How to cite: *Angew. Chem. Int. Ed.* **2025**, *64*, e202504459
doi.org/10.1002/anie.202504459

Electrosynthesis **Hot Paper**

Electrochemical Amination of Aryl Halides with NH_3

*Yaowen Liu, Yanfei Sun, Yuan Deng, and Youai Qiu**

Abstract: Primary arylamines are the most pivotal class of organic motifs in pharmaceuticals, agrochemicals, ligands and natural products. Ammonia (NH_3) is an ideal nitrogen source in terms of reactivity, atom economy, and environmental compatibility. Despite significant progress in the synthesis of primary arylamines, the development of a general method for rapid access to diversely functionalized primary arylamines is still urgent and necessary. Herein, we developed a method for the direct synthesis of primary arylamines through electrochemical amination of aryl halides with NH_3. Notably, the weak nucleophilic reagent NH_3 was directly used as an ammonia surrogate, allowing for efficient conversion of carbon-halogen bonds to diverse primary arylamines with good functional group tolerance. A broad scope of functionalized primary arylamines has been achieved in moderate to excellent yields.

Aniline compounds are highly valuable, ubiquitous skeletons that serve as important organic intermediates and basic chemical raw materials.[1,2] They are widely applied in pharmaceuticals,[3–5] agrochemicals,[6–8] dyes,[9–11] and functional materials.[12–15] The prevalence of primary arylamines underscores the significance of C─N bond formation, which is one of the most valuable and widespread transformation in synthetic chemistry.[16–19] As a result, enduring efforts have been devoted to the development of efficient and versatile methods for the synthesis of primary arylamine derivatives, such as Buchwald–Hartwig and Ullmann–Ma amination.[20–37] With the continuous development and innovation in organic chemistry, new synthetic technologies, for example photochemical C─N coupling is emerging as a fundamental and indispensable process, providing more options for the synthesis of primary arylamines.[38–50] Moreover, the diversification and improvement of synthetic routes have driven cutting-edge research and development in the field of organic chemistry. Last year, Hartwig and co-workers reported the palladium-catalyzed amination of aryl and heteroaryl halides with aqueous ammonia and potassium hydroxide base enabled by the development of a new ligand (KPhos) based on a bipyrazole backbone to form the primary arylamine with high selectivity.[25] Despite that significant progress has been made in establishing methods for the synthesis of primary arylamines,[51–58] the development of general and greener methods to access diverse functionalized aromatic amines still remains highly desirable, especially for the direct synthesis of primary arylamines.

In the past few years, the emergence of electrochemistry has brought opportunities and development in organic synthesis,[59–84] where it has not only improved the efficiency and selectivity of reactions but has also enabled reactions to be carried out under milder conditions, reducing environmental pollution and energy consumption.[85–107] Buoyed by the superiority of this strategy, it has been widely applied in C─N coupling.[108–123] Notably, the Baran,[124,125] Mei,[126,127] and other research groups,[128–131] respectively achieved the electrochemical amination of aryl halides through C─N coupling. However, the ammonia source was mainly derived from primary and secondary amines (Figure 1a), then form relatively stable and less easily oxidized non-primary arylamines. In sharp contrast, the direct synthesis of primary arylamines through electrochemical C─N coupling of halides with NH_3 is still elusive. The reason might be primary arylamines have a lower oxidation potential and are more prone to oxidation compared to non-primary arylamines (Figure 1a).[132–134] Thus, the development of a greener and direct method to synthesize primary arylamines from halides under mild reaction conditions remains challenging and in high demand.

Driven by our continued interests in electrochemical reduction and small molecule transformation,[135–146] herein, we report a direct and efficient protocol to synthesize a series of primary arylamines through electrochemical amination of aryl halides with NH_3 gas (Figure 1b). Notable features of this strategy include: a) a direct method for the synthesis of various primary arylamine derivatives; b) it uses a weak nucleophilic reagent NH_3 (1 atm) as the nitrogen source with high atom economy; c) it achieves general amination of various aryl halides with high selectivity; and d) demonstrates good functional group tolerance that is compatible with substrates bearing sensitive groups. Moreover, the examples of facile scalability to gram-scale and sequential modification of drug molecules show the potential of this methodology for further applications.

To test our hypothesis for the synthesis of primary arylamines, NH_3 and 1-bromo-4-methylbenzene (**1a**) were used as the model substrates to evaluate the reaction conditions.

[*] Y. Liu, Y. Sun, Y. Deng, Y. Qiu
State Key Laboratory and Institute of Elemento-Organic Chemistry, Frontiers Science Center for New Organic Matter, Haihe Laboratory of Sustainable Chemical Transformations, College of Chemistry, Nankai University, 94 Weijin Road, Tianjin 300071, China
E-mail: qiuyouai@nankai.edu.cn
Homepage: https://www.x-mol.com/groups/qiu_youai

Additional supporting information can be found online in the Supporting Information section

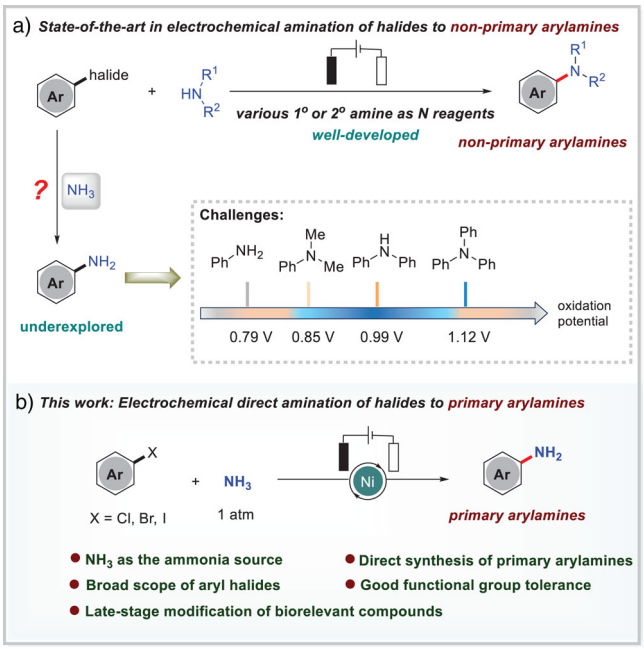
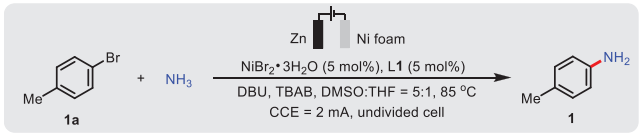
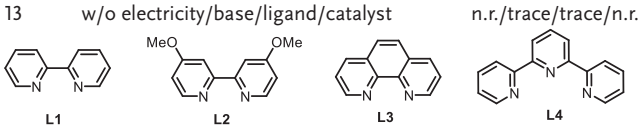


Figure 1. Electrochemical amination of aryl halides.

Table 1: Optimization of reaction conditions.[a]



Entry	Variation	Yield (%)[b]
1	**None**	**82**
2	$Ni(ClO_4)_2{\cdot}6H_2O$ instead of $NiBr_2{\cdot}3H_2O$	45
3	$Ni(acac)_2$ instead of $NiBr_2{\cdot}3H_2O$	28
4	$FeBr_2$ instead of $NiBr_2{\cdot}3H_2O$	n.r.
5	$CuCl_2$ instead of $NiBr_2{\cdot}3H_2O$	n.r.
6	Mg/Al instead of Zn	23/15
7	**L2**/**L3**/**L4** instead of **L1**	20/trace/trace
8	rt/40 °C/60 °C instead of 85 °C	trace/trace/20
9	5 mA/8 mA instead of 2 mA	42/25
10	$TBAClO_4$/$TBAPF_6$ instead of TBAB	25/55
11	DMSO/THF instead of DMSO:THF (5:1)	35/25
12	DMAP/DABCO/TBD instead of DBU	trace/trace/trace
13	w/o electricity/base/ligand/catalyst	n.r./trace/trace/n.r.



