



Electrochemical C–H Amination

Electrochemical Amination of Less-Activated Alkylated Arenes Using Boron-Doped Diamond Anodes

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Abstract: The anodic C–H amination of aromatic compounds is a powerful and versatile method for the synthesis of aniline derivatives. By using boron-doped diamond (BDD) anodes, a method initially described by Yoshida et al. for electron-rich arenes was expanded to less-activated aromatic systems e.g.,

Introduction

Primary aromatic amines are important precursors for the synthesis of pharmaceuticals,^[1] dyes,^[2] polymers or materials,^[3] and natural products.^[4] A typical protocol for the amination of aromatic compounds is nitration followed by reduction. However, regioselectivity as well as functional group tolerance is usually low.^[5] State-of-the-art methods for the regioselective, catalytic construction of aryl C–N bonds are transition-metal or copper catalyzed (Buchwald–Hartwig, Chan–Lam) aminations of aryl halides or organometallics.^[6] Modern versions of such conversions use ammonia as a nitrogen source.^[7] However, these methods require significant loading of toxic and expensive transition-metal catalysts as well as the prior installation of leaving groups e.g., halogens or metals. Recently, approaches for the direct transformation of aromatic carbon–hydrogen into carbon–nitrogen bonds were established.^[8]

Alternatively, photochemical aminations of arenes based on photoredox catalysis were developed.^[9] Unfortunately, this approach involves the initial conversion of electricity to light and requires the use of a photo-sensitizer. Therefore, a direct application of electric current would be highly desirable.

Electroorganic synthesis has recently experienced significant attention and a renaissance of electrosynthesis was observed.^[10] Electroorganic transformations can avoid reagent waste because only electrons are shifted for oxidizing or reducing substrates. Nowadays, the increase of renewable energy re-

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201600048. simple alkylated benzene derivatives. Anodes based on sp³ carbon seem to be the key for the electrochemical amination reaction. The corresponding primary anilines are obtained in good yields. Despite the cationic intermediates of the electrolytic reaction *tert*-butyl moieties are tolerated.

sources can lead to surplus electricity since generation and demand do not match. The use in discontinuously operated electrochemical processes offers direct valorization and makes this methodology even more attractive. Therefore, electrosynthetic conversions can be considered as "green chemistry".^[11]

Recently, Yoshida and co-workers reported a powerful method for the electrochemical amination of electron-rich arenes.^[12] The key step in this approach is the nucleophilic trapping of the arene radical cation by pyridine resulting in the formation of positively charged Zincke intermediates **2**.^[13] Those intermediates **2** are protected from further anodic degradation because of the strong electron-withdrawing effect of the positive charge. After the electrolysis, the amine moiety is released by ring opening of the pyridinium moiety by piperidine. A broad variety of arenes has been aminated in good to excellent yields of up to 99 % by using carbon felt as the anode material (Scheme 1). However, the approach is limited to activated, quite electron-rich substrates e.g., methoxy-substituted arenes.



Scheme 1. Electrochemical amination reaction of activated arenes.^[12]

The introduction of the amino moiety occurs *ortho* or *para* to the methoxy group at the most electron-rich position. If the formation of regioisomers is possible they will be formed. Similarly, *N*-mesyl-protected imidazole fragments can be installed at aromatic cores, which provides an elegant access to *N*-arylimid-azoles. If benzylic positions are present the use of *N*-mesyl imid-azole as the nucleophile leads exclusively to their functionalization.^[14] Here, we report the electrochemical amination of less-activated, alkylated arenes.

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Results and Discussion

Initially we envisioned the amination of the benzylic position of alkyl arenes, e.g. m-xylene by the Yoshida protocol. The initial challenge was to find suitable electrolysis conditions for such less-activated substrates. Specific attention was given to the electrode material, since in previous studies this turned out to be the key to success.^[15] Initially, using a carbon felt anode we obtained only moderate results and interestingly, no functionalization of the benzylic positions of *m*-xylene (4) was observed under the applied electrolysis conditions. The only product obtained was 2,4-dimethylaniline (5). However, the results by using carbon felt were moderate and prompted us to further study the direct anodic core amination of *m*-xylene. For this specific amination at the aromatic core different electrode materials, e.g. carbon felt, carbon fleece, platinum, glassy carbon, were investigated (Scheme 2). For carbon fleece and carbon felt anodes, where the surface area could not be exactly defined, the current was varied from 6-36 mA (geometric size carbon felt: $5.0 \times 1.0 \times 0.5$ cm; carbon fleece: 5.0×1.0 cm). For planar platinum and glassy carbon anodes, the current density was altered in the range 2-12 mA/cm². Screening experiments were conducted in divided teflon cells with a porous glass-frit as separator (for the detailed experimental setup see Supporting Information). This simple but efficient screening method which operates at ambient conditions has the advantage that many different electrolysis parameters, e.g. the current density, can be varied in a highly efficient way.[15b,16]



