nature portfolio

Peer Review File

# Paired Electrolysis Enables para-C–H Amination of Phenols with Nitroarenes and Mechanistic Visualization via Multifunctional Electrochemical Mass Spectrometry

Corresponding Author: Professor Aiwen Lei

**This file contains all reviewer reports in order by version, followed by all author rebuttals in order by version.**

Version 0:

Reviewer comments:

Reviewer #1

(Remarks to the Author)
In the manuscript titled “Paired Electrolysis enables para-C-H Amination of Phenols with Nitroarenes to p-Hydroxy Diphenylamines Guided by Multifunctional Electrochemical Mass Spectrometry”, the authors Yi，Lei and Wei investigate a paired electrolysis strategy for selective para-C–H amination of phenols with nitroarenes, enabling the one-step synthesis of unprotected p-hydroxy diphenylamines without relying on transition-metal catalysts or external reductants.. The study presents a comprehensive analysis of para-C-H amination of phenols with nitroarenes to p-hydroxy diphenylamines, which is of broad interest to the field of electrochemical organic synthesis. The findings are novel and potentially significant, as they provide new insights into forming the C-N bond. My recommendation is minor revision, and my specific comments are as follows.

Comment 1: Phenols are commonly found in natural products. To further demonstrate the practical utility of this methodology, it would be valuable to include one or two examples using structurally complex phenols, which could help illustrate the applicability of this approach in natural product synthesis.
Comment 2: In the substrate scope studies, various substituted phenols were examined. It would be helpful if the authors could comment on the relative reaction rates observed for phenols bearing electron-donating versus electron-withdrawing groups, along with a brief explanation of the electronic effects influencing reactivity.
Comment 3: The Supporting Information includes attempts with aromatic amine derivatives (page 7). Have the authors also explored the reactivity of Ts-protected anilines in this transformation?
Comment 4: There appears to be an inconsistency between the structural formula of intermediate 6 in Figure 6a and that in Figure 7. The authors should verify and correct this discrepancy.
Comment 5: The 13CNMR spectrum provided for compound 4d in the Supporting Information seems to be partially cut off. A complete spectrum should be provided.
Comment 6: In the Supporting Information, Section 10 (“Constant Potential Test”) states that reactions were performed at cathodic potentials of –0.4 V, –0.6 V, and –1.0 V. However, Figure S25 is labeled with “2.6 V”. This likely represents a typographical error and should be corrected to “0.6 V” for consistency.
Comment 7: There are several minor spelling and formatting errors that require attention. For example, on page 20 of the Supporting Information, “Arylhydrazine” should be removed and “Phenol” should be changed to “phenol”. A thorough proofreading of the manuscript and SI is recommended to correct similar inaccuracies.

Reviewer #2

(Remarks to the Author)
In this manuscript, the authors present an electrochemical, metal-free one-step strategy for C–N bond formation directly from nitroarenes, enabling the synthesis of unprotected p-hydroxy diphenylamines. This approach is further integrated with the AIEC-MS platform for rapid screening, demonstrating a broad substrate scope. In-depth mechanistic studies using in situ EC-MS uncover key intermediates, including aryl nitrenes and related species. However, I would like to recommend its publication in this journal after the following comments have been addressed.
1. Since the reaction involves the generation of phenoxy radical species, which have the potential to undergo self-

dimerization, did the authors observe such byproducts in the reaction mixture, or does this process interfere with the overall reaction?
2. Why do nitroarenes bearing electron-donating substituents lead to lower product yields?
3. What factors govern the selective reduction of only one nitro group while leaving the second nitro group intact, as observed in products 4ab–4ad?
4. If the para position of the phenol ring is substituted with an alkyl group, does the reaction still proceed? Furthermore, what would be the expected outcome if both the para and ortho positions are sterically blocked?
5. For completeness, the authors might consider citing “Org. Lett. 2022, 24, 12, 2310–2314”, where a related approach for the oxidation of phenol has been demonstrated.

Reviewer #3

(Remarks to the Author)
General Assessment
This manuscript describes a paired electrolysis strategy for para-C–H amination of phenols with nitroarenes, guided by multifunctional electrochemical mass spectrometry (EC-MS). The approach allows for one-step synthesis of p-hydroxy diphenylamines under mild, metal-free conditions, and provides mechanistic insight via in situ monitoring of reactive intermediates. While the work presents an innovative combination of electrochemistry and EC-MS analysis, several aspects of experimental design, mechanistic interpretation, and substrate scope require substantial clarification before it is suitable for publication. Therefore, I recommend major revision.
Minor Comments
• Line 245: The text refers to “Scheme 3c,” but no such scheme exists. This should be corrected.
• Line 265: Figure 7b is said to show compound 4i, but it appears to correspond to 5i, which creates confusion.
• Figure 3: The content resembles a table of compounds rather than a figure. It should be reformatted or consistently described.
• In Fig. 5a, could the observed positive shift in peak potential in the presence of HFIP be attributed to proton involvement in the electrochemical reduction of nitrobenzene?
• Figure 6a: Intermediates should be labeled consistently with the text. For example, the compound currently labeled “1” should be labeled as 1i-1 to avoid confusion with starting materials.
• Line 232: The manuscript states that 1i-1 is p-nitrotoluene, but based on mass data and mechanistic context, this should be nitrosobenzene. Similarly, 1i-2 should be N-(p-tolyl)hydroxylamine instead of p-hydroxytoluene.
• Figure S25 (Supporting Information): X-axis potentials should be reported as negative.
• Figure 8c: The MS of 7e1 and 7f appear to be incorrect.
• Several sentences are vague or incomplete. For example, Lines 210–212 (“Comparative analysis of nitrobenzene’s reduction potential…”) should be rewritten more clearly with quantitative electrochemical data.
Major Comments
• The complete reduction of nitrobenzene is usually a six-electron process. Could the authors monitor the reaction progress using cyclic voltammetry and, ideally, perform constant-potential electrolysis to confirm the paired electrolysis mechanism?
• Supporting Information: Electrode polarity switching frequency is reported inconsistently (1, 2, 5 Hz vs 0, 2, 5 Hz in Table X). This should be clarified. Also, indicate if the reaction was performed in a two-compartment cell under constant current without polarity switching.
• Authors suggest a nitrene intermediate (based on mass spectrometry), but there is no direct evidence of its participation in C–H amination. Observing traces in MS does not confirm it as a key intermediate; the reaction may proceed via classical nitroso/hydroxylamine pathways.
• The modified electrolysis conditions used for mass spectrometry are very different from bulk electrolysis conditions. It is unclear how the mechanism can be reliably studied under such differing conditions.
• Many products could potentially be accessed more easily via anilines, so the synthetic advantage is unclear.
• It is recommended to replicate NMR spectra of 4ab and 4ac to ensure reproducibility and accuracy.

Reviewer #4

(Remarks to the Author)
The manuscript by Prof Lei and colleagues have described Paired Electrolysis enables para-C-H Amination of Phenols with Nitroarenes to p-Hydroxy Diphenylamines Guided by Multifunctional Electrochemical Mass Spectrometry. There are several key aspects in mass spectrometry that need to be clarified and further verified to enhance the scientific rigor and impact of the research. I recommend accepting the paper after revisions.
1. Mass spectra with a certain mass range should be provided to facilitate the reader's understanding of the actual situation of the entire reaction. The mass spectra should show isotopic peaks in Figure S4. By observing the intensity and position of the isotopic peaks, more information about the elemental composition of the sample can be observed.
2. Discussion of fragmentation processes of tandem mass spectra in Figure 7, Figure S5 and Figure S6should be added in Supporting Information.
3. Specific experimental operations for offline in Figure 7b should be added in Supporting Information.
4. Central to this approach is a multifunctional automated injection electrochemical mass spectrometry (AIEC-MS) platform. Its ionization mode is described as APCI. But from the perspective of Device Setup, what is the difference from ESI? Theoretically, ESI is more reflective of the reaction species than APCI.

Version 1:

Reviewer comments:

Reviewer #1

(Remarks to the Author)
The author has addressed all my concerns. I hereby approve the publication of this article in Nature Communications.

Reviewer #2

(Remarks to the Author)
The manuscript can be accepted.

Reviewer #3

(Remarks to the Author)
The authors have adequately addressed all of my previous comments, and the revised manuscript is now clearer and more complete. The methodology is sound and meets the expected standards for publication in Nature Communications.

Reviewer #4

(Remarks to the Author)
There are several key aspects in mass spectrometry that need to be clarified and further verified to enhance the scientific rigor and impact of the research. My specific comments are as follows.
1. Mass spectra with a certain mass range should be provided to facilitate the reader's understanding of the actual situation of the entire reaction. This allows readers to have a comprehensive understanding of the entire response system. The mass range should be from 80 to 220 Da. Figure R16 should be primary mass spectra for both the electrolysis on and off and a local magnification. Figure R16 is not a tandem mass spectra. Figure R16 also does not give tandem mass spectrometry data.
2. The ionization of APCI results in a significant increase in fragmentation of certain compounds relative to ESI. It is recommended to increase the contrast between APCI and ESI to exclude that some of these ions are generated in APCI.

