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Electrochemical oxidative radical cascade cyclization of dienes and diselenides towards the synthesis of seleno-benzazepines†

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Selenium-containing compounds are important scaffolds owing to their value in medicinal chemistry, biochemistry and material chemistry. Herein, we report an electrochemical approach to access seleno-benzazepines through an oxidative radical cascade cyclization of dienes with diselenides under metal-free, external oxidant-free and base-free conditions. In a simple undivided cell, various dienes and diselenides were suitable for this transformation, generating the desired products in up to 84% yields. This method provides a green and convenient route for the synthesis of valuable selenium-containing seven-membered N-heterocycles from simple starting materials.

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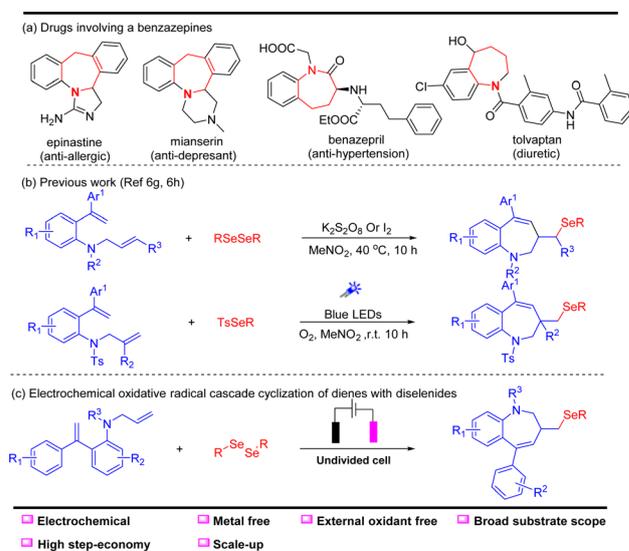
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Benzazepine derivatives are a significant family of seven-membered heterocycles with unique bioactive and pharmaceutical properties (Scheme 1).^{1–4} As shown in Scheme 1a, the selected examples of benzazepine medicine exhibit properties such as anti-allergic, anti-depressant, anti-hypertension and diuretic.^{5–8} Therefore, chemists have devoted considerable efforts to develop various ways for the rapid construction of benzazepine derivatives. To date, the benzazepine skeletons can be synthesized by the expansion of smaller rings,^{9–11} Beckmann rearrangements,^{12–14} transition-metal-catalyzed oxidative annulations,^{15–22} radical reactions^{23–30} and others.^{31–34} Among these elegant methods, the radical cascade reaction stands out owing to its high efficiency and simple reaction conditions. For instance, in 2022, Sun and coworkers²⁹ reported a $K_2S_2O_8/I_2$ -promoted electrophilic selenylative cyclization to access seleno-benzo[*b*]azepines (Scheme 1b). Very recently, the same group³⁰ developed a visible-light-promoted selective sulfonylation and selenylation of dienes using O_2 as the terminal oxidant to afford seleno-benzazepines. Despite these advances, developing new methods to prepare selenium-containing seven-membered N-heterocycles under sustainable conditions at an affordable cost is still highly desirable.

Over the past few decades, electrosynthesis has offered a green and efficient strategy for redox transformations by employing traceless electrons as redox agents instead of stoichiometric oxidants or reductants.^{35–38} In recent years, some breakthroughs have been made in electrochemical radical

cascade selenocyclization to prepare selenium-containing heterocycles.^{39–48} In 2019, Lei and coworkers developed an electrochemical oxidative cyclization of olefinic carbonyls and diselenides towards the synthesis of seleno-dihydrofurans and oxazolines.³⁹ Soon after, Sarkar,⁴⁰ Pan,⁴¹ Xu⁴² and other groups^{43–48} reported a series of related works, respectively. As part of our ongoing focus on radical cascade selenocyclization,^{44,45} herein, we report a facile and efficient method for the selenocyclization of dienes *via* electrochemical synthesis under metal-free and external oxidant-free conditions (Scheme 1c).



Scheme 1 (a) Drugs with benzazepine structures, (b) previous work, (c) electrochemical oxidative radical cascade cyclization of dienes with diselenides.