Scheme 2. Electrochemical amination of *m*-xylene, employed as test substrate for screening of electrolytic conditions.

One advantage of carbon felt and carbon fleece is the high surface area. However, reactive intermediates, e.g. radical cations, need to diffuse from the electrode surface into the bulk solution for subsequent chemical reactions. Especially for carbon felt as the anode, mass transport from the electrode into the bulk is more difficult because reactive intermediates might get absorbed by the highly porous material. With carbon fleece as the anode material, only trace amounts of the desired 2,4-dimethylaniline (**5**) were obtained. In contrast, carbon felt showed a better performance with a maximum yield of up to 38 % at a current of 30 mA (Figure 1).

In addition to carbon felt and carbon fleece, glassy carbon and platinum with a planar geometry were used as anodes in this transformation. However, the desired aniline **5** was obtained in less than 10 % yield (GC, internal standard) with these materials. Mostly, only trace amounts were found (Figure 2). Furthermore, fouling of the anode was observed for both platinum and glassy carbon (see Supporting Information). Isostatic graphite as the anode gave higher yields of up to 14 % at a current density of 12 mA/cm² (Figure 2). However, for isostatic graphite strong corrosion of the anode was observed. Since the





Figure 1. Electrochemical amination of *m*-xylene; screening of carbon felt $5.0 \times 1.0 \times 0.5$ cm (red dots) and carbon fleece 5.0×1.0 cm (black squares) at different currents. [a] GC, internal standard: *n*-octylbenzene.

anode materials investigated, either showed low performance or exhibited insufficient electrolytic stability, we decided to employ boron-doped diamond (BDD). This novel and innovative electrode material has recently attracted a lot of attention in C-C cross-coupling reactions.^[15b,17] The material, based on sp³ carbon usually shows a higher performance at more positive potentials than other sp²-carbon-based electrodes.^[15c,18]



Figure 2. Electrochemical amination of *m*-xylene; screening of BDD (green triangles), platinum (blue triangles), glassy carbon (red dots), isostatic graphite (black squares) at different current densities. [a] GC, internal standard: *n*-octylbenzene.

Indeed, the best results were obtained at commercially available boron-doped diamond anodes. At all current densities applied, BDD showed a significantly better performance than platinum, glassy carbon, carbon felt, carbon fleece, or isostatic graphite. The highest isolated yield at BDD anodes was 60 % at a current density of 8 mA/cm² (Figure 2). Furthermore, we investigated the effect of different concentrations (0.1 M–0.6 M) of tetrabutylammonium tetrafluoroborate as the supporting electrolyte. A high concentration of anions in the electrolyte might help to stabilize anodically formed, highly reactive radical cationic species. With a yield of 60 %, the best results were obtained with 0.2 M and 0.3 M electrolyte solutions. Consequently, a 0.2 M tetrabutylammonium tetrafluoroborate solution



was used as the electrolyte for the following studies (see Supporting Information).

The applied charge was varied in a range of 2 F to 3.2 F. As optimized electrolysis conditions a charge of 2.5 F was determined (see Supporting Information).

To gain an insight into the different performances of the above-investigated electrode materials in the anodic amination of less-activated aromatic compounds, CV studies were conducted. However, at isostatic graphite no CV data could be obtained due to corrosion of the working electrode. Furthermore, no CV measurements were possible with carbon fleece and carbon felt as working electrodes due to the difficulty of contacting those materials. Thus, only for platinum, BDD, and glassy carbon, CV data which provided a rationale for the different behavior of the anode could be obtained. Using a platinum working electrode, *m*-xylene (1 mM) exhibits an oxidation peak at +1.80 V vs. Fc/Fc⁺ (Figure 3). Upon addition of 12.4 mM pyridine (same excess as in screening experiments), the oxidation peak of *m*-xylene was no longer observed. Only the oxidation peak of pyridine (+2.32 V vs. Fc/Fc⁺) was found (Figure 3).



