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Scalable Electrochemical Transition-Metal-Free Dehydrogenative Cross-Coupling Amination Enabled Alkaloid Clausines Synthesis

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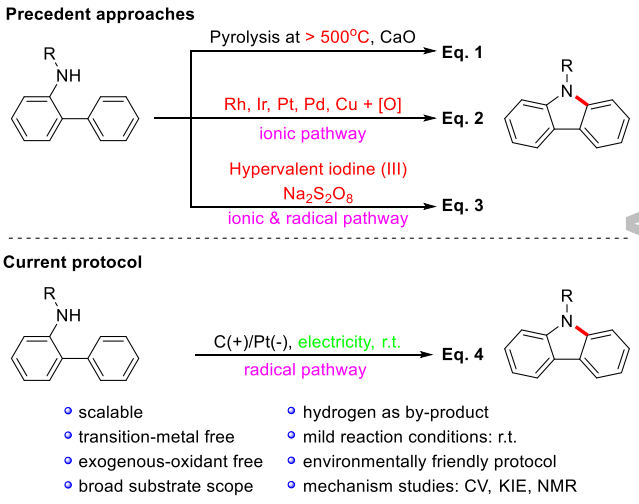
Abstract. Reported herein is an environmentally benign electrochemical C-H bond dehydrogenative amination protocol for the construction of privileged carbazole moiety with broad generality. Preliminary mechanistic investigations implied a radical reaction pathway. Compared with traditional ionic routes, the scalable transition-metal and exogenous-oxidant free strategy highlighted the green and sustainable nature of this method.

Keywords: electrosynthesis; dehydrogenative cross-coupling; amination; alkaloid clausines; C-H activation

Carbazole is a ubiquitous motif that constitutes the core structure for a diverse array of natural and non-natural products. Notably, a wide range of biological and physiological properties, including antitumor, antiplatelet aggregative, antibiotic, antiviral, antiplasmodial, anticonvulsant and sigma receptor antagonist, have been demonstrated.[1] Moreover, carbazole is commonly treated as electronic materials, such as photoconducting polymers and organic optoelectronic materials, owing to their excellent photophysical characteristics.[2] Consequently, the development of synthetic strategies for carbazole scaffolds holds potential significance in biological and material fields.

Although some valuable approaches for the synthesis of carbazole skeletons have been reported, such as Fischere-Borsche synthesis, Graebee-Ullmann synthesis, and conversion of indole derivatives to carbazoles,[3] developing a step-economic procedure is still highly desired.[4] For instance, direct cyclization of 2-aminobiaryl, represented as one of the most straightforward ways, has attracted tremendous attention. Specifically, Horaguchi *et al* reported a pyrolysis cyclization reaction over calcium oxide at high temperature (> 500 °C), affording carbazole scaffolds in moderate yields (**Eq. 1**, **Scheme 1**).[5] From the point of green and sustainable chemistry, there are currently three generations regarding to the C-H bond amination strategy. Firstly, transition-metal-catalyzed (Rh,[6] Ir,[7] Pt,[8] Pd,[9] Cu[10]) C-H bond activation of *N*-substituted 2-aminobiaryl enables carbazole synthesis with the assistance of chemical oxidants (**Eq. 2**, **Scheme 1**). Secondly, transition-metal-free strong chemical oxidant mediated carbazole construction via radical and/or nitrenium ion intermediates. For example, Antonchick, Chang, and Mal's group disclosed the hypervalent iodine (III)-mediated protocols towards carbazole scaffolds, respectively (**Eq. 3**, **Scheme 1**).[11] Despite these meaningful advances, the approaches described above have disadvantages associated with the requirements of costly transition-metal,[12] elevated reaction

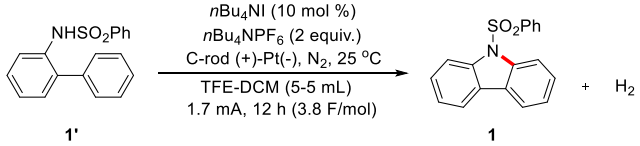


Scheme 1. Representative protocols for the C-H bond amination towards carbazole.

