nature portfolio

Peer Review File

Electrosynthesis of Arylglycines from Carbon Dioxide, Nitrite, and Aldehydes

Corresponding Author: Professor Hailiang Wang

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

Attachments originally included by the reviewers as part of their assessment can be found at the end of this file.

Version 0:

Reviewer comments:

Reviewer #1

(Comments for the Author)
In this manuscript, Wang and co-workers presented an electrochemical route for synthesizing arylglycines using low-cost feedstocks including CO2, nitrite, and aldehydes. The integration of nitrite reduction with oxime carboxylation represents a creative approach to high-value unnatural amino acids. The manuscript contains some interesting results and conclusions. I think it can be considered for publication in Nature Synthesis after revision..
1. The authors should provide specific reaction conditions for the traditional Strecker reaction and Bucherer-Bergs reaction (e.g., precise temperature, pressure, and typical reaction times).
2. The manuscript lacks essential details regarding the initial steps of the cascade reactions. The authors should provide characterizations of hydroxylamine and oximes.
3. Formulas of how the conversion and FE for these intermediates were calculated are missed.
4. In Figure 2, the authors describe the synthesis of free NH2OH followed by condensation to form oximes. This pathway has been recently presented in literature. I suggest the authors cite and discuss more related studies here.
5. Regarding the formation of BnNH2 mentioned on Page 4, the origin of the protons is unclear. What is the specific hydrogen source for this reduction?
6. Is it possible that the product exists as a zinc-coordinated complex rather than a free amine in the reaction mixture?
7. Figure 3a depicts what appears to be an open-vessel single cell. However, even in the absence of added water, trace amount of water from the atmosphere can significantly impact the carboxylation efficiency.
8. Metallic lithium was used in the control experiments, and the air atmosphere exerted a further influence. The author should comment on this point.
9. In addition, I strongly recommend the authors provide more details on the cell. Was the experiment performed under an inert atmosphere (e.g., Ar)?
10. If inert atmosphere is absence, the authors should discuss the influence of atmosphere on the reaction outcomes.
11. While I recognize that cell voltage is critical for dual-electrode systems, the primary novelty of this work lies in the cathodic reduction. The use of a two-electrode system led to the lack of individual electrode potentials. I suggest the authors perform additional experiments using a reference electrode to provide more data on carboxylation.
12. In Figure 5d, could the authors provide further experimental evidence regarding the presence of carbanions and radical species?
13. In Figure 5c, the author mentioned that the instability of the intermediates is the reason why alkane substrates fail to yield amino acids. The reviewer is curious whether the reaction could be driven forward if the alkane moiety were to bear substituents capable of stabilizing the intermediate species through polarization effects?
14. I highly appreciate the discussion in Figure 6 regarding the interplay between different aryl groups and the FE. This is an aspect often lacking in current electrocatalysis research. However, to be a bit more ambitious, could the authors provide some quantitative analysis like the reference (Science, 2024, 383, 6678).
15. Regarding Figure 6, the authors provide a detailed discussion of the electronic structure of the aryl groups. How about the steric effects?
16. Throughout the manuscript and SI, the authors frequently use the term of 100% conversion. From a catalytic and analytical chemistry perspective, this is technically imprecise. It is more accurate to state that the substrate concentration fell below the limit of detection of the analytical instrument. I think 100% can be replaced with > 99% or similar terminology to maintain rigorous scientific standards.

Reviewer #2

(Comments for the Author)
This manuscript by Wang et al. reports a new electrosynthesis reaction from CO_2, nitrite and aromatic aldehydes to arylglycines, a type of unnatural amino acids of great value. The heart of this synthesis route is a new electroreduction reaction from aryl oximes and CO_2 to arylglycines. Previously, people used the reaction between imines and CO_2 to form amino acids. Here, the use of oximes in the place of imines not just poses a different scientific question, but also enables the use of NOx such as nitrite as the nitrogen source and the formation of the C-N bond in aqueous media. The authors overcome the challenge of oxime carboxylation via a metal ion mediated electrocatalytic process. Besides reaction development and mechanistic understanding, this work demonstrates the synthesis of a series of arylglycines with high yield and faradaic efficiency. Product separation and purification is also taken into account. Therefore, I believe the high intellectual novelty and potential impact of this work suits the level of Nature Synthesis, but the following questions should be properly addressed before publication is considered.
On the first step of the synthesis route:
1) While electroreduction of nitrite is relatively easy, the Pd catalyst used in this work can selectively generate NH_2OH at quite positive electrode potentials, which is rare and noteworthy. I believe the performance here is better than most other catalysts. More detailed explanation should be provided.
2) The authors used nitrite in their experiments. Why was it selected? What about other forms of NOx? More discussion is needed here.
On the second step:
3) Why was Pb chosen as the catalyst? What about other metals or materials? More control experiments are needed here to clarify the roles played by the Pb electrode.
4) This step uses a DMF electrolyte. What about aqueous electrolyte or mixed electrolyte? More experiments are also needed here.

Reviewer #3

(Comments for the Author)
See attached file

Version 1:

Reviewer comments:

Reviewer #1

(Comments for the Author)
The authors have revised the manuscript based on the comments and suggestions of the reviewers. The manuscript is significantly improved and now suitable for publication. I recommend acceptance in its current form.

Reviewer #2

(Comments for the Author)
The authors have well addressed all my concerns.

Reviewer #3

(Comments for the Author)
After extensive revision and incoprportation of new data and conclusion, the manuscript has improved considerable and therefore I recommend its publication since the topic is very appealing to the community.

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Reviewer #1

In this manuscript, Wang and co-workers presented an electrochemical route for synthesizing arylglycines using low-cost feedstocks including CO2, nitrite, and aldehydes. The integration of nitrite reduction with oxime carboxylation represents a creative approach to high-value unnatural amino acids. The manuscript contains some interesting results and conclusions. I think it can be considered for publication in Nature Synthesis after revision.

Response:

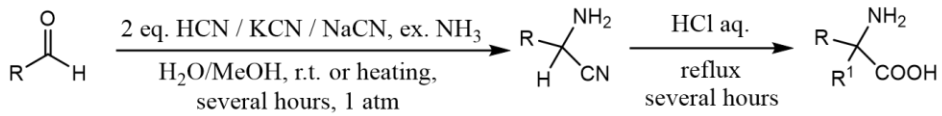
We thank the reviewer for the positive evaluation of our work and for recognizing the novelty and potential significance of integrating nitrite reduction with oxime carboxylation for the synthesis of arylglycines. We are pleased that the reviewer finds the approach creative and the results interesting. We have carefully revised the manuscript according to the reviewer's comments and suggestions to further improve its clarity, rigor, and overall quality. We hope that the revised version is suitable for publication.

1-1 The authors should provide specific reaction conditions for the traditional Strecker reaction and Bucherer-Bergs reaction (e.g., precise temperature, pressure, and typical reaction times).

Response:

We thank the reviewer for this helpful suggestion. Representative specific reaction conditions for the traditional Strecker and Bucherer–Bergs reactions are shown below in **Figure R1**. As can be seen, the Strecker reaction requires an aldehyde to react with cyanide and ammonia in aqueous/alcoholic media at room temperature or under heating for several hours, followed by hydrolysis in acid under reflux conditions. The Bucherer–Bergs reaction is typically conducted with KCN and $(NH_4)_2CO_3$ in H_2O/EtOH at elevated temperature (e.g., 75 °C) for extended time (e.g., 24 h), followed by hydrolysis in base under reflux and subsequent workup with acid. Providing these conditions in the manuscript allows a direct comparison and highlights the key advantages of our method in voiding toxic cyanide reagents and eliminating the need for harsh hydrolysis steps under strongly acidic or basic reflux conditions.

Strecker reaction



Bucherer-Bergs reaction

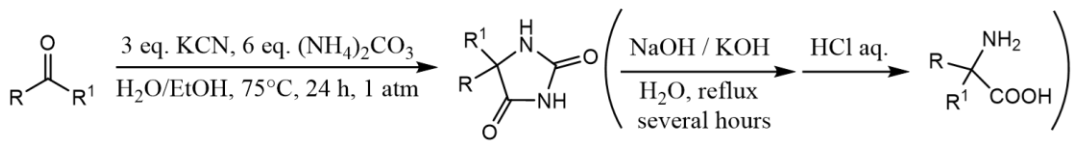


Figure R1 (new Figure S1). Representative conditions of Strecker and Bucherer–Bergs reactions.

Revision made:

We have added Figure R1 to the Supporting Information (SI) as new Figure S1 to clarify the specific reaction conditions of the conventional synthesis routes.

1-2 The manuscript lacks essential details regarding the initial steps of the cascade reactions. The authors should provide characterizations of hydroxylamine and oximes.

Response:

We thank the reviewer for this helpful suggestion. We agree that providing characterization of the hydroxylamine and oxime products in the initial cascade steps is important for supporting the overall reaction sequence. Following the reviewer's suggestion, we have characterized the products of the NO_2^- reduction step, as shown below in **Figure R2**; we have also added the ^1H NMR spectra of the oxime products formed from aldehydes and hydroxylamine, as shown below in **Figure R3**.

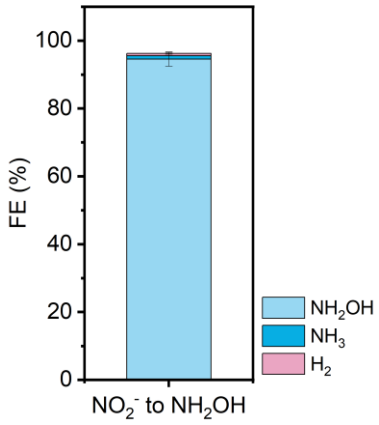


Figure R2 (new Figure S2). The FE results of 0.1 M of NO_2^- electroreduction in 0.5 M phosphate buffer (pH 7) solution by Pd cathode at −0.1 V vs RHE. The products were characterized following our previous work (ACS Catal. 2022, 12, 9135).

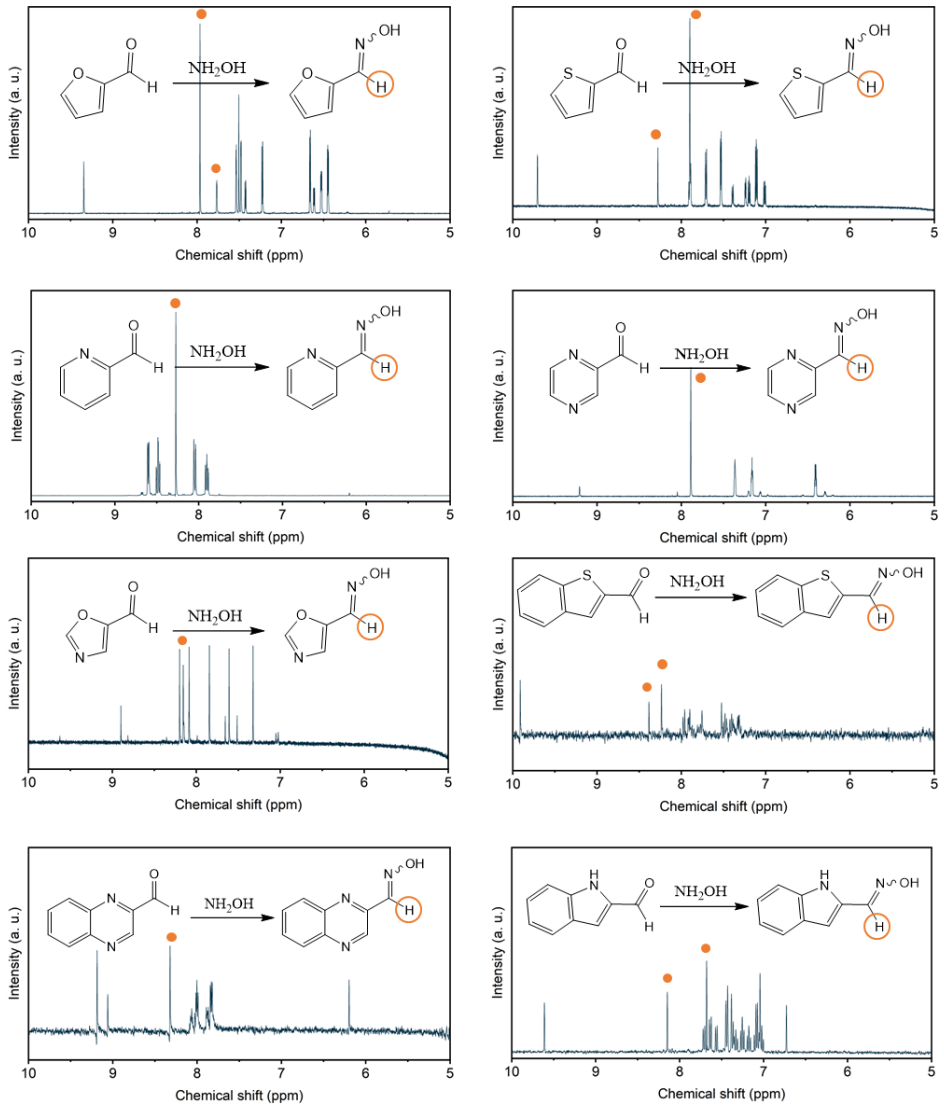


Figure R3 (new Figure S36). ^{1}H NMR results of aryl oximes synthesized by aryl aldehydes and NH_2OH.