Version 2:

Reviewer comments:

Reviewer #4

(Remarks to the Author)
The manuscript can be accepted.

**Reviewer #1 (Remarks to the Author):**

In the manuscript titled "Paired Electrolysis enables *para*-C-H Amination of Phenols with Nitroarenes to *p*-Hydroxy Diphenylamines Guided by Multifunctional Electrochemical Mass Spectrometry", the authors Yi, Lei and Wei investigate a paired electrolysis strategy for selective *para*-C–H amination of phenols with nitroarenes, enabling the one-step synthesis of unprotected p-hydroxy diphenylamines without relying on transition-metal catalysts or external reductants.. The study presents a comprehensive analysis of *para*-C-H amination of phenols with nitroarenes to *p*-hydroxy diphenylamines, which is of broad interest to the field of electrochemical organic synthesis. The findings are novel and potentially significant, as they provide new insights into forming the C-N bond. My recommendation is minor revision, and my specific comments are as follows.

Response: We thank the reviewer for the positive evaluation of our work and for recognizing the significance of the paired-electrolysis strategy developed for the *para*-C–H amination of phenols with nitroarenes. We are grateful for the reviewer's acknowledgment that the method offers a transition-metal-free and reductant-free route to unprotected *p*-hydroxy diphenylamines, and that the mechanistic insights provided by multifunctional electrochemical mass spectrometry contribute meaningfully to the broader field of electrochemical organic synthesis.

Comment 1: Phenols are commonly found in natural products. To further demonstrate the practical utility of this methodology, it would be valuable to include one or two examples using structurally complex phenols, which could help illustrate the applicability of this approach in natural product synthesis.

**Response:** Thank you very much for your comments. Phenolic frameworks are indeed widespread in pharmaceutical agents and natural products, and protecting-group manipulations are often unavoidable in their conventional synthetic routes. To further demonstrate the practical utility and structural generality of our method, we applied the paired-electrolysis protocol directly to a commercially available drug precursor, achieving the one-step synthesis

of the hydroxyl-containing ester **R-3**. This intermediate can be readily converted into 4′-hydroxy diclofenac, an established anti-inflammatory and analgesic compound.

By comparison, traditional synthetic routes to this target typically require *four discrete steps*, rely on stoichiometric nitrite and boron tribromide, and involve a copper(I) iodide catalyst, thereby increasing the operational burden and necessitating additional purification. Our method circumvents these limitations, underscoring its efficiency and applicability to structurally complex, pharmaceutically relevant phenols.

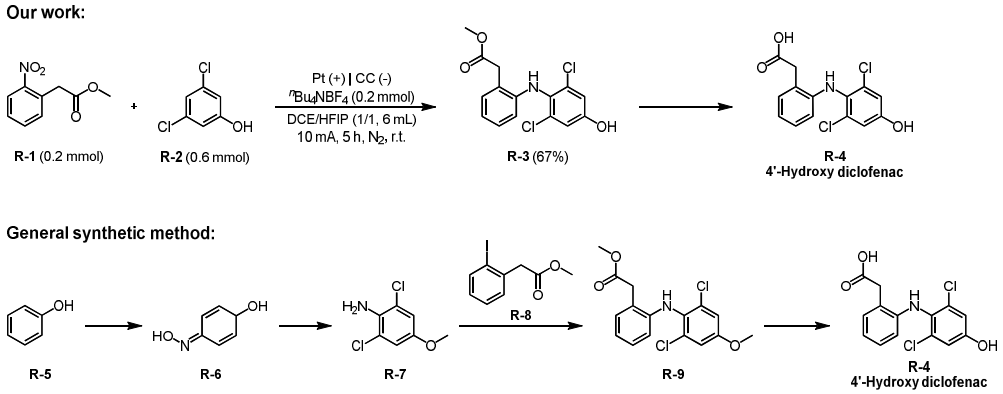


**Figure R1**. Comparison between the synthesis of the drug-related molecule and the corresponding conventional synthetic route.

Comment 2: In the substrate scope studies, various substituted phenols were examined. It would be helpful if the authors could comment on the relative reaction rates observed for phenols bearing electron-donating versus electron-withdrawing groups, along with a brief explanation of the electronic effects influencing reactivity.

**Response:** Thanks very much for your comments. To evaluate the influence of electronic effects on reaction kinetics, we compared the consumption rates of *m*-cresol and *m*-bromophenol under the standard reaction conditions. Within the first forty minutes, *m*-cresol exhibited a significantly faster consumption rate than *m*-bromophenol.

To further probe the electronic origins of this reactivity difference, we performed cyclic voltammetry (CV) measurements on both substrates. The CV data show that *m*-cresol features

an earlier onset potential and a more positive half-wave potential compared with *m*-bromophenol, along with a higher peak current. These results collectively indicate that phenols bearing weak electron-donating substituents are more easily oxidized than those containing weak electron-withdrawing groups.

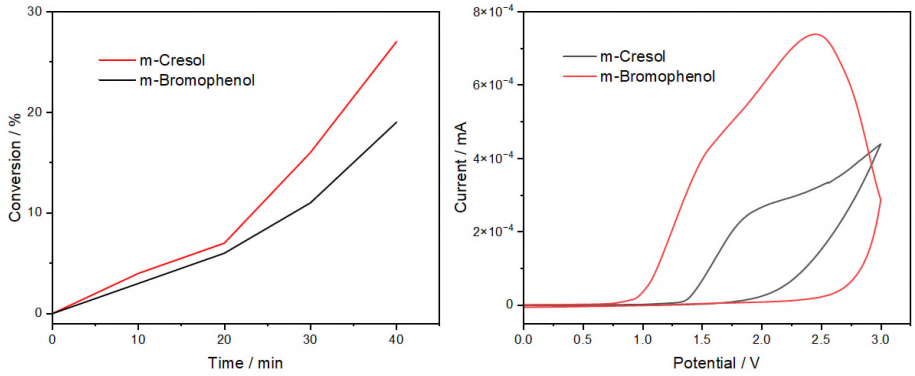


**Figure R2. Conversion profiles and cyclic voltammograms of phenols bearing different substituents.**

Comment 3: The Supporting Information includes attempts with aromatic amine derivatives (page 7). Have the authors also explored the reactivity of Ts-protected anilines in this transformation?

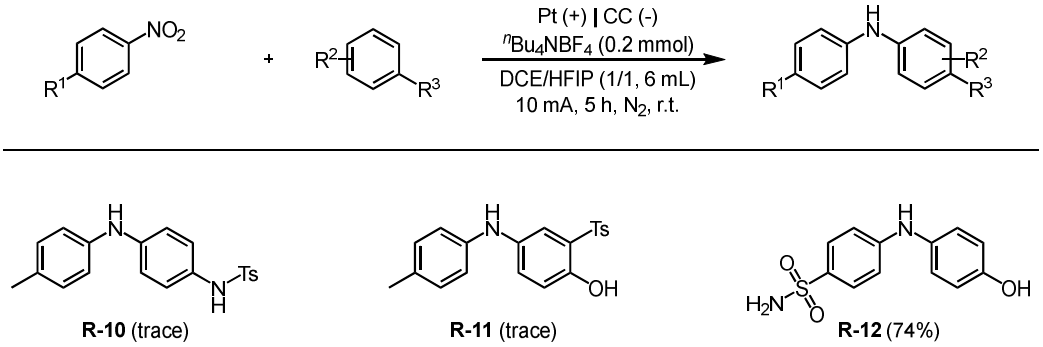


**Figure R3. Substrate evaluation involving Ts-protected anilines and related derivatives.**

**Response:** Thanks very much for your comments. We conducted the suggested experiments, and the results are summarized in Figure R3. When Ts-protected anilines were subjected to the standard reaction conditions, no desired product (**R-10**) was obtained. Likewise, Ts-substituted

phenols failed to deliver the corresponding coupling product (**R-11**). We attribute this lack of reactivity to the strong electron-withdrawing nature of the Ts group, which likely raises the oxidation potential of the substrates beyond the operative window of the system.

In contrast, when a nitroarene—bearing an electron-withdrawing group of comparable strength to Ts—was directly employed as the nitrogen source, the reaction proceeded smoothly to afford the desired product (**R-12**) in high yield. This outcome suggests that while electron-withdrawing substituents are not inherently incompatible, their position and participation in the redox processes critically determine reactivity.

Comment 4: There appears to be an inconsistency between the structural formula of intermediate 6 in Figure 6a and that in Figure 7. The authors should verify and correct this discrepancy.

