OL | Organic Letters

pubs.acs.org/OrgLett Letter

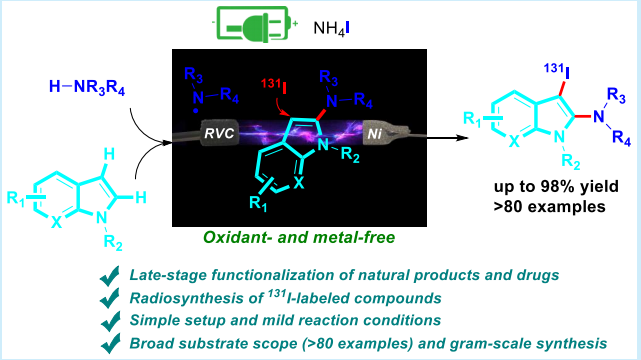
Electrochemical Iodoamination of Indoles Using Unactivated Amines

Ning Lei, Yanling Shen, Yujun Li, Pan Tao, Liquan Yang, Zhishan Su, and Ke Zheng*

Cite This: https://dx.doi.org/10.1021/acs.orglett.0c03158 Read Online

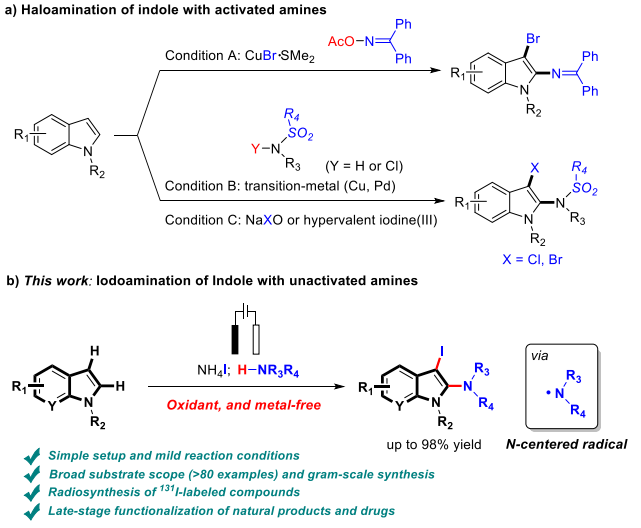
ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: An environmentally friendly electrochemical approach for iodoamination of various indole derivatives with a series of unactivated amines, amino acid derivatives, and benzotriazoles (more than 80 examples) has been developed. This strategy was further applied in late-stage functionalization of natural products and pharmaceuticals and gram-scale synthesis and radiosynthesis of ^{131}I-labeled compounds. Fundamental insights into the mechanism of the reaction based on control experiments, density functional theory calculation, and cyclic voltammetry are provided.



The indole scaffold is privileged structural motif that exists extensively in a wide range of natural products and pharmaceuticals, as well as agricultural chemicals.[1] The direct dual functionalization of indoles is of great interest to chemists because two functional groups can be introduced simultaneously. Specifically, the haloamination of indoles is synthetically attractive because the resulting haloaminated indoles are versatile synthetic blocks in both organic synthesis and biological applications due to their ability to readily facilitate further modification by the transformation of C3 halogen atoms. For instance, the Nicholas group described a copper-catalyzed bromoamination of indoles with oxime esters using a stoichiometric amount of CuBr.[2] Liu and Liang demonstrated a method for the chloroamidation of indoles with *N*-chlorosulfonamides by using a Pd/Cu-co-catalyst.[3] Moriyama and Togo reported the bromoamination of *N*-pivaloylindole with bis(tosyl)imide (Ts_2NH) by using hypervalent iodine-(III).[4] Recently, Yu, Tan, and co-workers developed the chloroamidation of indoles with sulfonamides and NaClO under metal-free conditions.[5] The concomitant introduction of a halogen and of a nitrogen functional group on indole derivatives has also been developed or observed with other strategies.[6] Despite the considerable progress that has been made in this field, the existing protocols usually require stoichiometric quantities of oxidant, hypervalent iodines(III), or transition metals (Cu and Pd), all with limited functional group tolerance (Scheme 1a). Specifically, the direct iodoamination of indole derivatives with unactivated amines remains challenging. Since the discovery of the Hofmann–Löffler–Freytag reaction,[7] it is well known that *N*-halo amines can readily undergo homolytic cleavage to form the corresponding N-centered radical species. In recent years,

Scheme 1. C–H Haloamination of Indoles



significant advances have been made in the field of generating N-centered radicals for building ubiquitous structural units by using photo- and electrochemistry.[8,10e,11d] Although considerable effort has been directed toward the development of

Received: September 22, 2020

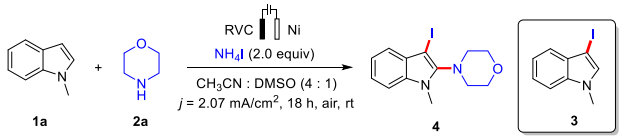
https://dx.doi.org/10.1021/acs.orglett.0c03158
Org. Lett. XXXX, XXX, XXX−XXX

these nitrogen radicals, most of them are viable on active amines, such as diarylamines,[9] amides,[10] *P*-methylbenzene sulfonamide derivatives,[11] etc., and using *N*-halo analogues of unactivated alkyl amines as N-centered radical precursors is still a paramount synthetic challenge.[12]

Compared to conventional chemical approaches, electrochemistry provides a green alternative for redox transformations and an environmentally friendly way to construct important organic molecules.[13] In recent years, electrochemical generation of N-centered radicals has drawn much interest, and several efficient protocols have been developed.[9,10,12e] The halogen-mediated amination of double bonds via an electron-driven process has also developed well.[13i,j,14] Furthermore, the electrochemical halogenation of indoles is a known process.[15] As part of our continuing pursuit of the discovery of new electrochemical methods,[16] herein, we report an environmentally friendly electrochemical dual functionalization of indole derivatives with the formation of C−N and C−I bonds in one step. The N-centered radical intermediates were demonstrated as key intermediates in this process. Using this strategy, more than 80 dual-functionalized indole derivatives are constructed with high yields under mild conditions [metal- and oxidant-free (Scheme 1b)].