Revisions made:

Figures R2 and R3 (new Figures S2 and S36) have been added to the revised SI.

We have also added related descriptions on Pages 4 and 14 of the revised manuscript:

"Pd is chosen for its high selectivity and low overpotential for electrochemically reducing NO_2^- to NH_2OH (Fig. S2)."

"we first convert the aldehyde substrates to their corresponding oximes by reacting with NH_2OH (Fig. S36)"

1-3 Formulas of how the conversion and FE for these intermediates were calculated are missed.

Response:

We thank the reviewer for pointing this out. The formulas used to calculate the conversion and FE values for the electroreductive carboxylation step and the overall two-step process are shown below.

$$\text{Conv.(electrocarboxyaltion)} = \frac{n_{final}(\text{PhGly})}{n_{initial}(\text{BzOx})} \times 100\%$$

$$\text{Conv.(two-step)} = \frac{n_{final}(\text{PhGly})}{n_{initial}(\text{PhCHO})} \times 100\%$$

$$\text{FE(electrocarboxyaltion)} = \frac{n_{final}(\text{PhGly}) \times n_{electrocarboxylation}(e) \times 96485\ \text{C/mol}}{Q_{electrocarboxylation}} \times 100\%$$

$$\text{FE(two-step)} = \frac{n_{final}(\text{PhGly}) \times \left(n_{electrocarboxylation}(e) + n_{nitrite\ electroreduction}(e)\right) \times 96485\ \text{C/mol}}{Q_{electrocarboxylation} + Q_{nitrite\ electroreduction}} \times 100\%$$

$$n_{electrocarboxylation}(e) = 4, \qquad n_{nitrite\ electroreduction}(e) = 4$$

Revision made:

We have added the corresponding equations and descriptions to the revised SI at the end of the "Electroreductive carboxylation of oximes" section.

"The formulas used to calculate the conversion and FE values for the electroreductive carboxylation step and the overall two-step process are below:

$$\text{Conv.(electrocarboxyaltion)} = \frac{n_{final}(\text{PhGly})}{n_{initial}(\text{BzOx})} \times 100\%$$

$$\text{Conv.(two-step)} = \frac{n_{final}(\text{PhGly})}{n_{initial}(\text{PhCHO})} \times 100\%$$

$$\text{FE(electrocarboxyaltion)} = \frac{n_{final}(\text{PhGly}) \times n_{electrocarboxylation}(e) \times 96485\ \text{C/mol}}{Q_{electrocarboxylation}} \times 100\%$$

$$FE(two-step) = \frac{n_{final}(PhGly) \times \left(n_{electrocarboxylation}(e) + n_{nitrite\ electroreduction}(e)\right) \times 96485\ C/mol}{Q_{electrocarboxylation} + Q_{nitrite\ electroreduction}} \times 100\%$$

$n_{electrocarboxylation}(e) = 4,\ n_{nitrite\ electroreduction}(e) = 4$"

1-4 In Figure 2, the authors describe the synthesis of free NH2OH followed by condensation to form oximes. This pathway has been recently presented in literature. I suggest the authors cite and discuss more related studies here.

Response:

We thank the reviewer for this helpful suggestion. Indeed, there has been quite a number of recent reports on electrochemical generation of NH_2OH followed by condensation with carbonyl compounds to form oximes. Different NO_x^{y-} reactants are used. Both one-step (NH_2OH is captured in situ by a carbonyl reactant during reduction) and two-step (free NH_2OH is first generated from electrolysis and then reacts with a carbonyl compound) approaches have been reported.

Revision made:

We have expanded the discussion of related NO_x^{y-}-to-oxime electrosynthesis studies on Page 2 of the revised manuscript:

"Oxime formation from reacting a carbonyl compound with electrochemically generated NH_2OH from nitrate (NO_3^-) reduction was initiated by our earlier work. Recent development has expanded this reaction to other NO_x^{y-} reactants including NO_2^- and nitrogen monoxide (NO). Both one-step (NH_2OH is captured in situ by a carbonyl reactant during electroreduction) and two-step (free NH_2OH is first generated from electrolysis and then reacts with the carbonyl compound) approaches have been reported."

1-5 Regarding the formation of BnNH2 mentioned on Page 4, the origin of the protons is unclear. What is the specific hydrogen source for this reduction?

Response:

We thank the reviewer for this insightful question regarding the proton source. In our system, the protons required for the formation of $BnNH_2$ originate primarily from the trace amount of water present in the DMF electrolyte. Although anhydrous solvents were used, completely eliminating water is challenging, and residual moisture can act as a proton donor during the electroreduction process. This is consistent with prior studies showing that even small amounts of water in

nonaqueous CO_2 electroreduction systems can significantly alter product pathways and promote hydrogenation reactions over carboxylation.

To further verify this point, we have conducted additional control experiments by systematically varying the water content in the DMF electrolyte. The results show a clear trend: under low water concentration conditions, the formation of PhGly is favored, while increasing the water content leads to a rapid decrease in PhGly FE and a corresponding increase in $BnNH_2$ formation (**Figure R4**). Notably, when the water content reaches 5%, PhGly formation is completely suppressed, and $BnNH_2$ becomes the dominant product. These results strongly support that water is the key proton source responsible for $BnNH_2$ formation and that a low-water environment is essential to suppress hydrogenation and favor the desired carboxylation pathway.

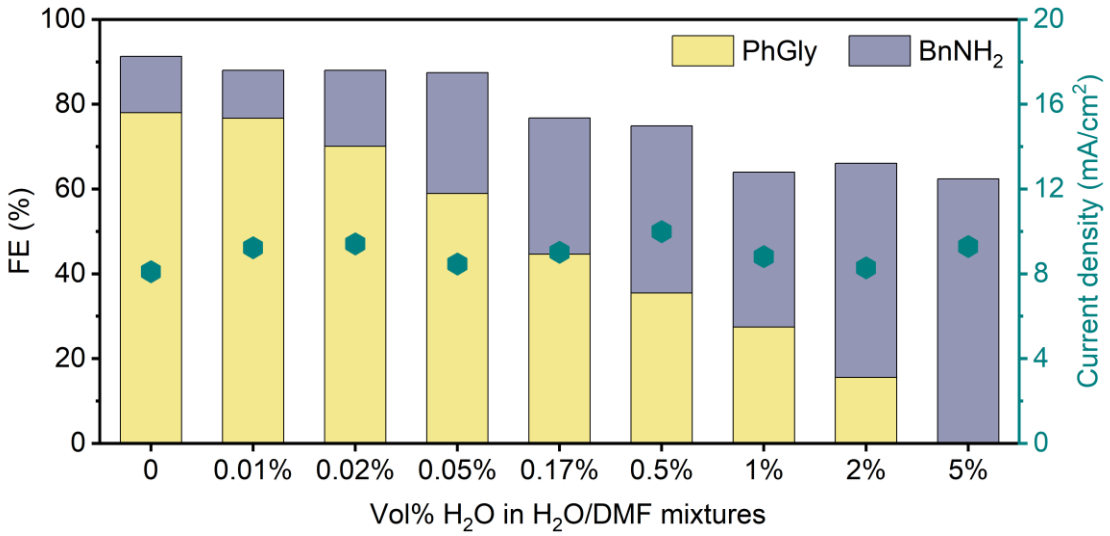


Figure R4 (new Figure S9). FEs and total current densities for electroreductive carboxylation of BzOx in H_2O/DMF mixed electrolyte with varied volume percentages of H_2O.

Revisions made:

Figure R4 (new Figure S9) has been added to the revised SI.

We have also added related discussion regarding the role of water and proton sources on Page 5 of the revised manuscript:

"The trace amount of H_2O that exists in the electrolyte solution is believed to be the proton source for the formation of $BnNH_2$. As we systematically vary the H_2O content in the DMF electrolyte, we find that increasing H_2O concentration rapidly decreases the FE for PhGly while markedly increasing $BnNH_2$ formation (Fig. S9). When the H_2O content reaches 5% by volume, no detectable PhGly is formed and $BnNH_2$ becomes the dominant product. These results confirm H_2O

as the proton source for $BnNH_2$ and indicate that aqueous or mixed electrolyte strongly shifts the reaction pathway from reductive carboxylation toward hydrogenation. This observation is consistent with our prior study showing efficient electroreduction of oximes to amines on Pb electrodes in aqueous electrolyte,[56] highlighting that a low-H_2O DMF electrolyte is essential for selective electroreductive carboxylation."

1-6 Is it possible that the product exists as a zinc-coordinated complex rather than a free amine in the reaction mixture?

Response:

We thank the reviewer for raising this interesting point regarding the possible coordination state of the amine product. It is indeed possible in principle for amines to coordinate with Zn^{2+} to form complexes in nonaqueous media. Nevertheless, under the specific conditions of this system, we believe such coordination is rather limited. Note that the typical concentration of $BnNH_2$ in the electrolyte after reaction is ~3 mM. The concentration of Zn^{2+} in the electrolyte is also low. Although Zn^{2+} is continuously generated at the anode, it is also simultaneously consumed through the precipitation processes, leading to a low steady-state concentration. Under these low concentration conditions, forming a stable Zn^{2+}-amine complex is unlikely. (Mater. Sci. Semicond. Process. 2015, 38, 278)

1-7 Figure 3a depicts what appears to be an open-vessel single cell. However, even in the absence of added water, trace amount of water from the atmosphere can significantly impact the carboxylation efficiency.

Response:

We thank the reviewer for reading our manuscript carefully and catching this mistake. The original schematic drawing in Figure 3a was not adequate in describing the actual structure of the electrochemical cell. A photograph of the cell is shown below in **Figure R5**. The cell is not open to the atmosphere. It is equipped with a sealed cap that fixes both the electrodes and the CO_2 inlet tubing, along with a dedicated gas outlet. During electrolysis, CO_2 is continuously purged into the cell, filling the headspace above the electrolyte. As a result, the system is effectively isolated from ambient air, and the presence of atmospheric moisture can be considered negligible. The corrected versions of Figures 3a and 4c are shown below as **Figures R6** and **R7**.

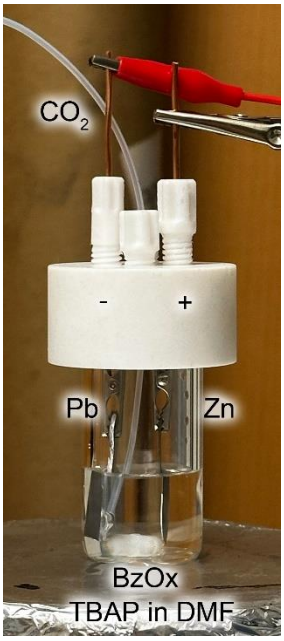


Figure R5 (new Figure S3). Photograph of two-electrode undivided cell used for electroreductive carboxylation.

Figure R6 (new Figure 3a). Schematic illustration of electrochemical reductive carboxylation of BzOx with CO_2.

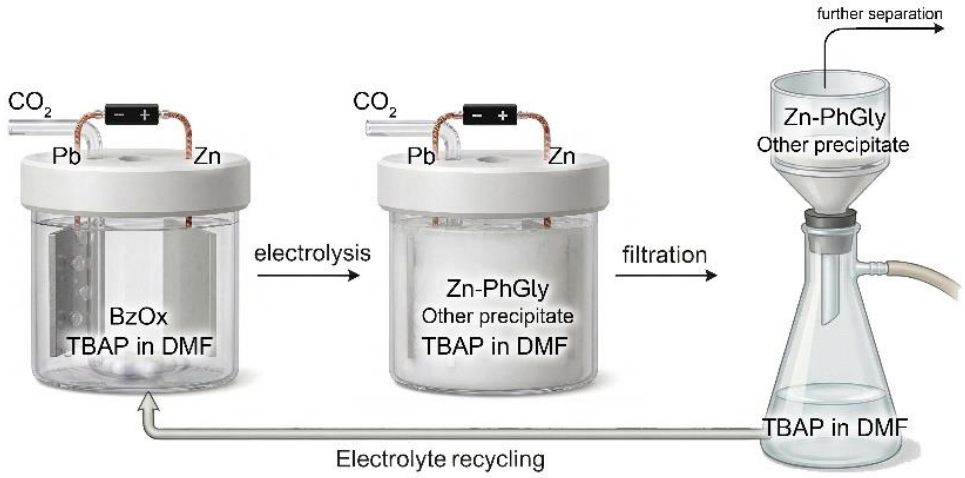


Figure R7 (new Figure 4c). Schematic illustration of PhGly production, separation.