**Response:** Thanks very much for your comments. We appreciate the reviewer's careful examination of the mechanistic figures. Upon re-evaluation, we confirmed that the structural representation of intermediate 6 was indeed inconsistent between Figure 6a and Figure 7. We have now corrected the structure to ensure full consistency across all mechanistic schemes and figures.

Comment 5: The $^{13}$C NMR spectrum provided for compound **4d** in the Supporting Information seems to be partially cut off. A complete spectrum should be provided.

**Response:** Thanks very much for your comments. We appreciate the reviewer's careful attention to the spectral data. The $^{13}$C NMR spectrum of compound **4d** in the Supporting Information was indeed incomplete due to an export error. We have now provided the full, uncut spectrum in the revised Supporting Information.

Comment 6: In the Supporting Information, Section 10 ("Constant Potential Test") states that

reactions were performed at cathodic potentials of –0.4 V, –0.6 V, and –1.0 V. However, Figure S25 is labeled with “2.6 V”. This likely represents a typographical error and should be corrected to “0.6 V” for consistency.

**Response:** Thanks very much for your comments. The discrepancy in Section 10 of the Supporting Information was indeed caused by a typographical error. We have corrected the mislabeled potential in Figure S25 and revised the corresponding textual description to ensure full consistency throughout the document.

Comment 7: There are several minor spelling and formatting errors that require attention. For example, on page 20 of the Supporting Information, “Arylhydrazine” should be removed and “Phenol” should be changed to “phenol”. A thorough proofreading of the manuscript and SI is recommended to correct similar inaccuracies.

**Response:** Thanks very much for your comments. Thanks very much for your comments. We have carefully corrected the spelling and formatting issues noted by the reviewer.

**Reviewer #2 (Remarks to the Author):**

In this manuscript, the authors present an electrochemical, metal-free one-step strategy for C–N bond formation directly from nitroarenes, enabling the synthesis of unprotected p-hydroxy diphenylamines. This approach is further integrated with the AIEC-MS platform for rapid screening, demonstrating a broad substrate scope. In-depth mechanistic studies using in situ EC-MS uncover key intermediates, including aryl nitrenes and related species. However, I would like to recommend its publication in this journal after the following comments have been addressed.

1. Since the reaction involves the generation of phenoxy radical species, which have the potential to undergo self-dimerization, did the authors observe such byproducts in the reaction mixture, or does this process interfere with the overall reaction?

**Response:** Thanks very much for your comments. We indeed observe trace amounts of phenoxy–phenoxy dimerization products at the end of the reaction. However, because phenol is employed in excess, this side process does not interfere with the formation of the desired product. In practice, these byproducts predominantly appear as deposits on the anode surface. Owing to the good solubility of these species in DCE, such deposition is barely detectable during the early stages of electrolysis. Monitoring the reaction over time indicates that the formation of these byproducts only leads to a slight increase in cell voltage, without affecting the overall efficiency of the transformation.

2. Why do nitroarenes bearing electron-donating substituents lead to lower product yields?

**Response:** Thanks very much for your comments. We initially hypothesized that the diminished yields observed for nitroarenes bearing electron-donating substituents might originate from differences in their electronic properties. To examine this possibility, we performed cyclic voltammetry measurements to compare their reduction potentials. Surprisingly, the onset potentials of *p*-nitrotoluene and *p*-nitroanisole showed no significant difference, suggesting that redox thermodynamics alone do not account for the observed reactivity trend.

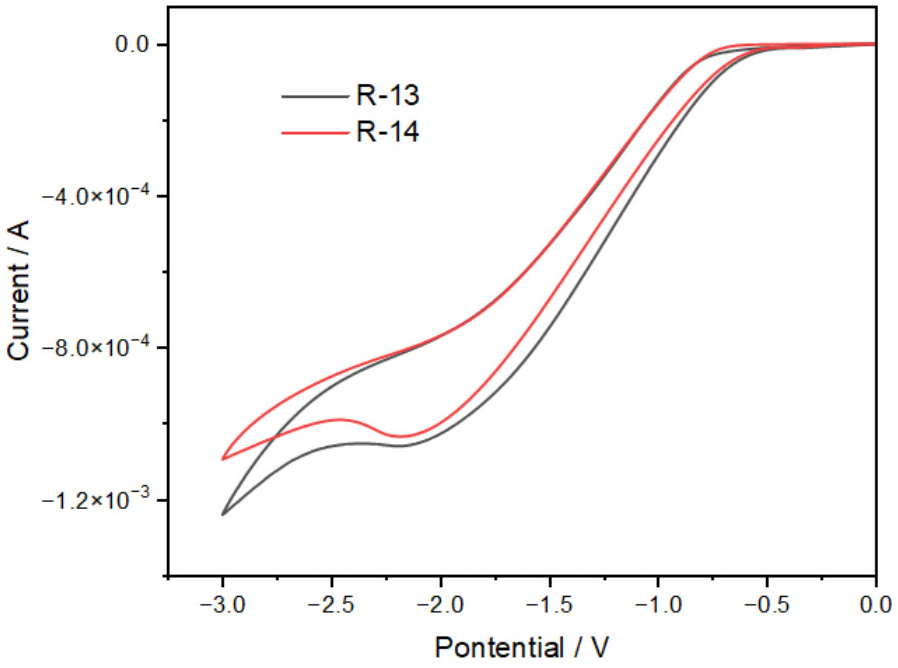


**Figure R4. Cyclic voltammetry experiments of nitrobenzenes bearing different substituents**

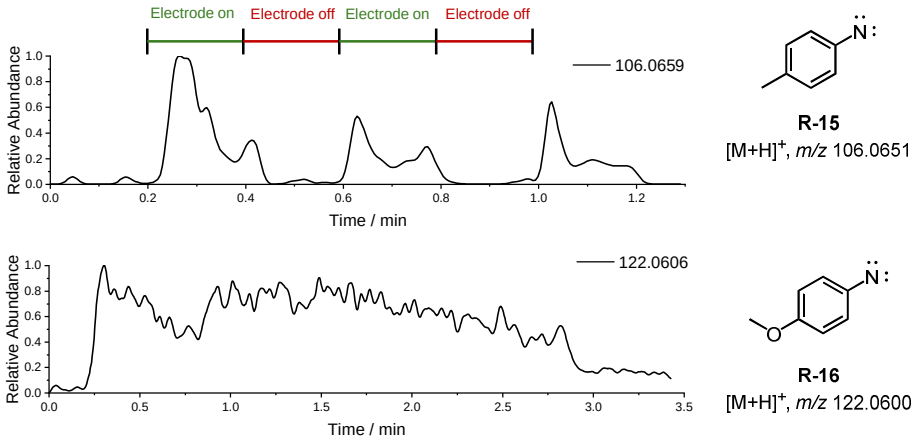


**Figure R5. Online electrochemical mass-spectrometric switching experiments for nitrobenzenes with different substituents**

To gain deeper mechanistic insight, we conducted online electrochemical mass-spectrometric switching experiments. For p-nitrotoluene, the corresponding reduction intermediate R-17 (*m/z* 106.0659) displayed a clear current-dependent fluctuation in ion intensity, indicating a short-lived species. In contrast, the reduction intermediate derived from *p*-nitroanisole, R-18 (*m/z* 122.0606), exhibited no such fluctuation, consistent with a markedly longer lifetime.

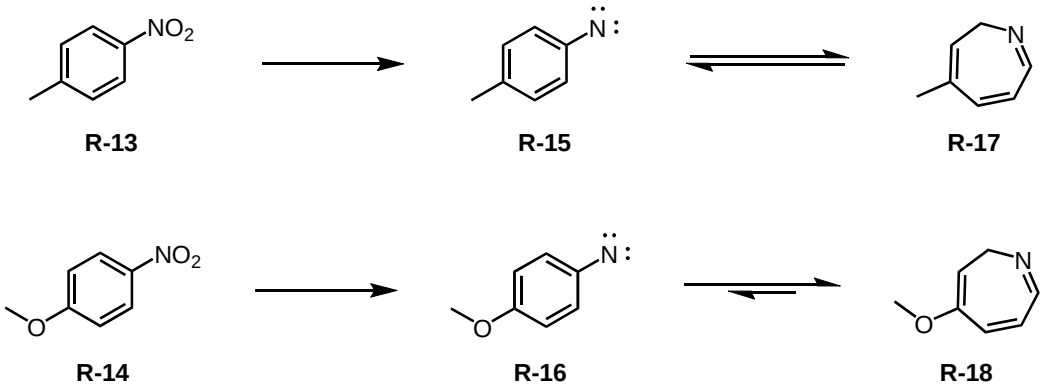


**Figure R6. Conversion pathways of the Nef reaction–related intermediates**

Our prior studies revealed that nitroso intermediates can undergo spontaneous ring expansion, which prolongs their lifetime while retaining reactivity. However, the *p*-nitroanisole–derived intermediate exhibits a significantly longer lifetime than other nitroarene intermediates. We propose that, due to its stronger electron-donating substituent, this species preferentially forms a nitrogen-containing seven-membered ring rather than interconverting between reactive intermediates. This structural divergence leads to loss of productive reactivity and, consequently, to the lower yield observed for reactions involving *p*-nitroanisole.