[a] Reaction conditions: undivided cell, **1a** (0.5 mmol), Catalyst (0.025 mmol, 5 mol%), Ligand (0.025 mmol, 5 mol%), DBU (3.0 mmol, 6.0 equiv.), TBAB (1.0 mmol, 2.0 equiv.) in DMSO: THF = 5: 1 (4.8 mL), 85 °C, 12 h, under NH_3, Zn as the anode, and Ni foam as the cathode, CCE = 2.0 mA, n.r. = no reaction. [b] Isolated yield. rt = room temperature, DBU = 1,8-Diazabicyclo[5,4,0]undec-7-ene, CCE = constant current electrolysis, TBAB = Tetrabutylammonium bromide, $TBAClO_4$ = Tetrabutylammonium perchlorate, $TBAPF_6$ = Tetrabutylammonium hexafluorophosphate, DMAP = 4-Dimethylaminopyridine, DABCO = Triethylenediamine. TBD = 1,5,7-Triazabicyclo[4.4.0]dec-5-ene. DMSO = Dimethyl sulfoxide, THF = Tetrahydrofuran.

After extensive optimization of the reaction parameters, we identified the use of 5 mol% of $NiBr_2{\cdot}3H_2O$, 5 mol% of bipyridine, DBU, and TBAB as the catalytic system in DMSO/THF = 5:1, under NH_3 atmosphere, in an undivided cell equipped with a Zn anode and Ni foam cathode with a constant current of 2 mA for 12 h at 85 °C as the optimal reaction conditions, which afforded the desired *p*-toluidine **1** in 82% isolated yield (Table 1, entry 1). First, the use of different metal catalysts including Ni, Fe, and Cu were explored, but no or low efficiency was observed (entries 2–5). After screening different electrode pairs, we found that the anode material had a significant effect on the reaction. In terms of anodes, Zn, Mg, and Al electrode materials are superior to Fe, Cu, GF, Pt, and GC electrode materials (Table S8). This preliminarily indicates that the use of Zn anode has a beneficial effect,[147] the reasons might be: i) the generated Zn^{2+} may serve as the role of Lewis acid catalyst, activating the C–X bond in the substrate and promoting nucleophilic attack of amines;[148,149] ii) the Zn potential is more positive in the THF (−1.25 V) than in the DMSO (−1.43 V);[84] iii) Zn sacrifices at the anode releases electrons, which can avoid over-oxidation reactions (entry 6). Moreover, despite using ligands such as **L2**, **L3**, and **L4**, the yield did not improve (entry 7). Subsequently, various factors such as temperature, electrolyte, and current intensity were examined. When the temperature is below 60 °C, no target product was detected, which probably attributed to the particularity of NH_3. The reasons might be: i) the high activation energy is required for the cleavage of N–H bond in NH_3; ii) NH_3 is prone to coordinate with Ni catalyst in the low temperature, causing catalyst deactivation by forming inert nickel-ammonia complex.[40,150,151] High temperatures not only prevent nickel deactivation but also thermodynamically favor NH_3 liberation (entry 8).[24,34] Increasing the current density unexpectedly inhibits the amination reaction (entry 9). The superior conductivity of the electrolyte, along with its compatibility with both the solvent and electrode materials, establishes TBAB as the optimal electrolyte choice (entry 10). After a series of solvent screening processes, a mixed solvent of DMSO:THF = 5:1 was found to be suitable for this reaction (entry 11). The reasons for using a mixed solvent might be that nickel complexes and NH_3 have good solubility in DMSO and DBU has high alkalinity in THF. Also, various bases were screened, but only trace amount of product were observed (entry 12). Reducing or increasing the amount of DBU is detrimental to the reaction (Table S4). Controlled experiments indicated that the nickel catalyst, ligand, base, and electricity were all essential to the success of this transformation, since there was no formation of product **1** in the absence of each of them (entry 13). Under the standard conditions, any oxidation products of primary arylamines have not been detected, although primary arylamines have a lower oxidation potential. A plausible reason is that the sacrificial Zn anode, combined with the NH_3 atmosphere, creating a reductive microenvironment. During the entire process of optimizing conditions, we found that the amount of DBU and the enough NH_3 probable are the important factors in preventing over-reduction products.

