

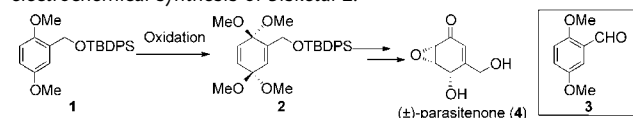
Anodic Oxidation on a Boron-Doped Diamond Electrode Mediated by Methoxy Radicals**

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The boron-doped diamond (BDD) electrode^[1a,b] is known to possess a wide range of applications for the direct generation of hydroxyl radicals and resulting inorganic peroxides such as persulfate,^[1c] perphosphate,^[1d] and hypochlorite.^[1e] In contrast to the extensive use of the BDD electrode in biological and inorganic chemistry, only a few examples exist in which electrochemically generated hydroxyl or alkoxy radicals have been employed to promote reactions of highly functionalized organic substances. The known applications include reactions of relatively simple substrates, such as acetal production by oxidative C–C bond cleavage,^[2] and BDD-mediated oxidative couplings to construct diaryl linkages.^[3] In general, alkoxy radicals,^[4] formed by anodic oxidation of the corresponding alcohols, function as mediators in reaction pathways that are different from those occurring under standard electrolysis conditions using carbon or platinum electrodes.

Dolson and Swenton have termed reactions that proceed by the generation of methoxy radicals, formed by anodic oxidation of MeOH followed by chemical reaction of the derived radical and ionic species, as EECrCp processes.^[5] In a previous effort focusing on the synthesis of (±)-parasitenone (**4**) (Table 1),^[6] we have used an oxidative quantitative dimethoxy-acetalization reaction (**1**→**2**), occurring in a basic MeOH solution at a Pt electrode,^[5] as the key step (entry 1). A similarly efficient reaction takes place when the BDD electrode is employed (entry 3), while the corresponding aldehyde **3**^[6] is produced from **1** in the oxidative reaction

Table 1: Synthesis of (±)-parasitenone (**4**) using anodic oxidation and electrochemical synthesis of bis-ketal **2**.



Entry	Anode/Oxidant	Potential (V vs. SCE)	Yield (Product) [%] ^[b]
1 ^[a]	Pt net	1.15	100 (2)
2 ^[a]	GC beaker	1.05	50 (3)
3 ^[a]	BDD plate	1.25	100 (2)
4	DDQ ^[c]	–	100 (3)
5	PhI(OAc) ₂ ^[d]	–	50 (3)
6	CAN ^[e]	–	70 (3)

[a] 40 mM solution of **1** in 5% KOH MeOH solution, Pt wire cathode. [b] Isolated yield. [c] 2,3-Dichloro-5,6-dicyano-*p*-benzoquinone, solvent: MeOH/CH₂Cl₂. [d] Solvent: MeOH. [e] Ammonium hexanitratocerate (IV), solvent: MeOH.

occurring on a glassy carbon (GC) electrode (entry 2). The process taking place in a basic MeOH solution (entry 1) might involve the intermediacy of methoxy radicals in the manner described by Swenton. Similarly, reaction at the BDD electrode (entry 3) is anticipated to produce the same radical species. These observations indicated that the acetalization reaction (**1**→**2**) at Pt or BDD electrodes proceeds through the EECrCp pathway in which the initially formed arene cation radical intermediate **A** is converted to a cation **B** that undergoes addition of methoxide, while the ECEC mechanism proceeds through radical **C** (Scheme 1). Also, the lack of production of methoxy radicals at the GC electrode enables the initially formed cation radical **A** to undergo proton loss (to **D**) in the route for formation of aldehyde **3**. Despite the plausibility of the mechanistic pathways suggested for the conversion of **1** to either **2** or **3**, no studies exist providing direct proof for the involvement of radical species in processes of this type. In the current study, we have carried out ESR experiments to determine if radical intermediates are generated in electrochemical oxidation reactions of methanol using BDD, Pt, and GC electrodes. In addition, we have probed electrochemical oxidation reactions of isoeugenol (**5**)^[5] as part of the biomimetic preparation of the neolignan, licarin A (**6**).

