Controlling One- or Two-Electron Oxidation for Selective Amine Functionalization by Alternating Current Frequency

Disni Gunasekera,[†,‡] Jyoti P. Mahajan,[†,‡] Yanick Wanzi,[†] Sachini Rodrigo,[†] Wei Liu,[⊥] Ting Tan[⊥], and Long Luo[†,*]

[†] Department of Chemistry, Wayne State University, Detroit, Michigan 48202, United States.

[⊥] Laboratory of Theoretical and Computational Nanoscience, CAS Center for Excellence in Nanoscience, National Center for Nanoscience and Technology, Chinese Academy of Sciences, Beijing 100190, China.

ABSTRACT: Here, we report a unique electrosynthetic method that enables selective one-electron oxidation of tertiary amines to generate α-amino radical intermediates over the two-electron oxidation to iminium cations, providing easy access to arylation products by simply applying an optimal alternating current (AC) frequency. More importantly, we have discovered an electrochemical descriptor from cyclic voltammetry studies to predict the optimal AC frequency for various amine substrates, circumventing the time-consuming trial-and-error methods for optimizing reaction conditions. This new development in AC electrolysis provides an alternative strategy to solving challenging chemoselectivity problems in synthetic organic chemistry.

INTRODUCTION

Controlling the degree of oxidation or reduction of substrates is critical to achieving the desired chemical transformation in organic synthesis. In the past decade, electroorganic synthesis has attracted significant attention because it allows, in principle, straightforward and accurate control over the redox transformations of a substrate by selecting the proper electrode potentials.[1-5] However, when the redox reactions of organic substrates directly occur on an electrode surface (i.e., direct electrolysis), a large overpotential is often required to initiate such a heterogeneous electron transfer process, prone to cause uncontrolled multielectron oxidation or reduction of the substrate.[6] For example, the Shono oxidation is a classical electrochemical reaction for functionalizing a C-H bond adjacent to a nitrogen atom.[7] In this transformation, amine substrate **I** is oxidized by two electrons to *N*-acyl-iminium cation species **II**, later trapped by nucleophiles such as MeOH and H_2O (**Figure 1A**). However, the functional-group compatibility of this method for both substrates and nucleophiles is limited by the high electrode potentials required to initiate electron transfer from the substrate during direct electrolysis, leading to the formation of overoxidized products.

Mediated electrolysis is a strategy to circumvent uncontrolled multielectron oxidation or reduction in organic electrosynthesis.[8-12] In mediated electrolysis, the electron transfer step is shifted to a homogeneous process that involves an electrochemically generated reagent that serves as a so-called "mediator". The mediator engages in a reversible single-electron redox cycle initiated at the electrode, followed by the single-electron transfer (SET) with the substrate (**Figure 1B**). This strategy provides access to the reactive intermediates formed by the SET events with substrates. For example, Ye and co-workers recently demonstrated using 2,2,6,6-tetramethylpiperidinooxy (TEMPO) as a mediator to perform one-electron oxidation of **I** to **III,** providing access to amino radicals after deprotonation of **III** for radical-radical cross-coupling reaction (**Figure 1B**).[9] However, finding a suitable mediator to achieve desired redox transformations remains a challenge.

More recently, AC electrolysis, where the flow of charge periodically changes direction, started to gain interest in the organic synthesis community.[13-21] One of the experimentally observed properties of AC electrolysis is its ability to reduce over-oxidation/reduction products without using any mediators relative to its direct current (DC) counterpart.[18] For example, Sattler et al.[15] demonstrated that AC electrolysis solved the problem of the over-oxidation of disulfides to oxo species and over-reduction of disulfides to unidentified black precipitate in synthesizing unsymmetrical disulfides by an electrochemical sulfur-sulfur bond metathesis reaction. More recently, Kawamata et al.[22] presented a unique chemoselective reduction of phthalimides to partially reduced hemiaminal or fully reduced lactam by applying different AC waveforms, which cannot be achieved by DC electrolysis, either. Despite these exciting findings, the mechanisms behind the controlled oxidation or reduction of substrates during AC electrolysis remain unclear. Due to the lack of mechanistic understanding, one must go through a time-consuming reiterative trial-and-error process to discover the optimal AC electrolysis conditions.

Here, we report a mechanism by which AC electrolysis controls the one- or two-electron oxidation of amines to amino radicals or iminium cations, enabling selective α-amine functionalization by simply adjusting the AC frequency. In this mechanism, the degree of amine oxidation is controlled by managing the redox environment where the amino radical cation **III** is deprotonated to amino radical **IV**, utilizing the alternating redox environment of AC electrolysis. When deprotonation of **III** occurs in an oxidizing environment, **IV** is further oxidized to iminium cation **II** for nucleophilic addition; otherwise, **IV** remains available for radical-based reactions (**Figure 1C**). Such delicate reaction control requires precise synchronization of the dynamic

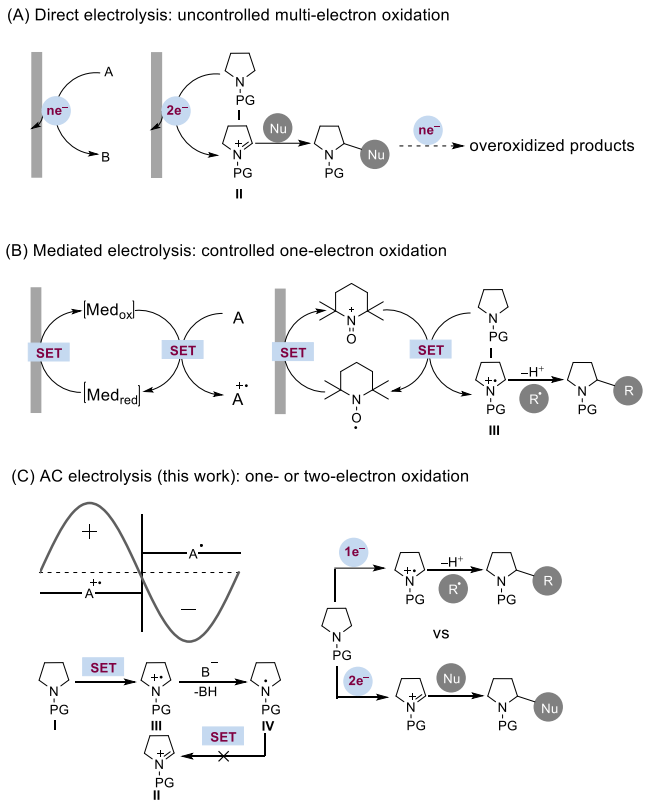


Figure 1. Existing and new strategies for controlling the degree of oxidation of amine substrates during electroorganic synthesis. (A) Direct electrolysis often leads to the two-electron oxidation of amine **I** to iminium cation **II** that can be captured by a nucleophile (Nu) and also causes multielectron oxidation to overoxidized products. PG stands for protecting group. (B) Mediated electrolysis enables one-electron oxidation of **I** to cation radical **III**, providing access to amino radical **IV** after deprotonation of **III** for radical-radical cross-coupling reaction. SET stands for single electron transfer. [Med_{ox}] and [Med_{red}] are the oxidized and reduced forms of the redox mediator, respectively. (C) Alternating current (AC) electrolysis controls one- or two-electron oxidation of amines by managing the redox environment during the deprotonation of **III** to **IV.**

