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Solvolysis, Electrochemistry, and Development of Synthetic Building Blocks from Sawdust

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Supporting Information

ABSTRACT: Either aldehyde or cinnamyl ether products can be selectively extracted from raw sawdust by controlling the temperature and pressure of a solvolysis reaction. These materials have been used as platform chemicals for the synthesis of 15 different synthetic substrates. The conversion of the initial sawdust-derived materials into electron-rich aryl substrates often requires the use of oxidation and reduction chemistry, and the role electrochemistry can play as a sustainable method for these transformations has been defined.

INTRODUCTION

Lignin is the second most abundant organic material on earth. It is one of the three main components of cell walls and comprises 15−30% of the dry weight of nonedible woody biomass.[1−5] Lignin (Figure 1) is synthesized in nature from coumaryl, coniferyl, and sinapyl alcohols. As such, its structure contains the same types of alkoxy-substituted, electron-rich aromatic rings commonly found in a variety of biological privileged structures and interesting new polymers of the type illustrated in Figure 2. In this regard, lignin is unique. Common biomaterials like proteins, DNA, carbohydrates, and lipids simply do not contain the types of electron-rich aromatic rings found in lignin.

Because of the unique structure of lignin and its availability, extensive effort is being expended to disassemble lignin into smaller materials.[1] These efforts have focused on reductive methods,[6] oxidative approaches,[7] redox neutral methods,[8] and solvolytic approaches. While significant success has been observed with model systems for lignin, there are fewer methods that successfully disassemble lignin itself. Of particular note are reductive methods that take advantage of catalysts to convert lignin into organic soluble smaller materials[6c−f] and redox neutral methods that allow lignin to be converted into potentially new "streams" of aromatic substrates.[8b] However, such methods often lead to mixtures of products that in turn require separation before processing selected components of the material into value-added materials. An overall strategy for rapidly acquiring isolated, pure synthetic building blocks from a raw form of lignin remains elusive.

We report here that the direct methanolysis of sawdust at lower temperature and pressure can be used to selectively extract cinnamyl ether derivatives from the wood, while the use of higher temperature and pressure affords aryl aldehyde products. Both families of products can be readily isolated and then converted into a wide variety of more advanced synthetic intermediates. Finally, redox reactions have proven to be critical for developing new materials from lignin, and the utility of electrochemical methods for meeting this need is highlighted.

RESULTS AND DISCUSSION

Solvolysis. The methanolysis conditions employed to obtain the initial starting materials from lignin took advantage of prior work from the Xu group on the reductive disassembly of lignin over Ni catalysts.[6f] In these reactions, sawdust was placed in a pressure reactor along with methanol and a Ni catalyst in order to afford reduction products from lignin that retained the three carbon side chain found in the original cinnamyl alcohol derivatives used by nature to make lignin (Figure 3).

We wondered if the catalyst was exclusively responsible for the disassembly of the lignin or if the solvolysis itself played a role in lignin disassembly. This idea was tested by treating birch sawdust under a variety of methanolysis conditions in the absence of catalyst. For the experiment, birch sawdust having particle sizes that ranged from approximately 2 mm × 1 mm to 1 mm long slivers was used. The sawdust was not milled in any way.

Prior to methanolysis, the birch sawdust was washed with 2:1 benzene:ethanol in a Soxhlet extractor in order to remove any oils from the surface of the wood (Scheme 1). The sawdust was then placed in a pressure reactor along with methanol and the mixture heated. The internal temperature of the reaction was monitored with a thermocouple. Following the reaction, the remaining wood (90−95% of the sawdust was recovered) was removed from the solution by filtration and the filtrate concentrated. Proton NMR spectra of the crude material obtained from three different sets of methanolysis conditions are shown in Figure 4. In the mixture obtained from the reaction using the lowest temperature and pressure (spectrum C), the vinyl protons of the cinnamate derivatives could be clearly seen (6−7 ppm). There was very little evidence for aldehyde formation. In the mixture obtained from the experiment run at the highest temperature and pressure (spectrum A), the presence of the syringealdehyde product was evident. Little evidence for cinnamate derivatives was observed. At an intermediate temper-

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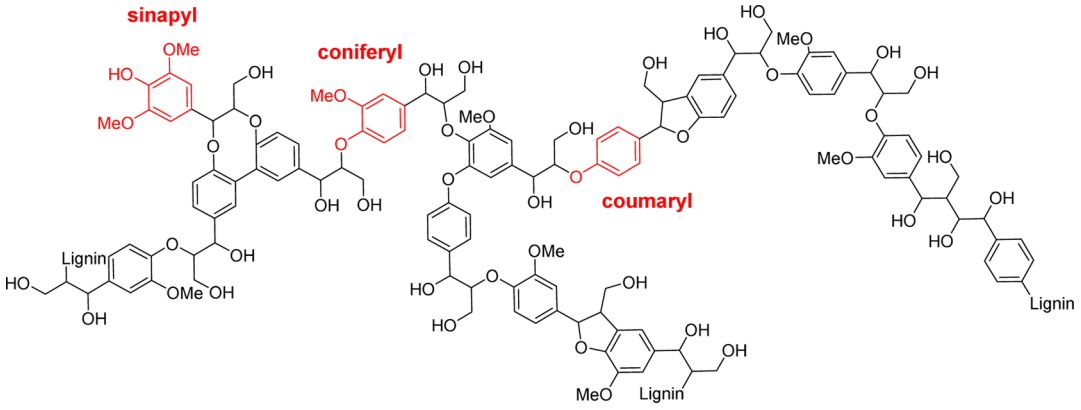


Figure 1. Example structure of lignin.

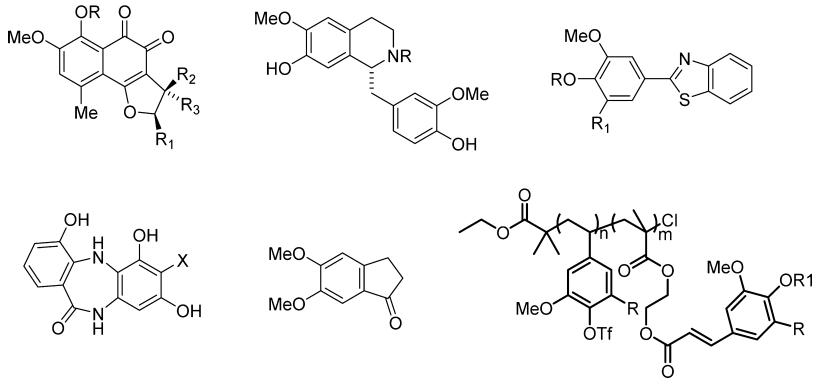


Figure 2. Electron-rich aromatic structures of interest.

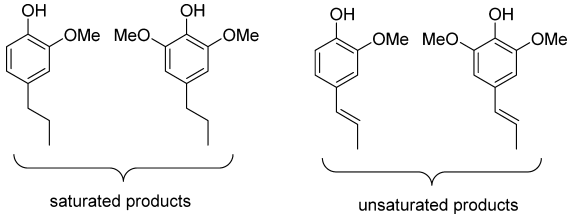
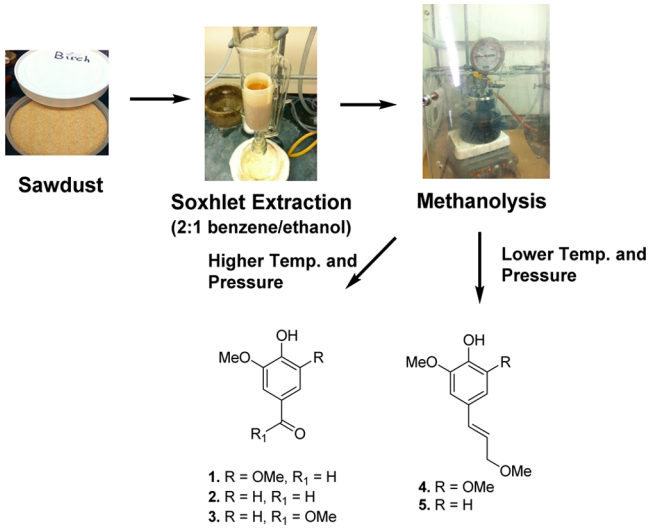


Figure 3. Products from the Ni-catalyzed reductive disassembly of lignin.

