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# Electrochemical oxidative C–H/N–H cross-coupling for C–N bond formation with hydrogen evolution†

Yi Yu,<sup>‡a</sup> Yong Yuan,<sup>§b</sup> Huilin Liu,<sup>a</sup> Min He,<sup>a</sup> Mingzhu Yang,<sup>a</sup> Pan Liu,<sup>a</sup> Banying Yu,<sup>a</sup> Xuanchi Dong<sup>a</sup> and Aiwen Lei<sup>§\*ab</sup>

**Under metal catalyst-free and exogenous-oxidant-free conditions, a series of C-3 aminated imidazo[1,2-*a*]pyridines were synthesized by electrochemical intermolecular oxidative C–H/N–H cross-coupling. Furthermore, by using a catalytic amount of ferrocene as the mediator, electrochemical intramolecular oxidative C–H/N–H cross-coupling for the synthesis of 10*H*-benzo[4,5]imidazo[1,2-*a*]indole derivatives has also been accomplished.**

An imidazo[1,2-*a*]pyridine core is a very important structural unit that widely occurs in many biologically active molecules,<sup>1</sup> particularly in many commercially available drugs (such as alpidem, zolpidem, necopidem and saripidem).<sup>2</sup> In order to obtain other new biologically active molecules, further modification or functionalization of imidazo[1,2-*a*]pyridines is highly necessary. Over the past few years, the modification of imidazo[1,2-*a*]pyridines has received much attention and studies have revealed that C-3 substituted imidazo[1,2-*a*]pyridines exhibit a better biological activity than imidazo[1,2-*a*]pyridines itself.<sup>3,4</sup> for example, C-3 sulfenylated or aminated imidazo[1,2-*a*]pyridines. However, compared with extensive research on C-3 sulfenylation, the C-3 amination of imidazo[1,2-*a*]pyridines still remains underexplored,<sup>5</sup> and the reported methods usually require stoichiometric oxidants, long reaction times, and/or high reaction temperature. Therefore, developing an alternative synthetic method to construct C-3 aminated imidazo[1,2-*a*]pyridines is desirable.

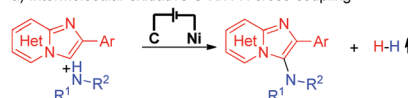
Electrochemical synthesis is an efficient and environmentally friendly synthetic method,<sup>6</sup> which can realize C–X bond formation *via* electrochemical oxidative C–H/X–H cross-coupling with hydrogen evolution under metal catalyst-free and exogenous-oxidant-free conditions. In recent years, electrochemical oxidative C–H/X–H cross-coupling with hydrogen evolution has gained significant attention.<sup>7</sup> However, until now, electrochemical oxidative

C–H/N–H cross-coupling with hydrogen evolution for the synthesis of C-3 aminated imidazo[1,2-*a*]pyridines has not been reported. As a part of our recent research interest in the field of electrochemical oxidative C–X bond formation,<sup>8</sup> we herein report an electrochemical oxidative C–H/N–H cross-coupling protocol for the synthesis of C-3 aminated imidazo[1,2-*a*]pyridines. Under metal catalyst-free and exogenous-oxidant-free conditions as well as using cheap and commercially available NaNO<sub>3</sub> as the electrolyte, a series of significant C-3 aminated imidazo[1,2-*a*]pyridines were synthesized with hydrogen evolution (Scheme 1a). Furthermore, under electrochemical oxidative conditions, intramolecular oxidative C–H/N–H cross-coupling for the synthesis of 10*H*-benzo[4,5]imidazo[1,2-*a*]indole derivatives has also been accomplished (Scheme 1b).

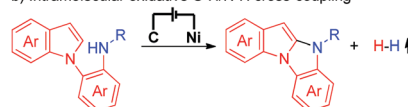
Our initial investigation started by using 2-phenylimidazo[1,2-*a*]pyridine (**1a**) and imidazole (**2a**) as the model substrates (Table 1). Interestingly, when the reaction was conducted at a constant current of 8 mA in MeCN/H<sub>2</sub>O/EtOH, the desired C–H/N–H cross-coupling product could be obtained in 78% <sup>1</sup>H NMR yield (Table 1, entry 1). Control experiments revealed that the mixed solvent (MeCN/H<sub>2</sub>O/EtOH) and electricity were important for the reaction efficiency (Table 1, entries 2–5). Some organic electrolytes were then investigated, but all were less effective than NaNO<sub>3</sub> (Table 1, entries 6 and 7). Either increasing the operating current to 16 mA or decreasing the operating current to 4 mA also led to a decreased reaction yield

## This work

### a) Intermolecular oxidative C–H/N–H cross-coupling



### b) Intramolecular oxidative C–H/N–H cross-coupling



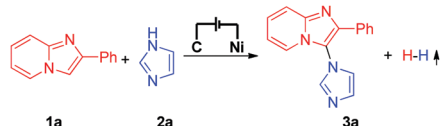
**Scheme 1** Electrochemical oxidative C–H/N–H cross-coupling for C–N bond formation with hydrogen evolution.

