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Replacing sulfuric acid with water in electrochemical metal-free mild aromatic C–H amidation: a direct route to *N*-phenylamides†

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In this work, we describe a mild electro-oxidative metal-, oxidant- and acid-free direct amidation of aromatic C–H bonds using nitrile solvents as a source of amide and amine moieties. We show that carrying out the reaction in a divided cell makes it possible to eliminate the use of an acid used in previous attempts, enabling at the same time this reaction for easily reducible substrates and paired electrosynthesis. This electrochemical approach was demonstrated on 60 examples of *N*-phenylamides, including propanil, which has not been obtained under electrochemical conditions so far, and 12 examples of benzoxazoles; it is also amenable to gram-scale synthesis. Mechanistic studies (voltammetry, EPR, and quantum chemical calculations) revealed that the process is initiated by the formation of hydroxyl radicals from residual water molecules on the anode, which attack the nitrile solvent, and the resulting amide radicals add to the arene.

Introduction

An efficient formation of amide bonds is important in organic and medicinal chemistry due to the presence of amide moieties in a wide range of natural products, pharmaceutical agents, and functional materials.[1] The amide bond is one of the most essential fragments that forms the backbone of proteins, peptides and many other biologically significant compounds. Currently, approximately 25% of all commercial drugs and two-thirds of all drug candidates contain at least one amide moiety.[2] Moreover, agrochemicals with herbicidal and antifungal activity (*e.g.* propanil and boscalid) and a lot of marketed drugs (paracetamol, niclosamide, imatinib, *etc.*) often contain the phenylamide framework (Fig. 1).[3]

Propanil is a contact herbicide commonly used in the US to control grass and broadleaf weeds in rice fields. In the factory, propanil is obtained by the following process: nitration of 1,2-

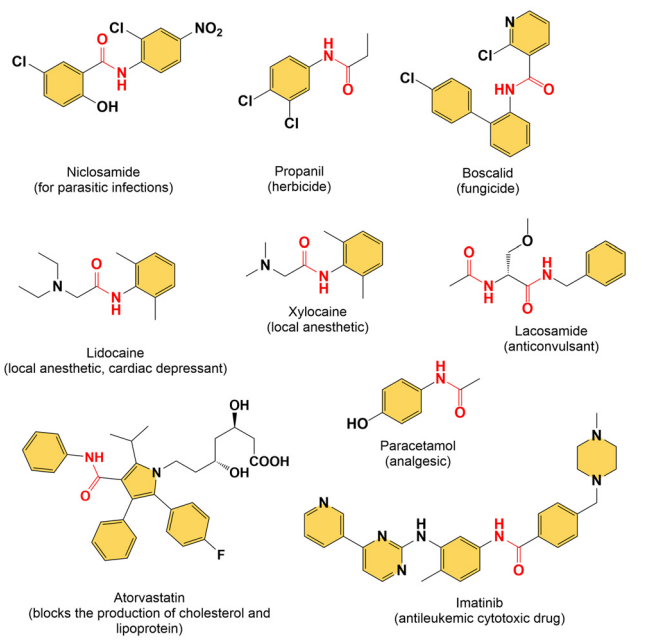

Fig. 1 Selected agrochemicals and drugs containing the phenylamide framework.

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dichlorobenzene produces 1,2-dichloro-4-nitrobenzene, and subsequent hydrogenation of the nitro group in the presence of a nickel or palladium catalyst forms 3,4-dichloroaniline. Then, acylation of the amino group with propionyl chloride gives propanil (Scheme 1).[4]

Another practically important phenylamide-containing compound is acetanilide, which is a starting compound in the synthesis of dyes and drugs (*e.g.* sulfa drugs) and is used as a fuel additive.[5] It is also used to stabilize hydrogen peroxide and as a plasticizer for cellulose nitrates. Acetanilide is commercially obtained by acylation of aniline with acetic acid or acetic anhydride at 120 °C followed by recrystallization from water (Scheme 1).

Thus, the importance of *N*-phenylamides is obvious, and the search for new ways to obtain them directly in one step under milder conditions still remains a challenge for chemists.

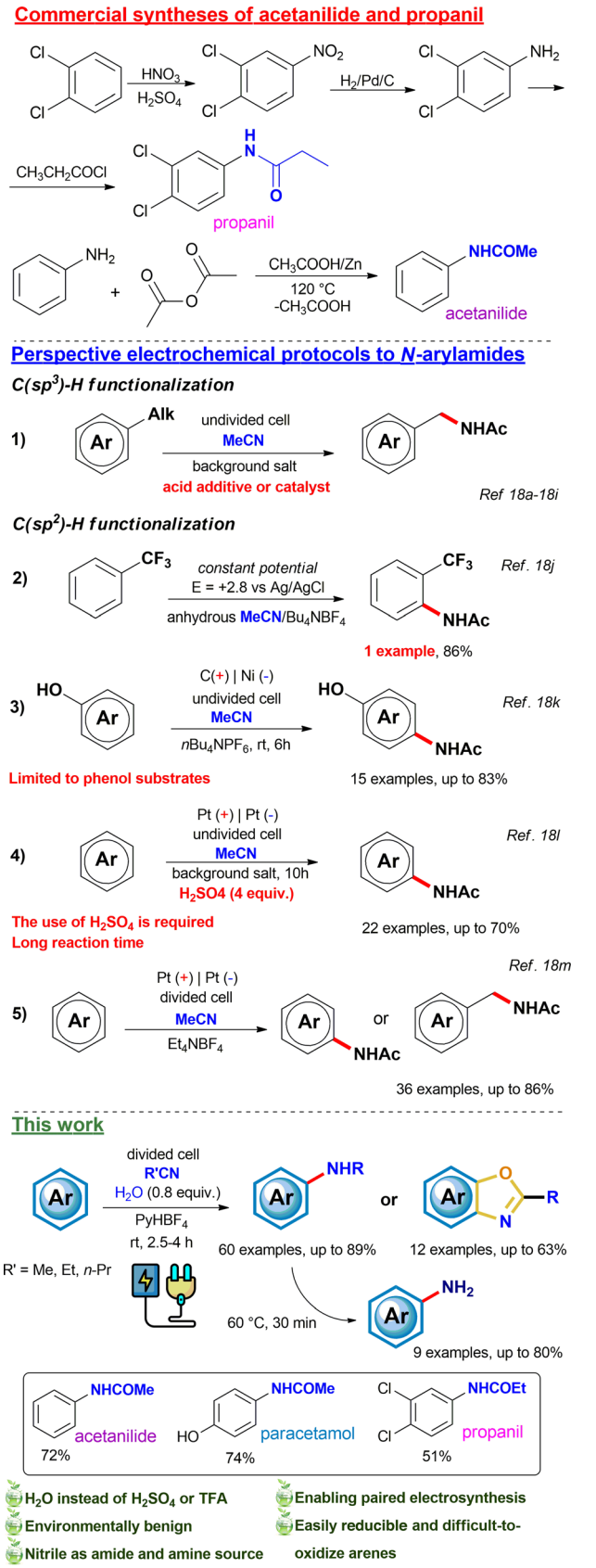
One of the most well-known methods for the preparation of *N*-substituted amides is the Ritter reaction.[6] To date, various variations of the Ritter-type reaction of carboxylic acid,[7] haloalkynes,[8] aldehydes,[9] triazenes,[10] arenediazonium tetrafluoroborates,[11] and cyclic diaryl iodonium salts[12] are known which allow one to obtain various *N*-substituted amides, in particular, *N*-benzylamides and *N*-arylamides. However, many of the established protocols require elevated temperatures, pre-functionalized aryl (or amide) halide precursors, expensive catalysts or the use of stoichiometric oxidants.[13]