Scheme 1. Solvolysis Approach



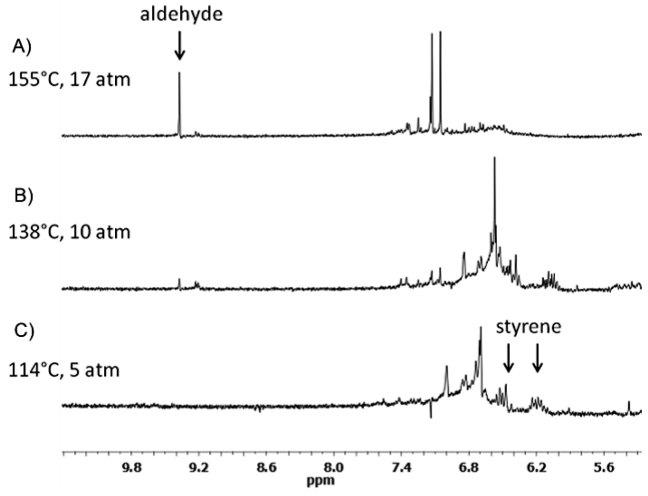


Figure 4. Proton NMR spectrum of the crude product from the solvolysis of birch sawdust at different temperatures and pressures.

ature (spectrum B), both products could be seen. In addition to the signals for these monomers, the proton NMRs of the crude material at all temperatures showed products that could best be assigned as lignin oligomers and products that were associated with the disassembly of cellulose.

Once the crude mixture was separated from the wood, the desired monomeric products could be easily isolated from the rest of the crude material by passing the filtrate through a very simple gravity flow silica gel chromatography column. Interestingly, the use of the birch sawdust in this manner led to only

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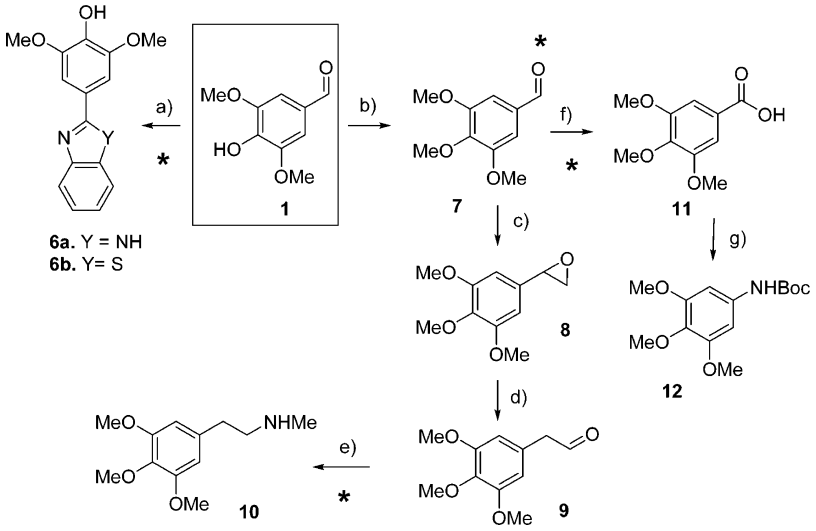
Scheme 2[a]



[a]Conditions: (a) Reticulated vitreous carbon (RVC) anode, carbon cathode, *o*-phenylenediamine or 2-aminothiophenol, 0.2 equiv of CAN, 0.1 M $LiClO_4$, 5:1 MeOH/THF, 4 mA, 2.3 F/mol, 80% (Y = N/by NMR), 83% (Y = S/by NMR); (b) KOH, DMSO/THF, MeI, 65%; (c) NaH, Me_3SI, DMSO/THF, 84%; (d) 10 mol % $Sc(OTf)_3$, CH_2Cl_2, 82%; (e) (i) $Ti(OiPr)_4$, MeOH, $MeNH_2$, (ii) $NaBH_4$, 46%; (f) H_2O_2–urea, NaOH, MeOH, 72%; (g) (i) DPPA, DMF, TEA, (ii) *t*-BuOH, 90 °C, 67%.

syringealdehyde (**1**) at the higher temperature and pressure. The yield of the syringealdehyde was approximately 1% by mass from the raw sawdust or approximately 5% from the lignin in the sawdust (assuming that the sawdust was roughly 20% lignin).[9] At the lower temperature and pressure, both the methyl ether of sinapyl alcohol (**4**) and the methyl ether of coniferyl alcohol (**5**) could be obtained. Both alcohols were isolated in about 0.6% by mass from the raw sawdust (3% from lignin). The products could be isolated in pure form with no difficulty. While the yield of the still unoptimized process is low, the ready availability of the sawdust starting material mitigates this issue, especially with the overall simplicity of the processes, the very high level of product selectivity obtained, and the fact that the remainder of the wood was recovered so that it could still be used for other purposes. This last point is important. For practical purposes, the solvolysis enables the selective extraction of desirable materials from the lignin in wood prior to processing the wood with more strenuous disassembly conditions that would more completely break apart the polymer and lead to mixtures of products.

The generality of the method was probed with the use of cedar sawdust in place of the previously used birch sawdust (Scheme 1). Once again, the selectivity of the solvolysis was controlled by the temperature and pressure of the reaction with more gentle conditions leading selectively to the methyl ether of coniferyl alcohol **5** (1.4% from the wood, 7% from lignin) and higher temperature and pressure leading to a mixture of vanillin **2** and the corresponding methyl ester **3** (yield = 1.4% from the wood, 7% from lignin in a 1:1.3 ratio of **2**/**3**). Interestingly, with the cedar sawdust no syringealdehyde or methyl ether from sinapyl alcohol was obtained. Thus, while the selectivity of the process was the same, the change in the source of lignin allowed for the isolation of products with different levels of aryl ring oxidation.

At the present time, the exact mechanism for the generation of the cinnamyl ether and aldehyde products is not clear. Do the products arise from fragmentation of the lignin polymer or are they simply end groups that are cleaved from the lignin during methanolysis? The observation that aldehyde products are absent at lower temperature and pressure and then appear at higher temperature and pressure in the absence of cinnamyl ether products does suggest that the aldehyde products may be thermodynamic products derived from the cinnamyl ethers during the solvolysis.

Not knowing the mechanism by which the products are generated complicates efforts to optimize the yield from the process. As mentioned above, most of the sawdust is recovered at the end of the solvolysis. The recovered sawdust does have a darker appearance than it did at the start of the reaction but otherwise appears unchanged. Resubmission of the sawdust to the methanolysis did lead to more of the desired product but afforded those products as a more difficult to separate mixture. Hence, efforts to optimize the yield of the process will focus less on driving the current reactions to completion and more on the role of particle size and milling of the sawdust prior to the methanolysis.

The observations made suggest a target-driven approach to obtaining aromatic materials from sawdust. If syringealdehyde **1** is needed as the starting material for a synthetic sequence then birch sawdust can be solvolyzed at high temperature and pressure to extract the desired substrate before continuing to process the wood. If the desire is to build a product from coniferyl alcohol **5** then it is best to start with cedar sawdust and maintain a lower temperature and pressure during the solvolysis. Presumably, other sources of lignin will afford alternative aromatic substrates.

Chemical Processing of Sawdust-Derived Materials. Of course, the use of lignin as a sustainable source of substrates for synthesis involves not only the disassembly of lignin but also conversion of the products obtained from that process into synthetic building blocks for constructing larger molecules of interest. With this in mind, we examined the conversion of lignin-derived aldehydes and cinnamyl ethers into a series of value-added synthetic building blocks. Each of the building blocks selected was identified as a key intermediate or platform chemical used in other synthetic efforts. The goal of the work was to identify "global" challenges that would need to be addressed for the overall strategy to be effective.