To gain information about whether or not radical species are involved in electrochemical oxidation reactions conducted in MeOH, we have carried out an ESR study using the radical trapping agent 5,5-dimethyl-1-pyrroline-*N*-oxide (DMPO) (Scheme 2). Anodic oxidations of methanolic solutions of DMPO were performed employing constant

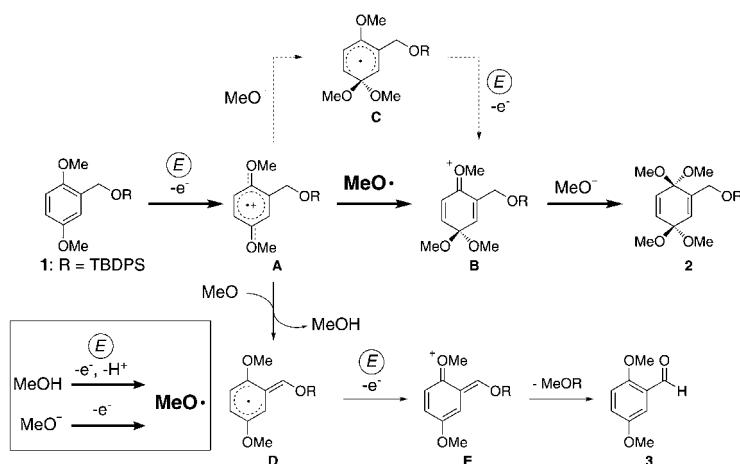
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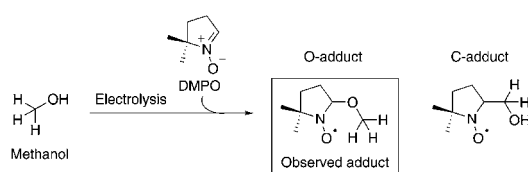
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Scheme 1.
Anodic oxidation pathway for construction of bisdimethyl acetal (**2**).



Scheme 2. Trap reaction of the methoxy radical by DMPO.

potential electrolysis (CPE) conditions (1.06 V vs. the saturated calomel electrode, SCE, 0.1 M LiClO₄ as supporting salt) with BDD, Pt, and GC electrodes as anodes, and Pt wire as the cathode. ESR of the product mixtures led to signals, displayed in Figure 1, which occur at the magnetic field value anticipated for nitroxyl radicals generated by reaction of DMPO with methoxy and not hydroxymethyl radicals.^[7] The intensities of the ESR signal for the formed radical varied with the

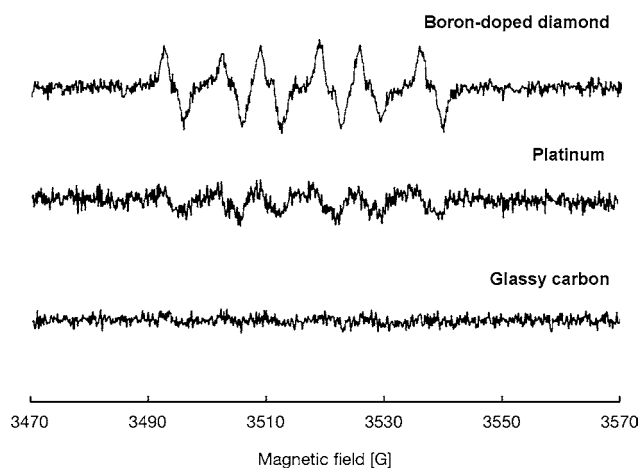
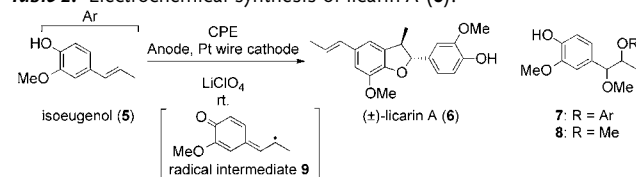


