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Research Article

# Selective Electrosynthesis of Benzimidazole *N*-Oxides and Benzimidazoles from *o*-Nitroanilides Using Metal-Free Electrodes

Eric F. R. Pertermann,[#] Sebastián O. Simonetti,[#] Sebastian B. Beil, and Siegfried R. Waldvogel*

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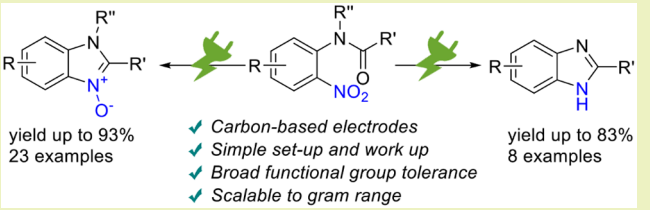
**ABSTRACT:** The electrochemical synthesis of benzimidazole *N*-oxides was achieved by tuning the pH and current density during the reduction of *o*-nitroanilides. By using boron-doped diamond cathodes and glassy carbon anodes in undivided cells, a collection of various aryl-, acyl-, and nitrogen-substituted benzimidazoles and their *N*-oxide derivatives was obtained in up to very good yields. The simple setup and purification steps render this methodology a powerful tool for synthesizing valuable heterocyclic motifs on up to a gram scale in a sustainable way. Additionally, our methodology allows for the electrochemical access to benzimidazole-containing active pharmaceutical ingredients, including clemizole, thiabendazole, and, in an unprecedented way, chlormidazole *N*-oxide as well as precursors of bendamustine *N*-oxide derivatives.




**KEYWORDS:** *nitro reduction, cathodic reduction, carbon-based electrodes, heterocycle N-oxides, nitrogen heterocycles*



## INTRODUCTION

Nitrogen heterocycles are predominant motifs in a wide variety of active pharmaceutical ingredients (APIs).[1] Among these, the benzimidazole structural pattern is of particular significance within the pharmaceutical industry due to its isostructural pharmacophore similarity to naturally occurring active biomolecules.[2,3] Relevant examples of benzimidazole-containing APIs include the antitumoral bendamustine **1**, the antiparasitic thiabendazole **2**, the antifungal chlormidazole **3**, and the antihistaminic clemizole **4** (Figure 1).[4,5]

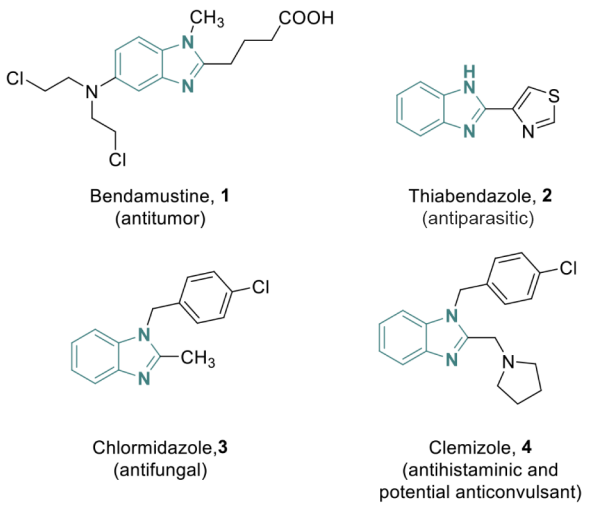



**Figure 1.** Selected examples of commercial benzimidazole-containing APIs.

Therefore, synthetic access to these motifs is of high importance, and their synthesis commonly entails the condensation reaction between *o*-phenylenediamine and carboxylic acids or their surrogates.[6] These *o*-phenylenediamines are obtained by the reduction of the corresponding dinitroarenes, usually involving high-pressure hydrogenation reactions with precious and toxic metals such as palladium or nickel, raising sustainability concerns within the process.[7] While the nitroarenes are stable, widely available, and affordable starting materials, alternative methods for providing hydrogen equivalents are imperative to circumvent these issues.[8]

In this regard, electrosynthesis, and electroreduction in particular, has emerged as a safer and more sustainable strategy.[9,10] With the sole use of electricity, which can be provided by renewable sources (e.g., photovoltaics and wind power), and protons from acidic reaction media, the mentioned concerns with reagent waste and safety risks of the classical synthetic approach can thus be avoided.[11,12] Moreover, in recent years, the development of galvanostatic conditions, the use of carbon-based electrodes, and the capability to be coupled to further technology, like flow, render electrosynthesis an incredibly useful tool to make syntheses of high-value-added products more efficient,

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**Scheme 1. Electrochemical Approaches for the Synthesis of the Benzimidazole (*N*-Oxide) Motif**