Revisions made:

Figures R5–R7 (new Figures S3, 3a, and 4c) have been added to the revised manuscript and SI to clearly illustrate the sealed structure of the cell.

We have also clarified the atmosphere inside the cell on Page 5 of the revised manuscript:

"The next step is electrochemical carboxylation of BzOx, which is carried out in an undivided cell with a Pb foil working electrode, a Zn foil counter electrode, and a dimethylformamide (DMF) electrolyte solution containing 0.10 M tetrabutylammonium perchlorate (TBAP) under CO_2 atmosphere (Fig. 3a, S3)."

1-8 Metallic lithium was used in the control experiments, and the air atmosphere exerted a further influence. The author should comment on this point.

Response:

We thank the reviewer for this careful attention to the experimental details. In the control experiment involving metallic Li, the electrode was handled under strictly controlled conditions to minimize influence from air. Specifically, the Li foil was polished inside a glovebox to remove the surface oxide layer, and then immediately immersed in the DMF-based electrolyte. Only after this immersion step was the assembled system removed from the glove box for subsequent experiments. Therefore, direct exposure of the Li counter electrode to ambient air was effectively avoided.

Revision made:

We have added the procedure for handling Li anode to the revised SI:

"In experiments where a Li anode was used, a piece of Li foil was first polished inside a glove box and immersed in the DMF electrolyte before being transferred out of the glove box for assembly into the electrochemical cell."

1-9 In addition, I strongly recommend the authors provide more details on the cell. Was the experiment performed under an inert atmosphere (e.g., Ar)?

Response:

We thank the reviewer for this helpful suggestion regarding the experimental conditions. As described in detail in the response to Comment 1-7 above, the electroreductive carboxylation reaction was conducted under CO_2 atmosphere.

1-10 If inert atmosphere is absence, the authors should discuss the influence of atmosphere on the reaction outcomes.

Response:

We thank the reviewer for this comment. As described in detail in the response to Comment 1-7 above, the electroreductive carboxylation reaction was conducted under CO_2 atmosphere.

1-11 While I recognize that cell voltage is critical for dual-electrode systems, the primary novelty of this work lies in the cathodic reduction. The use of a two-electrode system led to the lack of individual electrode potentials. I suggest the authors perform additional experiments using a reference electrode to provide more data on carboxylation.

Response:

We thank the reviewer for this valuable suggestion. Indeed, in this work we chose to use a two-electrode system and report the cell voltage because it is more convenient to use and relevant to synthesis. That said, we completely agree with the reviewer that it is important to provide a more accurate measure of the working electrode potential under which the reductive carboxylation reaction happens. To this goal, we carried out additional experiments using a three-electrode configuration. A silver wire was employed as a quasi-reference electrode, and its potential was calibrated against the Fc/Fc^+ redox couple. The linear sweep voltammogram of the electroreductive carboxylation system of benzaldoxime (BzOx) is shown below in **Figure R8**. At the potential of approximately −2.6 V vs Fc/Fc^+, a current density of ~10 mA/cm^2 is achieved, comparable to that measured under optimal working conditions in the standard two-electrode setup. Therefore, we chose this potential to conduct electrolysis for 1 h. The FEs of phenylglycine (PhGly) and benzylamine ($BnNH_2$) closely match those obtained under the original two-electrode

conditions (**Figure R9**). This result confirms that −2.6 V vs Fc/Fc^+ is a representative working potential for the electroreductive carboxylation reaction of BzOx.

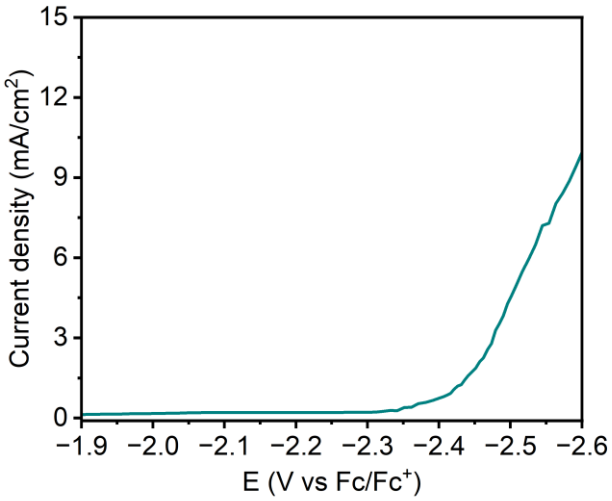


Figure R8 (new Figure S7). Linear sweep voltammogram at a scan rate of 10 mV/s for electroreductive carboxylation of BzOx in a three-electrode undivided cell.

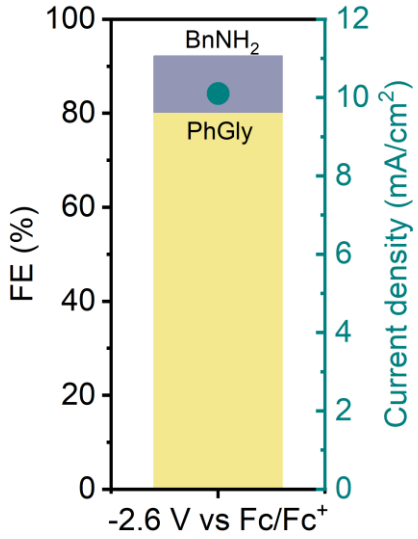


Figure R9 (new Figure S8). FEs and total current density for electroreductive carboxylation of BzOx at −2.6 V vs Fc/Fc^+ measured in a three-electrode undivided cell.

Revisions made:

Figures R8 and R9 (new Figures S7 and S8) have been added to the revised SI.

We have also added the corresponding three-electrode results on Page 5 of the revised manuscript and included the experimental details in the revised SI:

"To identify the working electrode potential for the electroreductive carboxylation reaction, we perform three-electrode measurements using a Ag wire quasi-reference electrode that is calibrated against the redox couple of Fc/Fc^+. As shown in the linear sweep voltammogram (Fig. S7), the reduction reaction onsets at approximately −2.3 V vs Fc/Fc^+ and reaches a current density comparable to that under the standard two-electrode conditions at −2.6 V vs Fc/Fc^+. Electrolysis performed at −2.6 V vs Fc/Fc^+ gives similar FEs for PhGly and $BnNH_2$ to those obtained in the two-electrode system (Fig. S8), confirming that this potential is representative of the optimal working conditions for electroreductive carboxylation of BzOx."

"Three-electrode measurements were carried out in the same undivided cell with a Ag wire serving as a quasi-reference electrode. All the other conditions were the same as the two-electrode measurements. The potential of the Ag wire quasi-reference electrode was calibrated against the Fc/Fc^+ redox couple by adding 5 mM Fc into the electrolyte after the electrochemical measurement and recording the cyclic voltammogram."

1-12 In Figure 5d, could the authors provide further experimental evidence regarding the presence of carbanions and radical species?

Response:

We thank the reviewer for this important question. To test possible involvement of radical species in the electroreductive carboxylation reaction, we performed a control experiment by adding 1 equivalent of butylated hydroxytoluene (BHT) as a radical scavenger to the electrolyte (ACS Omega 2022, 7, 18552; Chem. Phys. Lipids 2004, 130, 189). As shown in **Figure R10**, both the FE and current density remain essentially unchanged compared to the standard conditions. This result indicates that radical pathways are not involved in the reaction, as the radical scavenger would otherwise significantly suppress product formation. Therefore, it is more likely that the oxime carboxylation reaction in this work goes through the carbanion intermediate. Since we have sufficient evidence that the oxime is first reduced to the corresponding imine before carboxylation. This carbanion pathway is fully consistent with current understanding in the field. Electroreductive carboxylation of imines has been extensively reported to proceed via nucleophilic carbanion-type intermediates (Chem Catal. 2024, 4, 101158; J. Org. Chem. 2021, 86, 15953; React. Chem. Eng., 2017, 2, 871).

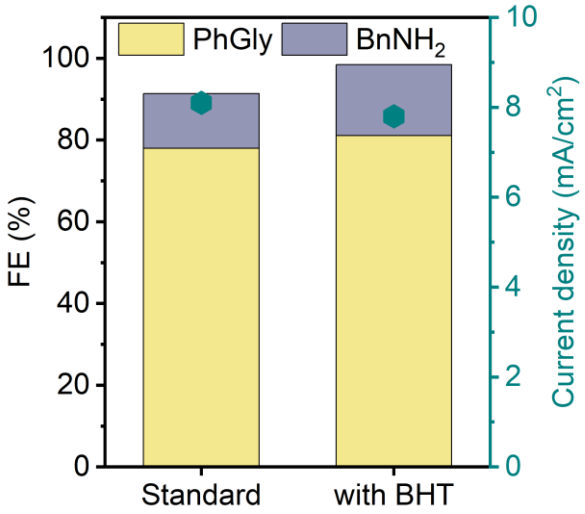


Figure R10 (new Figure S28). FEs and total current densities for electroreductive carboxylation of BzOx without (left) vs with (right) 0.1 M BHT added to the electrolyte.

Revisions made:

Figure R10 (new Figure S28) has been added to the revised SI.

We have also added the corresponding mechanistic discussion on Page 11 of the revised manuscript:

"A control experiment with butylated hydroxytoluene added as a radical scavenger[61,62] gives FE and current density values almost identical to the standard conditions (Fig. S28), suggesting that anion pathways, instead of radical pathways, are dominant in this reaction. This interpretation is also consistent with previous reports showing that electroreductive carboxylation of imines generally proceeds through nucleophilic carbanion-type intermediates rather than via free-radical pathways.[50,63,64]"

1-13 In Figure 5c, the author mentioned that the instability of the intermediates is the reason why alkane substrates fail to yield amino acids. The reviewer is curious whether the reaction could be driven forward if the alkane moiety were to bear substituents capable of stabilizing the intermediate species through polarization effects?

Response:

We thank the reviewer for this insightful and constructive suggestion. We agree that introducing substituents that are capable of stabilizing reactive intermediates through polarization or electronic effects is, in principle, a reasonable strategy to promote the reaction. To evaluate this possibility, we performed additional experiments using two representative substrates. First, we synthesized trifluoroacetaldehyde oxime and subjected it to the standard electroreductive carboxylation

conditions (two-electrode single-cell system, Pb cathode, Zn anode, TBAP/DMF electrolyte under continuous CO_2 flow, −3 V for 1 h). Under these conditions, neither the corresponding trifluoroalanine product nor trifluoroethylamine was detected. We also synthesized acrolein oxime for this test. Under the same electroreductive carboxylation conditions, no corresponding amino acid or amine products were observed. These two negative results show that neither a strong electron-withdrawing $-CF_3$ group nor a vinyl group on the C atom of the oxime is able to provide sufficient stabilization for the key intermediates involved in this electroreductive transformation. At this point, it seems that an aryl group is necessary for this reaction to occur. Our future work will look into more reactant structures in a more systematic way to further test this hypothesis and understand the reactivity.

1-14 I highly appreciate the discussion in Figure 6 regarding the interplay between different aryl groups and the FE. This is an aspect often lacking in current electrocatalysis research. However, to be a bit more ambitious, could the authors provide some quantitative analysis like the reference (Science, 2024, 383, 6678).