Electrochemistry is a powerful and green strategy compared to traditional organic reactions and allows one to access valuable *N*-containing compounds in an atom- and step-economical manner under mild conditions.[14] The electrochemical C(sp^3)–H Ritter-type amidation reaction of alkanes,[15] esters,[16] and ketones[17] has been well documented, as early as the 1970s. Since then, the study of Ritter-type electrochemical reactions has continued to develop rapidly. In the last few years, the world's leading scientists have proposed new electrochemical protocols for Ritter type C(sp^3)–H amidation of benzylic sites (Scheme 1, ex. 1) and Ritter type C(sp^2)–H amidation of aromatic sites (Scheme 1, ex. 2–4).[18]

Barba[18j] *et al.* proposed an anodic oxidation of 1-(trifluoromethyl)benzene in dry acetonitrile/Bu_4NBF_4 under constant potential conditions (Scheme 1, ex. 2). 2-(Trifluoromethyl)acetanilide was obtained as the main product in this reaction, but the scope consisted of only one reaction.

Banerjee[18k] and co-workers reported a regioselective electrochemical Ritter-type reaction at the C(sp^2)–H of phenol derivatives toward an environmentally benign and direct synthesis of different *N*-arylacetamides, in particular paracetamol (Scheme 1, ex. 3). The reaction proceeds under exogenous oxidant- and catalyst-free conditions, but was limited to phenol substrates.

In 2023, Ye's group[18l] reported a general approach for amidation of aromatic C(sp^2)–H bonds (Scheme 1, ex. 4). It has a good substrate scope but takes 10 hours and requires the use of excess sulfuric acid (4 equiv.), which makes it environmentally unfriendly.



Scheme 1 Commercial routes to acetanilide and propanil production, recent advances in Ritter-type electrochemical reactions to produce *N*-arylamides, and our green and wide-scope approach to them.

Strikingly, also in 2023, some of us[18m] achieved good yields in a very similar electrochemical amidation in the absence of sulfuric acid or any other reagent except water (Scheme 1, ex. 5). In this work, we compare our conditions to those of Ye's group[18l] and show that getting rid of sulfuric acid becomes possible simply by the use of a divided cell. We optimize the conditions for this amidation and extend its scope by synthesizing 60 distinct *N*-arylamides (*vs.* 22 in our previous article), including propanil, which has not been obtained under electrochemical conditions previously, as well as 12 benzoxazoles. We also show that nitriles can be a source of not only amides, but also the corresponding amines.

Results and discussion

Although in some studies[18l] H_2SO_4 is considered an indispensable reagent, which forms persulphates, thus initiating the reaction, examples 2, 3 and 5 in Scheme 1 suggest that electrochemical amidation of arenes by nitriles can proceed in its absence. We have hypothesized that the presence of an acid simply alleviated the reduction of easily reducible substrates[19] and products on the cathode when the reaction is carried out in an undivided cell. Then it should be easy to get rid of the acid by using a divided cell. This would not only "greenify" the process by removing the hazardous reagent, but also make it more economical by allowing pairing with some cathode process (see below for an example).

We chose 1,4-bis(trifluoromethyl)benzene (**1a**) as a model substrate for optimizing the conditions of acid-free divided-cell electrolysis, since it is very difficult to oxidize and CF_3-bearing arylamides are potential drug candidates.[20]

Initially, we explored the oxidation of a solution of **1a** in acetonitrile (20 mL) in a divided cell equipped with Pt–Pt electrodes at a constant current of 35 mA at room temperature for 2.5 hours under air; the salt $PyHBF_4$ (3 equiv.) as a supporting electrolyte was placed only in the cathodic compartment (Table 1, entry 1). As a result, *N*-(2,5-bis(trifluoromethyl) phenyl)acetamide (**2a**) was obtained in 63% yield with no detection of other products. We hypothesized that the amount of water present in acetonitrile (~0.02%, Merck) was limiting the reaction yield, since it is the only available source of oxygen for the amide group. Indeed, adding 0.8 equiv. of water allowed us to obtain **2a** in 97% yield under the same conditions (Table 1, entry 2). However, the reaction turned out to be water-sensitive, with excess water negatively affecting the formation of **2a** (Table 1, entries 3 and 4). Expectedly, no product was observed when the reaction was carried out in freshly dried MeCN under an inert atmosphere and using molecular sieves (Table 1, entry 5), or without electricity (Table 1, entry 6).

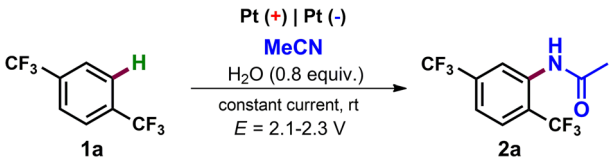
Replacing $PyHBF_4$ with Et_4NBF_4 had little effect on the yield of the resulting **2a** (Table 1, entry 7); however, Et_4NBF_4 must be added to both compartments (cathodic and anodic) to improve electrical conductivity, whereas $PyHBF_4$ needs to be added only to the cathodic compartment due to its easier diffusion through the membrane and it can be easily recovered from the reaction mixture after electrolysis (see the ESI† for details). The electrolytes Et_4NBr and Et_4NCl proved to be less efficient for this reaction (Table 1, entries 8 and 9) due to their hygroscopicity and lower oxidation potentials (+1.40 and +1.43 *vs.* Ag/AgCl, respectively). These salts can also act as nucleophiles, promoting unwanted halogenation processes.

