Chemical Science

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: Q. Wang, P. Wang, X. Gao, D. Wang, S. Wang , X. Liang, L. Wang, H. Zhang and A. Lei, *Chem. Sci.*, 2020, DOI: 10.1039/C9SC05729C.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/chemical-science

View Article Online
DOI: 10.1039/C9SC05729C

ARTICLE

Regioselective/Electro-oxidative Intermolecular [3+2] Annulation for the Preparation of Indolines

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

Qingqing Wang, [a] [†] Pan Wang, [a] [†] Xinlong Gao, [a] Dan Wang, [a] Shengchun Wang, [a] Xingan Liang, [a] Liwei Wang, [a] Heng Zhang, *[a] and Aiwen Lei*[a,b]

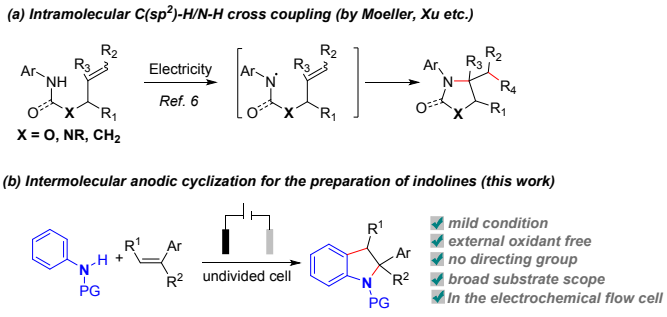
Compared with the reported intramolecular electro-oxidative cyclization of alkenyl amines or vinyl anilines for the preparation of pyrrolidines or indolines, the intermolecular version is less studied. Herein, this electrochemical intermolecular oxidative annulation of anilines and alkenes for the preparation of indolines was proceeded under external oxidant-free conditions. The most noteworthy achievement of our work is the facile generation of indolines with quaternary centers at the 2-position. In addition, alkenes and anilines bearing with various functional group can be well tolerated. Remarkably, the electrolyte-free conditions were performed in an electrochemical flow cell, which show application potential for this method.

Introduction

Indoline derivatives are the core skeletons widely found in natural products, pharmaceuticals and functionalized materials, such as physovenine, vallesamidine, indapamide and cannabinoid receptor modulators.[1] In recent years, substantial efforts have been paid to develop efficient methods for the synthesis of indolines. The dearomatization of indoles is the classical method to synthesize indolines.[2] In addition, transition metal-catalyzed dehydrogenative C-H/N-H coupling reactions to synthesize indolines have occupied the predominant position via inter- or intramolecular annulation.[3] Despite major progress in this field, stoichiometric amount of oxidants, such as Cu(II)[3a-c], Ag(I)[3d], benzoquinone(BQ)[3e-f] or selectfluor[3g] (with or without transition metal catalysts[3h-l]) are generally required. Under these reaction conditions, toxic or undesirable byproducts are not avoidable. It is more appealing to develop external oxidant-free reaction protocols to access the indoline derivatives directly based upon the rule of atom economy and sustainable chemistry.

Electrochemical oxidation offers an efficient and mild alternative to the use of hazardous chemical oxidants and sometimes demonstrates unique reaction selectivity compared with the chemical oxidation.[4-5] Besides, electro-oxidation-induced direct C-H bond functionalization might be an efficient and environmentally friendly strategy to construct C-C and C-X bonds.[5] Many ways have been prepared to synthesize functionalized indolines. Among them, the electrosynthesis methods can significantly reduce pollution. In the seminal works on electrochemical cyclization of alkenyl amines,[6] anodic oxidative coupling have provided pyrrolidines or lactams under mild conditions either through direct electrolysis or using redox catalyst (Scheme 1a).[6a-f, 6h] However, these studies have focused on intramolecular C-N coupling. It is very difficult to achieve intermolecular annulation for the synthesis of the indolines. Herein, we report a versatile regioselective/electrooxidative intermolecular [3+2] annulation under oxidant-free conditions to synthesize susbstitued indolines (Scheme 1b).

Scheme 1. Electrochemical synthesis for *N*-containing heterocycles



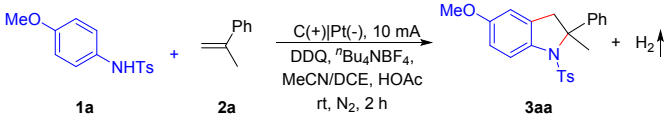
Results and discussion

Our studies commenced with *N*-(4-methoxyphenyl)-4-methylbenzenesulfonamide (**1a**) and α-methylstyrenes (**2a**) (Table 1). The reaction was carried out in an undivided cell under constant current electrolysis (CCE) with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 10 mol%) and $^{n}Bu_4NBF_4$ as the supporting electrolyte. After considerable efforts, 94 % yield of the product **3aa** could be obtained at 10 mA for 2 h with excellent regioselectivity (Table 1, entry 1). DDQ is well known for facilitating many transformations relying on the electron and hydrogen abstraction.[7] Notably,

[a] College of Chemistry and Molecular Sciences, Institute for Advanced Studies (IAS), Wuhan University, Wuhan 430072, P. R. China.
[b] National Research Center for Carbohydrate Synthesis, Jiangxi Normal University, Nanchang 330022, P. R. China.
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

lower yields were obtained in this transformation in the absence of DDQ or HOAc (entries 2 and 3). Moreover, the yield was diminished (62%) by using Na_2CO_3 instead of HOAc (entry 5). Thereafter, the solvent effect was also explored. Inferior reactivity could be observed by using acetonitrile or 1,2-dichloroethane (entries 6 and 7). In addition, slightly lower yields were obtained by either decreasing or increasing the operating current (entries 8 and 9). In order to test the electrode effect, carbon cloth, nickel plate, or iron plate were applied as cathode and furnished **3aa** in 57-78% yields (entries 10-12). The reaction yield was decreased dramatically when the reaction was opened to air (entry 13). No reaction took place without electric current under air atmosphere (entries 14 and 15).

