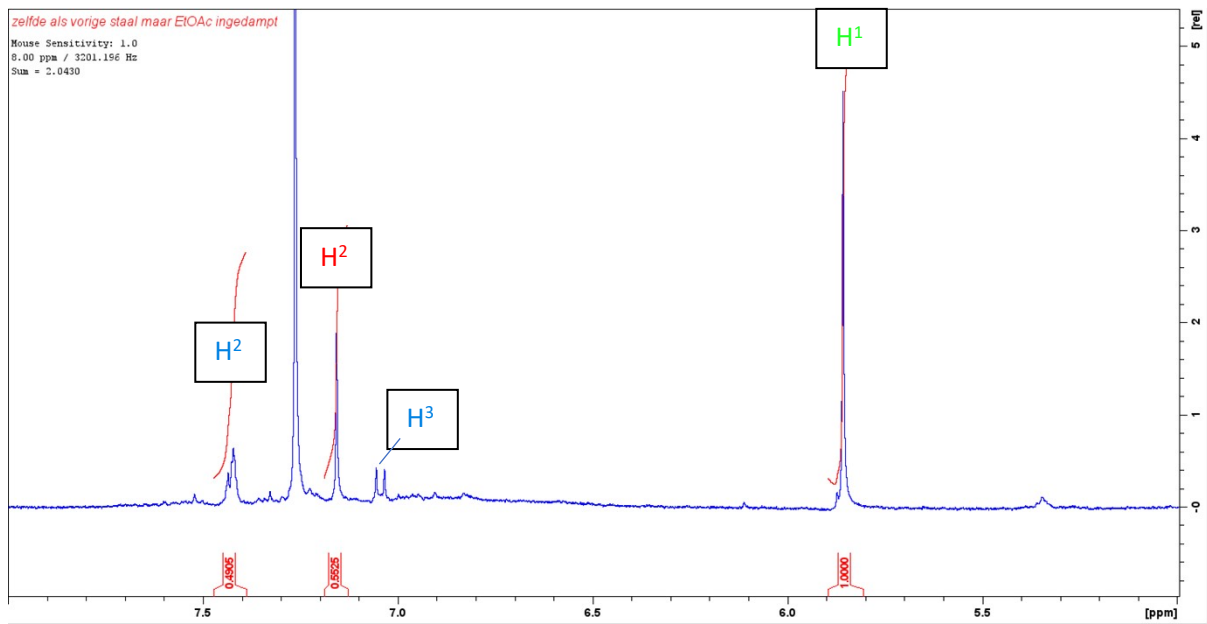
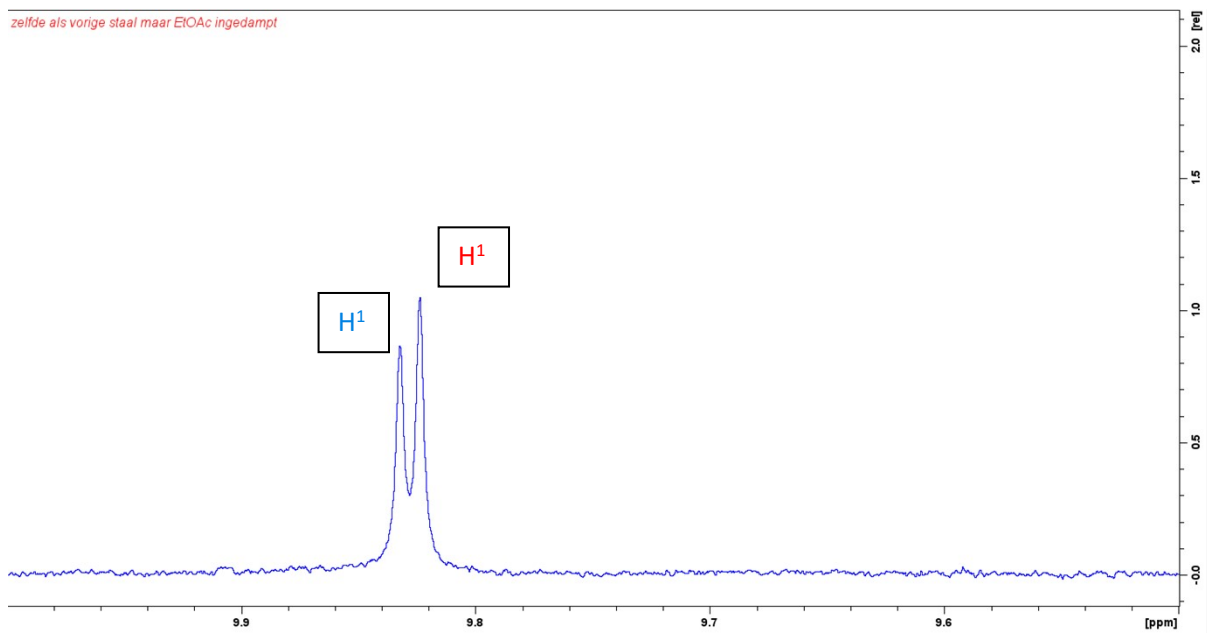


