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A Mild and Selective Method for the Catalytic Hydrodeoxygenation of Cyanurate Activated Phenols in Multi-Phasic Continuous Flow.

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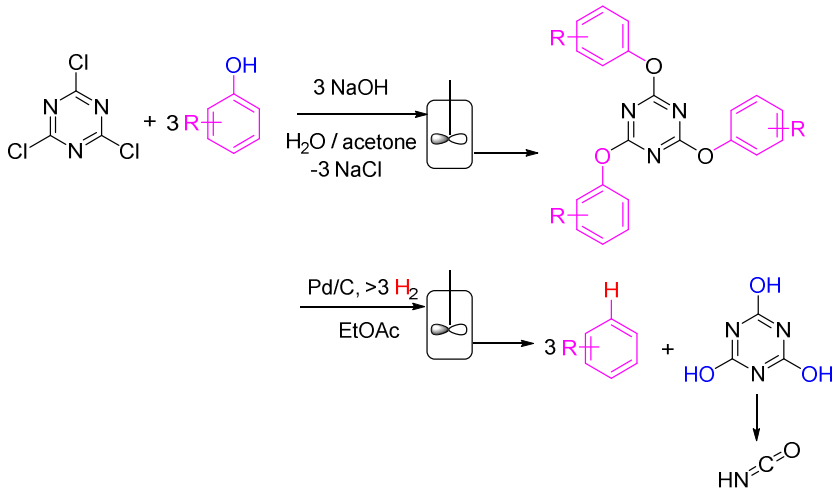


ABSTRACT

A low energy, high selectivity approach to the catalytic hydrodeoxygenation of phenols is reported using batch or continuous flow methods to react 3 equivalents of phenol with cyanuric chloride then hydrogenolyzing the triarylcyanurate intermediate to give 3 equivalents of de-oxo aromatic. The use of cyanuric chloride compares favorably with existing activation methods, showing improved scalability, atom efficiency and economics. The scope of both the activation and hydrogenolysis stages are explored using lignin-related phenols. Initial development has identified that continuous stir tank reactors (CSTRs) enable a multi-phasic process for converting guaiacol to anisole, and at steady-state overcome the catalyst deactivation issues observed in batch, seemingly caused by the cyanurate by-product. Green chemistry aspects, and the potential for industrial adoption are discussed.

KEYWORDS

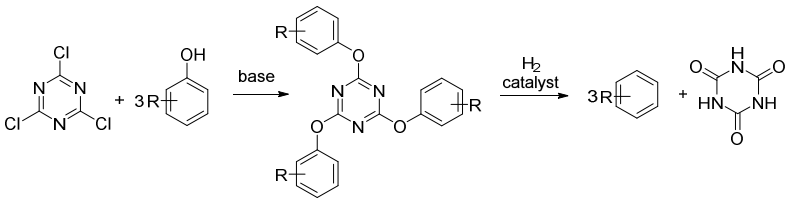
Aromatic phenol deoxygenation; catalytic hydrodeoxygenation; continuous stirred tank reactor; multi-phasic continuous flow; lignin derived phenols; guaiacol

INTRODUCTION

The use of lignin-derived poly-oxo aromatics as biorenewable replacements for petrochemical-derived phenols has so far been limited to specific applications such as the flavor, vanillin.[1,2] A part of the difficulty is breaking-down lignin, part the separation of complex mixtures, and part the removal of functional groups such as oxygen. Regarding the latter, hydrodeoxygenation (HDO) is a process to replace aromatic oxygen with hydrogen,[3] The conversion of lignin model compounds to benzene and cyclohexane has been reported recently using mild 200-240 ^{o}C

conditions,[4] however it has often required catalytic reforming at >300 ^{o}C temperature, resulting in over-reduction with complex product mixtures and catalyst deactivation.[5] For example cobalt molybdenum sulfide on alumina catalyst at 300 ^{o}C and 50 bar has been shown to convert 84% of the guaiacol to give 34% phenol, 11% catechol, 3% anisole, 1% benzene and the remainder saturated products.[6] The extreme conditions are required because the aromatic C-O bond is strong with a length of 1.37 Å and bond energy of 460 kJ.mol^{-1}, compared to the aliphatic C-O bond of 1.43 Å and 358 kJ.mol^{-1}.[7] In the organic laboratory the hydrogenolysis of phenolic compounds is usually carried out by activation with trifluoromethanesulfonyl chloride followed by reduction; however the cost of making triflates and the associated waste make this method too expensive and wasteful to consider for bulk production.[8] Reports of aryl-alkyl ether reduction, using either nickel catalysts and silane reductants, or better from an industrial perspective, a combination of metal triflate and palladium catalysts with hydrogen, both illustrate the difficulties in this transformation.[9] Another reported phenol activation method is reacting *N*-phenyl tetrazolium chloride with the phenol to make the corresponding 5-aryloxy-1-phenyltetrazoyl ethers, with similar disadvantages and low atom efficiency.[10] The electron-withdrawing and resonance stabilizing tetrazolyl group can weaken the aromatic C-O bond, facilitating its cleavage by catalytic hydrogenolysis. Alves has used X-ray crystal structures to show lengthening of the aromatic C-O bond to 1.42 Å, with the bond energy reduced by around 100 kJ.mol^{-1}.[11] A better industrial reagent is cyanuric chloride, made from cyanogen chloride. It is used widely in the manufacture of fiber-reactive dyes and agrochemicals, and is produced at >100 ktpa at about £1.50/kg.[12] Furthermore it has the benefit of 3 electrophilic centers, with only one third of a mole equivalent required in the S_NAr reaction with phenolate, Scheme 1.