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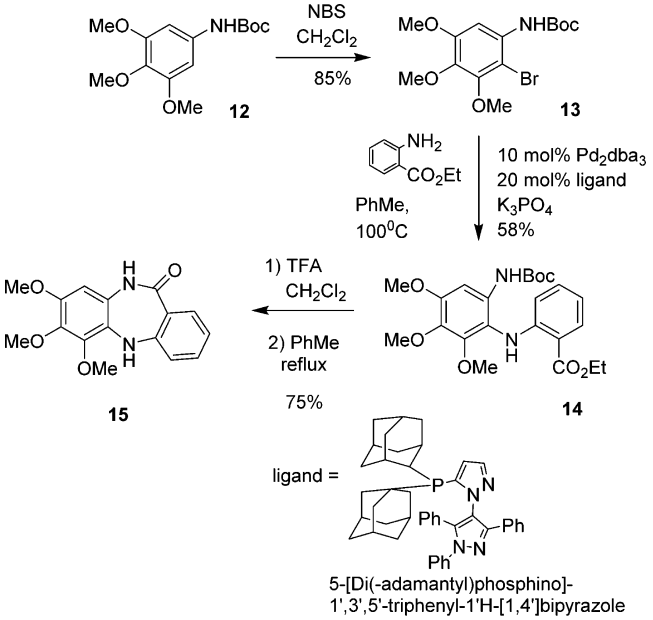
The work proceeded along two themes, one for each class of lignin-derived material. In the first (Scheme 2), syringealdehyde **1** was converted into a series of synthetic substrates, each of which can serve as a platform chemical for the construction of alkaloids. The first set of molecules made was benzimidazole and benzthiazole structures (**6**). Benzimidazole and benzthiazoles are privledged structures used for the development of a variety of medicinally active compounds.[10,11] The molecules could be made from syringealdehyde with an oxidative condensation reaction and thus were available from raw sawdust in just two steps. The next pair of molelcules made were aldehyde **9** and amine **10**. These two molecules were selected as targets because of their overall utility in the construction of polycyclic alkaloids.[12] The work started by protecting the phenol as a methyl ether in order to simplify isolation of the products and highlighted how very simple transformations can be used to access important synthetic intermediates from sawdust-derived material. Finally, syringealdehyde was converted into the electron-rich alanine derivative **12** that was targeted because of its use as a building block for assembling electron-rich benzodiazepenes (Scheme 3).

Scheme 3. Benzodiazepene Synthesis



Clearly, channeling the disassembly of lignin toward isolation of a clean aldehyde substrate can provide the starting materials needed to synthesize a variety of interesting new electron-rich materials.

As mentioned above, the reason for converting lignin-derived materials into more complex structures was to identify any global synthetic themes that would need to be addressed moving forward. During the work highlighted in Scheme 2 (and Scheme 4 below) one such theme was identified. The asterisks in the scheme denote oxidation and reduction reactions, reactions that played a key role in all three synthetic pathways.

A similar trend was found when sinapyl alcohol methyl ether **4** was converted into a series of synthetic substrates (Scheme 4). In this case, the phenol was protected as a methyl ether to form **16**, and then compound **16** was converted into electron-rich monomers (**17**, **19**) for the construction of new polymers, the indanone ring system found in numerous biological molecules (**20**), and substrates for electrochemical oxidation reactions (**22**, **23**). Of the reactions shown, it should be noted that the cross-metathesis reaction used in the construction of styrene derivative **17** is still under development. At this point, the mass balance for the reaction is high but the conversion low. Since this reaction lies outside the main theme of this paper, that effort will not be included here. Instead, note that once again oxidation and reduction reactions play a key role in the synthetic sequences and that in each case the syntheses take advantage of the carbon side chain on the aromatic ring that is available because of the milder conditions used for the solvolysis reaction.

In all, 9 of the 17 synthetic steps shown in Schemes 2 and 4 were redox reactions. Clearly, for the sustainable production of new synthetic building blocks from lignin, a generally applicable method for conducting a wide range of sustainable redox reactions is required.

Electrochemical Methods. Electrochemistry can serve as a very versatile method for meeting this need.[13] For example, the conversion of **1** into **6** highlighted in Scheme 2 takes advantage of an oxidative condensation between the aldehyde derived from lignin and either a diamine or an aminothiol. Such reactions are typically conducted with the use of a stoichiometric oxidant.[14] However, in the reaction shown, ceric ammonium nitrate was used in a catalytic fashion by recycling it at an anode.[15] Both reactions can be driven with the use of a renewable source of electricity, and both reactions produced hydrogen gas as the byproduct from the required reduction.[16,17] Such indirect methods are compatible with the use of a wide variety of chemical oxidants.[18]

Direct electrochemical reactions are also effective tools for processing lignin-derived materials. For example, molecules **22** and **23** highlighted in Scheme 4 have both been used as electrolysis substrates (Scheme 5). The first was used to convert the acyclic alcohol **22** into an aryl-substituted tetrahydrofuran derivative **24**. The reaction illustrated the utility of the lignin-derived aryl ring as an initiating group for subsequent oxidative cyclizations, reactions that have proven useful for the construction of aryl-functionalized C-glycosides.[19] Because the potential at the anode in such reactions automatically adjusts to that of the substrate,[16] the method can be used to oxidize molecules having a range of oxidation potentials and hence should be compatible with lignin-derived materials having varying alkoxy substitution patterns.

The second reaction was used to construct the bicyclic aldehyde **25**. This example was conducted in order to demonstrate the compatibility of the lignin-derived styrene moiety with oxidative C−C bond forming reactions,[20] a reaction that sets the stage for further synthetic transformations and the construction of polycyclic ring skeletons.

The use of electrochemistry for the processing of the lignin-derived materials is not limited to oxidation reactions. In Scheme 4, compound **19** was hydrogenated during the production of the indanone derivative. This reaction can be accomplished with the use of electrochemically generated hydrogen gas as illustrated in Scheme 6. The hydrogen gas was generated by the reduction of methanol at a cathode. For this particular reaction, the methanol solvent was also oxidized at the anode to form formaldehyde and the protons needed to neutralize the methoxide generated at the cathode. A photovoltaic was used to generate the electricity needed.[16,17] The reaction was conducted as part of a larger effort to improve the overall sustainability of reactions by generating the reagents needed for the reactions "on-site", thereby avoiding the need to isolate, package, and transport the reagent.

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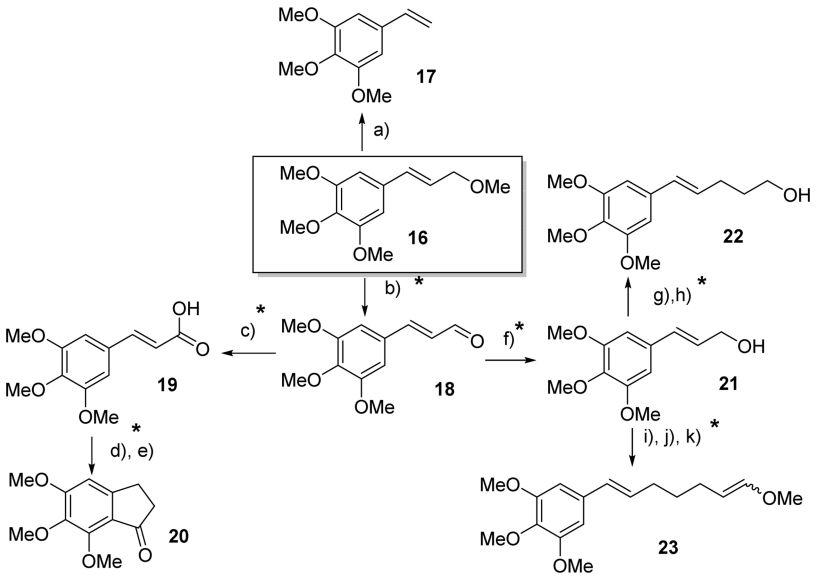
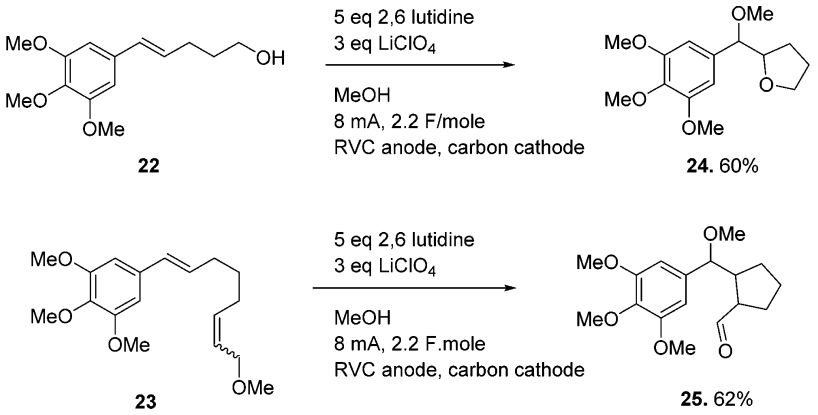
Scheme 4[a]

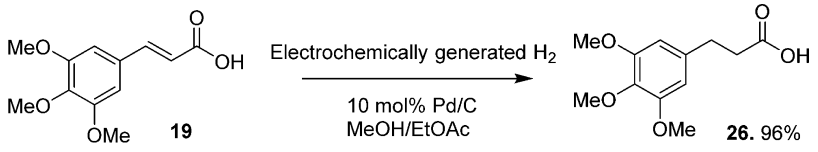


[a]Conditions: (a) Grubbs' 2nd-generation catalyst (8 mol %), THF, ethylene (1 atm), 55 °C, 34% (50% recovered starting material); (b) DDQ, CH_2Cl_2, 76%; (c) NaH_2PO_4, NaOClO, DMSO, H_2O, 83%; (d) Pd/C, H_2, MeOH, EtOAc, 100%; (e) P_2O_5, CH_3SO_3H, 100 °C, 73%; (f) $NaBH_4$, MeOH, 84%; (g) (i) MsCl, triethylamine, CH_2Cl_2, (ii) vinylmagnesium bromide, THF, 53%; (h) (i) 9-BBN, THF, −78 °C to RT, (ii) H_2O_2, H_2O, NaOH, −78 °C to RT, 75%; (i) (i) MsCl, triethylamine, CH_2Cl_2, (ii) allylmagnesium bromide, THF, 41%; (j) (i) 9-BBN, THF, −78 °C to RT, (ii) H_2O_2, H_2O, NaOH, −78 °C to RT, 77%; (k) (i) $(COCl)_2$, DMSO, THF, −78 °C, (ii) triethylamine, −60 °C to RT, (iii) $MeOCH_2PPh_3Cl$, THF, *t*-BuLi, pentane, 0 °C, 70%.