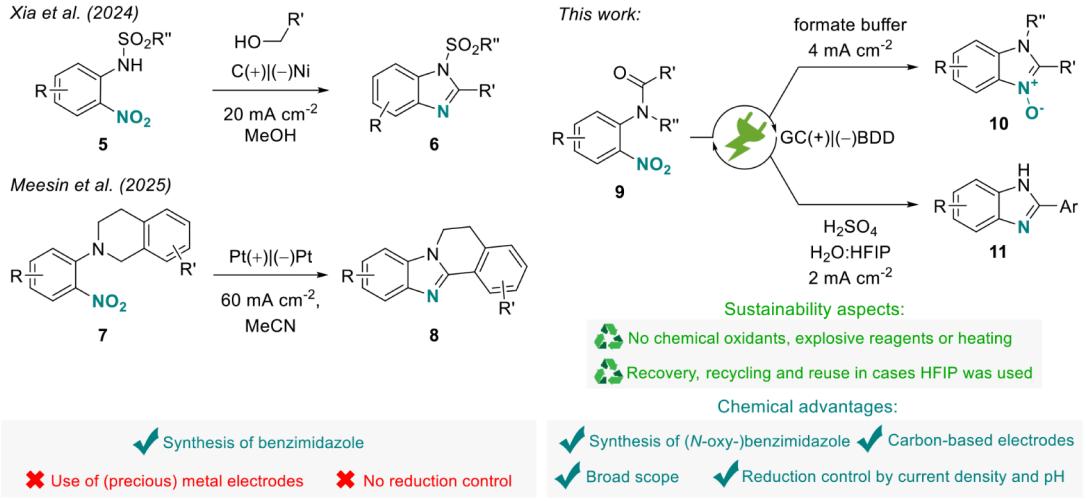
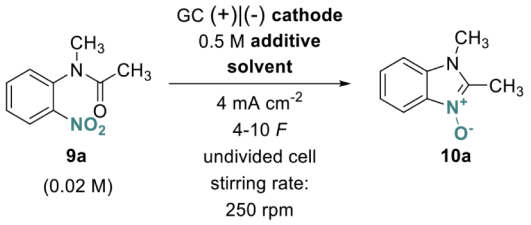



**Table 1. Optimization of the Reaction Conditions**[a]




| Entry | Cathode | Additive | Solvent | Current density (mA/cm$^2$) | Amount of applied charge (F) | Yield **10a**[b] (%) | Recov. **9a** (%) |
|---|---|---|---|---|---|---|---|
| 1 | BDD | 0.5 M $H_2SO_4$ | MeOH:$H_2O$ (1:1) | 4 | 4 | 61 | 8 |
| 2 | GC | 0.5 M $H_2SO_4$ | MeOH:$H_2O$ (1:1) | 4 | 4 | 54 | 6 |
| 3 | Pt | 0.5 M $H_2SO_4$ | MeOH:$H_2O$ (1:1) | 4 | 4 | 45 | 7 |
| 4 | BDD | 0.5 M $H_2SO_4$ | MeOH:$H_2O$ (1:9) | 4 | 4 | 55 | 10 |
| **5** | **BDD** | **0.5 M $H_2SO_4$** | **HFIP:$H_2O$** (1:1) | **4** | **4** | **84** | **15** |
| 6 | BDD | 0.5 M $H_2SO_4$ | HFIP | 4 | 5 | 0 | 36 |
| 7 | BDD | - | $HCO_2H$:$H_2O$ (1:1) | 4 | 5 | 56 | 14 |
| 8 | BDD | - | 0.5 M Formate buffer[c] | 4 | 5 | 55 | 44 |
| **9** | **BDD** | - | **0.5 M Formate buffer**[c] | **4** | **8** | **86** | **0** |
| 10 | BDD | - | 0.5 M Formate buffer[c] | 4 | 10 | 32 | 0 |
| 11[d] | BDD | - | 0.5 M Formate buffer[c] | - | - | - | 100 |

[a]Reaction carried out on a 0.1 mmol scale in 5 mL Teflon electrolysis cell with 1.8 cm$^2$ cathode surface. [b]NMR yields using 2,3,4-trimethoxytoluene as the internal standard. [c]0.5 M formate buffer prepared from sodium formate and formic acid in water (pH = 3.75). [d]No electricity was applied

sustainable, and scalable.[13−16] Especially, the cathodic reduction of nitro groups can be successfully applied to a multitude of different *N*-heterocyclic motifs by tuning the current density and pH to modulate the oxidation state of the nitrogen atom, affording aniline, phenylhydroxylamines, and nitroso compounds as reactive intermediates.[17] Possible *N*-heterocyclic motifs include quinolines,[18] quinazolines,[19] indoles,[20] indazoles,[21] benzotriazoles,[22] and benzisoxazoles.[23] Due to the high importance of benzimidazoles in public health, sustainable access to benzimidazole derivatives is highly desirable.

