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Synthesis of Renewable Bisphenols from Creosol

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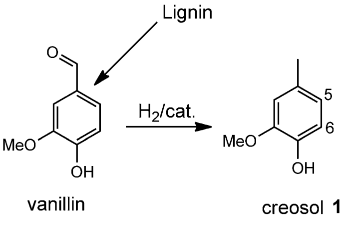
Dedicated to Dr. Albert R. Harvey on the occasion of his retirement.

A series of renewable bisphenols has been synthesized from creosol (2-methoxy-4-methylphenol) through stoichiometric condensation with short-chain aldehydes. Creosol can be readily produced from lignin, potentially allowing for the large scale synthesis of bisphenol A replacements from abundant waste biomass. The renewable bisphenols were isolated in good yields and purities without resorting to solvent-intense purification methods. Zinc acetate was shown to be a selective catalyst for the *ortho*-coupling of formaldehyde, but was unreactive when more sterically demanding aldehydes were used. Dilute HCl and HBr solutions were shown to be effective catalysts for the selective coupling of aldehydes in the position *meta* to the hydroxyl group. The acid solutions could be recycled and reused multiple times without decrease in activity or yield.

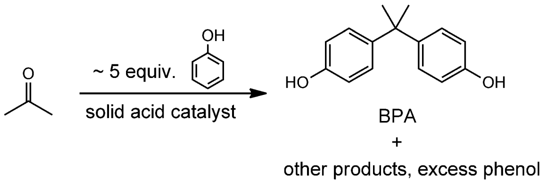
Introduction

A myriad of approaches have been developed for the efficient conversion of biomass to custom chemicals and fuels.[1] In parallel with these efforts, routes to renewable and sustainable polymer systems have been investigated and, in some cases, commercialized.[2] Although triglycerides and cellulose have been examined as the preferred feedstocks for many of these polymers, well-defined polymers from lignin have been largely unexplored, which is probably attributable to the difficulty of isolating pure, well-defined monomers on a large scale.[3] Given the clear benefits of highly aromatic polymer systems, including good thermal and mechanical properties, the study of methods for the efficient utilization of lignin has the potential to yield industrially relevant quantities of renewable polymers that meet the demanding requirements of conventional aromatic-based resins.[4] The utilization of renewable polyphenols as precursors to epoxy resins, polycarbonates, and high-temperature thermosetting resins, such as cyanate esters, provides an opportunity to develop full-performance materials while reducing the use of petroleum-based feedstocks. This approach diminishes the overall environmental impact of resin production, due to its use of a sustainable source of phenols. As a tangential benefit, renewable phenols may have significantly lower toxicities than typical precursors such as bisphenol A (BPA).[5]



Scheme 1. Isolation of **1** from lignin.

Creosol (**1**),a reduced form of vanillin (Scheme 1), is a compelling feedstock for the synthesis of bisphenols. The large scale isolation of vanillin from lignin is a demonstrated commercial process,[6] and the straightforward hydrogenation of vanillin has been shown to produce **1** in 99% yield.[7] The condensation of **1** with short-chain aldehydes has the potential to produce bisphenols that can be converted to resins with tunable physical characteristics, which include melting point, hydrophobicity, and toughness. The methyl group in **1** effectively blocks the position *para* to the hydroxyl group, while the methoxy and phenol groups direct coupling to the 5- and 6-positions, respectively (Scheme 1). Thus, although renewable phenols often have additional functional groups on the aromatic ring, the steric hindrance and directing effects of these groups can be utilized to control product distribution in some cases. In contrast, aldehyde and ketone condensation reactions using simple phenol must be run at a high phenol/(aldehyde or ketone) ratio to reduce side products, which include *o,p*-bisphenols and novolac-type resins (Scheme 2).[8] As an example



Scheme 2. Synthesis of BPA.