temperature, and strong oxidants used in stoichiometric amounts.[13] These raises concern regarding to atom economy and environmental issues.[14] Therefore, the development of a green and sustainable approach for highly efficient preparation of carbazole framework remains a desirable task. Fortunately, organic electrochemistry offers a facile and mild alternative to traditional chemical approaches.[15] The easily scalable feature and absence of exogenous chemical oxidants highlighted the green nature. Interestingly, Francke and Nishiyama's group independently described the electrochemically phenyl iodide-mediated carbazole scaffolds synthesis, in which hypervalent iodine was anodically generated.[16] However, the preparation of the electrocatalyst was time- and energy-consuming. Considering the forementioned synthetic challenge of bioactive carbazoles, we[17] envisioned the third generation, namely, a transition-metal and exogenous-oxidant free protocol for the preparation of carbazole derivatives via a dehydrogenative cross-coupling strategy (**Eq. 4**, **Scheme 1**).[18]

We commenced the study by optimizing the electrochemical conditions for the dehydrogenative C-H bond amination of arylsulfonamide **1'** (**Table 1**). The optimal reaction condition was obtained as followed: 10 mol % of tetrabutylammonium iodide (nBu$_4$NI) as the catalyst, 2 equivalents of tetrabutylammonium hexafluorophosphate (nBu$_4$NPF$_6$) as an electrolyte, a commercially available graphite rod as the anode, a platinum plate as the cathode, under constant current electrolysis of 1.7 mA at room temperature in the solvent mixture of trifluoroethanol and dichloromethane (TFE/DCM, 1:1, **entry 1**). And the target carbazole product **1** was afforded in 81% yield. Interestingly, a good result was still observed in the absence of nBu$_4$NI catalyst (69%, **entry 2**). However, when ferrocene (Cp$_2$Fe) was utilized as the catalyst, an inferior yield was detected (34%, **entry 3**). Compared with the original choice of electrodes, alternative niether the anode material, reticulated vitreous carbon (RVC), nor the cathode material, nickel foam (with greater overpotential for proton reduction), was effective in promoting the product formation (**entries 4 & 5**). Both replacing of the electrolyte (potassium hexafluorophosphate, KPF$_6$ instead of nBu$_4$NPF$_6$, **entry 6**) and increasing the proportion of TFE in the solvent (**entry 7**) resulted in decreasing product yields. Besides, neither decreasing nor increasing the current could improve the efficiency any further (**entries 8** & **9**).

Table 1. Optimized condition.