Scheme 1. Hydrodeoxygenation of phenolic compounds by activation with cyanuric chloride and catalytic hydrogenolysis.

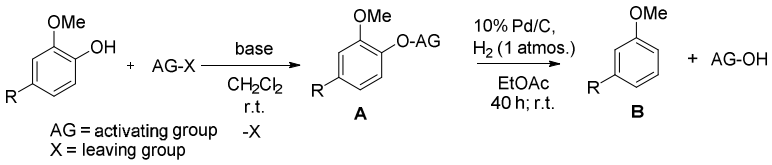


Allan et al have reported its reaction with a variety of phenols to produce the 1,3,5-triaryloxy-2,4,6-triazines in moderate to good yields,[13] though characterization of the compounds was limited to melting point and CHN analysis; whilst Sagar increased the yields using a microwave synthesis.[14] Forbes made triarylcyanurates with phenols, then used these in cross-linking reactions of lignosulfonate.[15] Van Muijlwijk showed that, as with the tetrazole, the tricyanurate esters are also able to activate the aromatic C-O bond toward cleavage under catalytic hydrogenolysis, though no lignin-related phenols were studied.[16] A more recent study by Iranpoor has used homogenous dichloronickel-bis-tricyclohexyl phosphine catalysts with super-stoichiometric zinc and potassium iodide to effect the same hydrogenolysis.[17] We reasoned that the use of tri-cyanurate esters for deoxygenation of guaiacol, vanillin and related phenols might have industrial potential.

RESULTS AND DISCUSSION

We herein report scoping studies and development of continuous flow aryloxylation and hydrodexygenation of lignin-related phenols. Initially phenol activation and hydrogenolysis of sulfonated phenols, Scheme 2.

Scheme 2. Reactions of guaiacol and vanillin with phenol activation reagents and catalytic hydrogenolysis.



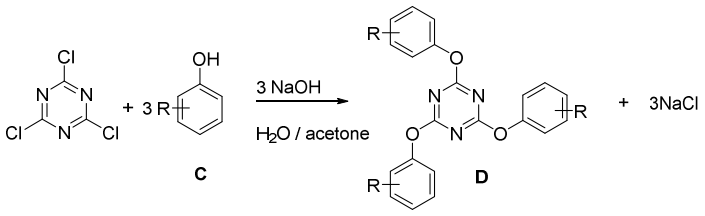
entry	R	AG-X	% yield A	% yield B	product name B
1	H	Tf-OTf[f]	95	33	anisole
2	CHO	Tf-OTf[f]	60	42[a]	*m*-methyl anisole
3	H	Ms-Cl[g]	97	0[b]	anisole
4	CHO	Ms-Cl	62	0[c]	*m*-methyl anisole
5	H	*p*Ts-Cl[h]	81	0[b]	anisole
6	CHO	*p*Ts-Cl	71	0[d]	*m*-methyl anisole
7	H	Tz-Cl[i]	75	39[e]	anisole

a. 30% *m*-methoxy benzyl alcohol co-product formed; b. recovered starting material; c. *p*-(hydroxymethyl)-2-methoxyphenyl methanesulfonate isolated in 81% yield; d. *p*-methyl-2-methoxyphenyl-*p*-toluenesulfonate isolated in 53% yield; e. compared to 60% published yield;[10] f. Tf-OTf = trifluoromethanesulfonic anhydride; g. Ms-Cl = methansulfonyl chloride; h. *p*Ts-Cl = *p*-toluenesulfonyl chloride; i. Tz-Cl = 5-chloro-1-phenyl-1*H* tetrazole.

Whilst activation of both guaiacol and vanillin with triflic anhydride followed by hydrogenolysis was successful the overall yields were low, despite a long reaction time, Entries 1 and 2; which is similar to previous observations.[8] Aryl mesylates and tosylates are inactive in oxidative addition and Grignard reactions, and the hydrogenolysis of guaiacyl or vanillin mesylate or tosylate compounds were also unsuccessful; the only reaction being reduction of the formyl group to give the benzyl alcohol and tolyl derivatives (Entries 3-6). The activation of

guaiacol with 5-chloro-1-phenyl-1H tetrazole and its hydrogenolysis was reconfirmed, Entry 7.[10] However, the modest yield, atom inefficiency and cost of this reagent make it unsuitable for industry use, as too with the aforementioned activating reagents. Attention was therefore turned to preparing 1,3,5-triaryloxy-2,4,6-triazines from cyanuric chloride and *in-situ* generated sodium phenolates, Scheme 3.

Scheme 3. Reaction of cyanuric chloride with different phenols to produce 1,3,5-triaryloxy-2,4,6-triazines.

