1,2-Amino oxygenation of alkenes with hydrogen evolution reaction

Shengzhang Liu1,2,4, Shengchun Wang3,4, Pengjie Wang3, Zhiliang Huang3, Tao Wang1 & Aiwein Lei1,3

1,2-Amino oxygenation of alkenes has emerged as one of the most straightforward synthetic methods to produce β-amino alcohols, which are important organic building blocks. Thus, a practical synthetic strategy for 1,2-amino oxygenation is highly desirable. Here, we reported an electro-oxidative intermolecular 1,2-amino oxygenation of alkenes with hydrogen evolution, removing the requirement of extra-oxidant. Using commercial oxygen and nitrogen sources as starting materials, this method provides a cheap, scalable, and efficient route to a set of valuable β-amino alcohol derivatives. Moreover, the merit of this protocol has been exhibited by its broad substrate scope and good application in continuous-flow reactors. Furthermore, this method can be extended to other amino-functionalization of alkenes, thereby showing the potential to inspire advances in applications of electro-induced N-centered radicals (NCRs).

As one type of basic frame with unique physiological activity, β-amino alcohol motifs widely exist in pharmaceuticals1, natural products2, and ligands3 (Fig. 1a). Due to their significant importance, the synthesis and transformation of β-amino alcohols have drawn much attention from synthetic chemists and pharmacists4–6. Forming β-amino alcohols in a single-step, 1,2-amino oxygenation of alkenes represents one of the ideal routes toward this synthetic goal. Over the last decades, 1,2-amino oxygenation has achieved several breakthroughs7–9. Since 1975, transition-metal (such as Pd, Os, Rh, Cu, Fe, Mn, Ir, etc.) catalyzed alkenes 1,2-amino oxygenation has undergone a flourishing development7,10–19. Despite their excellent regioselectivity, expensive transition-metal catalysts and/or complex ligands have propelled the development of alternative approaches. To avoid the use of metal-catalyst, oxidation-induced strategy has recently served as another fascinating way to synthesize β-amino alcohols with sacrificial oxidants (including hypervalent iodines9,20–21, peroxides22, diazodicarboxylates23, fluor-containing oxidants24–25, TEMPO26–27, etc.). While these methods ensure efficient approaches, their compatibility with oxygen and nitrogen sources may be problematic. As green and powerful tools, photo-induced organic transformations have been attractive synthetic methods to produce amino alcohol derivatives28–32. With a unique property for sustainable and practical synthetic methods, electro-induced alkenes transformation involving N-centered radicals (NCRs) has attracted extensive attention from chemists33–35. A representative report is an azidooxygenation of alkenes via electro-oxidation, in which TEMPO and N3 were applied as oxygen and nitrogen sources, respectively36.

Although numerous attractive methods have been developed for this ideal synthesis, several challenges still remain in the 1,2-amino oxygenation approach (Fig. 1b). One internal challenge is the precise control of regio- and chemoselectivity in this transformation. Since the reacting oxygen and nitrogen nucleophiles generally showed similar reactivity, other potential reactions, including diamination, 1,2-oxyamination, and dioxygenation, might adversely affect the desired 1,2-amino oxygenation. Another challenge in the application is the development of mild methods with good compatibility for both oxygen and nitrogen sources, especially for O–H and N–H compounds that represent a direct and atom-economical route. Thus, developing an efficient, cheap, and easy-to-handle method to...
accomplish alkene 1,2-amino oxygenation with simple O–H and N–H functionalities are desirable, yet challenging.

Based on our previous works on electro-induced NCR chemistry37–39, we conceived a feasible electro-oxidative 1,2-amino oxygenation of alkenes to address these challenges (Fig. 1c). As the initiation of this hypothesis, an anti-Markovnikov addition between NCRs and alkenes can provide high regioselectivity for such organic transformation. Moreover, the hydrogen evolution in the cathode can increase the concentration of alkoxy anions (–OR), which may further promote the formation of C–O bonds. Meanwhile, the direct utilization of O–H and N–H compounds may ensure the wide applicability of this synthetic method. Therefore, we report here an efficient, transition-metal-catalyst- and oxidant-free alkene 1,2-amino oxygenation via an electro-induced NCRs pathway, providing a practical route toward synthesizing β-amino alcohol derivatives.

