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Unexpected Highly Chemoselective Anodic *ortho*-Coupling Reaction of 2,4-Dimethylphenol on Boron-Doped Diamond Electrodes

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Anodic conversion of 2,4-dimethylphenol on boron-doped diamond (BDD) electrodes under solvent-free conditions results in an unusual highly selective formation of the desired 2,2′-biphenol, representing the best electrochemical synthesis for this particular compound.

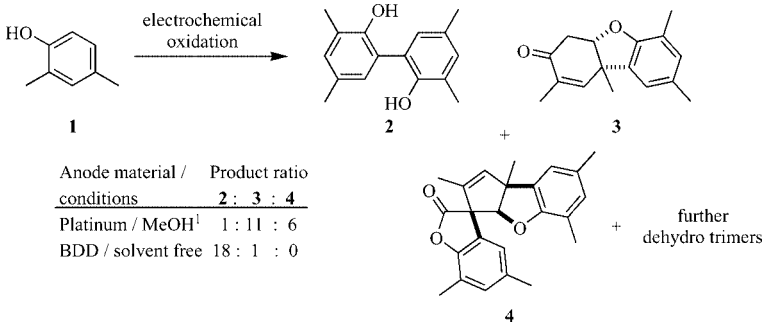
Introduction

The selective oxidative coupling reaction of simple methyl-substituted phenols like 2,4-dimethylphenol (**1**) is challenging because several by-products are formed. Besides the desired biphenol **2**, Pummerer's ketone **3** represents usually the major product. Additionally, dehydrotrimers with unique pentacyclic scaffolds (e.g. **4**) are produced in significant amounts (Scheme 1).[1]

To overcome this lack of selectivity, we developed recently a template-directed electrochemical synthesis: The phenols are converted to tetraphenoxy borate species,[2] which represent superb substrates for the anodic transformation.[3] Although this process can be performed on a large scale and exhibits excellent selectivity for **2**, it requires a multi-step sequence, including the isolation of the templated substrate and hydrolytic work-up after electrochemical conversion.[4]

Results and Discussion

In order to simplify the process, the direct electrochemical conversion of **1** was tested on a variety of different electrode materials. Initial experiments with boron-doped diamond (BDD) electrodes revealed promising results for the aspired *ortho*-coupling reaction. Surprisingly, the anodic conversion of **1** gave the biphenol **2** in almost exclusive selectivity of 18:1 for **2**/**3**. (Scheme 1). Noteworthy, except for traces of ketone **3**, no other by-product was observed when performing the electrolysis on BDD electrodes. These results were fully unexpected because BDD electrodes are



Anode material / conditions	Product ratio 2 : 3 : 4
Platinum / MeOH[1]	1 : 11 : 6
BDD / solvent free	18 : 1 : 0

Scheme 1. Product diversity (major components) from the electrochemical oxidation of **1**.

commonly used for total oxidation and mineralization of organic pollution in waste water.[5] BDD electrodes exhibit completely different characteristics compared to other carbon electrodes. The main features are unusual chemical and electrochemical stability, a high overpotential for oxygen

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evolution, and the capability of efficient anodic formation of very reactive hydroxyl radicals.[6] Recently, these properties led to the electrosynthesis of trimethyl orthoformate.[6] Furthermore, these particular electrodes were applied in the oxidation of propargylic alcohols and aromatic side chains.[7]

Therefore, the anodic conversion of **1** on BDD electrodes was systematically studied. Electrolysis cells for conversions on BDD in aqueous media were developed by CSEM and described as *Modular Electrochemical Cell*s for continuous-flow applications.[8] These are specific in size and restricted to relatively large electrodes. In order to work on a smaller scale and to apply various reaction conditions for preparative purposes, a novel cell geometry was developed. The boron-containing polycrystalline diamond layer (1–10 μm) was employed on a silicon or niobium support as commercially available.[9] Despite the superior chemical stability of the diamond layer, BDD electrodes create two challenges. The brittle nature of crystalline silicon limits the mechanical stability of the support, causing occasionally loss of the BDD electrode by friction. Furthermore, any contact with the electrolyte has to be strictly eliminated, because silicon or niobium suffer from corrosion. To allow only contact by the resistant BDD surface an arrangement with flange fittings was constructed (Figure 1).