In the beginning of our investigation, 1-methylindole (**1a**) and morpholine (**2a**) were used for optimization studies. The desired yield of dual-functionalization product **4** (98%) was obtained by employing NH_4I as the electrolyte and a CH_3CN/DMSO (4:1) solvent, under a constant current of 12 mA under atmospheric conditions (Table 1, entry 1). Lower yields were

Table 1. Optimization of Reaction Conditions[a]



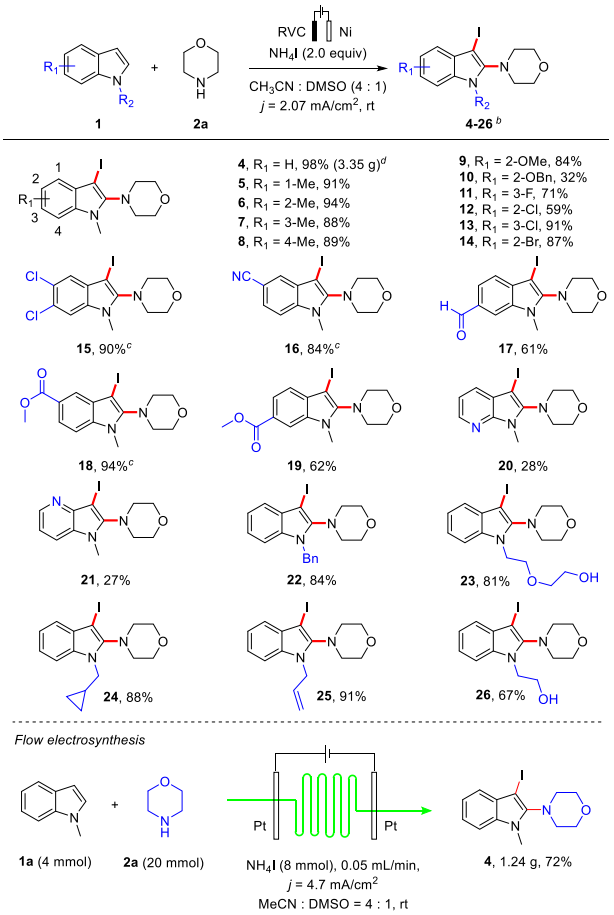
entry	variation from the "standard conditions"	yield[b] (%)
1	none	98
2	without DMSO	76[c]
3	without CH_3CN	82
4	RVC (+)|Pt (−) instead of RVC (+)|Ni (−)	78[c]
5	Pt (+)|Ni (−) instead of RVC (+)|Ni (−)	87
6	8 mA instead of 12 mA	71[c]
7	16 mA instead of 12 mA	81
8	without current	no reaction

[a]Reaction conditions: RVC anode (100 PPI, 1.2 cm × 1.0 cm × 1.0 cm), foamed Ni cathode (1.0 cm × 1.0 cm), constant current of 12 mA (j = 2.07 mA/cm^2), **1a** (0.2 mmol), **2a** (0.6 mmol), NH_4I (0.4 mmol), solvent (5.0 mL), undivided cell, air, room temperature, 18 h. RVC is reticulated vitreous carbon. [b]Isolated yield. [c]Iodination product **3** was obtained as a byproduct.

observed without the mixed solvent (Table 1, entries 2 and 3). When a reticulated vitreous carbon (RVC) anode or a nickel foam cathode was replaced, the efficiency of transformation was lower (Table 1, entry 4 or 5, respectively). Decreasing or increasing the current had a minimal effect on the facilitation of transformation (Table 1, entry 6 or 7, respectively). Electricity is indispensable for the reaction (Table 1, entry 8).

A wide variety of indole derivatives with different substituents were examined under optimized conditions (Scheme 2). The indoles with different substituents, including

Scheme 2. Scope of Indoles[a]