Figure 3. Cyclic voltammograms of 1.0 mm *m*-xylene (red line) and 1.0 mm *m*-xylene + 12.4 mm pyridine (blue line); working electrode: platinum; electrolyte: 0.1 m Bu_4NBF_4/CH_3CN ; scan rate: 100 mV/s.

Using glassy carbon as the working electrode, an oxidation peak of 1.71 V vs. Fc/Fc⁺ is observed (Figure 4). The oxidation of *m*-xylene takes place at a potential 90 mV less positive than those at platinum and BDD. Upon addition of pyridine the oxidation peak of *m*-xylene is no longer detectable and only the oxidation peak of pyridine is visible. The oxidation of pyridine at a glassy carbon working electrode takes place at 2.72 V vs. Fc/Fc⁺ (Figure 4). These data and the formation of a thick black film at both platinum and glassy carbon anodes are in accordance with the fact that 2,4-dimethylaniline (**5**) is only obtained in trace amounts.

Boron-doped diamond as the working electrode gives rise to an oxidation peak of *m*-xylene at 1.80 V vs. Fc/Fc⁺ (Figure 5). This oxidation peak is still visible upon addition of pyridine, which is in line with the results mentioned. Interestingly, at BDD the oxidation of pyridine can be observed at a more positive potential (2.64 V vs. Fc/Fc⁺) than at platinum ($\Delta E = 320$ mV). This can be attributed to an over-potential for the oxidation of pyridine at BDD. So far we cannot explain why the oxidation





Figure 4. Cyclic voltammograms of 1.0 mm *m*-xylene (red line) and 1.0 mm *m*-xylene + 12.4 mm pyridine (blue line); working electrode: glassy carbon; electrolyte: 0.1 m Bu_4NBF_4/CH_3CN ; scan rate: 100 mV/s.

peak of *m*-xylene disappears upon addition of pyridine in the case of platinum and glassy carbon as the working electrode. However, the CV data match the results obtained in the screening experiments and provide a highly consistent picture.



Figure 5. Cyclic voltammograms of 1.0 mM *m*-xylene (red line) and 1.0 mM *m*-xylene + 12.4 mM pyridine (blue line); working electrode: BDD; electrolyte: $0.1 \text{ M Bu}_4\text{NBF}_4/\text{CH}_3\text{CN}$; scan rate: 100 mV/s.

The optimized electrolysis conditions were applied to a broad range of alkylated arenes. The 1,3-alkyl substitution pattern leads to the corresponding aniline derivatives in good yields up to 60 %. Isopropyl substituents on the substrate 6 do not interfere with the amination process and the corresponding aniline 7 is obtained in 50 % isolated yield (Table 1, entry 2). Substrates with non-branched alkyl substituents can also be successfully treated. Tetrahydronaphthalene 12 is preferentially aminated at the less-hindered position (Table 1, entry 5). Interestingly, despite the cationic nature of the intermediates even tert-butyl groups are compatible with this particular method. However, functionalization ortho to a tert-butyl moiety is sterically hindered leading to slightly lower yields (Table 1, entries 6 and 7). Most remarkably, the amino moiety is installed adjacent to a tert-butyl group in a significant amount forming 16 (Table 1, entry 6). Steric demand from both adjacent positions are even more pronounced in the amination of mesitylene,





wherein the corresponding aniline **21** is obtained in only 24 % (Table 1, entry 8).

Table 1. Substrate scope of the anodic amination of alkylated arenes using boron-doped diamond as electrode material.



[a] Isolated yield. All reactions were carried out using a boron-doped diamond anode, 0.2 \rm_M Bu_4NBF_4/CH_3CN, 1 mmol substrate at room temperature (22 °C).

Conclusions

To conclude, boron-doped diamond shows an outstanding performance for the direct electrochemical amination of less-activated alkylated arenes. The Yoshida method was significantly expanded and improved. Ongoing studies are focused on the functionalization of benzylic positions by this method using sterically more demanding pyridine derivatives, e.g. 2,6-lutidine.

Experimental Section

Supporting Information (see footnote on the first page of this article): For experimental details and analytical data see SI.

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