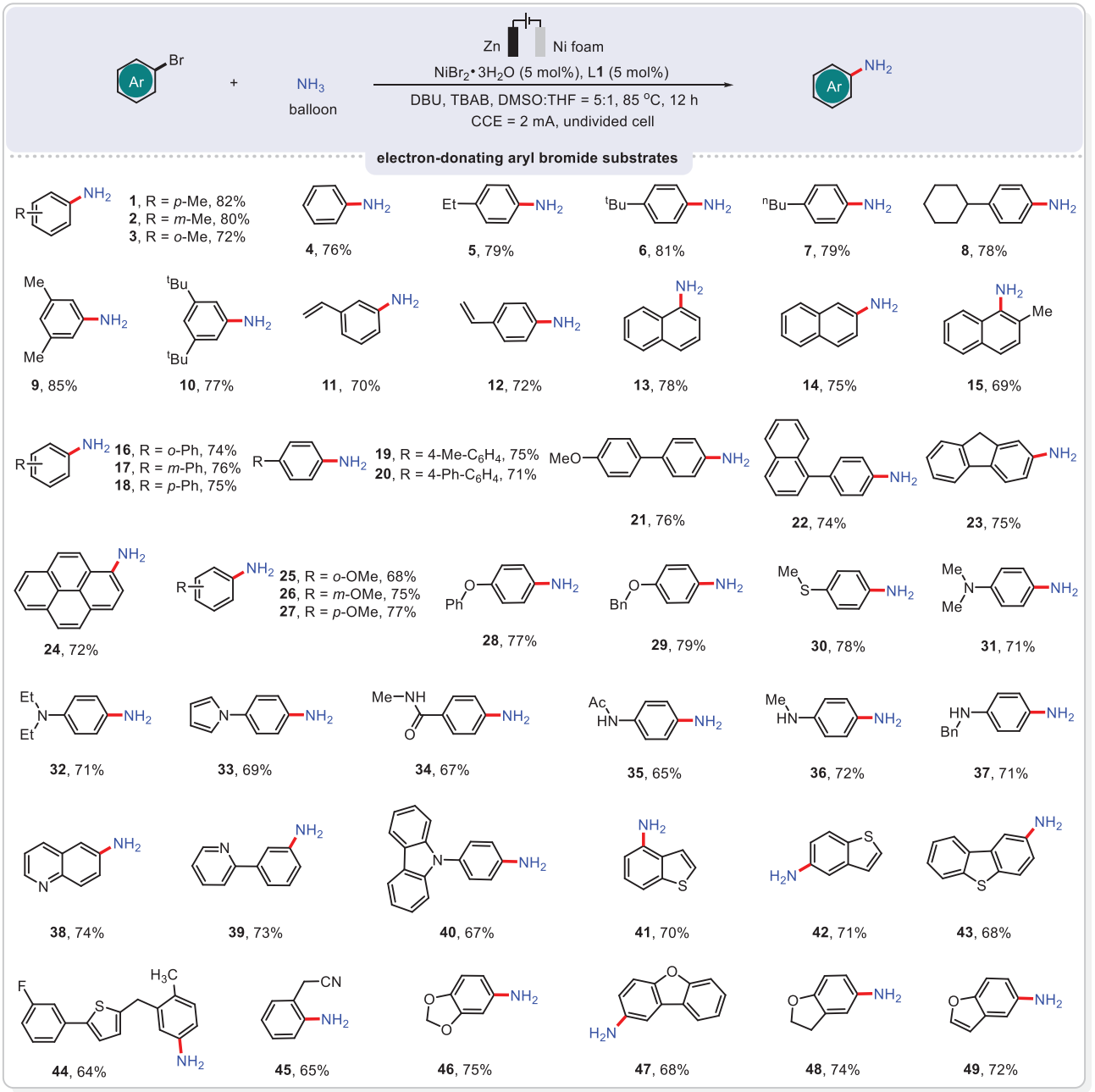


Figure 2. Scope of aryl bromide substrates. Reaction conditions: aryl bromide (0.5 mmol), $NiBr_2{\cdot}3H_2O$ (0.025 mmol, 5 mol%), L1 (0.025 mmol, 5 mol%), DBU (3.0 mmol, 6.0 equiv.), TBAB (1.0 mmol, 2.0 equiv.) in DMSO: THF = 5: 1 (4.8 mL), 85 °C, 12 h, under NH_3, Zn as the anode, and Ni foam as the cathode, CCE = 2.0 mA. Isolated yield.

With the optimal electrochemical conditions in hand, we transferred our attention on exploring the scope of aryl bromides with different substitutions (Figure 2). As shown in Figure 2, the system exhibits excellent functional group tolerance. Initially, a diverse array of weak electron-donating aryl bromides, including —Me, —Et, —^{t}Bu, —^{n}Bu, —Cy, and —Vinyl, regardless of their position on the aromatic ring, were readily accommodated, and afforded the desired products in excellent yields under the standard conditions (**1**–**12**). Also, regardless of the position of the bromo group on the naphthalene ring, the substrates underwent the desired transformation to afford the corresponding products in 69%–78% yields (**13**–**15**). Similarly, amine products of polycyclic substituted aromatic compounds were obtained in good yields (**16**–**24**). Then, for strong electron-donating groups, such as —OMe, —OPh, —OBn, —SMe, —$N(Me)_2$, —$N(Et)_2$ and nitrogen heterocycle, the corresponding products were furnished in good yields (**25**–**33**). It was worth noting that, aryl bromides containing secondary amines were smoothly transformed to primary arylamine products without any unwanted amination by-products detected, and the secondary amines remained intact (**34**–**37**). Encouraged by the above results, a broad range of aryl bromides with heterocyclic and alkyl substituents (**38**–**49**) were examined, and all successfully

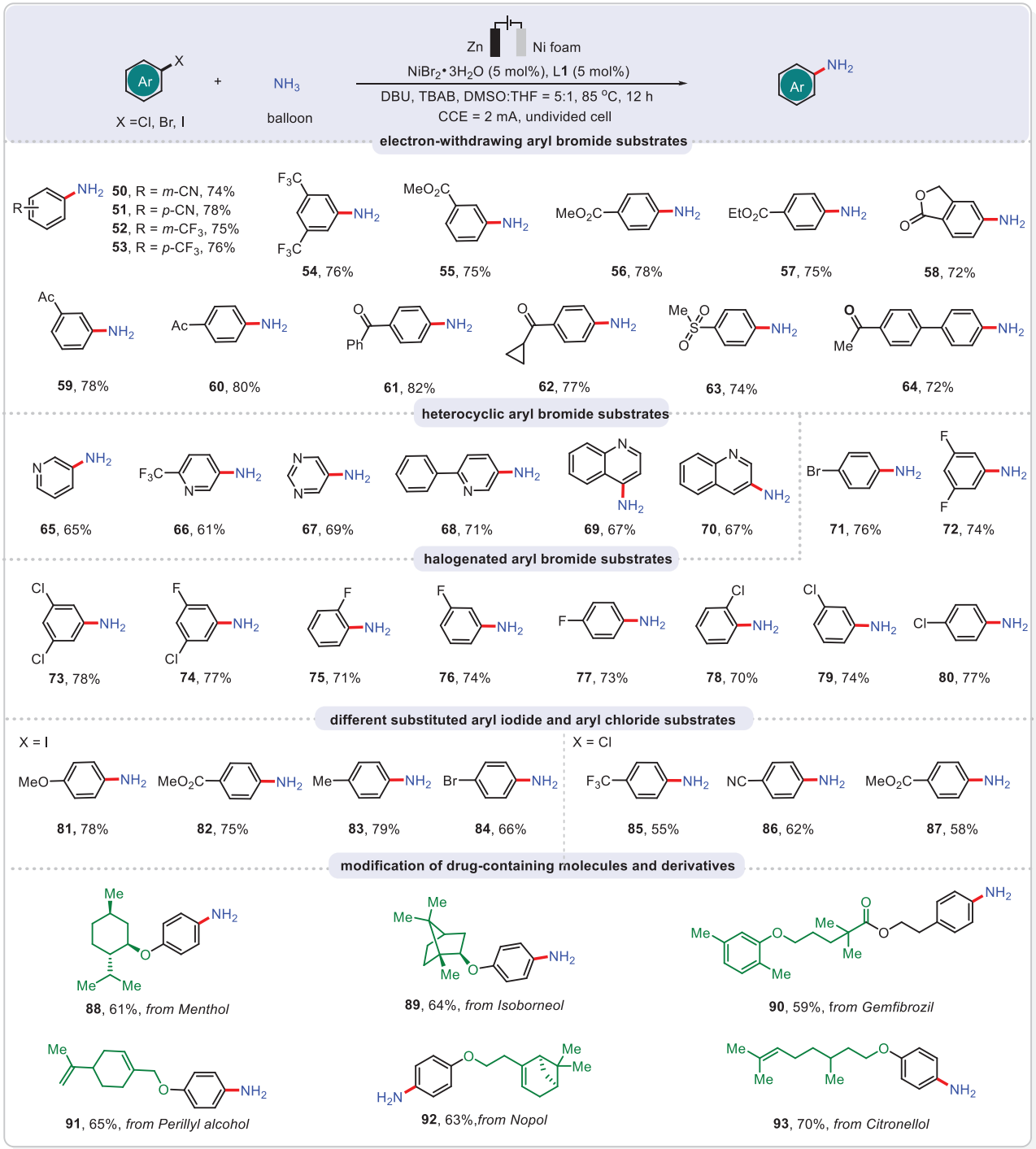


Figure 3. Scope of aryl halide substrates and late-stage modification of biorelevant compounds. Reaction conditions: aryl halide (0.5 mmol), $NiBr_2{\cdot}3H_2O$ (0.025 mmol, 5 mol%), L1 (0.025 mmol, 5 mol%), DBU (3.0 mmol, 6.0 equiv.), TBAB (1.0 mmol, 2.0 equiv.) in DMSO: THF = 5: 1 (4.8 mL), 85 °C, 12 h, under NH_3, Zn as the anode, and Ni foam as the cathode, CCE = 2.0 mA. Isolated yield.

underwent the electrochemical transformation with high reactivity to deliver the primary arylamines in good yields.

