Electrooxidation enables highly regioselective dearomative annulation of indole and benzofuran derivatives

Kun Liu¹, Wenxu Song¹, Yuqi Deng¹, Huiyue Yang¹, Chunlan Song¹, Takfaoui Abdelilah¹, Shengchun Wang⁶¹, Hengjiang Cong¹, Shan Tang¹ & Aiwen Lei¹*

The dearomatization of arenes represents a powerful synthetic methodology to provide three-dimensional chemicals of high added value. Here we report a general and practical protocol for regioselective dearomative annulation of indole and benzofuran derivatives in an electrochemical way. Under undivided electrolytic conditions, a series of highly functionalized five to eight-membered heterocycle-2,3-fused indolines and dihydrobenzofurans, which are typically unattainable under thermal conditions, can be successfully accessed in high yield with excellent regio- and stereo-selectivity. This transformation can also tolerate a wide range of functional groups and achieve good efficiency in large-scale synthesis under oxidant-free conditions. In addition, cyclic voltammetry, electron paramagnetic resonance (EPR) and kinetic studies indicate that the dehydrogenative dearomatization annulations arise from the anodic oxidation of indole into indole radical cation, and this process is the rate-determining step.

¹ College of Chemistry and Molecular Sciences, Institute for Advanced Studies (IAS), Wuhan University, Wuhan 430072, P. R. China. *email: aiwenlei@whu.edu.cn
Breaking the aromatic systems of electron-rich arenes or heteroarenes provides three-dimensional chemicals of high added value. In this field, polycyclic indoline-based alkaloids derived from indole dearomatization have promoted chemists to develop numerous methods for their efficient preparation owing to the important biological activities. Over the past several decades, deative annulation of indoles has served as one of the most popular avenues for preparing polycyclic indoline skeletons. Some powerful protocols like cyclopropanation, 1,3-dipolar cycloadditions, [2 + 2] photo-cycloadditions, Diels-Alder, and cascade electrophilic addition/annulation reactions have been well established. In these cases, most of the strategies took advantage of the C2–C3 π bond or the inherent strong nucleophilicity of C3 position, and had the advantage of rapid construction for highly functionalized indoline frameworks in one step. On the other hand, recent advances in oxidation-induced C–H functionalization have opened up other possibilities for constructing various polycyclic indolines. In this regard, many efficient strategies for activating indoles have been developed under milder conditions. In 2012, Ma and coworkers reported an attractive procedure to prepare polycyclic pyrroloidines with iodine as oxidizing agents. In 2014, the group of Xiao developed a visible light-induced intramolecular oxyamidation reaction of indoles using molecular oxygen as the oxidant. Obviously, significant progress has been made in the synthesis of five-membered ring-fused 2,3-indolines. As compared with this, these types of methodologies failed to provide a practically efficient route toward biologically valuable six to bigger-membered heterocycle-fused indolines (Fig. 1a). Therefore, it is highly appealing to develop efficient approaches to allow for their preparation.

Electrochemical oxidation offers a mild and efficient alternative to the use of hazardous chemical oxidants and demonstrates unique reaction selectivity compared with the results under thermal conditions. With sufficient potential bias, organic substrates can lose one electron at the anode to generate highly reactive intermediates. In 2017, our group developed an electrochemical deative [3 + 2] annulation between phenols and N-acetyl indoles for the synthesis of benzo[3,2-b]indolines (Fig. 1b). This deative annulation was proved to be proceeded through the radical/radical cross-coupling between in situ generated indole radical cations and phenol radicals, but only five-membered ring-fused 2,3-indolines were afforded. The approach toward dehydrogenative [4 + 2] deative annulation of indoles has been rare. Fascinated by the distinctive reactivity of indole radical cation, we anticipate that the reports for adequately studied alkene radical cation may give a hand to the development of dehydrogenative [4 + 2] annulation of indoles. For example, in 2018, our group has demonstrated a dehydrogenative [4 + 2] annulation of styrenes with alkynes to afford a variety of six-membered aromatic rings. This reaction went through the nucleophilic attack of dienophile to alkene radical cation and second nucleophilic attack from arene to in situ generated alkynl carbon cation to afford the cyclic intermediates. Therefore, we envision that introducing a reagent that incorporates separate radical and nucleophilic centers or two nucleophilic centers to react with indoles radical cation may achieve the desired [4 + 2] deative annulation. Very recently, Vincent