Scheme 5. Direct Electrochemical Cyclizations



Scheme 6. Hydrogenation with Electrochemically Generated H_2.



What makes the on-site generation of reagents at a cathode for reductions like the one shown in Scheme 6 particularly attractive is that the energy required for the reaction can be supplied by any oxidation reaction, for example, considering the paired electrolysis reaction shown in Scheme 7a.[21] In this reaction, veratryl alcohol is oxidized to the corresponding aldehyde at the anode. The reaction was coupled to generation of hydrogen gas and the subsequent hydrogenation of cinnamic acid derivative **19**.

Since the hydrogen gas from the reaction is allowed to bubble off into a second flask where the hydrogenation takes place, one can imagine that the paired electrolysis is not restricted to this one reduction. In Scheme 7b, a paired electrochemical reaction is illustrated that couples the oxidation of veratryl alcohol to the hydrogenolysis of a benzyl carbamate protecting group to form phenylalanine (**28**). In such processes, the oxidation reaction can be varied as well.

The success of the paired electrolyses illustrated above suggests an opportunity to rethink how we use the oxidation reactions in schemes like **2** and **4** and their overall value to a synthetic effort. Cathodic reductions can be used to make hydrogen gas, CO, syn-gas, bases, reductants, etc. Thus, in

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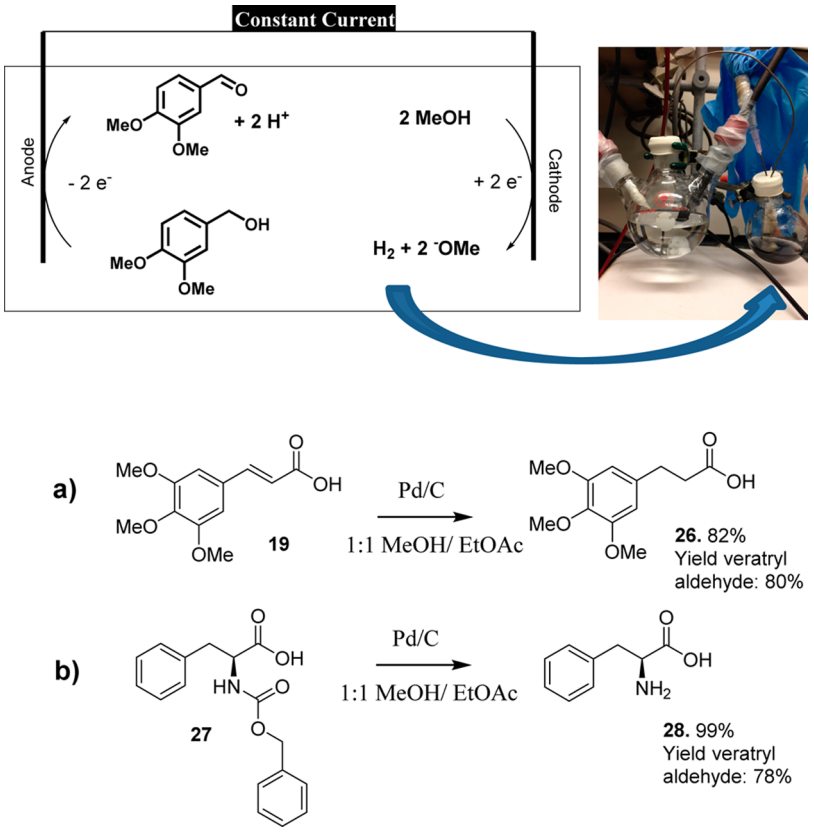
Scheme 7. Pairing Electrochemical Reactions



principle an oxidation reaction can be used to not only accomplish a desired oxidative transformation in a synthetic sequence but also to generate a variety of reagents for other steps in a synthesis. Efforts to demonstrate the generality of such processes are underway.

CONCLUSIONS

We have demonstrated the potential for converting raw sawdust into synthetic substrates that contain electron-rich aromatic rings. The process begins with the temperature- and pressure-controlled solvolysis of sawdust in order to generate one of two families of products. Solvolysis reactions conducted at lower temperature and pressure lead to cinnamyl ether products, while solvolysis reactions conducted at higher temperature and pressure afford aryl aldehyde products. The number of alkoxy substituents on the products obtained reflects the nature of the sawdust used. The method provides a very simply way of accessing both families of molecules so that they can be used to synthesize a variety of more complex platform chemicals for synthesis. In this subsequent effort, redox reactions play a key role, and electrochemistry has been identified as a potential sustainable method for accomplishing these transformations.

The efforts provide a starting point for the target-driven disassembly of lignin and the development of paired electrochemical reactions.

EXPERIMENTAL SECTION

General Experimental Methods. All glassware was flame dried prior to use, and all reactions were conducted under an argon atmosphere unless otherwise noted. Tetrahydrofuran was distilled from sodium benzophenone ketyl, and dichloromethane was distilled from calcium hydride. All other reagents and solvents were used as received from commercial sources unless otherwise noted. Chemical shifts are reported downfield from TMS. NMR yields were obtained using coumarin as an internal standard. High-resolution mass spectra (HRMS) were obtained using electrospray ionization (ESI) with Q-TOF detection. Infrared spectra were obtained using an FT-IR spectrophotometer.

Sample Sawdust Pretreatment Conditions. A paper thimble containing roughly 10 g of sawdust was loaded into a Soxhlet extractor containing benzene (200 mL) and ethanol (100 mL), and the system was refluxed overnight. The sawdust was transferred from the thimble to a Petri dish where it was allowed to dry completely before use.

Sample Solvolysis Conditions. A Parr Series 4600 pressure vessel was charged with 1 g of pretreated sawdust in 10 mL of MeOH. The reactor was heated with a small heating mantle to the desired temperature overnight. The temperature was measured using a thermocouple, and the pressure was measured from the pressure gauge. Once the reactor was cooled to room temperature, the sawdust was filtered and washed with MeOH. The resulting solvents were collected and removed in vacuo. The resulting crude oil was purified by silica gel chromatography (1:1 hexanes:ethyl acetate) to give clean products.

Synthetic Procedures. *3,4,5-Trimethoxybenzaldehyde (**7**).* To a solution of syringealdehyde (1.1399 g, 6.3 mmol) and KOH (0.70 g, 12.5 mmol) in DMSO (8 mL) and THF (4 mL) was added methyl iodide (0.78 mL, 12.5 mmol). The reaction was stirred overnight and then diluted and washed with water. The aqueous wash was extracted with ethyl acetate. The organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by silica gel column chromatography (1:1 hexanes:ether) to afford product (0.8345 g, 4.3 mmol) in 65% yield as a white solid. Spectral data matched that previously reported in the literature[24]

*2-(3,4,5-Trimethoxyphenyl)oxirane (**8**).* To a solid mixture of trimethylsulfonium iodide (4.0 g, 20 mmol) and NaH (60% in mineral oil, 0.80 g, 20 mmol) was added DMSO (6.5 mL) followed by THF (4.5 mL). The solution was stirred for 30 min at room temperature. 7 (2.08 g, 10.6 mmol) was then added in portions over 15 min. The reaction was

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stirred overnight and then quenched with water. The layers were separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were then washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by silica gel column chromatraphy (slurry packed using 1% triethylamine in 2:1 hexanes:ether) to give epoxide product (1.88 g, 8.9 mmol) in 84% yield as a white solid, mp 53−55 °C. ^{1}H NMR (300 MHz, $CDCl_3$): 6.52 (s, 2H), 3.86 (s, 6H), 3.84 (s, 3H), 3.82 (m, 1H), 3.12 (dd, J = 5.7, 3.9 Hz, 1H), 2.76 (dd, J = 5.7, 2.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 153.3, 137.5, 133.3, 102.0, 60.5, 55.8, 52.3, 51.0. IR (neat, KBr): 3051, 2941, 2831, 2629, 2250, 2005, 1592 cm^{-1}. HRMS (ESI/TOF-Q) m/z: $[M + H]^+$ calcd for $C_{11}H_{14}O_4H$ 211.0965; found 211.0966.