Heterocycle *N*-oxides and *N*-hydroxides have demonstrated remarkable pharmacological features as drugs and metabolites.[24] Among these properties are the modulation of enzyme interaction,[25−27] acting as prodrugs,[28,29] and the potential for membrane modulation.[30,31] However, the conventional synthesis of these compounds is limited to the use of strong oxidizers,[32,33] often incompatible with labile functional groups, with concomitant concerns about safety and environmental aspects.[34] Very few conventional methods use nitro reduction to obtain benzimidazole *N*-oxides or *N*-hydroxides by catalytic heterogeneous hydrogenation, and these methods are usually difficult to control.[35−38] Electrosynthesis also offers a valuable alternative here. While *N*-heterocycles can be oxidized with electrochemically generated peroxodicarbonate,[39] the electroreduction of nitroarenes enables direct access to heterocycle *N*-oxides and *N*-hydroxides, respectively.[23,40−42]

The electrosynthesis of benzimidazoles was achieved only to a very limited extent. Our group reported the anodic desulfurization of the corresponding thiones to generate imidazoles and benzimidazoles.[43] Xia et al. reported the synthesis of benzimidazoles **6** from *o*-nitro-sulfonamides **5** by *in situ* oxidation of the alcohol and subsequent cyclization but were limited to mostly tosyl-protected substrates (Scheme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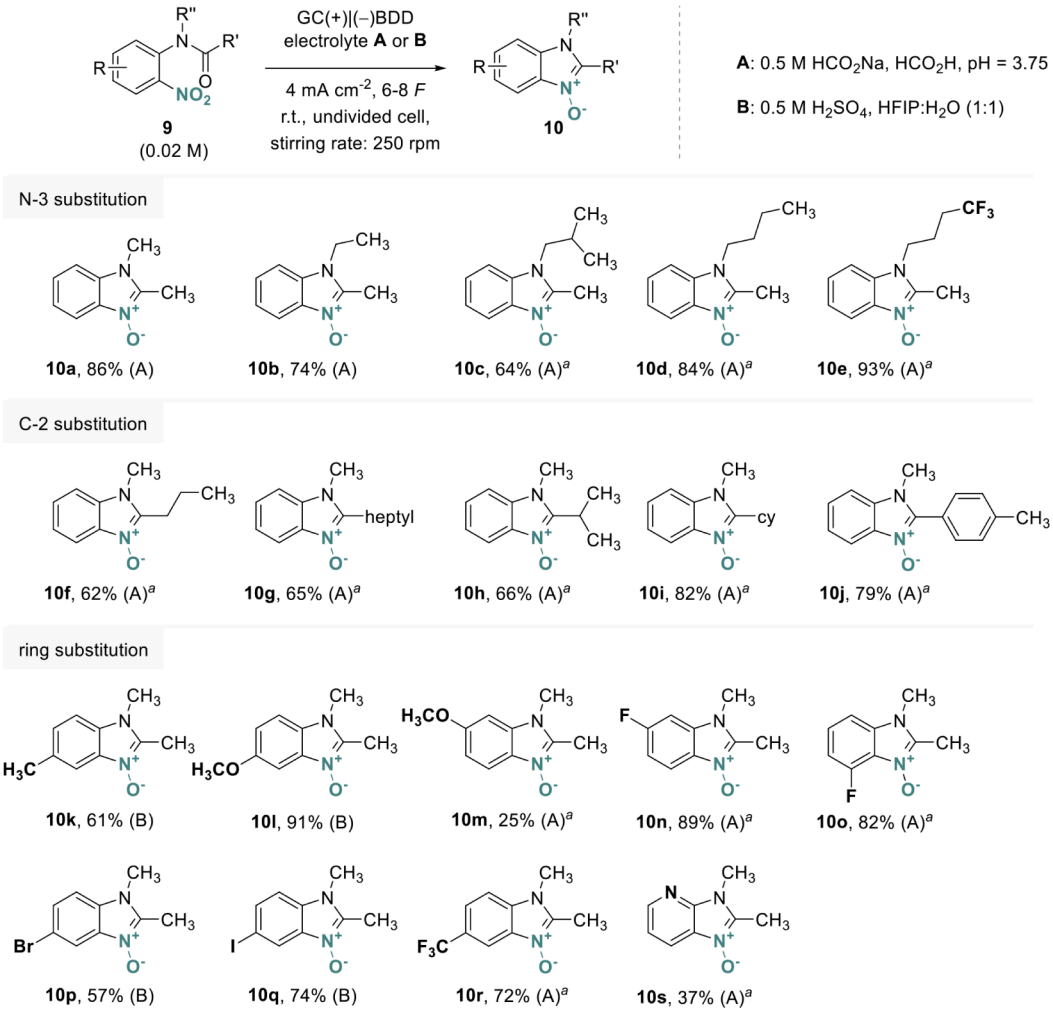
**Scheme 2. Synthesis of Benzimidazole *N*-Oxides 10**[a]




[a]Reactions carried out on a 0.5 mmol scale. Electrolyte systems are given in brackets with Electrolyte A: 0.5 M $HCO_2Na$, $HCO_2H$, pH = 3.75; Electrolyte B: 0.5 M $H_2SO_4$, HFIP:$H_2O$ (1:1). [a] 20% HFIP was added.

