



Cite this: *Chem. Sci.*, 2020, **11**, 2181

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 12th November 2019
Accepted 9th January 2020

DOI: 10.1039/c9sc05729c
rsc.li/chemical-science

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 effort has been made 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 *via* inter- or intramolecular annulation have occupied a predominant position.³ Despite major progress in this field, stoichiometric amounts 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 indoline derivatives directly based on 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 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

Regioselective/electro-oxidative intermolecular [3 + 2] annulation for the preparation of indolines[†]

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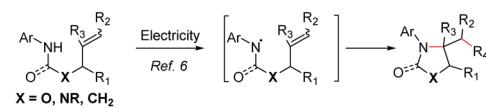
Compared with the reported intramolecular electro-oxidative cyclization of alkenyl amines or vinyl anilines for the preparation of pyrrolidines or indolines, the intermolecular version is less studied. Herein, this electrochemical intermolecular oxidative annulation of anilines and alkenes for the preparation of indolines 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 various functional groups can be well tolerated. Remarkably, electrolyte-free conditions were used in an electrochemical flow cell, which shows the application potential of this method.

bonds.⁵ Many methods have been developed to synthesize functionalized indolines. Among them, electrosynthesis methods can significantly reduce pollution. In the seminal studies on electrochemical cyclization of alkenyl amines,⁶ anodic oxidative coupling reactions have provided pyrrolidines or lactams under mild conditions either through direct electrolysis or using redox catalysts (Scheme 1a).^{6a–f,h} However, these studies have focused on intramolecular C–N coupling. It is very difficult to achieve intermolecular annulation for the synthesis of indolines. Herein, we report a versatile regioselective/electrooxidative intermolecular [3 + 2] annulation method under oxidant-free conditions to synthesize substituted indolines (Scheme 1b).

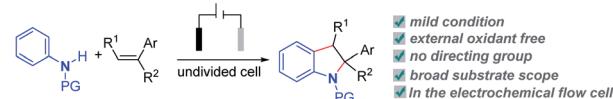
Results and discussion

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 $^7\text{Bu}_4\text{NBF}_4$ as

(a) *Intramolecular C(sp²)-H/N-H cross coupling (by Moeller, Xu etc.)*



(b) *Intermolecular anodic cyclization for the preparation of indolines (this work)*



Scheme 1 Electrochemical synthesis of N-containing heterocycles.

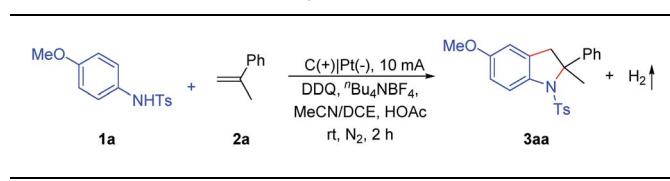
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[†] Electronic supplementary information (ESI) available. See DOI: 10.1039/c9sc05729c

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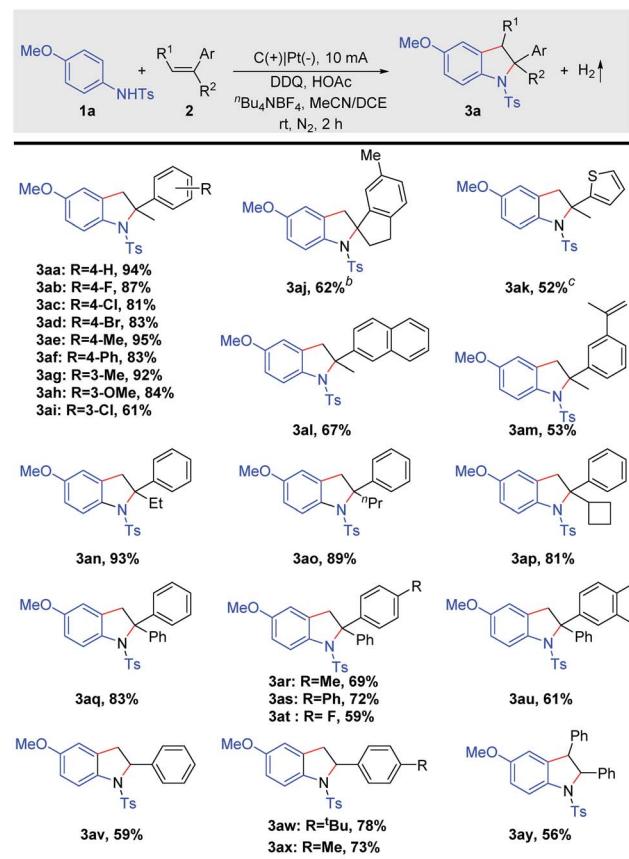
Table 1 Effect of the reaction parameters^a