---

**Fig. 1** Electrooxidation enables deative annulation of indoles to synthesize polycyclic indoline derivatives. **A** Important molecules containing six to bigger-membered heterocycle-fused indolines. **B** Electrochemical [3 + 2] annulation between indole and phenol to access benzo[3,2-b]indolines. **C** Electrochemical [3 + 2], [4 + 2], [5 + 2], and [6 + 2] deative annulation of indoles and benzo[3,2-b]indolines with various bis-nucleophiles.
and coworkers reported an electrochemical deearomatative dia- 
llkylation and diazidation of indoles with methanol or TMSN₃, 
albeit only one example of intermolecular deearomatization 
annulation was reported in 43% yield with ethylene glycol[69]. Here 
we present a versatile protocol for efficient electrooxidative [4 + 
2] deearomatization annulation between indoles and various bis-
nucleophiles that contain O-, N-, and S-nucleophilic groups. This 
method can be extended to intermolecular [3 + 2], [5 + 2], and 
[6 + 2] annulations. Many biologically valuable five to eight-
membered heterocycle- fused 2,3-indolines are constructed under 
electrolysis (Table 1, entry 11). No reaction took place without 
electric current under air atmosphere accompanied by the residue 
of almost all of starting materials (Table 1, entry 12). Notably, the 
reaction could be conducted under air atmosphere with a good 
yield (Table 1, entry 13).

Scope of bis-nucleophiles. To demonstrate the applicability of 
this transformation, we first evaluated the applicability of various 
bis-nucleophiles (Fig. 2). With 1-phenylethane-1,2-diol and 
hexane-1,2-diol, two products were obtained with ratio of 1:1 
(3ab) and 3ac in enhanced yield. If ethylene glycol with bigger 
steric hindrance was applied, the reaction selectivity could be 
increased to 3:4:1 with 82% yield (3ad). Deearomatative [4 + 3] 
animations could also be achieved efficiently from indole and 
functionalized 1,3-diols (3ae–3ag). 1,3-Diols bearing another 
rings could afford the spirocyclic compounds in 63% and 66% 
yield, respectively (3ah and 3ai). Moreover, eight-membered 
ring-fused 2,3-indoline (3aj) was obtained via [6 + 2] annulation 
from indole and 1,2-phenylenedimethanol in 50% yield. We then 
tested the possibility of forming C-N and C-S bonds instead of 
C-O bonds. With tert-butyl (2-hydroxyethyl)carbamate as 
bis-nucleophile, [4 + 2] dearomatative annulation happened 
regioselectively with C2-O and C3-N bond formation (3ak) 
owing to the different nucleophilicity. At the same time, we have 
done much efforts to construct two C-N bonds with indoles. 
After a number of screening, we found that sulfuric diamide 
could act as a dinitrogen nucleophile to couple with 1a in 58% 
yield (3al). The cyclic sulfamide with six or seven-membered ring 
afforded the desired product in higher yield (3am and 3an). The 
diamines without the protection of electron-withdrawing sub-
stituent could not react with indole under the standard reaction 
conditions as for the lower oxidation potential. Remarkably, 
mercaptoethanol and 3-mercaptopropan-1-ol could also couple 
with indole to afford the six- to seven-membered rings with 
regioselective C2-O and C3-S bond formation (3ao and 
3ap). Interestingly, 58% yield was obtained for the annulation 
of ethane-1,2-dithiol with indole to afford bioactive 1,4-dithiane 
(3aq).
**Scope of indoles.** Next, various indoles were applied to couple with bis-nucleophiles under standard conditions (Fig. 3). The effect of substituents on the benzene ring was firstly scrutinized. Indole rings bearing electron-donating groups and halogens at different positions could afford the annulation product in high efficiency (3aa–3da). Moderate yield was obtained with electron-withdrawing group (3ea). The major side reaction was the decomposition of the indole under the reaction conditions. Free hydroxyl group at phenyl moiety was well tolerated with 65% yield (3fa). Phenyl substituent at C3 position of indole could also furnish the annulation product in 69% yield (3ga). N-acetyl indoles bearing different C-3 substituents such as simple functionalized alkyl, alkenes and phenyl groups were suitable in this oxidative [4 + 2] dearmative annulation reaction (3ha–3na). Highly functional groups such as alkene, iodide, ester, amide, ketone, azide, and cyano were all well tolerated without hydrolysis or nucleophilic substitution by ethylene glycol. As for the reaction with unsubstituted and 2-substituted indoles (3oa–3ra), moderate yields were obtained, presumably owing to the less-stable reaction intermediates. By using mercaptoethanol as bis-nucleophile, [4 + 2] dearmative annulation also proceeded well with different phenyl- and C3 substituted indoles (3sa–3sa). When more sterically hindered 2,3-disubstituted indoles were applied, good reaction efficiency as well as regio- and stereo-selectivity were achieved (3va–3xa). The structure of 3wa was confirmed by X-ray crystallographic analysis.