1).[44] Recently, Meesin et al. used nitro reduction to synthesize fused benzimidazoles **8** with limited compatibility to activated benzylic substrates **7**.[45] Further methods involve electrochemistry for the synthesis of benzimidazoles by an addition-desulfurization cascade or the formation of *N*-arylamidine intermediates.[46] Neither of these reports was able to omit transition metal electrodes, nor did they report selectivity in the synthesis of benzimidazole *N*-oxide products. Therefore, we aim for the direct electroreduction of *o*-nitroanilides **9** under galvanostatic conditions and envision selectivity control over the formation of the parent benzimidazole **11** and its *N*-oxide derivatives **10** by adjusting pH and current density, respectively (Scheme 1).

## RESULTS AND DISCUSSION

The substrate **9a** was chosen as a test system for the optimization of the cathodic reduction. Anilide **9a** is readily obtained by methylation of commercial *o*-nitroacetanilide.[47] Based on previous work by our group, we chose methanol as an electrically conductive solvent and used boron-doped diamond (BDD) as the cathode for the initial conditions, applying a current density of 4 mA $cm^{-2}$ and an applied charge of 4 *F*.[15,40,41,48,49] The substrate concentration was 0.02 M, and 0.5 M sulfuric acid was employed as the supporting electrolyte, affording a 61% yield of benzimidazole *N*-oxide **10a** (Table 1, Entry 1). Glassy carbon (GC) and platinum cathodes were tested but gave lower yields of 54% and 46%, respectively (Table 1, Entries 2 and 3). This underlines the outstanding features of BDD for the nitro reduction, with its chemical and electrochemical stability and striking electrochemical properties, such as the large overpotential for the HER, which is an important aspect of our electrochemical transformation.[15,50] A different ratio of methanol:water (1:9) indicated a slightly lower yield (55%, Table 1, Entry 4). The yield was improved by the use of 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) as a cosolvent, obtaining 84% yield with an additional 15% of remaining starting material (Table 1, Entry 5). HFIP was found to substantially improve the outcome of electrochemical reductions by strong hydrogen-bonding to oxygenated intermediates, controlling the reactivity of such intermediates, and preventing unwanted side reactions, such as radical recombination.[50−52] Additionally, HFIP can polarize substrates, lowering the reduction potential, and the solvent's low nucleophilicity avoids direct bond formation reactions, as shown in the past.[53] However, the use of a 0.5 M solution of sulfuric acid in HFIP showed decomposition of the product,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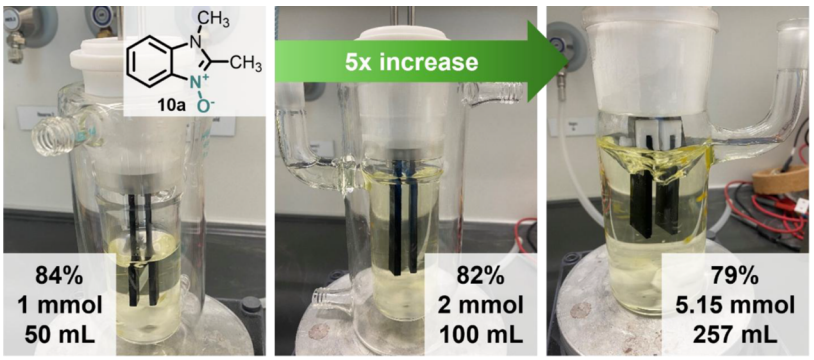


**Figure 2.** Scale-up in undivided glass cells: 1 mmol in 50 mL (left), 2 mmol in 100 mL (middle), and 5.15 mmol in 257 mL (right).

indicating that the use of water can play an important role in the outcome of the reaction (Table 1, Entry 6). Noteworthy, the use of HFIP has been shown to be key for several anodic coupling reactions.[54,55] Some of these reactions have even been scaled up to a technical level, where HFIP is handled in a closed loop to avoid losses. The recovery of this highly fluorinated solvent can be efficiently achieved by distillation at 70 °C and enables its recycling and direct reuse to facilitate sustainable processes (see the SI).[56,57] Therefore, no HFIP is released or accumulated as chemical waste in circular systems. Furthermore, a REACH report that assesses the mobility and persistence of toxic substances estimates the half-life of HFIP to be only 91 days, indicating a half-life that is orders of magnitude lower than that of PFAS listed in the same report.[58] As the primary metabolite of the common anesthetic sevoflurane, HFIP has also been shown to be safe in direct human exposure and is released upon employment.

