Anodic Phenol–Arene Cross-Coupling Reaction on Boron-Doped Diamond Electrodes**

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The cross-coupling reaction to give nonsymmetric biaryls is a very versatile and synthetically useful transformation.^[1] This particular C-C bond formation has found application in natural product synthesis^[2] and molecular catalysis,^[3] as well as material sciences.^[4] In most examples leaving groups on both reaction partners are required. Furthermore, toxic transition-metal catalysts based, for example, on palladium are necessary for the arylation reaction.^[5] The most prominent methods utilize arylboronic acids,^[6] arylstannanes,^[7] benzoic acid derivatives,^[8] arylzinc,^[9] or arylmagnesium^[10] reagents, thereby creating waste by the employed leaving groups. In a modern approach, the catalytically active transition-metal species effects C-H activation at one reaction partner and accomplishes the C-C bond formation by a common cross-coupling step. This particular version of biaryl formation requires only one leaving group and has recently found significant attention.^[11] The direct oxidative crosscoupling of arenes is a cutting-edge concept which sacrifices only hydrogen atom substituents and is consequently very attractive in terms of atom economy. This approach requires a specific reactivity of one reaction partner towards the employed oxidant which induces the reaction sequence. The oxidized intermediate then attacks the other partner and the transformation can be accomplished. This concept was demonstrated by Kita and co-workers using stoichiometric amounts of phenyliodine(III) bis(trifluoroacetate).^[12]

Electrochemical approaches for redox transformations are highly attractive in ecological and economical terms since solely electrons are used and virtually no reagent waste is produced.^[13] Anodic treatment of arenes results usually in the formation of the homo-coupling product because the oxidation potential is the key property.^[14] In a few examples the reactive radical cation can be trapped by an abundant reaction partner which is not affected by the electrode in the applied potential range.^[15] Boron-doped diamond (BDD)

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is a very appealing innovative electrode material which opens up novel synthetic pathways since alkoxyl or hydroxyl radicals are formed directly with high efficiency.^[16] The high reactivity and oxidative power of such oxyl intermediates lead to chemical incineration of substrates. Therefore, BDD electrodes are mostly used for disinfection purposes or wastewater treatment.^[17] In particular, at high current densities the mineralization presents a challenge in forming a specific product without degradation. To exploit the advantages of BDD electrodes and circumvent the mineralization, the electrolysis can be conducted in almost neat substrates like 2,4-dimethylphenol.^[18] Since this particular methodology is limited to a few substrates, we recently developed a protocol that employs highly fluorinated alcohols as additives in the electrolyte, allowing conversion of a broad scope of phenolic substrates into symmetric biphenols.^[19] Best results were obtained with 1,1,1,3,3,3-hexafluoroisopropyl alcohol (HFIP) as additive.

Herein we report the first anodic and selective phenolarene cross-coupling reaction employing boron-doped diamond (BDD) electrodes. The chemoselectivity of the crosscoupling reaction is induced by preferential formation of oxyl spin centers on the BDD electrodes.

The screening of a variety of different electron-rich phenols for the anodic conversion on the BDD electrodes led to an unusual result for 4-methylguaiacol (1). A selective and symmetric coupling *ortho* to the phenolic hydroxy group was anticipated; however, the reactions exclusively provided the *ortho/meta* coupled product **2** (Scheme 1). The previously



Scheme 1. Anodic coupling of 4-methylguaiacol (1).

elaborated electrolysis conditions with HFIP with respect to temperature, applied current, and concentrations were used.^[20] The yield of **2** is strongly dependent on the current density. In the range of 2.8–4.7 mA cm⁻² **2** is directly obtainable in about 30 % yield (Table 1, entries 1 and 2).