redox environment and the deprotonation reaction kinetics at the "correct" AC frequency. However, because the deprotonation kinetics of substrates varies significantly, each substrate requires individual reaction optimization, making the empirical trial-and-error reaction optimization approach impractically time-consuming (several days per substrate). Therefore, we developed a convenient electroanalytical method to identify the optimal AC frequency in a few minutes to address it.

RESULTS AND DISCUSSION

In this study, our model reaction is the α-amino C-H arylation reaction, which was first discovered by MacMillan and co-workers using the strategy of accelerated serendipity. This reaction was initially accomplished by photoredox catalysis.[23] We selected this model reaction for two reasons.

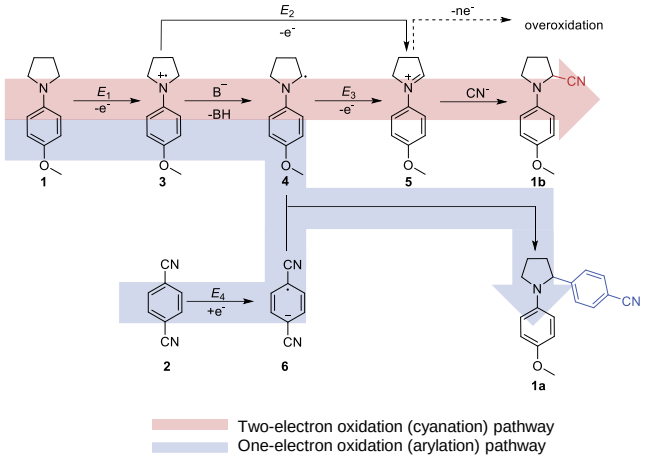


Figure 2. One- and two-electron oxidation pathways during electrochemical α-amino C-H functionalization reactions. One-electron oxidation pathway leads to the arylation product **1a**, while the two-electron oxidation pathway results in the cyanation product **1b**.

First, it can be completed by electrochemically oxidizing amine **1** to amine radical cation **3** and reducing 1,4-dicyanobenzene **2** to the corresponding arene radical anion **6** at electrodes (rather than via SET with a photoredox catalyst). The C–H bonds adjacent to the nitrogen atom in **3** are weakened and undergo deprotonation by a base, $\mathbf{B}^-$ such as NaOAc, to give α-amino radical **4**. A radical-radical coupling reaction between intermediates **4** and **6** yields the aromatized benzylic amine product **1a** after elimination of CN^- (one-electron oxidation (arylation) pathway in **Figure 2**). Second, unlikely photoredox catalysis, electrosynthesis produces a significant amount of cyanation byproduct **1b** because of the overoxidation of **1** to iminium cation **5** (the two-electron oxidation (cyanation) pathway in **Figure 2**), enabling us to study how AC electrolysis alters the degree of amine oxidation and controls product selectivity.

First, we carried out the model reaction using a DC electrolysis setup where **1** was oxidized at a carbon anode and **2** was reduced at a carbon cathode to initiate the reaction (**Figure S1**). **Figure 3A** shows the isolated yields of **1a** and **1b** at an applied voltage from 2 V to 4 V. A mixture of arylation and cyanation products were observed in all cases. At 2.5 V, the best overall conversion of 70% was attained with 30% arylation and 40% cyanation products (**1a:1b** = 0.7). After lowering the voltage to 2.0 V, the product selectivity did not show any obvious changes (**1a**:**1b** = 0.8), suggesting that the lowered voltage does not favor the one-electron oxidation pathway over the two-electron one. At high voltages of 3.0 V and 4.0 V, the product selectivity slightly shifted to the two-electron oxidation product **1b** (**1a**:**1b** = ~0.4-0.5), and the overall conversion dropped to ~50% due to further oxidation of **1** by multiple electrons.

The inevitable two-electron oxidation of amine **1** to iminium **5** and the consequent formation of cyanation product **1b** during DC electrolysis can be explained by the cyclic voltammograms (CVs) of **1** collected in the absence and presence of the base, NaOAc, in **Figure 3B**. Without NaOAc,

the CV of **1** (red curve) clearly shows two well-separated anodic peaks. The peak at E_1=~0.3 V vs. Ag/Ag^+ belongs to the reversible single-electron oxidation of amine **1** to its corresponding cation radical **3**, and the other one at E_2 = ~0.9 V arises from the further oxidation of **3** to **5** by another electron. However, when NaOAc was added, the anodic peak at 0.9 V shifted negatively and merged with the 0.3 V peak (black curve), indicating that one- and two-electron oxidation of **1** can take place under similar potentials. The drastically lowered potential for the second-electron oxidation of **1** in the presence of NaOAc is because iminium cations are generated via the low-potential α-amine radical route (E_3 < E_2, **Figure 2**).[24] As a result, the arylation product **1a** is always accompanied by the cyanation product **1b** under DC electrolysis, regardless of the applied voltage.

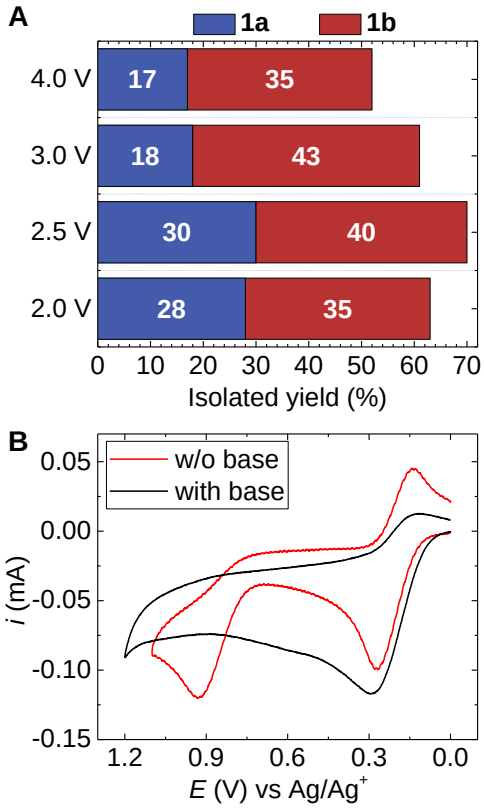


Figure 3. (A) Isolated yields of arylation and cyanation products (blue: **1a** and red: **1b**) using DC electrolysis at different cell voltages. (B) Cyclic voltammograms of **1** in the presence (black) and absence (red) of the base, NaOAc, in *N*, *N*-dimethylacetamide (DMA) containing 0.1 M $LiClO_4$. Scan rate: 1 V/s.