Tuning the outcome of the reaction simply by pH and current density represents major advantages in the cathodic reduction of nitroarenes.[17,41] For this reason, we envisioned the use of formic acid and formate buffer to promote the formation of the product of interest. Furthermore, the use of formate buffer solutions has been shown to form dimeric structures, mediated by hydrogen bonding.[59] These structures can facilitate proton delivery, thereby emulating the effects observed for HFIP. Employing 0.5 M formic acid afforded only 56% of the product (Table 1, Entry 7). However, using a 0.5 M formate buffer prepared from sodium formate and formic acid in water at pH 3.75 and 5 F as the amount of applied charge yielded 55% of **10a**, with 44% of the remaining starting material showing incomplete conversion without product decomposition (Table 1, Entry 8). The use of 8 *F* provided 86% yield without any remaining starting material being left over (Table 1, Entry 9), whereas even larger amounts of applied charge (10 *F*) afforded a lower yield (32%, Table 1, Entry 10). Full recovery of the starting material was observed without the use of electricity (Table 1, Entry 11). The underlying mechanism of the electrochemical reduction of nitroarenes is extensively discussed in the literature and outlined in the SI with performed CV studies compatible with the literature-proposed mechanism (see SI, Section 4).[17,40,41]

With the optimized conditions in hand, we carried out the reactions on a 0.5 mmol scale and expanded this method to a collection of suitable substrates (Scheme 2). In this process, we employed a fast and simple workup protocol by neutralizing the pH, recovering the solvent by distillation, extracting with methanol or acetonitrile, and performing reversed phase silica purification with water−acetonitrile mixtures. We started to use our method on nitroarenes with a substitution pattern at the nitrogen atom of the anilide. Benzimidazole *N*-oxides with different substituents at position 3 were obtained in good yields, such as 74% of **10b** with an ethyl substituent, 64% of **10c** with an isobutyl substituent, 84% of **10d** with an *n*-butyl substituent, and 93% of **10e** with a 4,4,4-trifluorobutyl substituent. Substitution at the acyl moiety gave synthetically useful yields, with 62% **of 10f** with a propyl substituent, 65% of **10g** with an *n*-heptyl substituent, 66% of **10h** with an isopropyl substituent, and 82% of **10i** with a cyclohexyl substituent, while no significant effect of the increasing steric demands of the substituents was observed. This electrolysis process could also be applied to benzoylated substrates, affording the 2-(4'-tolyl)benzimidazole *N*-oxide **10j** in 79% yield.

Additionally, this protocol was also amenable to a broad collection of different substitution patterns at the aromatic ring. A methyl group afforded the benzimidazole *N*-oxide **10k** in 61% yield, and a methoxy group gave **10l** in an excellent 91% yield. The benzimidazole *N*-oxide **10m**, equipped with a methoxy substitution at position 5, was obtained in only 25% yield due to the electron-releasing groups increasing the reduction potential of nitroarenes. Interestingly, experiments carried out with lower amounts of applied charge, followed by LC-MS analysis, allowed us to observe the formation of deoxygenated *N*-benzimidazole, even when the starting material had not been fully consumed.

Electron-withdrawing groups improved the performance of the electrolysis, e.g., a fluoro substituent in the *para* position to the nitro group affording 89% yield of the corresponding *N*-oxide **10n**, whereas *ortho*-fluoro gave an 82% yield of **10o**. This protocol tolerates even more labile halide substituents, providing the bromo benzimidazole *N*-oxide **10p** in 57% yield, as well as the iodo congener **10q** in 74% yield. A trifluoromethyl-substituted substrate gave the *N*-oxide **10r** in 74% yield, whereas a pyridine moiety in the substrate afforded the desired **10s** in a modest 37% yield.

The use of lower amounts of applied charge was generally necessary for the substrates **10b-s** in order to avoid overreduction to the deoxygenated benzimidazole, while some substrates gave better yields with Method B, employing sulfuric acid and HFIP. For the substrates **10c−j, 10m−o**, and **10r−s** the employment of 20% HFIP as a cosolvent was necessary to ensure the solubility of the starting material and to promote the conversion. The HFIP used was distilled from the reaction mixtures and used directly for further reactions (see the SI, Section 1.8).


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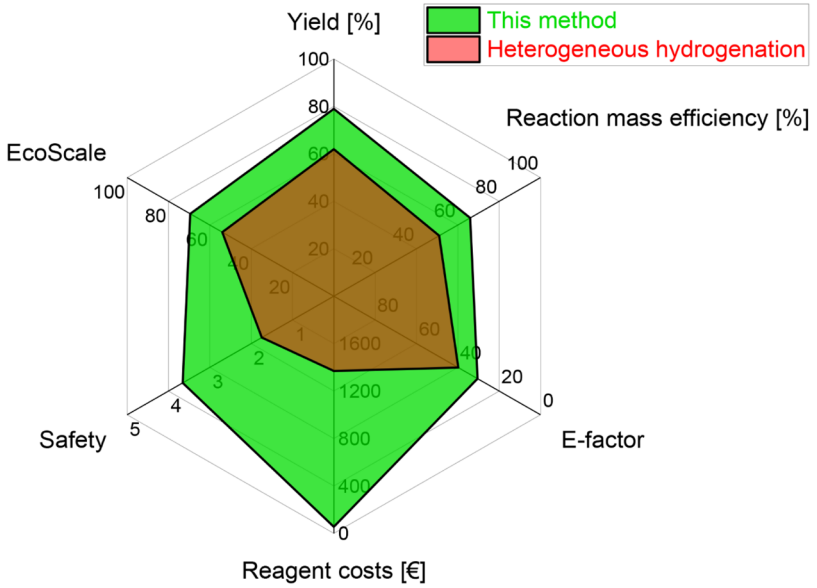


**Figure 3.** Comparison of green metrics of our method with heterogeneous hydrogenation. For details on the calculations, see the SI.