Table 1. Effect of the reaction parameters[a]



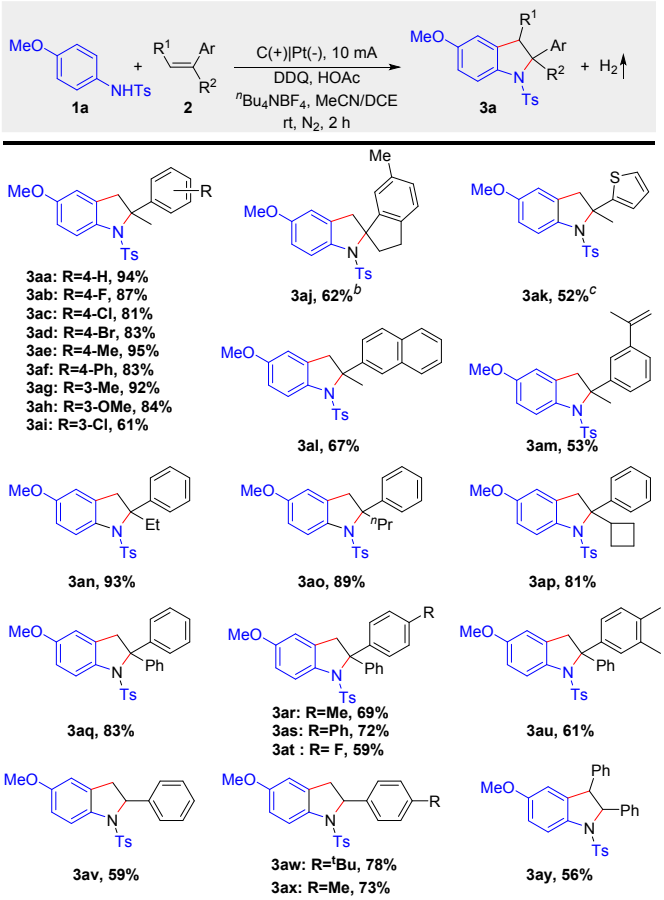
1a 2a 3aa

Entry	Variation from standard conditions	Yield (%)[b]
1	standard conditions	94
2	no DDQ	45
3	no HOAc	54
4	BQ instesd of DDQ	61
5	Na_2CO_3 instesd of HOAC	62
6	MeCN only	54
7	DCE only	37
8	6 mA, 4 h	78
9	15 mA, 2 h	85
10	carbon cloth as cathode	75
11	Ni plate as cathode	57
12	Fe plate as cathode	78
13	in air	60
14	no electric current	N.D.[c]
15	no electric current， in air	N.D.[c]

[a] Reaction conditions: graphite rod anode (ϕ 6 mm), Pt plate cathode (15 mm×15 mm×0.3 mm), constant current = 10 mA, **1a** (0.20 mmol), **2a** (0.40 mmol), $^nBu_4NBF_4$ (0.20 mmol), MeCN/DCE (4/2 mL), rt, 2 h (3.7 F/mol), undivided cell, nitrogen. [b] Isolated yields. [c] N.D. = not detected.

With the optimized reaction conditions in hand, we screened the substrate scope of alkenes (Scheme 2). Various α-methylstyrenes **2b**-**2i** with meta- or para-substitution could be converted to the corresponding indolines **3ab**-**3ai** in 61-95% yields. Notably, the electrophilic functional groups, such as fluoro, chloro, and bromo, were well tolerated. Gratifyingly, 6-methyl-1-methylene-2,3-dihydro-1H-indene (**2j**) also reacted efficiently to obtain the spiroindoline derivative (**3aj**, 62%). Remarkably, thiophene derivative **2k** and 2-isopropenylnaphthalene (**2l**) reacted with anilines to furnish final products **3ak**-**3al** in good to moderate yields. Importantly, diene **2m** underwent selective electro-oxidative [3+2] annulation smoothly, giving the mono-cyclization product **3am** in 53% yield. Subsequently, α-alkylstyrenes bearing linear or cyclic alkyl groups **2n**-**2p** proved to be suitable substrates, and the desired indolines **3an**-**3ap** were isolated in 81-93% yields. Additionally, 1,1-diphenylethylene derivatives **2q**-**2u** were converted to the corresponding 2,2-diarylindolines which were difficult to be accessed because of significant steric issues. To our delight, the desired products **3aq**-**3au** were formed in high yields. Moreover, the reaction could be extended to styrenes **2v**-**2x** and afforded the indoline products **3av**-**3ax** in 59% -78% yields. Notably, this method could also be efficiently extended to (*E*)-1,2-diphenylethene to afford the 2,3-fused indolines (**3ay**). Moreover, other olefins (e.g. alkyl olefins) have been tried, only a trace amount of the desired products could be obtained (Scheme S4).