Entry	Variation from standard conditions	Yield ^b (%)
1	Standard conditions	94
2	No DDQ	45
3	No HOAc	54
4	BQ instead of DDQ	61
5	Na ₂ CO ₃ instead 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 \times 15 mm \times 0.3 mm), constant current = 10 mA, **1a** (0.20 mmol), **2a** (0.40 mmol), $^n\text{Bu}_4\text{NBF}_4$ (0.20 mmol), MeCN/DCE (4/2 mL), rt, 2 h (3.7 F mol^{-1}), undivided cell, and nitrogen. ^b Isolated yields. ^c N.D. = not detected.

the supporting electrolyte. After considerable effort, 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 electron and hydrogen abstraction.⁷ Notably, 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, a nickel plate, or an iron plate was applied as the cathode which furnished **3aa** in 57–78% yields (entries 10–12). The reaction yield decreased dramatically when the reaction was opened to air (entry 13). No reaction took place without electric current under an air atmosphere (entries 14 and 15).

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-1*H*-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

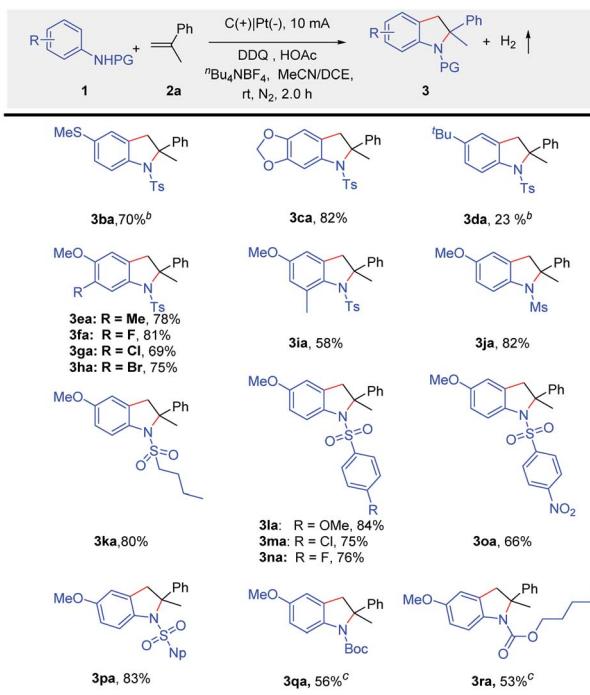


Scheme 2 Substrate scope of alkenes.^a ^a Reaction conditions: carbon rod anode (ϕ 6 mm), Pt plate cathode (15 mm \times 15 mm \times 0.3 mm), constant current = 10 mA, **1a** (0.20 mmol), **2** (0.40 mmol), HOAc (0.20 mmol), 10 mol% DDQ, solvent (MeCN/DCE = 4/2 mL), undivided cell, nitrogen, and 2 h (3.7 F mol^{-1}). Isolated yields are shown. ^b 4 h. ^c 8 mA, and 3 h.

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-diaryliindolines which were difficult to access 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, but only a trace amount of the desired products could be obtained (Scheme S4†).