**Scope of benzofurans.** Interestingly, benzofurans could also couple with ethylene glycol to achieve the [4 + 2] dearmative annulation (Fig. 4). Successful reports in the oxidative dearmatization annulation of benzofurans were very limited. This reaction tolerated electron-donating groups, halogens or electron-withdrawing groups at 3-phenyl rings (5a–5c). Unsubstituted benzofuran could also couple with 2a in moderate yield and high stereo-selectivity (5f). Enhanced yields were obtained from 2,3-disubstituted benzofuran (5d and 5e). Moreover, benzofuran-bearing dibenzofuran group could also participate in this transformation (5g).

**Gram scale synthesis and product transformation.** To further explore the utilities of this electrooxidative dearmative annulation for synthesizing polycyclic indolines, 10 mmol scale reactions were performed with four kinds of transformation in a simple beaker with 3 × 3 cm² carbon cloth as both anode and cathode under air atmosphere. Using 50 mA high constant current, gram scale of polycyclic indolines could be obtained (Fig. 5a–d). The transformations for heterocycle-fused 2,3-indolines were also conducted. In the presence of K₂CO₃ and MeOH under reflux conditions, N-Ac protected 3aa-delivered compound 6a in 95% yield (Fig. 6a). Besides, the deprotection of N-Boc group occurred smoothly upon the treatment of 3ak with trifluoroacetic acid, affording 6b in 82% yield without affecting N-Ac group (Fig. 6b). The functional group of azide or iodine inside the indoline alkaloids could undergo the click or sonogash reactions with drug molecules to afford the product 6c and 6d, respectively (Fig. 6c, d).

**Discussion**
Since the method has been established, efforts were then paid to understand the mechanism for this selectively oxidative dearmatization reaction. First, cyclic voltammetry experiments of 3-methyl N-acetyl indole (1a), ethane-1,2-diol (2a), tert-butyl (2-hydroxyethyl)carbamate (2k), and sulfuric diamide (2l) were
conducted (Fig. 7a). 3-Methyl N-acetyl indole started to be oxidized at ~1.20 V. By contrast, the oxidation onset of ethane-1,2-diol (2a), tert-butyl (2-hydroxyethyl)carbamate (2k), and sulfuric diamide (2l) was at ~1.86 V, so 1a would be oxidized before 2a, 2k and 2l. Then, the controlled potential electrolysis was carried out. If controlling the potential of anode to 0.8 V where both of the substrates could not be oxidized, no product was detected (Fig. 7b). If controlling the potential of anode to 1.4 V where only 1a could be oxidized, 62% yield of product was afforded (Fig. 7c). Meanwhile, P(OEt)3 was added into the standard reaction to explore the existence of indole radical cation intermediate. An indole phosphorylation product could be isolated in 6% yield and 69% yield of [4 + 2] annulation product was obtained (Fig. 7d). The oxidation peak of P(OEt)3 was observed at 1.9 V, which was higher than that of indoles, so P(OEt)3 would not be oxidized under the standard reaction conditions. The large amount of ethylene glycol had better capacity of capturing in situ generated indole radical cation than P(OEt)3, which led to the low yield of phosphorylation product. These results indicated that the anodic oxidation of 3-methyl N-acetyl indole might initiate this transformation, albeit the ethane-1,2-diol (2a), tert-butyl (2-hydroxyethyl)carbamate (2k) and sulfuric diamide (2l) have not been oxidized and just acted as bis-nucleophiles. In-depth analysis of the regioselectivity issue in the case of 2k, which contained both OH and NH nucleophilic group, C2-O and C3-N bond formation happened selectively with 1a. We reasoned that the radical of indole radical cation mainly delocalized at C2 position of indole radical cation to afford the stabilization of phenyl group, and cation mainly existed at C2 position via the formation of imine. Since the nucleophilicity of OH is stronger than that of NHBoc, the nucleophilic attack of OH happened first at C2 position of indole radical cation to afford the benzyl radical carbon. The second oxidation of benzyl carbon radical gave carbon cation, followed by the intramolecular attack of NHBoc to form C-N bond at C3 position.

In addition, in-operando infrared spectroscopy analysis of the electrooxidative dearomative annulation between 1a and 2a by...
react-IR technology did not show any sign for an induction period (see Supplementary Fig. 1a). Kinetic studies of this process were performed by detecting the initial reaction rate with different current, different loading of 3-methyl N-acetyl indole (1a) and ethylene glycol (2a). It was found that the initial rate increased in a linear fashion with increasing current (see Supplementary Fig. 1b). As for the kinetic profiles of substrates, the first-order dependencies at low concentration of 1a was observed.