Next, we tested AC electrolysis for its effect on product selectivity**.** During AC electrolysis, oxidation of **1** and reduction of **2** occurred sequentially at the same electrode driven by the alternating voltage polarity. Other reaction conditions, including electrodes, electrolytes, and chemical reagents, were identical to the DC electrolysis conditions (**Figure S2**). We applied sine waveforms with a frequency from 1 Hz to 30 Hz at a fixed AC peak amplitude of 2.5 V. This amplitude was calculated from the potential difference between the oxidation peak of **1** (0.28 V) and the reduction peak of **2** (-2.22V) in the CVs after *iR* drop correction (**Figures S4-6**). **Figure 4A** shows the product yields and selectivity for DC and AC electrolysis. All AC experiments exhibited a higher selectivity toward the one-electron oxidation pathway (arylation) product **1a** than DC electrolysis, meaning a reduced degree of amine oxidation. At 10 Hz, we observed the maximum yield of 68% for **1a** and the biggest six-fold selectivity improvement toward **1a** over DC electrolysis (**1a**: **1b** = 4.3 vs. 0.7).

To understand the AC frequency-dependent product selectivity, we conducted the following experiments to examine the time-resolved amine oxidation behavior. The CVs of **1** were acquired in the presence (black) and absence (red) of NaOAc at different scan rates from 0.02 to 20 V/s (**Figure 4B**). As previously discussed, **1** undergoes a reversible one-electron redox cycle in the absence of NaOAc, so its anodic peak current (i_0) is an ideal reference of a one-electron oxidation process. After introducing NaOAc to the reaction, two-electron oxidation of **1** becomes possible at low potentials (<0.6 V). If two-electron oxidation does happen, the anodic peak current (i_1) would be larger than i_0; otherwise, $i_1 = i_o$. By varying the scan rate, we can control the oxidation time (t_{ox}): the higher scan rate, the shorter t_{ox}. In this study, t_{ox} is defined as the time to scan the electrode potential from the onset potential where the oxidation of **1** starts to the anodic peak potential. For example, at a scan rate of 0.02 V/s, t_{ox} is ~8 s and i_1 is approximately twice of i_o (**Figure 4B**), suggesting that two-electron oxidation of **1** is dominant for t_{ox} =8 s. Interestingly, the difference between i_1 and i_o decreases with increasing scan rate, suggesting that two-electron oxidation of **1** is suppressed as t_{ox} is shortened. At 5 V/s or t_{ox} = ~45 ms, i_1 became equal to i_o and part of the CV curve overlapped with the reference CV (red curve), meaning that only one-electron transfer occurred during the 45-ms-long anodic potential scan. Recall that the second-electron oxidation of **1** at low potentials is achievable only after deprotonation of **3** to **4**. Therefore, when t_{ox} is short, the second-electron oxidation is hindered possibly due to the slow deprotonation of **3**, resulting in such t_{ox}-dependent oxidation behavior.

Based on the CV results above, we propose the following mechanism for the product selectivity change during AC electrolysis: due to the slow deprotonation of **3**, a portion of **3** formed in the positive half-cycle of AC waveform cannot be immediately deprotonated and thus stays intact until the subsequent negative half-cycle. In the reducing environment of the negative half-cycle, deprotonation continues but the further oxidation of the deprotonated product **4** to **5** is prohibited, thereby shifting the product selectivity toward **1a** (**Figure 4C**). According to the CV data, **3** can be hardly deprotonated to **4** and then oxidized to **5** within ~45 ms. Thus, the AC frequency that provides t_{ox} of 45 ms (*i.e.*, f_{pred} = 11 Hz, see **Figure S7**) should result in the highest selectivity toward **1a**. The f_{pred} of 11 Hz from the CV measurements is in excellent agreement with the experimentally observed optimal frequency (f_{exp}) of 10 Hz. At even higher frequencies such as 20 or 30 Hz, the deprotonation of **3** might not finish in one AC period and thus is carried over to the following AC period, resulting in deprotonation in an

oxidizing environment again and an increased yield for two-electron oxidation product **1b**.

The intriguing agreement between the CV-derived frequency (f_{pred}) and f_{exp} led us to think if we can predict f_{exp} for other amine substrates from their CVs without running the time-consuming trial-and-error reaction optimization. To test this idea, we collected the CVs of a variety of amines, including *N*-aryl pyrrolidines bearing electron-donating and withdrawing groups (**7-18**), *N*-aryl piperidine (**19**), *N*-aryl tetrahydroisoquinoline (**20**), and aliphatic amine (**32**). These amines showed similar scan-rate dependent CVs as **1** (**Figures S14-27** and **S39**): the ratio between i_1 and i_o ($|i_1/i_o|$) generally decreases with increasing scan rate, suggesting the slow deprotonation of amine cation radicals by NaOAc is true for all tertiary amines. We determined f_{pred} from the scan rate that produced $|i_1/i_o|$ that is most close to one (**Figure S8**).

