Redox Chemistry

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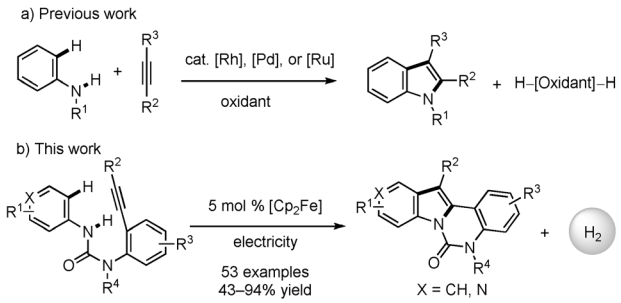
Electrochemical C–H/N–H Functionalization for the Synthesis of Highly Functionalized (Aza)indoles

Zhong-Wei Hou, Zhong-Yi Mao, Huai-Bo Zhao, Yared Yohannes Melcamu, Xin Lu, Jinshuai Song, and Hai-Chao Xu**

Abstract: *Indoles and azaindoles are among the most important heterocycles because of their prevalence in nature and their broad utility in pharmaceutical industry. Reported herein is an unprecedented noble-metal- and oxidant-free electrochemical method for the coupling of (hetero)arylamines with tethered alkynes to synthesize highly functionalized indoles, as well as the more challenging azaindoles.*

Indoles and azaindoles are prevalent in pharmaceutical agents and natural products.[1] Therefore, the development of general, efficient, and sustainable methods for the construction of these structures have long been pursued by organic chemists. In this context, the noble-metal-catalyzed coupling of anilides or anilines with internal alkynes by C–H/N–H functionalization has emerged in recent years as a modular and step-economical approach for the synthesis of indoles (Scheme 1 a).[2] This approach advantageously eliminates the need for prefunctionalized substrates (e.g., *ortho*-haloanilines) which are commonly required in the widely employed Larock indole synthesis.[3] Nonetheless, the reported methods frequently suffer from one or more of the following disadvantages, such as low regioselectivity when applied to similarly substituted alkynes (e.g., diaryl[2h] or dialkyl alkynes[2a]), as well as the requirement for noble-metal reagents and terminal oxidants.[4] Therefore, it is highly desirable to develop a more efficient and sustainable method for constructing indoles from easily available building blocks without relying on a noble-metal catalyst or oxidant.[5]



Scheme 1. (Aza)indole synthesis by C–H/N–H functionalization. Cp = cyclopentadiene.

Azaindoles are indole bioisosteres and possess a variety of beneficial biological properties.[6] However, access to structurally diverse azaindoles remains challenging. Traditional methods including the Fischer indole synthesis often fail[7] or are inefficient when electron-deficient pyridine-derived substrates are employed.[6] In contrast, preparation of azaindoles by annulation of alkynes with aminopyridines has been reported only once, in which a series of 7-azaindoles were constructed using a rhodium-based catalyst and a stoichiometric amount of silver oxidant.[8]

Organic electrosynthesis,[9] which employs electrons as reagents, has been demonstrated to be a versatile and environmentally friendly synthetic tool and attracted renewed interests.[10] We[11] have recently developed an electrochemical method for generating amidyl radicals and demonstrated in one example that they could participate in cascade cyclization reactions to afford indolines.[12] Inspired by this work and that of Nevado and co-workers on cascade radical reactions,[13] we report herein an unprecedented electrochemical synthesis of highly functionalized indoles and azaindoles by C–H/N–H functionalization of (hetero)-arylamines using tethered alkynes (Scheme 1 b). The noble-metal reagent- and oxidant-free reaction employs inexpensive ferrocene ([Cp_2Fe]) [14] as the redox catalyst, is compatible with a broad range of sensitive functional groups, and produces valuable H_2 as the only theoretical byproduct.[15]