Scheme 2. Substrate scope of alkenes.[a]

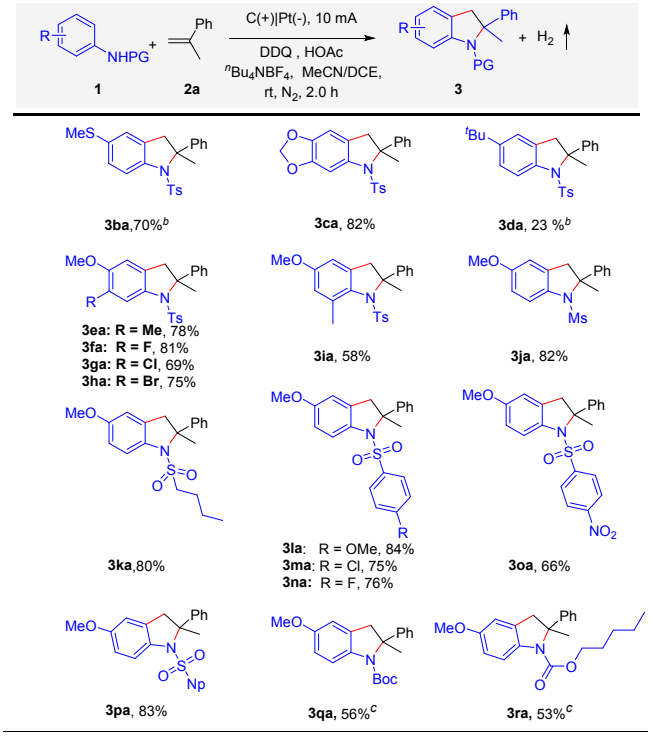


[a]Reaction conditions: carbon rod anode (ϕ 6 mm), Pt plate cathode (15 mm × 15 mm × 0.3 mm), constant current = 10 mA, **1a** (0.20 mmol), **2** (0.40 mmol), HOAc (0.20 mmol), 10 mol% DDQ, solvent (MeCN/DCE = 4/2 mL), undivided cell, nitrogen, 2 h (3.7 F/mol). Isolated yields were shown. [b] 4 h. [c] 8 mA, 3 h.

Subsequently, the scope of anilines was explored (Scheme 3). The strong electron-rich substituted amines 4-methyl-*N*-(4-

(methylthio)phenylbenzenesulfonamide **1b** and *N*-(benzo[d] [1,3] dioxol-5-yl)-4-methylbenzenesulfonamide **1c** could be tolerated to obtain the products **3ba** and **3ca** in high yield under constant current electrolysis. As for the reaction of *N*-(4-(tert butyl) phenyl)-4-methylbenzenesulfonamide (**3d**), low yield was obtained. At the same time, considering the effect of electronic effect, we also have made efforts to try other substituted amines in an undivided cell under constant current or constant voltage electrolysis. We found that a trace amount of products could be monitored in these reactions (Scheme S2). When substituted *N*-tosylanilines **1e**-**1i** were used, indolines **3ea**-**3ia** were furnished in good yields (58-82%). Subsequently, we speculated that applying sulfonyl group as the protecting group might be helpful in manipulating reactivity. Therefore, different *N*-sulfonylanilines **1j**-**1p** were prepared and well tolerated under the standard reaction conditions, giving indolines **3ja**-**3pa** in high yields (66-84%). Except for *N*-Ts, the aniline with other protecting groups (**1q** and **1r**) have been tried, which could give the desired products **3qa** and **3ra** in 53% and 56% yields.

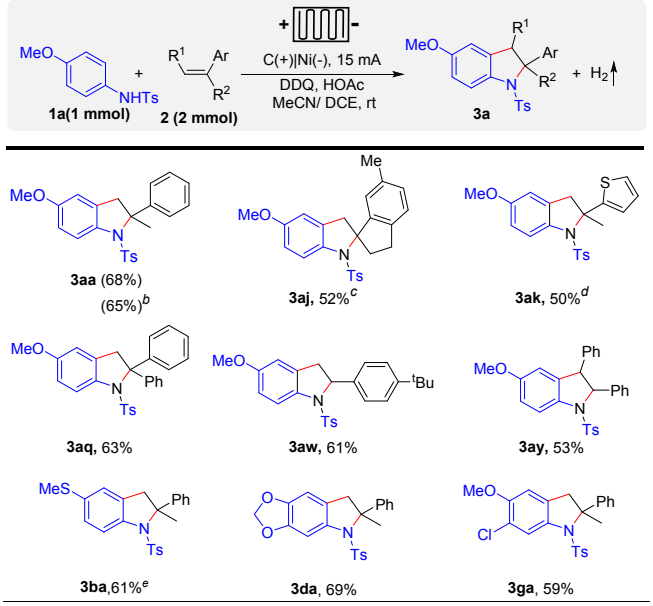
Scheme 3. Substrate scope of amines [a]



[a]Reaction conditions: carbon rod anode (ϕ 6 mm), Pt plate cathode constant current = 10 mA, **1** (0.2 mmol), **2a** (0.4 mmol), HOAc (0.2 mmol), 10 mol% DDQ, solvent (MeCN/DCE = 4/ 2 mL), undivided cell, N_2, 2 h (3.7 F/mol). Isolated yields were shown. [n]Bu_4NBF_4 (0.1 M) was added as supporting electrolyte. [b] Na_2CO_3 (0.2 mmol), I = 8 mA, 5 h. [c] Na_2CO_3 (0.2 mmol), I = 10 mA, 4 h.