3. What factors govern the selective reduction of only one nitro group while leaving the second nitro group intact, as observed in products 4ab–4ad?

**Response:** Thanks very much for your comments. We believe that two factors govern the selective reduction of only one nitro group in products **4ab–4ad.** First, the selectivity is strongly time-dependent: in our standard protocol, the reaction is quenched before complete consumption of the dinitro substrate. When the reaction time is intentionally extended in control experiments, high-resolution mass spectrometry clearly detects the formation of the doubly aminated product.

Second, we propose that the diamination product possesses a significantly lower oxidation potential than the corresponding monoamination product. As a result, any small amount of diamine generated under the standard conditions is preferentially re-oxidized at the anode and

thus removed from the reaction mixture. This electrochemical self-regulation accounts for the exclusive formation of monoaminated products under the optimized conditions.

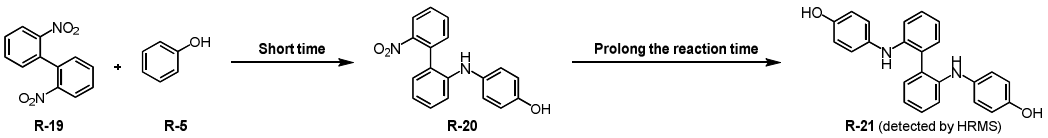


**Figure R7. Formation of the diamination product upon extending the reaction time with dinitro substrates**

4. If the para position of the phenol ring is substituted with an alkyl group, does the reaction still proceed? Furthermore, what would be the expected outcome if both the para and ortho positions are sterically blocked?

**Response:** Thanks very much for your comments. We investigated both scenarios experimentally. When *p*-cresol (**R-22**) was used as the substrate, the reaction mixture became considerably more complex. Online electrochemical mass spectrometry revealed the formation of benzylamine (**R-23**) as well as an ortho-aminated product (**R-24**), indicating that blocking the para position redirects the reaction toward alternative pathways.

Furthermore, when 2,4,6-trimethylphenol (**R-25**) was subjected to the standard conditions, we observed virtually no conversion of the phenol substrate. Instead, most of the *p*-nitrotoluene was reduced to aniline (**R-26**), accompanied by the formation of a small amount of azobenzene (**R-27**). These results suggest that when both the para and ortho positions are sterically hindered, C–N bond formation is effectively suppressed, and the reaction predominantly follows reductive pathways of the nitroarene.

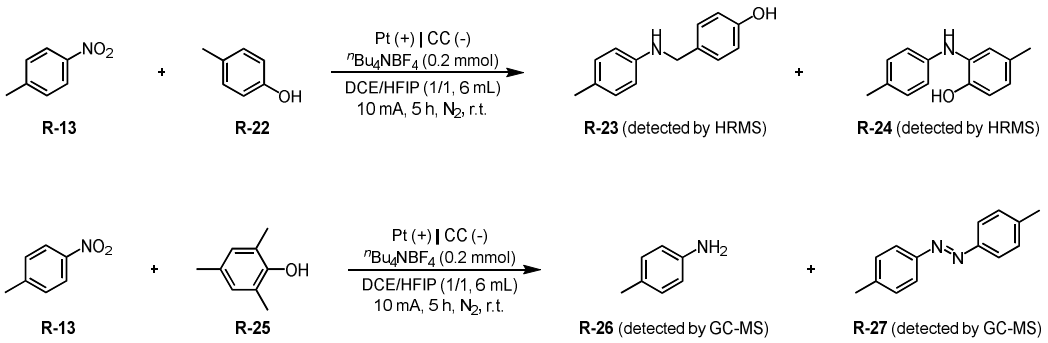


**Figure R8. Reactions involving phenols with different substitution patterns**

5. For completeness, the authors might consider citing "Org. Lett. 2022, 24, 12, 2310–2314", where a related approach for the oxidation of phenol has been demonstrated.

**Response:** Thanks very much for your comments. We agree that the referenced work is highly relevant to the background of our study. We have now included "*Org. Lett.* 2022, 24, 2310–2314" in the revised manuscript to provide a more complete contextual framework.

**Reviewer #3 (Remarks to the Author):**

This manuscript describes a paired electrolysis strategy for *para*-C–H amination of phenols with nitroarenes, guided by multifunctional electrochemical mass spectrometry (EC-MS). The approach allows for one-step synthesis of *p*-hydroxy diphenylamines under mild, metal-free conditions, and provides mechanistic insight via in situ monitoring of reactive intermediates. While the work presents an innovative combination of electrochemistry and EC-MS analysis, several aspects of experimental design, mechanistic interpretation, and substrate scope require substantial clarification before it is suitable for publication. Therefore, I recommend major revision.

**Response:** Thanks very much for your comments. We sincerely appreciate the reviewer's careful evaluation of our work. In the revised manuscript, we have addressed all concerns regarding experimental design, mechanistic interpretation, and substrate scope. Specifically, we have expanded the mechanistic studies, provided additional control experiments, clarified key aspects of the electrochemical setup, and enriched the substrate scope with more structurally diverse examples. We believe these revisions significantly strengthen the robustness and clarity of our conclusions, and we hope the improved version will meet the standards required for publication.

Minor Comments

• Line 245: The text refers to "Scheme 3c," but no such scheme exists. This should be corrected.

**Response:** Thanks very much for your comments. We have revised accordingly.

• Line 265: Figure 7b is said to show compound 4i, but it appears to correspond to **5i**, which creates confusion.

**Response:** Thanks very much for your comments. We have revised accordingly.

• Figure 3: The content resembles a table of compounds rather than a figure. It should be reformatted or consistently described.

**Response:** Thanks very much for your comments. We have revised accordingly.

◦

• In Fig. 5a, could the observed positive shift in peak potential in the presence of HFIP be attributed to proton involvement in the electrochemical reduction of nitrobenzene?

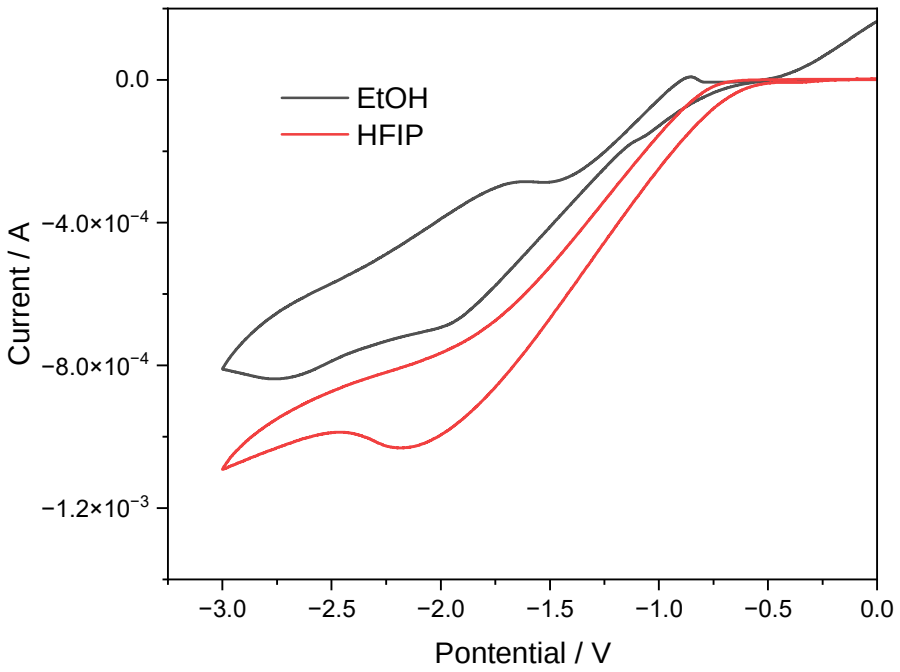


**Figure R9. CV experiments of the reaction under different solvent conditions**

**Response:** Thanks very much for your comments. To clarify the origin of the positive shift in peak potential observed in the presence of HFIP, we conducted comparative CV experiments in which HFIP was replaced by ethanol (EtOH). As shown in Figure R9, although the absolute currents differ slightly between the two solvent systems, the key electrochemical features remain essentially unchanged: both electrolytes display nearly identical onset potentials (≈ –0.5 V) and reach the first cathodic peak at approximately –2.0 V. These results indicate that, for the cathodic reduction of nitrobenzene, the acidity or proton-donating ability of HFIP can indeed be substituted by other protic solvents without significantly altering the fundamental

reduction behavior.