Fig. 4 Scope of benzofurans. Reaction conditions: graphite rod anode (ϕ 6 mm), platinum plate cathode (15 mm × 15 mm × 0.3 mm), constant current = 10 mA ($J_{anode} \approx 11.2$ mA cm$^{-2}$), 4 (0.30 mmol), 2a (1.0 mL), nBu$_4$NBF$_4$ (0.30 mmol), MeCN (5.0 mL), 4 h, N$_2$. 20 mA ($J_{anode} \approx 22.4$ mA cm$^{-2}$).

Fig. 5 Large-scale synthesis. a Gram scale synthesis of 3aa. b Gram scale synthesis of 3af. c Gram scale synthesis of 3ao. d Gram scale synthesis of 3am.
and the reaction rate was saturated at high concentrations (see Supplementary Fig. 1c). This might be attributed to the current controlled result at high concentration of 1a. However, the initiate rate constants showed to be independent of the concentration of 2a (see Supplementary Fig. 1d). Combining these kinetic behaviors with mechanism study above, it suggested that the anodic oxidation of 1a to indole radical cation was the rate-determining step.

Next, cyclic voltammograms of 3-methyl N-acetyl indole (1a), 2-mercaptoethanol (2o), and ethane-1,2-dithiol (2q) were measured (Fig. 8a). 3-Methyl N-acetyl indole (1a), mercaptoethanol (2o), and ethane-1,2-dithiol (2q) all started to be oxidized at about 1.20 V. These results indicated that 3-methyl N-acetyl indole (1a), mercaptoethanol (2o), and ethane-1,2-dithiol (2q) might all be oxidized at the same time during the electrolysis to generate reactive intermediates. As both of the substrates could be oxidized, electron paramagnetic resonance (EPR) experiments were performed to explore the radical species with adding free radical cross-coupling agent DMPO (5,5-dimethyl-1-pyrroline N-oxide) into the reaction system. When DMPO was added to the reaction mixture of 3-methyl N-acetyl indole (1a), mercaptoethanol (2o), and ethane-1,2-dithiol (2q) a new signal was observed, which was suggested as an alkyl sulfur radical. This radical was quickly trapped by DMPO to an obvious EPR signal was observed, which was suggested as an alkyl sulfur radical. This radical was quickly trapped by DMPO to the formation of imine radical cation (Fig. 8b). Next, when DMPO was added to the reaction mixture of 1a and 2o, the same radical signal was observed, which further proved the existence of sulfur-center radical during the reaction of 1a and 2o (Fig. 8c). On the other hand, if adding six equivalent of triethyl phosphate into the standard reaction, 12% yield of [4 + 2] annulation product could be gained. At the same time, an indole phosphorylation product 6e could be isolated in 22% yield, which proved the existence of indole radical cation intermediate (Fig. 8d). Then, the controlled potential electrolysis was carried out. Controlling the potential of anode to 1.4 V where both of 1a and 2o could be oxidized, 55% corresponding product was obtained (Fig. 8e). These results indicated that the reaction might go through the cross-coupling of sulfur radical with indole cation radical intermediate. Subsequent intramolecular annulation afforded the [4 + 2] deamoratization annulation product. As for the regioselective issue in the case of 1a with 2o where C-S bond formed at C3 position and C-O bond formed at C2 position selectively, we speculated that the reaction proceeded through the cross-coupling of sulfur radical with indole radical cation at C3 position where the radical species was stabilized by phenyl group. Subsequent intramolecular nucleophilic attack of OH to imine cation afforded the corresponding product.

Then, kinetic studies for the deamoratization annulation of 1a with 2o were performed to determine the order of reaction components in this deamoratization annulation with different loading of 3-methyl N-acetyl indole (1a) and mercaptoethanol (2o). As for the kinetic profiles of the substrates, the first-order dependencies of 1a was observed (see Supplementary Fig. 2a). However, the initiate rate was almost invariant when using different concentrations of 2o, indicating that the reaction rate is independent of the concentration of 2o (see Supplementary Fig. 2b). Similar to the kinetic behavior of 1a with 2a, the results suggested that the anodic oxidation of 1a into indole radical cation was the slowest step throughout the transformation, and the processes of anodic oxidation of S-H into sulfur radical, radical–radical cross-coupling and cascade nucleophilic attack might be relative fast steps.