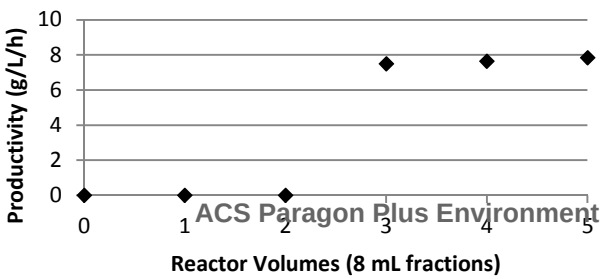


Entry	R	product number **D**	yield (%)[a,b] **D**
1	H	**1**	89
2	2-OMe	**2**	94
3	3-OMe	**3**	92
4	4-OMe	**4**	92
5	4-CHO	**5**	85
6	2-OMe, 4-CHO	**6**	62
7	2-CO_2Me	**7**	22[c]
8	2-OMe, 4-CO_2Me	**8**	10[c]
9	2-CO_2H	**9**	76
10	2-OMe, 4-CO_2H	**10**	71

a. isolated mass yields, with product identities and purity confirmed by GC, see ESI; b. run in water:acetone 1:1, 3h at ambient temp.; c. run in THF with di*iso*propylethylamine instead of NaOH;

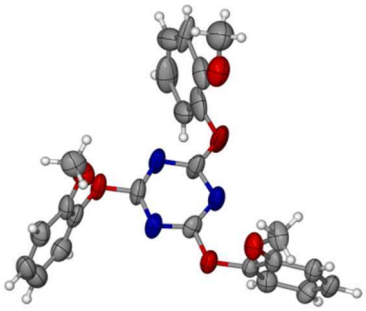
The reaction proceeds at ambient temperature in water/acetone with 3 equiv. phenol, during which the products precipitate, are separated by filtration, and can be recrystallized from methanol. The isolated products yields are satisfactory except Entries 7 and 8, methyl salicylate and methyl vanillate that are insoluble in water and were run in THF with soluble organic base DIPEA. No evidence of the intermediate mono- or di- addition products was observed, however these were seen and isolated as mixtures when fewer equivalents of phenol/base were used: 1 equiv. of sodium guaiacolate gave a ratio of 2:12:3 mono:di:tri-substituted triazine; 2 equiv. gave a 0:1:1 ratio. This indicates that each aryl oxide addition activates the product for the next reaction and may indicate a change from S_NAr to a concerted mechanism as proposed by Williams.[18] Increasing the base had no benefit, other than for Entries 9 and 10 to neutralize the carboxylic acids. To improve efficiency and productivity, the reaction was evaluated in continuous flow. Since solids are formed during the reaction a plug-flow reactor was considered inappropriate; instead a newly developed lab-scale 4-stage continuous stirred tank reactor (CSTR) (being reported separately) of 8 mL total volume was used, see ESI. An acetone solution of cyanuric chloride was pumped simultaneously with a thrice-concentrate aqueous solution of sodium guaiacolate at combined flow rate of 0.26 mL/min and residence time (T_{res}) of 30 min.; no blockages were observed during the 150 min. operation. 16% conversion of **2** was realized at steady-state after 90 min., and 8 mL fractions or reactor volumes (RV) were collected for a further 60 min., Figure 1.

Figure 1. Continuous reaction of sodium guaiacolate with cyanuric chloride using lab-scale 4-stage cascade CSTR.



The productivity achieved was 8 g/L/h which compares to 10 g/L/h achieved in batch. A higher conversion might be achieved by heating and work on this is on-going. The identity of the product **2**, was confirmed by single-crystal x-ray analysis Figure 2.

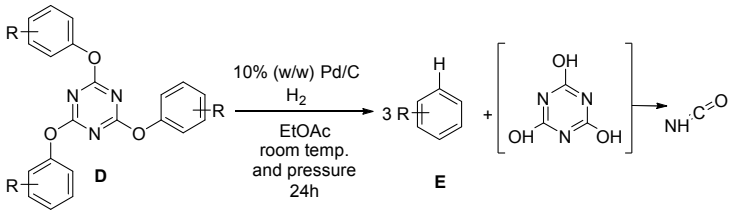
Figure 2. X-ray crystal structure of 1,3,5-triazolinyl-2,4,6-triguaiacolate, **2**.



Interestingly the bond lengths across the diarylether are significantly different: 1.453 Å aryl to oxygen and 1.361 Å triazole to the same oxygen atom. The longer bond is the one to be hydrogenolyzed. Having prepared a range of 1,3,5-triaryloxy-2,4,6-triazines at the 10's g scale, several hydrodeoxygenation catalysts were evaluated using combinations of water and solvent to ensure solubility of **2**. A screen of Pd/C, Pt/C, Ru/C and Raney® Ni catalysts under hydrogen transfer conditions with aqueous hydrazine, triethylamine/formic acid, sodium phosphinate or iso-propanol failed to show any conversion of **2**; however direct hydrogenation was more successful. The most promising catalyst was Johnson-Matthey 87L 10% Pd/C, used at 5% (w/w) vs substrate, TOF = 0.58 min^{-1}, giving 58% yield of anisole isolated by fractional distillation. Batch reactions were run with triazines **1**-**10**, initially at ambient temperature and hydrogen

pressure, with sampling and NMR analysis confirming full conversion of starting materials in 24 hours, Scheme 4.

Scheme 4. Isolated yields of aromatics **E**, at complete conversion of **D**.



	product number	product name	yield (%)[a,b]
Entry	**D**	**E**	**E**
1	**1**	benzene	10
2	**2**	anisole	86
3	**3**	anisole	68
4	**4**	anisole	68
5	**5**	benzyl alcohol	30
6	**6**	3-methylanisole	14
7	**7**	methyl benzoate	10
8	**8**	methyl 3-methoxybenzoate	12
9	**9**	benzoic acid	21
10	**10**	3-methoxybenzoic acid	58

a. isolated mass yields, with product identities and purity confirmed by GC, see ESI b. no by-products or impurities were identified in the crude isolate.