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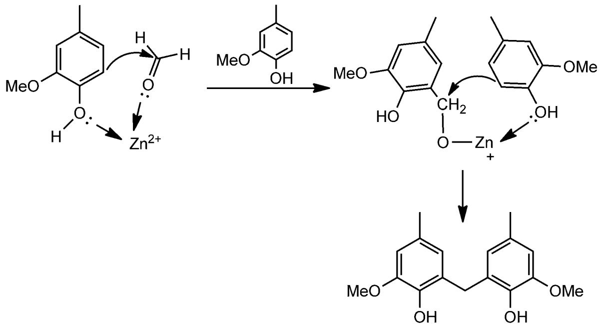
of the low selectivity of conventional substituted phenols in aldehyde condensation reactions, a total of six isomers were reported when a 3-methylphenol/formaldehyde ratio of 50:1 was allowed to react.[9] In the special case of renewable materials, atom economy is at a premium, making a stoichiometric process considerably more favorable. In this report, we describe the efficient, selective, and stoichiometric synthesis of bisphenols from **1**.

Results and Discussion

Synthesis of bisphenols

As an initial entry into this chemistry, we sought to condense one equivalent of an aldehyde or ketone with two equivalents of **1**. In an effort to reduce the environmental impact of the process, we first evaluated Nafion as a heterogeneous acid catalyst for the condensation reactions. Surprisingly, Nafion was ineffective at catalyzing the condensation reaction between **1** and formaldehyde, acetaldehyde, propionaldehyde, and acetone, respectively. Regardless of the aldehyde or ketone used, no reaction was observed even at temperatures in excess of 100 °C. Next, a Lewis acid catalyst, $Zn(Ac)_2$, was used at very moderate loadings (0.8 mol %), and the *ortho*-coupled product, 6,6′-methylenebis(2-methoxy-4-methylphenol) (**2**),[10] was isolated in 41 % yield (Table 1). Zn^{II} has been reported to be selective for *ortho*-condensation products based on a chelating effect[11] (Scheme 3). In agreement with the report, **2** was the only observed product. Although it has been suggested that other simple aldehydes, such as acetaldehyde, can be effectively condensed with **1** by using this method,[10] no reaction was observed with either acetaldehyde or propionaldehyde, even after 72 h of heating to reflux and using up to ten times the standard catalyst loading. This difference in reactivity is attributed to the electron-donating effect of the alkyl substituents, which could potentially be overcome with a stronger Lewis acid.



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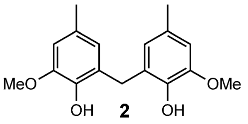
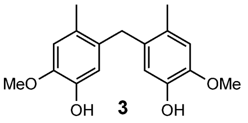
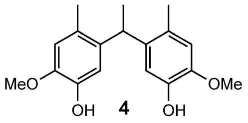
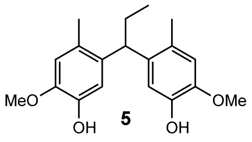
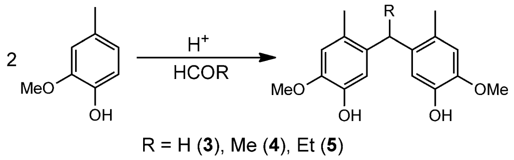
Scheme 3. Proposed mechanism for the $Zn(Ac)_2$-mediated coupling of **1** with formaldehyde.

Table 1. Synthesis of bisphenols from **1**.		
Product	Catalyst	Yield [%]
 **2**	$Zn(Ac)_2$	41[a]
 **3**	2.5 M HCl	63[b]
 **4**	2.5 M HCl	68[c]
 **5**	6 M HBr	67[d]

[a] 0.8 mol % catalyst, 16 h, reflux. [b] 3 h, reflux. [c] 4 h, reflux, phenol/aldehyde ratio of 1.5. [d] 16 h, ambient.