*(3,4,5-Trimethoxyphenyl)acetaldehyde (**9**).* To a solution of **8** (0.1874 g, 0.89 mmol) in CH_2Cl_2 (9 mL) was added $Sc(OTf)_3$ (40 mg). The reaction was stirred at room temperature for 1 h, after which water was added. The layers were separated and the aqueous layer extracted with dichloromethane. The combined organic layers were then washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified via silica gel chromatography (1:1 hexanes:ethyl acetate) to give aldehyde product (0.1533 g, 0.73 mmol) in 82% yield as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): 9.74 (t, J = 2.5 Hz, 1H), 6.42 (s, 2H), 3.86 (s, 6H), 3.85 (s, 3H), 3.62 (d, J = 2.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): 199.1, 153.5, 137.1, 127.3, 106.4, 60.7, 56.0, 50.7. IR (neat, KBr): 2940, 2839, 1722, 1590, 1508, 1460, 1423 cm^{-1}. HRMS (ESI/TOF-Q) m/z: $[M + H]^+$ calcd for $C_{11}H_{14}O_4H$ 211.0965; found 211.0969.

*3,4,5-Trimethoxybenzoic Acid (**11**).* To a solution of **7** (0.527 g, 2.69 mmol), 1:1 H_2O_2−urea complex (3.7 g, 39 mmol) in MeOH (14 mL) was added 6 M NaOH (1 mL). The solution was refluxed for 1 h, followed by addition of more H_2O_2−urea complex (0.80 g, 8.5 mmol). The reaction was refluxed for 1 h and then cooled to room temperature. The pH of the solution was adjusted to pH = 2 using 1 M HCl and then extracted with ethyl acetate. The organic layers were then washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified via silica gel chromatography (gradient 1:1 to 3:1 ethyl acetate:hexanes) to give acid product (0.4119 g, 1.9 mmol) in 72% yield as a white solid. Spectral data matched that previously reported in the literature.[25]

*tert-Butyl(3,4,5-trimethoxyphenyl)carbamate (**12**).* To a solution of **9** (0.1775 g, 0.84 mmol) in DMF (0.7 mL) was added diphenyl phosphoryl azide (0.26 mL, 1.2 mmol). The solution was cooled to 0 °C followed by addition of triethylamine (0.18 mL, 1.3 mmol). The reaction was then stirred at room temperature for 1 h. *tert*-Butyl alcohol (1.2 mL, 12.5 mmol) was then added, and the solution was heated to 90 °C for 5 h. The reaction was then cooled to room temperature. The *tert*-butyl alcohol was removed in vacuo, and the remaining residue was diluted with water and brine. The aqueous solution was extracted with CH_2Cl_2. The organic layers were dried over Na_2SO_4 and the solvent removed in vacuo (using high vacuum to remove residual DMF). The crude product was purified via silica gel chromatography (3:1 hexanes:ethyl acetate) to give amide product (0.1592 g, 0.56 mmol) in 67% yield as a white solid, mp 151−153 °C. ^{1}H NMR (300 MHz, $CDCl_3$): 6.73 (br s, 1H), 6.64 (s, 2H), 3.77 (s, 6H), 3.76 (m, 3H),1.48 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): 153.2, 152.8, 134.6, 133.4, 95.9, 60.8, 55.8, 28.2, 22.0. IR (neat, KBr): 3303, 2976, 2938, 1718, 1608, 1508 cm^{-1}. HRMS (ESI/TOF-Q) m/z: $[M + H]^+$ calcd for $C_{14}H_{21}NO_5H$ 284.1497; found 284.1497.

*Methyl(E)-3-(3,4,5-trimethoxyphenyl)acrylate (**S1**).* To solution of NaH (60% in mineral oil, 51 mmol) in THF (110 mL) was added methyl diethyl phosphonoacetate (10.5 mL, 57 mmol) dropwise at 0 °C. The mixture was stirred at 0 °C for 30 min, followed by dropwise addition of a solution of **7** (4.0 g, 20.3 mmol) in THF (15 mL). The reaction was stirred overnight at room temperature and then quenched with water. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were dried over Na_2SO_4. The solvent was removed in vacuo, and the crude product was purified via silica gel chromatography (1:1 hexanes:ether) to give the ester product (4.69 g, 18.6 mmol) in 92% yield as a white solid. Spectral data matched that previously reported in the literature.[26]

*(E)-3-(3,4,5-Trimethoxyphenyl)prop-2-en-1-ol (**21**).* To a solution of **18** (0.1000g, 0.45 mmol) in MeOH (1 mL) at 0 °C was added $NaBH_4$ (0.017 g, 0.45 mmol). The solution was stirred at room temperature for 30 min, followed by dilution with acetone, saturated aqueous NH_4Cl, and water. This was extracted with ethyl acetate, and the organic layers were washed with brine and dried over Na_2SO_4. Solvent was removed in vacuo to afford **19** (0.0847 g, 0.38 mmol) in 84% yield as a clear oil.

Alternatively (in order to quickly make bulk amounts of **21** from commercial starting materials), to a solution of **S1** (4.69 g, 18.6 mmol) in CH_2Cl_2 (120 mL) at 0 °C was added a solution of DIBAL-H (1 M in toluene, 47 mL, 47 mmol) dropwise. The reaction was allowed to warm to room temperature overnight. The reaction was then quenched with a saturated aqueous solution of Rochelle salt and stirred until both layers were mostly clear in appearance. The layers were separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed in vacuo, and the crude product was purified via silica gel chromatography (2:1 ether:hexanes) to give alcohol product (3.81 g, 17.0 mmol) in 91% yield as a clear oil. Spectral data matched that previously reported in the literature.[27]

*1,2,3-Trimethoxy-5-[(1E)-3-methoxyprop-1-en-1-yl]benzene (**4**).* To a solution of **19** (0.2214 g, 0.99 mmol) in THF (5 mL) was added NaH (60% in mineral oil, 80 mg, 2 mmol) slowly. The solution was stirred for 1 h at room temperature, after which methyl iodide (0.12 mL, 1.9 mmol) was added dropwise. The reaction was stirred overnight and then quenched with water. The layers were separated and the aqueous layer extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by silica gel chromatography (1:1 hexanes:ether) to give ether product (0.1863 g, 0.78 mmol) in 79% yield as a yellow oil. Spectral data matched that previously reported in the literature.[28]

*tert-Butyl (2-bromo-3,4,5-trimethoxyphenyl)carbamate (**13**).* To a solution of **12** (0.0453 g, 1.60 mmol) in CH_2Cl_2 (10.5 mL) was added NBS (0.29 g, 1.6 mmol) at −78 °C. The reaction was warmed to 0 °C, stirred for 1 h, then warmed to room temperature, and stirred 1 h. The crude mixture was concentrated onto silica gel in vacuo and purified by silica gel chromatography (eluting with 5:1 hexanes:ether) to give brominated product (0.5796 g, 1.36 mmol) as a colorless oil in 85% yield. ^{1}H NMR (300 MHz, $CDCl_3$): 7.72 (s, 1H), 7.71 (br s, 1H), 3.910 (s, 3H), 3.906 (s, 3H), 3.85 (s, 3 H), 1.55 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): 152.6, 151.9, 150.2, 137.9, 132.2, 99.2, 98.2, 80.2, 60.4, 60.3, 55.4, 27.7. IR (neat, KBr): 2975, 2934, 1730, 1581, 1514 cm^{-1}. HRMS (ESI/TOF-Q) m/z: $[M + Na]^+$ calcd for $C_{14}H_{20}BrNO_5Na$ 384.0417, found 384.0400.