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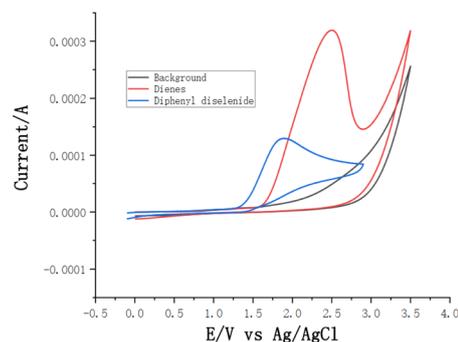
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produced in a 70% yield. Inspired by the above results, we examined the effect of the substitution pattern on the nitrogen atom of substrates. Alkyl sulfonamides were shown to be good candidates for this transformation (**3o**, **3p**). Moreover, various substituents on their benzene rings (*p*-OMe, *p*-^tBu, *p*-F, *p*-Cl, *p*-Br, *p*-CF₃, 3, 5-difluoro) were evaluated and shown to be good candidates for this transformation (**3q–3v**). To our delight, naphthalene-2-sulfonamide was also compatible and afforded the corresponding benzazepines in 78% yield (**3w**). To further exhibit the reaction generality, a variety of diselenides, including alkyl diselenides and aryl diselenides, were tested to couple with **1a**, afforded the desired products in moderate yields (**3x–3zc**). Unfortunately, the diphenyl ditelluride (**3zd**) and a substituent on the terminal carbon of the *N*-allyl part (**3ze**, **3zf**) were not tolerated in the standard reaction conditions.

To verify the practicability of this protocol, the scalability of this electrochemical oxidative radical cascade cyclization of dienes with diselenides was evaluated by performing a 5.0 mmol scale reaction. The reaction of **1a** and **2a** afforded the desired product **3a** in 55% yield (Scheme 3). Besides, the desired product **3a** could be transformed into non-selenated heterocycles **4a** through a simple treatment, which showed the application potential of this protocol.

To gain insight into the mechanism of this electrochemical oxidative radical cascade cyclization reaction, related control experiments (Scheme 4) and cyclic voltammetry (CV) experiments (Scheme 5) were carried out. First, radical trapping experiments were conducted. The reaction was completely suppressed when 2.0 equiv. radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was added. The adduct **5a** was detected by LC-MS in the reaction mixture when 2.0

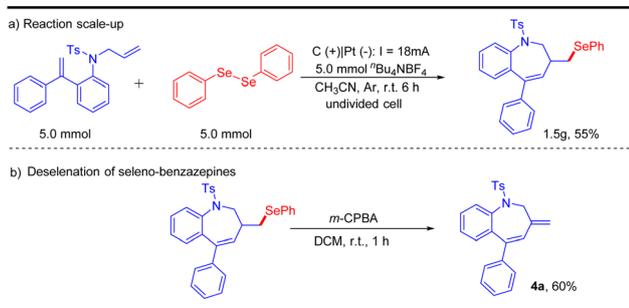


Scheme 5 Cyclic voltammetry.

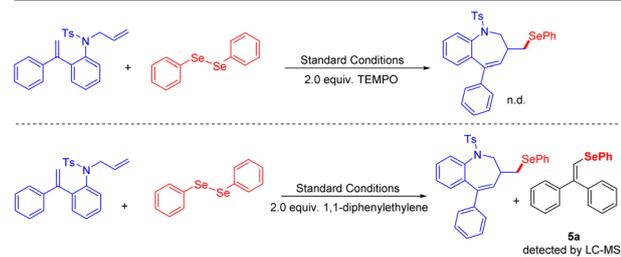
equiv. 1,1-diphenylethylene was added. These results indicated that this cascade cyclization reaction probably underwent a radical pathway, and selenium radical intermediate might be involved in this transformation. Furthermore, cyclic voltammetry (CV) experiments of *N*-allyl-4-methyl-*N*-(2-(1-phenylvinyl)phenyl) benzenesulfonamide **1a** and 1,2-diphenyldiselenane **2a** were performed, respectively. An obvious oxidation peak of **1a** was observed at 2.49 V, whereas the oxidation peak of **2a** was observed at 1.98 V (see ESI† for details). This result indicated that **2a** was oxidized preferentially at the anode in this system.

Based on the experimental results above (Scheme 4) and the previous reports,⁴⁶ a possible reaction mechanism was proposed in Scheme 5. Initially, diphenyl selenide was oxidized at the anode to generate a radical cation intermediate **A**, which divided into phenyl-selenium radical **B** and phenyl-selenium cation **C**, respectively. Phenyl-selenium cation **C** was reduced to diphenyl-selenide at the cathode for the next cycle. Then, the phenyl-selenium radical **B** added to the C=C double bond of diene to generate the alkyl radical **D**. Subsequently, the intermediate **D** underwent radical cyclization to provide the intermediate **E**. Finally, the intermediate **E** was further oxidized at the anode and then deprotonated to afford the desired seleno-benzazepines **3a**. At the cathode, the proton was reduced to give hydrogen gas during the reaction (Scheme 6).

