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Anodic Coupling of Guaiacol Derivatives on Boron-Doped Diamond Electrodes

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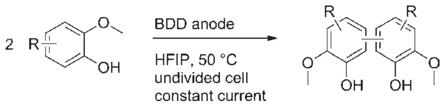
ABSTRACT



The anodic treatment of guaiacol derivatives on boron-doped diamond electrodes (BDD) provides a direct access to nonsymmetrical biphenols, which would require a multistep sequence by conventional methods. Despite the destructive nature of BDD anodes they can be exploited for chemical synthesis.

The cross-coupling reaction to nonsymmetrical biaryls represents a very versatile and synthetically useful transformation.[1] This method for C,C bond formation belongs to the standard repertoire in natural product synthesis,[2] molecular catalysis,[3] and material science.[4] In general, such conversions rely on traditional leaving groups, and toxic transition metal catalysts based, e.g., on palladium.[5−10] More recent approaches exploit that a catalytically active transition metal species allows C,H activation on one reaction partner and accomplishes the C,C bond formation by a common cross-coupling step.[11] Activation of the reaction partner can also be performed by an organocatalytic protocol.[12] A direct oxidative cross-coupling of arenes without the use of leaving functionalities is a cutting edge concept and is very attractive in terms of atom economy.[13] Electrochemical transformations exhibit an

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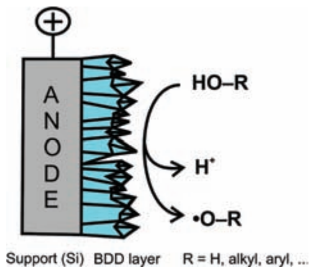

Figure 1. Mode of action for BDD anodes in aqueous or alcoholic media.

outstanding ecological and economical attractiveness since only electrons are employed as reagents. Consequently, reagent waste is avoided.[14] Oxidative synthesis of biphenols often results in the formation of the homocoupling product.[15] Recently, we found that the boron-doped diamond (BDD) as a very appealing innovative electrode material which can be used for the conversion of a broad scope of phenolic substrates to symmetrical biphenols.[16,17] The addition of fluorinated alcohols significantly reduces the oxidative degradation of the substrates and products. Furthermore, the additive allows the conversion of solid substrates[18] and suppresses the formation of complex molecular architectures.[19] The best results were obtained with 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) as an additive. This created the basis for the first anodic phenol-arene cross-coupling reaction and gave an indication for the electrochemical generation of nonsymmetrical biphenol coupling products.[20,21]

Here, we report the direct anodic dehydrodimerization to nonsymmetrical biphenols using BDD electrodes. The chemoselectivity of this unusual coupling reaction is based on the preferential formation of oxyl spin centers on BDD electrodes (Figure 1).[22]

Guaiacol derivatives occur abundantly in nature. Many plants, e.g. the guaiac tree, contain these phenolic compounds such as vanillin, syringic aldehyde, eugenol, or syringol (**6**) in significant amounts. The biopolymer lignin represents the largest renewable source for aromatic compounds and provides these guaiacol derivatives in huge quantities upon oxidative treatment.[23] They represent the future feedstock for a sustainable arene chemistry. Consequently, the chemistry of these phenols will be of particular interest for future applications.

Table 1. Electrochemical Oxidation of Guaiacol Derivatives on BDD[a]

entry	guaiacol derivative R =	yield (%) of biphenols 2	3
1[b]	CH_3 (**1a**)	33% (**2a**)	–
2	C_3H_7 (**1b**)	21% (**2b**)	–
3	$CH(CH_3)_2$ (**1c**)	5% (**2c**)	5% (**3c**)
4	$C(CH_3)_3$ (**1d**)	–	18% (**3d**)
5	Cl (**1e**)	4% (**2e**)	–
6	Br (**1f**)	8% (**2f**)	–

[a] Electrolysis conditions: constant current; undivided cell; BDD anode on silicon; nickel net cathode; j = 4.7 mA/cm^2; 1 F per mol phenol (1930 C); 0.02 mol of phenol; 30 mL of HFIP; 0.7 g of $[MeNEt_3]O_3SOCH_3$; 50 °C. [b] This entry is taken from ref 16.

A direct oxidation of guaiacol derivatives by transition metal ions with a high oxidation potential, such as Mn^{7+} or Fe^{3+}, leads to the formation of corresponding *ortho-ortho*-coupled biphenols. The naturally occurring dehydrodieugenol is available in this way.[24,25] By serendipity we found that 4-methylguaiacol (**1a**) gave the *ortho-meta* coupled **2a** upon anodic treatment on boron-doped diamond electrodes and 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) as solvent. This nonsymmetrical biphenol **2a** was formed exclusively (Table 1, entry 1). Since the remaining starting material was recovered by short-path distillation the subsequent workup was easy. Although the yield is moderate, fast access without requiring prior installation of leaving functionalities on the respective positions made this approach interesting.[20,26] Therefore, we studied the scope of the BDD/HFIP protocol in more detail. A variety of differently substituted guaiacol derivatives was subjected to this electrochemical oxidation.