Response:

We thank the reviewer for this encouraging comment and for suggesting a more quantitative treatment. Following this suggestion, we performed additional analysis inspired by the mentioned article to identify a suitable molecular descriptor that correlates with the observed FE. After evaluating several candidates, we selected polarizability (α) of molecules corresponding to each substituent (Ar−H) as the descriptor for the aryl oxime (ArCH=NOH) substrates shown in Figure 6. As shown in **Figure R11a**, the FE of arylglycine formation increases with α, while the selectivity toward amine decreases correspondingly (**Figure R11b**). This indicates that substrate polarizability drastically influences the competition between carboxylation and hydrogenation. Substrates with higher polarizability, particularly fused aromatic systems, can better stabilize the anionic intermediate through π-electron delocalization, thereby facilitating its nucleophilic attack to CO_2. Meanwhile, the relatively small variation in the oxime reduction current density with α (**Figure R11c**) suggests that polarizability primarily affects reaction selectivity instead of substantially changing the overall reaction rate. Overall, these results are consistent with our proposed carboxylation pathway via a carbanion intermediate. A higher polarizability reflects a more easily deformable electron cloud, which enhances the stabilization of the charged intermediate formed in the reduction step. Higher polarizability in this case is also correlated with stronger solvation in the electrolyte, which further contributes to stabilizing the key carbanion intermediate and promoting the desired carboxylation pathway. This newly added analysis provides a quantitative framework that complements our earlier qualitative observations and highlights the critical role of substituent structure in governing reaction efficiency.

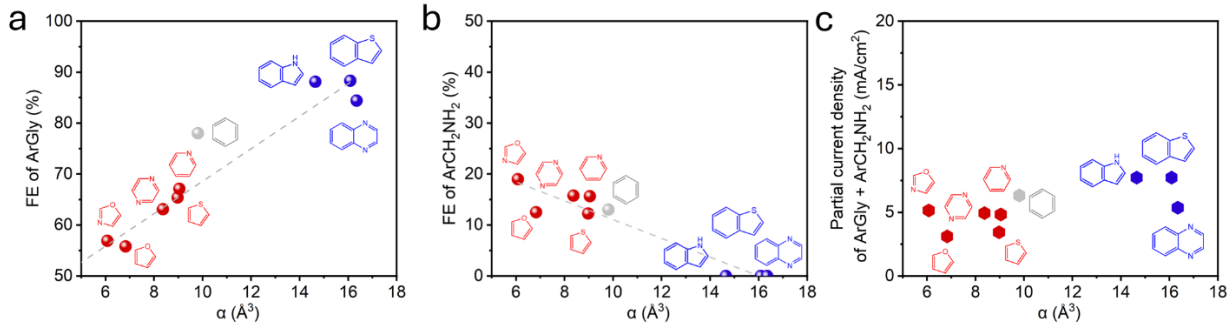


Figure R11 (new Figure S46). Correlation of molecular polarizability (α) of Ar−H with (a) ArGly FE, (b) $ArCH_2NH_2$ FE, and (c) combined partial current density of ArGly and $ArCH_2NH_2$ in electroreductive carboxylation reactions of ArCH=NOH. The static isotropic polarizabilities were determined via density functional theory (DFT) calculations at the B3LYP/6-311+G(d,p) level with the *Polar* keyword in Gaussian 16, utilizing fully optimized geometries.

Revisions made:

Figure R11 (new Figure S46) has been added to the revised SI.

We have also added the corresponding discussion on Page 14 of the revised manuscript:

"We find that the polarizability (α) of the molecule (Ar−H) corresponding to the aryl group in the oxime reactant exhibits a strong correlation with the product selectivity. As shown in Fig. S46a and b, the FE of arylglycine increases while the selectivity toward amine formation decreases with increasing α, suggesting that substrates with higher polarizability favor the carboxylation pathway and suppress the competing hydrogenation pathway. Meanwhile, the relatively small variation in the oxime reduction current density (Figure S46c) suggests that the polarizability descriptor primarily affects reaction selectivity instead of substantially altering the overall reaction rate. These results are consistent with the proposed carbanion-mediated carboxylation pathway, in which substrates with higher polarizability can better stabilize the charged reaction intermediate through π-electron delocalization and stronger solvation in the electrolyte, thereby promoting its reaction with CO_2."

1-15 Regarding Figure 6, the authors provide a detailed discussion of the electronic structure of the aryl groups. How about the steric effects?

Response:

We thank the reviewer for this insightful comment. We agree that considering steric effects is important, particularly for reactions involving surface adsorption and transformation of intermediates. In principle, steric hindrance could influence the accessibility of the reactive site

and thus affect the reaction efficiency. However, based on our experimental results, no obvious relationship is found between changes in FE and variations in steric hindrance across the substrate scope, as the FE values remain within a relatively narrow range despite structural differences.

From a structural perspective, this can be rationalized by the fact that all substrates examined in this study contain relatively small and non-bulky aryl groups, and the reactive C=N moiety of the oxime remains sterically accessible. Since the electrochemical reductive carboxylation proceeds via adsorption and transformation of this C=N unit on the electrode surface, the absence of significant steric congestion near the reaction center minimizes steric limitations. Therefore, we conclude that steric effects are not important, at least for the substrates investigated in this work, and the observed trends are primarily governed by electronic factors.

Revision made:

We have added additional discussion regarding substrate steric effects on Page 14 of the revised manuscript:

"No obvious steric effect is observed in the electroreductive carboxylation process involving these oxime substrates."

1-16 Throughout the manuscript and SI, the authors frequently use the term of 100% conversion. From a catalytic and analytical chemistry perspective, this is technically imprecise. It is more accurate to state that the substrate concentration fell below the limit of detection of the analytical instrument. I think 100% can be replaced with > 99% or similar terminology to maintain rigorous scientific standards.

Revision:

We thank the reviewer for this valuable suggestion. We agree that rigorous terminology is important when describing conversion in catalytic and analytical contexts. In our manuscript, the term "100% conversion" was not intended to describe experimentally quantified results, but rather to denote a theoretical value used for setting reaction parameters (the total charge corresponding to full consumption of the substrate). To avoid any potential ambiguity and to better align with standard analytical conventions, we will revise the manuscript to replace such numerical expressions with more appropriate wording, such as "complete conversion/complete Faradaic selectivity" where applicable. This change will improve clarity and ensure more precise communication of the experimental results.

Revisions made:

We have revised the related descriptions throughout the revised manuscript and SI to improve the precision of the terminology:

“In both routes, the total charge passed in the electrolysis is set at 20 mAh, corresponding to a theoretical NH_2OH concentration of 15.5 mM assuming complete Faradaic selectivity.”

“Electrolysis proceeds until total charge reaches the theoretical value corresponding to complete conversion of BzOx.”

“The first step follows Route S2 as shown in Fig. 2, and the second step is carried out with a total charge of 20 mAh, corresponding to full conversion of 15.5 mM BzOx into PhGly assuming complete Faradaic selectivity.”

Reviewer #2

This manuscript by Wang et al. reports a new electrosynthesis reaction from CO2, nitrite and aromatic aldehydes to arylglycines, a type of unnatural amino acids of great value. The heart of this synthesis route is a new electroreduction reaction from aryl oximes and CO2 to arylglycines. Previously, people used the reaction between imines and CO2 to form amino acids. Here, the use of oximes in the place of imines not just poses a different scientific question, but also enables the use of NOx such as nitrite as the nitrogen source and the formation of the C−N bond in aqueous media. The authors overcome the challenge of oxime carboxylation via a metal ion mediated electrocatalytic process. Besides reaction development and mechanistic understanding, this work demonstrates the synthesis of a series of arylglycines with high yield and faradaic efficiency. Product separation and purification is also taken into account. Therefore, I believe the high intellectual novelty and potential impact of this work suits the level of Nature Synthesis, but the following questions should be properly addressed before publication is considered.

Response:

We sincerely thank the reviewer for the thorough evaluation and for recognizing the significance, novelty, and potential impact of this work. We particularly appreciate the reviewer's insightful summary of the key advances, including the use of oximes as intermediates, the integration of NO_x-derived nitrogen sources, and the development of a metal ion-mediated electrocatalytic strategy for arylglycine synthesis. We are also grateful for the positive assessment of the reaction scope, efficiency, and the consideration of product separation and purification.

We have carefully addressed all of the reviewer's comments and questions in detail below. We believe that these revisions have significantly strengthened the manuscript and clarified several important aspects of the reaction design and mechanism.

2-1 While electroreduction of nitrite is relatively easy, the Pd catalyst used in this work can selectively generate NH2OH at quite positive electrode potentials, which is rare and noteworthy. I believe the performance here is better than most other catalysts. More detailed explanation should be provided.

Response:

We thank the reviewer for this comment. We agree that the ability of the Pd catalyst to selectively generate NH_2OH at relatively positive potentials is noteworthy. This behavior is also consistent with our previous work, where Pd catalysts were shown to efficiently mediate the electroreduction of NO_2^- in the presence of ketones to form ketoximes at similarly mild potentials (J. Am. Chem. Soc. 2025, 147, 9378).

A more detailed and systematic investigation of direct NH_2OH production on Pd, including mechanistic analysis and catalyst optimization, is currently underway and will be reported in a follow-up study (**Figure R12**).

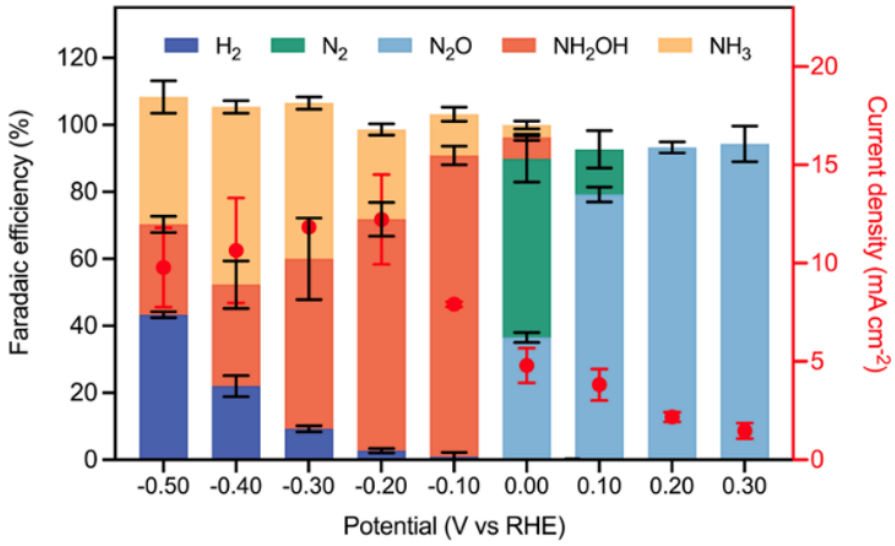


Figure R12. FEs and current densities of NO_2^- electroreduction using Pd cathode.

Revision made:

We have added related discussion regarding Pd-catalyzed NH_2OH formation on Page 3 of the revised manuscript:

"Pd is chosen for its high selectivity and low overpotential for electrochemically reducing NO_2^- to NH_2OH (Fig. S2)."

2-2 The authors used nitrite in their experiments. Why was it selected? What about other forms of NOx? More discussion is needed here.

Response:

We thank the reviewer for this comment. In principle, this reaction strategy should be applicable to other forms of NO_x^{y-} species, including NO_3^-, NO_2^-, and NO. As reported in the literature (Chem Catalysis 2022, 2, 1807; Nat. Commun. 2023, 14, 3057; J. Am. Chem. Soc. 2024, 146, 6294; J. Am. Chem. Soc. 2024, 146, 10934; Nat. Synth. 2025, 4, 1598.), all of them can be electrochemically reduced to NH_2OH or NH_3 (probably via NH_2OH). Since NH_2OH is the key nitrogen-containing species involved in the subsequent condensation and transformation steps in this work, Therefore, all these NO_x^{y-} sources could in principle be employed within the same reaction framework with appropriate control of reduction selectivity. In this study, NO_2^- was

specifically chosen as the nitrogenous reactant because it is a harmful environmental contaminant (~10 times more toxic than NO_3^-), making its direct utilization particularly meaningful from a sustainability perspective. We will clarify this issue in the revised manuscript.

Revision made:

We have added additional discussion regarding the selection of NO_2^- and other possible NO_x^{y-} reactants on Page 2 of the revised manuscript:

"NO_2^- is selected in this work because it is a harmful environmental contaminant, making its direct utilization especially meaningful from a sustainability perspective, but the synthesis can be readily extended to other NO_x^{y-} reactants such as NO_3^- and NO."

2-3 Why was Pb chosen as the catalyst? What about other metals or materials? More control experiments are needed here to clarify the roles played by the Pb electrode.

Response:

We thank the reviewer for this important question. Pb was initially selected as the cathode material based on our prior work. In our previous study, we found that Pb is effective for the electroreduction of oximes to amines in near neutral aqueous electrolytes, indicating that Pb has a capability to activate the N−O bond and facilitate oxime hydrogenation without triggering substantial size reactions. This provided a solid basis for employing Pb in the present system, where oxime activation is also a key step. Luckily, Pb demonstrated superior performance in this reaction system as well.