Employment of glass flange connections offers the use of every planar type of BDD electrode, which is easily contacted by a metal foil on the back. Particular attention was given to the sealing between BDD electrode and the flange of glass. Several materials have been tested.[10] Best results were obtained by a sealing made of ethylene-propylene-diene rubber (EPDM). This rubber is a highly resistant terpolymer. The sealings were stamped out of a 2-mm EPDM sheet. Thermal stability was found up to 120 °C. Hot organic and aggressive media as well as highly anodic potentials seem not to affect the sealing over a long process time. The depicted cell geometry offers the possibility to heat the electrolyte. Usually, a sand bath or silicon oil was applied. The cooling jacket in the upper part kept the more volatile components in the electrolysis vessel.

Initially, alcohols as common solvents for organic transformations on BDD electrodes were applied in the oxidative coupling reaction of phenol **1** (Table 1).

For sufficient conductivity of the electrolyte a protic solvent and a supporting electrolyte were required (Table 1). All electrochemical conversions gave the desired compound **2** only in modest yield. Except for **3**, no other low-molecular-weight by-products could be isolated indicating that oligomeric species were predominantly formed.[11] These findings were additionally supported by notable low current

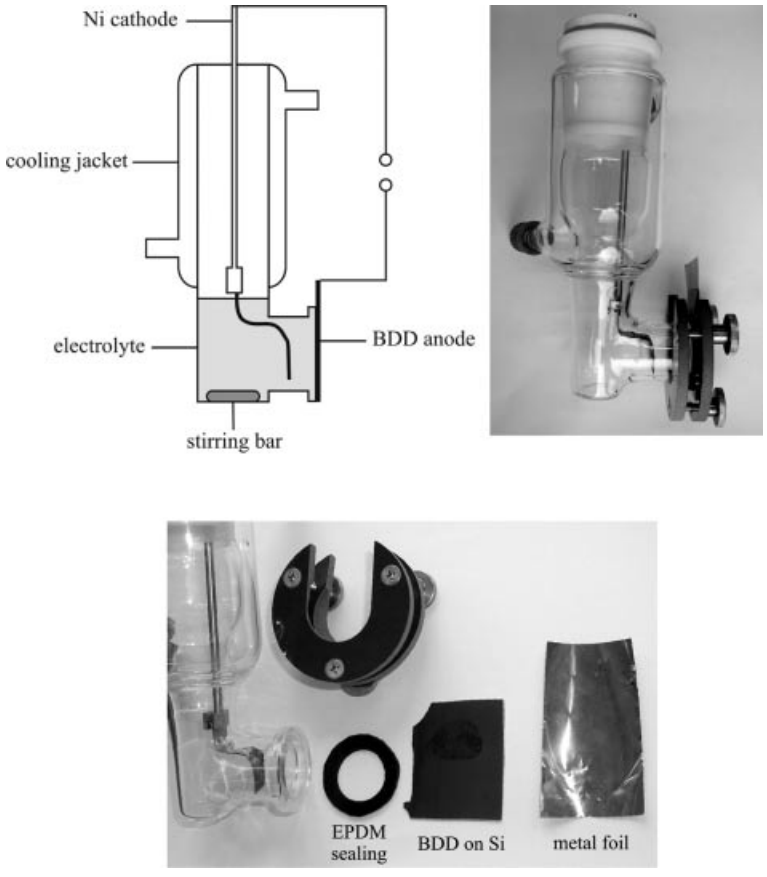


Figure 1. Flange electrolysis cell design for BDD electrodes (top) and assembly (bottom).

Table 1. Anodic treatment of **1** in organic solvents.[a]

Entry	Electrolyte	**2** [%][b]	*CE*[c] [%]	**2/3**
1	0.1 M Bu_4NBF_4 in MeOH	17	7	10:1
2	0.1 M NaOH in MeOH	15	6	3:2
3	0.1 M H_2SO_4 in MeOH	15	10	4:1
4	0.1 M Bu_4NBF_4 in CH_3CN/*t*BuOH	16	4	20:1
5	0.1 M Bu_4NBF_4 in CH_2Cl_2/MeOH	11	3	4:3
6	$FeSO_4$, Bu_4NHSO_4, H_2O/*t*BuOMe	3	n.d.	n.d.

[a] Reaction conditions: 1.5 g **1**, 35 mL electrolyte, BDD anode (layer thickness: 1 μm), j = 20 mA/cm^2, nickel cathode, room temp. [b] Determined from the crude product by GC using an internal standard. [c] Current efficacy.

efficacies. The surface of the electrode stood intact when performing the transformation in acidic or neutral media, whereas basic electrolyte caused significant corrosion. Within this study a variety of solvent mixtures and an iron-based mediator were tested, but with less success (Table 1).