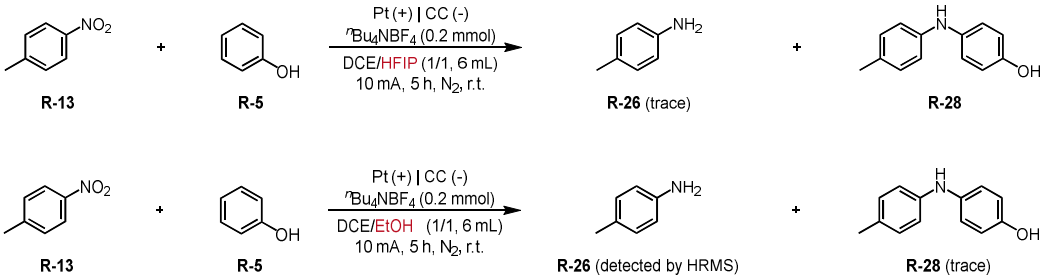


**Figure R10. Product distributions obtained after the reaction under different solvent conditions**

However, a clear divergence emerges during the reverse scan starting from –3.0 V. Under our standard HFIP-containing conditions, only trace amounts of *p*-toluidine are detected after electrolysis. By contrast, when HFIP is replaced with EtOH, the target amination product is not observed at all; instead, *p*-nitrotoluene is almost completely reduced to p-toluidine (Figure R10). These observations demonstrate that although HFIP and EtOH provide similar CV profiles in terms of reduction potentials, they exert markedly different influences on the overall reaction pathway and product distribution.

Therefore, the positive shift in peak potential cannot be attributed to proton involvement in the reduction process. Rather, it likely originates from solvent–solute interactions or co-solvent effects unique to HFIP, which play a critical role in steering the downstream reactivity.

• Figure 6a: Intermediates should be labeled consistently with the text. For example, the compound currently labeled "**1**" should be labeled as **1i-1** to avoid confusion with starting materials.

**Response:** Thanks very much for your comments. We have revised the labeling of intermediates in Figure 6a to ensure consistency with the text; for example, the compound previously labeled as "**1**" is now correctly labeled as **1i-1** to avoid confusion with the starting materials.

• Line 232: The manuscript states that **1i-1** is p-nitrotoluene, but based on mass data and mechanistic context, this should be nitrosobenzene. Similarly, **1i-2** should be N-(*p*-tolyl)hydroxylamine instead of p-hydroxytoluene.

**Response:** Thanks very much for your comments. We have corrected the errors in the manuscript: **1i-1** is now properly identified as nitrosobenzene, and **1i-2** has been corrected to N-(p-tolyl)hydroxylamine.

• Figure S25 (Supporting Information): X-axis potentials should be reported as negative.

**Response:** Thanks very much for your comments. We have revised accordingly.

• Figure 8c: The MS of 7e1 and 7f appear to be incorrect.

**Response:** Thanks very much for your comments. We have revised accordingly.

• Several sentences are vague or incomplete. For example, Lines 210–212 ("Comparative analysis of nitrobenzene's reduction potential…") should be rewritten more clearly with quantitative electrochemical data.

**Response:** Thanks very much for your comments. We have revised accordingly.

Major Comments

• The complete reduction of nitrobenzene is usually a six-electron process. Could the authors monitor the reaction progress using cyclic voltammetry and, ideally, perform constant-potential electrolysis to confirm the paired electrolysis mechanism?

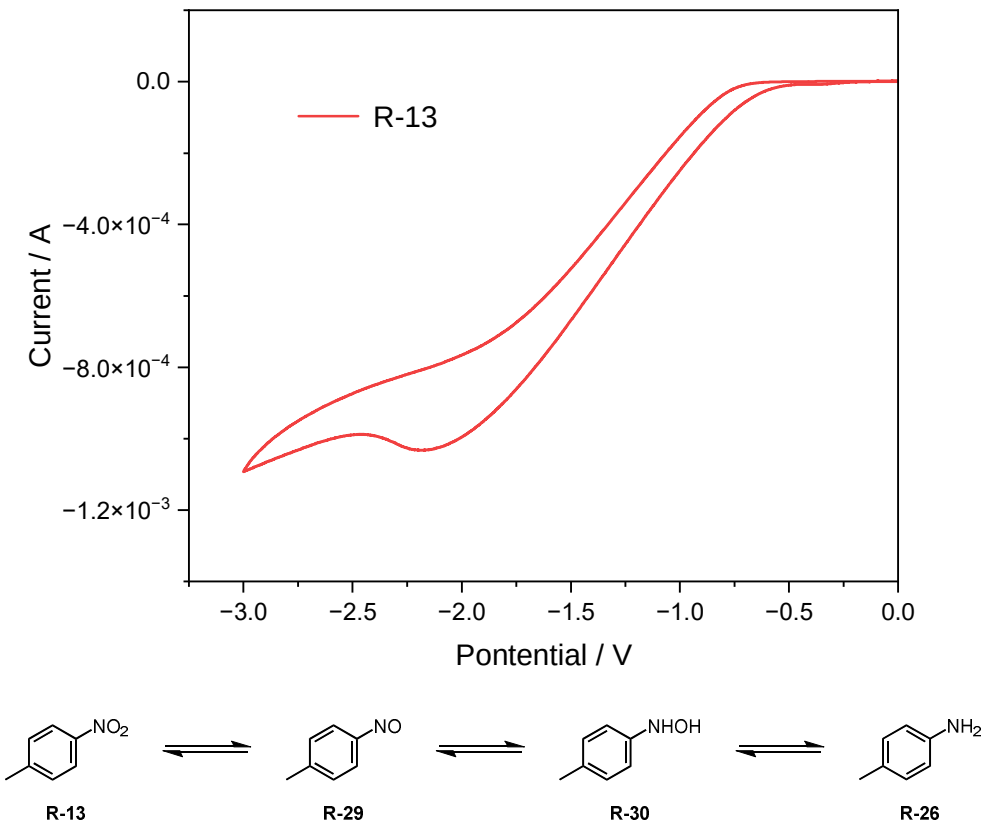


**Figure R11. Nitrobenzene CV reduction curves under reaction conditions and possible explanations**

**Response:** Thanks very much for your comments. The electrochemical reduction of nitrobenzene has been extensively studied. Although the overall process involves a six-electron transfer through two intermediates—nitrosobenzene and hydroxylamine—these steps are largely reversible. As a result, cyclic voltammetry (CV) monitoring typically shows a broad peak, analogous to catalytic current behavior.

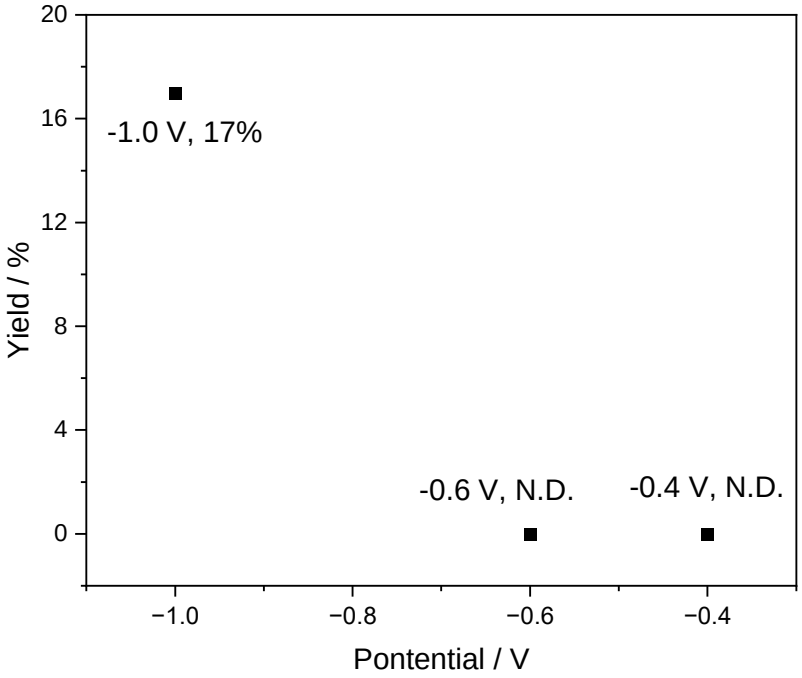


**Figure R12. Results of constant cathodic potential electrolysis**

We also performed constant-potential electrolysis experiments, as described in the Supporting Information. At a cathodic potential of –0.4 V, no significant reduction of nitrobenzene or formation of the target product was observed, although phenol oxidation occurred, leading to detectable phenol dimer formation. At –1.0 V, nitrobenzene reduction commenced, and the target product **R-23** was obtained in 17% yield. These results confirm that the reaction proceeds only when phenol oxidation and nitrobenzene reduction occur concurrently, providing strong evidence that the transformation follows a paired electrolysis mechanism.