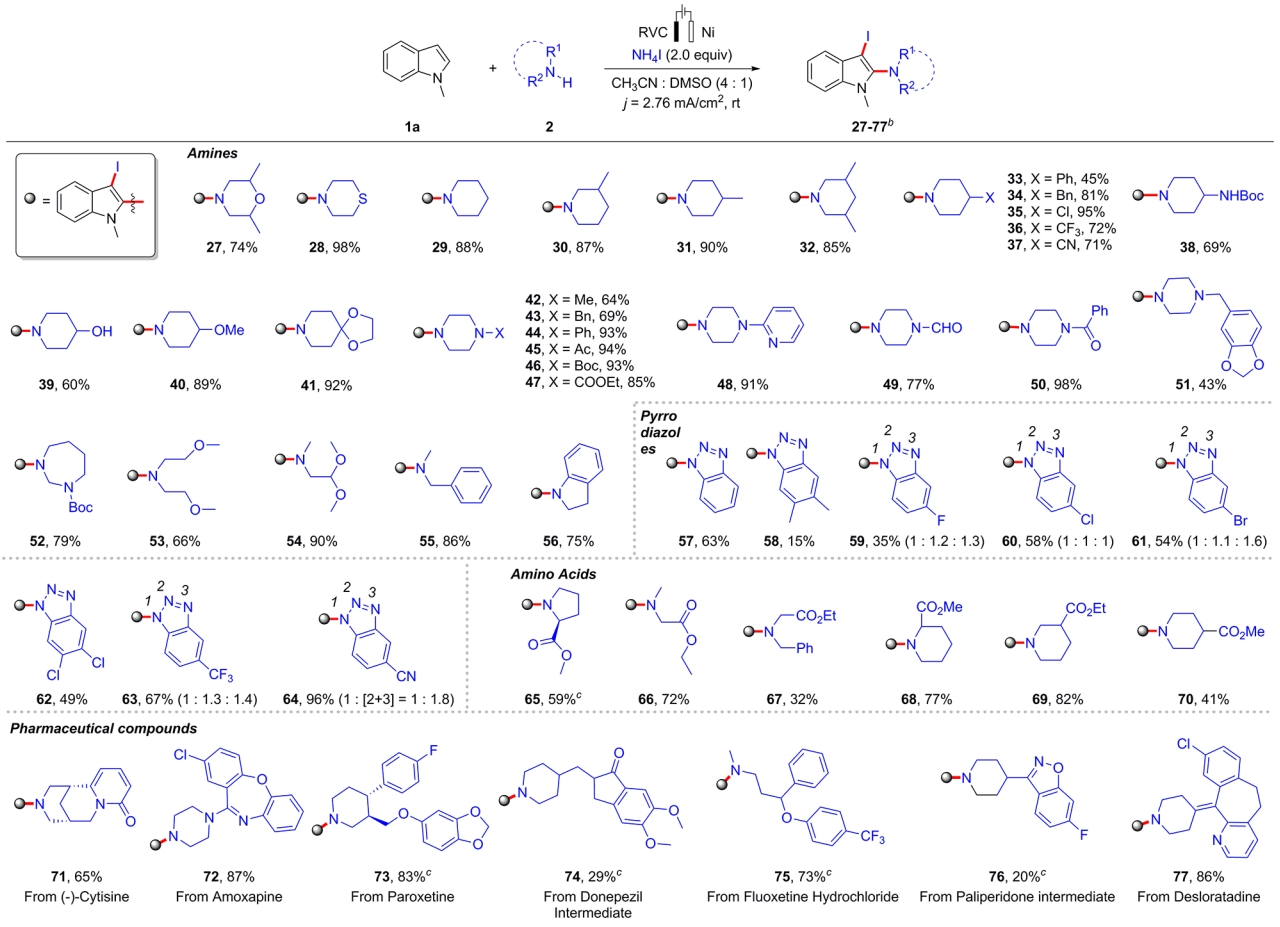
[a]Standard conditions. [b]Isolated yields. [c]With 10.0 equiv of morpholine. [d]Gram-scale synthesis.

alkyl (**5**−**8**), alkoxy (**9** and **10**), halogen (**11**−**15**), cyan (**16**), aldehyde (**17**), and ester (**18** and **19**) groups, had been successfully applied to the reaction, giving the iodoamination products in good to excellent yields. The reaction was also successful with heteroaryl indoles, including 7-aza-*N*-methylindole **20** and 4-aza-*N*-methylindole **21**, though with a decreased yield. The N-substituted indole derivatives with different groups, such as benzyl (**22**), 2-ethoxyethan-1-ol (**23**), cyclopropylmethyl (**24**), allyl (**25**), and hydroxy (**26**) groups, were well tolerated, producing the corresponding products in high yields. Furthermore, the success of gram-scale synthesis via either a batch protocol (3.35 g, 98% yield) or flow chemistry (1.24 g, 72% yield) provided promising results for further applications in industry.

Next, a large variety of amines were explored under similar conditions by using a constant current of 16 mA. As described in Scheme 3, the reaction displayed a broad scope with amines, and high to excellent yields were achieved (≤98% yield). 2,6-Dimethylmorpholine (**27**) and thiomorpholine (**28**) could react smoothly with 1-methylindole **1a**. We also evaluated a wide range of piperidine (**29**−**41**) and piperazine (**42**−**51**) derivatives, which are the most prevalent N-heterocycles in pharmaceuticals and often used as links in drug modifications. The mild reaction conditions were compatible with various functional groups, including halide, hydroxy, aldehyde, cyan, amide, ether, and ester groups, which are sometimes troublesome in the classical coupling method.

https://dx.doi.org/10.1021/acs.orglett.0c03158
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 3. Scope of Amines[a]



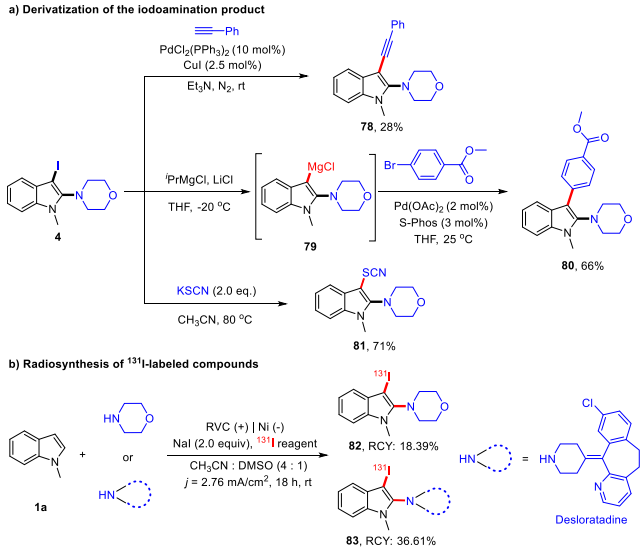
[a]Standard conditions with a constant current of 16 mA (j = 2.76 mA/cm^2). [b]Isolated yields. [c]Reaction performed with 2.0 equiv of Na_2CO_3.