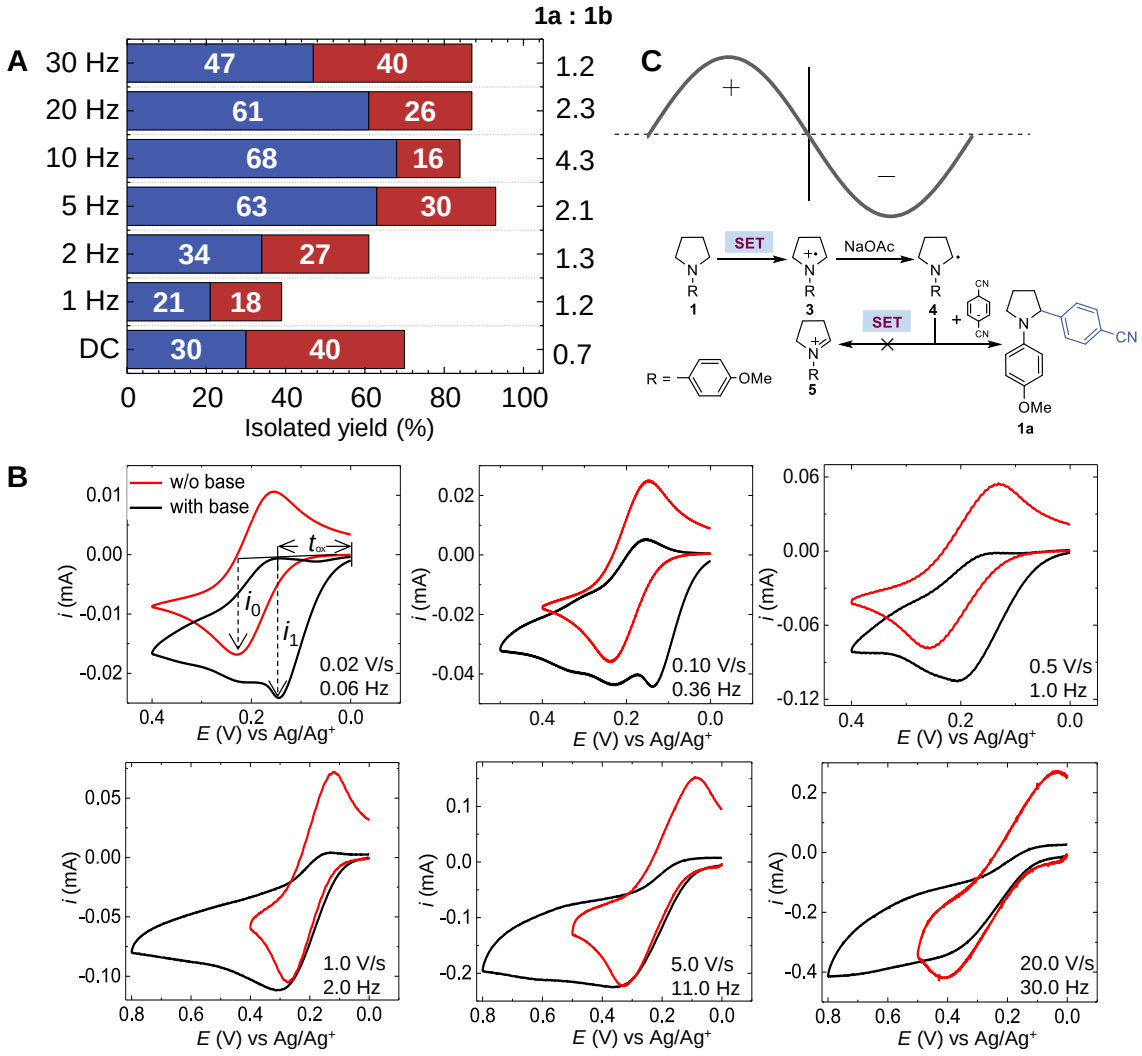


Figure 4. (A) Isolated yields and selectivity of arylation and cyanation products (**1a** and **1b**) at different AC frequencies from 1 to 30 Hz. (B) Cyclic voltammograms of **1** in the presence and absence of NaOAc in DMA containing 0.1 M $LiClO_4$ at different scan rates and their equivalent AC frequencies. (C) Proposed mechanism for the reduced degree of amine oxidation during AC electrolysis.

In parallel, we experimentally identified f_{exp} via conventional reaction optimization (i.e., running reactions at different AC frequencies and determining the selectivity from crude NMR, **Figure S8**). **Figure 5A** shows the excellent agreement between f_{exp} and f_{pred} for various amines, confirming the predictive power of the simple electrochemical descriptor (i.e., $|i_1/i_o|$) in finding the optimal frequency for selective arylation over cyanation. We also attempted to understand the dispersed f_{exp} values (by two orders of magnitude) for different amines from the calculated pKa values of their corresponding cation radicals (**Figure S9**, **Table S1**). However, we did not find any obvious correlation between f_{exp} and pKa (**Figure S10**), suggesting that the deprotonation rate is not solely determined by the acidity of these cation radical intermediates. We further varied the cyanoaromatic coupling partners, including 1,2-dicyanobenzene

(**35**), ethyl 4-cyanobenzoate (**36**), 4,4'-biphenylcarbinitrile (**37**) and 2,5-dicyanotoulene (**38**) and bases, including LiOAc, CsOAc, NaOMe, NaOH, Na_2CO_3 and $NaHCO_3$ to examine their effects on f_{exp}. Cyanoaromatics **35**-**38** show similar reversible redox behaviors with a reduction potential of ~-2 V vs Ag/Ag^+ as **2** (**Figure S42**) and have little impact on f_{exp} because they are not involved in the deprotonation of **3**. In contrast, **Figure 5B** shows that base strongly influences f_{exp} and the CV-based method accurately predicts f_{exp} (**Figure S43-48**), further supporting our proposed mechanism that the deprotonation step plays an essential role in controlling the degree of amine oxidation and product selectivity during AC electrolysis.

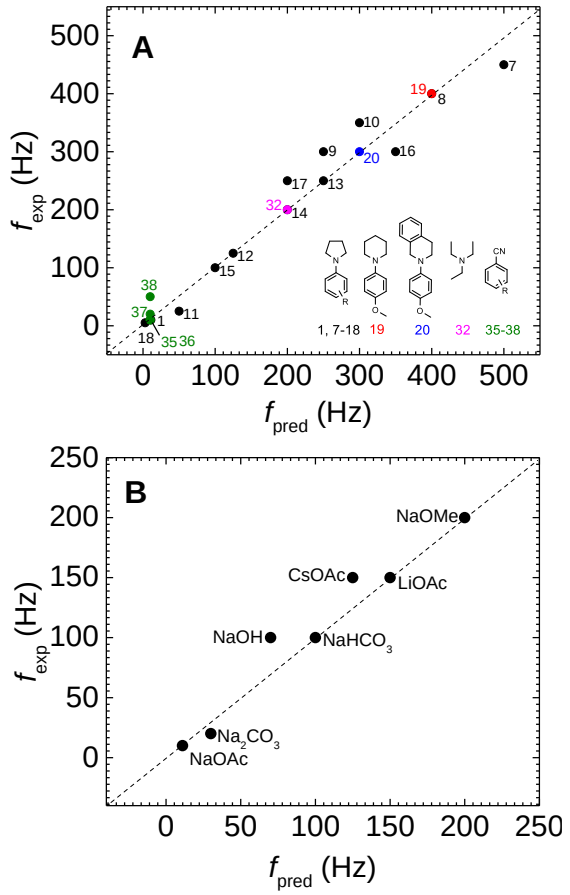


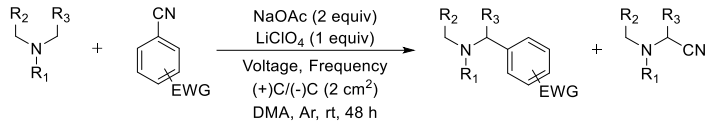
Figure 5. (A) The plot of experimentally determined optimal frequency (f_{exp}) vs predicted optimal frequency (f_{pred}) for various tertiary amines and cyanoaromatics. (B) The plot of f_{exp} vs. f_{pred} for **1** with different bases.