Figure 1. ESR spectra obtained for the methoxy radical on several electrode materials. Standard condition: 10 mM solution of 5,5'-dimethyl-1-pyrroline *N*-oxide (DMPO) in 0.1 M LiClO₄/MeOH, Pt-wire cathode (Applied potential: 1.06 V vs. SCE), *A_N* (hyperfine coupling constant of N) value: 13.37 G (cf. 13.58 G), *A_H* (hyperfine coupling constant of H) value: 7.98 G (cf. 7.61 G).

anode used in the order BDD > Pt > GC. Thus, the ESR spectroscopic data suggested that methoxy radicals are generated in electrochemical oxidation reactions of MeOH and that they are produced with greater efficiency when the BDD anode is used.

We have probed an application of anodic oxidation using the BDD electrode in the context of the preparation of the benzofuran-type neolignan,^[8] (±)-licarin A (**6**). In nature, neolignans are known to be biosynthesized by enzymatic oxidation of corresponding phenol precursors.^[9] Several biomimetic syntheses of **6**, starting with isoeugenol (**5**) and employing a variety of oxidants, have been described previously.^[10] Included in these approaches was one that employed an electrochemical protocol,^[11] in which electrolysis using a Pt electrode was reported to provide **6** in 29%. In contrast to that occurring at a Pt anode, anodic oxidation of **5** in MeOH solution employing the BDD electrode was anticipated to involve or be accompanied by the formation of methoxy radicals. To probe the consequences of this factor, we have investigated product distributions of reactions of **5** promoted using BDD, Pt, and GC anodes. The reactions were conducted under CPE conditions and the used potentials were larger than the oxidation potential of **5** (from linear sweep voltammetry, LSV, measurements). The results of these experiments, displayed in Table 2, showed that licarin A (**6**) is produced in 10–25% yield (entries 1–4), along with substantial amounts of recov-

Table 2: Electrochemical synthesis of licarin A (**6**).



Entry	Anode	Solvent	Potential [V vs. SCE]	Yields [%] ^[b]		
				6	7	8
1	Pt plate	MeOH	0.80 ^[c]	20	9	–
2			0.90 ^[d]	25	19	–
3 ^[e]	GC plate	MeOH	0.69 ^[c]	17	16	–
4			0.92 ^[d]	10	17	–
5	BDD on Si plate	MeOH	0.74 ^[c]	21	6	–
6			1.06 ^[d]	40	18	16
7 ^[f]		MeCN	1.27 ^[d]	–	–	–
8 ^[f]		MeNO ₂	1.19 ^[d]	–	–	–

[a] 10 mM solution of **5** in 0.1 M LiClO₄ solution, Pt wire cathode, 1.0 F mol^{−1}. [b] Isolated yield. [c] The first oxidation potential. [d] The second oxidation potential. [e] 0.5 F mol^{−1}. [f] 0.1 F mol^{−1}.

ered **5**, when Pt and GC electrodes were used. The highest yield (40%) of **6** is obtained (entry 6) when the oxidation is performed using the BDD anode. In this case, the vicinal substituted products^[12] **7** and **8**^[13] were also produced, likely through a pathway involving 1) the formation of radical intermediate **9** through sequential electron transfer and deprotonation, 2) self-coupling of **9** to form **7** and coupling

of **9** with a methoxy radical to form **8**, and 3) MeOH addition.^[14] Additional observations made in this effort suggested that methoxy radicals participated in the mechanism for the formation of **6**. For example, **6** is not formed in electrochemical oxidation reactions occurring in non-alcoholic solvents like MeCN and MeNO₂ (entries 7–8). In addition, when alcohols other than MeOH were employed as solvents for this process, **6–8** were generated in decreased yields. Finally, in contrast to phenol oxidation reactions in hexafluoroisopropyl alcohol, which have been reported to take place in higher yields,^[2b–d] the reaction of **5** promoted by a BDD electrode in trifluoroethanol (TFE) is not efficient.