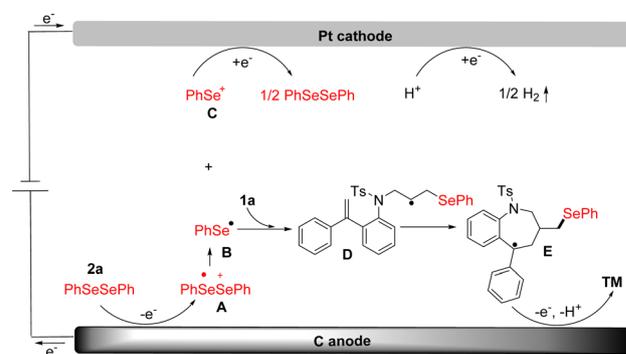
In summary, a general and efficient electrochemical oxidative radical cascade cyclization of dienes and diselenides has been successfully achieved. Using this eco-friendly method, we were able to synthesize the seleno-benzazepines under metal-



Scheme 3 Gram-scale synthesis and derivatizations.



Scheme 4 Control experiments.



Scheme 6 Proposed reaction mechanism.



free, external oxidant-free and additive-free conditions. Preliminary mechanistic studies indicated that this reaction underwent a radical pathway, and selenium radical intermediate might be involved in this transformation. Further applications of electrochemical oxidative radical cascade cyclization of dienes are currently underway in our group.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