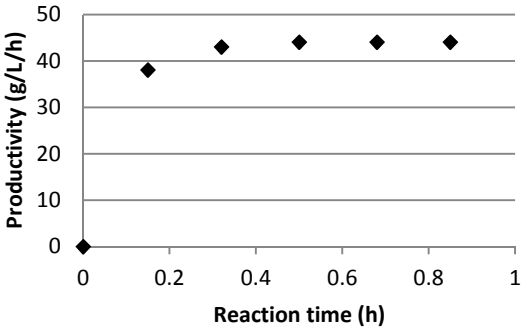
Whilst the conversion of **1** was high, the yield of benzene was low, though this may reflect difficulty in isolation due to evaporation during work-up, Entry 1. On the other hand, the yield of anisole from any of the regioisomers **2**, **3** or **4** was good, Entries 2-4. The overall conversion of

guaiacol to anisole was 81% over both the activation and hydrogenolysis steps. Aldehyde **5** from 4-hydroxy benzaldehyde, and **6** from vanillin were reduced under these conditions to produce benzyl alcohol and 3-methylanisole (via the corresponding benzyl alcohol), Entries 5 and 6; whilst the triazine from methyl vanillate produced methyl 3-methoxybenzoate, Entry 8. Monitoring the rate of hydrogen uptake with **2** under the same conditions showed a maximum productivity of 4.5 g/L/h after 1 hour that slowed over 5 hours. Examination of the catalyst at the end of reaction showed a grey surface coating that may be linked to the low recovery of cyanuric acid by-product. Washing the catalyst with water enabled isolation of small amounts of cyanuric acid, as determined by comparison of the IR spectrum to an authentic standard, see ESI. A control reaction in which cyanuric acid was exposed to the same catalyst and conditions provided recovery of only half the mass. Moreover, higher hydrogen pressures resulted in lower cyanuric acid recovery. These results indicate both catalyst surface poisoning and cyanuric acid decomposition, possibly to *iso*cyanate or the corresponding acid. The addition of triethylamine had no effect on the reaction rate, however the physical appearance of the catalyst was significantly different with change in median particle size from 20 μm, to two maxima at 4 and 50 μm.[19] Energy dispersive X-ray (EDX) spectroscopy showed that once-used catalyst had a higher Pd:C ratio of 53:5, compared with fresh, 79:11, or a reaction co-fed with triethylamine, 73:11. Study of the kinetics of the hydrogenolysis of **2** showed the order of reaction to be 0.9; probably less than unity because of the catalyst deactivation. The reaction rate constant k_{obs} was determined to be 0.012 min^{-1}. An aspect of this study was to develop methods that have potential for industrial exploitation therefore a continuous hydrogenolysis process was also evaluated. A 2-stage cascade CSTR was determined appropriate for the multiphase reaction, (see ESI). Using the same 10% (w/w) catalyst loading, at 5 bar hydrogen pressure and 50^{o}C, and a flow rate of 4

mL/min ethyl acetate solution of **2** to give a Tres of 8 minutes, the steady-state conversion of starting material was >95% with reactions carried out for 1 hour (7 reaction volumes). The isolated anisole yield was 70%, and remaining mass was identified as cresol 15%, along with 15% unidentified impurities.

Using the CSTR the reaction reaches steady-state after 20 mins and the catalyst appears not to decompose over 1 hour operation, Figure 3.

Figure 3. Productivity of anisole by Pd/C catalysed hydrogenolysis of **2** at Tres = 8 min. in CSTR.



The productivity was 45 g/L/h, catalyst TOF 100 h^{-1}, and represents a 10-fold improvement over the batch method. Further development is likely to improve this. At twice the flow rate the conversion dropped to 60%, whilst reuse of the catalyst gave 20% less anisole.

CONCLUSIONS

A mild and selective continuous flow process has been developed, in which a variety of lignin-related phenols have been activated with cyanuric chloride and catalytically hydrodeoxygenated at mild temperatures and pressures by Pd/C and H_2. Further work will look at telescoping the two processes and using mixtures of phenols typical of lignin digests. Guaiacol has been converted to

anisole with 81% yield over 2 steps using one third of a mole equivalent of cyanuric chloride. The atom efficiency of the overall process is 48% and the Process Mass Intensity is 81, 96% of which is due to the solvents water, acetone and ethyl acetate. A process for the continuous production of anisole has been developed giving 45 g/L/h over an hour, but clearly further improvements would need to be made before being commercially viable, including extended run-times and a more thorough evaluation of the catalyst deactivation. Anisole is being increasingly used as a green solvent and reactant in the Pharma, Fine Chemical, Agrochemical and Perfumery industries. Assuming guaiacol from lignin could be produced at £1/kg, and more efficient use was made of the Pd/C catalyst, the hydrodeoxygenation process described herein has potential to compete with the petrochemical produced price of anisole.[20]

EXPERIMENTAL

Analytical Methods for the Determination of Chemical Purity by GC. Analyses were performed on an Agilent HP6890 chromatograph, using a capillary column HP-5 (5% phenyl methyl siloxane) HP 19091J-413; dimensions: 30 m × 320 μm × 0.25 μm; pressure: 4.3 psi; nominal initial flow: 1.6 mL/min; average velocity: 33 cm/sec; equilibration time: 3; injection volume: 1 μl; oven: initial temperature: 60 °C; ramp: 20 °C/min to 200 °C; hold for 3 min; total run time = 16 min; inlet:mode: split ratio 10.7:1; temperature: 250 °C; split flow: 17.5 mL/min; total flow: 28.3 mL/min; gas saver: 20 mL/min; detector: temp: 250 °C; mode: constant flow; H_2 flow: 30 mL/min; air flow: 300.0 mL/min; makeup flow: 10 mL/Min (N_2). Quantitative product analysis was calculated using the following method: a 0.10 mL solution of biphenyl (10 mg/L) containing a standard of the specific compound of interest (0.05 mL) in MeOH (1.00 ml). The retention times of commercial standards and pure products: (min)

anisole 2.00; benzene 0.63; phenol 3.28; cresol 4.80; toluene 1.13; 3-methylanisole 5.80; 3-methoxybenzyl alcohol 8.96; 3-methoxybenzaldehyde 8.09; 2,4,6-*tris*(2-methoxyphenoxy)-1,3,5-triazine 19.86.