Next, the facile synthesis of primary arylamines through examining the scope of aryl halides bearing structurally complex and highly reactive functional groups further demonstrates the utility of this strategy (Figure 3). There is no doubt that a variety of electron-withdrawing groups were well tolerated in the reaction, such as —CN, —CF_3, —COOMe, —Ac, etc. (**50**–**64**). Notably, regardless of the brominated nitrogen heterocycle, e.g., pyridine, pyrimidine, and quinoline, the reaction proceeded efficiently in NH_3 atmosphere and afforded the desired primary arylamines in good yields (**65**–**70**). Moreover, disubstituted and multi-substituted aryl halides with more than one halogen atom could also participate in the process efficiently. Notably, only a single mono-primary arylamine was generated in each case (**71**–**80**). This is probably due to the

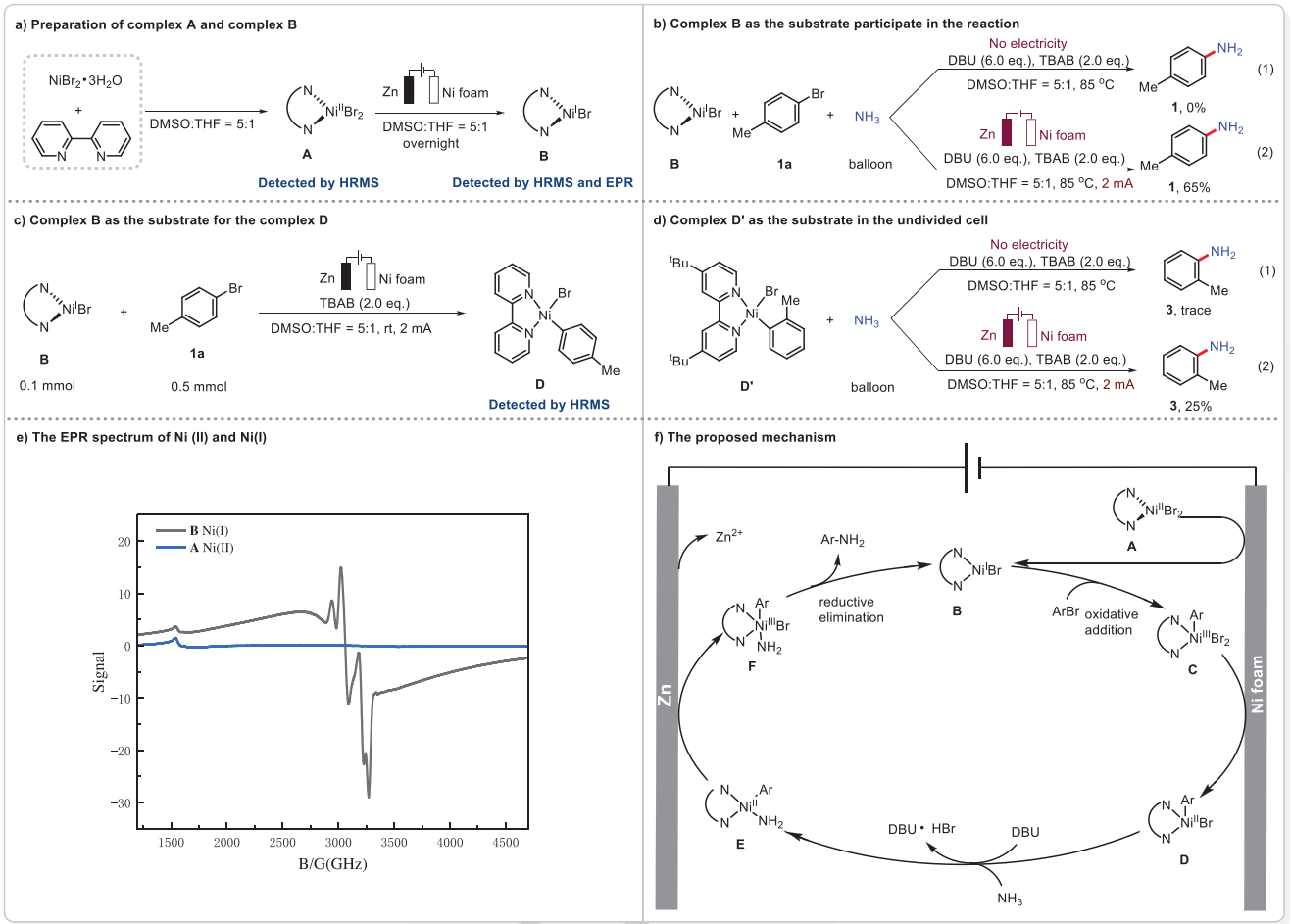


Figure 4. Mechanistic studies and the proposed mechanism. a) Preparation of complex **A** and complex **B**. b) Complex **B** as the substrate participate in the reaction. c) Complex **B** as the substrate for the complex **D**. d) Complex **D'** as the substrate in the undivided cell. e) The EPR spectrum of Ni (II) and Ni(I). f) The proposed mechanism.

fact that the bond energies of the C─F and C─Cl bonds are much higher than that of a C─Br bond. It is noteworthy that when 1,4-dibromobenzene was employed as the substrate, one bromine atom was retained, while the other participated in the amination reaction, and no *p*-phenylenediamine was detected (**71**). Encouraged by the above results, we conducted preliminary investigations on iodobenzene derivatives and chlorobenzene derivatives. We found that iodide primary arylamines are almost unaffected by the type of functional group, while aryl chlorides can only obtain primary arylamine products smoothly with electron withdrawing groups (**81**–**87**). To further demonstrate the viability of the present methodology, late-stage modifications of drug molecules were carried out (Figure 3). A series of bioactive compounds and drugs such as Menthol (**88**), Isoborneol (**89**), Gemfibrozil (**90**), Perillyl alcohol (**91**), Nopol (**92**), and Citronellol (**93**) could be coupled with NH_3 efficiently, which resulted in the desired corresponding primary arylamines. The promising results suggested that basic scaffolds of future drugs and natural products could be directly obtained through a simple and efficient halide and ammonia gas reductive amination strategy.

To verify the mechanism of this electroreduction protocol, we conducted a series of mechanistic studies (Figure 4). $NiBr_2{\cdot}3H_2O$ is firstly complexed with bipyridine, generating Ni(II) complex **A**. The complex **A** is then subjected to electrochemical reduction, affording the Ni(I) complex **B**, which was confirmed by both HRMS and EPR (Figure 4a,e). Employing Ni(I) complex **B** and 4-bromotoluene (**1a**) as substrates, the reaction was carried out under NH_3 atmosphere, with variations in electrochemical versus non-electrochemical conditions. The expected *p*-toluidine product was only obtained under electricity conditions (Figure 4b-(2)), while no product was detected in the absence of electricity condition (Figure 4b-(1)). These results indicate that the mechanism is probably initiated by Ni(I) complex **B**. Subsequently, we attempted to trap intermediate **D** by reacting complex B with 4-bromotoluene (**1a**) under conditions devoid of both NH_3 and DBU (Figure 4c). This indicates that the oxidation addition of Ni(II) complex **B** with aryl halides to obtain Ni(III) intermediate **C**, followed by electroreduction to form Ni(II) intermediate **D** is feasible in this transformation. To further clarify the entire mechanistic cycle, we also performed experiments related to the intermediates. A large number of stability Ni(II) intermediate **D'** was successfully obtained at room temperature by using 4,4′-di-tert-butyl-2,2′-dipyridyl, an equimolar amount of Ni(0), and 2-bromotoluene