Based on the above experiment results, a plausible mechanism for these electrooxidative deamoratization annulations was shown in Fig. 9. In the first step, 1a would be oxidized at carbon anode to generate a radical cation where radical mostly lied at C3 position with stablization of phenyl group and cation mostly lied at C2 position stabilized by the formation of imine cation. This reactive intermediate could undergo two different transformations by making use of radical and cation centers. If
ethane-1,2-diol (2a) was applied as bis-nucleophile, first nucleophilic attack at the C2 position of I afforded benzylic carbon radical intermediate II. The oxidation of benzylic carbon radical gave carbon cation, followed by the intramolecular attack of OH to form C-O bond at C3 position. If bis-nucleophiles contains mercaptan, single-electron oxidation of mercaptan could generate sulfur-center radical in the meantime. Radical–radical cross-coupling between indole radical cation and sulfur radical at C3 position afforded intermediate V. Subsequently, the intramolecular attack of nucleophilic side chain to iminium moiety yielded the corresponding polycyclic indolines with excellent cis-dia-stereo-selectivity. The processes of radical–radical cross-coupling and nucleophilic attack might also happen at the same time.

In summary, we have developed an electrochemical method for the oxidative dearomatization annulation of indole and benzo-furan derivatives. Under undivided electrolytic conditions, [3 + 2], [4 + 2], [5 + 2], as well as [6 + 2] annulation happened regio- and setero-selectively with O-, N-, S-nucleophilic groups. A series of highly functionalized five to eight-membered heterocycle-2,3-fused indolines and dihydrobenzofurans were afforded, which are typically unattainable under thermal conditions. Notably, highly active functional groups such as iodide, hydroxyl, alkene, azide, ester, amide, cyano, carbonyl groups, etc. could all be well tolerated after electrolysis. A detailed mechanistic survey, including cyclic voltammetry, EPR, radical trapping experiments, and kinetic studies have been presented. These results demonstrate that anodic oxidation-induced indole radical cation has a vital role in these transformations and this process is the rate-determining step. The dearomative annulation of indoles with diols is believed to proceed through the two-step nucleophilic attack, whereas the annulation with mercapto group containing bis-nucleophiles proceeds through the radical–radical cross-coupling of indole radical cation and sulfur radical with subsequent nucleophilic attack. The unique reaction pathways have resulted in the high regio- and diastereo-selectivity. Finally, we believe this powerful strategy would stimulate broad interests in the journey of natural product total synthesis.

**Methods**

**General procedure for the reaction of 1a with 2a.** In an oven-dried undivided three-necked bottle (25 mL) equipped with a stir bar, N-acetyl indole (0.5 mmol), nBu4NBF4 (98.7 mg, 0.30 mmol), and MeCN/ethane-1,2-diol (9.0 mL/1.2 mL) were combined and added. The bottle was equipped with carbon cloths (20 mm × 20 mm) as both the anode and cathode and then charged with nitrogen. Then the electrolysis system was stirred at a constant current of 10 mA at room temperature until the complete consumption of N-acetyl indole (detected by thin-layer chromatography; TLC). When the reaction finished, the reaction mixture was washed with water and extracted with diethyl ether (10 mL × 3). The organic layers were combined, dried over Na2SO4, and concentrated. The pure product was obtained by flash column chromatography on silica gel (petroleum: ethyl acetate = 7:1).
**experimental details and characterization of the compounds are given in the Supplementary Information.**

**General procedure for the reaction of 1a with 2o.** In an oven-dried undivided three-necked bottle (25 mL) equipped with a stir bar, N-acetyl indole (0.5 mmol), nBu4NBF4 (98.7 mg, 0.3 mmol), 2o (8 eq.), and MeCN/DCM (5.0 mL/4 mL) were combined and added. The bottle was equipped with carbon cloths (20 mm × 20 mm) as both the anode and cathode and then charged with nitrogen. Then the electrolysis system was stirred at a constant current of 15 mA at room temperature until the complete consumption of N-acetyl indole (detected by TLC). When the reaction finished, the reaction mixture was washed with water and extracted with...

**Fig. 8 Mechanism study for the reaction of 1a with 2o.** a Cyclic voltammograms on a glassy carbon electrode (ϕ 3 mm) at 0.1Vs⁻¹ under nitrogen. Black line, 3-methyl N-acetyl indole (1a); red line, mercaptoethanol (2o); blue line, ethane-1,2-dithiol (2q). b EPR measurements of 2o in the presence of DMPO under constant current conditions for 6 min. c EPR measurements of 1a and 2o in the same conditions. d Radical cation trapping experiment by P(OEt)_3. e Controlled potential electrolysis.