*Ethyl 2-((6-((tert-Butoxycarbonyl)amino)-2,3,4-trimethoxyphenyl)amino)benzoate (**14**).* To a degassed solution of **13** (0.0919 g, 0.2537 mmol), K_3PO_4 (0.11 g, 0.52 mmol), and ethyl anthranilate (0.045 mL, 0.30 mmol) in toluene (1.3 mL) was added 5-[di(1-adamantyl)phosphino]-1′,3′,5′-triphenyl-1′*H*-[1,4′]bipyrazole (0.034 g, 0.051 mmol, 20 mol %) and Pd_2dba_3 (0.023 g, 0.025 mmol, 10 mol %). The reaction mixture was heated at 100 °C overnight, cooled to room temperature, and filtered through Celite with CH_2Cl_2. The filtered solution was concentrated in vacuo and then purified via silica gel chromatography (eluting with 5:1 hexanes:ether) to afford coupled product (0.0636 g, 0.147 mmol) in 58% yield as a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): 8.71 (s, 1H), 8.01 (d, J = 9.0 Hz, 1H), 7.68 (s, 1H), 7.26 (t, J = 9.0 Hz, 1H), 7.06 (s, 1 H), 6.75 (t, J = 9.0 Hz, 1H), 6.37 (d, J = 9.0 Hz, 1H), 4.40 (q, J = 9.0 Hz, 2H), 3.93 (s, 3H), 3.81 (s, 3H), 3.66 (s, 3H), 1.46 (s, 9H), 1.44 (t, J = 9.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 168.8, 153.1, 152.7, 151.3, 150.6, 137.8, 134.6, 133.6, 131.5, 117.5, 115.4, 114.3, 112.4, 97.8, 61.4, 60.9, 56.3, 18.5, 14.5. IR (neat, KBr): 3405, 3314, 2977, 2933, 1726, 1682, 1600, 1581, 1518 cm^{-1}. HRMS (ESI/TOF-Q) m/z: $[M + H]^+$ calcd for $C_{23}H_{30}N_2O_7H$ 447.2126, found 447.2110.

*6,7,8-Trimethoxy-5,10-dihydro-11H-dibenzo[b,e][1,4]diazepin-11-one (**15**).* To a solution of **14** (37 mg, 0.0856 mmol) in CH_2Cl_2 (1.0 mL) was added trifluoroacetic acid (0.05 mL, 0.65 mmol) dropwise. The solution was stored overnight, and the solvent was removed in vacuo. Toluene (6.0 mL) was then added and the solution refluxed for 2 days.

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The solvent was removed in vacuo and the crude material purified via silica gel chromatography (eluting with 3:1 ethyl acetate:hexanes) to give cyclized product (19.3 mg, 0.064 mmol) in 75% yield as a light purple oily solid. . ^{1}H NMR (300 MHz, $CDCl_3$): 8.33 (br s, 1H), 8.20 (dd, J = 7.8, 1.5 Hz, 1H), 7.63 (td, 7.8, 1.5 1H), 6.97 (t, J = 7.2 Hz, 1H), 6.79 (d, J = 8.1 Hz, 1 H), 6.30 (s, 1H), 5.97 (br s, 1H), 3.94 (s, 3H), 3.83 (s, 3H), 3.79 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 169.4, 150.4, 149.5, 144.0, 139.5, 133.1, 126.8, 123.1, 122.1, 119.5, 100.5, 61.8, 61.3, 56.5. IR (neat, KBr): 2934, 1658, 1604 cm^{-1}. HRMS (ESI/TOF-Q) m/z: [M + Na]$^+$ calcd for $C_{16}H_{16}N_2O_4Na$ 323.1002, found 323.0990.

*3,4,5-Trimethoxy Styrene (**17**).* A solution of Grubbs second-generation catalyst (23 mg, 8 mol %) in THF (3.3 mL) was purged with ethylene gas. The catalyst solution was then added to **16** under 1 atm of ethylene. The reaction was stirred at 55 °C overnight, cooled to room temperature, and diluted with ether. The solvent was then removed in vacuo and the crude residue purified by silica gel chromatography (5:1 hexanes:ether) to give styrene product (22.6 mg, 0.12 mmol) in 34% yield as a light brown oil (along with 50% recovered starting material). Spectral data matched that previously reported in the literature.[29]

*3,4,5-Trimethoxy-trans-cinnamaldehyde (**18**).* To a solution of **14** (71.6 mg, 0.30 mmol) in CH_2Cl_2 (6 mL) was added DDQ (70 mg, 0.30 mmol). The reaction was stirred overnight and then filtered through a pad of Celite. The crude product was purified by silica gel chromatography (2:1 hexanes:ethyl acetate) to give aldehyde product (50.8 mg, 0.23 mmol) in 76% yield as a yellow solid. Spectral data matched that previously reported in the literature.[30]

*3,4,5-Trimethoxy-trans-cinnamic acid (**19**).* To a solution of **18** (0.1076 g, 0,48 mmol) in DMSO (2.8 mL) at 0 °C was added a solution of NaH_2PO_4 (58 mg, 0.48 mmol) in water (1 mL) followed by dropwise addition of a solution of $NaOCl_2$ (0.127 g, 1.1 mmol) in water (1 mL). The reaction was stirred at room temperature for 23 h, followed by dilution with water. The solution was acidified to pH 1 with 1 M HCl and then extracted with ether. The organic washes were then concentrated in vacuo, and the crude product was purified via silica gel chromatography (4:1 ether:hexanes) to give acid product (0.0954 g, 0.40 mmol) in 83% yield as a white solid. Spectral data matched that previously reported in the literature.[31]

3-(3,4,5-Trimethoxyphenyl)propanoic Acid. To a solution of **19** (0.5202 g, 2.2 mmol) in MeOH (3 mL) and EtOAc (3 mL) was added Pd/C (10 wt %, 18 mg). The solution was put under hydrogen atmosphere and stirred overnight. The solution was then filtered through a pad of Celite with excess EtOAc, and the solvent was removed in vacuo to give pure product (0.5240 g, 2.2 mmol) in 100% yield as a white solid.

Alternatively, the hydrogen used can be generated electrochemically by the reduction of MeOH. A RVC anode and Pt cathode were inserted into a solution of 1:1 MeOH and THF (12.5 mL, 12.5 mL) and 0.1 M $LiClO_4$ (270 mg), and current was passed at 25 mA overnight. The H_2 was transferred continuously via a cannula to a flask containing a solution of **19** (0.0899 g, 0.38 mmol) and Pd/C (10 wt %, 40 mg) in MeOH (4 mL) and EtOAc (4 mL). The resulting solution was filtered through a pad of Celite with excess EtOAc, followed by a short silica column in EtOAc to give pure product (0.0872 g, 0.36 mmol) in 96% yield as a white solid. Spectral data matched that previously reported in the literature.[32]

*5,6,7-Trimethoxy-2,3-dihydro-1H-inden-1-one (**20**).* To P_2O_5 (50 mg, 0.18 mmol) was added methanesulfonic acid (0.33 mL, 5.0 mmol). The mixture was heated at 100 °C for 30 min, followed by addition of the saturated acid **19** (96.7 mg, 0.40 mmol). The solution was heated at 100 °C for 30 min, cooled to room temperature, and quenched with ice water. The aqueous solution was extracted with dichloromethane, washed with saturated aqueous $NaHCO_3$ and brine, and dried over Na_2SO_4. The solvent was removed in vacuo and the crude product purified by silica gel chromatography (2:1 hexanes:ethyl acetate) to give cyclized product (65.3 mg, 0.29 mmol) in 73% yield as off white crystals. Spectral data matched that previously reported in the literature.[32]

*(E)-1,2,3-Trimethoxy-5-(penta-1,4-dien-1-yl)benzene (**S2**).* To a solution of **21** (1.978 g, 8.81 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added Et_3N (1.84 mL, 13.2 mmol). Mesyl chloride (0.82 mL, 10.5 mmol) was added dropwise, and the solution was stirred and warmed slowly to room temperature over 3 h. The solution was then diluted with CH_2Cl_2, washed with 1 M HCl, and dried over $MgSO_4$. The solvent was removed in vacuo to give crude mesylate. To a solution of this mesylate in THF at 0 °C was added vinylmagnesium bromide (1.0 M in THF, 9.6 mL, 9.69 mmol). The solution was stirred overnight, diluted with CH_2Cl_2, washed with satd NH_4Cl (aq), and dried over $MgSO_4$. The solvent was removed in vacuo, and the crude product was purified by silica gel chromatography (1:1 hexanes:diethyl ether) to give pure product (1.0891 g, 4.64 mmol) in 53% yield as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): 6.58 (s, 2H), 6.34 (d, 15.8 Hz, 1H), 6.14 (dt, 15.8, 7.0 Hz, 1H), 5.90 (ddt, 16.9, 10.1, 6.4 Hz, 1H), 5.12 (d, 17.0 Hz, 1H), 5.07 (d, 10.0 Hz, 1H), 3.87 (s, 6H), 3.85 (s, 3H), 2.96 (t, 6.2 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): 153.2, 133.4, 130.7, 127.7, 115.6, 102.9, 60.8, 55.9, 36.9. IR (neat, KBr): 2997, 2938, 2837, 1582, 1507 cm^{-1}. HRMS (ESI/TOF-Q) m/z: [M + H]$^+$ calcd for $C_{14}H_{18}O_3H$ 235.1337; found 235.1329.