For **entry 3**, following low weight aromatics were identified^a:



^asignals match with ¹H-NMR signals of isolated products and literature

$^1\text{H-NMR}$ of reaction mixture filtered over silica (SiO_2):**Region 3-5 ppm**

Region 5-8 ppm**Region 9.5-10 ppm**

Additional reactions

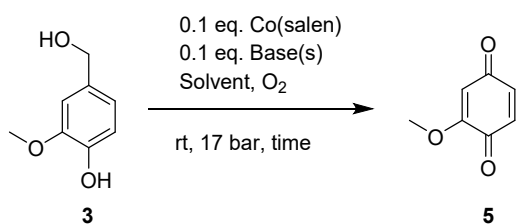


Table S1. Reaction of vanillyl alcohol towards methoxybenzoquinone in batch: greener solvents

Entry	Solvent	Base	Reaction time	Conversion (%) ^b	MBQ 5 (%) ^a
1	Cyrene/EtOH (1/1)	DIPEA + Pyridine	1 h	nd	8
2	Acetonitrile	DIPEA + Pyridine	1 h	37	28
3	Acetonitrile/EtOH (4/1)	DIPEA + Pyridine	30 min	65	43
			1 h	68	46
			2 h	72	51
4	Acetonitrile/Cyrene (4/1)	DIPEA + Pyridine	30 min	29	19
			1 h	41	24
			2 h	54	28
			43 h	88	47
5	EtOAc	DIPEA + Pyridine	1h	nd	4
6	2-MeTHF	DIPEA + Pyridine	30 min	nd	4
			1h	nd	5
7	EtOH	DIPEA + Pyridine	1h	83	38
8	EtOH	Pyridine	30 min	59	40
			1 h	66	44
			3h	76	46

^aYield obtained via quantitative HPLC analysis of crude reaction mixture

^bYield obtained via ¹H-NMR integration

nd = not determined

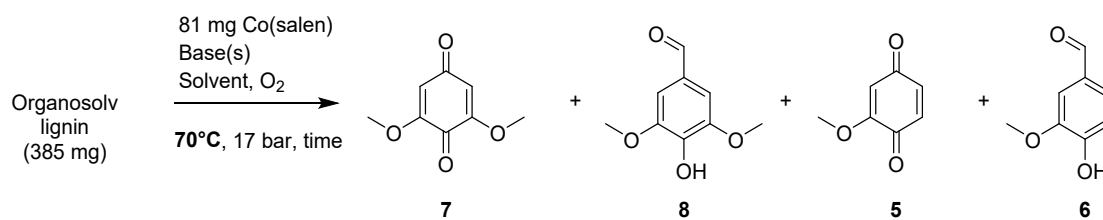


Table S2. Reaction of organosolv lignin towards low weight aromatics at 70°C

Entry	Solvent	Base	Reaction time	Products
1	DCM/MeOH (4/1)	DIPEA (32 mg)+ Pyridine (20 mg)	22h	7 (1.9 w%) ^a 8 (0.6 w%) ^b 6 (0.4 w%) ^b
2	MeOH	DIPEA (32 mg) + Pyridine (20 mg)	18h	7 (1.2 w%) ^a 6 (0.3 w%) ^b 8 (0.2 w%) ^b
3	MeOH	Pyridine (20 mg)	18h	7 (0.7 w%) ^a 8 (0.2 w%) ^b 6 (0.2 w%) ^b

^aYield obtained via quantitative HPLC analysis of crude reaction mixture

^bYield obtained via ¹H-NMR integration

LITERATURE DATA OXIDATION OF LIGNIN MODEL SUBSTRATES WITH CO(SALEN)

All references found of Co(salen)-catalyzed oxidation of G, S and H lignin model substrates are listed below. **(Table S3)** It is important to highlight that this research exclusively concentrates on Co(salen), and as a result, references related to derivatives of Co(salen) are not listed.