**Fig. 9 Plausible mechanism for the dearomative annulation of indole.** The plausible mechanism involves anodic oxidation of indole to generate indole radical cation. Two steps of nucleophilic attack by ethylene glycol accompanied with an oxidation process would afford product 3aa. On the other hand, radical-radical cross-coupling with in situ generated sulfur radical and subsequent intramolecular nucleophilic attack would furnish product 3ao.
diethyl ether (10 mL × 3). The organic layers were combined, dried over Na2SO4, and concentrated. The pure product was obtained by flash column chromatography on silica gel (petroleum: ethyl acetate = 7:1). Full experimental details and characterization of the compounds are given in the Supplementary Information.

Data availability

The X-ray crystallographic coordinates for structures reported in this article have been deposited at the Cambridge Crystallographic Data Centre (CCDC), under deposition numbers CCDC 1963165 (3aa), CCDC 1963166 (3ma), CCDC 1963167 (3na), CCDC 1963168 (3o), CCDC 1963169 (3na). The data can be obtained free of charge from The Cambridge Crystallographic Data Centre [http://www.ccdc.cam.ac.uk/data_request/cif].

The data supporting the findings of this study are available within the article and its Supplementary Information files. Any further relevant data are available from the authors on request.

Received: 4 August 2019; Accepted: 29 November 2019; Published online: 07 January 2020

References

1. Zhuo, C.-X., Zheng, C. & You, S.-L. Transition-metal-catalyzed asymmetric dehalogenation reactions. Acc. Chem. Res. 47, 2558–2573 (2014).

2. Fan, L., Liu, J., Bai, L., Wang, Y. & Luan, X. Rapid assembly of diversely functionalized spiroindenes by a three-component palladium-catalyzed C–H amination/phenol deamortation domino reaction. Angew. Chem. Int. Ed. 56, 14257–14261 (2017).

3. Wu, W.-T., Zhang, L. & You, S.-L. Catalytic asymmetric deamortation (CADA) reactions of phenol and aniline derivatives. Chem. Soc. Rev. 45 (2016).

4. Wertjes, W. C., Southgate, E. H. & Sarlah, D. Recent advances in chemical graphity on silica gel (petroleum: ethyl acetate = 7:1). Full experimental details and characterization of the compounds are given in the Supplementary Information.

5. Bartoli, G., Bencivenni, G. & Dalpozzo, R. Organocatalytic strategies for the characterization of the compounds are given in the Supplementary Information.

6. Roche, S. P., Youte Tendoung, J.-J. & Tréguier, B. Advances in allylic dearomatization reactions.

7. Austin, J. F., Kim, S.-G., Sinz, C. J., Xiao, W.-J. & MacMillan, D. W. C. Enantioselective indole functionalizations.

8. Hari Narayana Moorthy, N. S., Karthikeyan, C. & Trivedi, P. Design, synthesis of 2-substituted indoline derivatives.

9. Nagaraju, K. & Ma, D. Oxidative coupling strategies for the total synthesis of indoline alkaloids.

10. Menozzi, C., Dalko, P. I. & Cossy, J. Concise synthesis of the (±)-nb-desmethyl-meso-chimonanthine. Chem. Commun. 38, 4638–4640 (2006).

11. Hua, T.-B., Xiao, C., Yang, Q.-Q. & Chen, J.-R. Recent advances in asymmetric functionalization of indoles. Nat. Catal. 1, 601–608 (2018).

12. Cheng, H.-G. et al. Highly enantioselective friedel-crafts alkylation/n-hemiectatic cascade reaction with indoles. Angew. Chem. Int. Ed. 52, 3250–3254 (2013).

13. Denizot, N. et al. Bioinspired direct access to benzofoindolines by oxidative (3 + 2) annulation of phenols and indoles. Org. Lett. 16, 5752–5755 (2014).

14. Liu, Q. et al. A trans diacyloxilation of indoles. Chem. Commun. 48, 3239–3241 (2012).

15. Shen, M., Duan, Y., Li, W., Cheng, Y. & Zhu, C. Visible-light-induced aerobic deamortation reaction of indole derivatives: access to heterocycle fused spiroindolenine-containing pentacyclic frameworks.

16. Depew, K. M. et al. Total synthesis of 5-N-acetylardeemin and amauromine: practical routes to potential mrdr reversal agents. J. Am. Chem. Soc. 121, 11953–11963 (1999).

17. Han, L., Liu, C., Zhang, W., Shi, X.-X. & You, S.-L. Deamortization of tryptophols via a vanadum-catalyzed asymmetric epoxidation and ring-conversion cascade. Angew. Chem. Int. Ed. 50, 1213–1217 (2011).

18. Zhu, W., Zuo, Z. & Ma, D. Intramolecular deamortative oxidative coupling of indoles: a unified strategy for the total synthesis of indole alkaloids. Acc. Chem. Res. 48, 702–711 (2015).