Other N-heterocycles with seven- and five-membered rings were also well tolerated (**52** and **56**). To our delight, this transformation was not limited to cyclic systems; acyclic dialkyl amines were also suitable, as demonstrated by the successful formation of **53**−**55**. Various benzotriazoles also proved to be tolerable, giving iodoamination products in good to excellent yields, whereas the benzotriazoles with electron-donating groups usually gave lower yields (**57**−**64**). Introducing different amino acids is a popular strategy in medicinal chemistry and is aimed at balancing the biocompatibility of lead compounds. We were pleased to see that the amino acid derivatives were also suitable for this strategy (**65**−**70**).

The broad substrate scope of the method, as well as the promising functional group compatibility, encouraged us to futher envaluate its application in late-stage functionalization of natural products and bioactive molecules (**71**−**77**). (−)-Cytisine underwent electrochemcial iodoamination to afford **71** in 65% yield. Amoxapine and paroxetine were efficiently functionalized in excellent yields to afford **72** (87% yield) and **73** (83% yield), respectively. The Donepezil intermediate, Fluoxetine, and the Paliperidone intermediate underwent functionalization in moderate to high yields (**74**−**76**, respectively). Electrochemcial iodoamination has been achieved on Desloratadine, affording **77** in 86% yield.

To further evaluate the potential of this method, the derivatization of iodoamination products was extended. As shown in Scheme 4, Sonogashira coupling of **4** with phenylacetylene gave product **78** in an acceptable yield. Coupling of **4** with bromobenzene via Grignard reagent produced **80** in good yield. Furthermore, sulfurcyanation of **4** can be performed easily to give **81** in 71% yield. As ^{131}I is one of the most important radioisotopes in the radiopharmaceut-

Scheme 4. Derivatization of the Iodoamination Product and Radiosynthesis

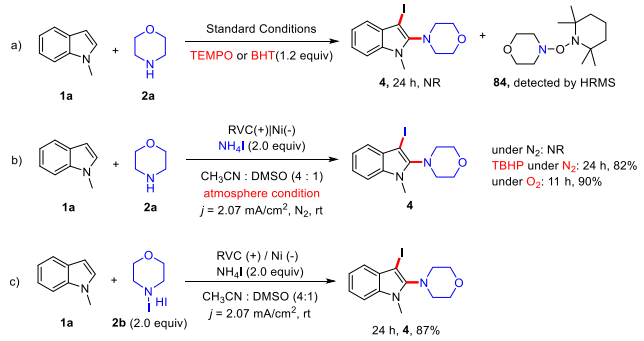


https://dx.doi.org/10.1021/acs.orglett.0c03158
Org. Lett. XXXX, XXX, XXX−XXX

ical industry,[17] we further explored application of this strategy to the radiosynthesis of ^{131}I-labeled compounds. To our delight, ^{131}I-labeled products **82** and desloratadine analogue **83** could be easily prepared by using this electrochemical iodoamination protocol with 18.4% and 36.7% radiochemical yields, respectively (the radiochemical yield was determined by radio-TLC).

To gain insight into the mechanistic details, control experiments and cyclic voltammetry (CV) analysis were conducted (for more details, see Figures S4, S5, and S8). When TEMPO or BHT as a radical inhibitor was subjected to the reaction, no reaction took place with concomitant detection of TEMPO adduct **84**, indicating that the N-centered radical intermediate was formed during this process (Scheme 5a). Only a trace of product **4** was formed under a N_2

Scheme 5. Control Experiments



atmosphere without O_2 (Scheme 5b). Desired product **4** can be established in high yield under O_2 conditions (O_2 balloon at 1 atm) or with addictive TBHP under a N_2 atmosphere (for more details, see the Supporting Information).[18,19] To further elucidate the mechanism that is responsible for this electrochemical iodoamination, **2b** was directly subjected to reaction and gives **4** with 87% yield in 24 h (Scheme 5c). The results of the CV experiment showed that the oxidative peak potential for the mixture of NH_4I and morphiline ($E_{p/2}$ = 0.81 and 1.17 V vs Ag/AgCl), which was similar to that of **2b** ($E_{p/2}$ = 0.85 and 1.16 V vs Ag/AgCl), was significantly lower than those of **1a** and **2a** [$E_{p/2}$ = 1.41 and 1.24 V vs Ag/AgCl, respectively (Figure S8)]. These experimental observations provide evidence for the formation of highly reactive intermediate **2b** in this electrochemical protocol. Moreover, the DFT calculations demonstrate that the N-centered radical could be easily formed by the homolysis of **2b** (ΔG = 23.7 kcal/mol, at the B3LYP/Def2-SVP level of theory).

On the basis of the mechanistic results presented above, the proposed mechanism is depicted in Figure 1. This electrochemical iodoamination reaction is initiated by oxidation of the iodide ion at the anode, which leads to the formation of iodine (Figure 1). Then, key intermediate **2b** can be generated in situ as morphiline reacts with iodine. N-Centered radical species **I** is generated by homolysis of a weak N−I bond of **2b**, followed by radical addition to the indole at position 2 to afford radical intermediate **II**.[9a,c,11c,20] Radical intermediate **II** is trapped by superoxide radical $HO_2^{\bullet}$ to furnish intermediate **III**,[21] which can be easily converted to amination product **V** under standard conditions. As an alternative pathway, radical intermediate **II** can also be oxidized at the anode to form carbocation **IV**.[21] Meanwhile, O_2 was oxidized at the anode to form $O_2^{\bullet-}$, which abstracts a hydrogen atom from intermediate **IV** to produce