Following the reviewer's suggestion, we tested more cathode materials, including Zn metal, Ni metal, boron-doped diamond (BDD), graphite, Ti metal, and Cu metal, for the electroreductive carboxylation reaction of benzaldoxime (BzOx). As shown below in **Figure R13**, while all these electrode materials can perform the carboxylation reaction, they all exhibit lower selectivity toward the desired product, phenylglycine (PhGly), than Pb. These results justify the selection of Pb as the cathode material.

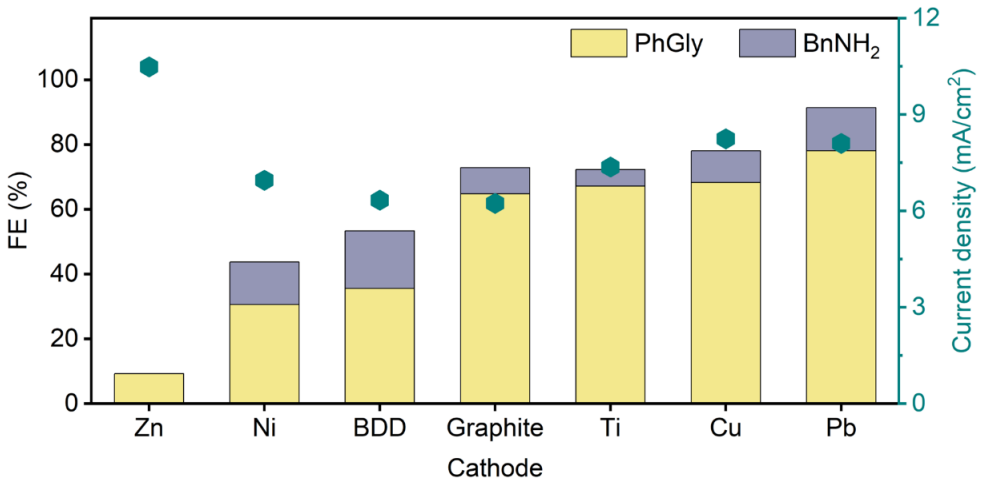


Figure R13 (new Figure S34). FEs and total current densities for electroreductive carboxylation of BzOx performed at −3.1 V vs Fc/Fc^+ for 1 h in a three-electrode H-cell with varied amount of anhydrous $Zn(OTf)_2$ added in the catholyte.

Revisions made:

Figure R13 (new Figure S34) has been added to the revised SI.

We have also added the corresponding cathode comparison discussion in the revised manuscript:

"Replacing the Pb cathode with other materials, including Ti, Ni, Cu, Zn, boron-doped diamond, and graphite, can also drive the electroreductive carboxylation reaction of BzOx, but with lower selectivity toward PhGly formation (Fig. S34). This result is consistent with our previous work showing that Pb can effectively catalyze electroreduction of oximes through N–O bond activation,[56] thereby justifying its selection as the cathode material in this study."

2-4 This step uses a DMF electrolyte. What about aqueous electrolyte or mixed electrolyte? More experiments are also needed here.

Response:

We thank the reviewer for this valuable suggestion. To address this point, we carried out additional experiments by systematically varying the water content in the DMF electrolyte. The new results are shown below in **Figure R14**. A clear trend can be observed: once a noticeable amount of water is introduced into the electrolyte, the FE for PhGly decreases rapidly, while the FE for benzyl amine ($BnNH_2$) increases markedly. When the H_2O content reaches 5%, no PhGly is detected and $BnNH_2$ becomes the dominant product. These results indicate that the mixed electrolyte strongly shifts the reaction pathway from reductive carboxylation toward simple hydrogenation of the

oxime-derived intermediate. This result is also consistent with our previous study, in which oximes were efficiently reduced on Pb electrodes to amines in aqueous electrolyte (J. Am. Chem. Soc. 2025, 147, 43692). Taken together, these results suggest that a low-water DMF electrolyte is essential for maintaining high selectivity for the electroreductive carboxylation pathway, whereas aqueous or mixed electrolytes favor hydrogenative electroreduction to the amine product instead.

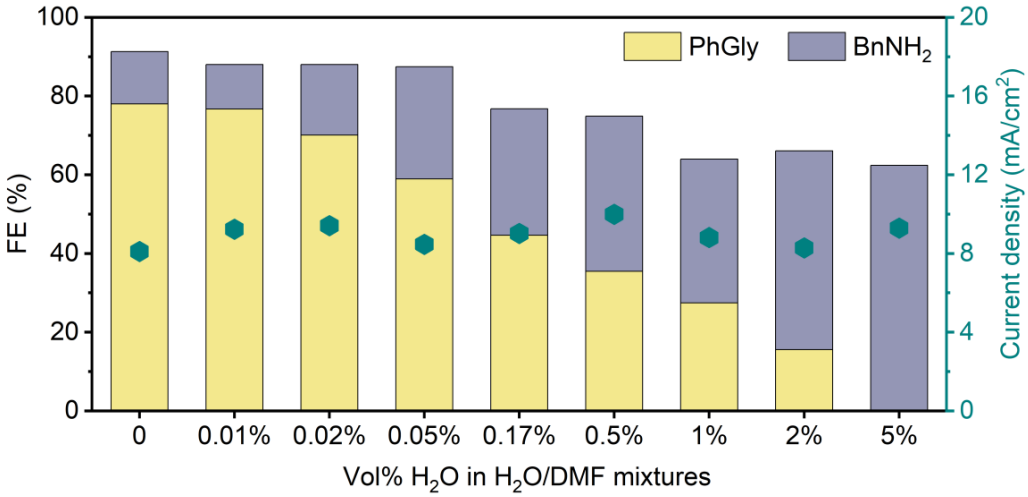


Figure R14 (new Figure S9). FEs for PhGly and $BnNH_2$ and current densities of BzOx electrocarboxylation in H_2O/DMF mixture solvents of different water volume percentages.

Revisions made:

Figure R14 (new Figure S9) has been added to the revised SI.

We have also expanded the discussion of aqueous and mixed electrolytes on Page 5 of the revised manuscript:

"The trace amount of H_2O that exists in the electrolyte solution is believed to be the proton source for the formation of $BnNH_2$. As we systematically vary the H_2O content in the DMF electrolyte, we find that increasing H_2O concentration rapidly decreases the FE for PhGly while markedly increasing $BnNH_2$ formation (Fig. S9). When the H_2O content reaches 5% by volume, no detectable PhGly is formed and $BnNH_2$ becomes the dominant product. These results confirm H_2O as the proton source for $BnNH_2$ and indicate that aqueous or mixed electrolyte strongly shifts the reaction pathway from reductive carboxylation toward hydrogenation. This observation is consistent with our prior study showing efficient electroreduction of oximes to amines on Pb electrodes in aqueous electrolyte,[56] highlighting that a low-H_2O DMF electrolyte is essential for selective electroreductive carboxylation."

Reviewer #3

The transformation is conceptually attractive, combining nitrogen and carbon waste streams into value-added amino acid derivatives, and the reported substrate scope is promising. The authors further propose a mechanistic pathway in which oximes are converted to arylglycines via an imine intermediate, with dissolved metal ions (e.g., Zn^{2+}) playing a crucial enabling role. While the overall concept is compelling and well aligned with the scope of Nature Synthesis, the mechanistic claims are currently stronger than the experimental evidence fully supports. In particular, the imine pathway is inferred largely through exclusion experiments and reactivity of preformed intermediates, rather than direct observation under catalytic conditions. Similarly, although the importance of dissolved metal ions is convincingly demonstrated, their precise role in the reaction mechanism remains insufficiently resolved. Given that mechanistic insight constitutes a central pillar of the manuscript, additional experimental support, such as in situ / operando spectroscopy, isotopic labeling, and more detailed electrochemical analysis would significantly strengthen the work. Overall, I find the study promising but not yet at the level of mechanistic rigor expected for publication in Nature Synthesis. I therefore recommend major revision.

Response:

We sincerely thank the reviewer for the insightful and constructive comments and appreciate the recognition of the conceptual significance of this work. While we would argue that the primary innovation of this work lies in the discovery of a new reaction (electroreductive carboxylation of oximes with CO_2) and its use in synthesis (formation of amino acids electrochemically from aldehydes, CO_2, and NO_x^{y-}), we agree with the reviewer that mechanistic insight is also an important part of this work and we could further strengthen our conclusions with more evidence. In this revision, we carried out additional experiments and have expanded the discussion of reaction pathways and mechanisms with newly obtained results and analysis. We believe these revisions have significantly strengthened the mechanistic section of this manuscript, and we thank the reviewer for making this happen.

3-1 The authors conclude that the reaction proceeds via an imine intermediate rather than via hydroxylamine-derived species, based on (i) the lack of reactivity of a synthesized hydroxylamine intermediate and (ii) the successful conversion of a preformed imine. While these results are suggestive, they do not constitute direct evidence for the formation of the imine intermediate under electrochemical conditions.

Can the authors provide direct evidence for the imine intermediate under reaction conditions (e.g., operando IR, Raman, or NMR)?

Is it possible to perform time-resolved or in situ spectroscopy to monitor oxime to imine conversion?

Are there kinetic or isotope-labeling experiments that could distinguish between competing pathways more rigorously?

Response:

We thank the reviewer for this insightful and constructive comment. As the reviewer correctly pointed out, our control experiment with the synthesized hydroxylamine intermediate can effectively rule out the hydroxylamine pathway, but it does not directly confirm the imine pathway. To unambiguously verify the formation of the imine intermediate during the reaction, we chose to detect benzaldehyde (PhCHO) that is formed during the reaction. Unlike benzaldoxime (BzOx) is highly stable against hydrolysis, benzaldehyde imine (BzIm) quickly hydrolyzes in the presence of water. While most of the formed BzIm intermediate will be quickly reduced electrochemically to phenylglycine (PhGly) or benzylamine ($BnNH_2$), some will still hydrolyze to give PhCHO. In this experiment, we treated the electrolyte after reaction with a 0.1 M NaOH aqueous solution, which is sufficient to dissolve the precipitate but not adequate for the hydrolysis of BzOx to PhCHO. We observed ~0.15 mM of PhCHO after reaction (**Figure R15**), which is considerably higher than the concentration before reaction (residue that is not fully converted by NH_2OH in the preparation of BzOx). This result provides indirect but strong evidence for the formation of BzIm during the reaction. To further strengthen this point, we carried out additional experiments by systematically varying the water content in the DMF electrolyte and using the same method to analyze PhCHO after reaction. As shown in **Figure R16**, the amount of formed PhCHO increases with water content in the electrolyte, as a result of enhanced hydrolysis of the imine intermediate due to increased water concentration.

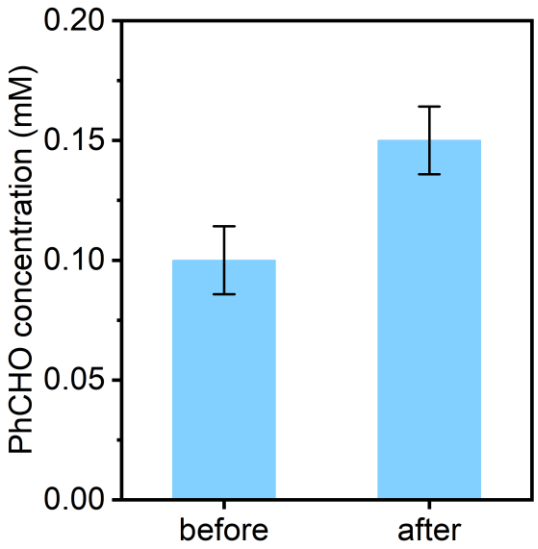


Figure R15 (new Figure S26). Measured PhCHO concentrations in the electrolyte before and after electroreductive carboxylation of BzOx. The electrolyte was treated with 0.1 M aqueous NaOH before PhCHO quantification, which was sufficient to dissolve the precipitate but not strong enough to hydrolyze unreacted BzOx.