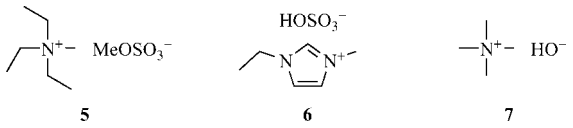
Significant amelioration was achieved when **1** was used neat at higher reaction temperature. The yield as well as the selectivity of the transformation could be considerably improved (Table 2). A good conductivity was obtained by addition of 11% of water and 6% ammonium salt (Figure 2). For a sustainable process development, reduction in the amount of solvent is important and applying a green additive like water will be beneficial. Despite of the large excess of phenol a mediating role of water by preliminary formed hydroxyl radicals can not be excluded. Moreover, a mediated mechanism is confirmed by a slightly lower oxidation potential for water of 1.23 V vs. SCE compared to phenols with 1.3–1.65 V vs. SCE.[12] The oxidation of **1** by intermediate hydroxyl radicals is supposed to proceed immediately, because no peroxides were detected in the electrolyte.

Table 2. Anodic coupling reaction of **1** on BDD electrodes.[a]

Entry	Ammonium salt	BDD support, thickness	**2** [%][b]	*CE*[c] [%]	**2/3**
1	**5**	Si, 1 μm	56	29	17:1
2	**6**	Si, 1 μm	46	42	16:1
3	**7**	Si, 1 μm	39	30	17:1
4	**5**	Nb, 10 μm	49	43	18:1
5	**5**	Si, 10 μm	47	32	19:1

[a] Reaction conditions: 30 g **1**, 4 mL water, 2.2 g ammonium salt, BDD anode, j = 10 mA/cm^2, nickel cathode, Q = 0.4 F per mol **1**, 70 °C. [b] From the crude product after distillative removal of excess **1**, determined by GC using internal standard. [c] Current efficacy.

The electrolysis was only performed to a conversion of about 0.4 F per mol **1** in order to depress the formation of by-products. For work-up excess of **1** was easily removed by a short-path distillation. The residue was then fractioned with water and *tert*-butyl methyl ether in order to remove the supporting electrolyte. Upon concentration of the organic layer and slow addition of heptane the desired biphenol **2** was afforded as pure crystalline material. This is the most efficient electrochemical access to this particular compound. Variation of the ammonium salt resulted in the same selectivity but differed significantly in the current efficacy (Table 2, Entries 1, 2, and 3). On the 1 μm diamond-coated silicon BDD, neutral electrolysis conditions employing **5** gave the best yields in the desired biphenol **2** (Entry 1). However, the acidic ionic liquid **6** turned out to be superior concerning the current efficacy of the phenolic oxidation (Entry 2).The basic ammonia salt **7** lead to moderate yields and inferior current efficacies (Entry 3). When 10 μm-diamond-coated supports were employed for electrolysis, the tetraalkylammonium methyl sulfate (**5**) gave better results (Entry 4). Surprisingly, the nature of the support seems to play a crucial role for the current efficacy (Entries 4 and 5). Because the very same chemoselectivity for the transformation was observed, the loss of efficacy is not based on the oxidative coupling step.



5 **6** **7**

Figure 2. Ammonium salts as supporting electrolytes in the oxidation of **1**.

However, the BDD electrodes exhibit an aging process. In general, prolonged lifetime of the electrodes is achieved by continuous reversion of polarity. Still, the polarity was not reversed with regard to the oxidation of the nickel electrode. After multiple runs the selectivity and the appearance looked the very same, whereas the current efficacy dropped from 43% to about 20–25% (e.g. for Entry 4). To enhance the purity of **2** and to avoid the formation of overoxidation products, a series of electrolyses were performed to a certain conversion (Figure 3).

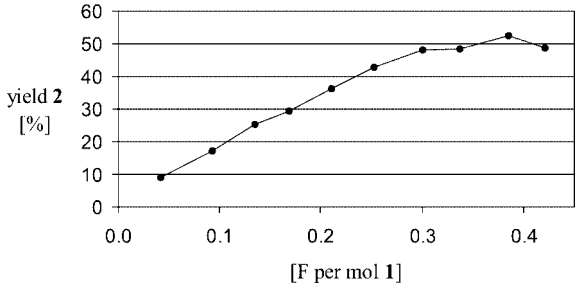


Figure 3. Progress of the oxidation of **1** on BDD electrode.