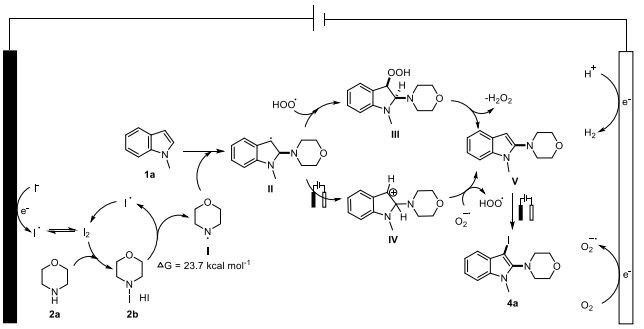


Figure 1. Proposed mechanism.

amination product **V**. Finally, iodination amination product **V** furnishes the desired dual-functionalization product.

In summary, an efficient electrochemical approach was developed for dual functionalization of indoles with a series of unactivated amines. The approach generates a variety of useful iodoamination products with good tolerance of functional groups under mild electrochemical conditions. Mechanism studies demonstrated that the N-centered radical intermediate was formed facilely in this process. The success of gram-level synthesis and radiosynthesis of ^{131}I-labeled compounds, as well as the potential of late-stage functionalization, provides promising results for further applications in industrial settings and medicinal chemistry. Further synthetic application research, as well as the application of ^{131}I-labeled compounds, is ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03158.

General procedures, analytical data, NMR spectra, and DFT calculation data (PDF)

Accession Codes

CCDC 2006856 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, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

Ke Zheng − *Key Laboratory of Green Chemistry & Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, P. R. China;* orcid.org/0000-0002-3345-7715; Email: kzheng@scu.edu.cn

Authors

Ning Lei − *Key Laboratory of Green Chemistry & Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, P. R. China*

Yanling Shen − *Key Laboratory of Green Chemistry & Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, P. R. China*

https://dx.doi.org/10.1021/acs.orglett.0c03158
Org. Lett. XXXX, XXX, XXX−XXX

Yujun Li − *Key Laboratory of Green Chemistry & Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, P. R. China*
Pan Tao − *Key Laboratory of Green Chemistry & Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, P. R. China*
Liquan Yang − *Key Laboratory of Green Chemistry & Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, P. R. China*
Zhishan Su − *Key Laboratory of Green Chemistry & Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, P. R. China;* orcid.org/0000-0001-5168-3823

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c03158

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors acknowledge the National Natural Science Foundation of China (21602142) and the Fundamental Research Funds for the Central Universities. The authors thank the Xiaoming Feng laboratory (SCU) for access to equipment and Yuqiao Zhou (SCU) for X-ray structural analysis. The authors thank Chuanqin Xia (SCU) and Huawei Cai (SCU) for radiochemical analysis. The authors also thank the comprehensive training platform of the Specialized Laboratory in the College of Chemistry at Sichuan University for testing of compounds.

■ REFERENCES

(1) (a) Iwasa, E.; Hamashima, Y.; Fujishiro, S.; Higuchi, E.; Ito, A.; Yoshida, M.; Sodeoka, M. Total Synthesis of (+)-Chaetocin and its Analogues: Their Histone Methyltransferase G9a Inhibitory Activity. *J. Am. Chem. Soc.* **2010**, *132*, 4078−4079. (b) Somei, M.; Yamada, F. Simple indole alkaloids and those with a non-rearranged monoterpenoid unit. *Nat. Prod. Rep.* **2005**, *22*, 73−103. (c) Crich, D.; Banerjee, A. Chemistry of the Hexahydropyrrolo[2,3-b]indoles: Configuration, Conformation, Reactivity, and Applications in Synthesis. *Acc. Chem. Res.* **2007**, *40*, 151−161. (d) Ruiz-Castillo, P.; Buchwald, S. L. Applications of Palladium-Catalyzed C−N Cross-Coupling Reactions. *Chem. Rev.* **2016**, *116*, 12564−12649.

(2) John, A.; Nicholas, K. M. Copper-Mediated Multiple C−H Functionalization of Aromatic N-Heterocycles: Bromoamination of Indoles and Pyrroles. *Organometallics* **2012**, *31*, 7914−7920.

(3) Liu, X.-Y.; Gao, P.; Shen, Y.-W.; Liang, Y.-M. Palladium-/Copper-Catalyzed Regioselective Amination and Chloroamination of Indoles. *Org. Lett.* **2011**, *13*, 4196−4199.

(4) Moriyama, K.; Ishida, K.; Togo, H. Regioselective Csp2−H dual functionalization of indoles using hypervalent iodine(iii): bromoamination via 1,3-migration of imides on indolyl(phenyl)iodonium imides. *Chem. Commun.* **2015**, *51*, 2273−2276.

(5) (a) Liu, X.; Tong, K.; Zhang, A.; Tan, R.; Yu, S. Metal-free chloroamidation of indoles with sulfonamides and NaClO. *Org. Chem. Front.* **2017**, *4*, 1354−1357. (b) Li, Z.; Tang, M.; Hu, C.; Yu, S. Atroposelective Haloamidation of Indoles with Amino Acid Derivatives and Hypohalides. *Org. Lett.* **2019**, *21*, 8819−8823. (c) Tong, K.; Liu, X.; Zhang, Y.; Yu, S. Visible-Light-Induced Direct Oxidative C-H Amidation of Heteroarenes with Sulfonamides. *Chem. - Eur. J.* **2016**, *22*, 15669−15673.