**Results**

**Condition optimization for electro-oxidative 1,2-amino oxygenation**

Usually, solvents affect the lifetime and reactivity of NCRs. Therefore, various solvents involving O–H functionalities were initially examined with N-methyl-p-toluenesulfonamide 1a and styrene 2aa as the model substrates. Unfortunately, the desired 1,2-amino oxygenation products were not detected in AcOH, EtOH, 2,2,2-trifluoroethanol (TFE), and hexafluorisopropylalcohol (HFIP) (see Supplementary Table 1). Though the 1,2-amino oxygenation was successfully achieved in MeOH, those tested reactions were limited in their moderate yields (see details in Supplementary Table 2). Combined with our previous works, the mixed solvents were attempted, including dichloromethane (DCM)/TFE, MeCN/TFE, and DCM/HFIP. When the mixture of DCM (4 mL) and TFE (2 mL) was used, the 1,2-amino oxygenation was successfully accomplished to form target product 4aa in 76% isolated yield by using 2 equivalents 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as the base (Table 1, entry 1). DBU is essential for the high yield, as the low conversion of 1aa and no target product detected in its absence (entry 2), while lower yields were obtained with the use of K3PO4 or Cs2CO3 instead of DBU (entries 3 and 4). The separated yield of 4aa slightly reduced when the electron current was decreased to 2 mA or increased to 10 mA, even with the same electron quantity (entries 5 and 6). The utilization of carbon rod or Ni plate as cathode could also furnish the product 4aa, but in lower yields (entries 7 and 8). This electro-chemical conversion was compatible with air in which the products were formed in 60% yield (entry 9). The control experiment showed that the current is necessary for this transformation (entry 10).

**Scope of substrates**

With the optimized protocol for alkene 1,2-amino oxygenation, we examined the scope of alkenes using N-methyl-p-toluenesulfonamide
### Table 1 | Optimization of the electro-oxidative 1,2-amino oxygenation of alkenes

| Entry | Variations | Yield (%) \(^a\) |
|-------|------------|------------------|
| 1     | No         | 71               |
| 2     | Without DBU | n.d.            |
| 3     | K₂PO₄ instead of DBU | 55 |
| 4     | Cs₂CO₃ instead of DBU | 38 |
| 5     | 2 mA, 10 h | 74               |
| 6     | 10 mA, 2.5 h | 70               |
| 7     | Carbon rod as cathode | 66 |
| 8     | Ni plate as cathode | 67 |
| 9     | Under air  | 60               |
| 10    | Without current | n.d.             |

Standard conditions: graphite rod anode (Ø 6 mm), Pt plate cathode (15 mm × 15 mm × 0.3 mm), constant current = 4 mA, 1a (0.30 mmol), 2aa (0.90 mmol), DBU (0.60 mmol), TBABF₄ (0.30 mmol), DCM/TFE (4 mL/2 mL), r.t., 5 h, undivided cell, and nitrogen.

\(^a\) Isolated yields.

---

**Fig. 2 | Scope of substrates.**

**a** Scope of alkenes. Reaction conditions: graphite rod anode (Ø 6 mm), Pt plate cathode (15 mm × 15 mm × 0.3 mm), constant current = 4 mA, sulfonamides (0.3 mmol, 1 equiv.), alkenes (0.9 mmol, 3 equiv.), DBU (0.6 mmol), TBABF₄ (0.30 mmol), DCM/TFE (4 mL/2 mL), r.t., 5 h, undivided cell under N₂.