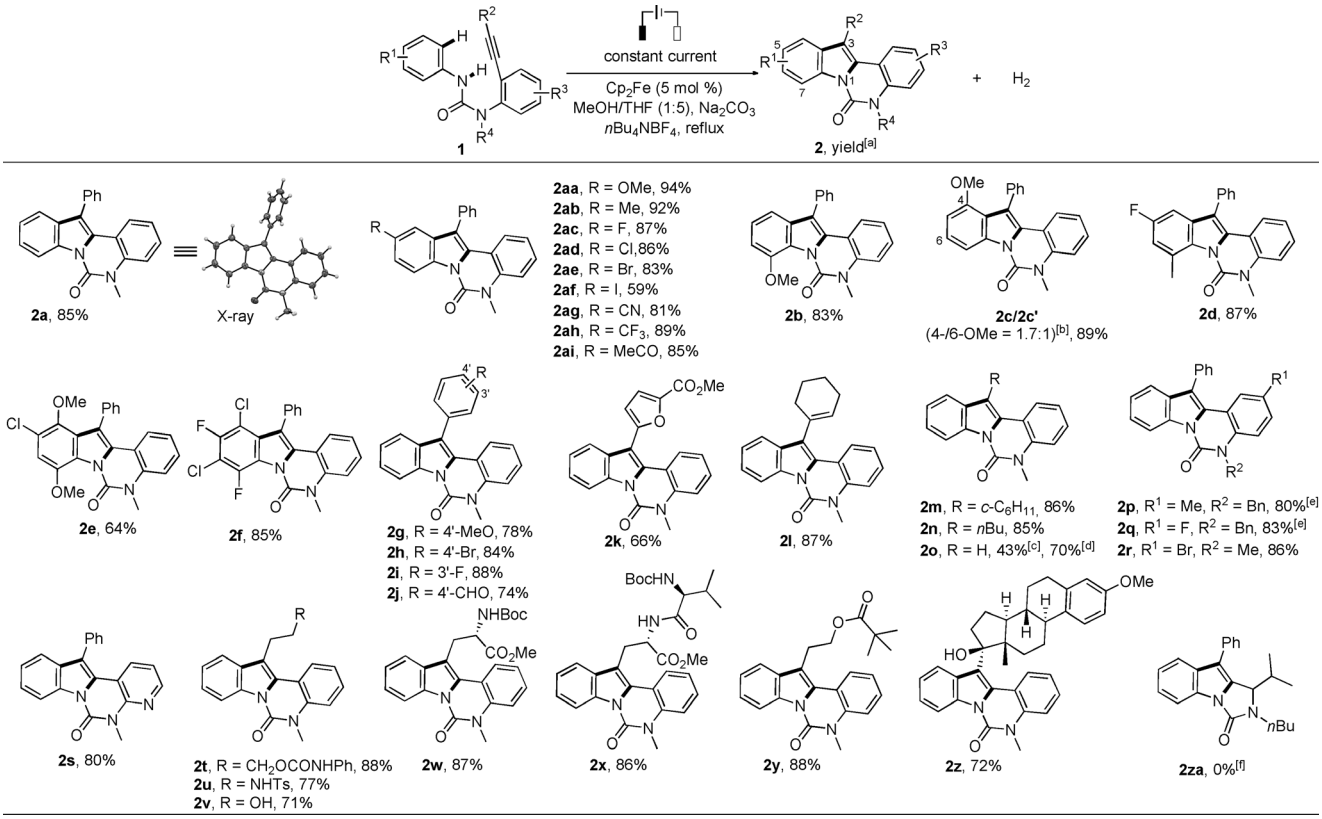
The easily available urea **1a** (see Scheme 2, $R^1 = R^3 = H$, $R^2 = Ph$, $R^4 = Me$) was chosen as a model substrate and electrolyzed in a round-bottom flask under the reaction conditions we recently developed for the electrochemical olefin hydroamidation reaction but without addition of the reducing reagent 1,4-cyclohexadiene.[11] Regiospecific formation of the unsymmetrical 2,3-diarylsubstituted indole **2a** was achieved in 85% yield with 5 mol% of [Cp_2Fe] as the redox catalyst. The structure of **2a** was confirmed by single-crystal X-ray diffraction studies.[16] The ferric catalyst and electricity were indispensable for the success of the transformation (see Table S1 in the Supporting Information). Importantly, conducting the electrolysis under air exerted no significant impact on reaction efficiency (see Table S1).

[*] Z.-W. Hou, Z.-Y. Mao, H.-B. Zhao, Y. Y. Melcamu, Prof. Dr. X. Lu, Dr. J. Song, Prof. Dr. H.-C. Xu
Collaborative Innovation Center of Chemistry for Energy Material
State Key Laboratory of Physical Chemistry of Solid Surfaces
Key Laboratory of Chemical Biology of Fujian Province and Department of Chemistry, Xiamen University
Xiamen 361005 (P.R. China)
E-mail: xinlu@xmu.edu.cn
haichao.xu@xmu.edu.cn
Homepage: http://chem.xmu.edu.cn/groupweb/hcxu/index.asp
Dr. J. Song
Fujian Institute of Research on Structure of Matter
Chinese Academy of Sciences, Fuzhou 350002 (P.R. China)
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under http://dx.doi.org/10.1002/anie.201602616.