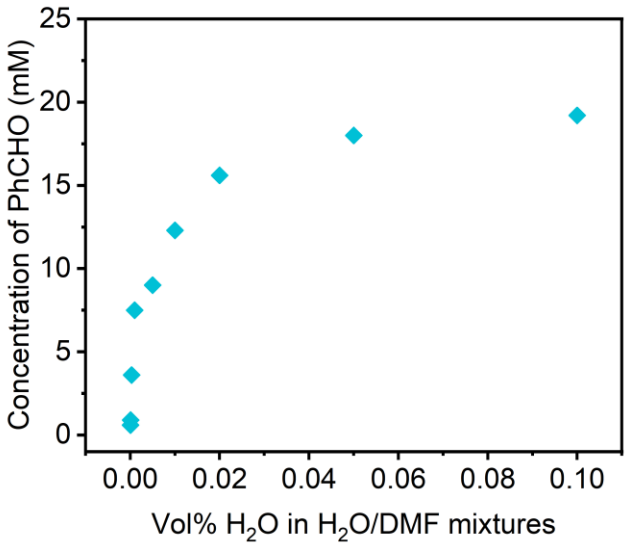


Figure R16 (new Figure S27). Measured PhCHO concentrations in the electrolyte after electroreductive carboxylation of BzOx in H_2O/DMF mixed electrolyte with varied volume percentages of H_2O. The electrolyte was treated with 0.1 M aqueous NaOH before PhCHO quantification.

We also appreciate the reviewer's suggestion of using in-situ Raman or IR spectroscopy to detect the BzIm intermediate. However, this experiment is highly challenging. The C=N stretching signal of BzIm significantly overlaps with those of BzOx (C=N) and the DMF solvent (C=O), making spectral discrimination difficult. In addition, the Pb electrode does not have strong surface enhancement, which is typically required in Raman and IR measurement of surface intermediates.

Revisions made:

Figures R15 and R16 (new Figures S26 and S27) have been added to the revised SI.

We have also added the corresponding discussion of the imine intermediate on Page 10 of the revised manuscript:

"Additional evidence for the formation of the BzIm intermediate is obtained from analyzing PhCHO generated during the reaction. Unlike BzOx, which is relatively stable against hydrolysis, BzIm can readily hydrolyze in the presence of H_2O to form PhCHO. After electrolysis under standard conditions, ~0.15 mM PhCHO can be detected, which is significantly higher than the residual concentration before electrolysis (Fig. S26). Furthermore, the amount of generated

PhCHO increases with increasing H_2O content in the electrolyte (Fig. S27), consistent with enhanced hydrolysis of the imine intermediate."

3-2 The manuscript clearly demonstrates that dissolved metal ions are essential for product formation. However, their precise role remains unclear.

Can the authors distinguish between Lewis acid activation vs precipitation-driven effects?

Is there spectroscopic evidence (e.g., UV–vis, NMR, EXAFS) for coordination between Zn^{2+} and intermediates?

How does the reaction rate or selectivity correlate with metal ion identity, concentration, and Lewis acidity?

Could the authors rule out that the observed effect is primarily post-electrode (solution-phase) chemistry rather than electrochemical activation?

Response:

We thank the reviewer for these insightful questions. We agree that clarifying the role of dissolved metal ions is essential, and we have performed additional experiments and analysis to address this point.

Several of our results support a Lewis acid activation role played by Zn^{2+} rather than a precipitation-driven effect. First, as shown in **Figure R17** below, significant PhGly formation can still occur at low Zn^{2+} concentrations (20 mM or lower), where no precipitation was observed, indicating that precipitation is not required for the reaction to proceed. Second, as shown in Figure 6 in the manuscript, substrates bearing fused aromatic substituents can effectively react to form the corresponding amino acid products without precipitation, further excluding precipitation as the primary driving force. Moreover, as we vary the identity of the added metal ions, a strong influence on the electroreductive carboxylation reaction can be observed (**Figure R18**). Cations of relatively weak Lewis acidity such as K^+ and Na^+ do not produce detectable PhGly. Li^+ with stronger Lewis acidity can enable product formation. Even stronger Lewis acids such as Mg^{2+}, Zn^{2+}, and Al^{3+} can generate PhGly with high FE values. All these results strongly support that Lewis acid activation is essential for the electroreductive carboxylation reaction of BzOx.

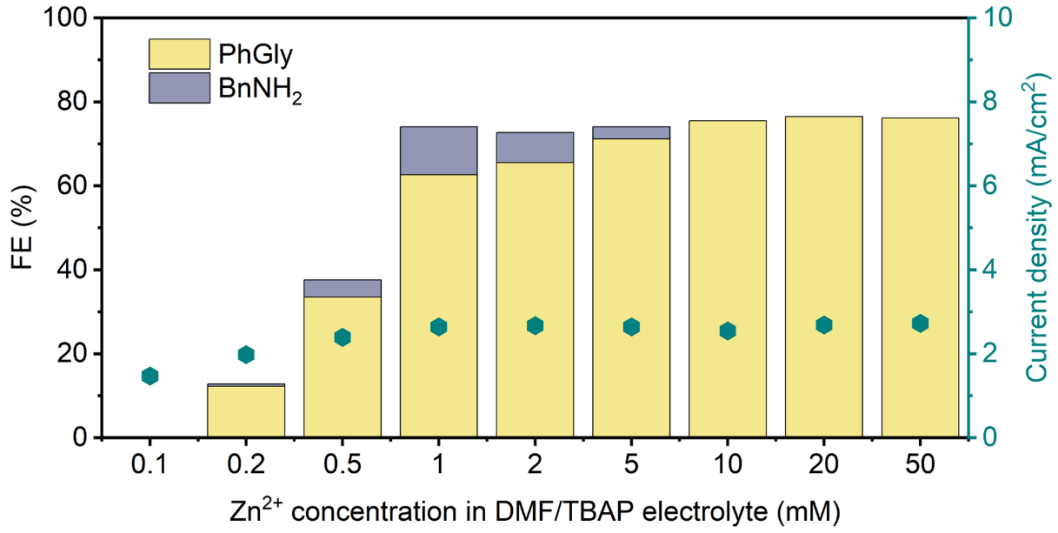


Figure R17 (new Figure S34). FEs and total current densities for electroreductive carboxylation of BzOx performed at −3.1 V vs Fc/Fc^+ for 1 h in a three-electrode H-cell with varied amount of anhydrous $Zn(OTf)_2$ added in the catholyte.

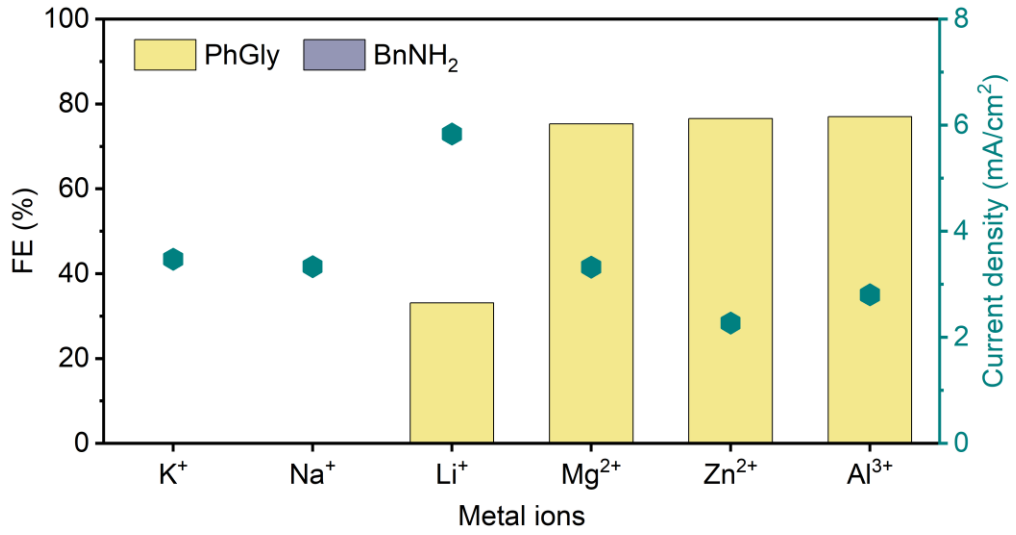


Figure R18 (new Figure S29). FEs and total current densities for electroreductive carboxylation of BzOx performed at −3.1 V vs Fc/Fc^+ for 1 h in a three-electrode H-cell with 50 mM of anhydrous $KClO_4$, $NaClO_4$, $LiClO_4$, $MgCl_2$, $Zn(OTf)_2$, or $AlCl_3$ added in the catholyte.

The activation role played by Zn^{2+} as a Lewis acid in the electroreductive carboxylation reaction of BzOx is fully consistent with our understanding of the kinetics of this reaction, which we will

present in detail in our response to Comment 3-4. The rate-determining step (RDS) of this reaction is the initial reduction of the oxime, which leads to cleavage of the N−O bond and formation of the imine intermediate. Metal ions play a crucial role in this electrochemical step, and the reaction efficacy is positively correlated with their Lewis acidity. The precipitation step, a solution-phase process that happens well after the RDS and is only observed for a fraction of oxime substrates at relatively high metal ion concentrations, is not an indispensable component of the oxime carboxylation reaction.

Revisions made:

Figures R17 and R18 (new Figures S34 and S29) have been added to the revised SI.

We have also expanded the discussion of the Lewis acid activation effect on Page 12 of the revised manuscript:

"Replacing Zn^{2+} with other metal ions such as Li^{+}, Na^{+}, K^{+}, Mg^{2+}, and Al^{3+} leads to different results. Systems containing Na^{+} or K^{+} do not generate any detectable amount of PhGly, whereas Li^{+}, Mg^{2+}, and Al^{3+} can all enable BzOx carboxylation (Fig. S29). This positive correlation between reaction efficacy and Lewis acidity of the added metal ions strongly supports the role of Zn^{2+} as a Lewis acid activating the oxime structure for electrochemical reduction into the corresponding imine."

3-3 Can the authors perform a $^{13}CO_2$ labeling experiment to directly confirm carbon incorporation? Is there any possibility that carbon originates from solvent decomposition or side reactions under the applied conditions?

Response:

We thank the reviewer for this valuable suggestion. Our control experiment already strongly supports that the carbon in the carboxylation product originates from the supplied CO_2 rather than solvent decomposition or other side reactions. As shown in **Figure R19** below, when CO_2 was replaced by Ar under otherwise identical conditions, no PhGly product was detected, while only $BnNH_2$ formation remained. This result rules out the possibility of PhGly formation from solvent decomposition or other side reactions. PhGly can be obtained only in the presence of CO_2, confirming that external CO_2 is an indispensable reactant of the carboxylation step. Since our control experiment has unambiguously confirmed CO_2 as the carbon source, we believe the use of expensive $^{13}CO_2$ is not need here.

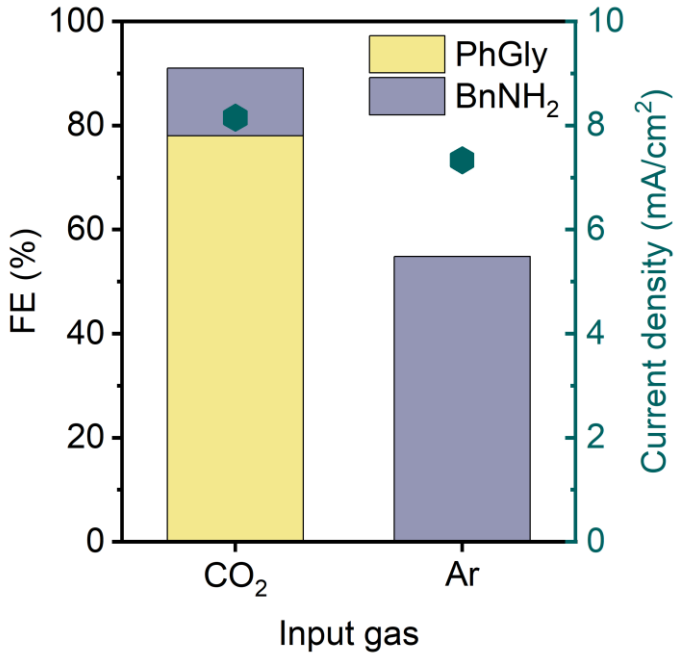


Figure R19 (new Figure S4). FEs and total current densities for electroreductive carboxylation of BzOx in CO_2 vs Ar gas atmosphere.

Revisions made:

Figure R19 (new Figure S4) has been added to the revised SI.

We have also added the corresponding discussion regarding the carbon source on Page 11 of the revised manuscript:

"A control experiment under otherwise identical conditions in Ar instead of CO_2 atmosphere yields no PhGly but only $BnNH_2$ from BzOx reduction (Fig. S4), which unambiguously rules out the possibility that the carboxyl carbon originates from solvent decomposition or other side reactions under the applied electrochemical conditions."

3-4 The electrochemical characterization remains relatively limited given the mechanistic ambition of the study. For example, the manuscript reports a zero-order dependence on oxime concentration, attributed to surface saturation, but this interpretation is not further developed.

What is the rate-determining step in the proposed mechanism?

How does the rate depend on potential, CO_2 concentration, and metal ion concentration?