*(E)-5-(3,4,5-Trimethoxyphenyl)pent-4-en-1-ol (**22**).* To a solution of **S2** (0.2637 g, 1.12 mmol) in THF (10 mL) at −78 °C was added 9-BBN (0.5 M, 4.4 mL, 2.24 mmol). The solution was stirred and warmed slowly to room temperature. After 3 h, the solution was cooled to −78 °C, followed by addition of NaOH (3 M, 1 mL) and H_2O_2 (30% w/w, 1 mL). The solution was then allowed to warm to room temperature overnight. The solution was diluted with a sodium phosphate buffer (pH = 7), extracted with CH_2Cl_2, and dried over $MgSO_4$. The solvent was removed in vacuo, and the crude product was purified by silica gel chromatography (2:1 diethyl ether: hexanes) to give pure product (0.2108 g, 0.83 mmol) in 75% yield as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): 6.57 (s, 2H), 6.35 (d, 15.8 Hz, 1H), 6.15 (dt, 15.8, 7.0 Hz, 1H), 3.87 (s, 6H), 3.84 (s, 3H), 3.72 (t, 6.4 Hz, 2H), 2.31 (q, 7.0 Hz, 2H), 1.76 (quintet, 6.9 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): 153.3, 137.2, 133.5, 130.2, 129.7, 102.9, 62.3, 60.9, 56.1, 32.2, 29.3. IR (neat, KBr): 3400, 2995, 2935, 2839, 1582, 1507 cm^{-1}. HRMS (ESI/TOF-Q) m/z: [3M + Na]$^+$ calcd for $C_{42}H_{60}O_{12}Na$ 779.3997; found 779.3998

*2-(Methoxy(3,4,5-trimethoxyphenyl)methyl)tetrahydrofuran (**24**).* A 3-neck round-bottom flask was charged with **20** (180 mg, 0.71 mmol), 2,6-lutidine (0.41 mL, 3.55 mmol), and $LiClO_4$ (228 mg, 2.13 mmol) in anhydrous MeOH (12 mL). The flask was capped with a reticulated vitreous carbon anode and carbon cathode. After 2.2 F/mol was passed at a current of 8 mA, the solution was diluted with CH_2Cl_2, washed with 1 M HCl, and dried over $MgSO_4$. The solvent was removed in vacuo, and the crude product was purified by silica gel chromatography (1:1 hexanes:diethyl ether) to give a major diasteromer (94 mg, 0.33 mmol) in 47% yield and minor diastereomer (26 mg, 0.09 mmol) in 13% yield, both as colorless oils. ^{1}H NMR (300 MHz, $CDCl_3$) (major diasteromer): 6.55 (s, 2H), 4.00 (m, 1H), 3.92−3.81 (m, 3H), 3.87 (s, 6H), 3.86 (s, 3H), 3.28 (s, 3H), 1.85−1.75 (m, 2H), 1.66−1.48 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): 153.3, 137.7, 137.5, 134.8, 104.2, 86.9, 82.4, 60.9, 57.0, 56.2, 28.5, 25.7. IR (neat, KBr): 2936, 2873, 1591, 1505 cm^{-1}. HRMS (ESI/TOF-Q) m/z: [M + Na]$^+$ calcd for $C_{15}H_{22}O_5Na$ 305.1359; found 305.1368. ^{1}H NMR (300 MHz, $CDCl_3$) (minor diasteromer): 6.56 (s, 2H), 4.11−3.99 (m, 2H), 3.95−3.73 (m, 2H), 3.87 (s, 6H), 3.85 (s, 3H), 3.28 (s, 3H), 1.93−1.80 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): 153.3, 137.8, 137.4, 135.24, 110.17, 104.24, 86.0, 82.4, 68.8, 60.9, 57.3, 56.2, 27.4, 25.8. IR (neat, KBr): 2939, 2837, 1591, 1505 cm^{-1}. HRMS (ESI/TOF-Q) m/z: [M + Na]$^+$ calcd for $C_{15}H_{22}O_5Na$ 305.1359; found 305.1353.

*(E)-5-(Hexa-1,5-dien-1-yl)-1,2,3-trimethoxybenzene (**S3**).* To a solution of **21** (2.115 g, 9.43 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added Et_3N (2 mL, 14.1 mmol). Mesyl chloride (0.87 mL, 11.3 mmol) was added dropwise, and the solution was stirred and warmed slowly to room temperature over 3 h. The solution was then diluted with CH_2Cl_2, washed with 1 M HCl, and dried over $MgSO_4$. The solvent was removed in vacuo to give crude mesylate. To a solution of this mesylate in THF at 0 °C was added allylmagnesium bromide (1.0 M in THF, 10.4 mL, 10.4 mmol). The solution was stirred overnight, diluted with CH_2Cl_2, washed with satd NH_4Cl (aq), and dried over $MgSO_4$. The solvent was removed in vacuo, and the crude product was purified by silica gel chromatography (1:1 hexanes:diethyl ether) to give pure product (0.9672 g, 3.89 mmol) in 41% yield as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): 6.57 (s, 2H), 6.34 (d, 16.4 Hz, 1H), 6.15 (dt, 15.8, 7.0

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Hz, 1H), 5.87 (ddt, 16.9, 10.6, 6.2 Hz, 1H), 5.07 (d, 15.8 Hz, 1H), 5.00 (d, 10.0 Hz, 1H), 3.88 (s, 6H), 3.84 (s, 3H), 2.31 (q, 7.0 Hz, 2H), 2.24 (dt, 7.0, 6.4 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): 153.2, 138.0, 137.2, 133.5, 130.1, 129.6, 114.9, 102.9, 60.9, 56.0, 33.5, 32.3. IR (neat, KBr): 2937, 2873, 1591, 1505, 1460, 1419 cm^{-1}. HRMS (ESI/TOF-Q) m/z: $[M + Na]^+$ calcd for $C_{15}H_{20}O_3Na$ 271.1305; found 271.1305.

*(E)-6-(3,4,5-Trimethoxyphenyl)hex-5-en-1-ol (**S4**).* To a solution of **S3** (0.967 g, 3.89 mmol) in THF (10 mL) at −78 °C was added 9-BBN (0.5 M, 15.5 mL, 7.78 mmol). The solution was stirred and warmed slowly to room temperature. After 3 h, the solution was cooled to −78 °C, followed by addition of NaOH (3 M, 3.5 mL) and H_2O_2 (30% w/w, 3.5 mL). The solution was then allowed to warm to room temperature overnight. The solution was diluted with a sodium phosphate buffer (pH = 7), extracted with CH_2Cl_2, and dried over $MgSO_4$. The solvent was removed in vacuo, and the crude product was purified by silica gel chromatography (2:1 diethyl ether: hexanes) to give pure product (0.7984 g, 2.99 mmol) in 77% yield as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): 6.57 (s, 2H), 6.32 (d, 15.8 Hz, 1H), 6.14 (dt, 15.8, 7.0 Hz, 1H), 3.87 (s, 6H), 3.84 (s, 3H), 3.68 (t, 6.4 Hz, 2H), 2.25 (q, 6.6 Hz, 2H), 1.67−1.53 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): 152.8, 136.7, 133.3, 129.8, 129.5, 102.5, 61.9, 60.4, 55.5, 32.3, 31.8, 25.2. IR (neat, KBr): 3408, 2995, 2935, 2838, 1582, 1507, 1458 cm^{-1}. HRMS (ESI/TOF-Q) m/z: $[M + H]^+$ calcd for $C_{15}H_{22}O_4H267.1591$; found 267.1601.