General information. All reagents and solvents were obtained from commercial suppliers and used as supplied unless stated otherwise. All yields refer to chromatographically and spectroscopically pure products unless stated otherwise. All NMR spectra were recorded on Bruker DPX-300 and DRX-500 spectrometers in the solvents specified. Infrared spectra were recorded neat on NaCl plates or as a solid on a diamond transmission accessory using a Perkin Elmer FT-IR spectrometer; details are reported as νmax in cm^{-1}. Mass spectra were carried out using a Microsmass LCT (ES mode), Bruker Daltonic (ES mode) and Waters GCT Premier (EI and FI mode) apparatus and are reported as values in atomic mass units followed by the peak intensity relative to the base peak (100%). Elemental analysis was done using a Carlo Erba 1108 Elemental Analyser apparatus. Crystal and molecular structures were determined using single crystal X-ray diffraction using Nonius KappaCCD and Bruker-Nonius FR591/X8Apex apparatus. Melting points were measured using a Griffin melting point apparatus and are uncorrected. Sulfonylated phenols used were synthesized and hydrogenolyzed using standard procedures, see ESI. Tetrazoylguaicol was synthesized using the method of Alves,[11] see ESI

General method for synthesis of 1,3,5-triaryloxy-2,4,6-triazines 1 to 10. A solution of cyanuric chloride (1 equiv.) in acetone (300 mL) was added drop wise to a solution of the phenol (3 equiv.) in water (300 mL) with NaOH (3 equiv.) and the resulting solution stirred at room temperature for 3 h. The reaction mixture was filtered, the resulting solid was washed with water (2 × 100 mL) and crystallized.

1,3,5-triphenoxy-2,4,6-triazine, 1. Recrystallized from MeOH to give a white solid (2.26g, 6.32 mmol, 89%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35 (ddd, *J* = 8.3, 7.4, 0.9 Hz, 9H, C3H/C4H/C5H), 7.16–7.10 (m, 6H, C2H/C6H). Lit ^{1}H NMR: δ = 7.25–6.60 (m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.68, 151.61, 129.44, 126.03, 121.39. HRMS (ES+ mode): *m/z* = 380.1020 [100%, MNa^+]; calculated for $C_{21}H_{15}N_3O_3$ requires [MNa^+]: *m/z* = 380.1006. Mpt. (MeOH) 230–232 °C; Lit.[21] Mpt. ($CHCl_3$/hexane) 230–231°C.

1,3,5-tri(2-methoxyphenoxy)-2,4,6-triazine, 2. Recrystallized from MeOH to give a white crystalline product (19.68 g, 44.03 mmol, 78%). ^{1}H NMR (500 MHz, DMSO-d6): δ = 7.22 (ddd, *J* = 8.2, 7.4, 1.6 Hz, 3H, C5), 7.13 (ddd, *J* = 30.5, 8.1, 1.5 Hz, 6H, C4/C6), 6.93 (td, *J* = 7.7, 1.4 Hz, 3H, C3), 3.85 (s, 9H, OCH_3). ^{13}C NMR (125 MHz, DMSO-d6): δ = 173.62, 151.16, 140.86, 126.80, 122.35, 120.60, 112.66, 55.79. HRMS (ES+ mode): *m/z* = 448.1509 [100%, MH^+]; calculated for $C_{24}H_{22}N_3O_6$ requires [MH^+]: *m/z* = 448.1506. IR υ_{max}/ cm^{-1} (film): 3017, 2836, 2097, 1695, 1596, 1476, 1253, 1202, 1166, 743. Analysis calculated (%) for $C_{24}H_{21}N_3O_6$: C, 64.42; H, 4.73; N, 9.39. Found: C, 64.15; H, 4.75; N, 9.25. Mpt. (MeOH) 139–141°C; Lit.[22] Mpt. 145 °C.

1,3,5-tri(3-methoxyphenoxy)-2,4,6-triazine, 3. Recrystallized from MeOH to give the product as a white solid (2.34 g, 5.24 mmol, 92%). ^{1}H NMR (501 MHz, $CDCl_3$) δ = 7.24 (s, 3H, C5H), 6.75 (dddd, *J* = 16.1, 8.1, 2.4, 0.8 Hz, 6H, C5H/C6H), 6.69 (t, *J* = 2.3 Hz, 3H, C2H), 3.76 (s, 9H, OCH_3). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 173.63, 160.49, 152.45, 129.80, 113.59, 111.88, 107.52, 55.41. LC-MS: *m/z* = 448.20 [100%, MH^+]; calculated for $C_{24}H_{21}N_3O_6$ requires [MH^+]: *m/z* = 448.15. IR υ_{max}/ cm^{-1} (film): 3011, 2840, 1576, 1269, 1146, 1040, 776. Mpt. 145−147 °C.