(Mechanistic studies (f) in the Supporting Information). Subsequently, the intermediate **D'** was employed as the substrate under NH_3 atmosphere without electricity, no corresponding product was produced (Figure 4d-(1)). While the primary arylamine **3** was obtained in 25% under electricity (Figure 4d-(2)). These experimental results demonstrated that the Ni(II) intermediate **D** is essential throughout the catalytic cycle. To verify process of oxidation of Ni(II) **E** to Ni(III) **F** on the anode, we conducted divided cell experiments, using **D'** as the substrate under NH_3 atmosphere, the primary arylamine product (19%) was successfully obtained in the anodic cell (Mechanistic studies (h) in the Supporting Information). These results suggest the possible occurrence of a Ni(II) **E** to Ni(III) **F** oxidation process at the anode. To further verify the oxidation process, we independently measured the oxidation potential of the Ni(bpy)Br_2 complex via cyclic voltammetry (CV), two oxidative peaks appearing at −0.84 V and 0.32 V versus Ag/Ag^+ and revealing an oxidation potential range of −0.1 V to 0.73 V (Figure S9, a green line). Simultaneously, through a three-electrode system, we monitored the real-time potential variation of the anode during the reaction (Table S10). The recorded real-time anode potential consistently exceeds the oxidation potential of Ni(bpy)Br_2 complex measured by CV, further supporting the possible occurrence of Ni(II) **E** to Ni(III) **F** oxidation at the anode. In addition, to further demonstrate the practical application of this methodology, we conducted the gram-scale experiment of **79a** using a simple two-necked flask, which provided the desired product in 60% yield (Figure S2).

Based on previous literatures and our experiments,[124–127] we proposed a possible mechanism (Figure 4f). First, Ni(II) species **A** was reduced to Ni(I) intermediate **B** at the cathode. Subsequently, **B** underwent oxidative addition with an aryl halide to form Ni(III) intermediate **C**. Then, the key Ni(II) intermediate **D** is obtained through cathodic reduction of Ni(III) species **C**. After that, under an atmosphere of DBU and NH_3 gas, **D** possible underwent oxidation to form the relatively Ni(III) intermediate **F**. Finally, the reductive elimination of **F** to obtain the primary arylamines and regenerate the Ni(I) intermediate **B** that completes the entire cycle.

In conclusion, we have developed a method for the direct synthesis of primary arylamines through electrochemical amination of aryl halides using NH_3. In this process, the weak nucleophile, NH_3, acts as an efficient nitrogen source to achieve the synthesis of primary arylamines. We have achieved good functional group tolerance and a broad scope of functionalized primary arylamines in moderate to excellent yields. Moreover, the facile scalability to gram-scale and the sequential modification of drug molecules shows the potential of this methodology for further applications. Detailed mechanistic studies supported the proposed mechanism, where the aryl Ni(II) intermediate is crucial for realizing the Ni(I/III) cycle. This electrochemical system offers a powerful strategy for the synthesis of primary arylamines, which play a key role as versatile precursors, and in late-stage derivatization of biorelevant compounds. Further research on electrochemical transformations of NH_3 are currently underway in our laboratory.

Acknowledgements

Financial support from National Key R&D Program of China (2022YFA1503200), National Natural Science Foundation of China (Grant No. 22371149, 22401158, 22188101), the Natural Science Foundation of Tianjin (24JCJQJC00210), the Fundamental Research Funds for the Central Universities (No. 63224098), Frontiers Science Center for New Organic Matter, Nankai University (Grant No. 63181206), China Postdoctoral Science Foundation (Grant No. 2024M751515 and Grant No. 2024T170435) and Nankai University are gratefully acknowledged. The authors thank the Haihe Laboratory of Sustainable Chemical Transformations for financial support.

Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

Materials and methods, optimization studies, experimental procedures, mechanistic studies, ^1H NMR, ^{13}C NMR spectra, and high-resolution mass spectrometry data are available in the Supplementary Information.

Keywords: Amination · Aryl halides · Electrochemistry · NH_3 · Primary arylamines

[1] H. N. C. Wong, M. Y. Hon, C. W. Tse, Y. C. Yip, J. Tanko, T. Hudlicky, *Chem. Rev.* **2015**, *115*, 3388–3432.
[2] P. Ruiz-Castillo, S. L. Buchwald, *Chem. Rev.* **2016**, *116*, 12564–12649.
[3] J. A. Smith, B. C. Johnson, *J. Med. Chem.* **2020**, *63*, 6543–6572.
[4] L. Wang, X. Zhang, *Cancer Res. Rev.* **2019**, *45*, 234–250.
[5] R. T. Brown, M. L. Davis, *Eur. J. Med. Chem.* **2018**, *150*, 1–15.
[6] C. Lamberth, S. Jeanmart, T. Luksch, A. Plant, *Science* **2013**, *341*, 742–746.
[7] W. Zhang, J. Jiang, *J. Agric. Food Chem.* **2019**, *67*, 4085–4098.
[8] P. Jeschke, *Pest Manag. Sci.* **2017**, *73*, 1053–1066.
[9] A. Bafana, S. Devi, T. Chakrabarti, *Environ. Rev.* **2011**, *19*, 350–371.
[10] S. K. Shorey, V. K. Gupta, *J. Chem. Pharm. Res.* **2012**, *4*, 508–514.
[11] R. M. Christie, *Color. Technol.* **2001**, *117*, 1–8.
[12] R. C. Gupta, *Mater. Sci. Eng. R Rep.* **2018**, *131*, 1–22.
[13] M. A. Ibrahim, *J. Polym. Sci. A Polym. Chem.* **2017**, *55*, 902–918.
[14] S. Kumar, *J. Mater. Chem. C* **2020**, *8*, 12–27.
[15] P. Zhang, *Prog. Polym. Sci.* **2019**, *96*, 1–27.
[16] J. F. Hartwig, *Nature*, *455*, 314–322.
[17] P. Ruiz-Castillo, S. L. Buchwald, *Chem. Rev.* **2016**, *116*, 12564–12649.
[18] J. Bariwal, E. Eycken, *Chem. Soc. Rev.* **2013**, *42*, 9283.
[19] C. L. Allen, J. M. Williams, *Chem. Soc. Rev.* **2011**, *40*, 3405.
[20] J. L. Klinkenberg, J. F. Hartwig, *J. Am. Chem. Soc.* **2010**, *132*, 11830–11833.
[21] R. J. Lundgren, B. D. Peters, P. G. Alsabeh, M. A. Stradiotto, *Angew. Chem. Int. Ed.* **2010**, *49*, 4071–4074.