Replacing the platinum anode with a glassy carbon (GC) or graphite anode (C) led to a decrease in the yield of **2a** (Table 1, entries 10 and 11), which is probably associated with higher overvoltage that can cause higher adsorption of aromatics on the electrode, leading to the inhibition of the target process. The platinum electrode is optimal since it is more reliable and stable in most electrochemical reactions.

Carrying out the reaction in dichloromethane (DCM) using a **1a** : MeCN ratio of 1 : 1–1 : 10 resulted in no products (Table 1, entry 12). Product **2a** was formed in moderate yields when an excess of nitrile relative to the substrate was used (Table 1, entries 13 and 14). This is likely linked to the necessity for the formed OH-radical to encounter a MeCN molecule before it encounters an aryl (see below for mechanism investigation).

A constant current of 35 mA turned out to be optimal. A decrease in the current led to slower and incomplete conver-

Table 1 Electrochemical oxidation of 1,4-bis(trifluoromethyl)benzene, optimization of reaction conditions[a]



Entry	Variation from the standard conditions	Yield of **2a**,[b] %
1	Without water (≪0.8 equiv.)	63
2	None	97 (87)[c]
3	H_2O (1/1.5/3/10 equiv.)	92/88/81/32
4	MeCN : H_2O (3 : 1), or ~232 equiv. of H_2O	0[d]
5	Under N_2, freshly dried MeCN, M.S.[e]	0[d]
6	No cell potential	n.r.
7	Et_4NBF_4 instead of $PyHBF_4$	94
8	Et_4NCl instead of $PyHBF_4$	38
9	Et_4NBr instead of $PyHBF_4$	29
10	GC(+)–Pt(−)	74
11	C(+)–Pt(−)	43
12	DCM solvent, MeCN (1–10 equiv.)	0[d]
13	DCM solvent, MeCN (30–100 equiv.)	<42
14	DCM : MeCN (1 : 1)	57
15	25 mA for 3.5 hours	76
16	50 mA for 1.5 hours	87
17	Undivided cell	27
18	Undivided cell, H_2SO_4 (4 equiv.)	59
19	Heating 50 °C	53

[a] General conditions: **1a** (1.2 mmol), $PyHBF_4$ (3 equiv.) only in the cathodic compartment, MeCN (20 mL), divided cell, Pt anode (20 cm^2), Pt cathode (10 cm^2), rt, 35 mA for 2.5 hours (2.4 F mol^{-1}). [b] Yield determined by ^1H NMR using trimethoxybenzene as an internal standard. [c] Isolated yield. [d] The solution changes its color, but no **2a** could be detected. [e] Molecular sieves. n.r. = no reaction.

sion of the starting substrate and longer synthesis time, whereas its increase somewhat lowered the product yield (Table 1, entries 15 and 16).

The yield of the model reaction expectedly decreased when it was carried out in an undivided cell (Table 1, entry 17) due to the higher propensity of **1a** to undergo reduction than to undergo oxidation (see below). But addition of sulfuric acid, indeed, inhibited reduction, somewhat improving the product yield (Table 1, entry 18). Heating the reaction mixture to 50 °C led to a decrease in the yield of the target product **2a** (Table 1, entry 19), since in this case the resulting amide decomposes into an amine.

To compare our optimal conditions with those proposed in ref. 18*l*, we carried out the oxidation of **1a** and 1-chloro-4-nitrobenzene (**1o**), one of the most easily reducible substrates from their article (Fig. 2). We considered the reaction in an undivided cell with 4 equiv. of sulfuric acid ("Ye's conditions" (A), as close as possible to the conditions from ref. 18*l*), the same conditions but without the acid ("acid-free Ye's conditions" (B)), and our optimized conditions ("our conditions" (C)). The formation of products was monitored by TLC, GC-MS and ^{1}H NMR. See Scheme 2 for the results.

Oxidation of **1a** under acid-free Ye's conditions (B) produced **2a** in only 27% yield, and 21% of the starting substrate remained in the reaction mixture unreacted (Scheme 2). The low product yield was due to gum formation during electrosynthesis due to the reduction of acetonitrile at the cathode to 3-aminocrotononitrile and trimers,[22] which can polymerize quite easily, forming a film on the electrodes. Adding sulfuric acid (Ye's conditions, **A**) indeed improved the product yield to 59% and significantly reduced gum formation (Scheme 2). However, 19% of the starting material was still present, and the formation of 8% of a dimer was observed. Our conditions (C), on the other hand, allowed us to obtain the desired product **2a** in an excellent yield and with no gum formation or dimerization.

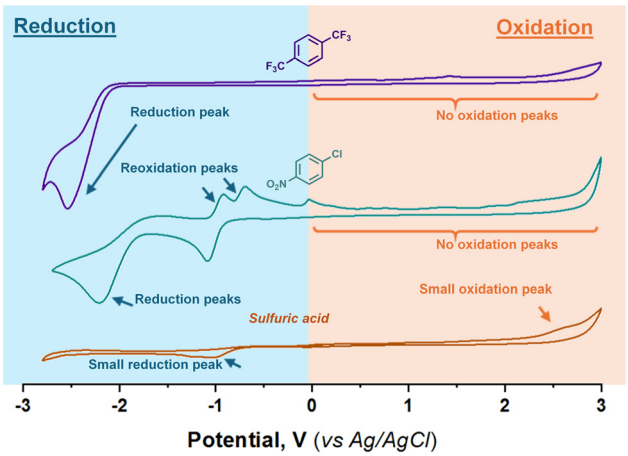
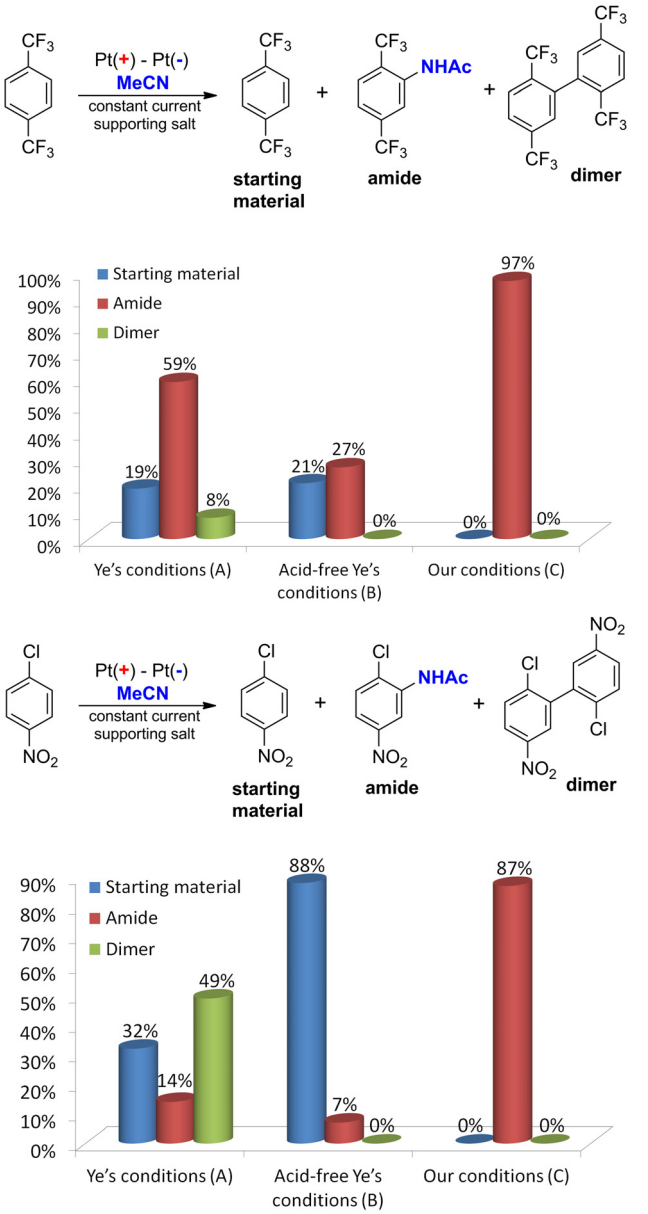