**b** Scope of sulfonamides. Alkenes (1.8 mmol, 6 equiv.) were used. Constant current = 5 mA, 6 h, DBU (0.39 mmol, 1.3 equiv.). Alkenes (3.0 mmol, 10 equiv.) were used. All yields are isolated yields.
1aa in the mixture of DCM and TFE (Fig. 2a). Various mono-functionalized styrenes with ortho-, meta- or para-substituents were suitable radical acceptors to afford the corresponding products in moderate to good yields (4aa–4am). Notably, though alkenes with electron-withdrawing groups transformed to the target products smoothly (4an and 4ao), this 1,2-amino oxygenation was completed in low yields using alkenes with strong electron-donating groups (4ar). In addition, alkene with a sensitive functional group, for example, benzyl chloride, was well tolerated in this condition (4as). Moreover, alkenyl ether derivatives were also compatible with this electro-oxidative 1,2-amino oxygenation. Various alkyl ether ethers were smoothly transformed to target products in moderate yields (4at–4ba). In addition, unactivated 1,1-disubstituted alkene 2bb successfully realized amino oxygenation to afford products 4bb.

Subsequently, further exploration of sulfonamides was carried out under electro-oxidative conditions (Fig. 2b). A series of functionalized benzenesulfonamides with electron-donating or electron-withdrawing groups were satisfactory amination reagents (5a–5j). Moreover, sulfonamides with (hetero)cyclic motifs were also suitable for producing products in moderate yields (5k–5m). Furthermore, other N-alkyl substituted sulfonamides well performed in this 1,2-amino oxygenation (5n–5r). With the respect to limitation, secondary alkylamines and primary amides failed toward the target products under the optimized conditions. When the activated methylene was present on the nitrogen atom, the amino oxygenation was also achieved in low yields (5s, 5t). More efforts to address these limitations are currently going on.

Strategic expansions and synthetic applications

Next, a series of experiments were performed to demonstrate the expansion of this strategy (Fig. 3A). Additional scope of alkenes with HNOAc illustrated that this method could be well expanded to other acids with good functional group compatibility (Fig. 3A-a, 6a–6j). In addition, this electro-induced alkenes di-functionalizations were successfully achieved with other nucleophiles, including acids, alcohols, and even pyrazoles (Fig. 3A-b, 6k–6s).

To show the potential in further application, this synthetic method was also demonstrated in a continuous-flow reactor (Fig. 3B-c). At the flow rate of 0.8 mL min⁻¹, the desired 1,2-amino oxygenation was completed smoothly to produce 1.88 g products in 81% isolated yield. In addition, 4ba and 6a were also well performed in continuous-flow conditions toward a gram-scale synthesis of β-amino alcohol derivatives. Furthermore, this transformation was applied in the synthesis of 8, which could further furnish a natural product, halostachine (Fig. 3B-d).

Mechanistic studies

Then, several experiments were carried out to explore the mechanism of this electro-chemical 1,2-amino oxygenation (Fig. 4A). As shown in Fig. 4A-a, the NMR experiments supported a proton transfer mechanism. To show the potential in further application, this synthetic method was also demonstrated in a continuous-flow reactor (Fig. 3B-c). At the flow rate of 0.8 mL min⁻¹, the desired 1,2-amino oxygenation was completed smoothly to produce 1.88 g products in 81% isolated yield. In addition, 4ba and 6a were also well performed in continuous-flow conditions toward a gram-scale synthesis of β-amino alcohol derivatives. Furthermore, this transformation was applied in the synthesis of 8, which could further furnish a natural product, halostachine (Fig. 3B-d).
In addition, the radical clock experiment was carried out with the use of alkene 11 (Fig. 4A-c). The formation of the corresponding ring-opening adduct 11a further supported the radical addition of in-situ formed NCRs to alkenes. Afterward, a series of CV studies were performed to explore the anodic reaction (Fig. 4A-d). Although the oxidative peak of 1a was not observed in the range of 0–2.5 V, the catalytic current of DBU obviously increased with the addition of 1a. These results revealed that DBU was electroactive, supporting a fast electron-transfer process between oxidized DBU and 1a. While styrene 2a showed an electro-redox activity, styrenes with electron-donating groups led to low yields (Supplementary Fig. 6). Therefore, the direct oxidation of alkenes may not be the initial step of this electro-oxidative transformation. Based on the above results and previous studies37,39, a plausible mechanism was proposed for this electro-oxidative 1,2-amino oxygenation (Fig. 4B). Firstly, a proton transfer between sulfonamide 1a and DBU happened to generate N-centered cation I, which could be oxidized toward NCR II in the anode. Another mechanism could not be ruled out that a mixture of 1a and DBU was directly oxidized in the anode to afford NCR II. Subsequently, such NCR II was added to the alkene 2a to form a C-centered radical III, which could further be oxidized for the formation of C-centered cation IV. Then intermediate IV was attacked by trifluoroethanol 3 with the release of a proton. In the cathode, two protons were reducted to evolve hydrogen.