[22] A. Borzenko, N. L. Rotta-Loria, P. M. Macqueen, C. M. Lavoie, R. McDonald, M. Stradiotto, *Angew. Chem. Int. Ed.* **2015**, *54*, 3773–3777.
[23] R. Green, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2015**, *54*, 3768–3772.
[24] P. Ruiz-Castillo, S. L. Buchwald, *Chem. Rev.* **2016**, *116*, 12564–12649.
[25] K. Choi, J. N. Brunn, K. Borate, R. Kaduskar, C. L. Pueyo, H. Shinde, R. Goetz, J. F. Hartwig, *J. Am. Chem. Soc.* **2024**, *146*, 19414–19424.
[26] E. R. Raguram, J. C. Dahl, K. F. Jensen, S. L. Buchwald, *J. Am. Chem. Soc.* **2024**, *146*, 33035–33047.
[27] K. Feng, E. R. Raguram, J. R. Howard, E. Peters, C. Liu, M. S. Sigman, S. L. Buchwald, *J. Am. Chem. Soc.* **2024**, *146*, 26609–26615.
[28] J. Kim, S. Chang, *Chem. Commun.* **2008**, 3052.
[29] N. Xia, M. Taillefer, *Angew. Chem. Int. Ed.* **2009**, *48*, 337–339.
[30] L. Jiang, X. Lu, H. Zhang, Y. Jiang, D. Ma, *J. Org. Chem.* **2009**, *74*, 4542–4546.
[31] H. Xu, C. Wolf, *Chem. Commun.* **2009**, 3035–3037.
[32] M. K. Elmkaddem, C. Fischmeister, C. M. Thomas, J. L. Renaud, *Chem. Commun.* **2010**, *46*, 925–927.
[33] M. Fan, W. Zhou, Y. Jiang, D. Ma, *Org. Lett.* **2015**, *17*, 5934–5937.
[34] S. Bhunia, G. Goroba Pawar, S. VijayKumar, Y. Jiang, D. Ma, *Angew. Chem. Int. Ed.* **2017**, *56*, 16136–16179.
[35] C. Sambiagio, S. P. Marsden, A. J. Blacker, P. C. McGowan, *Chem. Soc. Rev.* **2014**, *43*, 3525–3550.
[36] Y. Zhang, J. Wang, *Adv. Synth. Catal.* **2022**, *364*, 876–894.
[37] X. Guo, M. Rueping, *ACS Catal.* **2022**, *12*, 4567–4580.
[38] G. Song, Q. Li, J. Song, D. Nong, J. Dong, G. Li, J. Fan, C. Wang, D. Xue, *ACS Catal.* **2024**, *14*, 4968–4974.
[39] M. R. Lasky, E. Liu, M. S. Remy, M. S. Sanford, *J. Am. Chem. Soc.* **2016**, *138*, 10080–10083.
[40] G. Song, J. Song, Q. Li, D. Nong, J. Dong, G. Li, J. Fan, C. Wang, J. Xiao, D. Xue, *Angew. Chem. Int. Ed.* **2024**, *63*, e202314355.
[41] R. Kancherla, K. Muralirajan, S. Dutta, K. Pal, B. Li, B. Maity, L. Cavallo, M. Rueping, *Angew. Chem. Int. Ed.* **2024**, *63*, e202314508.
[42] B. D. Akana-Schneider, D. J. Weix, *J. Am. Chem. Soc.* **2023**, *145*, 16150–16159.
[43] G. Song, L. Yang, J. Li, W. Tang, W. Zhang, R. Cao, C. Wang, J. Xiao, D. Xue, *Angew. Chem. Int. Ed.* **2021**, *60*, 21536–21542.
[44] G. Li, L. Yang, J. Liu, W. Zhang, R. Cao, C. Wang, Z. Zhang, J. Xiao, D. Xue, *Angew. Chem. Int. Ed.* **2021**, *60*, 5230–5234.
[45] J. Wang, S. Li, C. Yang, H. Gao, L. Zuo, Z. Gao, P. Yang, Y. Jiang, J. Li, L-Z, W.u, Z. Tang, *Nat. Commun.* **2024**, *15*, 6907.
[46] W. S. Ham, J. Hillenbrand, J. Jacq, C. Genicot, T. Ritter, *Angew. Chem. Int. Ed.* **2019**, *58*, 532–536.
[47] Y. Zheng, B. Chen, P. Ye, K. Feng, W. Wang, Q. Meng, L-Z. Wu, C.-H. Tung, *J. Am. Chem. Soc.* **2016**, *138*, 10080–10083.
[48] N. A. Romero, K. A. Margrey, N. E. Tay, D. A. Nicewicz, *Science* **2015**, *349*, 1326–1330.
[49] V. A. Pistritto, M. E. Schutzbach-Horton, D. A. Nicewicz, *J. Am. Chem. Soc.* **2020**, *142*, 17187–17194.
[50] L. Zhang, L. Liardet, J. Luo, D. Ren, M. Grätzel, X. Hu, *Nat. Catal.* **2019**, *2*, 366–373.
[51] R. Y. Liu, J. M. Dennis, S. L. Buchwald, *J. Am. Chem. Soc.* **2020**, *142*, 4500–4507.
[52] J. Li, P. Wang, B. Bai, Y. Xiao, Y. Wan, Y. Yan, F. Li, G. Song, G. Li, C. Wang, X. Zhang, J. Dong, T. Kang, D. Xue, *J. Am. Chem. Soc.* **2025**, *147*, 5851–5859.
[53] G. Song, J. Song, Q. Li, T. Kang, J. Dong, G. Li, J. Fan, C. Wang, D. Xue, *J. Am. Chem. Soc.* **2024**, *146*, 26936–26946.
[54] F. Li, H. Lu, H. Liao, W. Xiong, J. Dong, G. Li, D. Xue, *Org. Chem. Front.* **2024**, *11*, 6089–6095.