• Supporting Information: Electrode polarity switching frequency is reported inconsistently (1, 2, 5 Hz vs 0, 2, 5 Hz in Table X). This should be clarified. Also, indicate if the reaction was performed in a two-compartment cell under constant current without polarity switching.

**Response:** Thanks very much for your comments. The correct electrode polarity switching frequencies are 1, 2, and 5 Hz; the 0 Hz reported in the text was a typographical error. Although all experiments reported in this study were performed under alternating polarity conditions, we

also conducted constant-current electrolysis in a two-compartment cell. In these experiments, the target product was successfully detected at the end of the reaction, confirming the viability of the reaction under constant-current conditions.

• Authors suggest a nitrene intermediate (based on mass spectrometry), but there is no direct evidence of its participation in C–H amination. Observing traces in MS does not confirm it as a key intermediate; the reaction may proceed via classical nitroso/hydroxylamine pathways.

Response: Thanks very much for your comments. Nitrosobenzene is a well-established intermediate in the electroreduction of nitrobenzene, and our experiments similarly confirm that it is formed during the reaction. However, existing deuterium-labeled online electrochemical mass spectrometry (EC-MS) experiments do not support the direct participation of nitrosobenzene in the C–H amination coupling. In our proposed mechanism, nitrobenzene is first reduced to nitrosobenzene, which must undergo further reduction to generate a nitrene intermediate before it can participate in the coupling reaction. This proposal is based on two key observations: first, nitrosobenzene can be further reduced to form the nitrene intermediate, and second, the formation of the target product requires this further reduction of nitrosobenzene. To verify this, we performed the following control experiments (Fig. R13):

A) Replacing nitrobenzene with authentic nitrosobenzene and monitoring the reaction by online EC-MS revealed the same series of intermediates, including the nitrene, confirming that nitrosobenzene can undergo further reduction to generate the nitrene species.

B) Cyclic voltammetry determined that the nitroso → nitrene reduction occurs at –0.51 V vs Ag/AgCl. Constant-potential electrolysis at –0.40 V or –0.60 V for 4 h yielded no p-hydroxy diphenylamine, while holding the cathode at –1.0 V for 4 h afforded the amination product (17%), indicating that further reduction of nitrosobenzene is necessary for product formation.

C) Taken together with our previous online EC-MS results, these findings confirm that nitrosobenzene cannot directly participate in the coupling reaction. In the reaction system, nitrobenzene is first reduced to nitrosobenzene, which is subsequently reduced to a nitrene intermediate that undergoes C–H amination to generate the target p-hydroxy diphenylamine.

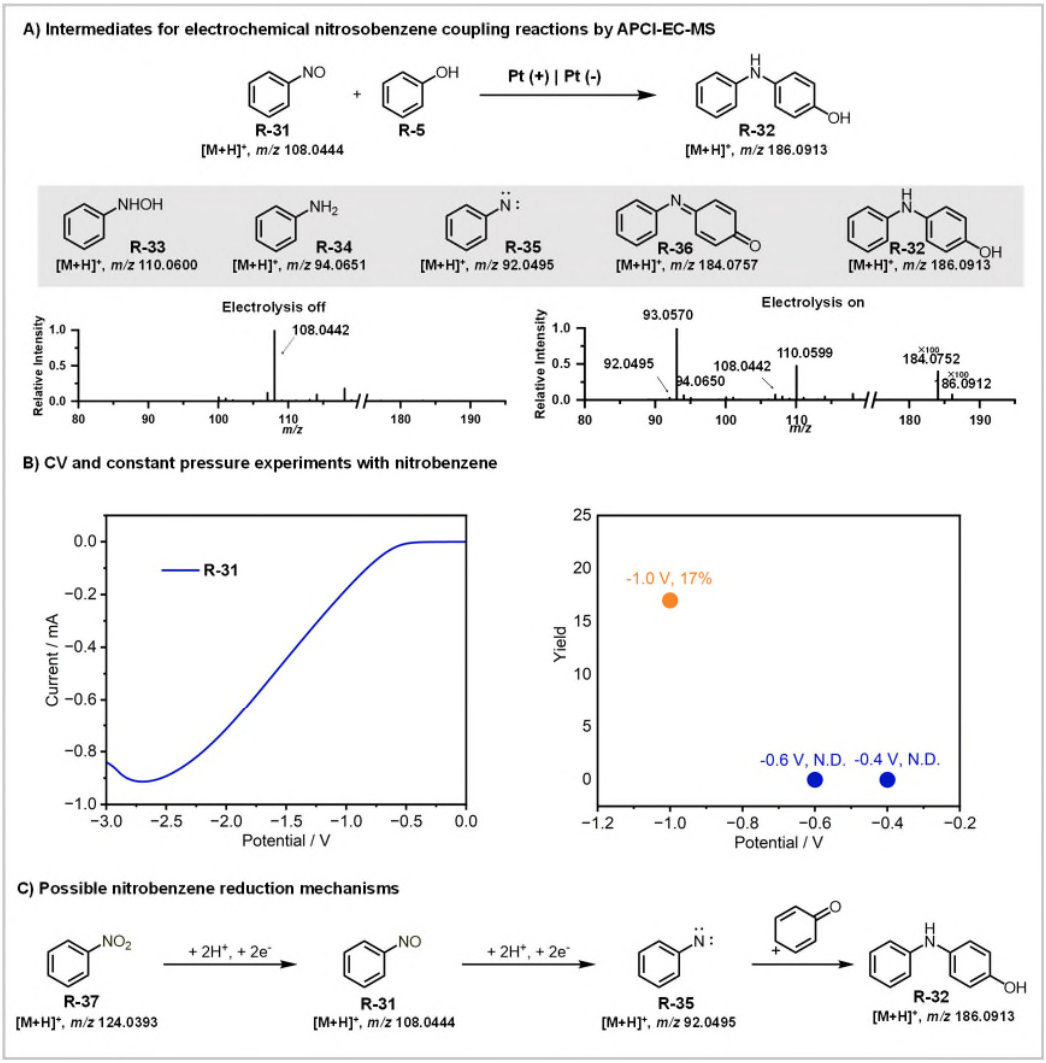


**Figure R13. A**) Intermediates for electrochemical nitrosobenzene coupling reactions by APCI-EC-MS; **B**) LSV and constant pressure experiments with nitrobenzene; **C**) Possible nitrobenzene reduction and coupling mechanism

• The modified electrolysis conditions used for mass spectrometry are very different from bulk electrolysis conditions. It is unclear how the mechanism can be reliably studied under such differing conditions.

Response： Thanks for your comments. We acknowledge your concern regarding the modification of electrolysis conditions for compatibility with the mass spectrometry (MS) system and its potential impact on the reaction mechanism. To address this, we undertook a

comprehensive investigation to ensure that the underlying mechanism remains consistent despite the altered conditions.

1. **Scale-Up Experiments:** We conducted milligram-scale reactions using the modified conditions. Although there was a slight decrease in yield, we successfully obtained a substantial amount of the desired product, indicating that the core reaction remains effective under these adjusted parameters.
2. **Online Mass Spectrometry Detection:** Target products were reliably detected using the online MS setup. This demonstrates that the modifications necessary for MS compatibility do not hinder the formation of the intended products.

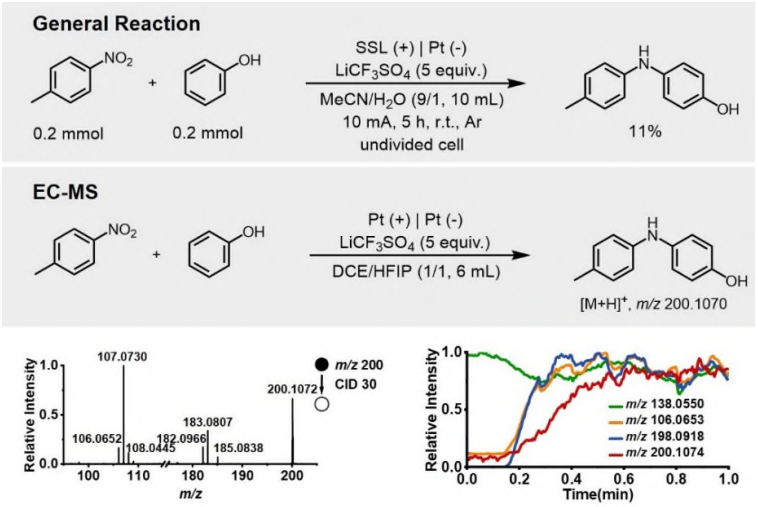


**Figure R14**. General and APCI-MS conditioned control experiments.

Based on these findings, we conclude that the changes made to accommodate the MS system primarily influence the reaction yield and efficiency. Importantly, they do not alter the fundamental reaction pathway or mechanism. Therefore, we are confident that the mechanistic insights derived under the modified conditions are representative of those under the original reaction conditions.