Much lower current densities result in decreased yields. The anticipated reaction sequence requires a second electrochemical oxidation step which apparently does not occur rapidly enough to form the stable product. Increased current density rendered **2** in a significant lower yield as well (Table 1,



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Entry	<i>j</i> [mA cm ⁻²]	Yield [%]	Current efficiency [%]
1	2.8	27	27
2	4.7	33	33
3	9.5	14	14

[a] Current: 1.0 Fmol^{-1} (based on 1).

entry 3). Since the current efficiency (CE) equals the chemical yield, mineralization and over-oxidation of **2** are plausible side reactions (see the Supporting Information). Despite the anodic treatment of electron-rich arenes the electrolyte is colorless. If slightly colored substrates are subjected to this electrolysis a decolorizing effect is observed which reveals the bleaching and mineralizing nature of oxyl radicals. The architecture of previously unknown **2** is confirmed by a complete set of spectroscopic and spectrometric data as well as by X-ray analysis of a suitable single crystal (Figure 1). In the solid state the biaryl is tilted by $64.41(8)^{\circ}$.^[21] A hydrogen-bonding network between different molecules of **2** accounts for the dominating interactions for the dense packing allowing a mutual distance between the similarly arranged arene moieties of about 3.4 Å.



Figure 1. Molecular structure of 2 by X-ray analysis.

A rationale for the formation of 2 includes the generation of phenoxyl radicals on the BDD electrode. The applied conditions result in a concentration of oxyl spin centers far too low for recombination to 2,2'-biphenol derivatives. Anodic treatment might cause an umpolung effect because the electron-rich phenol is oxidized.^[15,22] Despite the liberation of a proton after the oxidation step the phenoxyl species still represents an electrophile.^[23] Consequently, 1 experiences an electrophilic attack on the most electron-rich position which results in the connectivity of 2 (Scheme 1). This reaction pathway points the strategy for a novel anodic cross-coupling reaction exploiting oxyl spin-center formation and then electrophilic arylation, and subsequent anodic termination. The specific role of HFIP is not yet clear, but without it the conversion does not proceed.^[19] The previously anticipated role as mediator^[19] can definitely be excluded since the electrochemical window on BDD is larger than the individual oxidation potentials of the substrates (see the Supporting Information). However, the non-nucleophilic and protic nature of HFIP enhances the stability of radical intermediates by several magnitudes.[24]

After oxidation the acidity of the phenol radical cation is increased by several magnitudes and in contrast to the studies of Eberson,^[24] deprotonation occurs immediately. These



Scheme 2. Concept of the anodic phenol-arene cross-coupling reaction and the potential mechanism. HOR^{F} = fluorinated alcohol.

unique properties of HFIP allow realization of this novel concept with a postulated mechanistic picture (Scheme 2). Although the mean free path length of the phenoxyl species **I** is increased, it is still a highly reactive intermediate. Consequently, an excess of arene **B** for an efficient quenching step is beneficial.^[25] The intermediate **II** will be formed and is in a tautomeric equilibrium with **III**. Final oxidation on the anode furnishes product **AB**. In general, for the last step two pathways are possible. Either a phenoxyl moiety is specifically generated on the BDD electrode, or a cation, which immediately undergoes extrusion of a proton.

A variety of different electron-rich arenes (component **B**) were used for the cross-coupling with the 4-methylguaiacol system A. Remarkably, under these conditions no dehydro dimer 2 was detected. First, 4-methylguaiacol was electrolyzed in the presence of 1,2,4-trimethoxybenzene (Table 2, entry 1), and due to the electron-rich nature of 3, this arene undergoes oxidative homo-coupling. If the amount of electric current is doubled, the yield, as well as the selectivity for the cross-coupling product 11, is increased. The architecture of 11 was also unequivocally determined by X-ray analysis of a suitable single crystal (see the Supporting Information). Most probably the homo-coupling product is anodically degraded to some extent. Dramatic amelioration with respect to selectivity and yield is found by lowering the current density to 2.8 mA cm^{-2} . Enhancement of applied current at these conditions leads to inferior results (Table 2, entry 1 d). These findings are supported by cyclovoltammetric studies at BDD

Table 2: Converted substrates under electrolysis conditions.^[a]