[55] H. Ai, S. Kim, C. Liu, S. L. Buchwald, *J. Am. Chem. Soc.* **2024**, *146*, 25949–25955.
[56] M. J. Strauss, K. X. Liu, M. E. Greaves, J. C. Dahl, S. Kim, Y. Wu, M. A. Schmidt, P. M. Scola, S. L. Buchwald, *J. Am. Chem. Soc.* **2024**, *146*, 18616–18625.
[57] S. Kim, M. J. Strauss, A. Cabré, S. L. Buchwald, *J. Am. Chem. Soc.* **2023**, *145*, 6966–6975.
[58] S. M. Papidocha, H. R. Wilke, K. J. Patej, M. Isomura, T. J. Stucky, L. Rothenbühler, E. M. Carreira, *J. Am. Chem. Soc.* **2025**, *147*, 11675-11681.
[59] M. Yan, Y. Kawamata, P. S. Baran, *Chem. Rev.* **2017**, *117*, 13230–13319.
[60] P. Xiong, H.-C. Xu, *Acc. Chem. Res.* **2019**, *52*, 3339–3350.
[61] C. W. Anson, S. S. Stahl, *Chem. Rev.* **2020**, *120*, 3749–3786.
[62] L. F. T. Novaes, J.-J. Liu, Y.-F. Shen, L.-X. Lu, J. M. Meinhardt, S. Lin, *Chem. Soc. Rev.* **2021**, *50*, 7941–8002.
[63] C. Zhu, N. W. J. Ang, T. H. Meyer, Y. Qiu, L. Ackermann, *ACS Cent. Sci.* **2021**, *7*, 415–431.
[64] J. C. Siu, N. Fu, S. Lin, *Acc. Chem. Res.* **2020**, *53*, 547–560.
[65] Y. Qiu, C. Zhu, M. Stangier, J. Struwe, L. Ackermann, *CCS Chem.* **2020**, *2*, 1529–1552.
[66] C.-Y. Cai, H.-C. Xu, *Nat. Commun.* **2018**, *9*, 3551.
[67] L.-X. Lu, J. C. Siu, Y. Lai, S. Lin, *J. Am. Chem. Soc.* **2020**, *142*, 21272–21278.
[68] S.-Z. Li, S.-C. Wang, P.-J. Wang, Z.-L. Huan, T. Wan, A. Lei, *Nat. Commun.* **2022**, *13*, 443.
[69] C.-Y. Cai, Y.-T. Zheng, J.-F. Li, H.-C. Xu, *J. Am. Chem. Soc.* **2022**, *144*, 11980–11985.
[70] K. Liang, Q. Zhang, C. Guo, *Sci. Adv.* **2022**, *8*, eadd7134.
[71] N. Fu, G. S. Sauer, A. Saha, A. Loo, S. Lin, *Science* **2017**, *357*, 575–579.
[72] P. Zhou, K. Niu, H. Song, Y. Liu, Q. Wang, *Green Chem.* **2022**, *24*, 5760–5763.
[73] E. J. Horn, B. R. Rosen, Y. Chen, J. Tang, K. Chen, M. D. Eastgate, P. S. Baran, *Nature* **2016**, *533*, 77–81.
[74] Y. Liang, S.-H. Shi, R. Jin, X. Qiu, J. Wei, H. Tan, X. Jiang, X. Shi, S. Song, N. Jiao, *Nat. Catal* **2021**, *4*, 116–123.
[75] K.-J. Jiao, Y.-K. Xing, Q.-L. Yang, H. Qiu, T.-S. Me, *Acc. Chem. Res.* **2020**, *53*, 300–310.
[76] Q.-L. Yang, Y.-Q. Li, C. Ma, P. Fang, X.-J. Zhang, T.-S. Mei, *J. Am. Chem. Soc.* **2017**, *139*, 3293–3298.
[77] N. Sauermann, T.-H. Meyer, C. Tian, L. Ackermann, *J. Am. Chem. Soc.* **2017**, *139*, 18452–18455.
[78] G.-Q. Sun, P. Yu, W. Zhang, W. Zhang, Y. Wang, L.-L. Liao, Z. Zhang, L. Li, Z. Lu, D.-G. Yu, S. Lin, *Nature* **2023**, *615*, 67–72.
[79] W. Zhang, L.-L. Liao, L. Li, Y. Liu, L.-F. Dai, G.-Q. Sun, C.-K. Ran, J.-H. Ye, Y. Lan, D.-G. Yu, *Angew. Chem. Int. Ed.* **2023**, *62*, e202301892.
[80] D. S. Chung, S. H. Park, S. G. Lee, H. Kim, *Chem. Sci.* **2021**, *12*, 5892–5897.
[81] S. H. Park, G. Bae, A. Choi, S. Shin, K. Shin, C. H. Choi, H. Kim, *J. Am. Chem. Soc.* **2023**, *145*, 15360–15369.
[82] Y.-M. Jiang, Y.-Y. Lin, L. Zhu, Y. Yu, Y. Li, Y. Lin, K.-Y. Ye, *CCS Chem.* **2024**, *6*, 2021–2030.
[83] F. Bu, Y. Deng, J. Xu, D. Yang, Y. Li, W. Li, A. Lei, *Nature* **2024**, *634*, 592–599.
[84] Z. Su, R. Deng, S. S. Stahl, *Nat. Chem.* **2024**, *16*, 2036–2043.
[85] S.-S. Xu, H. Qiu, P.-P. Xie, Z. H. Wang, X. Wang, C. Zheng, S.-L. You, T.-S. Mei, *CCS Chem* **2025**, *7*, 245–255.
[86] P. Li, Y. Wang, H. Zhao, Y. Qiu, *Acc. Chem. Res.* **2025**, *58*, 113–129.
[87] Q. Wang, X. Zhang, P. Wang, X. Gao, H. Zhang, A. Lei, *Chin. J. Chem.* **2021**, *39*, 143–148.
[88] M. Chen, Z.-J. Wu, J. Song, H.-C. Xu, *Angew. Chem. Int. Ed.* **2022**, *61*, e202115954.
[89] C. Huang, W. Ma, X. Zheng, M. Xu, X. Qi, Q. Lu, *J. Am. Chem. Soc.* **2022**, *144*, 1389–1395.