During the electrolysis the amount of **2** increases in a linear fashion up to 0.3 F per mol **1**. Then side reactions appear limiting the amount of isolated **2**. Thus, a partial conversion of about 30% gives the best results. Because excess of **1** is easily recovered virtually no loss of material occurs, creating a good basis for a continuous preparation of **2**.[13] The elaborated protocol for the oxidative coupling process was applied to a series of low-melting phenols.[14] Either no conversion was observed or the substrate was completely destructed. Even in mixtures of several phenolic substrates the sole product that was detected was **2**. The

reason for this exclusive substrate selectivity and the particular nature of 2,4-dimethylphenol (**1**) are unclear but currently under investigation.

Conclusions

BDD electrodes are novel and appealing materials of organic electrochemistry, which give access to unusual selective reactions. Under controlled conversion almost no overoxidation or mineralization is observed. The anodic coupling reaction of **1** on BDD provides **2** in an excellent selectivity and represents the most efficient electrochemical synthesis of this technically relevant biphenol. The electrolysis is performed under solvent-free conditions; additional water is required to enhance the conductivity. Partial conversion provides the biphenol **2** in good quality. 2,4-Dimethylphenol (**1**) is exclusively transformed by this protocol. Furthermore, an easy to handle electrolysis cell for BDD electrodes in electroorganic synthesis was developed.

Experimental Section

General Remarks: All reagents were used in analytical grades. Solvents were desiccated if necessary by standard methods. Melting points were determined with a Melting Point Apparatus SMP3 (Stuart Scientific, Watford Herts, UK) and were uncorrected. Microanalysis was performed with a Vario EL III (Elementar-Analysensysteme, Hanau, Germany). NMR spectra were recorded with a Bruker ARX 300, (Analytische Messtechnik, Karlsruhe, Germany) by calibration on $CHCl_3$ with δ = 7.26 ppm for ^{1}H NMR; chemical shifts were expressed in ppm. Gas chromatography was performed with a Shimadzu GC-2010 (Shimadzu, Japan) using a HP 5 column (Agilent Technologies, USA; length: 30 m, inner diameter: 0.25 mm, film: 0.25 μm, carrier gas: hydrogen). GC calibration was accomplished with analytically pure 3,3′,5,5′-tetramethyl-2,2′-biphenol (**2**) and (*E*)-stilbene as internal standard.

Anodic Oxidation of 2,4-Dimethylphenol: 2,4-Dimethylphenol (**1**) (35.2 g, 0.29 mol), water (4.8 mL) and $(Et)_3MeNSO_4Me$ (**5**) (2.4 g) were mixed in a nondivided electrolysis cell equipped with a BDD anode and a nickel cathode. At 70 °C, a galvanostatic electrolysis with a current density of 10 mA/cm^2 was performed. After 11760 C (ca. 0.4 F per mol **1**) the electrolysis was stopped and excess of **1** was recovered by a short-path distillation. The remaining crude product was dissolved in water (50 mL) and *tert*-butyl methyl ether (30 mL). The layers were separated and the aqueous layer was extracted with *tert*-butyl methyl ether (2 × 30 mL). The combined organic layers were washed with brine (80 mL), dried ($MgSO_4$), and concentrated in vacuo yielding a brown oil (12.9 g). Upon slow addition of heptane (20 mL) the desired product crystallized and could be isolated by filtration and subsequent washings with heptane (2 × 10 mL). The mother liquor was concentrated in vacuo and a second crop was isolated as described above. Compound **2** was obtained as colorless solid (6.3 g, 26 mmol, 49% referring to the organic fraction). M.p. 135 °C (cyclohexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.27 (s, 12 H, CH_3), 5.04 (s, 2 H, OH), 6.85 (s, 2 H, 4-H), 6.98 (s, 2 H, 6-H) ppm. $C_{16}H_{18}O_2$ (242.13): calcd. C 79.31, H 7.49; found C 79.21, H 7.35.

Acknowledgments

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[9] 1 μm BDD on Si: Adamant Technologies, La-Chaux-de-Fonds, Switzerland; 10 μm BDD on Si or Nb: CONDIAS GmbH, Itzehoe, Germany.
[10] Diverse silicon materials and PTFE have been applied. Either the electrochemical stability was not sufficient or leaching was observed after prolonged electrolysis.
[11] Oligomeric and polymeric species were isolated as deep brown colored material but not further characterized.
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[14] The following substrates were tested under the described conditions: *ortho*-cresol, *para*-cresol, sesamole, 4-*tert*-butylphenol, 4-allyl-2-methoxyphenol, 2-methoxy-4-methylphenol.

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