Recently, electrochemical flow cells have been successfully used in a variety of organic transformations.[9-16], Considering the difficulty of electrolyte post-treatment and the price of electrolyte, we tried to achieve this transformation in the flow cells in the absence of the electrolyte. Gratifyingly, the indoline derivatives could be obtained under free electrolyte conditions in the presence of only 5 mol% DDQ, which shows application potential for this method (Scheme 4). Various alkenes (e.g. α-methylstyrenes, styrene, 1,1-diphenylethylene derivatives, Heterocyclic olefin) could be well tolerated.

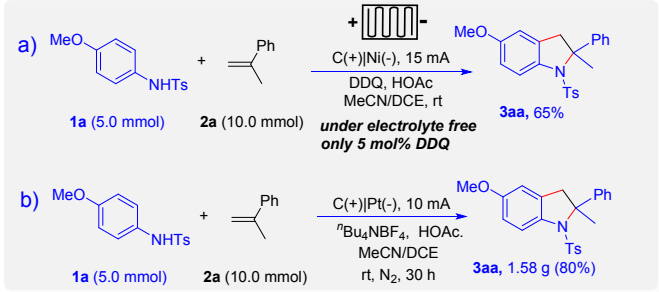
Scheme 4. Substrate scope in the electrochemical flow cell



[a]Reaction conditions: I= 10 mA, **1a** (1.0 mmol), **2** (2.0 mmol), HOAc (0.2 mmol), 5 mol% DDQ, solvent (MeCN/ DCE = 10/5 mL), in the electrochemical flow cell, nitrogen, 8 h. Isolated yields were shown. [b] 4 mmol Scale, MeCN/ DCE (50 mL/ 25 mL. [c] 10 h. [d] 8 mA, 10 h. [e] 8 mA, 5 h.

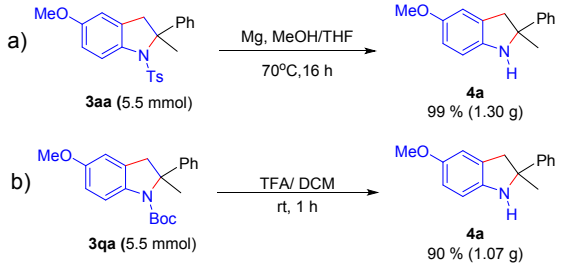
To further demonstrate the utility of the electrochemical method, the scale-up reaction was carried out in 5 mmol scale. Considering the price of platinum electrode, nickel plate was employed as cathode. In continuous-flow reactor, indoline **3aa** could be obtained in 65 % yield with a good selectivity and efficiency in a gram scale synthesis (Scheme 5a). Furthermore, the optimized conditions were applied for electro-oxidative [3+2] annulation in an undivided cell under 5.0 mmol scale. Thus, indoline **3aa** could be got in 80 % yield (Scheme 5b).

Scheme 5. Gram scale experiment.

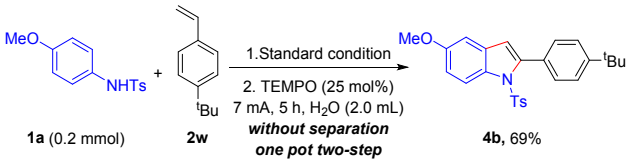


Moreover, as illustrated in Scheme 6, deprotection of the *N*-Ts or *N*-Boc group proceeded smoothly to separately give the 2-methyl-2-phenylindoline (**4a**) in 99% and 95% yields on a larger scale (up to 5.5 mmol). Disubstituted indolines own significant synthetic value in medicinal chemistry.[8] Interestingly, we envisioned that the oxidative dehydrogenation of indoline (**3aw**) may achieve 2-position indole derivative (**4b**) in 69% yield by one pot two-step method in the same undivided cell under constant current electrolysis without separation of the **3aa** (Scheme 7).