- M. B. Murphy, C. Murray and G. D. N. Shorten, *Engl. Med. J.*, 2001, **345**, 1548–1557.
- F. Hou, X. Zhang, G. Zhang, D. Xie, P. Chen, W. Zhang, J. Jiang, M. Liang, G. Wang, Z. Liu and R. N. Geng, *Engl. Med. J.*, 2006, **354**, 131–140.
- J. H. Ryan, C. Hyland, A. G. Meyer, J. A. Smith and J. X. Yin, *Prog. Heterocycl. Chem.*, 2012, **24**, 493–536.
- K. Ramig, *Tetrahedron*, 2013, **69**, 10783–10795.
- J. A. Balfour and K. L. Goa, *Drugs*, 1991, **42**, 511–539.
- S. Pradhan, K. Abhishek and F. Mah, *Expert Opin. Drug Metab. Toxicol.*, 2009, **5**, 1135–1140.
- P. Roszkowski, J. K. Maurin and Z. Czarnocki, *Beilstein J. Org. Chem.*, 2015, **11**, 1509–1513.
- B. J. Kramers, M. D. A. van Gastel, E. Meijer and R. T. Gansevoort, *BMC Nephrol.*, 2018, **19**, 157.
- H. Tabata, T. Yoneda, T. Tasaka, S. Ito, T. Oshitari, H. Takahashi and H. Natsugari, *J. Org. Chem.*, 2016, **81**, 3136–3148.
- A. Gini, J. Bamberger, J. L.-M. Barrera, R. Zurro, R. Mas-Ballesté, J. Alemán and O. G. Mancheño, *Adv. Synth. Catal.*, 2016, **358**, 4049–4056.
- M. Bakthadoss, P. V. Kumar, T. T. Reddy and D. S. Sharada, *Org. Biomol. Chem.*, 2018, **16**, 8160–8168.
- E. C. Horning, V. L. Stromberg and H. A. Lloyd, *J. Am. Chem. Soc.*, 1952, **74**, 5153–5155.
- P. E. Eaton, G. R. Carlson and J. T. Lee, *J. Org. Chem.*, 1973, **38**, 4071–4073.
- J. D. Armstrong, K. Eng, J. L. Keller, R. M. Purick, F. W. Hartner, W. B. Choi, D. Askin and R. P. Volante, *Tetrahedron Lett.*, 1994, **35**, 3239–3242.
- L. Wang, J. Huang, S. Peng, H. Liu, X. Jiang and J. Wang, *Angew. Chem., Int. Ed.*, 2013, **52**, 1768–1772.
- A. A. Peshkov, V. A. Peshkov, O. P. Pereshivko, K. Van Hecke, R. Kumar and E. V. Van der Eycken, *J. Org. Chem.*, 2015, **80**, 6598–6608.
- B. Cendón, N. Casanova, C. Comanescu, R. GarcíaFandiño, A. Seoane, M. Gulías and J. L. Mascareñas, *Org. Lett.*, 2017, **19**, 1674–1677.
- G.-W. Wang and J. F. Bower, *J. Am. Chem. Soc.*, 2018, **140**, 2743–2747.
- B. Niu, Q. Nie, B. Huang and M. Cai, *Adv. Synth. Catal.*, 2019, **361**, 4065–4074.
- B. M. Trost, Z. Zuo and J. E. Schultz, *Chem. - Eur. J.*, 2020, **26**, 15354–15377.
- Á. Velasco-Rubio, J. A. Varela and C. Saá, *Adv. Synth. Catal.*, 2020, **362**, 4861–4875.
- X.-Q. Shen, X.-W. Yan and X.-G. Zhang, *Chem. Commun.*, 2021, **57**, 10234–10237.
- L. Z. Yu, Q. Xu, X. Y. Tang and M. Shi, *ACS Catal.*, 2016, **6**, 526–531.
- Z. Zhang, X. Fang, A. Aili, S. Wang, J. Tang, W. Lin, L. Xie, J. Chen and K. Sun, *Org. Lett.*, 2023, **25**, 4598–4602.
- Y. Zhao, J. R. Chen and W.-J. Xiao, *Org. Lett.*, 2018, **20**, 224–227.
- D. Zhao, K. Sun, M. Tian, B. Yan, W. Li, Q. Sun, G. Zheng and Q. Zhang, *Org. Chem. Front.*, 2023, **10**, 3313–3320.
- Y. Li, M. Hu and J. H. Li, *ACS Catal.*, 2017, **7**, 6757–6761.
- B. S. Bhakuni, A. Kumar, S. J. Balkrishna, J. A. Sheikh, S. Konar and S. Kumar, *Org. Lett.*, 2012, **14**, 2838–2841.
- Z. Zhang, S. Wang, P. Tan, X. Gu, W. Sun, C. Liu, J. Chen, J. Li and K. Sun, *Org. Lett.*, 2022, **24**, 2288–2293.
- Z. Zhang, P. Tan, S. Wang, H. Wang, L. Xie, Y. Chen, L. Han, S. Yang and K. Sun, *Org. Lett.*, 2023, **25**, 4208–4213.
- W. Mazumdar and T. G. Driver, *Synthesis*, 2021, **53**, 1734–1748.
- I. Y. Danyliuk, R. I. Vas'kevich, A. I. Vas'kevich and M. V. Vovk, *Chem. Heterocycl. Compd.*, 2019, **55**, 802–814.
- M. Kaur, S. Garg, S. D. Malhi and S. H. Sohal, *Curr. Org. Chem.*, 2021, **25**, 449–506.
- Á. Velasco-Rubio, J. A. Varela and C. Saá, *Adv. Synth. Catal.*, 2020, **362**, 4861–4875.
- B. A. Frontana-Urbe, R. D. Little, J. G. Ibanez, A. Palma and R. Vasquez-Medrano, *Green Chem.*, 2010, **12**, 2099–2119.
- A. Wiebe, T. Gieshoff, S. Mohle, E. Rodrigo, M. Zirbes and S. R. Waldvogel, *Angew. Chem., Int. Ed.*, 2018, **57**, 5594–5619.
- Y. Li, Q. Yang, L. Yang, N. Lei and K. Zheng, *Chem. Commun.*, 2019, **55**, 4981–4984.
- G. M. Martins, G. C. Zimmer, S. R. Mendes and N. Ahmed, *Green Chem.*, 2020, **22**, 4849–4870.
- Z. Guan, Y. Wang, H. Wang, Y. Huang, S. Wang, H. Tang, H. Zhang and A. Lei, *Green Chem.*, 2019, **21**, 4976–4980.
- S. Mallick, M. Baidya, K. Mahanty, D. Maiti and S. D. Sarkar, *Adv. Synth. Catal.*, 2020, **362**, 1046–1052.
- X. Y. Wang, Y. F. Zhong, Z. Y. Mo, S. H. Wu, Y. L. Xu, H. T. Tang and Y. M. Pan, *Adv. Synth. Catal.*, 2021, **363**, 208–214.
- W. Gao, B. Li, L. Zong, L. Yu, X. Li, Q. Li, X. Zhang, S. Zhang and K. Xu, *Eur. J. Org. Chem.*, 2021, **2021**, 2431–2435.
- D. Maiti, A. Halder, A. S. Pillai and S. D. Sarkar, *J. Org. Chem.*, 2021, **86**, 16084–16094.



- 44 F. Lu, J. Xu, H. Li, K. Wang, D. Ouyang, L. Sun, M. Huang, J. Jiang, J. Hu, H. Alhumade, L. Lu and A. Lei, *Green Chem.*, 2021, **23**, 7982–7986.
- 45 H. Li, F. Lu, J. Xu, J. Hu, H. Alhumade, L. Lu and A. Lei, *Org. Chem. Front.*, 2022, **9**, 2786–2791.
- 46 P. Tan, L. Lu, S. Wang, J. Wang, J. Chen, Y. Zhang, L. Xie, S. Yang, J. Chen and Z. Zhang, *J. Org. Chem.*, 2023, **88**, 7245–7255.
- 47 N. Mukherjee and T. Chatterjee, *Adv. Synth. Catal.*, 2023, **365**, 2255–2263.
- 48 P. Qu, Y. Q. Jiang, Y. H. Wang and G. Q. Liu, *Green Chem.*, 2023, **25**, 7485–7507.