(6) (a) Tu, D.; Luo, J.; Jiang, C. Copper-mediated domino C−H iodination and nitration of indoles. *Chem. Commun.* **2018**, *54*, 2514−2517. (b) Wu, W.-B.; Huang, J.-M. Highly Regioselective CN Bond Formation through C-H Azolation of Indoles Promoted by Iodine in Aqueous Media. *Org. Lett.* **2012**, *14*, 5832−5835. (c) Beukeaw, D.; Udomsasporn, K.; Yotphan, S. Iodine-Catalyzed Oxidative Cross-Coupling of Indoles and Azoles: Regioselective Synthesis of N-Linked 2-(Azol-1-yl)indole Derivatives. *J. Org. Chem.* **2015**, *80*, 3447−3454. (d) Ghosh, S. K.; Nagarajan, R. NIS-mediated regioselective amidation of indole with quinazolinone and pyrimidine. *RSC Adv.* **2014**, *4*, 20136−20144. (e) Liu, X.; Hu, Q.; Yuan, Z.; Liu, P. AcOH-mediated dichloroimination of indoles using chloramine-B: a facile access to 2,3-functionalized indolines. *Org. Biomol. Chem.* **2014**, *12*, 7494−7497.

(7) (a) Wolff, M. E. Cylization of N-halogenated amines (The Hofmann-Löffler Reaction). *Chem. Rev.* **1963**, *63*, 55−64. (b) Stella, L. Homolytic Cyclizations of N-Chloroalkenylamines. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 337−422. (c) Pellissier, H.; Santelli, M. Functionalization of The 18-Methyl Group of Steriods. *Org. Prep. Proced. Int.* **2001**, *33*, 455−476.

(8) (a) Zard, S. Z. Recent progress in the generation and use of nitrogen-centred radicals. *Chem. Soc. Rev.* **2008**, *37*, 1603−1618. (b) Chen, J.-R.; Hu, X.-Q.; Lu, L.-Q.; Xiao, W.-J. Visible light photoredox-controlled reactions of N-radicals and radical ions. *Chem. Soc. Rev.* **2016**, *45*, 2044−2056. (c) Xiong, T.; Zhang, Q. New amination strategies based on nitrogen-centred radical chemistry. *Chem. Soc. Rev.* **2016**, *45*, 3069−3087. (d) Zhao, Y.; Xia, W. Recent advances in radical-based C−N bond formation via photo-/electrochemistry. *Chem. Soc. Rev.* **2018**, *47*, 2591−2608. (e) An, X.-D.; Yu, S. Photoredox-catalyzed C(sp2)−N coupling reactions. *Tetrahedron Lett.* **2018**, *59*, 1605. (f) Jiang, H.; Studer, A. Intermolecular radical carboamination of alkenes. *Chem. Soc. Rev.* **2020**, *49*, 1790−1811. (g) Kärkäs, M. D. Photochemical Generation of Nitrogen-Centred Amidyl, Hydrazonyl, and Imidyl Radicals: Methodology Developments and Catalytic Applications. *ACS Catal.* **2017**, *7*, 4999−5022. (h) Tang, S.; Gao, X.; Lei, A. Electrocatalytic intramolecular oxidative annulation of N-aryl enamines into substituted indoles mediated by iodides. *Chem. Commun.* **2017**, *53*, 3354−3356.

(9) (a) Li, Y.; Ye, Z.; Chen, N.; Chen, Z.; Zhang, F. Intramolecular electrochemical dehydrogenative N−N bond formation for the synthesis of 1, 2,4-triazolo[1,5-a]pyridines. *Green Chem.* **2019**, *21*, 4035−4039. (b) Lv, S.; Han, X.; Wang, J.-Y.; Zhou, M.; Wu, Y.; Ma, L.; Niu, L.; Gao, W.; Zhou, J.; Hu, W.; Cui, Y.; Chen, J. Tunable Electrochemical C-N versus N-N Bond Formation of Nitrogen-Centred Radicals Enabled by Dehydrogenative Dearomatization: Biological Applications. *Angew. Chem., Int. Ed.* **2020**, *59*, 11583−11590. (c) Zhang, P.; Li, B.; Niu, L.; Wang, L.; Zhang, G.; Jia, X.; Zhang, G.; Liu, S.; Ma, L.; Gao, W.; Qin, D.; Chen, J. Scalable Electrochemical Transition-Metal-Free Dehydrogenative Cross-Coupling Amination Enabled Alkaloid Clausines Synthesis. *Adv. Synth. Catal.* **2020**, *362*, 2342−2347. (d) Chen, J.; Yan, W.-Q.; Lam, C. M.; Zeng, C.-C.; Hu, L.-M.; Little, R. D. Electrocatalytic Aziridination of Alkenes Mediated by n-Bu_4NI: A Radical Pathway. *Org. Lett.* **2015**, *17*, 986−989.

(10) (a) Zhang, S.; Li, L.; Xue, M.; Zhang, R.; Xu, K.; Zeng, C. Electrochemical Formation of N-Acyloxy Amidyl Radicals and Their Application: Regioselective Intramolecular Amination of sp2 and sp3 C−H Bonds. *Org. Lett.* **2018**, *20*, 3443−3446. (b) Li, L.; Xue, M.; Yan, X.; Liu, W.; Xu, K.; Zhang, S. Electrochemical Hofmann rearrangement mediated by NaBr: practical access to bioactive carbamates. *Org. Biomol. Chem.* **2018**, *16*, 4615−4618. (c) Day, J. C.; Govindaraj, N.; McBain, D. S.; Tanko, J. M.; Skell, P. S. Imidyl Radicals. The Chemistries of 1,8-Naphthalenedicarboximidyl and Phthalimidyl Radicals. *J. Org. Chem.* **1986**, *51*, 4959−4963. (d) Kim, H.; Kim, T.; Lee, D. G.; Roh, S. W.; Lee, C. Nitrogen-centred radical-mediated C−H imidation of arenes and heteroarenes via visible light induced photocatalysis. *Chem. Commun.* **2014**, *50*, 9273−9276. (e) Song, L.; Zhang, L.; Cheng, J.-P.; Luo, S. Visible-Light Promoted Catalyst-Free Imidation of Arenes and Heteroarenes. *Chem. - Eur. J.* **2014**, *20*, 14231−14234. (f) Shono, T.; Matsumura, Y.; Katoh, S.; Takeuchi, K.; Sasaki, K.; Kamada, T.; Shimizu, R. Electroorganic Chemistry. 120. New Patterns of Anodic Oxidation of Amides.