Scheme 6. The deprotection of *N*-Ts and *N*-Boc group

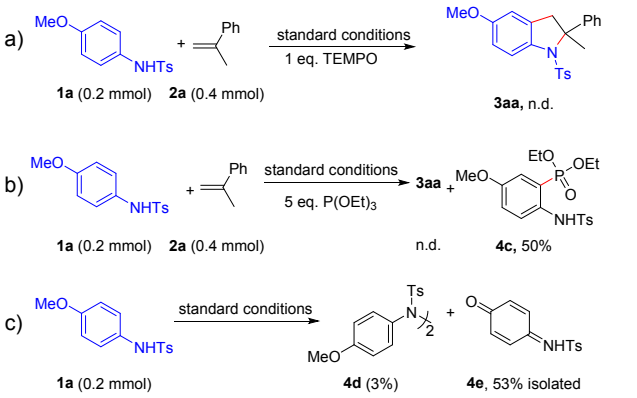


Scheme 7. One pot two-step process for 2-position indole synthesis



In order to clarify the reaction pathway of this reaction, some control experiments were carried out as shown in Scheme 5. When (2,2,6,6-tetramethylpiperidin-1-yl) oxy (TEMPO, 1 equiv.) was added in the reaction between **1a** and **2a** under the standard conditions, no desired product was observed (Scheme 8a). Thus, this transformation was proposed to proceed via a radical pathway. Then 5.0 equiv. of triethyl phosphite was added to the reaction mixture to trap the radical intermediates.[4o,17] Interestingly, the phosphorylation product **4c** was obtained in 50% yield, which suggested the generation of a carbon radical during the reaction (Scheme 8b). Moreover, in the absence of **2a** and DDQ, the homocoupling product **4d** could be obtained with the formation of **4e** in 53% yield at the same time, which suggested that nitrogen radicals were generated and then transformed into carbon radicals subsequently (Scheme 8c). Furthermore, the electron paramagnetic resonance (EPR) experiments were carried out when electrolysis was performed for 30 minutes in the absence of styrene **2a** and DDQ. The EPR spectra show that an organic conjugated radical is formed (see the figure S1). Therefore, the above control experiments and EPR results might reveal the existence of a carbon radical intermediate under the reaction conditions.

Scheme 8. Mechanistic studies.



To gain a deeper insight into the mechanism of this transformation, the cyclic voltammetry (CV) experiments were conducted. Firstly, as shown in Figure 1a, no obvious oxidation peak was observed for α-methylstyrenes **2a** in the region of 0.0-2.0 V *vs*. Ag/AgCl. Whereas, the *N*-(4-methoxyphenyl)-4-methylbenzenesulfonamide **1a** gave oxidation wave at 1.49 V *vs*. Ag/AgCl. The results suggested that **1a** was easier to be oxidized over **2a**. However, the electrochemical behavior of **1a** did not change in the presence of HOAc, indicating that HOAc may mainly serve as proton source for hydrogen evolution. However, when α-methylstyrene **2a** was added, the catalytic current was observed, which showed radical addition between **1a** and alkene **2a** was proceeded. (Fig. 1a, the red line). Moreover, when DDQ was added, a slight catalytic current was observed; the peak currents of Ox1 and Ox2 increase slightly from 16.8 to 17.9 μA, which proposed that aniline **1a** was not mainly oxidized by DDQ. In other words, it may only mean that the reaction was slow and did not occur at the electrode surface. (see Figure S3). Furthermore, UV experiments also demonstrated that there was no interaction between DDQ and **1a** (Fig. 1b).

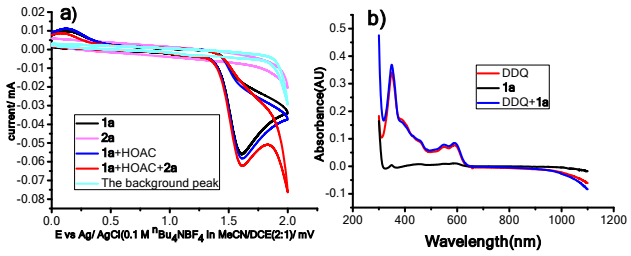
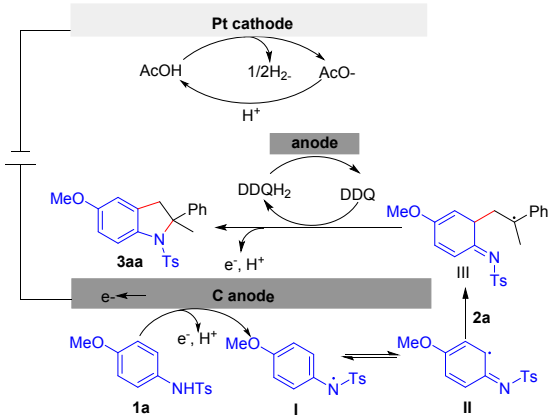


Figure 1. a) Cyclic voltammograms. b) UV experiments

In addition, kinetic studies of this reaction were carried out by detecting the initial rate with different concentrations of **1a** and **2b** by HPLC analysis. The reaction demonstrated a first order dependence on **1a**, and was independent of the concentration of **2b**, which indicted the anodic oxidation of **1a** may be the rate determining step (for the details see the figure S5).

Scheme 9. Proposed mechanism



Based on the experimental results and literature reports,[10] a plausible mechanism is outlined in Scheme 9. The reaction is initiated by the anodic oxidation of aniline **1a**. The following deprotonation can produce *N*-radical species **I**, which can resonate to liberate the C-radical species **II**. The intermediate **III** can be formed through the radical addition between **II** and alkene **2a**. Subsequently, the intermediate **III** is oxidized either through anodic oxidation or by DDQ. Finally, the target molecule **3aa** is generated through the intermolecular cyclization. Concomitant cathodic reduction of proton leads to the formation of dihydrogen.

Conclusions

In conclusion, we have developed a novel method for the electrochemical intermolecular [3+2] annulation of anilines and alkenes. This method was external oxidant-free, which provided a simple and atom-economic way to synthesize functionalized indolines. A wide range of functional groups were proved to be compatible under our optimized conditions. Besides, in the absence of electrolyte, indolines could be obtained in the electrochemical flow cell, which shows great application potential for this method. Control experiments and mechanistic studies suggested that carbon radical was involved in the reaction pathway.