Fig. 2 Cyclic voltammograms (CVs): **1a** (purple), **1o** (green) and sulfuric acid (orange). Conditions: 5 mM, MeCN, 0.1 M Bu_4NBF_4. GC – working electrode, Ag/AgCl – reference electrode, scan rate –100 mV s^{-1}.



Scheme 2 Electro-oxidation of arenes. Ye's conditions (A): arene (1.2 mmol), H_2SO_4 (4.8 mmol), MeCN (15 mL), Pt–Pt (14 mm × 32 mm × 1 mm both electrodes), undivided cell, nBu$_4$NBF$_4$ background salt. Acid-free Ye's conditions (B): arene (1.2 mmol), H_2O (0.8 equiv.), MeCN (15 mL), Pt–Pt (14 mm × 32 mm × 1 mm both electrodes), undivided cell, nBu$_4$NBF$_4$ background salt. Our conditions (C): arene (1.2 mmol), H_2O (0.8 equiv.), MeCN (20 mL), Pt anode (20 cm^2), Pt cathode (10 cm^2), divided cell, PyHBF$_4$ background salt. Yield was determined by ^{1}H NMR.

However, as widely known in the machine learning field,[21] it is incorrect to compare different conditions on a reaction that was used to optimize one of them but not others. So, we compared these conditions on **1o**, which was used in ref. 18*l*. Oxidation of **1o** under conditions **B** provided **2o** in a very low yield of 7%, while 88% of the starting substrate remained in the reaction mixture (Scheme 2). No gum formation was observed, however. This behavior can be explained by the

ability of nitroarenes to easily reduce, but then oxidize back under electrochemical conditions (Fig. 2).

Expectedly, addition of 4 equivalents of sulfuric acid increased the product yield, but only to 14% (Scheme 2). Strikingly, the yield of the dimer was twice as large (49%), and 32% of the starting **1o** remained unreacted. Our greener conditions (C) allowed us to obtain **2o** in 87% yield with no traces of starting materials or dimers (Scheme 2). Thus, our conditions are clearly eco-friendlier and more efficient.

With the optimized conditions in hand, the scope of aromatic derivatives with electron-donating and electron-withdrawing functional groups was expanded to 60 entities (Table 2). The data on the redox properties of all arenes in the C–H amidation are summarized in Table S2 (see the ESI†).

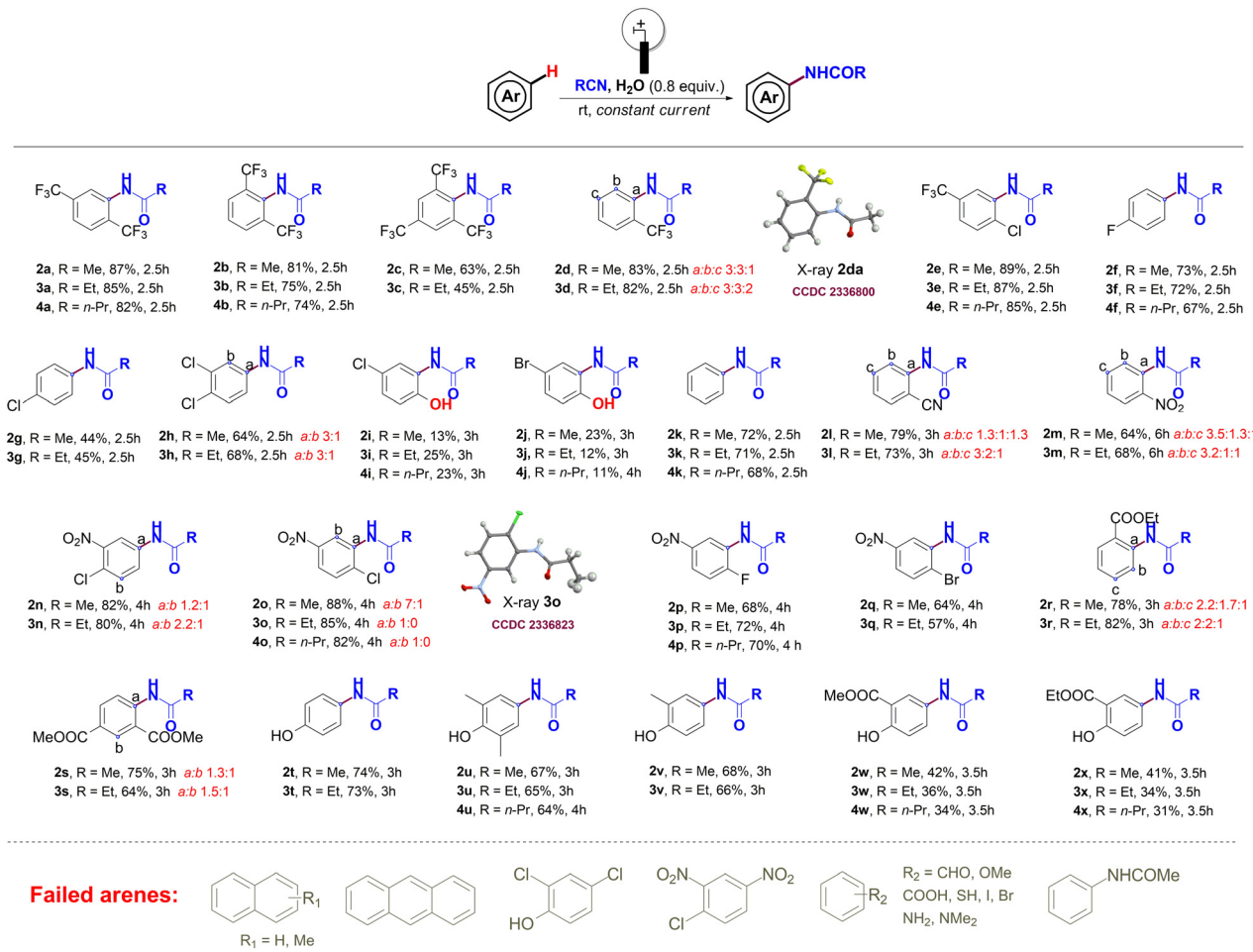
Electrochemical oxidation of 1,3-bis(trifluoromethyl) benzene (**1b**) in MeCN, EtCN and *n*-PrCN led to anilides **2b**, **3b** and **4b** as the main isomers in 81%, 75% and 74% yields, respectively, with trace formation of other regioisomers. The product yield decreased in the case of 1,3,5-tris(trifluoromethyl)benzene (**1c**), probably due to the steric factor. Oxidation of trifluoromethylbenzene (**1d**) gave *ortho*- and *meta*-substituted anilides **2d**-*a*, **3d**-*a*, **2d**-*b*, and **3d**-*b* as the major regioisomers with an *ortho*/*meta*/*para* ratio of 3 : 3 : 1 (**2d**) and 3 : 3 : 2 (**3d**). The structure of **2d**-*a* was also confirmed by single-crystal X-ray analysis (CCDC 2336800†).