1,3,5-tri(4-methoxyphenoxy)-2,4,6-triazine, 4. Recrystallised from MeOH to give the title product as a white solid (3.08 g, 6.97 mmol, 85%). ^{1}H NMR as described in the literature.[23] ^{13}C NMR (125 MHz, $CDCl_3$): 190.9, 173.6, 156.0, 134.8, 131.7, 122.6. HRMS (ES+ mode): *m/z* = 464.0870 [100%, MNa^+]; calculated for $C_{24}H_{15}N_3O_6$ requires [MNa^+]: *m/z* = 464.0853. Mpt. (MeOH) 168–170°C; Lit.[24] Mpt. (EtOAc) 174–176 °C.

1,3,5-tri(4-formylphenoxy)-2,4,6-triazine (5). Filtered to give the product as a yellow solid (2.84 g, 6.35 mmol, 92%). ^{1}H NMR and Mpt. as described in the literature.[25]

1,3,5-tri(2-methoxy-4-formylphenoxy)-2,4,6-triazine (6). Recrystallised from MeOH to give the title product as a white solid (2.16 g, 4.07 mmol, 62%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.01 (s, 1H, CHO), 7.50 (d, *J* = 1.8 Hz, 1H, C5H), 7.49 (d, *J* = 1.8 Hz, 1H, C3H), 7.30 (d, *J* = 8.4 Hz, 1H, C6H), 3.86 (3H, s, OCH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 190.79, 173.70, 151.70, 145.04, 135.73, 124.72, 122.71, 111.48, 56.26. HRMS (ES+ mode): *m/z* = 554.1176 [100%, MNa^+]; calculated for $C_{27}H_{21}N_3O_9$ requires [MNa^+]: *m/z* = 554.1170. IR υ_{max}/ cm^{-1} (film): 3012, 2835, 2563, 2097, 1694, 1593, 1466, 1263, 1202, 1174, 812, 732. Mpt. (MeOH) 238–240 °C.

1,3,5-tri(4-methoxycarbonylphenoxy)-2,4,6-triazine (7). Recrystallised from CH_2Cl_2 to give the title product as white solid (1.54 g, 2.90 mmol, 66%). ^{1}H NMR (501 MHz, $CDCl_3$): δ = 8.05 (d, *J* = 8.7 Hz, 6H, C3H/C5H), 7.19 (d, *J* = 8.8, 6H, C2H/C6H), 3.93 (3H, s, $COOCH_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.10, 166.80, 159.74, 131.92, 122.87, 115.89, 51.89. HRMS (ES+ mode): *m/z* = 554.1176 [100%, MNa^+]; calculated for $C_{27}H_{21}N_3O_9$ requires [MNa^+]: *m/z* = 554.1170. IR υ_{max}/ cm^{-1} (film): 2986, 1726, 1538, 1357, 1286, 1117, 739. Mpt. 148–151 °C.

1,3,5-tri(2-methoxy-4-methoxycarbonylphenoxy)-2,4,6-triazine (8). Recrystallised from CH_2Cl_2 to give the title product as a white solid (0.19 g, 0.30 mmol, 33%). ^{1}H NMR (500 MHz,

$CDCl_3$): δ = 7.67 (dd, *J* = 8.3, 1.9 Hz, 3H, C5H), 7.62 (d, *J* = 1.9 Hz, 3H, C3H), 7.16 (d, *J* = 8.3 Hz, 3H, C6H), 3.93 (s, 9H, OCH_3), 3.83 (s, 9H, $COOCH_3$). ^{13}C NMR (125 MHz, DMSO-d6): δ = 166.71, 164.10, 150.84, 142.00, 129.16, 124.62, 117.64, 112.29, 56.19, 52.07. LC-MS: *m/z* = 622.22 [100%, MH^+]; calculated for $C_{30}H_{27}N_3O_{12}$ requires [MH^+]: *m/z* = 622.16. IR υ_{max}/ cm^{-1} (film): 2975, 1718, 1538, 1357, 1291, 1174, 739. Mpt. 251–253 °C.

1,3,5-tri(4-benzoyloxy)-2,4,6-triazine (9). After filtration and vacuum drying, the product was obtained as a white solid (1.54 g, 3.15 mmol, 76%). ^{1}H NMR as described in the literature.[26] ^{13}C NMR (126 MHz, DMSO-d6): δ = 172.70, 166.41, 154.53, 130.90, 128.59, 121.61. HRMS (ES+ mode): m/z = 490.0883 [100%, MH^+]; calculated for $C_{24}H_{15}N_3O_9$ requires [MH^+]: *m/z* = 490.0881. Mpt. 329−331 °C; Lit.[26] Mpt. > 300 °C

1,3,5-tri(2-methoxy-4-carboxy)-2,4,6-triazine (10). After filtration and vacuum drying, the product was obtained as a yellow solid (1.40 g, 2.41 mmol, 71% yield). ^{1}H NMR (501 MHz, DMSO-d6): δ = 13.04 (brs, 3H, COOH), 7.61–7.50 (m, 6H, C5H/C6H), 7.31 (d, *J* = 8.3 Hz, 3H, C3H), 3.78 (s, 9H, OCH_3). ^{13}C NMR (126 MHz, DMSO-d6): δ = 172.74, 166.40, 150.45, 143.24, 129.88, 122.48, 122.11, 113.40, 55.99. HRMS (ES+ mode): m/z = 580.1209 [100%, MH^+]; calculated for $C_{27}H_{21}N_3O_{12}$ requires [MH^+]: *m/z* = 579.1198. IR υ_{max}/ cm^{-1} (film): 3071, 2957, 1618, 1497, 1367, 1292, 1179, 805. Mpt. 313−315 °C