In the next stage of this study, we explored electrochemical oxidation reactions of **5** using the BDD electrode in a flow cell system (Figure 2).^[15] We anticipated that the use of this type of system would lead to improved current efficiencies and avoidance of secondary oxidation reactions of the

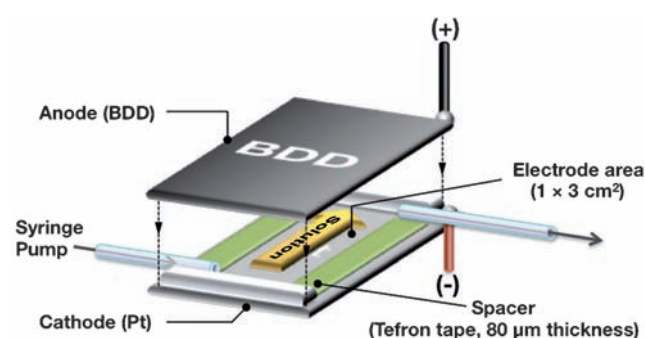


Figure 2. The flow cell system by means of BDD electrode.

formed products. Although when conducted using the batch electrochemical system, **6** is produced in higher yields when the BDD electrode is employed as the anode in contrast to the Pt and GC electrodes. However, long reaction times (13 h for a 1 mmol scale) were required to generate 1 Fmol⁻¹ of electricity. As a result, the prolonged exposure of the products to the oxidation conditions causes over-oxidation leading to formation of undesired polymerization and/or decomposition products. Use of a flow cell system would circumvent this problem. Moreover, it was expected to generate high concentrations of methoxy radicals at the anode, which would facilitate highly efficient one-electron oxidation processes.

To determine if these expectations were correct and to explore more generally the scope and limitations of electrochemical oxidation reactions mediated by the BDD electrode, methanolic solutions of **5** were submitted to electrochemical oxidation reactions in the flow cell system. Studies, in which the current density and flow rate were varied, established optimized conditions (current density 1.0 mA cm⁻², flow rate 0.05 mL min⁻¹, entry 6) for the conversion of **5** to **8** as the major product. Interestingly, product distributions from reactions in the flow system are different from those obtained using the batch system discussed above (see Table 2). This observation suggests that the radical intermediate **9**, produced from **5** by sequential one-electron oxidation and

deprotonation reacts rapidly with methoxy radicals formed in high concentration at the surface of the electrode in the pathway for generation of **8** (Table 3). Because the diffusion layer of the flow-type cell system is thinner than in the batch-type cell system,^[15] it might be associated with a high probability of the reaction between radical **9** and methoxy radicals.

Table 3. Electrochemical flow reaction of **5** by means of the BDD electrode.^[a]

Entry	<i>j</i> [mA cm ⁻²]	Flow rate [mL min ⁻¹]	Yields [%] ^[b]			
			6	7	8	sm
1	0.5	0.1	7	8	30	43
2	1.0		7	9	68	7
3	1.5		8	9	67	9
4	2.0		8	9	66	10
5	1.0	0.025	3	3	60	1
6		0.05	4	3	90	1
7		0.15	7	9	40	42
8 ^[c]	1.0	–	12	12	24	32

[a] 10 mM solution of **5** in 0.1 M LiClO₄ MeOH solution, BDD anode, Pt-plate cathode, 1.0 Fmol⁻¹. [b] Isolated yield. [c] Batch-type cell (potential: > 5.55 vs. Pt wire).

We have demonstrated that methoxy radicals were generated by electrochemical oxidation of MeOH using a BDD anode. In addition, the results showed that the electrooxidative reaction of isoeugenol (**5**) using the BDD electrode produced (±)-licarin A (**6**) in higher yields than related processes employing Pt and GC electrodes. Finally, electrooxidation of **5** in a BDD-electrode-based flow system formed the coupling product **8** highly efficiently, and the coupling reaction was facilitated by high concentrations of methoxy radicals formed at the anode. Further studies on the applicability of electrochemical oxidation reactions taking place at the BDD electrode and in particular those reactions that lead to the formation of biologically important low-molecular-weight substances are in progress.

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