To confirm the one-electron oxidation of amines to α-amine radicals at the optimal frequency, we performed the radical trapping experiment on amine **1** and **20**. 5 equiv of TEMPO was added to the reaction mixture under the optimal AC electrolysis conditions. We did not observe the formation of arylation product **1a** or **20a**. However, the formation TEMPO-adduct of **1** and **20** (**Figures S11-12**) indicates that this reaction proceeds via α-amine radical pathway.

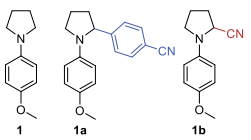
Finally, we evaluated the substrate scope and compared the product selectivity between AC and DC electrolysis in **Figure 6**. For all substrates, we performed AC electrolysis under f_{exp} and DC electrolysis. For *N*-aryl pyrrolidine bearing electron-donating groups such as methyl, tertiary butyl, 2,6-dimethyl, indane, dioxole, ethylacetate and phenyl, the arylation product yields were significantly improved from 5-30% under DC electrolysis to 43-68% under AC electrolysis (**1a, 7a-14a**) while the cyanation product yields dropped from 11-40% to 0-38% (**1b, 7b-14b**). The product selectivity shifted from the cyanation products under DC electrolysis to the arylation products under AC electrolysis. The *N*-aryl pyrrolidine substituted with electron-withdrawing groups such as F, Cl, and Br also afforded one-electron transfer products (**15a-17a**) with greater selectivity and yields under AC electrolysis than the DC counterpart. In the case of *N*-aryl pyrrolidine without any substituent on ring (**18**) afforded poor yield (<20%) and selectivity in both electrolysis conditions (**18a** and **18b**). The reaction of six-membered cyclic amine, *N*-aryl piperidine **19,** with **2** under both AC and DC electrolysis conditions provided poor yield for **19a** and **19b**, possibly because the impaired overlap between the lone pair of amine and the unpaired electron at the α-carbon significantly destabilizes the α-amino radical intermediate.[25]

Encouraged by the broad generality of our approach on five-membered cyclic amines, we tested it on another class of tertiary amines, *N*-aryl tetrahydroisoquinoline. Tetrahydroisoquinoline alkaloids are an important class of bioactive natural products and display a myriad of biological activities.[26-27] *N*-aryl ring bearing electron-donating and electron-withdrawing groups such as methoxy, fluoro, dioxine, dimethyl, trifluoromethyl (**20-26**) and *N*-benzyl (**27**) all afforded arylated and cyanation products (**20a-27a** and **20b-27b**). Under DC electrolysis, formation of cyanation product was predominantly observed in good yield 36-63% because the benzylic position is prone to overoxidation to form iminium cation.[28-30] Under AC electrolysis, arylation product formation significantly improved to good/moderate yields of 26-51%. However, the cyanation product yields were comparable to the DC electrolysis results, even though the CV data in **Figures S27-34** predicts that the two-electron oxidation of *N*-aryl tetrahydroisoquinolines should be largely reduced at f_{exp}, like the *N*-aryl pyrrolidine oxidation. A possible explanation for the discrepancy is that there are alternative pathways to generate iminium cations that does not require NaOAc, for example, via deprotonation by in situ generated CN^-[30] or dicyanobenzene **2**.[31] This explanation is in part supported by the formation of arylation and cyanation products at moderate yields for tetrahydroisoquinoline **20** even in the absence of NaOAc (**Table S2**).

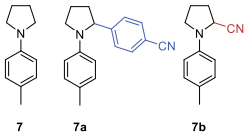
We have also identified the tertiary amine-containing heteroaromatic rings as a suitable class of substrates (**28-31**). Various *N*-benzyl/alkyl thienopyridines containing susceptible functional groups such as ester and allyl were tested. The reaction of **28** with benzonitrile **2** under DC electrolysis provided poor yield and selectivity for arylation product **28a** relative to cyanation product **28b**. In contrast, the yield of **28a** improved from 17 % to 54 % under AC



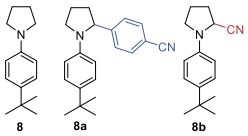
N-Aryl Pyrrolidines



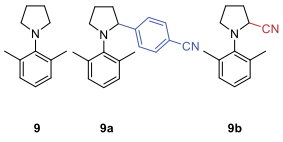
AC	68	16	(4.3:1)
DC	30	40	(0.8:1)



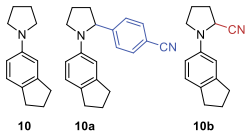
AC	64	15	(4.3:1)
DC	14	30	(0.5:1)



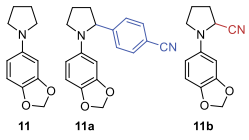
AC	56	38	(1.5:1)
DC	9	20	(0.5:1)



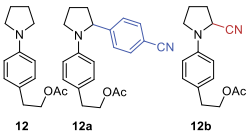
AC	62		(>99)
DC	16	27	(0.6:1)



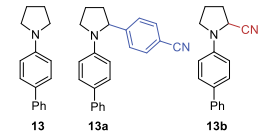
AC	52	11	(4.7:1)
DC	5	25	(0.2:1)



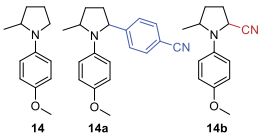
AC	43	12	(3.6:1)
DC	14	15	(0.9:1)



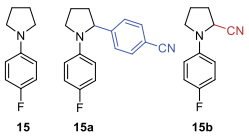
AC	63	32	(2:1)
DC	22	18	(1.2:1)



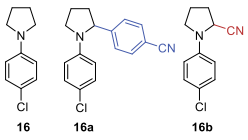
AC	51	32	(1.6:1)
DC	6	13	(0.5:1)