[90] Z. Zhao, Y. Liu, S. Wang, S. Tang, D. Ma, Z. Zhu, C. Guo, Y. Qiu, *Angew. Chem. Int. Ed.* **2023**, *62*, e202214710.
[91] M. J. Kim, D. J. Wang, K. Targos, U. A. Garcia, A. F. Harris, I. A. Guzei, Z. K. Wickens, *Angew. Chem. Int. Ed.* **2023**, *135*, e202303032.
[92] X. Zhang, X. Cheng, *Org. Lett.* **2022**, *24*, 8645–8650.
[93] L.-B. Li, X.-Y. Wang, N.-K. Fu, *Angew. Chem. Int. Ed.* **2024**, *63*, e202403475.
[94] S.-L. Fang, K.-H. Zhong, S.-G. Zeng, X.-W. Hu, P.-H. Sun, Z.-X. Ruan, *Chem. Commun.* **2023**, *59*, 11425–11428.
[95] H.-T. Tang, H.-Y. Zhou, Y.-M. Pan, J.-L. Zhang, F.-H. Cui, W.-H. Li, D. Wang, *Angew. Chem. Int. Ed.* **2024**, *136*, e202315032.
[96] T. Wang, F. He, W. Jiang, J. Liu, *Angew. Chem. Int. Ed.* **2024**, *63*, e202316140.
[97] S.-Z. Sun, Y.-M. Cai, D.-L. Zhang, J.-B. Wang, H.-Q. Yao, X.-Y. Rui, R. Martin, M. Shang, *J. Am. Chem. Soc.* **2022**, *144*, 1130–1137.
[98] S. P. Blum, T. Karakaya, D. Schollmeyer, A. Klapars, S. R. Waldvogel, *Angew. Chem. Int. Ed.* **2021**, *60*, 5056–5062.
[99] J. Liu, A. Guðmundsson, J. E. Bäckvall, *Angew. Chem. Int. Ed.* **2021**, *60*, 15686–15704.
[100] J. Zhang, B. Das, O. Verho, J. E. Bäckvall, *Angew. Chem. Int. Ed.* **2022**, *61*, e202212131.
[101] X.-Y. Wang, Y.-Z. Pan, J. Yang, W.-H. Li, T. Gan, Y.-M. Pan, H.-T. Tang, D. Wang, *Angew. Chem. Int. Ed.* **2024**, *22*, e202404295.
[102] H.-T. Tang, H.-Y. Zhou, Y.-M. Pan, J.-L. Zhang, F.-H. Cui, W.-H. Li, D.-S. Wang, *Angew. Chem. Int. Ed.* **2024**, *63*, e202315032.
[103] T. J. DeLano, S. E. Reisman, *ACS Catal.* **2019**, *9*, 6751–6754.
[104] J. L. Hofstra, A. H. Cherney, C. M. Ordner, S. E. Reisman, *J. Am. Chem. Soc.* **2018**, *140*, 139–142.
[105] W. Yi, P. C. Xu, T. He, S. Shi, S. Huang, *Nat. Commun.* **2024**, *15*, 9645.
[106] G. Kou, P. Li, G. Yang, Y. Qiu, *CCS Chem.* **2024**, https://doi.org/10.31635/ccschem.024.202404697.
[107] A. Shi, Y. Liu, R. Zhang, Z. Zhu, Y. Qiu, *eScience* **2024**, *4*, 100255.
[108] Y. Zhong, H. Xiong, J. Low, R. Long, Y. Xiong, *eScience* **2023**, *3*, 100086.
[109] X. Peng, L. Zeng, D. Wang, Z. Liu, Y. Li, Z. Li, B. Yang, L. Lei, L. Dai, Y. Hou, *Chem. Soc. Rev.* **2023**, *52*, 2193–2237.
[110] Y. Wang, D. Chen, C. Chen, S. Wang, *Acc. Chem. Res.* **2024**, *57*, 247–256.
[111] T. Morofuji, A. Shimizu, J. Yoshida, *J. Am. Chem. Soc.* **2014**, *136*, 4496–4499.
[112] B. Zhang, S. L. Homölle, T. Bauch, J. C. A. Oliveira, S. Warratz, B. Yuan, X. Gou, L. Ackermann, *Angew. Chem. Int. Ed.* **2024**, *63*, e202407384.
[113] S.-K Zhang, R. C. Samanta, N. Sauermann, L. Ackermann, *Chem. - Eur. J.* **2018**, *24*, 19166–19170.
[114] T. Morofuji, A. Shimizu, J. Yoshida, *J. Am. Chem. Soc.* **2013**, *135*, 5000–5003.
[115] H. Huang, T. H. Lambert, *Angew. Chem. Int. Ed.* **2021**, *60*, 11163–11167.
[116] H. Huang, K. A. Steiniger, T. H. Lambert, *J. Am. Chem. Soc.* **2022**, *144*, 12567–12583.
[117] L. Qian, M. Shi, *Chem. Commun.* **2023**, *59*, 3487–3506.
[118] H. Zhao, P. Xu, J. Song, H. Xu, *Angew. Chem. Int. Ed.* **2018**, *57*, 15153–15156.
[119] H. Zhao, Z. Liu, J. Song, H. Xu, *Angew. Chem. Int. Ed.* **2017**, *56*, 12732–12735.
[120] C. Guan, J. Yin, J. Ji, J. Liu, X. Wu, T. Zhu, *Org. Lett.* **2023**, *25*, 5383–5388.
[121] J. Xu, Y. Liu, Q. Wang, X. Tao, S. Ni, W. Zhang, L. Yu, Y. Pan, Y. Wang, *Nat. Commun.* **2024**, *15*, 6116.
[122] N. Sauermann, R. Mei, L. Ackermann, *Angew. Chem. Int. Ed.* **2018**, *57*, 5090–5094.
[123] Z. Zhu, P. Li, Y. Qiu, *Chin. J. Org. Chem.* **2024**, *44*, 871.
[124] C. Li, Y. Kawamata, H. Nakamura, J. C. Vantourout, Z. Liu, Q. Hou, D. Bao, J. T. Starr, J. Chen, M. Yan, P. S. Baran, *Angew. Chem. Int. Ed.* **2017**, *56*, 13088–13093.
[125] Y. Kawamata, J. C. Vantourout, D. P. Hickey, P. Bai, L. Chen, Q. Hou, W. Qiao, K. Barman, M. A. Edwards, A. F. Garrido-Castro, J. N. Gruyter, H. Nakamura, K. Knouse, C. Qin, K. J. Clay, D. Bao, C. Li, J. T. Starr, C. Garcia-Irizarry, N. Sach, H. S. White, M. Neurock, S. D. Minteer, P. S. Baran, *J. Am. Chem. Soc.* **2019**, *141*, 6392–6402.
[126] D. Liu, Z. Liu, C. Ma, K. Jiao, B. Sun, L. Wei, J. Lefranc, S. Herbert, T.-S. Mei, *Angew. Chem. Int. Ed.* **2021**, *60*, 9444–9449.
[127] Z. Liu, S. Herbert, H. Schirok, C. Ma, T.-S. Mei, *Org. Lett.* **2024**, *26*, 9034–9039.
[128] J. Luo, M. T. Davenport, C. Callister, S. D. Minteer, D. H. Ess, T. L. Liu, *J. Am. Chem. Soc.* **2023**, *145*, 16130–16141.
[129] J. Morvan, K. P. L. Kuijpers, D. Fanfair, B. Tang, K. Bartkowiak, L. Eynde, E. Renders, J. Alcazar, P. J. J. A. Buijnsters, M. Carvalho, A. X. Jones, *Angew. Chem. Int. Ed.* **2025**, *64*, e202413383.
[130] C. Zhu, A. P. Kale, H. Yue, M. Rueping, *JACS Au* **2021**, *1*, 1057–1065.
[131] S. Sengmany, F. Daili, I. Kribii, E. Léonel, *J. Org. Chem.* **2023**, *88*, 675–683.
[132] S. Liu, X. Cheng, *Nat. Commun.* **2022**,*13*, 425.
[133] S. Liu, W. Zhao, J. Li, N. Wu, C. Liu, X. Wang, S. Li, Y. Zhu, Y. Liang, X. Cheng, *CCS Chem* **2022**, *4*, 693–703.
[134] X. Zhang, R. Jiang, X. Cheng, *J. Org. Chem.* **2021**, *86*, 16016–16025.
[135] Y.-W. Wang, Q. Wang, L. Wu, K.-P. Jia, M.-Y. Wang, Y. Qiu, *Nat. Commun.* **2024**, *15*, 2780.
[136] M. Liu, T. Feng, Y.-W. Wang, G.-S. Kou, Q. Wang, Q.-Y. Wang, Y. Qiu, *Nat. Commun.* **2023**, *14*, 6467.
[137] P.-F. Li, G.-S. Kou, T. Feng, M.-Y. Wang, Y. Qiu, *Angew. Chem. Int. Ed.* **2023**, *62*, e202311941.
[138] K.-M. Yang, T. Feng, Y. Qiu, *Angew. Chem. Int. Ed.* **2023**, *62*, e202312803.
[139] M. Liu, Y.-W. Wang, C. Gao, J. Jia, Z. Zhu, Y. Qiu, *Angew. Chem. Int. Ed.* **2025**, e202425634.
[140] R. Zhang, M. Liu, Z. Zhao, Y. Qiu, *Green Chem.* **2025**, *27*, 1658–1666.
[141] Z. Zhao, R. Zhang, Y. Liu, Z. Zhu, Q. Wang, Y. Qiu, *Nat. Commun.* **2024**,*15*, 3832.
[142] X. Liu, R. Liu, J. Qiu, X. Cheng, G. Li, *Angew. Chem. Int. Ed.* **2020**, *59*, 13962–13967.
[143] P. Li, Y. Wang, H. Zhao, Y. Qiu, *Acc. Chem. Res.* **2025**, *58*, 113–129.
[144] Y. Liu, P. Li, Y. Wang, Y. Qiu, *Angew. Chem. Int. Ed.* **2023**, *62*, e202306679.
[145] W. Zeng, Y. Wang, C. Peng, Y. Qiu, *Chem. Soc. Rev.* **2025**, https://doi.org/10.1039/d4cs01142b.
[146] W. Zeng, C. Peng, Y. Qiu, *J. Am. Chem. Soc.* **2025**, https://doi.org/10.1021/jacs.5c00259.
[147] L. Cardinale, G. L. Beutner, C. Y. Bemis, D. J. Weix, S. S. Stahl, *J. Am. Chem. Soc.* **2024**, *146*, 32249–32254.
[148] M. Wang, C. Zhang, C. Ci, H. Jiang, P. H. Dixneuf, M. Zhang, *J. Am. Chem. Soc.* **2023**, *145*, 10967–10973.
[149] M. Wang, C. Zhang, H. Zhao, H. Jiang, P. H. Dixneuf, M. Zhang, *CCS Chem* **2024**, *6*, 342–352.
[150] J. Schranck, A. Tlili, *ACS Catal.* **2018**, *8*, 405–418.
[151] G. Song, D. Nong, Q. Li, Y. Yan, G. Li, J. Fan, W. Zhang, R. Cao, C. Wang, J. Xiao, D. Xue, *ACS Catal.* **2022**, *12*, 15590–15599.

Manuscript received: February 24, 2025
Revised manuscript received: April 09, 2025
Accepted manuscript online: April 09, 2025
Version of record online: April 21, 2025