Oxidation of fluorobenzene (**1f**) and chlorobenzene (**1g**) in MeCN and EtCN resulted only in *para*-substituted anilides (**2f**, **2g**, **3f** and **3g**), while oxidation of bromobenzene and iodobenzene failed to give any amidation product. Oxidation of **1g** led to the formation of a dimer in addition to the anilide, which was confirmed by mass spectrometry and ^{1}H NMR.

Oxidation of 1,2-dichlorobenzene (**1h**) in propionitrile and acetonitrile resulted in the formation of *N*-(3,4-dichlorophenyl) propionamide (propanil, **3h**-*a*) and *N*-(3,4-dichlorophenyl)acetamide (**2h**-*a*) as the main products.

Oxidation of 4-chloro-1-(trifluoromethyl)benzene (**1e**) in MeCN, EtCN and PrCN afforded anilides **2e**, **3e** and **4e** with the amide group at the *ortho* position to chlorine in high yields of 89%, 87% and 85%, respectively. Upon oxidation of 1-chloro-4-fluorobenzene (**1i**) and 1-bromo-4-fluorobenzene

Table 2 Substrate scope in Ritter-type electro-oxidative aromatic C–H amidation of arenes[a]



[a] General conditions: arene (1.2 mmol), RCN (20 mL), $PyHBF_4$ (3 equiv., 3.6 mmol) in the cathodic compartment, Pt anode (20 cm^2), Pt cathode (10 cm^2), divided cell, rt, constant current I = 35 mA. Isolated yield.

(**1j**) under selected conditions, fluorine was replaced by a hydroxyl group, resulting in the formation of *N*-arylamides **2i**, **3i**, **4i**, **2j**, **3j**, and **4j** in low yields since benzoxazoles **2ii**, **2jj**, **3ii**, **3jj**, **4ii**, and **4jj** were formed predominantly (Scheme 3). Electro-oxidation of ester **1r** in both MeCN and EtCN led to *ortho*/*meta*/*para* regioisomers with the formation of the *ortho*- and *meta*-substituted anilides (**2r**-*a*, **3r**-*a*, **2r**-*b*, and **3r**-*b*) as the main products. Oxidation of dimethyl isophthalate (**1s**) in MeCN led to the formation of **2s** with a yield of 75% and an *a* : *b* isomer ratio of 1.3 : 1. The oxidation reaction of **1s** in EtCN resulted in the formation of **3s** in an *a* : *b* ratio of 1.5 : 1, but with a lower yield of 64%.

Phenols reacted solely at the *para* position to the hydroxyl group to afford phenylamides **2t–2v** and **3t–3v**. Acetaminophen or paracetamol (**2t**) was formed in 74% yield directly from phenol under mild conditions. The *para*-protected phenol did not give any anilide product, as was shown for 2,4-dichlorophenol.

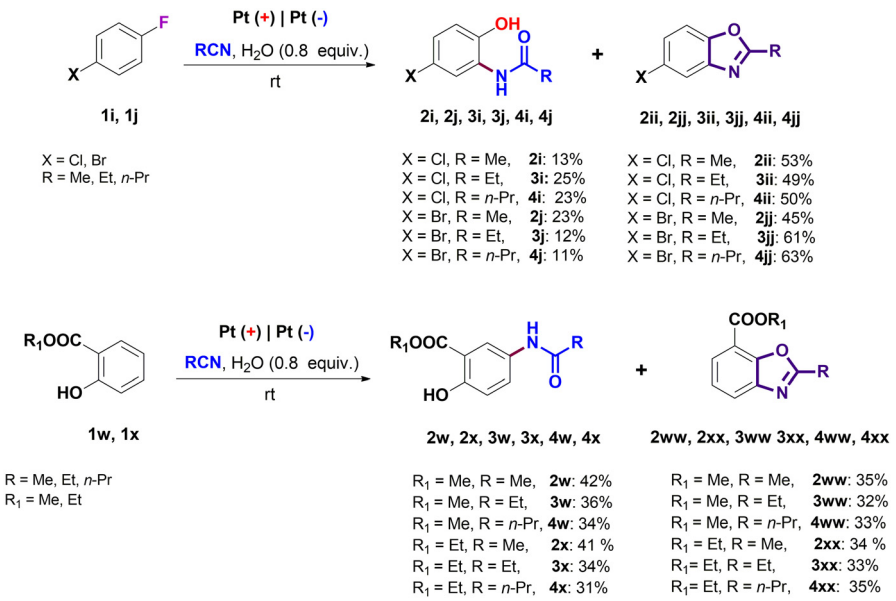
Oxidation of methyl salicylate (**1w**) and ethyl salicylate (**1x**) in aceto-, propio- and butyronitrile led to the formation of two products: anilides **2w**, **3w**, **4w**, **2x**, **3x**, and **4x** and benzoxazoles **2ww**, **3ww**, **4ww**, **2xx**, **3xx**, and **4xx** (Scheme 3). On passing more electricity (4.8 F mol^{-1}), benzoxazoles were predominantly formed rather than anilides. The formation of amidation products with two or more amide groups was not detected in each case by ^{1}H NMR and HRMS.