Turning to Brønsted acid catalysts, we explored the use of biphasic systems consisting of a mineral acid, an aldehyde, and a stoichiometric amount of **1** (Scheme 4).[12] HCl (2.5 M) was determined to be the most effective catalyst for the condensation of **1** with formaldehyde.[13] In contrast to the zinc-catalyzed reaction, formaldehyde coupled almost exclusively at the position *meta* to the hydroxyl group with a selectivity of 97 %.[14] As opposed to the acid-catalyzed condensation of simple phenol with formaldehyde, the steric constraints of **1** along with the *para*- and *ortho*-directing effects of the methoxy and methyl groups, respectively, resulted in the product specificity. In a similar manner, the stoichiometric condensation product **4** was prepared in 68 % yield from **1** and acetaldehyde.



Scheme 4. Brønsted acid-catalyzed coupling of **1** with aldehydes.

Propionaldehyde proved to be a considerably more demanding substrate than acetaldehyde[15] and could not be condensed even by using concentrated HCl. H_2SO_4 (5 M) also produced no reaction, whereas 9 M and concentrated H_2SO_4 produced black solutions with multiple products. Although the dark color suggested the presence of quinones, concentrated H_2SO_4 has been reported to convert aryl methyl ethers to phenols, which may further complicate the product distribution.[16] Interestingly, HBr (6 M) cleanly produced bisphenol **5** in 67 % yield at room temperature. This is probably the result of the enhanced reactivity of the intermediate carbocation due to the greater polarizability of bromide compared to chloride.

Table 2. Selectivity of aldehyde coupling reactions using **1**.

Aldehyde	*meta,meta* Isomer [%]	*meta,ortho* Isomer [%]
CH_2O	97	3
CH_3CHO	96	4
CH_3CH_2CHO	100	–

The *meta,meta* isomers were almost exclusively isolated, regardless of the aldehyde (Table 2). Significant differences in the selectivity were not observed between formaldehyde and acetaldehyde, but when propionaldehyde was condensed, no trace of the *meta,ortho* product was found. This suggests that, in addition to electronic and steric effects inherent to the phenol, the alkyl group on the aldehyde plays a role in the selectivity of the reaction.

The biphasic approach to bisphenol synthesis has a number of advantages over conventional techniques. The initial reaction requires no organic solvent and the crude product can be isolated by using a simple decantation followed by a water wash. Although subsequent steps utilize solvents for purification, the phenols can also be purified by sublimation, which results in a solvent-free process. In addition, the procedure is performed at moderate temperatures and does not require protection from atmospheric conditions. Perhaps one of the most attractive aspects of this method is the potential to reuse the acid solutions. To examine the feasibility of recycling the acid solutions, **4** was prepared according to the standard conditions with HCl (2.5 M). The acid solution was then reused in two subsequent reactions without any purification. The yields actually increased slightly in later reactions, perhaps due to residual reagents that were solubilized in the aqueous phase. Although the use of mineral acids may be considered detrimental for a sustainable process, the ability to reuse the solutions greatly reduces the environmental impact of this approach.

Structures and properties of bisphenols

To confirm the structures and evaluate the suitability of various phenols as precursors to thermoplastics and thermosetting resins, the X-ray structures of the bisphenols were determined.[17] Compound **2**, in addition to exhibiting intermolecular hydrogen bonding, has two intramolecular hydrogen bonds of 1.83(2) and 2.24(2) Å between the two phenol units and between a phenol and a methoxy oxygen, respectively. This interaction is possible due to the close proximity of the phenols resulting from the *ortho* coupling and gives rise to a symmetrical molecule in the solid state (Figure 1). The bisphenols substituted at the *meta* position also participate in intramolecular hydrogen bonding, but the aromatic substitution precludes the strong inter-ring hydrogen bonding observed in **2** and results in rotated aromatic groups; as an example, the structure of **4** is shown in Figure 2.[18] In contrast to the other phenols, pure **5** was isolated as an oil at room temperature. Although ^{13}C NMR spectroscopy and GC–MS confirmed the purity of this oil, ^1H NMR spectroscopy revealed the presence of residual water even after extended drying in a vacuum oven. This excess water was confirmed by elemental analysis, and leads to the conclusion that the oil is a water adduct of **5** with a stoichiometry of $\mathbf{5}\cdot 1.5\,H_2O$. In the presence of dimethylsulfoxide (DMSO), **5** formed a solvent adduct that readily crystallized, allowing for a structural comparison. The adduct is stabilized by a strong hydrogen bonding interaction between the phenol and DMSO.