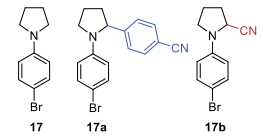
AC	45	5	(9:1)
DC	21	11	(2:1)



AC	55	9	(6:1)
DC	34	10	(3.4:1)

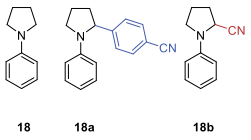


AC	43	8	(5.4:1)
DC	17	19	(0.9:1)

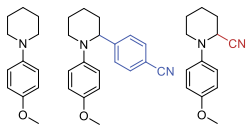


AC	56	14	(4:1)
DC	12	11	(1.1:1)

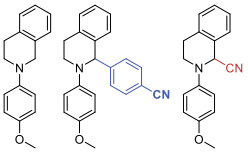
N-Aryl Tetrahydroisoquinolines



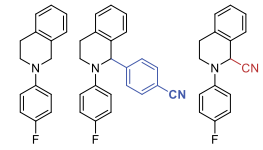
AC	16	13	(1.2:1)
DC	9	7	(1.3:1)



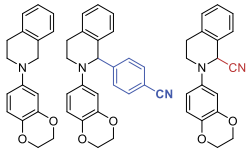
AC	18	14	(1.3:1)
DC	6	6	(1:1)



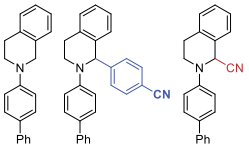
AC	50	57	(0.9:1)
DC	12	49	(0.2:1)



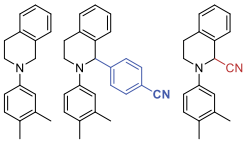
AC	49	39	(1.3:1)
DC	6	63	(0.1:1)



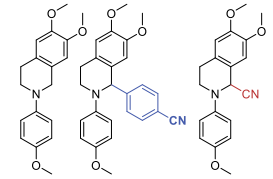
AC	26	29	(0.9:1)
DC	7	42	(0.2:1)



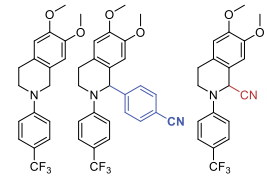
AC	40	53	(0.8:1)
DC	46		(>99)



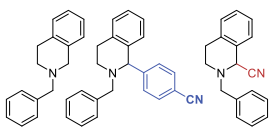
AC	47	47	(1:1)
DC	36		(>99)



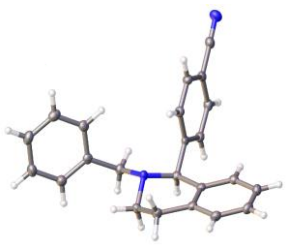
AC	48	40	(1.2:1)
DC	9	46	(0.2:1)



AC	33	43	(0.8:1)
DC	44		(>99)



AC	51	31	(1.6:1)
DC	51	51	(1:1)



X-ray structure of 27a

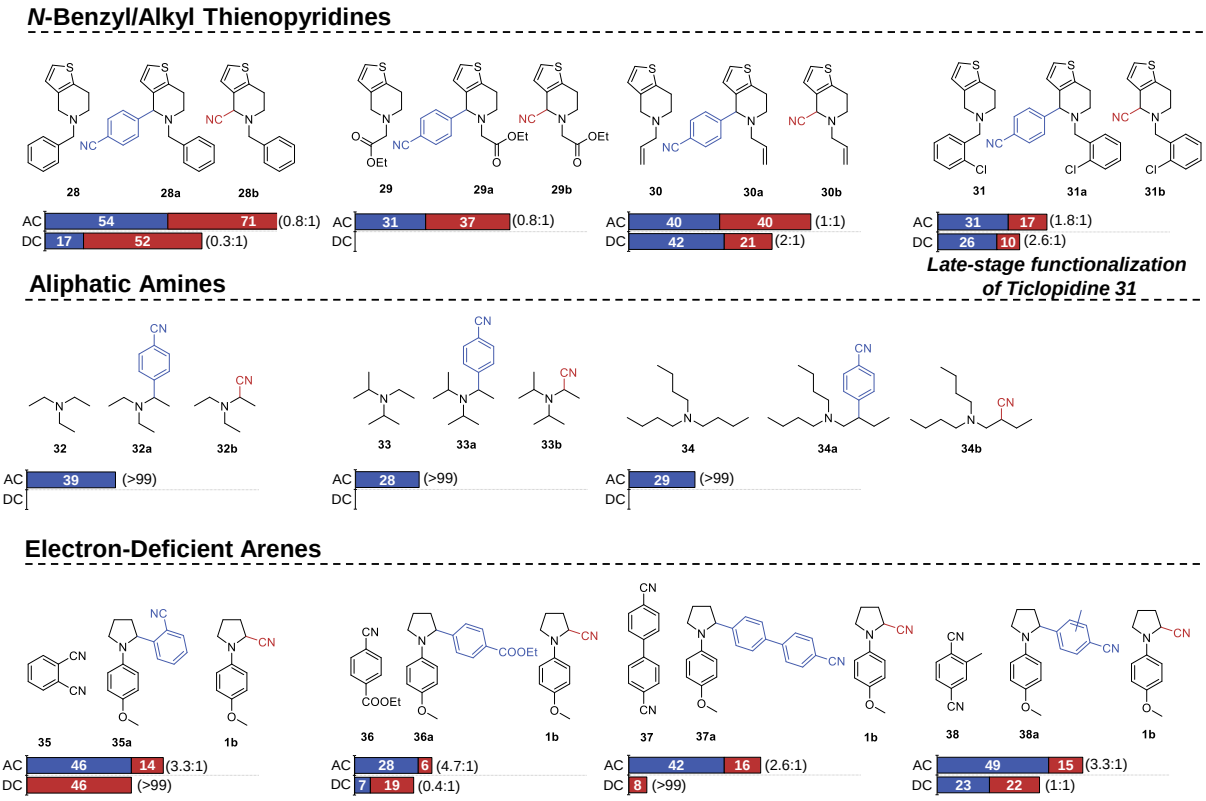


Figure 6. Substrate scope and product selectivity comparison between AC and DC electrolysis. Note: **18b** and **19b** were characterized using high-resolution mass spectrometry. Yields of **30a** and **30b** were determined using ^{1}H-NMR of the purified inseparable compounds. Regioisomers of **38a** were formed in 1:0.6 ratio. The experimental voltage and frequency for each substrate are provided in the SI.

conditions. Notably, the arylation occurred regioselectively at cyclic amine and the benzylic methylene group remained intact. In the presence of ester (**29**), DC electrolysis did not yield any products. This situation was altered when AC was applied, delivering both products at yield of 31% for **29a** and 37% for **29b**. In the case of *N*-allyl group, significant enhancement in yield and selectivity was not observed (**30a** and **30b**). For late-stage functionalization of antiplatelet drug Ticlopidine **31,** the arylation and cyanation product yields (**31a** and **31b**) slightly increased under AC electrolysis.