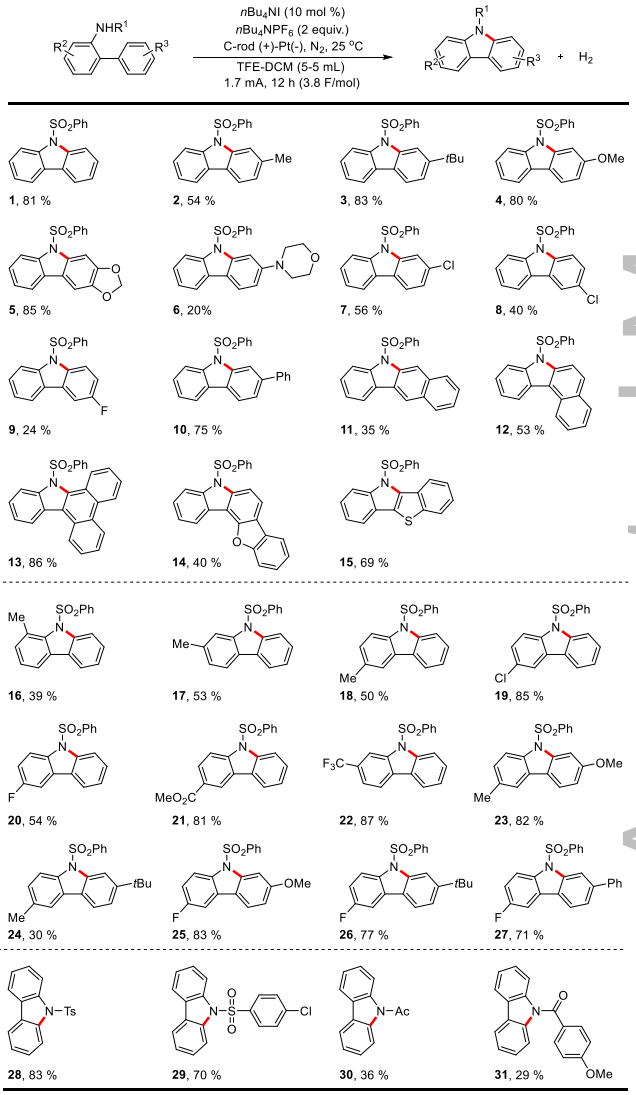


1' 1

Entry	Deviation from standard conditions	Yield (%)
1	none	81
2	No nBu$_4$NI	69
3	Cp$_2$Fe as catalyst	34
4	RVC as anode	0
5	Ni foam as cathode	64
6	KPF$_6$ as electrolyte	36
7	TFE-DCM (9:1) as solvent	50
8	1.5 mA instead of 1.7 mA	75
9	2.0 mA instead of 1.7 mA	77

With the optimized reaction conditions in hand, we next explored the substrate scope (**Table 2**). First, we explored the 2-amidobiaryls bearing various substituents on the benzene ring which was linked to the aniline moiety. The outcome indicated that

Table 2. Generality of the electrochemical dehydrogenative C-H bond amiation protocol.



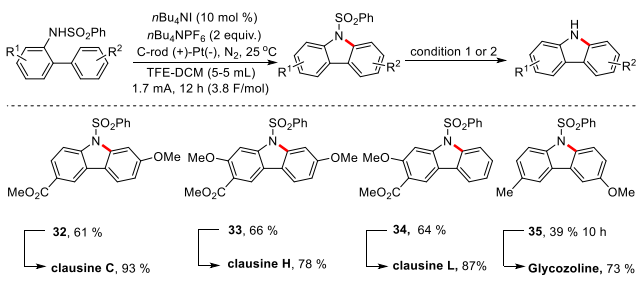
Reaction condition: Substrate (0.2 mmol), nBu$_4$NI (10 mol %), nBu$_4$NPF$_6$ (2 equiv.), graphite rod (ϕ 10 mm) as anode and platinum (10 mm × 10 mm), 1.7 mA, TFE/DCM (5/5 mL), 25 °C, N$_2$, 12 h (3.8 F/mol).

several 2-amidobiaryls were compatible with this reaction, affording the carbazole products **2-9** in moderate to good yields (20-85%), regardless of the presence of electron-donating substituents (methyl, *t*-butyl, methoxy, methylenedioxy) or electron-withdrawing substituents (chloro, fluoro). However, the morpholine-substituted compound **6** was achieved in relatively low yield presumably because of the oxidation labile feature.[19] In addtion, a phenyl group was introduced to the *para*-position of the benzene ring and the target product **10** was smoothly formed in 75% yield.

Remarkably, other aromatic ring, such as naphthalene and phenanthrene could also be cyclized and the related 2-amidobiaryls could be converted into carbazole products **11-13** in 35-86% yields. Significantly, heteroaromatic ring, such as dibenzofuran and thiophene could be annulated and the desired products **14** and **15** were obtained in 40% and 69% yield, respectively. Similarly, several 2-amidobiaryls bearing different substituents on the aniline ring were tested too. The related substrates bearing methyl, halo, ester, and trifluoromethyl at the *ortho*, *meta* or *para* position to the nitrogen atom were employed, and the desired products **16-22** were smoothly formed in moderate to high yields (39-87%). To broaden the generality of this methodology, substrates bearing funtional groups on both benzene rings were subjected to this protocol. And the corresponding di-substituted carbazole products **23-27** (30-82% yields) were formed as expected. Then, variation of the protecting group displayed that sulfonamide was better than amide (**28-31**). These results were presumably due to the varied acidity of the N-H bond in the presence of different protecting groups.[20]

To demonstrate the practical utility of this protocol, we tried to synthesize several natural alkaloids (**Clausine C**, **Clausine H**, **Clausine L**, and **Glycozoline**, **Scheme 1**). To our delight, *N*-substituted alkaloids **32-35** were provided from readily available substrates. After simple deprotection, the corresponding natural alkaloids, Clausine series, were obtained in good to excellent yields (73-93%, **Table 3**). Furthermore, the scalability was illustrated by the gram-scale synthesis with moderate efficiency

Table 3. Alkaloid Clausines synthesis.