• Many products could potentially be accessed more easily via anilines, so the synthetic advantage is unclear.

Thank you for your constructive comments. We have carefully addressed the mechanistic concerns and clarified the presentation of our work. Below, we outline the key advantages of our approach, which we believe offer substantial value to synthetic chemistry:

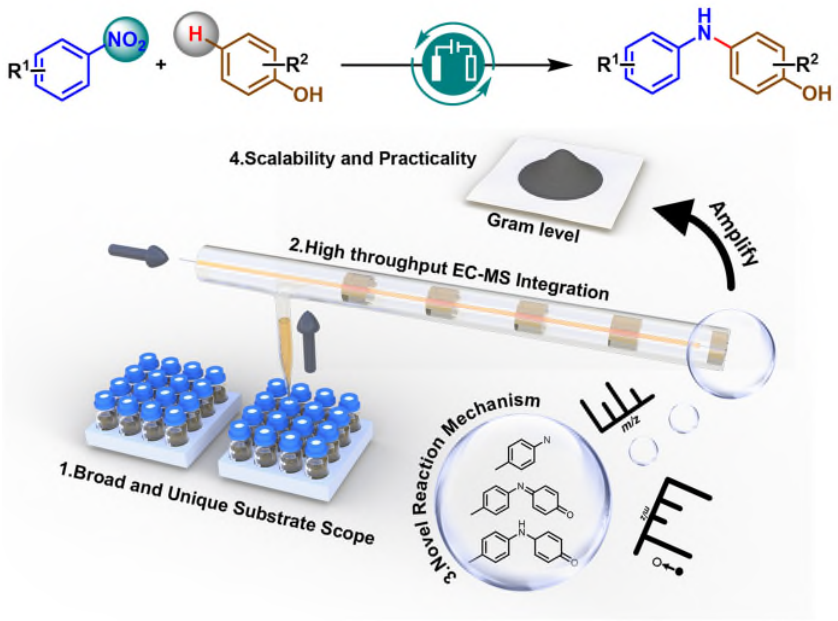


**Figure R15**. Mass Spectrometry Advantages and Expansion Prospects.

1) **Substrate Diversity**

Our reaction system accommodates a wide range of functional groups, including phenol, ethylbenzene, and benzyl ether. It also enables catalyst-free reduction amination of alkyl nitro compounds, which is rarely achieved under mild conditions.

2) **Scalability and Practical Application**

We have demonstrated gram-scale reactivity, highlighting the robustness and practicality of our method. The preparation of p-hydroxydiphenylamine—an important intermediate and pharmaceutical precursor—illustrates its efficiency. Compared with conventional protocols, our approach lowers raw material costs and avoids halogen waste.

3) **Advanced Mass Spectrometry Integration**

Automated mass spectrometry accelerates substrate screening while providing precise information on reaction intermediates. This strategy reduces experimental workload and offers clearer mechanistic insights than standard analytical methods.

4) **Real-time Mechanistic Clarifications**

Our study addresses longstanding questions in ortho amination of nitrobenzene and phenol. By optimizing reaction conditions, we expanded the range of compatible substrates without resorting to harsh protocols. This mechanistic understanding lays the groundwork for developing new reactions and refining established methodologies.

• It is recommended to replicate NMR spectra of **4ab** and **4ac** to ensure reproducibility and accuracy.

**Response:** Thanks very much for your comments. We have revised accordingly.

**Reviewer #4 (Remarks to the Author):**

The manuscript by Prof Lei and colleagues have described Paired Electrolysis enables para-C-H Amination of Phenols with Nitroarenes to *p*-Hydroxy Diphenylamines Guided by Multifunctional Electrochemical Mass Spectrometry. There are several key aspects in mass spectrometry that need to be clarified and further verified to enhance the scientific rigor and impact of the research. I recommend accepting the paper after revisions.

1. Mass spectra with a certain mass range should be provided to facilitate the reader's understanding of the actual situation of the entire reaction. The mass spectra should show isotopic peaks in Figure S4. By observing the intensity and position of the isotopic peaks, more information about the elemental composition of the sample can be observed.

**Response**: Thanks very much for your comments. We have now provided full-scan mass spectra covering the relevant mass ranges in the Supporting Information to offer a comprehensive view of the reaction progress. The updated spectra in Figure S4 clearly display the isotopic peak patterns, allowing readers to verify the elemental composition of the observed intermediates and products. By examining both the intensity and positions of these isotopic peaks, one can gain additional insight into the molecular identities and confirm the assignments made in the work.

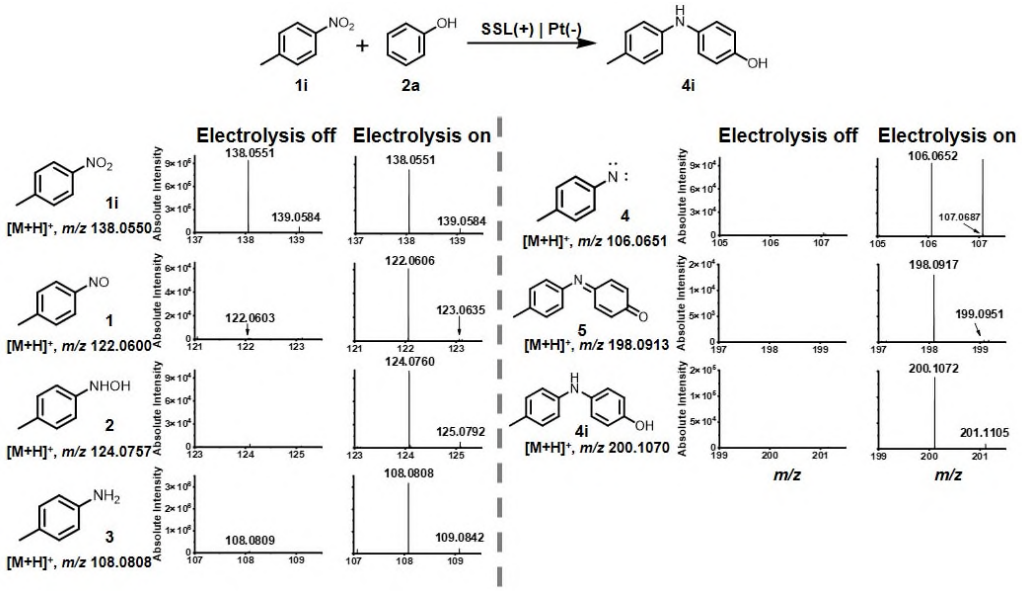

**Figure R16. Detected tandem mass spectrometry (MS/MS) data**

2. Discussion of fragmentation processes of tandem mass spectra in Figure 7, Figure S5 and Figure S6should be added in Supporting Information.

**Response**: Thanks very much for your comments. In this study, we employed high-resolution tandem mass spectrometry (MS/MS) to characterize the structures of both products and intermediates.

First, we analyzed and verified the structures of product 4i and intermediate 1i-5 in Figure 7a:

1. **Identification of product 4i:** Product 4i undergoes characteristic C–N bond cleavage on the aromatic ring, producing fragment ions C7H7N (m/z 105.0578), C7H8N (106.0657), and C7H9N (107.0735), as well as neutral losses corresponding to methyl (C12H11ON, 185.0841), hydroxyl (C13H12N, 182.0970), and amino (C13H11O, 183.0807) substituents. These fragment ions are fully consistent with the MS/MS data in Figure 7, confirming the product structure.
2. **Identification of intermediate 1i-5:** The intermediate 1i-5 exhibits similar C–N bond cleavage on the aromatic ring, indicating the presence of an aniline-type structure. The key differences from 4i are neutral losses at m/z 15.0235, 27.9949, 43.0184, and 55.0058, corresponding to CH3, CO, C2H3O, and C2HON, respectively. These losses are consistent with C–C bond cleavage in a quinone-type structure, suggesting that 1i-5 contains a quinone moiety. Based on the MS/MS spectrum in Figure 7b (left), the detected signal at m/z 198.0918 is attributed to intermediate 1i-5.

To further validate the structures of intermediates and products, deuterated reagents were employed:

1. **Validation of 1i-5 using D3-1i:** As shown in Figure 7b (right), the deuterated intermediate D3-1i-5 produced fragment ions C7H4D3N (108.0721), C7H5D3N (109.0835), and C7H6D3N (110.0916) upon C–N bond cleavage, consistent with the proposed 1i-5 structure.
2. **Validation of 1i-6 and product 4i using D3-1i:** Similar results were observed for D3-1i-derived intermediate D3-1i-6 and product D3-4i, showing the same aniline-type

fragment ions, confirming the structures of 1i-6 and 4i (Figure S6).