The tertiary aliphatic amines were also investigated. DC electrolysis did not furnish any arylation or cyanation products. In contrast, one-electron oxidation arylation product exclusively formed under AC conditions in moderate yields 28-39% (**32a-34a**). Tertiary amines containing strong electron-withdrawing functional groups such as nitro (**39**), pyrimidinyl (**40**), and benzenesulfonyl (**41**) did not result in any products (**Figure S13**).

Moreover, the substrate scope for aromatic partner **2** was also explored. Cyanoaromatics **35**-**38** successfully underwent coupling with **1** to furnish arylated products in moderate to good yields (**35a-38a**). In contrast, , the product involving two-electron transfer was predominantly obtained in most cases in moderate to low yields (**1b**) under DC electrolysis. The arylated product **38a** was a 1:0.6 mixture of two isomers due to lack of regioselectivity in elimination of CN^- group in reaction. The coupling of **1** with electron-deficient heteroaromatics such as 4-cyanopyridine (**43**), 2-chlorobenzthiozole (**44**) and 2-chlorobenzoxazole (**45**) were not successful using AC or DC electrolysis (**Figure S13**).

CONCLUSIONS

In conclusion, we have reported a mechanism by which AC electrolysis controls the one- or two-electron oxidation of amines to amino radicals or iminium cations, enabling selective α-amine functionalization by adjusting the AC frequency. We found that the selective one-electron oxidation of amines to amino radicals was achieved by providing a reducing environment for the deprotonation of amino radical cations. We have also developed a convenient electroanalytical method to identify the optimal AC frequency that maximizes the arylation product of the one-electron oxidation pathway, eliminating the time-consuming trial-and-error approach in conventional AC electrolysis condition optimization. We envision that this highly efficient and unique AC electrolysis protocol can be applied to achieve unique reactivities in synthetic and medicinal chemistry.

ASSOCIATED CONTENT

Supporting Information. The Supporting Information is available free of charge via the Internet at http://pubs.acs.org.

Details of experimental procedures, cyclic voltammetry studies, determination of the optimal voltage and frequency for each substrate, pKa calculations, X-ray crystallography data, full characterization data and copies of NMR spectra (PDF).

Accession Codes

CCDC 2150591 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

AUTHOR INFORMATION

Corresponding Author

* Long Luo − Department of Chemistry, Wayne State University, Detroit, Michigan 48202, United States; orcid.org/0000-0001-5771-6892; Email: long.luo@wayne.edu

Authors

Disni Gunasekera − Department of Chemistry, Wayne State University, Detroit, Michigan 48202, United States
Jyoti P. Mahajan− Department of Chemistry, Wayne State University, Detroit, Michigan 48202, United States; orcid.org/0000-0002-6071-6348
Yanick Wanzi− Department of Chemistry, Wayne State University, Detroit, Michigan 48202, United States
Sachini Rodrigo− Department of Chemistry, Wayne State University, Detroit, Michigan 48202, United States
Wei Liu − Laboratory of Theoretical and Computational Nanoscience, CAS Center for Excellence in Nanoscience, National Center for Nanoscience and Technology, Chinese Academy of Sciences, Beijing 100190, China
Ting Tan− Laboratory of Theoretical and Computational Nanoscience, CAS Center for Excellence in Nanoscience, National Center for Nanoscience and Technology, Chinese Academy of Sciences, Beijing 100190, China

Author Contributions

The manuscript was written through the contributions of all authors. All authors have given approval to the final version of the manuscript. DG and JPM contributed equally to this work.

Notes

Any additional relevant notes should be placed here.

ACKNOWLEDGMENT

DG, JPM, and LL gratefully acknowledge support from NIH (1R35 GM142590-01), the start-up funds, the Thomas C. Rumble University Graduate Fellowship, and the Faculty Competition for Postdoctoral Fellows ward from Wayne State University. We thank Cassandra Ward (the Lumigen Instrument Center) for assistance with X-ray crystallographic analysis.