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

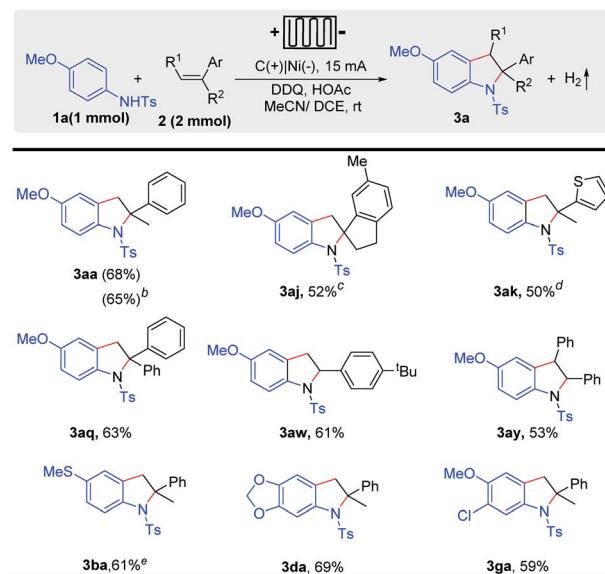




Scheme 3 Substrate scope of amines.^a ^aReaction conditions: carbon rod anode (ϕ 6 mm), Pt plate cathode constant current = 10 mA, 1 (0.2 mmol), 2a (0.4 mmol), HOAc (0.2 mmol), 10 mol% DDQ, solvent (MeCN/DCE = 4/2 mL), undivided cell, N_2 , and 2 h (3.7 F mol⁻¹). Isolated yields are shown. ^b Na_2CO_3 (0.2 mmol), I = 8 mA, 5 h. ^c Na_2CO_3 (0.2 mmol), I = 10 mA, and 4 h.

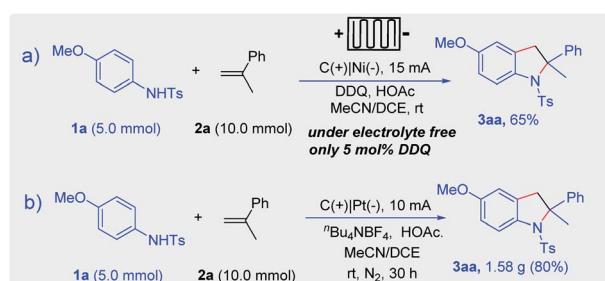
butyl) phenyl)-4-methylbenzenesulfonamide (**3d**), low yield was obtained. At the same time, considering the electronic effect, we have also made efforts to try other substituted amines in an undivided cell under constant current or constant voltage electrolysis. We found that a trace amount of products could be monitored in these reactions (Scheme S2†). When substituted *N*-tosylanilines **1e–1i** were used, indolines **3ea–3ia** were obtained in good yields (58–82%). Subsequently, we speculated that applying a 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, anilines with other protecting groups (**1q** and **1r**) have been tried, which could give the desired products **3qa** and **3ra** in 53% and 56% yields.

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 electrolytes, we tried to achieve this transformation in flow cells in the absence of the electrolyte. Gratifyingly, indoline derivatives could be obtained under electrolyte-free conditions in the presence of only 5 mol% DDQ, which shows the application potential of this method (Scheme 4). Various alkenes (e.g. α -methylstyrenes, styrene, 1,1-diphenylethylene derivatives, and heterocyclic olefin) could be well tolerated.

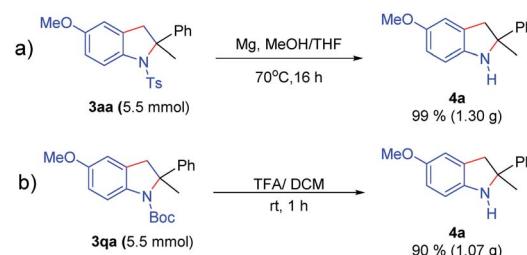


Scheme 4 Substrate scope in the electrochemical flow cell.^a ^aReaction conditions: I = 10 mA, 1a (1.0 mmol), 2 (2.0 mmol), HOAc (0.2 mmol), 5 mol% DDQ, solvent (MeCN/DCE = 10/5 mL), in the electrochemical flow cell, nitrogen, and 8 h. Isolated yields are shown. ^b 4 mmol scale, MeCN/DCE (50 mL/25 mL). ^c 10 h. ^d 8 mA, 10 h. ^e 8 mA, and 5 h.

To further demonstrate the utility of the electrochemical method, the scale-up reaction was carried out in the 5 mmol scale. Considering the price of platinum electrodes, a nickel plate was employed as the cathode. In a 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 to electro-



Scheme 5 Gram scale experiment.

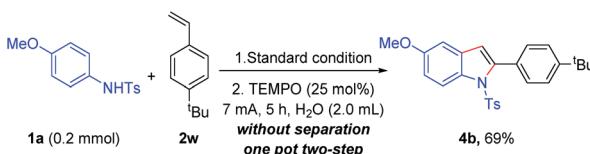


Scheme 6 The deprotection of the *N*-Ts and *N*-Boc group.