Condition 1 for products **32**, **33**, **34** with nBu$_4$NF (5 equiv.) in THF reflux and Condition 2 for product **35** with KOH (3 equiv.) in EtOH reflux.

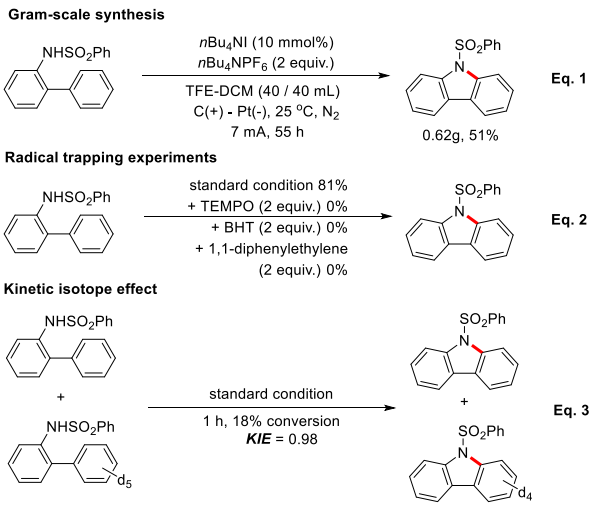


Figure 1. Control experiments.

without physically changing the electrode employed (**Eq. 1**, **Figure 1**). To obtain insights into the mechanism, a series of control experiments and cyclic voltammetry were conducted. First, the addition of radical scavengers, such as 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), butylated hydroxytoluene (BHT), and 1,1-diphenylethylene into the standard conditions completely shut down the reaction (**Eq. 2**, **Figure 1**). These phenomena indicated a radical nature of the process. Second, the intermolecular kinetic isotope effect was observed with a *KIE* value of 0.98, implying an inverse secondary kinetic isotope effect (**Eq. 3**, **Figure 1**). The scenario was in line with the configuration change of carbon center from sp^2 to sp^3 and demonstrated that C-H bond cleavage might be not involved in the amination step. Then, cyclic voltammetry analysis of each compound of interest was performed (**Figure 2**). The oxidative peak potentials for substrate **1'** and iodide anion were 2.2 V *vs* SCE and 0.95 V *vs* SCE in TFE/DCM, respectively. Notably, the peak potential for I^- was significantly shifted to 0.75 V *vs* SCE when the above two species were mixed, inferring a hydrogen

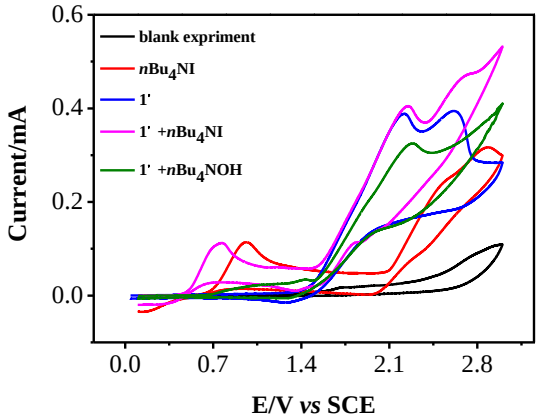
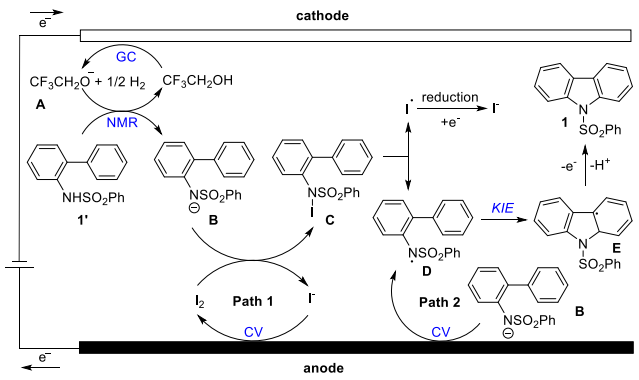