En	try	Arene B	j [mAcm ⁻²]	Current [Fmol ⁻¹] ^[28]	Coupling product AB	AB/BB (GC)	Yield of AB [%]	Current efficiency [%]
1	a b c d		4.7 4.7 2.8 2.8	1.0 2.0 2.0 3.0		1:1 1.5:1 5:1 1.5:1	17 39 47 34	34 39 47 22
2	a b		4.7 4.7	1.0 2.0		11:1 7:1	12 16	23 16
3	a b c	5 Br	4.7 4.7 2.8	1.0 2.0 2.0	ОН 13 Br	> 50:1 15:1 > 50:1	18 14 8	37 15 8
4	a b		4.7 4.7	1.0 2.0		> 50:1 13:1	11 18	23 15
5	a b		4.7 2.8	2.0 2.0	0 0H 15 0-	9:1 23:1	30 25	30 25
6	a b		4.7 4.7	1.0 2.0		> 50:1 > 50:1	10 18	19 15
7		e e	4.7	2.0	0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	12:1	33	33
8		10	4.7	1.0	0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	2.5:1	11	22

[a] BDD anode, nickel cathode, 30 mL HFIP, 50 °C, A/B 1:10.

electrodes with the employed electrolyte, wherein 1 and 2 show similar oxidation potentials. Furthermore, product 11 is more easily oxidized than the corresponding starting materials, which limits the chemical yield as a result of overoxidation (see the Supporting Information). Employing 1,3,5trimethoxybenzene (4) affords the mixed biaryl in good selectivity, wherein alteration of current density has only little influence on the formation of 12 (Table 2, entry 2). The crosscoupling reaction is compatible with bromo substituents. The biaryl 13 is almost exclusively observed when 4-bromo-1,3dimethoxybenzene (5) is anodically treated on BDD electrodes (Table 2, entry 3).

Electrochemical conversion of 3,4,5-trimethoxytoluene (6) results in the exclusive formation of the mixed biaryl 14 (Table 2, entry 4). O-methylated sesamol 7 turns out to be a

useful coupling partner, providing 15 in very good selectivity (Table 2, entry 5). If the less electron-rich arene component 5-methylbenzo-[1,3]dioxole (8) is subjected to the protocol, only the mixed biaryl is detected (Table 2, entry 6). The anodic cross-coupling is also applicable to methoxylated naphthalenes; 2-methoxynaphthalene (9) is arylated in the 1-position to give biaryl 17 in good yield and acceptable selectivity (Table 2, entry 7). Increased electron density on the arene component yields inferior results as well as lower selectivity in the formation of 18 (Table 2, entry 8).

All cross-coupling products 11-18 are novel compounds and accessible in a single step. In the workup procedure HFIP is almost completely recovered as it represents the most volatile component in the reaction mixture. Subsequently, the nonconverted starting materials can be recovered by short-path distillation in about 80% efficiency. Detailed studies of the conversion including mass balance reveal that only a small part of the reaction mixture undergoes electrochemical incineration and the cross-coupling products seem to undergo over-oxidation to give oligomeric and polymeric by-products (see the Supporting Information).

Compared to a Suzuki coupling sequence starting from arenes without the leaving functionalities, our approach is competitive in respect to the overall yield (see the Supporting Information). In

addition, the presented approach is faster and definitely more sustainable. The unique character of BDD is obvious when platinum or other carbon electrodes like graphite or glassy carbon are used instead (see the Supporting Information). In control experiments using carbon electrodes only the homo-dehydro dimers were found since the component with the lowest oxidation potential converts first.^[26] The transformation can successfully be extended to other 2,4-substituted electron-rich phenols, for example, 2,4-dimethylphenol.^[27]

In conclusion, we have discovered the first anodic phenolarene cross-coupling, which is performed on BDD electrodes. Our results demonstrate that such electrodes can be used for more than just destructive purposes. BDD electrodes represent a novel and innovative material to generate oxyl spin

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centers for selective transformations. In several examples novel mixed biaryls are formed in high selectivity allowing user-friendly purification. Although the yields are low, this particular direct method is easy and quick to perform, and the recycling of HFIP as well as the starting materials is easily achieved in high efficiency. The mineralization of substrates and products could be diminished by the addition of fluorinated alcohols. Since only hydrogen atoms are lost during the course of transformation, this electrochemical concept is a sustainable approach to biaryls. Taming of the intermediate oxyl spin centers through the development of suitable additives/mediators is the key to make this methodology attractive to several other anodic cross-coupling reactions.

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- [27] Analogous electrolysis of 2,4-dimethylphenol and 1,2,4-trimethoxybenzene yields 15% of cross-coupling product (see the Supporting Information).
- [28] Amount of current is given per equivalent of the minor component **1**.