Experimental

General procedure for Regioselective/Electro-oxidative Intermolecular [3+2] Annulation for the Preparation of Indolines: An undivided cell was equipped with a carbon anode and a platinum cathode and connected to a DC regulated power supply. *N*-(4-methoxyphenyl)-4-methylbenzenesulfonamide (0.20 mmol), prop-1-en-2-ylbenzene (0.40 mmol), $^{n}Bu_4NBF_4$ (0.1 M), 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (0.02 mmol), AcOH (0.2 mmol) and CH_3CN/DCE (4/2 mL) were combined and added. The bottle was equipped with graphite electrode as the anode and platinum electrode (1.5×1.5×0.3 cm^3) as the cathode and was then charged with nitrogen. The reaction mixture was stirred and electrolyzed at a constant current of 10 mA for 2.0 h. When the reaction was finished, the solution was extracted with EtOAc (3×10 mL) and H_2O (3×10 mL). The combined organic layer was dried with Na_2SO_4, filtered. The solvent was removed with a rotary evaporator. The pure product was obtained by flash chromatography on silica gel using petroleum ether and ethyl acetate as the eluent (10: 1).

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (21701127, 21520102003, 21390402), the Hubei Province Natural Science Foundation of China (2017CFB152, 2017CFA010), the Fundamental Research Funds for the Central Universities (213413000050), and the Scientific Research Foundation of Wuhan University (413100043, 413100021). The Program of Introducing Talents of Discipline to Universities of China (111 Program) is also appreciated. Qingqing Wang is grateful to the guidance and advice from Dr. Yi-Hung Chen in this work.

Notes and references

1. For selected examples, see: (a) E. J. Glamkowski, P. A. Eieitano, *J. Med. Chem*. **1979**, *22*, 106 -109. (b) K. Shishido, E. Shitara, H. Komatsu, K.Hiroya, K.Fukumoto, T.Kametani, *J. Org. Chem.*, **1986**, *51*, 3007 -3011. (c) M. Zhang, X.-M. Huang, L.-Q.Shen, Y. Qin, *J. Am. Chem. Soc.* **2009**, *131*, 6013 -6020. (d) J. D.Trzupek, D. J. Lee, B. M.Crowley, V. M. Marathias, J. S. Danishefsky, *J. Am. Chem. Soc.* **2010**, *132*, 8506 -8512. (e) S. Thakrar, N. Pandya, H. Vala, A. Bavishi, A. Radadiya, P annecouque, A. K. Shah, *Chem. Biol. Interface* **2012**, *2*, 107 -113. (f) Z.-D. Pan, S. M. Pound, N. R. Rondla, C. J. Douglas, *Angew. Chem., Int. Ed*. **2014**, *53*, 5170 -5174. (g) A. C. S. Reddy, V. S. K. Choutipalli, J. Ghorai, V. Subramanian, P. Anbarasan, *ACS Catal.* **2017**, *7*, 6283 -6288.
2. (a) R. Kuwano, K.Kaneda, T. Ito, K. Sato, T.Kurokawa, Y. Ito, *Org. Lett.* **2004**, *6*, 2213 -2215. (b) R.Kuwano, M. Kashiwabara, *Org. Lett.* **2006**, *8*, 2653 -2655. (c) D. Liu, G. Zhao, L. Xiang, *Eur. J. Org. Chem.* **2010**, *21*, 3975-3984.
3. (a) J.-J. Li, T.-S. Mei, J.-Q. Yu, *Angew. Chem . Int. Ed*. **2008**, *47*, 6452 -6455. (b) S. W.Youn, T. Y. Ko, Y. H. Jang, *Angew. Chem. Int.* Ed. **2017**, *56*, 6636 -6640. (c) E. S. Sherman, S. R. Chemler, T. B. Tan, O. Gerlits, *Org. Lett*. **2004**, *6*, 1573 -1575. (d) E. S. Sherman, P. H. Fuller, D. Kasi, S. R. Chemler, *J. Org. Chem*. **2007**, 72, 3896 -3905. (e) C. E. Houlden, C. D. Bailey, J. G. Ford, M. R. Gagne, G. C. Lloyd-Jones, K. I. Booker-Milburn, *J. Am. Chem. Soc*, **2008**, *130*, 10066 -10067. (f) M. K. Manna, A. Hossian, R. J. Jana, *Org. Lett.* **201**5, *17*, 672 -675. (g) G.-Z. Zhang, Y.-D. Luo, Y.-Z. Wang, L.-M. Zhang, *Angew. Chem. Int. Ed.* **2011**, *50*, 4450 -4454. (h) Y. Ni, Q.-L. Yu, Q.-H. Liu, H.-H. Zuo, H.-B. Yu, W.-J. Wei, R.-Z. Liao, F.-R. Zhong, *Org. Lett.*, **2018**, *20*, 1404 -1408. (i) U. Sharma, R. Kancherla, T. Naveen, S. Agasti, D. Maiti, *Angew. Chem. Int . Ed.* **2014**, *53*, 11895 -11899. (j) D.-B. Zhao, S. Vsquez-Cspedes,

F. Glorius, *Angew. Chem. Int. Ed*. **2015**, *54*, 1657 -1661. (k) Y. Gao, Y.-B. Huang, W.-Q. Wu, K.-F. Huang, H.-F. Jiang, *Chem. Commun.*, **2014**, *50*, 8370 -8373. (l) L. Ye, K.-Y. Lo, Q.-S. Gu, D. Yang, *Org. Lett.*, **2017**, *19*, 308 -311.