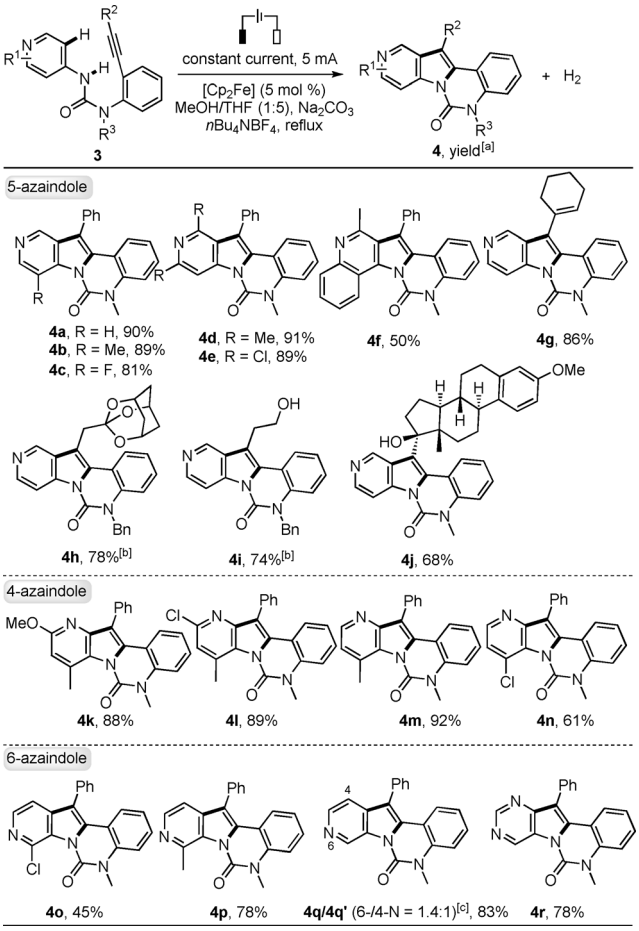
With the optimal reaction conditions defined, we conducted substrate scope analysis by varying the peripheral substituents (R^1, R^2, R^3, and R^4) of the scaffold **1** (Scheme 2). The electrolysis reaction exhibited excellent compatibility with a variety of electron-donating and electron-withdrawing groups at different positions of the reacting aryl ring (**2aa**–**ai**, **2b**, 59–94% yields), among which *meta* substitution was found to generate two separable regioisomeric indole products (**2c**/**2c′** = 1.7:1). Substrates with a multisubstituted N-aryl ring could also be used for constructing densely decorated indoles, most notably the fully substituted **2f**, with good efficiency (**2d**–**f**, 64–87% yields). In contrast, a wide range of substituents including aryl groups with different electronic properties (**2g**–**j**), a furan ring (**2k**), an alkenyl group (**2l**), and alkyl groups (**2m**, **2n**) were well tolerated on the alkyne moiety. 3-Unsubstituted indoles (**2o**), which are difficult for noble-metal-based methods,[2] could be prepared from either a terminal alkyne or, more efficiently, a trimethylsilyl-substituted alkyne through cyclization and in situ desilylation. Indoles bearing functionalized 2-aryl substituents could be conveniently synthesized in high yields (**2p**–**s**, 80–86% yields).

The broad functional-group tolerance of our electrochemical method was evidenced by the preparation of indoles bearing diverse substituents (Scheme 2), including the full-spectrum of halogens (**2ac**–**af**), a ketone (**2ai**), redox-sensitive aldehyde (**2j**), *N*-aryl carbamate (**2t**),[11] N-H sulfonamide (**2u**)[17] and free alcohol (**2v**), and acid/base-sensitive chiral Boc-amino ester (**2w**), dipeptide (**2x**), orthoester (see **4h**; Scheme 3), and acetal (see Scheme 4). Note that indole **2y** (Scheme 2) bearing a pivalate ester group did not undergo methanolysis and the current method can be applied for the late-stage modification of ethinyl estradiol, an active ingredient in oral contraceptives, to give the indole-functionalized estradiol **2z**. Further investigation revealed that the tether between the alkyne and the reactive nitrogen atom should ensure the formation of a six-membered ring in the first step of the cascade cyclization reactions. Substrates that form a relatively strained five-membered ring yielded no desired product, such as in the case of **2za**.[18]