In summary, we have developed an electro-oxidative 1,2-amino oxygenation of alkenes using readily available sulfonamides and alcohols as nitrogen and oxygen sources with H2 evolution. This method offers a convenient and powerful synthetic approach toward β-amino alcohols in one step without extra-oxidants. Moreover, the wide scope, good performance in continuous-flow electro-reactor, and the efficient synthesis of natural products illustrate the potential applicability of this method in the industry. Furthermore, this method can be extended to other alkene amino-functionalizations, thereby having the potential to inspire advances in other transformations via electro-induced NCRs.

**Methods**

In an oven-dried undivided three-necked bottle (10 mL) equipped with a stir bar, sulfonamide substrate 1a (0.3 mmol) and Bu4NF 4 (0.3 mmol) were combined and added. The undivided cell was equipped with graphite rod anode (φ 6 mm), platinum plate cathode (1.5 cm × 1.5 cm × 0.3 mm) and was then charged with nitrogen. Under the atmosphere of nitrogen, DBU (0.6 mmol), and alkenes 2 (0.9 mmol) were added, then DCM (4.0 mL) and TFE (2.0 mL) were injected respectively into the tubes via syringes. The mixture was electrolyzed using constant current conditions (4.0 mA) for 5 h at room temperature under magnetic stirring. When TLC analysis indicated that the electrolysis was complete (witnessed by the disappearance of the 1a), the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel using a mixture of PE/EA (v:v = 25:1) as eluent to afford the desired pure product.

**Data availability**

The authors declare that the data supporting the findings of this study are available within the paper and its Supplementary information files or from the authors upon request.