4. (a) C. B. Kazuhiro, T. A. Masahiro, *Chem. Com.* **1994**, *21*, 2485 -2486. (b) T. K. Nokami, R. J. Soma, Y. M.Yamamoto, T. Y. K. C. Kamei, J. I. Yoshida, *Beilstein J. Org. Chem.* **2012**, *8*, 456 -460. (c) A. Jutand, Contribution of Itami, *Chem. Rev.* **2008**, *108*, 2300 -2347. (d) E. J. Horn, B. R. Rosen, P. S. Baran, *ACS Cent. Sci.* **2016**, *25*, 302 -308. (e) J. I. Yoshida, A. Shimizu, R.Hayash, *Chem. Rev.* **2018**, *118*, 4702 -4730. (f) Y.-Y. Jiang, K. Xu, C. -C. Zeng, *Chem. Rev*. **2018**, *118*, 4485 -4540. (g). C. Ma, P. Fang, T.-S. Mei, *ACS Cat.* **2018**, *8*, 7179 -7189. (h) N. K. Fu, G. S. Sauer, A. Saha, A.Loo, S. Lin, *Science*, **2017**, *357*, 575 -579. (i) R. Francke, R. D. Little, *Chem. Soc. Rev.* **2014**, *43*, 2492 -2521. (j) S. Tang, Y.-C. Liu, A.-W. Lei, *Chem*. **2018**, *4*, 27 -45. (k) N. Sauermann, H. T. Meyer, Y. Qiu, L. Ackermann, *ACS Catal.* **2018**, *8*, 7086 -7103. (l) H. Yi, G. -T. Zhang, H. -M. Wang, Z.-Y. Huang, J. Wang, A. K. Singh, A.-W. Lei, *Chem. Rev.* **2017**, *117*, 9016 -9085. （m） J.-W. Wu, Y. Zhou, Zhou, Y.-C.; C. W. Chiang, A.-W. Lei,. *ACS Catal*. **2017**, *7*, 8320 -8323 （n） P. Wang, S. Tang, P. Huang, A. W. Lei, *Angew. Chem. Int. Ed.* **2017**, *56*, 3009 -3013. (o) Q.-Q. Wang, K. Xu, Y.-Y. Jiang, Y. - G. Liu, B. - G. Sun, C.-C. Zeng, *Org. Lett*. **2017**, *81*, 5517 -5520. (p) P.-F Huang, P. Wang, S.-C. Wang, S. Tang, A.-W. Lei, *Green Chem*. **2018**, *20*, 4870 -4874. (q) F. Xu, Y. -J. Li, C. Huang, H.- C. Xu, *ACS Catal.* **2018**, *8*, 3820 -3824. (r) P. Qian, Z.-C. Yan, Z. -H. Zhou, K. -F. Hu, J. -W. Wang, Z. -B. Li, Z, -G. Zha, Z. -Y. Wang, *Org. Lett.* **2018**, *20*, 6359 -6363. (s) Q.-Q. Wang, Y.-Y. Jiang, C.-C. Zeng, B.-G. Sun, *Chin. J. Chem.* **2019**, *37*, 352 -358. (t) J.-B. Chen, S.-D. Lv, S.-Y.Tian, *ChemSusChem.* **2019**, *12*, 115 -132.

5. (a) B. R.Rosen, E. W.Werner, A. G.O'Brien, P. S. Baran, *J. Am. Chem. Soc.* **2014**, *136*, 5571 -5574. (b) T.Gieshoff, A.Kehl, D. Schollmeyer, K. D .Moeller, S. R. Waldvogel, *J. Am. Chem. Soc.* **2017**, *139*, 12317 -12324. (c) T. Gieshoff, D. Schollmeyer, S. R. Waldvogel, *Angew. Chem., Int. Ed.* **2016**, *55*, 9437 -40. (d) P. Qian, J.-H. Su, Y.-K. Wang, M.-X. Bi, Z.-G. Zha, Z.-Y. Wang, *J. Org. Chem.* **2017**, *8212*, 6434 -6440. (e) M.-Y. Lin, K. Xu, Y.-Y. Jiang, Y.-G. Liu, B.-G. Sun, C.- C. Zeng, *Adv. Synth. Catal*. **2018**, *360*, 1665 -1672. (f) S. Tang, S.-Y. Wang, Y.-C. Liu, H.-J. Cong, A.-W. Lei, *Angew. Chem. Int. Ed.* **2018**, *130*, 4827 -4831. (g) H. Zhang, A.W. Lei, *Synthesis* **2018**, *50*, A–N. (h) X.-L. Gao, P. Wang, L. Zeng, S.Tang, A.-W. Lei, *J. Am. Chem. Soc.* **2018**, *140*, 4195 -4199. (i) Z.-W. Hou, Z.-Y.Mao, H.-B.Zhao, Y. Y. Melcamu, X. Lu, J. Song, H.-C. Xu, *Angew. Chem. Int. Ed.* **2016**, *55*, 9168 -9172. (j) N. Sauermann, R. Mei, L. Ackermann, *Angew. Chem. Int. Ed.* **2018**, *57*, 5090 -5094. (k) S. Tang, D. Wang, Y.-C. Liu, L. Zeng, A.-W. Lei, *Nat. Commun.*, **2018**, *9*, 798. (l) Q. L. Yang, X. Y. Wang, J. Y.Lu, L. P.Zhang, P. Fang, T. S. Mei, *J. Am. Chem. Soc.* **2018**, *140*, 11487 -11494. (m) Y.-T. Zhao, W.-J. Xia, *Chem. Soc. Rev.* **2018**, *47*, 2591 -2608. (n) X. Hu, G. T, Zhang, F. X. Bu, L. Nie,; A.W. Lei, *ACS Catal.* **2018**, *8*, 9370 -9375. (o) S. Zhang, L. J Li,. M.-Y. Xue, R.-K. Zhang, K. Xu, C.-C. Zeng, *Org. Lett*. **2018**, *20*, 3443 -3446. (p) K. Liu, S. Tang, T. Wu, S.-C. Wang, M.-Z.Zou, H.-J. Cong, A. W. Lei, *Nat. Commun.* **2019**, *10*, 1 -10. (q) J.-W. Wang, P.Qian, K.-F. Hu, Z.-G. Zha, Z.-Y. Wang, *ChemElectroChem.* **2019**, *6*, 1-6. (r) P. Qian, Z.-C.Yan, Z.-H. Zhou, K. F. Hu, J. W. Wang, Z. B. Li, Z. G. Zha, Z. Y. Wang, *J. Org. Chem*. **2019**, *84*, 3148 -3157. (s) J. C. Siu, J. B. Parry, S. Lin, *J. Am. Chem. Soc.* **2019**, *141*, 2825 -2831. (t) W. – J. Kong, L. H. Finger, A. M. Messinis, R. Kuniyil, J. C. A. Oliveira, L. Ackermann, *J. Am. Chem. Soc*. **2019**, *141*, 17198 -17206.