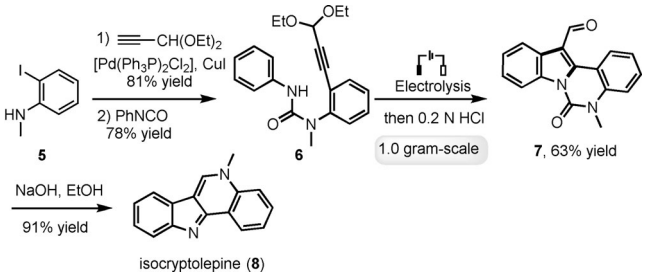
With the success of the indole synthesis, we next applied the electrochemical method to the more challenging task of constructing complex azaindoles (Scheme 3). Gratifyingly, 4- and 3-aminopyridine-derived substrates reacted efficiently under the standard reaction conditions, thus providing an unprecedented route to 5-, 4-, and 6-azaindoles. Similar to that observed earlier in the indole synthesis, the cyclization was largely unaffected by the electronic or steric properties of the pyridine ring and the alkyne substituent. As a result, a wide range of azaindole products bearing diverse substitu-



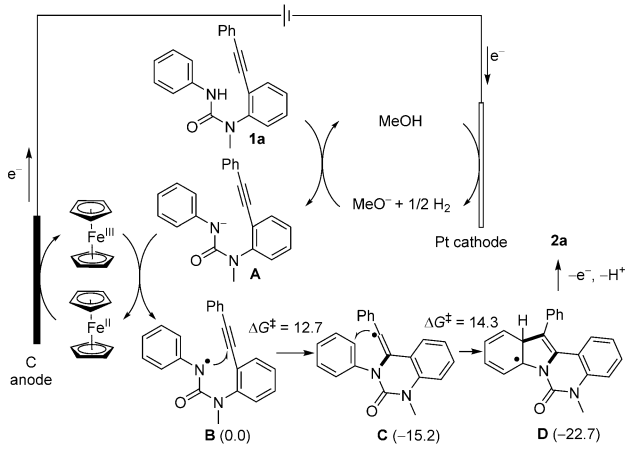
Scheme 2. Scope of indole synthesis. Reaction conditions: Reticulated vitreous carbon (RVC) anode, Pt cathode, constant current = 5 mA (ca. 0.05 mA cm^{-2}), **1** (0.3 mmol), THF (7.5 mL), MeOH (1.5 mL), nBu$_4$NBF$_4$ (0.9 mmol), reflux, argon, 4 h (2.5 F). [a] Yield of isolated product. [b] Two separable isomers were obtained. [c] A terminal alkyne (R^2 = H) was used as the starting material. [d] A trimethylsilyl-terminated alkyne (R^2 = TMS) was used as the starting material. [e] The reaction time was 5 h (3.1 F). [f] The substrate decomposed into unidentifiable material. Boc = *tert*-butoxycarbonyl, THF = tetrahydrofuran, TMS = trimethylsilyl, Ts = 4-toluenesulfonyl.



Scheme 3. Scope of azaindole synthesis. Reaction conditions were the same as those of Scheme 2. [a] Yield of isolated product. [b] The reaction time was 8 h (5 F). [c] Two separable isomers were obtained.



Scheme 4. Synthesis of the natural product isocryptolepine (**8**).



Scheme 5. Mechanistic proposal and computational studies. The values are DFT-derived energetics for the cyclization of the radical intermediate **B**. The energies (kcal mol^{-1}), shown within parentheses, are those relative to **B** and were calculated at the level of B3LYP/6-31G*.

ents at peripheral positions could be achieved. The use of unsubstituted 3-aminopyridine as the coupling partner afforded a separable mixture of 6-/4-azaindole (**4q**/**4q′**) in a ratio of 1.4:1. Finally, an aminopyrimidine-derived substrate bearing two basic nitrogen atoms reacted to afford the pyrrolo[3,2-*d*]pyrimidine **4r** in 78% yield. Taken together, the experimental results demonstrate the general applicability of the electrochemical protocol for constructing pyrrole-fused N-heterocycles.