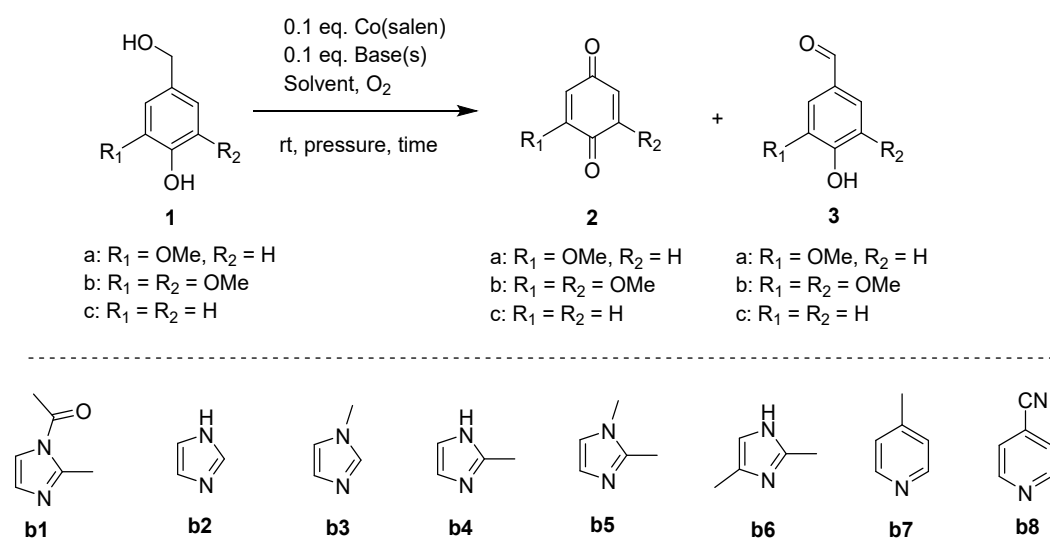


Table S3. Literature data of Co(salen)-catalyzed oxidation of model substrates

Substrate	Solvent	Base	RT	Pressure O ₂ (bar)	BQ 2 (%) ^a	Ald 3 (%) ^b
1a ^[4]	MeOH	TBD	22h	4.14	38 ^b	/
		DBU			59 ^b	/
		DBN			30 ^b	/
		DIPEA			68 ^b	/
		DABCO			0	/
		Pyridine			0	/
		2,6-lutidine			0	/
1b ^[4]	MeOH	Pyridine	1h	4.14	99 ^b	/
		2,6-lutidine	1h		52 ^b	26
			22h		58 ^b	15
			None		1h	36 ^b
			22h		41 ^b	8
1b ^[5]	MeOH	b1	17h	4.14	31	/
		b2	24h		5	/
		b3	17h		69	/
		b4	17h		63	/
		b5	17h		65	/
		b6	17h		67	/
		b7	17h		74	/
		b8	17h		64	/
1b ^[6]	MeOH	Pyridine	17h	3.45	88 ^a	4 ^a

1c ^[4]	MeOH	Pyridine	22h	4.14	/	/
		2,6-lutidine	22h		/	/

^aIsolated yield, unless specified otherwise

^bYield obtained via quantitative HPLC analysis of crude reaction mixture

MATERIALS AND METHODS

High Performance Liquid Chromatography (HPLC)

To quantify yield, high performance liquid chromatography was used with the help of a calibration curve. The 1200 Series LC/MSD SL is equipped with a Supelco ascentis express C18 column with an internal diameter of 4.6 mm. Additionally, the instrument possesses a UV-DAD detector and there was an Agilent 1100 Series MSD SL mass spectrometer with electrospray ionisation (ESI, 4000 V, 70 eV) and with a single quadrupole detector coupled to the machine. To elute the components, a solvent mixture of acetonitrile and water in different ratios is used.

Nuclear Magnetic Resonance Spectroscopy (NMR)

The spectra were taken by a Bruker Avance Nanobay III NMR spectrometer with a ¹H/BB z-gradient high resolution probe. The ¹H NMR was taken at 400 MHz. The software used to process and display the spectra was TOPSPIN version 3.6.4. To prepare the samples for usage, the compounds were dissolved in deuterated solvents. The solvent of choice was CDCl₃, but when it was seen that compounds were poorly soluble in the latter solvent, d₆-DMSO was chosen.

High-pressure batch reactor

For the high-pressure batch reactions, a Parr 4793 pressure vessel is used. The reactor vessel is made from stainless steel and has a reactor volume of 100 ml. The reactor can endure pressures up to 200 bar and temperatures up to 350 °C.

Continuous flow pumps

Two different pumps were used to perform continuous flow reactions:

-Knauer AZURA P 4.1S pump with pressure sensor and stainless steel pump head with a maximum flow rate of 10 ml/min and maximum pressure of 200 bar

-Wadose LITE HP HPLC pump with a pump head made of PEEK and a maximum with a maximum flow rate of 10 ml/min and maximum pressure of 400 bar

Mass flow controller (MFC)

To coordinate the oxygen flow towards the continuous flow reactor, an EL-FLOW metal sealed F-201 CM mass flow controller from Bronkhorst® was used. The mass flow controller can control gas flows up to 30 bar and has a maximum flow rate setpoint of 80 ml_N/min O₂ flow.

Continuous flow tubing

To build the continuous flow reactor, tubing made from polytetrafluoroethylene (PTFE) with an internal/external diameter of 0.8/1.6 mm was used.

Back pressure regulator

To maintain a constant pressure, BPR cartridges of IDEX Health & Science of the desired pressures were placed at the end of the reactor and regularly exchanged.

References

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