Synthesis of alpha-Amino Aldehyde Acetals and Pyrrolidines from Amines. *J. Am. Chem. Soc.* **1990**, *112*, 2368−2372.

(11) (a) Nikolaienko, P.; Jentsch, M.; Kale, A. P.; Cai, Y.; Rueping, M. Electrochemical and Scalable Dehydrogenative C(sp3)-H Amination via Remote Hydrogen Atom Transfer in Batch and Continuous Flow. *Chem. - Eur. J.* **2019**, *25*, 7177−7184. (b) Wang, F.; Stahl, S. S. Merging Photochemistry with Electrochemistry: Functional-Group Tolerant Electrochemical Amination of C(sp3)-H Bonds. *Angew. Chem., Int. Ed.* **2019**, *58*, 6385−6390. (c) Qin, Q.; Yu, S. Visible-Light-Promoted Remote C(sp3)−H Amidation and Chlorination. *Org. Lett.* **2015**, *17*, 1894−1897. (d) Qin, Q.; Ren, D.; Yu, S. Visible-light-promoted chloramination of olefins with N-chlorosulfonamide as both nitrogen and chlorine sources. *Org. Biomol. Chem.* **2015**, *13*, 10295−10298. (e) O'Broin, C. Q.; Fernandez, P.; Martínez, C.; Muñiz, K. N-Iodosuccinimide-Promoted Hofmann−Löffler Reactions of Sulfonimides under Visible Light. *Org. Lett.* **2016**, *18*, 436−439.

(12) (a) Wang, J.-D.; Liu, Y.-X.; Xue, D.; Wang, C.; Xiao, J. Amination of Benzoxazoles by Visible-Light Photoredox Catalysis. *Synlett* **2014**, *25*, 2013−2018. (b) Ruffoni, A.; Juliá, F.; Svejstrup, T. D.; McMillan, A. J.; Douglas, J. J.; Leonori, D. Practical and regioselective amination of arenes using alkyl amines. *Nat. Chem.* **2019**, *11*, 426−433. (c) Govaerts, S.; Angelini, L.; Hampton, C.; Malet-Sanz, L.; Ruffoni, A.; Leonori, D. Photoinduced Olefin Diamination with Alkylamines. *Angew. Chem., Int. Ed.* **2020**, *59*, 15021−15028. (d) Wang, Y.; Qian, P.; Su, J.-H.; Li, Y.; Bi, M.; Zha, Z.; Wang, Z. Efficient electrosynthesis of phosphinic amides via oxidative cross-coupling between N−H/P−H. *Green Chem.* **2017**, *19*, 4769−4773. (e) Yan, M.; Kawamata, Y.; Baran, P. S. Synthetic Organic Electrochemical Methods Since 2000: On the Verge of a Renaissance. *Chem. Rev.* **2017**, *117*, 13230−13319.

(13) (a) Nutting, J. E.; Rafiee, M.; Stahl, S. S. Tetramethylpiperidine N-Oxyl (TEMPO), Phthalimide N-Oxyl (PINO), and Related N-Oxyl Species: Electrochemical Properties and Their Use in Electrocatalytic Reactions. *Chem. Rev.* **2018**, *118*, 4834−4885. (b) Moeller, K. D. Using Physical Organic Chemistry to Shape the Course of Electrochemical Reactions. *Chem. Rev.* **2018**, *118*, 4817−4833. (c) Tang, S.; Liu, Y.; Lei, A. Electrochemical Oxidative Cross-coupling with Hydrogen Evolution: A Green and Sustainable Way for Bond Formation. *Chem.* **2018**, *4*, 27−45. (d) Wiebe, A.; Gieshoff, T.; Möhle, S.; Rodrigo, E.; Zirbes, M.; Waldvogel, S. R. Electrifying Organic Synthesis. *Angew. Chem., Int. Ed.* **2018**, *57*, 5594−5619. (e) Xiong, P.; Xu, H.-C. Chemistry with Electrochemically Generated N-Centered Radicals. *Acc. Chem. Res.* **2019**, *52*, 3339−3350. (f) Chang, X.; Zhang, Q.; Guo, C. Asymmetric Electrochemical Transformations. *Angew. Chem., Int. Ed.* **2020**, *59*, 12612−12622. (g) Qian, P.; Zha, Z.; Wang, Z. Recent Advances in C H Functionalization with Electrochemistry and Various Iodine-Containing Reagents. *ChemElectroChem* **2020**, *7*, 2527−2544. (h) Yuan, Y.; Lei, A. Electrochemical Oxidative Cross-Coupling with Hydrogen Evolution Reactions. *Acc. Chem. Res.* **2019**, *52*, 3309−3324. (i) Jiao, K.-J.; Xing, Y.-K.; Yang, Q.-L.; Qiu, H.; Mei, T.-S. Site-Selective C−H Functionalization via Synergistic Use of Electrochemistry and Transition Metal Catalysis. *Acc. Chem. Res.* **2020**, *53*, 300−310. (j) Tang, H.-T.; Jia, J.-S.; Pan, Y.-M. Halogen-mediated electrochemical organic synthesis. *Org. Biomol. Chem.* **2020**, *18*, 5315.