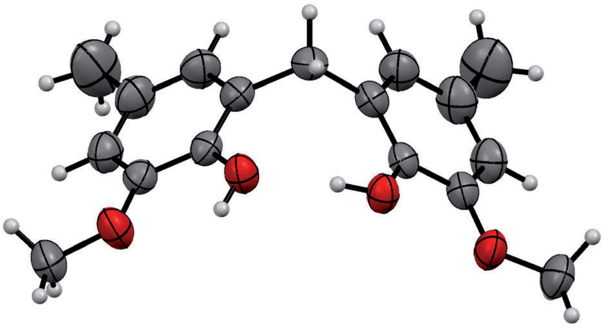


Figure 1. Solid-state structure of **2**.

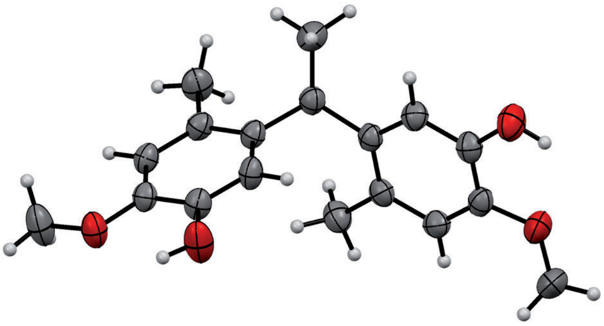


Figure 2. Solid-state structure of **4**.

One of the goals of this research was the development of a method that allowed for the selective modification of both the hydrophobicitiesand melting points of the phenols. Daughter resins (e.g., cyanate esters) are expected to inherit many of the properties of the parent phenols, and thus, this work will allow the resins to be custom-tailored based on the choice of aldehyde and the condensation catalyst.

Some insight into the effect of aldehyde choice can be gained by comparing the melting points of the bisphenols. Compound **2** has the lowest melting point (123–125 °C), followed by **3** (131–134 °C), and **4** (143–146 °C). The increase in melting point from **3** to **4** is surprising compared to the melting points of the related bisphenol F and bisphenol E, which are 162–164 and 123–127 °C, respectively (Figure 3). The 1,1-di-

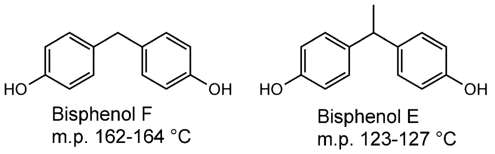


Figure 3. Structures of conventional bisphenols.

phenylethane framework typically results in depressed melting points compared to methylene or 2,2-diphenylpropane linkages.[19] Despite this discrepancy, the melting point exhibited a drastic decrease upon extension of the reaction from acetaldehyde to propionaldehyde, and **5** was isolated as a viscous oil. For applications as precursors to thermosetting composites, lower melting resins should allow simplified and lower-cost fabrication methods.

Conclusions

A series of bisphenols has been synthesized from creosol, a renewable phenol that can be produced from abundant waste lignin. The functional groups on the ring and choice of catalyst allow for control of the condensation productsand these reactions can be conducted with stoichiometric amounts of the phenol. The ability to recycle the acid catalysts, perform the reaction in the absence of organic solvents, and isolate the products without resorting to solvent-intense purification methods make these phenols intriguing renewable and sustainable precursors to a variety of polymeric materials. Further work on the conversion of these bisphenols to resins and polymers is ongoing.