3. **Validation of 1i-6 using D3-2a:** The reaction of D3-2a produced intermediate D2-6, which showed fragment ions C7H8N (106.0657), C7H9N (107.0735), and C7H10N (108.0808) corresponding to the aniline core, along with deuterated methyl (C12H9D2ON, 187.0964), hydroxyl (C13H10D2N, 184.1093), and amino (C13H9D2O, 185.0933) substituents. These results further support the structure of intermediate 1i-6.

Finally, as shown in Figure S5, we characterized intermediates and products formed during the electrochemical reduction of nitrobenzene:

1. **p-Tolylhydroxylamine:** Fragment ions at m/z 109.0522, 107.0490, and 106.0651 correspond to neutral losses of CH3 (15.0235), NO (29.9980), and H2O (18.0106), consistent with the proposed structure (Figure S5a).
2. **Nitrosotoluene:** Fragmentation produced m/z 92.0618 via neutral loss of NO (29.9980), consistent with the expected structure (Figure S5b).
3. **Aniline:** Fragment ion at m/z 93.0572 corresponds to neutral loss of CH3 (15.0235), consistent with the structure (Figure S5c).
4. **Arylnitrenium rearrangement product:** Detected m/z 106.0651 corresponds to a methyl-substituted N-hetero seven-membered ring formed via rearrangement, producing a fragment at m/z 79.0541 via HCN (27.0109) loss, consistent with the proposed N-hetero seven-membered ring structure (Figure S5c, reference: 10.1002/anie.202219302).

In summary, these MS/MS analyses, complemented by deuterium labeling, provide strong evidence supporting the structural assignments of both intermediates and products in our study.

3. Specific experimental operations for offline in Figure 7b should be added in Supporting Information.

**Response**: Thanks very much for your comments. The detection of product 4i was performed offline using high-resolution mass spectrometry (HRMS). Specifically, a solution of acetonitrile:water = 9:1 (v:v) containing 0.2 mM 4i was loaded into the EC-MS system with

electrolysis turned off. These experimental details have been added to Section 2.3 of the Supporting Information.

4. Central to this approach is a multifunctional automated injection electrochemical mass spectrometry (AIEC-MS) platform. Its ionization mode is described as APCI. But from the perspective of Device Setup, what is the difference from ESI? Theoretically, ESI is more reflective of the reaction species than APCI.

**Response**: Thanks very much for your comments. Compared to electrosp ray ionization (ESI), atmospheric pressure chemical ionization (APCI) offers two key advantages for constructing an in situ electrochemical cell in the AIEC-MS platform. First, the APCI process is physically separated from the electrochemical cell, minimizing interference between the electrochemical reaction and the ionization process. Second, APCI is more suitable for detecting and analyzing less polar species, including the nitro and nitroso compounds investigated in this work.

Reviewer #1 (Remarks to the Author):

The author has addressed all my concerns. I hereby approve the publication of this article in Nature Communications.

**Response:** We are grateful for your positive feedback on our work. Your constructive suggestions have significantly contributed to the improvement of our manuscript.

Reviewer #2 (Remarks to the Author):

The manuscript can be accepted.

**Response:** We are grateful for your positive feedback on our work. Your constructive suggestions have significantly contributed to the improvement of our manuscript.

Reviewer #3 (Remarks to the Author):

The authors have adequately addressed all of my previous comments, and the revised manuscript is now clearer and more complete. The methodology is sound and meets the expected standards for publication in Nature Communications.

**Response:** We are grateful for your positive feedback on our work. Your constructive suggestions have significantly contributed to the improvement of our manuscript.

Reviewer #4 (Remarks to the Author):

There are several key aspects in mass spectrometry that need to be clarified and further verified to enhance the scientific rigor and impact of the research. My specific comments are as follows.

**Response:** We would like to thank you for your valuable suggestions. Your prior recommendations have provided significant guidance for the mass spectrometry part of our study. We fully endorse your commitment to the rigor of scientific research.

1. Mass spectra with a certain mass range should be provided to facilitate the reader's understanding of the actual situation of the entire reaction. This allows readers to have a comprehensive understanding of the entire response system. The mass range should be from 80 to 220 Da.

**Response:** Thank you for your question. We indeed did not directly provide the mass spectrometry data in the range of 80–100 Da and 215–220 Da in the manuscript and supporting information. This is because we found no reaction-related substances in these ranges during the initial data processing. Phenol ($[M+H]^+$, *m/z* 95.0491), one of the starting materials, cannot be detected in the positive ion mode of APCI due to its electron-rich nature. To improve the completeness of our data, we hereby provide a comparison of mass spectra before and after the reaction in the range of 80–220 Da.

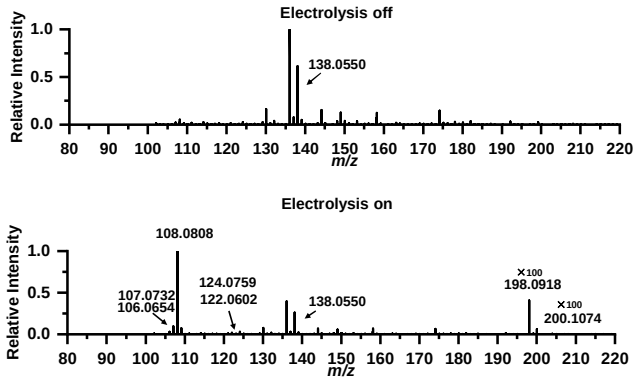


**Figure R1**. HR-MS before and after electrolysis

Figure **R16** should be primary mass spectra for both the electrolysis on and off and a local magnification. Figure **R16** is not a tandem mass spectra. Figure R16 also does not give tandem mass spectrometry data.

**Response:** Thank you for your question. As you correctly pointed out, there is an error in the legend of Figure R16. We have now revised it to (HR-MS before and after eletrolysis of reactant **1i**, *p*-nitrotoluene **1**, *p*-hydroxytoluene **2**, *p*-methylaniline **3**, N-oxide **4**, intermediate **5** and product **4i**).

2. The ionization of APCI results in a significant increase in fragmentation of certain compounds relative to ESI. It is recommended to increase the contrast between APCI and ESI to exclude that some of these ions are generated in APCI.

**Response:** Thank you for your question. We have supplemented the relevant data from the online mass spectrometry experiments using ESI, as shown in Figure **R2**. It is worth noting that no ion signals related to *p*-nitrotoluene and *p*-methylnitrosobenzene were detected by ESI either before or after the reaction. This indicates that such devices cannot effectively detect nitrobenzene and nitrosobenzene derivatives. In contrast, in the APCI data we provided, distinct ion signals were observed for both *p*-nitrotoluene in the reaction solution before electrolysis and *p*-methylnitrosobenzene formed after the reaction. Furthermore, for the relatively easily detectable amine intermediates and products, there was only a difference in ion intensity between ESI and APCI. These results confirm that the intermediates we detected are generated from the electrochemical reaction, rather than from the APCI process.

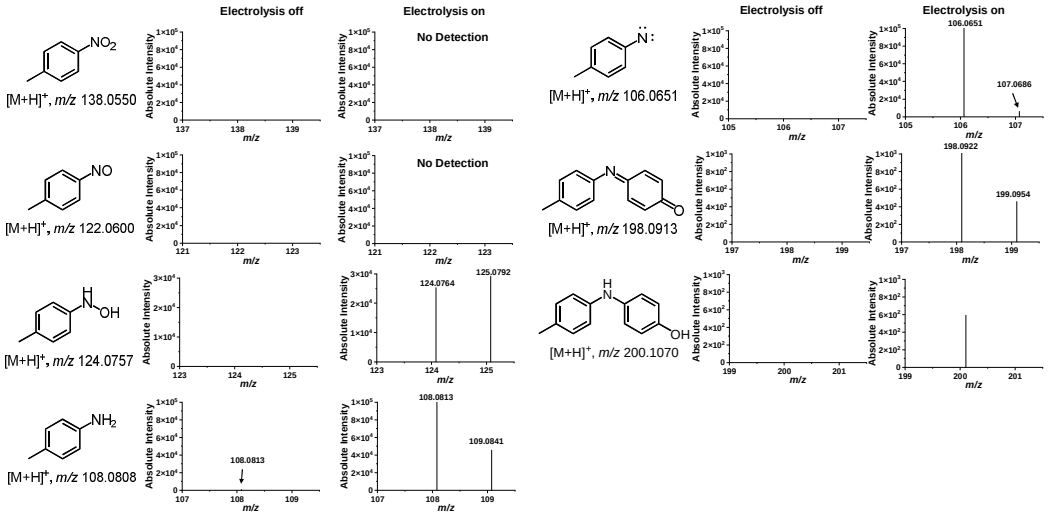


**Figure R2**. ESI-HR-MS spectra and data of the reaction mixture before and after electrolysis