(14) (a) Strehl, J.; Hilt, G. Electrochemical, Iodine-Mediated α-CH Amination of Ketones by Umpolung of Silyl Enol Ethers. *Org. Lett.* **2020**, *22*, 5968−5972. (b) Yang, Y.; Zhang, D.; Vessally, E. Direct Amination of Aromatic C−H Bonds with Free Amines. *Top. Curr. Chem.* **2020**, *378*, 37. (c) Tang, H.-T.; Jia, J.-S.; Pan, Y.-M. Halogen-mediated electrochemical organic synthesis. *Org. Biomol. Chem.* **2020**, *18*, 5315. (d) Wang, H.; Shi, J.; Tan, J.; Xu, W.; Zhang, S.; Xu, K. Electrochemical Synthesis of trans-2,3-Disubstituted Aziridines via Oxidative Dehydrogenative Intramolecular C(sp^3)−H Amination. *Org. Lett.* **2019**, *21*, 9430−9433.

(15) (a) Wu, J.; Abou-Hamdan, H.; Guillot, R.; Kouklovsky, C.; Vincent, G. Electrochemical synthesis of 3a-bromofuranoindolines and 3a-bromopyrroloindolines mediated by $MgBr_2$. *Chem. Commun.* **2020**, *56*, 1713−1716. (b) Zhang, P.; Chen, J.; Gao, W.; Xiao, Y.; Liu, C.; Xu, S.; Yan, X.; Qin, D. Electrochemical Umpolung of Bromide: Transition-Metal-Free Bromination of Indole C−H Bond. *Molecules* **2019**, *24*, 696. (c) Sun, L.; Zhang, X.; Wang, C.; Teng, H.; Ma, J.; Li, Z.; Chen, H.; Jiang, H. Direct electrosynthesis for N-alkyl-C3-haloindoles using alkyl halide as both alkylating and halogenating building blocks. *Green Chem.* **2019**, *21*, 2732−2738. (d) Sun, L.; Zhang, X.; Li, Z.; Ma, J.; Zeng, Z.; Jiang, H. A Versatile C−H Halogenation Strategy for Indole Derivatives under Electrochemical Catalyst- and Oxidant-Free Conditions. *Eur. J. Org. Chem.* **2018**, *2018*, 4949−4952.

(16) (a) Li, Y.; Yang, Q.; Yang, L.; Lei, N.; Zheng, K. A scalable electrochemical dehydrogenative cross-coupling of P(O)H compounds with RSH/ROH. *Chem. Commun.* **2019**, *55*, 4981−4984. (b) Yang, L.; Liu, Z.; Li, Y.; Lei, N.; Shen, Y.; Zheng, K. Electrochemically Enabled C3-Formylation and -Acylation of Indoles with Aldehydes. *Org. Lett.* **2019**, *21*, 7702−7707.

(17) (a) Darwish, W. M.; Bayoumi, N. A.; El-Shershaby, H. M.; Allahloubi, N. M. Targeted photoimmunotherapy based on photosensitizer-antibody conjugates for multiple myeloma treatment. *J. Photochem. Photobiol., B* **2020**, *203*, 111777. (b) Jia, X.; Guo, K.; Gao, R.; Yu, Y.; Yang, A. Radiosensitivity-related postirradiation hypothyroidism in Graves' disease patients. *Hormones* **2019**, *18*, 267−272. (c) Jin, Q.; Jiang, C.; Gao, M.; Zhang, D.; Yao, N.; Feng, Y.; Wu, T.; Zhang, J. Target exploration of rhein as a small-molecule necrosis avid agent by post-treatment click modification. *New J. Chem.* **2019**, *43*, 6121−6125.

(18) (a) Palominos, R.; Freer, J.; Mondaca, M. A.; Mansilla, H.D. Evidence for hole participation during the photocatalytic oxidation of the antibiotic flumequine. *J. Photochem. Photobiol., A* **2008**, *193*, 139−145. (b) Kou, J.; Li, Z.; Yuan, Y.; Zhang, H.; Wang, Y.; Zou, Z. Visible-Light-Induced Photocatalytic Oxidation of Polycyclic Aromatic Hydrocarbons over Tantalum Oxynitride Photocatalysts. *Environ. Sci. Technol.* **2009**, *43*, 2919−2924.

(19) Choi, S.; Park, J.; Yu, E.; Sim, J.; Park, C.-M. Electrosynthesis of Dihydropyrano[4,3-b]indoles Based on a Double Oxidative [3+3] Cycloaddition. *Angew. Chem., Int. Ed.* **2020**, *59*, 11886−11891.

(20) (a) Stateman, L. M.; Wappes, E. A.; Nakafuku, K. M.; Edwards, K. M.; Nagib, D. A. Catalytic β C−H amination via an imidate radical relay. *Chem. Sci.* **2019**, *10*, 2693−2699. (b) Becker, P.; Duhamel, T.; Stein, C. J.; Reiher, M.; Muñiz, K. Cooperative Light-Activated Iodine and Photoredox Catalysis for the Amination of C−H Bonds. *Angew. Chem., Int. Ed.* **2017**, *56*, 8004−8008.

(21) Intermediate **III** and carbocation **VI** were detected by HRMS (for more details, see the Supporting Information).

https://dx.doi.org/10.1021/acs.orglett.0c03158
Org. Lett. XXXX, XXX, XXX−XXX