*1,2,3-Trimethoxy-5-((1E)-7-methoxyhepta-1,6-dien-1-yl)benzene (**23**).* To a solution of **S4** (0.281 g, 1.05 mmol) in THF (10 mL) was added DMSO (0.94 mL, 12.6 mmol). The solution was cooled to −78 °C, followed by addition of $(COCl)_2$ (0.12 mL, 1.36 mmol). The solution was warmed gently to between −60 and −50 °C and stirred for 30 min, followed by addition of Et_3N (0.74 mL, 5.25 mmol). The solution was warmed slowly to room temperature, diluted with diethyl ether, and filtered. The solvent was removed in vacuo, leaving roughly 1 mL of crude aldehyde. To a solution of (methoxymethyl)-triphenylphosphonium chloride (0.719 g, 2.10 mmol) in THF at 0 °C was added *t*-BuLi (1.7 M in pentane, 1.23 mL, 2.10 mmol), and it was stirred for 30 min. To this solution was added the crude aldehyde dissolved in THF (5 mL), and the solution was stirred overnight. The solution was diluted with H_2O, extracted with CH_2Cl_2, and dried over $MgSO_4$. The solvent was removed in vacuo, and the product was isolated by silica gel chromatography (2:1 diethyl ether: hexanes) to give a 2:1 (trans:cis) mixture of isomers (0.2142 g, 0.73 mmol) in 70% yield as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): 6.57 (s, 2H), 6.31 (d, 15.2 Hz, 1.7H), 6.17 (q, 7.0 Hz, 0.7 H), 6.11 (q, 7.0 Hz, 0.3H), 5.90 (d, 6.4 Hz, 0.3H), 4.74 (dt, 12.9, 7.0 Hz, 0.7H), 4.36 (q, 7.0 Hz, 0.3H), 3.87 (s, 6.3H), 3.84 (s, 2.7H), 3.59 (s, 0.9H), 3.52 (s, 2.1H), 2.22 (q, 7.0 Hz, 2H), 2.13 (q, 7.0 Hz, 0.6H), 1.99 (q, 7.4 Hz, 1.4H), 1.53 (quintet, 7.6 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): 153.4, 153.2, 147.3, 146.3,137.6, 137.1, 133.7, 133.6, 130.5, 130.3, 129.9, 129.7, 106.7, 106.4, 102.8, 102.5, 102.1, 60.8, 59.4, 56.0, 55.8, 32.5, 32.2, 30.3, 29.5, 27.2, 23.4. IR (neat, KBr): 2995, 2935, 2837, 1655, 1582, 1507, 1463 cm^{-1}. HRMS (ESI/TOF-Q) m/z: $[M + Na]^+$ calcd for $C_{17}H_{24}O_4Na$ 315.1567; found 315.1575.

*2-(Methoxy(3,4,5-trimethoxyphenyl)methyl)cyclopentane-carbaldehyde (**25**).* A 3-neck round-bottom flask was charged with **21** (93 mg, 0.31 mmol), 2,6-lutidine (0.18 mL, 1.55 mmol), and $LiClO_4$ (99 mg, 0.93 mmol) in anhydrous MeOH (8 mL). The flask was capped with a reticulated vitreous carbon anode and a carbon cathode. After 2.3 F/mol was passed at a current of 8 mA, the solution was diluted with CH_2Cl_2, washed with 1 M HCl, and dried over $MgSO_4$. The product was isolated by silica gel chromatography (1:1 hexanes:diethyl ether) as a 2:2.5:1 mixture of 3 diastereomers (0.0595 g, 0.19 mmol) in 62% yield as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): 9.94 (d, 2.3 Hz, 0.34H), 9.64 (d, 2.9 Hz, 0.50H), 9.28 (d, 1.8 Hz, 0.16H), 6.51 (s, 2H), 3.95 (m, 0.16H), 3.88 (s, 3H), 3.87 (s, 3H), 3.86 (s, 3H), 3.82 (m, 0.84H), 3.23 (s, 0.48H), 3.18 (s, 1.50H), 3.08 (s, 1.02H), 2.74 (qd, 8.2, 2.9 Hz, 0.50H), 2.58 (m, 0.66H), 2.45 (quintet, 8.4 Hz, 0.50H), 2.1−1.2 (m, 6.34H). ^{13}C NMR (75 MHz, $CDCl_3$): 204.0, 203.8, 203.2, 153.34, 153.30, 137.43, 137.40, 136.7, 136.5, 136.2, 104.0, 103.83, 103.78, 88.1, 86.3, 84.6, 60.9, 57.1, 56.7, 56.3, 56.18, 56.17, 56.0, 54.1, 53.3, 51.2, 49.3, 48.7, 48.0, 29.7, 29.6, 29.3, 29.1, 27.0, 26.8, 25.8, 25.2, 25.0, 24.9, 24.2. IR (neat, KBr): 2939, 2872, 2825, 1719, 1592, 1505 cm^{-1}. HRMS (ESI/TOF-Q) m/z: $[M + Na]^+$ calcd for $C_{17}H_{24}O_5Na$ 331.1516; found 331.1526

*4-(1H-Benzo[d]imidazol-2-yl)-2,6-dimethoxyphenol (**6a**).* A 3-neck round-bottom flask was charged with *o*-phenylenediamine (34 mg, 0.31 mmol), **1** (63 mg, 0.34 mmol), ceric ammonium nitrate (33 mg, 0.06 mmol), and 0.1 M $LiClO_4$ (133 mg) in 5:1 THF:MeOH (12 mL). A RVC anode and carbon cathode were inserted into the flask, and 2.2 F/mol of charge was passed at 4 mA of current. The solution was diluted with H_2O, extracted with EtOAc, and washed with brine to give a 80% yield (by NMR). The product was isolated by silica gel chromatography (25:1 dichloromethane:methanol) as a light brown solid (53% isolated yield), mp 120−126 °C. ^{1}H NMR (300 MHz, CD_3OD): 7.57 (dd, 5.9, 2.9 Hz, 2H), 7.45 (s, 2H), 7.23 (dd, 5.9, 2.9 Hz, 2H), 3.97 (s, 6H). ^{13}C NMR (75 MHz, CD_3OD): 153.9, 149.7, 140.1, 139.1, 123.7, 121.3, 115.5, 105.3, 56.9. IR (neat, KBr): 3310, 2957, 2929, 1607, 1503 cm^{-1}. HRMS (ESI/TOF-Q) m/z: $[M + H]^+$ calcd for $C_{15}H_{14}N_2O_3H$ 271.1077; found 271.1084.

*4-(Benzo[d]thiazol-2-yl)-2,6-dimethoxyphenol (**6b**).* A 3-neck round-bottom flask was charged with 2-aminothiophenol (50 μL, 0.46 mmol), **1** (94 mg, 0.52 mmol), ceric ammonium nitrate (48 mg, 0.08 mmol), and 0.1 M $LiClO_4$ (125 mg) in 5:1 THF:MeOH (12 mL). A RVC anode and carbon cathode were inserted into the flask, and 2.2 F/mol of charge was passed at 4 mA of current. The solution was diluted with H_2O, extracted with EtOAc, and washed with brine to give a 83% yield (by NMR). The product was isolated by silica gel chromatography (ether) as a reddish brown solid (59% isolated yield), mp 115−119 °C. ^{1}H NMR (300 MHz, CD_3OD): 7.97 (dd, 8.5, 2.1 Hz, 2H), 7.51 (ddd, 8.2, 7.0, 1.2 Hz, 1H), 7.4 (ddd, 8.2, 7.2, 1.2 Hz, 1H), 7.38 (s, 2H), 3.97 (s, 6H). ^{13}C NMR (75 MHz, CD_3OD): 170.3, 154.7, 149.4, 140.1, 135.6, 135.0, 127.4, 126.0, 124.9, 123.0, 122.7, 105.7, 56.8. IR (neat, KBr): 3502, 3400, 3061, 3002, 2961, 2938, 2838, 1608, 1528 cm^{-1}. HRMS (ESI/TOF-Q) m/z: $[M + H]^+$ calcd for $C_{15}H_{13}NO_3SH$ 288.0689; found 288.0689.

Sample Paired Electrolysis Procedure. A 3-neck round-bottom flask was charged with 30 mmol of veratryl alcohol, 2,6-lutidine (5 equiv), and 0.1 M $LiClO_4$ in 1:1 THF:MeOH and fitted with a RVC anode and Pt cathode. A round-bottom flask was charged with 1 mmol of substrate and 10 mol % Pd/C in 1:1 MeOH:EtOAc. A cannula was inserted into the head space of the 3-neck round-bottom flask, and the other end was inserted into the round-bottom flask into the solution. After 2.2 F/mol was passed through the 3-neck round-bottom flask at 25 mA of current, the cannula was removed. The Pd/C solution was filtered through Celite and washed with EtOAc. The crude reduction product was purified through silica gel chromatography. The electrolysis solution was diluted with dichloromethane and washed with 1 M HCl. The organic layers were dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude oxidation product was then purified through silica gel chromatography.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01776.

Additional NMR spectra from the solvolysis reactions as well as NMR data for new compounds are provided (PDF)

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Notes

The authors declare no competing financial interest.

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