Synthesis of 1,3,5-tri(2-methoxyphenoxy)-2,4,6-triazine (2) in continuous flow

A solution of cyanuric chloride (0.083 g, 0.45 mmol) in acetone (25 ml) was added to one syringe. A solution of guaiacol (0.25 g, 2 mmols) in water (25 ml) and NaOH (0.25 g, 6.25 mmols) was added to the second syringe. The solutions were pumped through a 4-stage cascade CSTR, see ESI for picture, at 0.26 ml/ min, giving a residence time of 30 minutes. The reaction was run for 2.5 h and 5 RVs were collected. Each RV was then filtered and the solid washed

with water (2 x 15 ml), yielding off-white crystals of **2** (0.28 g, 16%). Each reactor volume was analysed by NMR and the spectra consistent with those reported for **2** above.

General procedure for hydrogenolysis of triaryloxytriazines in batch

To a solution of the triaryloxytriazine (1.00 equiv.) in ethyl acetate (60 mL) was added 10% Pd/C (10 weight percentage of the substrate) at room temperature. The mixture was degassed of oxygen by three times vacuum/nitrogen cycles. The flask was degassed of nitrogen by three times vacuum/hydrogen cycles and left under a reservoir of hydrogen at atmospheric pressure from a balloon. Separate reactions were stirred for 6−21 h at 20 °C or 40 °C. When the hydrogenation was complete the catalyst was removed by filtering through a plug of Celite. The filtrate was washed with water (20 mL) and the organic layer was separated and dried with $MgSO_4$ and concentrated *in vacuo*.

General procedure for hydrogenolysis of triaryloxytriazines in continuous flow

A two-stage cascade CSTR 0.6 L Hastelloy® automated Parr hydrogenator was employed, see ESI for picture. A 12.5 g/L solution of the triazine in EtOAc was pumped into the 1st reactor containing the resident volume of ethyl acetate, 10% (w/w) of catalyst mechanically stirred under a hydrogen atmosphere, controlled at a temperature of 40 °C. The hydrogen pressure, flow rate and residence volume were varied to optimise the reaction conditions, see ESI Table 2 for details. The residence volume could be changed by adjusting the length of the dip tube in both reactors, the product was collected continuously in a column connected in series. After venting the hydrogen the products were obtained by screening the catalyst using solvent-wet Celite on a sintered filter, washed with additional solvent, and the deoxygenated aromatic product was analysed directly in solution by quantitative GC against authentic standards. In some

experiments the solvent was carefully removed to give the product oils, and the structures were confirmed by ^{1}H NMR and found to be consistent with published data.

ASSOCIATED CONTENT

Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org."

Analytical details; Experimental information on other compounds discussed in the paper; details of continuous flow experiments using CSTRs; information about cyanuric acid decomposition and catalyst deactivation; raw material cost information; crystal structure x-ray data.

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Notes

The authors declare no competing financial interest.

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(20) See ESI. Current costs of lignin vary from £0.25-2/kg. Information available online from www.nnfcc.co.uk/ publications/nnfcc-renewable-chemicals-factsheet-lignin/at_download/file. [Accessed 08/04/2016]; indicative bulk pure anisole price £3/kg. www.alibaba.com [Accessed 24/08/16].

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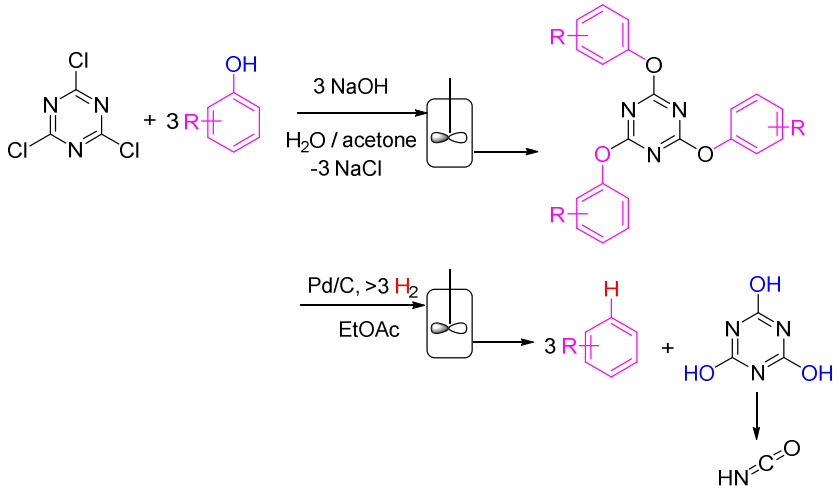
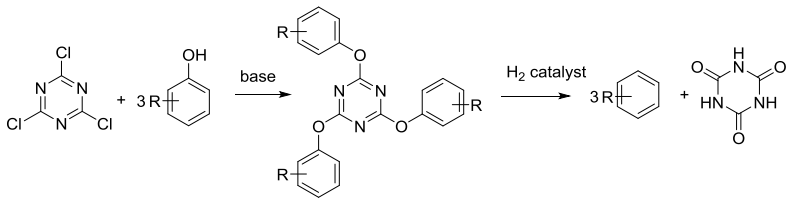
Table of Contents Graphic and Synopsis

A new approach to the hydrodeoxygenation of lignin-related aromatic building blocks is reported. This involves the reaction of three phenol equivalents with cyanuric chloride and hydrogenolysis of the resulting cyanurate esters. A continuous process has been developed for converting guaiacol to anisole.