Reactions involving an *N*-phenyl substitution, phthalimide, or lactams afforded the respective phenylhydroxylamine (detected by LC-MS), which was reluctant to cyclization, even after prolonged reaction times or under microwave heating, whereas trifluoromethyl substrates afforded only decomposition, even at lower current density. Involving an ester moiety attached to C2 afforded a set of benzimidazoles with the partially reduced ester moiety, wherein alcohol and aldehyde byproducts were traced by LC-MS.

Our electroreductive methodology proved to be scalable. At a 1 mmol scale of **9a**, the benzimidazole *N*-oxide **10a** was obtained in 84% yield. Enhancing to 2 or 5.15 mmol scale was accompanied only by a slightly lower yield. A visualization of the different undivided glass cells used is depicted in Figure 2.

The only reported conventional synthesis of benzimidazole *N*-oxides achieves yields of 43−77%, with very few examples.[38] Conventional synthetic approaches to benzimidazole *N*-hydroxides claim yields of 24−75% and 46−72%,[35,37] respectively, whereas our method achieves multiple examples above 70−80%, with a maximum of 93%. In this regard, our method not only addresses the aforementioned environmental and safety concerns but also achieves higher yields.

Additionally, the calculation of different green metrics was performed and compared to the only reported conventional method to access **10a** (see the SI, Section 6).[38] Both methods achieve the same atom economy of 83%, due to their similar nature to nitro reductions. This results in a reaction mass efficiency of 72% for our electrochemical methodology, whereas the compared conventional method achieves only 51%. Furthermore, we calculated the E-factor for this transformation, achieving a value as low as 30 on the 5.15 mmol scale. This value is in accordance with the lower range of E-factors for the pharmaceutical industry.[60] Once again, our method performs better than the conventional method due to their higher use of organic solvents. Moreover, our procedure offers significant cost and safety improvements. The use of heavy metals and explosive gas mixtures in the compared procedure is expensive and dangerous, whereas the use of electricity and cheap electrolytes is inexpensive and inherently safe, as the current and, consequently, the reaction can be instantly terminated. Finally, we considered the EcoScale, a tool developed by Van Aken for comparing different methodologies.[61] The EcoScale also strongly favors our methodology due to a combination of the aforementioned factors. The comparison of these different parameters is visualized in Figure 3.

Further important pharmaceutical motifs are 2-arylbenzimidazoles.[62,63] Therefore, this motif caught our attention, and we developed a successful electroreduction procedure. Initially, neither the phenylhydroxylamine nor the aniline intermediates of the *N*-benzoyl starting materials underwent cyclization under the initial electrochemical conditions. Adjusting the current density used for the aforementioned Method B to 2 mA $cm^{-2}$ proved to be optimal for the complete reduction of the nitro group to the aniline, which could subsequently be cyclized under microwave heating conditions. Employing this adjusted method, we afforded the use of benzoylated substrates **9t−y** afforded the corresponding benzimidazoles **11** in good yields.

As expected, involving electron-releasing groups in the benzoyl substitution required a larger amount of applied charge (8 *F*), whereas electron-withdrawing groups improved the efficiency of this electrolytic transformation (Scheme 3). On the other hand, the substitution pattern at the benzo moiety led to the inverse outcome, and donor groups afforded better yields at the same amount of applied charge (72%) compared to the electron-withdrawing groups at the same position.

Noteworthy, the reaction control by adjusted current density toward *N*-oxide derivatives was previously discovered through the cathodic reduction of 2-nitro azobenzenes to 2-arylbenzotriazoles.[22] However, in this transformation, control over benzimidazole *N*-oxides and their deoxygenated congeners is achieved synergistically by pH and current density.