6. (a) H.- C. Xu, K. D. Moeller, *J. Am. Chem. Soc.* **2008**, *130*, 13542 -13543. (b) H.- C Xu, J. M. Campbell, K. D. Moeller, *J. Org. Chem*. **2014**, *79*, 379 -391. (c) L. Zhu, P. Xiong, Z. -Y. Mao, Y. H. Wang, X. -M. Yan, X. Lu, H. -C Xu,. *Angew. Chem. Int. Ed.* **2016**, *55*, 2226 -2229. (d) F. Xu, L. Zhu, S. B. Zhu, X. Yan, H.-C. Xu, *Chem. Eur. J.* **2014**, *20*, 12740 -12744. (e) H.-B. Zhao, Z.-W.Hou, Z.-J. Liu, Z.-F. Zhou, J. Song, H.-C Xu,. *Angew. Chem. Int. Ed.* **2017**, *56*, 587 -590. (f) Z.-W. Hou, H. Yan, J.-S. Song, H.-C. Xu, *Chin. J. Chem*. **2018**, *36*, 909 -915. (g) S. Liang, C.-C. Zeng, X.-G. Luo, F.-Z. Ren, H.-Y. Tian, B.-G. Sun, D. Little, *Green Chem*. **2016**, *18*, 2222 -2230. (h) X.-L Yi, X. -L. Hu, *Angew. Chem. Int. Ed*. **2019**, *58*, 4700 -4704.

7. A. E. Wendlandt, S. S. Stahl, *Angew. Chem. Int. Ed*. **2015**, *54*, 14638 -14658.

8. (a) D. Robinson, T. Bertrand, W. Sherman, *J. Chem. Inf. Model*. **2016**, *56*, 886 -894. (b) X.-Y.Jiao, W. G. Bentrude, *J. Am. Chem. Soc*. **1999**, *121*, 6088 -6089.

9. M. B.Plutschack, B. Pieber, K. Gilmore, P. H. Seeberger, *Chem. Rev.* **2017**, *117*, 11796 -11893.

10. H., Chong; Qian, X. Yang, H.-C. Xu, *Angew. Chem. Int. Ed*. **2019**, *58*, 6650 -6653.

11. C., Gütz, A. Stenglein, S. R., Waldvogel, *Org. Process Res. Dev.* **2017**, *21*, 771–778.

12. G., Laudadio, W., de Smet, L., Struik, Y., Cao, T. J., Noël, *J. Flow Chem.* **2018**, 8, 157–165.

13. (a) D. Wang, P. Wang, S. C. Wang, Y.-H. Chen, H. Zhang, A. W. Lei, *Nature communications*, **2019**, *10*, 1-8.

14. A. A., Folgueiras-Amador, T. Wirth, *J. Flow Chem.***2017**, *7*, 94–95.

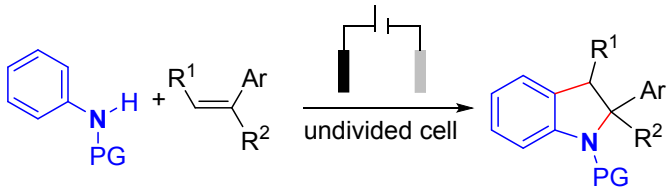
15. A. A., Folgueiras-Amador, K., Philipps, S., Guilbaud, J., Poelakker, T., Wirth, *Angew. Chem. Int. Ed.* **2017**, *56*, 15446–15450.

16. G. Laudadio, N. J. W., Straathof, M. D., Lanting, B., Knoops, V., Hessel, T., Noël, *Green Chem.***2017***, 19*, 4061–4066.

17. Schulz, M. Enders, B. Elsler, D. Schollmeyer, K. M. Dyballa, R. Franke, S. R. Waldvogel, *Angew. Chem. Int. Ed*. **2017**, *56*, 4877 -4881.

TOC

View Article Online
DOI: 10.1039/C9SC05729C



- ***mild condition***
- ***external oxidant free***
- ***no directing group***
- ***broad substrate scope***
- ***In the electrochemical flow cell***