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N
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+ 3 R
OH
base
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3 R
+
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N
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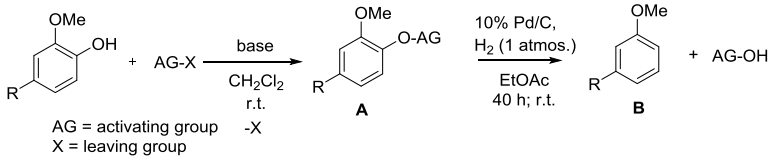
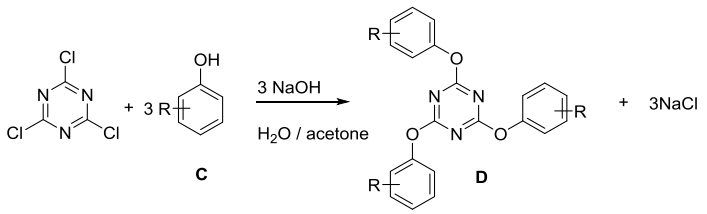
O
HN
NH
O

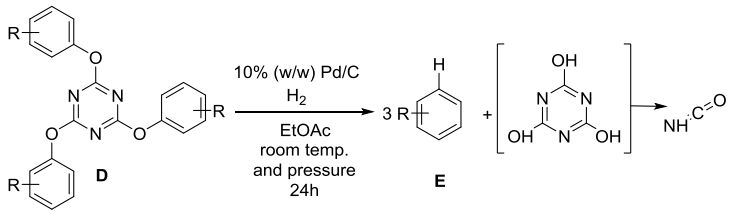


			% yield		product name
entry	R	AG-X	**A**	**B**	**B**
1	H	Tf-OTf[f]	95	33	anisole
2	CHO	Tf-OTf[f]	60	42[a]	*m*-methyl anisole
3	H	Ms-Cl[g]	97	0[b]	anisole
4	CHO	Ms-Cl	62	0[c]	*m*-methyl anisole
5	H	*p*Ts-Cl[h]	81	0[b]	anisole
6	CHO	*p*Ts-Cl	71	0[d]	*m*-methyl anisole
7	H	Tz-Cl[i]	75	39[e]	anisole

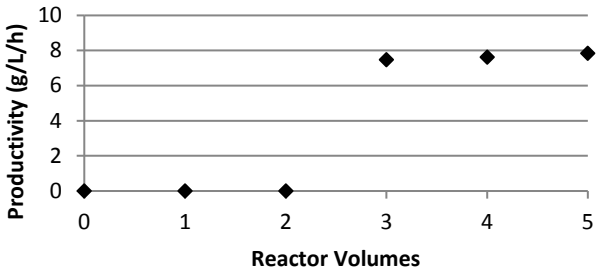


C D

		product number	yield (%)[a,b]
Entry	R	**D**	**D**
1	H	**1**	89
2	2-OMe	**2**	94
3	3-OMe	**3**	92
4	4-OMe	**4**	92
5	4-CHO	**5**	85
6	2-OMe, 4-CHO	**6**	62
7	2-CO_2Me	**7**	22[c]
8	2-OMe, 4-CO_2Me	**8**	10[c]
9	2-CO_2H	**9**	76
10	2-OMe, 4-CO_2H	**10**	71



Entry	product number **D**	product name **E**	yield (%)[a,b] **E**
1	**1**	benzene	10
2	**2**	anisole	86
3	**3**	anisole	68
4	**4**	anisole	68
5	**5**	benzyl alcohol	30
6	**6**	3-methylanisole	14
7	**7**	methyl benzoate	10
8	**8**	methyl 3-methoxybenzoate	12
9	**9**	benzoic acid	21
10	**10**	3-methoxybenzoic acid	58


Productivity (g/L/h)
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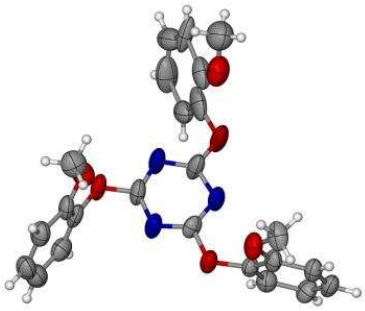
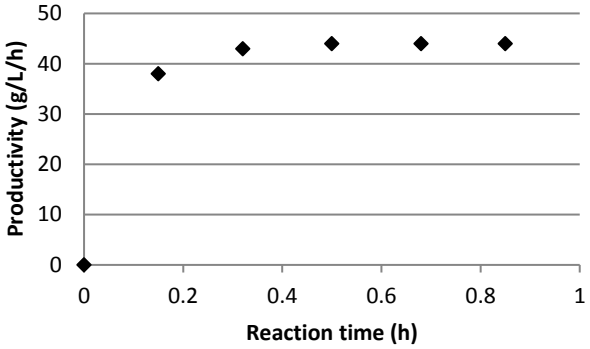
8
6
4
2
0
0
1
2
3
4
5
Reactor Volumes




Productivity (g/L/h)
50
40
30
20
10
0
0
0.2
0.4
0.6
0.8
1
Reaction time (h)