19. Gentry, E. C., Rono, L. J., Hale, M. E., Matsura, R. & Knowles, R. R. Enantioselective synthesis of pyrroleindolines via noncovalent stabilization of indole radical cations and applications to the synthesis of alkaloid natural products. J. Am. Chem. Soc. 140, 3394–3402 (2018).

20. Tomakinian, T., Guillot, R., Koutkovsky, C. & Vincent, G. Direct oxidative coupling of N-acetyl indoles and phenols for the synthesis of benzofoindolines related to phalarine. Angew. Chem. Int. Ed. 53, 11881–11885 (2014).

21. Tu, H.-F., Zhang, X., Zheng, C., Zhu, M. & You, S.-L. Enantioselective deamortative prenylation of indole derivatives. Nat. Catal. 2, 140–147 (2019).

22. Takayama, H. et al. New procedure to mask the 2,3-dialkyloxylation of indoles.

23. Araújo, L. D., Carvalho, I. M. & Almeida, M. M. Concise synthesis of polycyclic indolines: copper-catalyzed cascade reactions of substituted allylic carbamates and indoles.

24. Chi, Y., Bao, W.-Q., Li, Y.-B. & Guo, F. New method for the total synthesis of indoline alkaloids.

25. Tu, H.-F., Zhang, X., Zheng, C., Zhu, M. & You, S.-L. Enantioselective deamortative prenylation of indole derivatives. Nat. Catal. 2, 140–147 (2019).

26. Biedermann, S., Fopp, T., Lennstra, J. C., Weitkamp, J. & Wulff, K. W. Rhodium-catalyzed oxidative [3+2] annulation of phenols and indoles.

27. Okuda, Y. & Chiba, K. Redox-tag processes: Intramolecular electron transfer and its broad relationship to redox reactions in general. Chem. Rev. 118, 4592–4630 (2018).