Experimental Section

General

2-Methoxy-4-methylphenol (**1**), acetaldehyde, propionaldehyde, formaldehyde (37 %), $Zn(Ac)_2{\cdot}2\,H_2O$, and concentrated HBr (48 %) were purchased from Aldrich and used as received. Concentrated HCl and H_2SO_4 were purchased from Fisher Scientific and used as received. NMR spectra were collected by using a Bruker Avance II 300 MHz NMR spectrometer. Samples of bisphenols were prepared in [D$_6$]DMSO, and spectra were referenced to the solvent peaks ($\delta = 2.50$ and 39.5 ppm for ^{1}H and ^{13}C NMR spectra, respectively). The products were further analyzed by using an Agilent 6890-GC system with a Restek RTX-5MS 30-meter column. The GC inlet temperature was 250 °C, and the column oven temperature program began at 40 °C for three minutes and increased to 350 °C at 10 °C min^{-1}. An Agilent mass selective detector (MSD) 5973 system was used to identify various products. Elemental analysis was performed by Atlantic Microlabs Inc. Norcross, GA.

6,6′-Methylenebis(2-methoxy-4-methylphenol) (2)

Compound **1** (5 g, 36.2 mmol), 37 % formaldehyde (1.56 g, 19.2 mmol), and $Zn(ac)_2{\cdot}2\,H_2O$ (70 mg, 3.2×10^{-4} mol) were heated to reflux overnight under N_2. The resulting oil was washed with 10 % ethanol, and extracted into ether. The ether was removed on a rotary evaporator and the resulting oil was heated to 100 °C overnight under reduced pressure (133.3 Pa). The resulting solid was dissolved in ether and precipitated with heptane. The light-tan solid was collected by filtration, washed with excess heptane, and dried to yield 2.13 g (41 %) of **2**. m.p. 123–125 °C; ^{1}H NMR ([D$_6$]DMSO): $\delta = 2.11$ (s, 6 H), 3.71 (s, 2 H), 3.74 (s, 6 H), 6.35 (d, $J = 2$ Hz, 2 H), 6.58 (d, $J = 2$ Hz, 2 H), 8.20 ppm (s, 2 H); ^{13}C NMR ([D$_6$]DMSO): $\delta = 21.1$, 29.0, 56.2, 110.7, 122.7, 127.4, 127.7, 141.9, 147.5 ppm; MS: $m/z = 288$, 271, 255, 239, 212, 195, 165, 138, 121, 105. elemental analysis calcd. (%): C 70.81, H 6.99; found: C 70.84, H 7.13.

5,5′-Methylenebis(2-methoxy-4-methylphenol) (3)

Compound **1** (5.03 g, 36.4 mmol) and 37 % formaldehyde (1.47 g, 18.1 mmol) were diluted with deionized H_2O (40 mL). Concentrated HCl (10 mL) was slowly added, and the reaction was heated to reflux under N_2 for 3 h. A precipitate formed, the solution was decanted, and the solid was washed with 10 % ethanol solution. The solid was dissolved in ether and precipitated with heptane. Compound **3** was isolated as a crystalline white solid (3.29 g, 63 %). Crystals suitable for an X-ray diffraction study were obtained from the slow evaporation of an ether solution at room temperature. m.p. 131–134 °C; ^{1}H NMR ([D$_6$]DMSO): $\delta = 2.08$ (s, 6 H), 3.56 (s, 2 H), 3.71 (s, 6 H), 6.30 (s, 2 H), 6.72 (s, 2 H), 8.54 ppm (s, 2 H); ^{13}C NMR ([D$_6$]DMSO): $\delta = 19.0$, 35.0, 56.2, 115.0, 117.0, 126.3, 131.3, 144.8, 146.6 ppm; MS: $m/z = 288$, 273, 257, 241, 227, 213, 195, 181, 165, 150; elemental analysis calcd. (%): C 70.81, H 6.99; found: C 70.66, H 7.16.