REFERENCES

1. Yan, M.; Kawamata, Y.; Baran, P. S., Synthetic Organic Electrochemistry: Calling All Engineers. *Angew. Chem., Int. Ed.* **2018,** *57* (16), 4149-4155.
2. Yan, M.; Kawamata, Y.; Baran, P. S., Synthetic Organic Electrochemical Methods Since 2000: On the Verge of a Renaissance. *Chem. Rev.* **2017,** *117* (21), 13230-13319.
3. Yoshida, J.-i.; Kataoka, K.; Horcajada, R.; Nagaki, A., Modern Strategies in Electroorganic Synthesis. *Chem. Rev.* **2008,** *108* (7), 2265-2299.
4. Pletcher, D., Organic electrosynthesis – A road to greater application. A mini review. *Electrochem. Commun.* **2018,** *88*, 1-4.
5. Wiebe, A.; Gieshoff, T.; Möhle, S.; Rodrigo, E.; Zirbes, M.; Waldvogel, S. R., Electrifying organic synthesis. *Angew. Chem., Int. Ed.* **2018,** *57* (20), 5594-5619.
6. Chen, N.; Xu, H.-C., Electrochemically Driven Radical Reactions: From Direct Electrolysis to Molecular Catalysis. *The Chemical Record* **2021,** *21* (9), 2306-2319.
7. Shono, T.; Hamaguchi, H.; Matsumura, Y., Electroorganic chemistry. XX. Anodic oxidation of carbamates. *J. Am. Chem. Soc.* **1975,** *97* (15), 4264-4268.
8. Lennox, A. J. J.; Goes, S. L.; Webster, M. P.; Koolman, H. F.; Djuric, S. W.; Stahl, S. S., Electrochemical Aminoxyl-Mediated α-Cyanation of Secondary Piperidines for Pharmaceutical Building Block Diversification. *J. Am. Chem. Soc.* **2018,** *140* (36), 11227-11231.
9. Ma, Y.; Yao, X.; Zhang, L.; Ni, P.; Cheng, R.; Ye, J., Direct Arylation of α-Amino C(sp3)-H Bonds by Convergent Paired Electrolysis. . *Angew. Chem., Int. Ed.* **2019,** *58* (46), 16548-16552.
10. Wang, F.; Rafiee, M.; Stahl, S. S., Electrochemical Functional-Group-Tolerant Shono-type Oxidation of Cyclic Carbamates Enabled by Aminoxyl Mediators. *Angew. Chem., Int. Ed.* **2018,** *57* (22), 6686-6690.
11. Francke, R.; Little, R. D., Redox catalysis in organic electrosynthesis: basic principles and recent developments. *Chem. Soc. Rev.* **2014,** *43* (8), 2492-2521.
12. Wang, F.; Stahl, S. S., Electrochemical oxidation of organic molecules at lower overpotential: Accessing broader functional group compatibility with electron−proton transfer mediators. *Acc. Chem. Res.* **2020,** *53* (3), 561-574.
13. Rodrigo, S.; Um, C.; Mixdorf, J. C.; Gunasekera, D.; Nguyen, H. M.; Luo, L., Alternating Current Electrolysis for Organic Electrosynthesis: Trifluoromethylation of (Hetero)arenes. *Organic Letters* **2020,** *22* (17), 6719-6723.
14. Bortnikov, E. O.; Semenov, S. N., Coupling of Alternating Current to Transition-Metal Catalysis: Examples of Nickel-Catalyzed Cross-Coupling. *The Journal of Organic Chemistry* **2021,** *86* (1), 782-793.
15. Sattler, L. E.; Otten, C. J.; Hilt, G., Alternating Current Electrolysis for the Electrocatalytic Synthesis of Mixed Disulfide via Sulfur–Sulfur Bond Metathesis towards Dynamic Disulfide Libraries. *Chemistry – A European Journal* **2020,** *26* (14), 3129-3136.
16. Hilt, G., Basic Strategies and Types of Applications in Organic Electrochemistry. *ChemElectroChem* **2020,** *7* (2), 395-405.
17. Schotten, C.; Taylor, C. J.; Bourne, R. A.; Chamberlain, T. W.; Nguyen, B. N.; Kapur, N.; Willans, C. E., Alternating polarity for enhanced electrochemical synthesis. *Reaction Chemistry & Engineering* **2020**.
18. Rodrigo, S.; Gunasekera, D.; Mahajan, J. P.; Luo, L., Alternating current electrolysis for organic synthesis. *Current Opinion in Electrochemistry* **2021,** *28*, 100712.
19. Fährmann, J.; Hilt, G., Alternating Current Electrolysis as Efficient Tool for the Direct Electrochemical Oxidation of Hydroxamic Acids for Acyl Nitroso Diels–Alder Reactions. *Angew. Chem., Int. Ed.* **2021,** *60* (37), 20313-20317.
20. Zhong, J.; Ding, C.; Kim, H.; McCallum, T.; Ye, K., Alternating current electrolysis: a photoredox catalysis mimic and beyond. *Green Synthesis and Catalysis* **2022**, DOI: 10.1016/j.gresc.2022.01.003

21. Wang, D.; Jiang, T.; Wan, H.; Chen, Z.; Qi, J.; Yang, A.; Huang, Z.; Yuan, Y.; Lei, A., Alternating Current Electrolysis Enabled Formal C-O/O-H Cross-Metathesis of 4-Alkoxy Anilines with Alcohols. *Angew. Chem., Int. Ed.* **2022,** DOI: 10.1002/anie.202201543.
22. Kawamata, Y.; Hayashi, K.; Carlson, E.; Shaji, S.; Waldmann, D.; Simmons, B. J.; Edwards, J. T.; Zapf, C. W.; Saito, M.; Baran, P. S., Chemoselective Electrosynthesis Using Rapid Alternating Polarity. *J. Am. Chem. Soc.* **2021,** *143* (40), 16580-16588.
23. McNally, A.; Prier, C. K.; MacMillan, D. W., Discovery of an α-amino C-H arylation reaction using the strategy of accelerated serendipity. *Science* **2011,** *334* (6059), 1114-7.
24. Novaes, L. F. T.; Ho, J. S. K.; Mao, K.; Liu, K.; Tanwar, M.; Neurock, M.; Villemure, E.; Terrett, J. A.; Lin, S., Exploring Electrochemical C(sp3)–H Oxidation for the Late-Stage Methylation of Complex Molecules. *J. Am. Chem. Soc.* **2022,** *144* (3), 1187-1197.
25. Ma, Y.; Yao, X.; Zhang, L.; Ni, P.; Cheng, R.; Ye, J., Direct Arylation of α-Amino C(sp3)-H Bonds by Convergent Paired Electrolysis. *Angew. Chem., Int. Ed.* **2019,** *131* (46), 16700-16552.
26. Faheem; Karan Kumar, B.; Chandra Sekhar, K. V. G.; Chander, S.; Kunjiappan, S.; Murugesan, S., Medicinal chemistry perspectives of 1,2,3,4-tetrahydroisoquinoline analogs – biological activities and SAR studies. *RSC Advances* **2021,** *11* (20), 12254-12287.
27. Kaur, P.; Kumar, R., Recent advances in the C(1)-functionalization of tetrahydroisoquinolines via multicomponent reactions. *Chem. Heterocycl. Compd. (N. Y., NY, U. S.)* **2020,** *56*, 422 - 432.
28. Xie, W.; Liu, N.; Gong, B.; Ning, S.; Che, X.; Cui, L.; Xiang, J., Electrochemical Cross-Dehydrogenative Coupling of N-Aryl-tetrahydroisoquinolines with Phosphites and Indole. *Eur. J. Org. Chem.* **2019,** *2019* (14), 2498-2501.
29. Benmekhbi, L.; Louafi, F.; Roisnel, T.; Hurvois, J.-P., Synthesis of Tetrahydroisoquinoline Alkaloids and Related Compounds through the Alkylation of Anodically Prepared α-Amino Nitriles. *The Journal of Organic Chemistry* **2016,** *81* (15), 6721-6739.
30. Louafi, F.; Hurvois, J.-P.; Chibani, A.; Roisnel, T., Synthesis of Tetrahydroisoquinoline Alkaloids via Anodic Cyanation as the Key Step. *The Journal of Organic Chemistry* **2010,** *75* (16), 5721-5724.
31. Stevenson, B. G.; Spielvogel, E. H.; Loiaconi, E. A.; Wambua, V. M.; Nakhamiyayev, R. V.; Swierk, J. R., Mechanistic Investigations of an α-Aminoarylation Photoredox Reaction. *J. Am. Chem. Soc.* **2021,** *143* (23), 8878-8885.

Table of contents artwork