In the case of nitrobenzene (**1m**) oxidation, the addition of the amide fragment occurred predominantly at the *ortho* position to the nitro group. *N*-(2-Nitrophenyl)acetamide (**2m**) and *N*-(2-nitrophenyl)propionamide (**3m**) were obtained in moderate yields of 39% and 42%, respectively, with incomplete conversion of **1m** even after passing 7.2 F mol^{-1} of electricity. Addition of the amide fragment to the *ortho* position relative to the nitro group probably occurs due to the formation of a more stable intramolecular hydrogen bond of the N–H···O type which is the driving force for the regioselective formation of the *ortho* isomer. Oxidation of 1-chloro-4-nitrobenzene (**1o**) in EtCN and *n*-PrCN afforded *N*-(2-chloro-5-nitrophenyl)propionamide (**3o**) and *N*-(2-chloro-5-nitrophenyl)butyramide (**4o**) as the only isomers in 85% and 82% yields while oxidation of **1o** in MeCN gave two regioisomers (**2o**-*a* and **2o**-*b*) with an *a* : *b* ratio of 7 : 1 and a total yield of 88%. The structure of **3o** was confirmed by single-crystal X-ray analysis (CCDC 2336823†). Complete conversion of **1o** occurred after passing 4.8 F mol^{-1} of electricity while 1-chloro-2,4-dinitrobenzene failed to afford any amidation products.

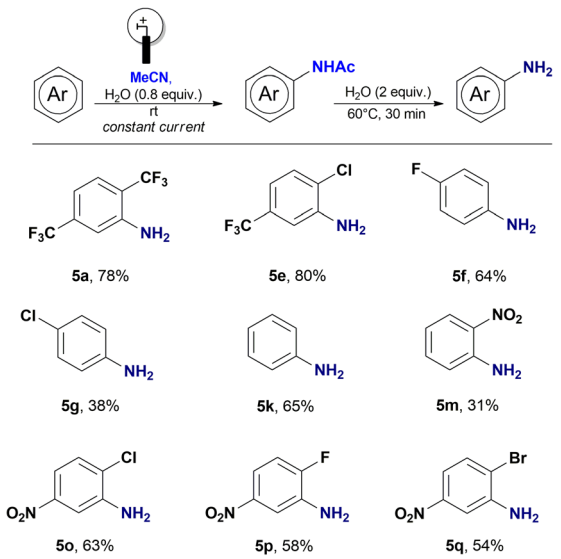
1-Fluoro-4-nitrobenzene (**1p**) in MeCN, EtCN and *n*-PrCN gave *N*-phenylamides **2p**, **3p** and **4p** in 68%, 72% and 70% yields, respectively. Oxidation of 1-bromo-4-nitrobenzene (**1q**) in nitrile solvents led to the formation of anilides **2q** and **3q** in lower yields (64% and 57%). Anilide formation with an amide bond predominantly at the *ortho* position to the halogen (Cl, F, Br) was probably due to the fact that the positive mesomeric effect of the halogen outweighs the formation of an intramolecular hydrogen bond between the amide radical and nitro group in the transition state (which probably directs the attack on the *ortho*-position in the case of nitrobenzene).

Electro-oxidation of a number of arenes that are quite easy to oxidize (below +2 V), such as methoxybenzene, naphthalene, 2,6-dimethylnaphthalene, 1,3,5-trimethoxybenzene, and anthracene, or arenes with bromine or iodine substituents under similar conditions resulted solely in a C–C coupling.[23]

When the reaction mixture after electrolysis was heated at 60 °C for half an hour, the resulting amides were converted



Scheme 3 Formation of benzoxazoles and *N*-phenylamides during electro-oxidation of arenes. [a] General conditions: arene (1.2 mmol), RCN (20 mL), $PyHBF_4$ (3 equiv.) in the cathodic compartment, divided cell, Pt anode (20 cm^2), Pt cathode (10 cm^2), rt, 35 mA. Isolated yield.

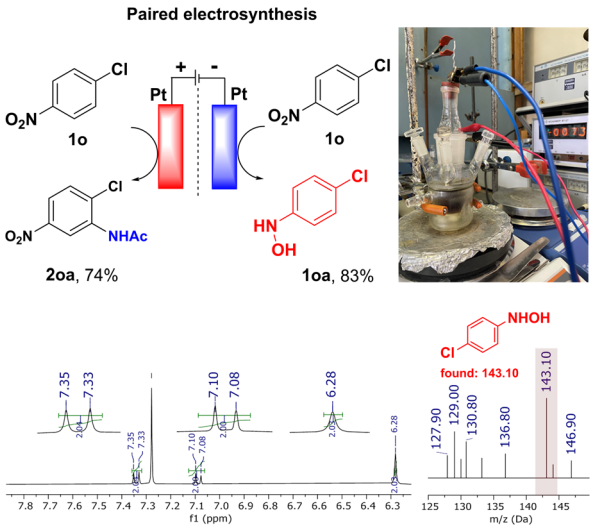


Scheme 4 Formation of amines from the obtained amides during hydrolysis and heating. Isolated yield according to arenes.

into amines due to hydrolysis, as shown for a number of the obtained *N*-phenylamides (Scheme 4). Heating of *p*-amidophenols **2t–2v** did not lead to the formation of amines.

To demonstrate the capabilities of the proposed approach, a paired electrosynthesis experiment in MeCN was carried out using **1o** as a model substrate (Scheme 5). Oxidation of **1o** resulted in **2o**-*a* with 74% yield, while reduction of **1o** gave *N*-(4-chlorophenyl)hydroxylamine (**1oa**) in 83% yield after passing 4.8 F mol^{-1} of electricity (see section 2.4 of the ESI†). Note that the substrates in the anode and cathode areas do not need to be identical.

To understand the underlying mechanism of this process, a detailed investigation involving electron paramagnetic resonance spectroscopy (EPR) and quantum chemical calculations was performed.



Scheme 5 Paired electrosynthesis: oxidation of **1o** in MeCN (left), reduction of **1o** in MeCN (right). Isolated yield.