The synthetic utility of the current method was further demonstrated by the construction of isocryptolepine (**8**), a bioactive natural product (Scheme 4).[19] The synthesis began with converting *N*-methyl-2-iodoaniline (**5**) into the electrolysis substrate **6** by urea formation followed by alkyne installation. The gram-scale electrolysis of **6** and subsequent acid-promoted hydrolysis of the acetal moiety resulted in the formation of the formyl-substituted indole **7** in 63% yield. The compound **7** was then converted into isocryptolepine (**8**) in one step by base-promoted hydrolysis of the urea linkage followed by spontaneous intramolecular condensation of the formyl group with the resultant secondary amino group.

A plausible mechanism for the electrochemical formation of (aza)indoles was proposed based on the results from both this and our previous studies (Scheme 5).[11] The process begins with the anodic oxidation of $[Cp_2Fe]$ to $[Cp_2Fe]^+$ and concomitant cathodic reduction of methanol solvent to form methoxide (MeO^-) and H_2. MeO^- then deprotonates substrate **1a** to furnish the anion **A**, which is a much better electron-donor than its neutral precursor. Single-electron transfer (SET) between **A** and $[Cp_2Fe]^+$ affords the electron-deficient nitrogen-centered radical[20] **B** and regenerates $[Cp_2Fe]$.[21] This efficient SET competes well with the cathodic reduction of $[Cp_2Fe]^+$, thus allowing the electrolysis to be carried out in an undivided cell rather than the relatively complicated and costly divided cell. Subsequently, **B** participates in a rare 6-*exo-dig* cyclization[22] to give the vinyl radical **C**, which then undergoes a second cyclization with the aryl ring to afford the delocalized radical **D**. Finally, the rearomatization of **D** by electron and proton eliminations generates the final product **2a**.[23]

To verify the mechanism proposed above, we first recorded cyclic voltammograms of $[Cp_2Fe]$ in the absence and presence of **1a** (see Figure S1). Results from these experiments suggested that efficient SET occurred between $[Cp_2Fe]^+$ and the conjugate base of **1a** (e.g., **A**, Scheme 5), and is consistent with our previous observations.[11] Density functional theory (DFT) calculations were then conducted to obtain the energetics for the bis(cyclization) of **B** to form **D**. The cascade cyclization was calculated to be a descending and

overall energetically favorable process with reasonable activation energies.[24] Together, the experimental and computational results offer strong support for the proposed mechanism.

In summary, we have developed an electrochemical method which achieved efficient coupling of aryl- and heteroarylamines with tethered alkynes for the highly chemo- and regioselective synthesis of indoles and azaindoles. Our method employs the inexpensive [Cp_2Fe] as the redox-relay reagent and proceeds through H_2 liberation and thus obviates the need for noble-metal catalysts and external oxidants.

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Keywords: electrochemistry · heterocycles · indoles · radicals · redox chemistry

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[23] An alternative mechanism of hydroamidation followed by oxidative cyclization was found to be unlikely (see Scheme S1 in the Supporting Information for details).
[24] Similar calculations were performed on the **1za**-derived radical (see Scheme S2 for details).

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Communications

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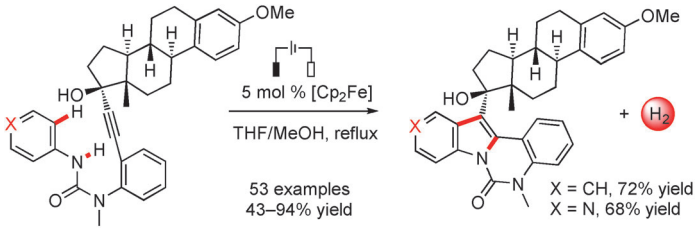
Z.-W. Hou, Z.-Y. Mao, H.-B. Zhao, Y. Y. Melcamu, X. Lu,* J. Song, H.-C. Xu* ——— ■■■■–■■■■

Electrochemical C–H/N–H Functionalization for the Synthesis of Highly Functionalized (Aza)indoles



It's electric: An electrochemical coupling of (hetero)arylamines with tethered alkynes has been developed and provides highly chemo- and regioselective access to densely functionalized indoles and azaindoles. The electrochemical reaction employs ferrocene ([Cp_2Fe]), an inexpensive organometallic reagent, as the redox catalyst and produces H_2 as the only theoretical byproduct.