Can the authors provide a more quantitative kinetic or microkinetic analysis supporting the surface-saturation hypothesis?

Response:

We thank the reviewer for raising these important points regarding the kinetics of this newly developed electroreductive carboxylation reaction of oximes. Following the reviewer's suggestion, in this revision, we have carried out additional kinetic studies and achieved a good understanding of the reaction mechanism. The details are described below.

First, we investigated the reaction's dependence on applied electrode potential. To accurately control the potential applied on the working electrode, we used a three-electrode system with a Ag wire quasi-reference electrode which was calibrated to the redox pair of Fc/Fc^+. As shown in **Figure R20** below, the target product PhGly starts to onset at the potential of −2.40 V vs Fc/Fc^+ and reaches its optimal FE and current density at −2.60 V. Tafel analysis based on these data near the onset potential gives a slope close to 120 mV/dec (**Figure R21**), suggesting that the first electron transfer step is the RDS. In the context of this reaction, this corresponds to the initial one-electron reduction of the oxime, leading to cleavage of the N−O bond. This is consistent with our previous findings about Pb-catalyzed oxime electroreduction to amine in aqueous media (J. Am. Chem. Soc. 2025, 147, 43692).

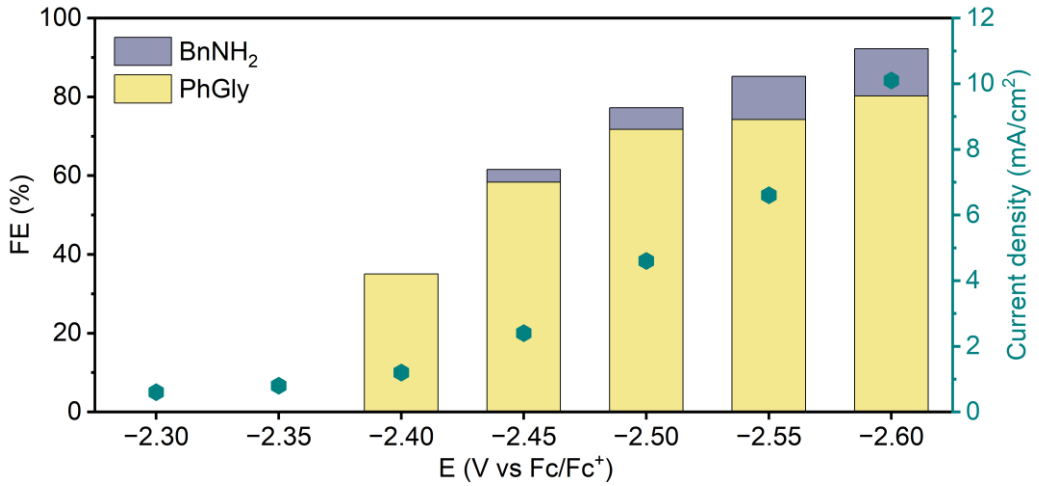


Figure R20 (new Figure S30). FEs and total current densities for electroreductive carboxylation of BzOx at varied electrode potentials measured in a three-electrode undivided cell.

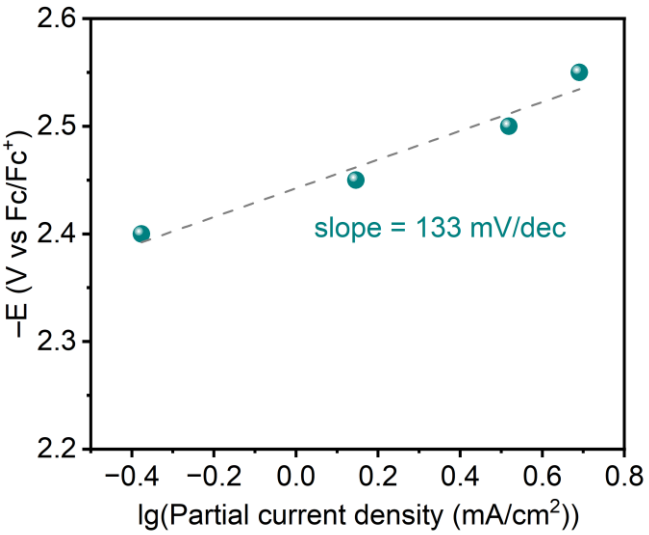


Figure R21 (new Figure S31). Tafel analysis for electroreductive carboxylation of BzOx.

We then studied the dependence of reaction rate on CO_2 concentration, by systematically varying the CO_2 partial pressure using CO_2/Ar mixtures. The results are plotted in **Figure R22**. As the CO_2 concentration decreases, the total current density decreases with decreasing FE for PhGly and increasing FE for $BnNH_2$. The relationship between the partial current density of PhGly and CO_2 partial pressure is shown in **Figure R23**. As the partial pressure of CO_2 decreases from 100 kPa to 80 kPa and then 60 kPa, the formation rate of PhGly (i.e., partial current density) remains the same. This zero-order kinetics reflects that the carboxylation step, namely the reaction between reduced BzIm and CO_2, occurs after the RDS. This agrees with the aforementioned Tafel analysis which shows the initial oxime reduction step is rate-limiting. As the CO_2 partial pressure further drops below 60 kPa, the reaction rate of PhGly formation becomes limited by the mass transport of CO_2 and consequently decreases with the partial pressure of CO_2.

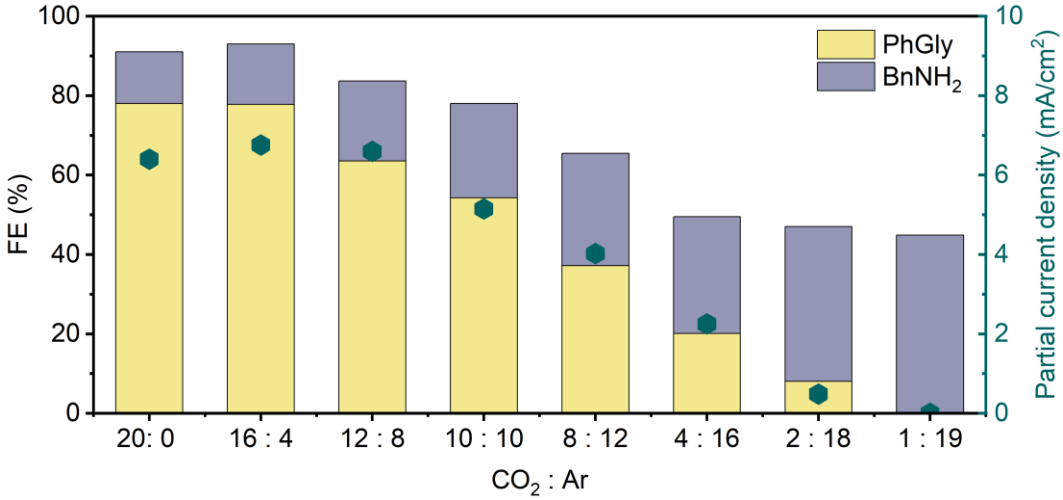


Figure R22 (new Figure S32). FEs and PhGly partial current densities for electroreductive carboxylation of BzOx in CO_2/Ar mixed atmosphere.

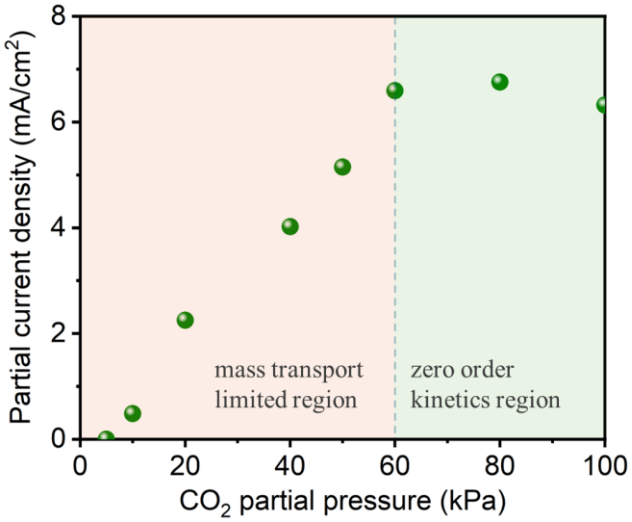


Figure R23 (new Figure S33). Dependence of PhGly partial current density on CO_2 partial pressure for electroreductive carboxylation of BzOx.

We also examined the dependence of reaction rate on Zn^{2+} concentration. The results are shown above in **Figure R17** in our response to Comment 3-2. The PhGly FE increases markedly when the Zn^{2+} concentration is raised from 0.1 to 1 mM, and then remains nearly unchanged at higher Zn^{2+} concentrations. The partial current density also increases with Zn^{2+} concentration in the lower region but reaches a plateau above 1 mM. The relationship between the production rate of PhGly and Zn^{2+} concentration is plotted in **Figure R24**. The linear correlation at Zn^{2+} concentrations lower than 1 mM reflects a first-order reaction with respect to Zn^{2+}. This indicates that Zn^{2+} directly

participates in the RDS of the electroreductive carboxylation reaction of BzOx, which we have confirmed to be the initial electrochemical reduction of the N−O bond in the oxime structure. This is consistent with the activation role played by Zn^{2+} as a Lewis acid, as discussed above.

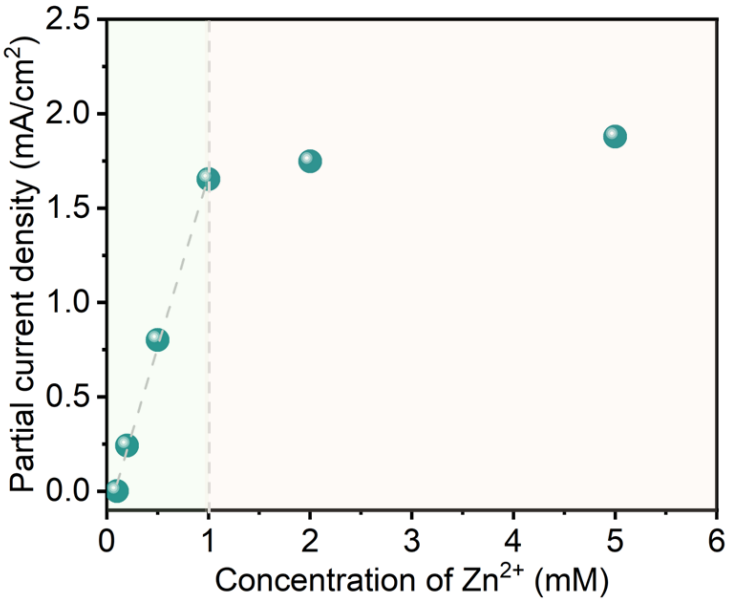


Figure R24 (new Figure S35). Partial current density of PhGly vs Zn^{2+} concentration in catholyte for electroreductive carboxylation of BzOx at −3.1 V vs Fc/Fc^+ measured in a three-electrode H-cell.

Taken together, these detailed kinetic results and analysis support a mechanism in which the initial one-electron reduction of BzOx, accompanied by N−O bond cleavage, is the RDS of the overall reaction (**Figure R25**). The subsequent carboxylation step between the imine (or its reduced intermediate) and CO_2 is kinetically fast under normal CO_2 concentration conditions. Participation of metal ions with strong Lewis acidity such as Zn^{2+} in the RDS is crucial. These results collectively support an electroreduction mechanism controlled primarily by the first electron-transfer step assisted by a Lewis acid.

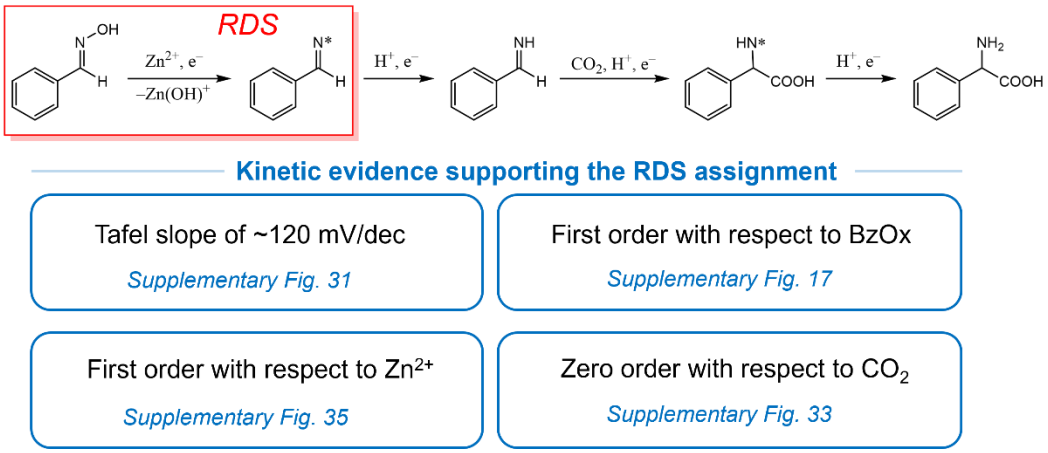


Figure R25 (new Figure 6). Identification of RDS for electroreductive carboxylation of BzOx to PhGly supported by kinetic study results.