Figure 2. Cyclic voltammetry.

bond existed. Remarkably, the initial oxidative potential for the nitrogen anion (E = 0.65 V *vs* SCE) was tremendously lower than that of the corresponding N-H starting material. Importantly, the hydrogen gas was detected from the headspace of the reactor by the gas chromatography (GC) after the completion of the model reaction (see Figure S2).

Based on the above information, a putative mechanism was proposed in **Scheme 3**. Cathodically reduction of the proton solvent initiated the transformation, giving a strong base **A**. Deprotonation of the substrate **1'** (see Figure S4) took place to generate the nitrogen anion **B**. Nucleophilic substitution to anodic generated iodine afforded intermediate C, followed by homolytic cleavage of the N-I bond delivering nitrogen-centered radical **D**. Then intramolecular nitrogen radical attacking to the aryl ring supplied species **E**. Eventually, anodic heterogeneous oxidation in a combination of the ensuing deprotonation furnished the desired carbazole scaffold **1**. Considering the comparatively low initial potential for the nitrogen anion which was similar to that of iodide, direct anodic oxidation of species **B** was also feasible and that was confirmed by **entry 2** in **Table 1**.



Scheme 2. Proposed mechanism.

In conclusion, we developed a transition-metal and exogenous-oxidant free C-H bond amination approach towards carbazole-derived alkaloid Clausine and Glycozoline synthesis. The scalability, very mild conditions, and broad generality highlighted the green and sustainable nature of this procedure. Preliminary mechanistic investigations including NMR, CV, GC, KIE, and radical trapping experiments substantially indicated a radical pathway. In light of the above-mentioned advantages, the newly developed protocol will promote the dehydrogenative C-H bond functionalization in organic community.

Experimental Section

To an oven-dried undivided three-necked flask (10 mL), arylamine (0.2 mmol), nBu$_4$NPF$_6$ (0.4 mmol, 2.0 equiv.), and nBu$_4$NI (0.02 mmol, 10 mol%) were added. The bottle was equipped with graphite rod (ϕ 10 mm, about 15 mm immersion depth in solution) as the anode and platinum plate (10 mm × 10 mm) as the cathode. Then the flask was charged with nitrogen, followed by the sequential addition of TFE (5.0 mL) and DCM (5.0 mL). The reaction mixture was stirred and electrolyzed at a constant current of 1.7 mA at 25 °C for 12 h. When the reaction was completed, as indicated by TLC, the solvent was removed with a rotary evaporator and the residue was purified by column chromatography on silica gel (ethyl acetate/petroleum ether = 1:20 as eluent) to give the pure carbazoles **1**-**35**.

Acknowledgements

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[18] In the indirect electrolysis of ref 16, the corresponding mediator was phenyl iodide which was electrochemically oxidized to hypervalent iodine. In contrast, our procedure was directly electrolysed of the starting material and/or the simple iodide anion.

[19] Generally speaking, tertiary amine has relatively low oxidative potential.

[20] A strong electron-withdrawing group was benefit to stabilize the nitrogen-radical species.

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Scalable Electrochemical Transition-Metal-Free Dehydrogenative Cross-coupling Amination Enabled Alkaloid Clausines Synthesis

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Pan Zhang, Baoying Li, Liwei Niu, Ling Wang, Guofeng Zhang, Xiaofei Jia, Guoying Zhang, Siyuan Liu,* Li Ma,* Wei Gao, Dawei Qin, Jianbin Chen*

20-87% yields, 35 examples

Clausine C, **H**, **L** and **Glycozoline**