Electron paramagnetic resonance spectroscopy (EPR)

The formation of reactive radicals during electrochemical oxidation of arenes in nitriles was monitored by electron paramagnetic resonance (EPR) spectroscopy. We began our research with the oxidation of a solution of acetonitrile (2 ml) in water (100 μl) in the presence of *N*-*tert*-butyl-α-phenylnitrone (PBN) as a spin-trap (C = 0.5 mg ml^{-1}). The EPR spectrum of PBN–OH$^{\bullet}$ spin adduct **A** was recorded (Fig. 3), which indicated that the process can begin with the formation of a hydroxyl anion radical that can further react with nitrile or arene.

To reveal the formation of other spin adducts, an EPR study was further carried out on the oxidation of a solution of benzene in MeCN and EtCN. Benzene was taken as a model arene because its oxidation potential is slightly lower (+2.56 V) than the oxidation potentials of other aromatic compounds (Table S1†). Oxidation of a benzene solution in MeCN and EtCN containing 0.8 equiv. of water in the presence of a PBN spin-trap provided the EPR spectra as shown in Fig. 4 and 5, which are notably distinct from each other. The EPR spectrum obtained during the oxidation in EtCN gave a clearer line splitting than the spectrum obtained in acetonitrile. The obtained values for the number of lines, constants and *g*-factor in both cases indicate a structure containing two nitrogen atoms and two protons, which may correspond to intermediates **B** and **C** (Fig. 4 and 5).

Unfortunately, we did not find the EPR spectra of similar structures in the literature. The high-resolution mass spectrum of an oxidized solution of benzene in acetonitrile with water (0.8 equiv.) in the presence of the spin-trap PBN also indicates the most likely formation of intermediate **B** (molecular peak 235.1441) (Fig. 4).

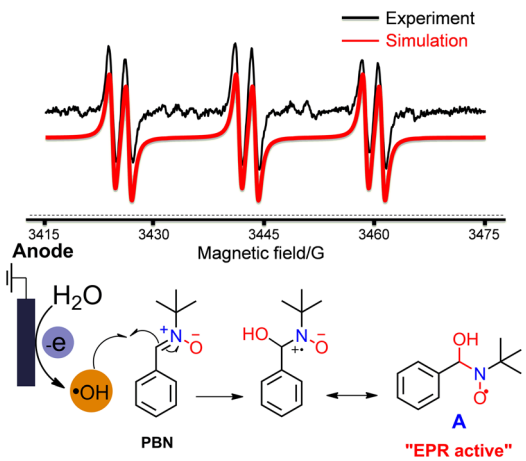


Fig. 3 EPR spectrum of PBN–OH$^{\bullet}$ recorded during oxidation of a solution of MeCN (2 ml) in water (100 μl) at 293 K with simulations. g = 2.001, a_N = 13.9 G, a_H = 2.3 G. C (PBN) = 0.5 mg ml^{-1}.

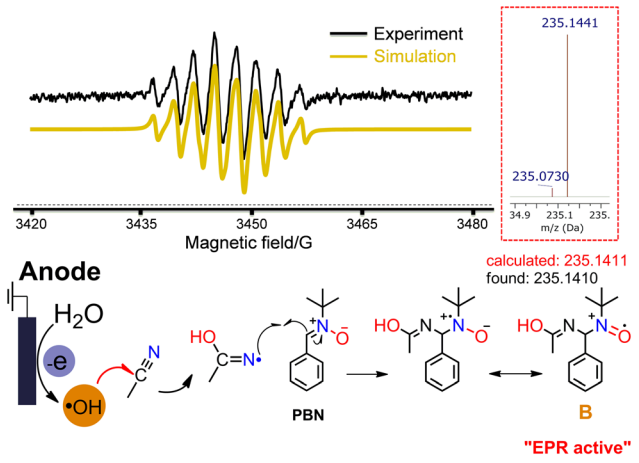


Fig. 4 EPR spectrum of spin-adduct **B** recorded during oxidation of a benzene solution in MeCN with water (0.8 equiv.) at 293 K with simulations. g = 2.009, a_{N1} = 5.2 G, a_{N2} = 4.4 G, a_{H1} = 5.3 G, a_{H2} = 9.2 G. C (PBN) = 1.5 mg ml^{-1}.

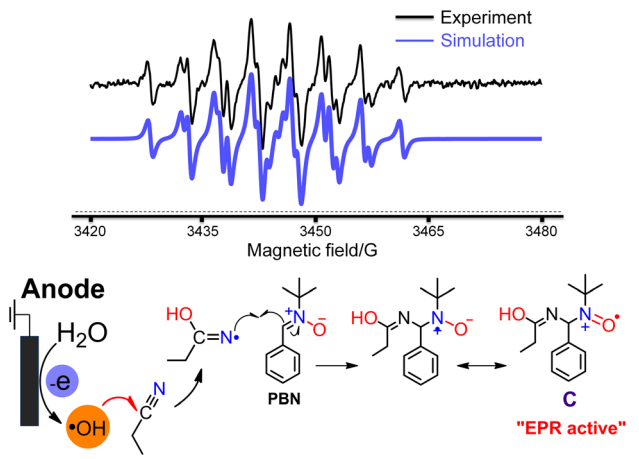
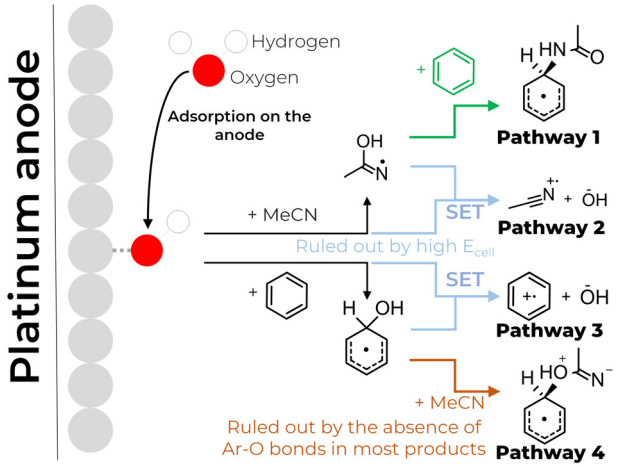


Fig. 5 EPR spectrum of spin-adduct **C** recorded during oxidation of benzene solution in EtCN with water (0.8 equiv.) at 293 K with simulations. g = 2.006, a_{N1} = 5.24 G, a_{N2} = 4.32 G, a_{H1} = 5.15 G, a_{H2} = 9.24 G. C (PBN) = 1.5 mg ml^{-1}.