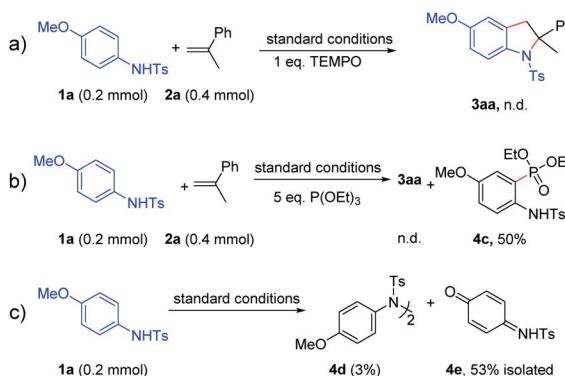
oxidative [3 + 2] annulation in an undivided cell in the 5.0 mmol scale. Thus, indoline **3aa** could be obtained in 80% yield (Scheme 5b).

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

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)oxyl (TEMPO, 1 equiv.) was added into 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.^{40,41} 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, 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 Fig. S1†). Therefore, the above control experiments



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



Scheme 8 Mechanistic studies.

and EPR results might reveal the existence of a carbon radical intermediate under the reaction conditions.

To gain a deeper insight into the mechanism of this transformation, cyclic voltammetry (CV) experiments were conducted. First, as shown in Fig. 1a, no obvious oxidation peak was observed for α -methylstyrenes **2a** in the region of 0.0–2.0 V vs. Ag/AgCl. However, *N*-(4-methoxyphenyl)-4-methylbenzenesulfonamide **1a** gave an oxidation wave at 1.49 V vs. Ag/AgCl. The results suggested that **1a** was easier to oxidize than **2a**. However, the electrochemical behavior of **1a** did not change in the presence of HOAc, indicating that HOAc may mainly serve as a proton source for hydrogen evolution. However, when α -methylstyrene **2a** was added, a catalytic current was observed, which showed radical addition between **1a** and alkene **2a** (Fig. 1a, the red line). Moreover, when DDQ was added, a slight catalytic current was observed; the peak currents of Ox1 and Ox2 increased slightly from 16.8 to 17.9 μ A, which indicated 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 Fig. S3†). Furthermore, UV experiments also demonstrated that there was no interaction between DDQ and **1a** (Fig. 1b).

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 indicated that the anodic oxidation of **1a** may be the rate determining step (for details see Fig. S5†).

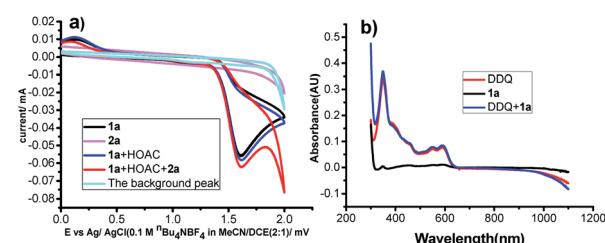
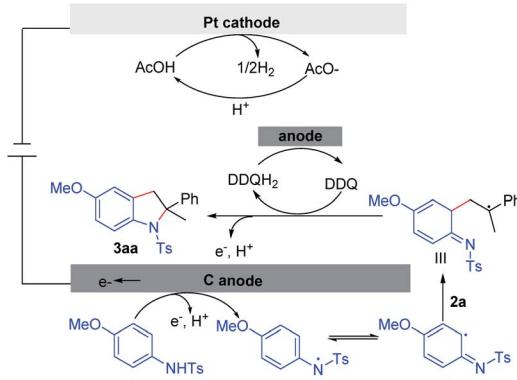


Fig. 1 (a) Cyclic voltammograms. (b) UV experiments.



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 subsequent deprotonation can produce N-radical species **I**, which can resonate to liberate the C-radical species **II**. Intermediate **III** can be formed through the radical addition between **II** and alkene **2a**. Subsequently, 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 the 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 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 the great application potential of this method. Control experiments and mechanistic studies suggested that a 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), ⁷Bu₄NBF₄ (0.1 M), 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.02 mmol), AcOH (0.2 mmol) and CH₃CN/DCE (4/2 mL) were combined and added. The bottle was equipped with a graphite electrode as the anode and a platinum electrode (1.5 × 1.5 × 0.3 cm³) 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 H₂O (3 × 10 mL). The combined organic layer was dried with Na₂SO₄ and 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, and 21390402),

the Hubei Province Natural Science Foundation of China (2017CFB152 and 2017CFA010), the Fundamental Research Funds for the Central Universities (213413000050), and the Scientific Research Foundation of Wuhan University (413100043 and 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.

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