Depending on the steric demand of the substituent in position 4 of phenol **1** either a symmetrical or nonsymmetrical biphenol was obtained (Scheme 1, Table 1). An elongation of an alkyl chain from 4-methyl to 4-propyl

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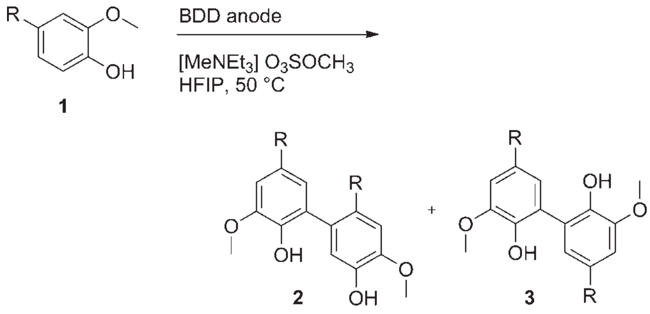
Scheme 1. Electrochemical Oxidation of 4-Substituted Guaiacol Derivatives on BDD in Hexafluoroisopropanol (HFIP)



guaiacol (**1b**) resulted in the corresponding nonsymmetrical biphenol **2b** as the sole product (entry 2).

Increasing steric demand at that position promotes the formation of the symmetrical product **3** since in **2** the aryl–aryl linkage is adjacent to this bulky substituent. An isopropyl moiety led to an equimolar mixture of the symmetrical **3c** and nonsymmetrical biphenol **2c**.

Because isopropyl groups on arenes are prone to oxidation, an anodic degradation of the biphenols resulted in low yields (entry 3). The enhanced bulkiness and stability of a *tert*-butyl moiety caused the regioselective formation of the symmetrical biphenol **3d** (entry 4). The less sensitive nature for overoxidation resulted also in a higher yield for **3d**. Additionally, guaiacol, eugenol, vanillin, and dihydroferulic acid were examined on BDD by this protocol, but no signficant amount of corresponding biphenols were detected.

The halogenated guaiacols are more difficult to be oxidized, and the corresponding nonsymmetrical biphenols **2e** and **2f** were obtained by the conversion of 4-chloroguaiacol (**1e**) and 4-bromoguaiacol (**1f**), respectively (entries 5 and 6). The steric demand of a chloro and bromo substituent in position 4 did not affect the regioselectivity. The formation of symmetrical or nonsymmetrical biphenols from guaiacols can be controlled by the steric influence of a substituent in position 4.

Suitable single crystals for X-ray analysis of **2e** and **2f** were obtained, and the structures could be elucidated (Figure 2).

In the course of our investigations 4-methoxyguaiacol (**4**) was oxidized on BDD in 1,1,1,3,3,3-hexafluoroisopropanol (Scheme 2). Surprisingly, the symmetrical dehydrodimer **5** was exclusively obtained and isolated in 45% yield. The electron rich nature of this substrate led to a *meta-meta* coupling product. Interestingly, **5** was not known before. The molecular structure was confirmed by consistent spectroscopic and spectrometric data as well as X-ray analysis of a suitable single crystal (Figure 2).

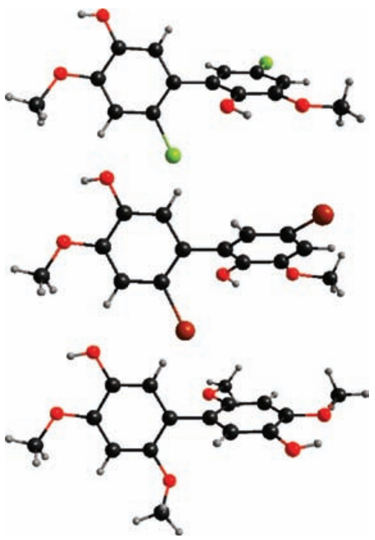
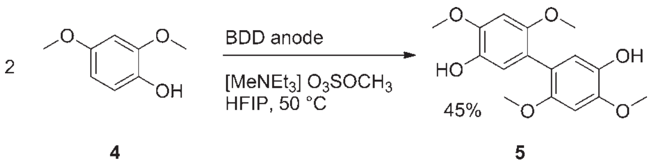


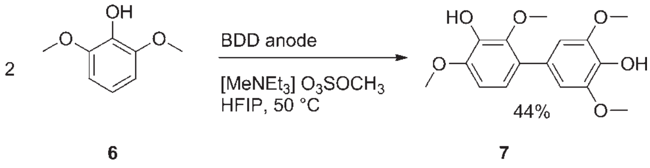
Figure 2. Molecular structures of **2e** (top) and **2f** (middle) and **5** (bottom) by X-ray analysis.

Scheme 2. Electrosynthesis of *meta-meta* Coupled Symmetrical Biphenol **5** Using BDD Anode



Switching the methoxy substituent from position 4 to 6 provides the naturally occurring syringol (**6**) as a substrate. Standard oxidation methods of 2,6-disubstituted phenols are well-known to form the *para-para* coupled dehydrodimers.[27,28] In contrast, the electrolysis on BDD of **6** revealed the exclusive formation of the nonsymmetrical *meta-para* coupled biphenol **7** in 44% isolated yield (Scheme 3). The product was completely characterized by spectrometric and spectroscopic means.