5,5′-(Ethane-1,1-diyl)bis(2-methoxy-4-methylphenol) (4)

Compound **1** (5.1 g, 37.0 mmol) and acetaldehyde (1.06 g, 24.1 mmol) were diluted with deionized H_2O (40 mL). Concentrated HCl (10 mL) was slowly added, and the mixture was heated to reflux under N_2 for 4 h. The supernatant was carefully decanted from the resulting dense oil. Compound **4** was obtained as a white solid after extraction into ether and precipitation with heptane (3.74 g, 68 %). Crystals suitable for an X-ray diffraction study were obtained from the slow evaporation of an ether solution at room temperature. m.p. 143–146 °C; ^{1}H NMR ([D$_6$]DMSO): $\delta = 1.30$ (d, $J = 7$ Hz, 3 H), 2.06 (s, 6 H), 3.69 (s, 6 H), 4.05 (t, $J = 7$ Hz, 1 H), 6.48 (s, 2 H), 6.66 (s, 2 H), 8.57 ppm (s, 2 H); ^{13}C NMR ([D$_6$]DMSO): $\delta = 18.5$, 21.3, 36.1, 56.0, 114.6, 115.0, 125.7, 137.0, 144.6, 145.5 ppm; MS: $m/z = 303$, 287, 269, 240, 211, 195, 164, 145, 128, 105; elemental analysis calcd.(%): C 71.50, H 7.33; found: C 71.58, H 7.46.

5,5′-(Propane-1,1-diyl)bis(2-methoxy-4-methylphenol) (5)

Compound **1** (5.02 g, 36.4 mmol) and propionaldehyde (1.04 g, 17.9 mmol) were diluted with deionized H_2O (10 mL). 48 % aqueous HBr (20 mL) was slowly added, and the reaction was stirred at room temperature overnight. The supernatant was carefully decanted from the resultant oil, and the product was washed with water. Work up by using the method described above yielded **5** as a viscous tan oil (3.82 g, 67 %). The product formed a solvent adduct with DMSO that crystallized from ether solutions upon standing at room temperature. ^{1}H NMR ([D$_6$]DMSO): $\delta = 0.85$ (t, $J = 7$ Hz, 3 H), 1.73 (t, $J = 7$ Hz, 2 H), 2.10 (s, 6 H), 3.69 (s, 6 H), 3.81 (t, $J = 7$ Hz, 1 H), 6.52 (s, 2 H), 6.65 (s, 2 H), 8.55 ppm (s, 2 H); ^{13}C NMR ([D$_6$]DMSO): $\delta = 13.1$, 18.9, 28.9, 43.3, 56.1, 114.9, 115.0, 126.3, 135.5, 144.5, 145.6 ppm; MS: $m/z = 316$, 287, 257, 240, 211, 195, 167, 151, 131, 115; elemental analysis calcd. for **5**$\cdot 1.5\,H_2O$: C 66.45, H 7.92; found: C 66.33, H 7.78.

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Keywords: aldehydes · biomass · bisphenols · catalysis · sustainable chemistry

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[14] The selectivity of the *m*,*m* isomer is based on GC–MS data—see the Supporting Information.
[15] Compound **5** has been reported as a condensation product by using dilute H_2SO_4 as a catalyst: S. Yasuda, K. Ota, *Mokuzai Gakkaishi* **1986**, *32*, 51 – 58. In our laboratory, dilute H_2SO_4 did not promote the condensation of **1** and propionaldehyde.
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[17] CCDC 831799 (**2**), 831800 (**3**), 831801 (**4**), and 831802 (**5**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre through www.ccdc.cam.ac.uk/data request/cif. A cif file that contains the structural information for each compound is available in the Supporting Information.
[18] The angles between the rings are 78.18, 81.49, and 72.34° for **3**, **4**, and **5**, respectively.
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