Aiming for pharmaceutically established motifs, bendamustine **1** precursors could be synthesized using the established conditions (Scheme 4). The benzimidazole *N*-oxides **12a** and **12b**, containing the central structural motif of bendamustine with bromo- and fluoro-substituents at position 5, were obtained in 56% and 50% yield, respectively. Follow-up


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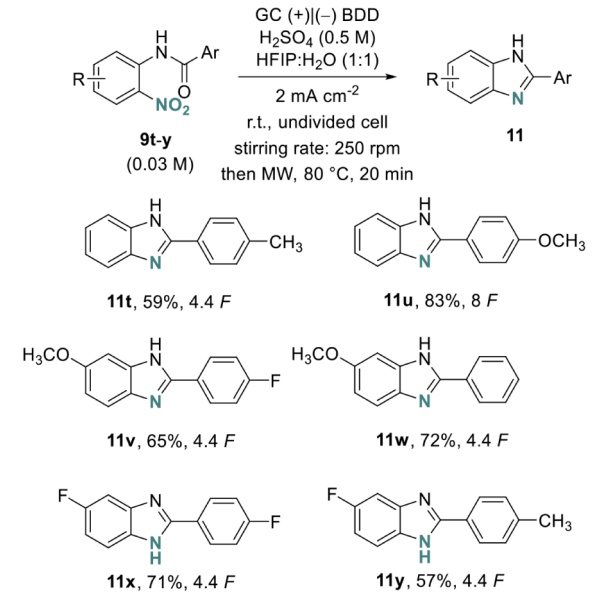
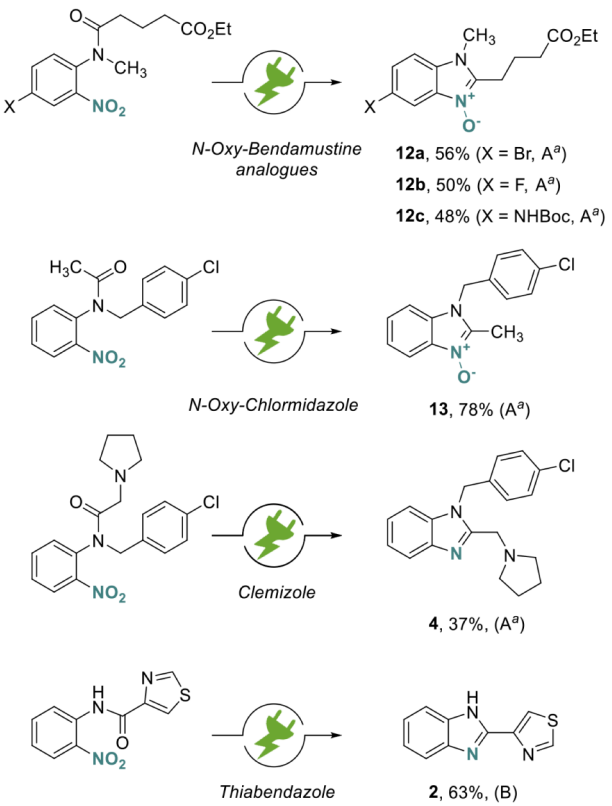
**Scheme 3. Synthesis of 2-Arylbenzimidazoles 11**




**Scheme 4. Electro-Reductive Formation of APIs (*N*-Oxides)**[a]




[a]Standard conditions used: GC(+)|(−)BDD, electrolyte A or B, 4 mA $cm^{-2}$, 6−12 *F*, r.t., undivided cell, stirring rate: 250 rpm. Electrolyte systems are given in brackets with Electrolyte A: 0.5 M $HCO_2Na$, $HCO_2H$, pH = 3.75; Electrolyte B: 0.5 M $H_2SO_4$, HFIP:$H_2O$ (1:1). With microwave heating for clemizole **4**: 30 min at 140 °C and thiabendazole **2**: 20 min at 80 °C. [a] 20% HFIP was added.

derivatization could further transform them into bendamustine *N*-oxide *via* Buchwald−Hartwig coupling or a nucleophilic aromatic substitution. Furthermore, the Boc-protected benzimidazole *N*-oxide bendamustine analogue **12c** was obtained in 48% yield and successfully deprotected to the free aniline. This compound could be further converted into bendamustine *N*-oxide following the standard and well-known alkylation routes.[64] These *N*-oxide derivatives, with potential as prodrugs with enhanced solubility, could lead to promising candidates for pharmaceutical use or are of interest as metabolites. Similarly, chlormidazole *N*-oxide **13** was obtained in a good yield of 78%. Additionally, our method enabled the electrosynthesis of clemizole **4** and thiabendazole **2** from the respective amides under subsequent microwave heating conditions, in 37% and 63% isolated yield, respectively.

## CONCLUSION

In conclusion, we established the first electrosynthetic method for synthesizing benzimidazole *N*-oxides by direct cathodic reduction and subsequently cyclizing stable, readily accessible *o*-nitroanilides. This electrolysis was carried out with sustainable, carbon-based electrodes using a formate buffer or sulfuric acid as the supporting electrolyte, allowing for defined selectivity of the oxidation state within the products. The easy and benign purification process enables efficient access to benzimidazole *N*-oxides in a clean way and provides a prerequisite for technical applications, since downstream processing often represents a cost driver.[65] Overall, 31 examples with yields up to 93%, with a wide diversity of substituents, were converted in an atom economy of up to 83% and were scalable to the gram scale. The methodology was complemented with the formation of promising *N*-oxide analogues to the APIs bendamustine and chlormidazole, as well as clemizole and thiabendazole, showcasing a critical structural motif for medicinal chemistry. Overall, this established electrochemical methodology is the first general approach to the sustainable and efficient synthesis of the benzimidazole *N*-oxide motif, which has inherent importance in organic synthesis and medicinal chemistry.