Scheme 3. Electrochemical Homo-Cross-Coupling Reaction of Syringol (**6**)



When 2,5-dimethoxyphenol (**8**) was electrolyzed by our protocol only the biphenol **9** was observed with an isolated yield of 83%. Interestingly, despite the potential stabilization by the methoxy substituents an

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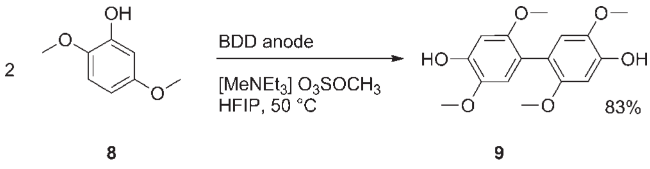
overoxidation to the quinoide structure was not detected (Scheme 4).

Scheme 4. Electrosynthesis of *para-para* Coupled Symmetrical Biphenol **9** on BDD

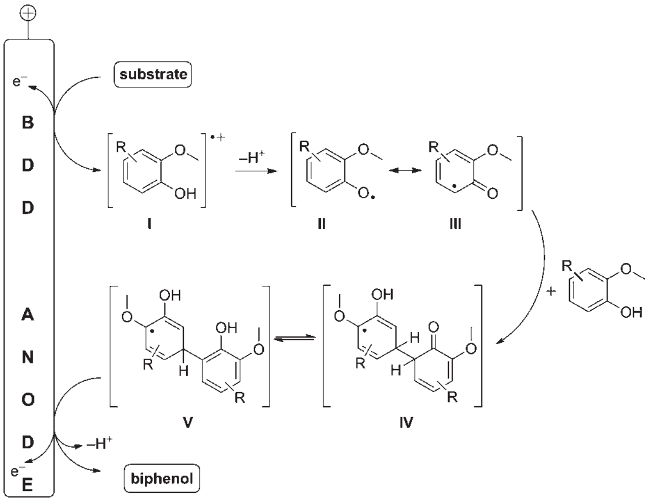


The formation of homo-cross-coupling products such as **7** indicates that it might not be generated by radical recombination. Otherwise, only symmetrical biphenols would be formed. A possible explanation is given by a mechanistic concept for phenol oxidation on a BDD anode (Scheme 5). This rationale commences with the anodic oxidation of the phenolic substrate. The radical cation **I** exhibits a dramatically enhanced acidity compared to the starting material. Consequently, an extrusion of a proton spontaneously occurs forming a phenoxyl radical with its mesomeric structures **II** and **III**, respectively. This part of the sequence can be considered as an anodic *Umpolung* reaction.[29] Subsequently, the electrophile **III** is trapped by another nucleophilic phenol, generating the tautomeric intermediates **IV** and **V**. A second oxidation step could follow directly or indirectly. A final rearomatization will result in the biphenol as a product of the electrolysis.

The results are in complete accordance with the rationale. When the steric demand in position 4 is low enough, the electrophile (**II**/**III**) will attack the guaiacol in position 5 forming a nonsymmetrical product. This is obviously the case for the generation of **2a**, **2b**, and **7**. If the steric demand in the vicinity increases, e.g. guaiacol **1d**, the C,C coupling occurs preferably in position *ortho* to the hydroxy group leading to a symmetrical product.

For the electrosynthesis of biphenol **5** this concept has to be slightly altered, because the positions for the spin center (species **II**/**III**) as well as the nucleophilic attack are dominated by the two methoxy groups, which are in a *meta* arrangement. With such electron rich substrates an alternative pathway via further oxidation of the spin centers **II** and **III** to corresponding cationic species cannot be excluded.

Scheme 5. Mechanistic Concept for the Oxidative Coupling Process of Guaiacol Derivatives on BDD



In conclusion, we established the selective anodic coupling of guaiacol derivatives on BDD electrodes. Despite the destructive nature of boron-doped anodes this new electrode material can be employed for electrosynthesis when 1,1,1,3,3,3-hexafluoroisopropanol is used as a solvent. The regioselectivity is strongly dependent on the steric demand close to the coupling position and additional electron releasing groups. In most cases a single product was observed and isolated. The isolated yields go up to 83%. Furthermore, the anodic coupling does not require prior installation of leaving functionalities and can therefore be performed with very simple substrates. Known tether strategies provide higher yields in the coupling step compared to our protocol but require in contrast high loadings of palladium catalyst, ligands, and significant quantities of base. In addition, those approaches rely on prior installation of the tether and subsequent removal.[30] Despite the quite moderate yields our approach provides a fast access to the reported molecules. The 2,3′,4,5′-tetramethoxy-3,4′-biphenol (**7**) represents directly the biaryl moiety of eupomatilone 2[31] and indicates the potential use of this method for natural products synthesis.

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Supporting Information Available. Experimental procedures and full spectroscopic data for all new compounds; complementary data to literature for substrates. This material is available free of charge via the Internet at http://pubs.acs.org.

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