**References**

1. Garofalo, A. W. et al. A series of C-terminal amino alcohol dipeptide A beta inhibitors. *Bioorg. Med. Chem. Lett.* **12**, 3051–3053 (2002).
2. Heravi, M. M., Lashaki, T. B., Fattahi, B. & Zadshirjan, V. Application of asymmetric Sharpless aminohydroxylation in total synthesis of natural products and some synthetic complex bio-active molecules. *RSC Adv.* **8**, 6634–6659 (2018).
3. Fache, F., Schulz, E., Tommasino, M. L. & Lemaire, M. Nitrogen-containing ligands for asymmetric homogeneous and heterogeneous catalysis. *Chem. Rev.* **100**, 2159–2232 (2000).
4. Bergmeier, S. C. The synthesis of vicinal amino alcohols. *Tetrahedron* **56**, 2561–2576 (2000).
5. Roughley, S. D. & Jordan, A. M. The medicinal chemist’s toolbox: an analysis of reactions used in the pursuit of drug candidates. J. Med. Chem. 54, 3451–3479 (2011).
6. Hemric, B. N. Beyond osmium: progress in 1,2-amino oxygenation of alkenes, 1,3-dienes, alkenes, and alkenes. Org. Biomol. Chem. 19, 46–81 (2021).
7. Yin, G., Mu, X. & Liu, G. Palladium(II)-catalyzed oxidative difunctionalization of alkenes: bond forming at a high-valent palladium center. Acc. Chem. Res. 49, 2413–2423 (2016).
8. Lan, X.-W., Wang, N.-X. & Xing, Y. Recent advances in radical difunctionalization of simple alkenes. Eur. J. Org. Chem. 2017, 5821–5851 (2017).
9. Romero, R. M., Wöste, T. H. & Muñiz, K. Vicinal difunctionalization of alkenes with iodine(III) reagents and catalysts. Chem. Eur. J. 9, 972–983 (2014).
10. Chemler, S. R., Chen, D., Karyakarte, S. D., Shikora, J. M. & Wdowik, T. Transition-metal-catalyzed aminoxygenation of alkenes. Org. React. 108, 421–769 https://doi.org/10.1002/0471264180.or108.02 (2021).
11. Kotov, V., Scarborough, C. C. & Stahl, S. S. Palladium-catalyzed aerobic oxidativeamination of alkenes: development of intra- and intermolecular Aza-Wacker reactions. Inorg. Chem. 46, 1910–1923 (2007).
12. Li, Z.-L., Fang, G.-C., Gu, Q.-S. & Liu, X.-Y. Recent advances in copper-catalysed radical-involved asymmetric 1,2-difunctionalization of alkenes. Chem. Soc. Rev. 49, 32–48 (2020).
13. Levites-Agababa, E., Menhaji, E., Perlson, L. N. & Rojas, C. M. Amiodagocysylation via metal-catalysed internal nitrogen atom delivery. Org. Lett. 4, 863–865 (2002).
14. Williamson, K. S. & Yoon, T. P. Iron catalyzed asymmetric oxygenation of olefins. J. Am. Chem. Soc. 134, 12370–12373 (2012).
15. Sun, X. et al. Mn-catalyzed highly efficient aerobic oxidativehydroxyazidation of olefins: a direct approach to β-azido alcohols. J. Am. Chem. Soc. 137, 6059–6066 (2015).
16. Shi, Y. et al. Rhodium-catalyzed aminohydroxylation of unactivated alkenes in aqueous media for the benign synthesis of 1,2-amine alcohols. Green. Chem. 21, 780–784 (2019).
17. Lei, H., Conway, J. H., Cook, C. C. & Rovis, T. Ligand controlled Ir-catalyzed regiodivergent oxyamination of unactivated alkenes. J. Am. Chem. Soc. 141, 11864–11869 (2019).
18. Wu, Y.-C., Xiao, Y.-T., Yang, Y.-Z., Song, R.-J. & Li, J.-H. Recent advances in Silver-mediated radical difunctionalization of alkenes. ChemCatChem 12, 5312–5329 (2020).
19. Bäckvall, J.-E. Stereosepecific palladium(II)-lead(IV)-promoted oxyamination of olefins. Tetrahedron Lett. 16, 2225–2228 (1975).
20. Wang, X. & Studer, A. Iodine(III) reagents in radical chemistry. Acc. Chem. Res. 50, 1712–1724 (2017).
21. Muñiz, K. In Hypervalent Iodine Chemistry (ed Wirth, T.) 105–133 (Springer International Publishing, 2016). https://doi.org/10.1007/1282015-663.
22. Xue, Q. et al. Metal-free, n-Bu4NI-catalyzed regioselective difunctionalization of unactivated alkenes. ACS Catal. 3, 1365–1368 (2013).
23. Schmidt, V. A. & Alexanian, E. J. Metal-free oxyaminations of alkenes using hydroxamic acids. J. Am. Chem. Soc. 133, 11402–11405 (2011).
24. Wu, F., Alom, N.-E., Ariyathatha, J. P., Naß, J. & Li, W. Regioselective formal [3+2] cycloadditions of urea substrates with activated and unactivated olefins for intermolecular olefin aminooxygenation. Angew. Chem. Int. Ed. 58, 11676–11680 (2019).