## EXPERIMENTAL SECTION

### General Information

Details about the used materials, analytical devices, characterization methods, equipment, and reaction setup can be found in Section S1 of the Supporting Information.

### Key Experiments

**Electrolysis of Substrate 9a to Benzimidazole *N*-Oxide 10a.** *N*-Methyl-*N*-(2-nitrophenyl)acetamide **9a** (0.5 mmol) was dissolved in 25 mL of a 0.5 M sodium formate/formic acid buffer solution in water (pH = 3.75). The mixture was subjected to a current of 11.2 mA, with an electrode surface area of 2.8 $cm^2$ (current density: 4 mA/$cm^2$), using a GC anode and a BDD cathode. After applying 8 *F* of charge, the reaction was complete, and the mixture was neutralized with a 1 M aqueous $NaHCO_3$ solution. The solvents were then evaporated from the resulting mixture under reduced pressure. The solid was redissolved in acetonitrile to separate it from the remaining salts. After 10 min of decantation, the acetonitrile layer was filtered and evaporated under reduced pressure. A short reverse-phase silica (C18) filter column using a water/acetonitrile (95:5 to 7:3) mixture afforded the benzimidazole *N*-oxide **10a** in 86% yield.

**Electrolysis of Substrate 9t to Benzimidazole 11t.** 4-Methyl-*N*-(2-nitrophenyl)benzamide **9t** (0.15 mmol) was dissolved in 2.5 mL of HFIP, and 2.5 mL of 1 M sulfuric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acid was added. The mixture was subjected to a current of 3.6 mA, with an electrode surface area of 1.8 $cm^2$ (current density: 2 $mA/cm^2$), using a GC anode and a BDD cathode. After an applied amount of charge of 4.4 *F*, the mixture was transferred to a microwave vial and heated at 80 °C for 20 min in a closed device. The mixture was neutralized with a 1 M aqueous $NaHCO_3$ solution. The resulting mixture was then distilled to recover the HFIP solvent. After the distillation was finished (at 70 °C), the remaining water solvent was removed under reduced pressure. The solid was redissolved in methanol to separate it from the remaining salts. After 10 min of decantation, the methanol layer was filtered and concentrated under reduced pressure. The crude product was purified by silica gel chromatography using a cyclohexane/ethyl acetate (9:1 to 6:4) mixture to afford the benzimidazole **11t** in 59% yield.

Electrolyses of all further substrates were performed according to these general protocols, with adjusted amounts of applied charge for the individual substrates. For details and the characterization of all isolated benzimidazole *N*-oxides and benzimidazoles, see Section 5 of the Supporting Information. Details about the synthesis and characterization of the substrates used in the electrolysis reactions can be found in Section 2 of the Supporting Information. The $^1H$, $^{13}C$, and $^{19}F$ NMR spectra of all isolated compounds are shown in Section 7 of the Supporting Information.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acssuschemeng.6c00249.

Experimental procedures, characterization, calculation of green metrics, and NMR spectra (PDF)

## ■ AUTHOR INFORMATION


### Corresponding Author

**Siegfried R. Waldvogel** − *Max-Planck-Institute for Chemical Energy Conversion, Department of Electrosynthesis, Mülheim an der Ruhr 45470, Germany; Karlsruhe Institute of Technology, Institute of Biological and Chemical Systems − Functional Molecular Systems (IBCS FMS), Karlsruhe 76131, Germany;* orcid.org/0000-0002-7949-9638; Email: siegfried.waldvogel@cec.mpg.de

### Authors

**Eric F. R. Pertermann** − *Max-Planck-Institute for Chemical Energy Conversion, Department of Electrosynthesis, Mülheim an der Ruhr 45470, Germany*

**Sebastián O. Simonetti** − *Max-Planck-Institute for Chemical Energy Conversion, Department of Electrosynthesis, Mülheim an der Ruhr 45470, Germany*

**Sebastian B. Beil** − *Max-Planck-Institute for Chemical Energy Conversion, Department of Electrosynthesis, Mülheim an der Ruhr 45470, Germany;* orcid.org/0000-0003-0373-3843

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### Author Contributions

#E.F.R.P. and S.O.S. contributed equally to this work. S.R.W. and S.B.B. conceived the project. S.O.S. conducted the optimization experiments. E.F.R.P. and S.O.S. synthesized the starting material, conducted the scope experiments, and analyzed the results. E.F.R.P. planned and carried out the synthesis of the APIs and their analogues and analyzed the results. E.F.R.P., S.O.S., S.R.W., and S.B.B. wrote and reviewed the manuscript. All authors have given approval to the final version of the manuscript.


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