28. Fu, T. & MacMillan, D. W. C. Oxidative coupling of benzofuran derivatives.

29. Nat. Catal. 2, 87–93 (2019).

30. Nat. Catal. 2, 41–47 (2019).

31. Acc. Chem. Res. 49, 1731–1743 (2016).

32. Angew. Chem. Int. Ed. 43, 1115–1121 (2004).

33. Angew. Chem. Int. Ed. 48, 6558–6562 (2010).

34. Angew. Chem. Int. Ed. 48, 151–157 (2009).

35. Angew. Chem. Int. Ed. 48, 1584–1591 (2009).

36. Angew. Chem. Int. Ed. 48, 1580–1588 (2009).

37. Angew. Chem. Int. Ed. 46, 5488–5508 (2007).

38. Angew. Chem. Int. Ed. 101, 5482 (2004).

39. Angew. Chem. Int. Ed. 48, 9608–9644 (2009).

40. Angew. Chem. Int. Ed. 49, 3550–3567 (2017).

41. Angew. Chem. Int. Ed. 50, 12008–12011 (2011).

42. Angew. Chem. Int. Ed. 49, 4469–4485 (2010).

43. Angew. Chem. Int. Ed. 100, 6558–6562 (2010).

44. Angew. Chem. Int. Ed. 104, 13594–13795 (2007).

45. Angew. Chem. Int. Ed. 105, 6253–6264 (2014).

46. Angew. Chem. Int. Ed. 103, 5833–5857 (2014).

47. Angew. Chem. Int. Ed. 102, 405–409 (2010).

48. Angew. Chem. Int. Ed. 101, 842–843 (2012).

49. Angew. Chem. Int. Ed. 100, 8644–8645 (2009).

50. Angew. Chem. Int. Ed. 104, 1553–1558 (2015).

51. Angew. Chem. Int. Ed. 109, 7979–7984 (2020).

52. Angew. Chem. Int. Ed. 107, 729–741 (2018).

53. Angew. Chem. Int. Ed. 105, 11881–11885 (2017).
47. Fu, N., Sauer, G. S. & Lin, S. Electrocatalytic radical dichlorination of alkenes with nucleophilic chlorine sources. J. Am. Chem. Soc. 139, 15548–15553 (2017).
48. Yang, Q.-L. et al. Palladium-catalyzed C(sp3)−H oxygenation via electrochemical oxidation. J. Am. Chem. Soc. 139, 3293–3298 (2017).
49. Yoshida, J.-i, Kataoka, K., Horcajada, R. & Nagaki, A. Modern strategies in electroorganic synthesis. Chem. Rev. 108, 2265–2299 (2008).
50. Siu, J. C., Parry, J. B. & Lin, S. Aminoxyl-catalyzed electrochemical diazidation of alkenes. Science 357, 575 (2017).
51. Fu, N., Sauer, G. S., Saha, A., Loo, A. & Lin, S. Metal-catalyzed electrochemical dearomatization of indoles. J. Am. Chem. Soc. 141, 2825–2831 (2019).
52. Xu, G. & Moeller, K. D. Anodic coupling reactions and the synthesis of C-glycosides. Org. Lett. 12, 2590–2593 (2010).
53. Huang, C., Qian, X.-Y. & Xu, H.-C. Continuous-flow electrosynthesis of benzofused S-heterocycles by dehydrogenative C−S cross-coupling. Angew. Chem. Int. Ed. 58, 6650–6653 (2019).
54. Xu, J. C., Parry, J. B. & Lin, S. Aminoxy-catalyzed electrochemical diazidation of alkenes mediated by a metastable charge-transfer complex. J. Am. Chem. Soc. 141, 2825–2831 (2019).
55. Xu, G. & Moeller, K. D. Anodic coupling reactions and the synthesis of C-glycosides. Org. Lett. 12, 2590–2593 (2010).
56. Huang, C., Qian, X.-Y. & Xu, H.-C. Continuous-flow electrosynthesis of benzofused S-heterocycles by dehydrogenative C−S cross-coupling. Angew. Chem. Int. Ed. 58, 6650–6653 (2019).
57. Xu, H.-C. & Moeller, K. D. Intramolecular anodic olefin coupling reactions: Use of the reaction rate to control substrate/product selectivity. Angew. Chem. Int. Ed. 49, 8004–8007 (2010).
58. Yan, H., Hou, Z.-W. & Xu, H.-C. Photoelectrochemical C−H alkylation of heteroarenes with organotrifluoroborates. Angew. Chem. Int. Ed. 131, 4640–4643 (2019).
59. Tang, S., Liu, Y. & Lei, A. Electrochemical oxidative cross-coupling with hydrogen evolution: a green and sustainable way for bond formation. Chem. 4, 27–48 (2018).
60. Waldvogel, S. R., Lips, S., Selt, M., Riehl, B. & Kampf, C. J. Electrochemical arylation reaction. Chem. Rev. 118, 6706–6765 (2018).
61. Sauerermann, N., Meyer, T. H., Tian, C. & Ackermann, L. Electrochemical cobalt-catalyzed C−H oxygenation at room temperature. J. Am. Chem. Soc. 139, 18452–18455 (2017).
62. Redden, A., Perkins, R. J. & Moeller, K. D. Oxidative cyclization reactions: Controlling the course of a radical cation-derived reaction with the use of a second nucleophile. Angew. Chem. Int. Ed. 52, 12865–12868 (2013).
63. Jiang, Y., Xu, K. & Zeng, C. Use of electrochemistry in the synthesis of heterocyclic structures. Chem. Rev. 118, 4485–4540 (2018).
64. Liu, K., Tang, S., Huang, P. & Lei, A. External oxidant-free electrooxidative [3 + 2] annulation between phenol and indole derivatives. Nat. Commun. 8, 775 (2017).
65. Cai, C.-Y. & Xu, H.-C. Dehydrogenative reagent-free annulation of alkenes with diols for the synthesis of saturated o-heterocycles. Nat. Commun. 9, 3551 (2018).
66. Ma, Y. et al. Electrochemical [4 + 2] annulation-rearrangement- aromatization of styrenes: Synthesis of naphthalene derivatives. Angew. Chem. Int. Ed. 58, 6756–6760 (2019).
67. Zhang, G. et al. Oxidative [4 + 2] annulation of styrenes with alkynes under external-oxidant-free conditions. Nat. Commun. 9, 1225 (2018).
68. Wu, J., Dou, Y., Guillot, R., Koukovsky, C. & Vincent, G. Electrochemical dearomatative 2,3-difunctionalization of indoles. J. Am. Chem. Soc. 141, 2832–2837 (2019).

Acknowledgements
This work was supported by the National Natural Science Foundation of China (21520102003) and the Hubei Province Natural Science Foundation of China (2017CFA010). The Program of Introducing Talents of Discipline to Universities of China (111 Program) is also appreciated.

Author contributions
A.L. and K.L. contributed to the conception and design of the experiments. K.L., W.S., Y.D., H.Y., C.S. and T.A. performed the electrochemistry synthesis. K.L. and S.W. performed the EPR experiments. H.C. resolved the X-ray structure. K.L., S.T. and A.L. co-wrote the manuscript contributed to data analysis and scientific discussion.

Competing interests
The authors declare that they have no conflicts of interest.

Additional information
Supplementary information is available for this paper at https://doi.org/10.1038/s41467-019-13829-4.

Correspondence and requests for materials should be addressed to A.L.

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

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

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

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

© The Author(s) 2020