Revisions made:

Figures R20–R25 (new Figures S28–S33 and Figure 6) have been added to the revised SI and manuscript.

We have also added additional kinetic analysis on Pages 11–12 of the revised manuscript:

"To further understand the mechanism of the electroreductive carboxylation reaction of BzOx, we perform systematic kinetic studies. First, the dependence of the reaction on applied potential is studied using a three-electrode system. PhGly formation starts to onset at approximately −2.40 V vs Fc/Fc^+ (Fig. S30). Tafel analysis based on the partial current density of PhGly near the onset region gives a slope close to 120 mV/dec (Fig. S31), suggesting that the rate-determining step (RDS) involves the first electron transfer. In the context of this reaction, this corresponds to the initial one-electron reduction of BzOx accompanied by N–O bond cleavage, consistent with our previous study on Pb-catalyzed electroreduction of oximes to amines in aqueous electrolyte.[56] We then investigate the dependence of reaction kinetics on CO_2 concentration using CO_2/Ar mixed gas feeds with controlled ratios. Decreasing the CO_2 partial pressure generally leads to lower FE toward PhGly together with increased $BnNH_2$ formation (Fig. S30). However, the partial current density for PhGly remains nearly unchanged as the CO_2 partial pressure is decreased from 100 to 60 kPa (Fig. S33), indicating an approximately zero-order dependence on CO_2 concentration within this range. This suggests that the carboxylation step between CO_2 and the reduced imine intermediate occurs after the RDS and is kinetically fast under normal CO_2 concentration conditions. When the CO_2 partial pressure is decreased below 60 kPa, the partial current density for PhGly decreases markedly because of CO_2 mass transport limitation. The dependence of reaction kinetics on Zn^{2+} concentration is also examined in the three-electrode H-cell setting. Both the FE and partial current density of PhGly increase significantly when the Zn^{2+} concentration is

increased from 0.1 to 1 mM, followed by a plateau at higher concentrations (Fig. S34). The approximately linear dependence of PhGly formation rate on Zn^{2+} concentration below 1 mM reflects first-order kinetics with respect to Zn^{2+}, suggesting direct participation of the metal ion in the RDS (Fig. S35). Combined together, these kinetic analysis results support a reaction mechanism in which Lewis acid-assisted initial reduction of the oxime N–O bond is the kinetically limiting step, whereas the subsequent carboxylation step is relatively fast under standard reaction conditions (Fig. 6)."

3-5 A more explicit comparison with existing electrochemical amino acid syntheses would strengthen the discussion.

Response:

We thank the reviewer for this helpful suggestion. In response, we have now included a more explicit and detailed comparison with previously reported electrochemical amino acid synthesis strategies, as summarized in the two tables below.

Table R1 makes a comparison with previous electrosynthetic routes based on α-keto or oxalic acid substrates. These substrates have two limitations compared to the reaction developed in this work. First, they already contain the carboxyl group in the structure, and therefore do not directly incorporate CO_2 in the synthesis. In contrast, our method directly converts CO_2 into the carboxyl group of the amino acid product. Second, some α-keto acids are difficult or expensive to synthesize, whereas our method uses simple aromatic aldehydes that can be easily sourced from biomass or commodity chemicals.

Table R2 makes a comparison with previous electrosynthetic routes based on imine substrates. These methods predominantly yield N-substituted α-amino acid derivatives because N-substituents are required to stabilize the imine reactants/intermediates in the electrochemical carboxylation. In contrast, our method avoids this constraint by employing an oxime-based pathway, enabling the direct synthesis of free arylglycines without preinstalled N-substitution. This difference not only simplifies the overall synthetic route and provides more direct access to practically useful amino acid products, but also allows direct valorization of NO_x^{y-} wastes.

Overall, this comparison highlights that our approach differs fundamentally from prior work by combining simple feedstocks, lower substrate cost, and direct CO_2 incorporation, thereby offering a more sustainable and potentially scalable route to amino acid synthesis.

Table R1 (new Table S1). Comparison with amino acid electrosynthesis based on α-keto acid substrates.

Category	**Methods based on α-keto acids/oxalic acids**	**This work**
Organic substrate	Pre-functionalized substrates (α-keto acids, α-hydroxyl acids, and oxalic/glyoxylic acid)	Simple aromatic aldehydes
Substrate origin	Typically derived from biomass upgrading or chemical pre-synthesis	Widely available commodity or biomass chemicals
Substrate cost	Higher, due to functionalization and limited availability	Lower, due to broad availability of aldehydes
Nitrogen source	NO_3^-/NO_2^-/NO	NO_2^-, extendable to NO_3^-/NO
Carbon source	Already in the organic substrate (no CO_2 incorporation)	CO_2 (directly incorporated)
Use of environmental waste feedstocks	NO_x^{y-} utilization	Dual utilization of CO_2 and NO_2^-
Overall feedstock sustainability	Limited by reliance on pre-functionalized organic acids	Higher sustainability due to simple inputs and waste valorization

Table R2 (new Table S2). Comparison with electrochemical amino-acid syntheses and this work

Category	**Methods based on electrochemical carboxylation of imines**	**This work**
Product type	N-substituted (N-aryl or N-acyl) α-amino acids	Unsubstituted (free) arylglycines
Requirement of N-substitution	N-substituents are required for substrate stability/reactivity	No preinstalled N-substituents, nitrogen introduced as NH_2OH from NO_2^-, enabling formation of free NH_2 groups

Nitrogen source	Already in the organic substrate (no NO_x^{y-} valorization)	NO_2^-, extendable to NO_3^-/NO
Post-synthesis treatment	Additional deprotection or transformation steps are required to access free amino acids	Direct access to free amino acids, avoiding extra post-treatment steps
Imine reactants/intermediates	Imines with stabilizing N-substituents as reactants	Imine intermediates generated in situ from oxime reduction

Revision made:

Tables R1 and R2 (new Tables S1 and S2) have been added to the revised SI.

3-6 The discussion of competing CO_2 reduction pathways (e.g., formate formation) could be expanded.

Response:

We thank the reviewer for this helpful suggestion to expand the discussion of competing CO_2 reduction pathways.

On Pb electrodes in nonaqueous media, competing CO_2 reduction pathways originate from the same initial step: one-electron transfer to CO_2 to form $CO_2^{\bullet-}$, which can either couple to give oxalate or follow proton-coupled routes to formate, CO, and other reduced products (Appl. Catal. B: Environ. 2010, 98, 65; Ind. Eng. Chem. Res. 2022, 61,14837). Which pathway dominates depends strongly on the local reaction environment. A low-proton, rigorously aprotic interface favors C–C coupling to oxalate, whereas even trace water shifts Pb toward formate and other proton-involving products (Sustain. Energy Fuels, 2023, 7, 509; ChemPhysChem 2025, 26, e202500136). Solvent properties further control this balance by changing CO_2 solubility, viscosity, conductivity, and mass transport, so that DMF, PC, and MeCN can give markedly different selectivities on Pb under otherwise similar conditions (Sustain. Energy Fuels 2023, 7, 509; ChemPhysChem 2025, 26, e202500136). In addition, the double-layer composition is important: alkali cations such as K^+ stabilize CO_2-derived intermediates near the surface and promote C–C coupling to C_{2+} products (J. Mater. Chem. A 2024, 12, 15829), while catalyst microenvironment engineering, such as polymer-confined interfaces, can suppress proton transport and retain reactive intermediates, again favoring oxalate formation over competing CO_2RR channels (Adv. Energy Mater. 2025, 15, 2501286). Surface structure also matters, since oxide-derived Pb suppresses competing H^+ reduction while maintaining CO_2 reduction activity (ACS Catal. 2015, 5, 465). In the present system, however, these conventional CO_2RR pathways are largely outcompeted

because the oxime/imine substrate is a more favorable electron acceptor than CO_2 under the applied conditions. As a result, electron transfer occurs preferentially to the organic substrate rather than generating a substantial surface population of $CO_2^{\bullet-}$, so pathways such as formate or oxalate formation are disfavored. CO_2 therefore behaves mainly as a coupling reagent in the subsequent carboxylation of the reduced organic intermediate, rather than as the primary species undergoing direct electroreduction.

Overall, this expanded discussion highlights that the suppression of competing CO_2RR pathways in our system arises from a fundamental shift in the reaction sequence, where electron transfer is directed toward the organic substrate, thereby preventing CO_2 from entering conventional reduction pathways such as formate formation.

Revision made:

We have expanded the discussion of competing CO_2 reduction pathways on Page 7 of the revised manuscript:

"For Pb-catalyzed CO_2 electroreduction in organic media, strictly aprotic conditions often favor C−C coupling to form oxalate, whereas proton sources promote formate formation. In this case, the trace amount of H_2O in the DMF electrolyte serves as the proton source for formate production when the BzOx reactant is not present."

Manuscript#: NATSYNTH-26030694
Corresponding Author: Hailiang Wang
Title: Electrosynthesis of Arylglycines from Carbon Dioxide, Nitrite, and Aldehydes

The manuscript presents an electrosynthetic route to arylglycines from nitrite, aldehydes, and CO_2. The transformation is conceptually attractive, combining nitrogen and carbon waste streams into value-added amino acid derivatives, and the reported substrate scope is promising. The authors further propose a mechanistic pathway in which oximes are converted to arylglycines via an imine intermediate, with dissolved metal ions (e.g., Zn^{2+}) playing a crucial enabling role.
While the overall concept is compelling and well aligned with the scope of *Nature Synthesis*, the mechanistic claims are currently stronger than the experimental evidence fully supports. In particular, the imine pathway is inferred largely through exclusion experiments and reactivity of preformed intermediates, rather than direct observation under catalytic conditions. Similarly, although the importance of dissolved metal ions is convincingly demonstrated, their precise role in the reaction mechanism remains insufficiently resolved. Given that mechanistic insight constitutes a central pillar of the manuscript, additional experimental support, such as in situ / operando spectroscopy, isotopic labeling, and more detailed electrochemical analysis would significantly strengthen the work.

Overall, I find the study promising but not yet at the level of mechanistic rigor expected for publication in *Nature Synthesis*. I therefore recommend **major revision**.

1. The authors conclude that the reaction proceeds via an imine intermediate rather than via hydroxylamine-derived species, based on (i) the lack of reactivity of a synthesized hydroxylamine intermediate and (ii) the successful conversion of a preformed imine. While these results are suggestive, they do not constitute direct evidence for the formation of the imine intermediate under electrochemical conditions.
Can the authors provide direct evidence for the imine intermediate under reaction conditions (e.g., operando IR, Raman, or NMR)? Is it possible to perform time-resolved or in situ spectroscopy to monitor oxime to imine conversion? Are there kinetic or isotope-labeling experiments that could distinguish between competing pathways more rigorously?

2. The manuscript clearly demonstrates that dissolved metal ions are essential for product formation. However, their precise role remains unclear. Can the authors distinguish between Lewis acid activation vs precipitation-driven effects? Is there spectroscopic evidence (e.g., UV–vis, NMR, EXAFS) for coordination between Zn^{2+} and intermediates? How does the reaction rate or selectivity correlate with metal ion identity, concentration, and Lewis acidity? Could the authors rule out that the observed effect is primarily post-electrode (solution-phase) chemistry rather than electrochemical activation?

3. Can the authors perform a $^{13}CO_2$ labeling experiment to directly confirm carbon incorporation? Is there any possibility that carbon originates from solvent decomposition or side reactions under the applied conditions?

4. The electrochemical characterization remains relatively limited given the mechanistic ambition of the study. For example, the manuscript reports a zero-order dependence on oxime concentration, attributed to surface saturation, but this interpretation is not further developed. What is the rate-determining step in the proposed mechanism? How does the rate depend on potential, CO_2 concentration, and metal ion concentration? Can the authors provide a more quantitative kinetic or microkinetic analysis supporting the surface-saturation hypothesis?

Minor Comments

- A more explicit comparison with existing electrochemical amino acid syntheses would strengthen the discussion.
- The discussion of competing CO_2 reduction pathways (e.g., formate formation) could be expanded.