As we did not detect any aromatic radicals with EPR, but detected products of OH-radical and RC(OH)N radical additions to PBN, we can conclude that the reaction starts with the oxidation of a water molecule on the anode (at least in the case of the platinum anode, which is known to adsorb OH radicals).

After the formation of an OH radical, the reaction can follow one of the four pathways shown in Scheme 6. However, conventional quantum chemistry methods are not well suited to modeling heterogeneous processes, or the processes directly occurring in the near-electrode layers of the solution, so we cannot reliably quantify their plausibilities *via* calculations.

Previous studies by Kissner *et al.* suggest[24] that the OH radical is capable of attacking acetonitrile (first stage of Pathways 1 and 2). On the other hand, Pathway 2 is, in fact, a



Scheme 6 Possible pathways involving the OH radical after its formation on the Pt anode.

formal SET reaction of the OH radical with acetonitrile, and this process can be expected to be thermodynamically unfavorable – nitriles have higher oxidation potentials compared to water.[25] Pathway 3 can be ruled out by the EPR studies of the reaction mixture, which have not shown any signs of aromatic radicals.

On the other hand, hydroxylated aromatics are widely recognized intermediates in such processes and have been extensively studied in the anodic oxidation of organic pollutants (Pathway 4).[26,27] However, this particular pathway results in the formation of an Ar–O bond, which only forms as a replacement of the Ar–F bond in our above examples (Scheme 3), but never of Ar–H (Table 2). So, we consider this mechanism unfeasible.

Thus, only Pathway 1 is in full agreement with our experimental observations.

Quantum chemical calculations

Molecular modeling involving concurrent quantum chemical methods can be used to establish the feasibility of the suggested mechanism (Pathway 1).

We have computed all steps of Pathway 1 at the DLPNO-CCSD(T)[28]/def2-TZVPP[29]/CPCM(CH_3CN)//B3LYP[30,31]-D3BJ[32,33]/def2-TZVP/CPCM(CH_3CN)[34] level of theory. Transition states were located using conformational searches in CREST,[35] followed by pre-optimization[36] and, finally, optimization in Orca (see the ESI†).[37] The computed free energy profile for Pathway 1 using benzene as a model aromatic compound is shown in Fig. 6.

Pathway 1 further splits into two possible routes with the attacking radical particle being **T1** or **T2** (Fig. 6). According to quantum chemical calculations, in both cases, the addition of **T1**/**T2** to benzene constitutes the rate-limiting step. The first route has a lower activation energy of ~21 kcal mol^{-1}, which is feasible for a reaction proceeding at room temperature.

Conversion to the final reaction product can proceed in two ways: through oxidation of the intermediate radical **I1** to **A1** at

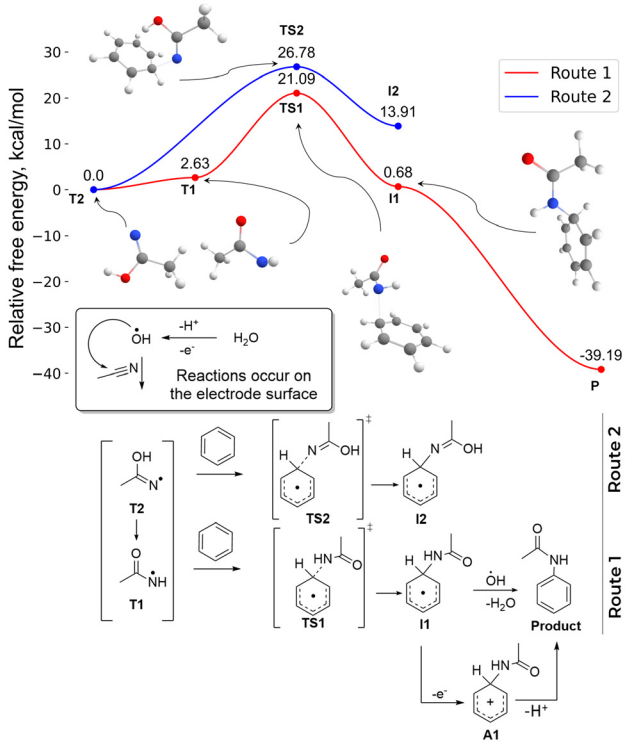


Fig. 6 Relative free energies along the reaction coordinate, calculated at the DLPNO-CCSD(T)/def2-TZVPP/CPCM(CH_3CN)//B3LYP-D3BJ/def2-TZVP/CPCM(CH_3CN) level of theory. Only the minimum energy structures are shown; different elements are shown in different colors: red – oxygen, grey – carbon, white – hydrogen and blue – nitrogen. The bottom section shows the modeled mechanism.

the anode and subsequent deprotonation, or *via* direct abstraction of the hydrogen atom by an OH radical (Fig. 6). To confirm that the second process is not rate limiting, we performed a relaxed PES scan that showed that it is barrierless (Fig. S16†).

Conclusions

Phenylamides are an important class of substances with practically significant properties, so the search for new sustainable approaches to obtain them is undoubtedly relevant. Organic electrosynthesis in which electrons are utilized as a traceless agent is of increasing interest in dehydrogenative C–H/N–H cross-coupling reactions. In this article, we have shown that the use of excess sulfuric acid in electrochemical C(sp^2)–H amidation can be replaced simply by the use of a membrane (*i.e.*, use of a divided cell instead of an undivided cell) and shown that these conditions are highly universal by synthesizing 60 *N*-phenylamides and 12 benzoxazoles directly from arenes using nitriles as a source of an amide or amine moiety. The only requirement is for the aryl to have a higher oxidation potential than that of water; otherwise, dimers are formed.[23] The established protocol features excellent yields of up to 89% under mild reaction conditions, allows functionalization of difficult-to-oxidize arenes, and is amenable to gram-scale synthesis and paired electrosynthesis. The reaction proceeds more selectively and with a higher product yield when difficult-to-oxidize (more positive than +3.2 V) arenes are used. Based on the data of preparative electrosynthesis, cyclic voltammetry, EPR studies in the presence of a spin-trap and quantum chemical calculations, it was shown that the process starts with the formation of hydroxyl radicals, which react with nitrile and then attach to arenes to afford desirable *N*-phenylamides.

Author contributions

Conceptualization: SOS, AIK, MGM. Methodology: AIK, SOS, VIM, MGM, EVK, OBB, VMB, KAI. Investigation: AIK, SOS, VIM, KVB, VIT. Data curation: AIK, SOS, VIM, KVB, VIT, MGM. Writing – original draft: SOS, AIK. Writing – reviewing and editing: SOS, AIK, MGM, YHB. Visualization: SOS, MGM. Supervision: SOS, AIK, MGM, YHB.

Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

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