25. Tao, Z., Gilbert, B. B. & Denmark, S. E. Catalytic, enantioselective syn-diamination of alkenes. J. Am. Chem. Soc. 141, 19161–19170 (2019).
26. Wang, T. & Jiao, N. TEMPO-catalyzed aerobic oxygenation and nitrogenation of olefins via C=C double-bond cleavage. J. Am. Chem. Soc. 135, 11692–11695 (2013).
27. Chen, F. et al. Oxoammonium salt-mediated vicinal oxyazidation of alkenes with Na[N3] access to β-aminooxy azides. Adv. Synth. Catal. 363, 5079–5084 (2021).
28. Zhao, Y. & Xia, W. Recent advances in radical-based C–N bond formation via photo-electrochemistry. Chem. Soc. Rev. 47, 2591–2608 (2018).
29. Xiong, T. & Zhang, Q. New amination strategies based on nitrogen-centered radical chemistry. Chem. Soc. Rev. 45, 3069–3087 (2016).
30. Yu, X.-Y., Zhao, Q.-Q., Chen, J., Xiao, W.-J. & Chen, J.-R. When light meets nitrogen-centered radicals: from reagents to catalysts. Acc. Chem. Res. 53, 1066–1083 (2020).
31. Lai, S.-Q., Wei, B.-Y., Wang, J.-W., Yu, W. & Han, B. Photocatalytic anti-Markovnikov radical hydro- and aminooxygenation of unactivated alkenes tuned by ketoine carbonates. Angew. Chem. Int. Ed. 60, 21997–22003 (2021).
32. Patra, T., Das, M., Daniluc, C. G. & Glorius, F. Metal-free photosensitized oxyamination of unactivated alkenes with bifunctional oxime carboxylates. Nat. Catal. 4, 54–61 (2021).
33. Shi, J. C., Fu, N. & Lin, S. Catalyzing electrosynthesis: a homogeneous electrocatalytic approach to reaction discovery. Acc. Chem. Res. 53, 547–560 (2020).
34. Yuan, Y. & Lei, A. Electrochemical oxidative cross-coupling with hydrogen evolution reactions. Acc. Chem. Res. 52, 3309–3324 (2019).
35. Xiong, P. & Xu, H.-C. Chemistry with electrochemically generated N-centered radicals. Acc. Chem. Res. 52, 3339–3350 (2019).
36. Shi, J. C. et al. Electrochemical azidoxygenation of alkenes mediated by a TEMPO–N3 charge-transfer complex. J. Am. Chem. Soc. 140, 12511–12520 (2018).
37. Hu, X., Zhang, G., Bu, F., Nie, L. & Lei, A. Electrochemical-oxidation-induced site-selective intramolecular C(sp3)–H amination. ACS Catal. 8, 9370–9375 (2018).
38. Hu, X., Zhang, G., Nie, L., Kong, T. & Lei, A. Electrochemical oxidation-induced intermolecular aromatic C-H imidation. Nat. Commun. 10, 5467 (2019).
39. Liu, Y. et al. Time-resolved EPR revealed the formation, structure, and reactivity of N-centered radicals in an electrochemical C(sp3)-H amination reaction. J. Am. Chem. Soc. 143, 20863–20872 (2021).
40. Engl, S. & Reiser, O. Catalyst-free visible-light-mediated iodooxygenation of olefins and synthetic applications. Org. Lett. 23, 5581–5586 (2021).
41. Martinez, C. & Muniz, K. An iodine-catalyzed Hofmann-Loffler reaction. Angew. Chem. Int. Ed. 54, 8287–8291 (2015).

Acknowledgements
This work was supported by the National Key R&D Program of China No. 2021YFA1500100 (A.L.), National Natural Science Foundation of China 22031008 (A.L.), 21762025 (T.W.), Science Foundation of Wuhan 2021YFA1500100 (A.L.), National Natural Science Foundation of China 21922106 (T.W.), Science Foundation of Wuhan 2020010601012192 (A.L.), and Key Projects of Natural Science Foundation of Jiangxi Province 20192ACBL20026 (T.W.). We thank W.L. (WHU) for the helpful discussions.

Author contributions
A.L. and S.W. conceived the work. S.L., S.W., P.W., Z.H., and T.W. designed the experiments and analyzed the data. S.L. performed the experiments. S.W. described the manuscript.

Competing interests
The authors declare no competing interests.
Additional information
Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41467-022-32084-8.

Correspondence and requests for materials should be addressed to Zhiliang Huang, Tao Wang or Aiwen Lei.

Peer review information Nature Communications thanks the anonymous reviewers for their contribution to the peer review of this work. Peer reviewer reports are available.

Reprints and permission information is available at http://www.nature.com/reprints

Publisher’s note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this license, visit http://creativecommons.org/licenses/by/4.0/.

© The Author(s) 2022