<sup>a</sup> National Research Center for Carbohydrate Synthesis, Jiangxi Normal University, Nanchang 330022, P. R. China. E-mail: aiwenlei@whu.edu.cn

<sup>b</sup> College of Chemistry and Molecular Sciences, Institute for Advanced Studies (IAS), Wuhan University, Wuhan 430072, P. R. China

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‡ Yi Yu and Yong Yuan contributed equally to this work.

Table 1 Optimization of the reaction conditions<sup>a</sup>


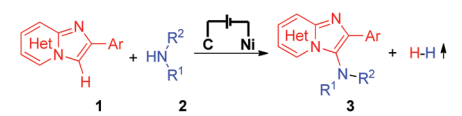
| Entry | Variation from the standard conditions                                     | Yield <sup>b</sup> (%) |
|-------|----------------------------------------------------------------------------|------------------------|
| 1     | Standard conditions                                                        | 78, 75 <sup>c</sup>    |
| 2     | No H <sub>2</sub> O (MeCN/EtOH = 5.8/1.2)                                  | 66                     |
| 3     | No EtOH (MeCN/H <sub>2</sub> O = 6/1)                                      | 67                     |
| 4     | No MeCN (H <sub>2</sub> O/EtOH = 1/6)                                      | 40                     |
| 5     | No constant current                                                        | 0                      |
| 6     | <sup>n</sup> Bu <sub>4</sub> NBF <sub>4</sub> instead of NaNO <sub>3</sub> | 73                     |
| 7     | <sup>n</sup> Bu <sub>4</sub> NPF <sub>6</sub> instead of NaNO <sub>3</sub> | 67                     |
| 8     | 16 mA, 2.5 h                                                               | 65                     |
| 9     | 4 mA, 10 h                                                                 | 46                     |
| 10    | C(+) Fe(-) instead of C(+) Ni(-)                                           | 56                     |

<sup>a</sup> Standard conditions: graphite rod anode, nickel plate cathode, constant current = 8 mA, **1a** (0.3 mmol), **2a** (2.0 equiv.), NaNO<sub>3</sub> (0.3 mmol), MeCN (4.8 mL), H<sub>2</sub>O (1.0 mL), EtOH (1.2 mL), 50 °C, 5 h (5.0 F mol<sup>-1</sup>), undivided cell. <sup>b</sup> Yields were determined by <sup>1</sup>H NMR using naphthalene as the internal standard. <sup>c</sup> Isolated yields.

(Table 1, entries 8 and 9). Further investigation showed that the carbon rod anode and the nickel plate cathode were the best choice for the electrode materials (Table 1, entry 10).

With the optimized reaction conditions in hand, we subsequently explored the substrate scope of this electrochemical oxidative C-H/N-H cross-coupling reaction with different imidazo[1,2-*a*]pyridines and *N*-nucleophiles (Table 2). First, the effect of different substituents on the 2-phenyl moiety of imidazo[1,2-*a*]pyridines was investigated. Imidazo[1,2-*a*]pyridine bearing an electron-neutral methyl substituent at the 2-phenyl moiety produced the C-H/N-H cross-coupling product in 75% yield (Table 2, **3a**), while imidazo[1,2-*a*]pyridines with phenyl or electron-withdrawing -F and -CF<sub>3</sub> substituents at the 2-phenyl moiety gave the corresponding products in moderate to good yields (Table 2, **3b** to **3f**). Moreover, substrates with a methyl group at the C-5, C-6, or C-7 position of 2-phenylimidazo[1,2-*a*]pyridines reacted smoothly with imidazole (**2a**) and afforded the C-3 aminated products in moderate to good yields (Table 2, **3g** to **3i**). It is worth noting that important benzo[*d*]imidazo[2,1-*b*]thiazole derivatives were also compatible with the reaction conditions, generating the corresponding C-H/N-H cross-coupling products in moderate to high yields (Table 2, **3j** to **3l**). Different azoles and other *N*-nucleophiles were also applied as substrates in this electrochemical oxidative C-H/N-H cross-coupling reaction. Delightedly, 2-methyl-1*H*-imidazole, 1*H*-benzo[*d*]imidazole, 2-methyl-1*H*-benzo[*d*]imidazole, and even 3,5-dimethyl-1*H*-pyrazole and morpholine all were suitable substrates for this transformation (Table 2, **3m** to **3q**). However, when long-chain aliphatic amines, such as *n*-butylamine, were employed in the reaction, no desired product was detected (Table 2, **3r**).

Having successfully established the feasibility of the electrochemical intermolecular oxidative C-H/N-H cross-coupling of imidazo[1,2-*a*]pyridines with *N*-nucleophiles, we became enthusiastic about the synthesis of significant 10*H*-benzo[4,5]imidazo[1,2-*a*]indole derivatives<sup>9</sup> using the electrochemical intramolecular oxidative C-H/N-H cross-coupling strategy (Table 3). Unfortunately, under

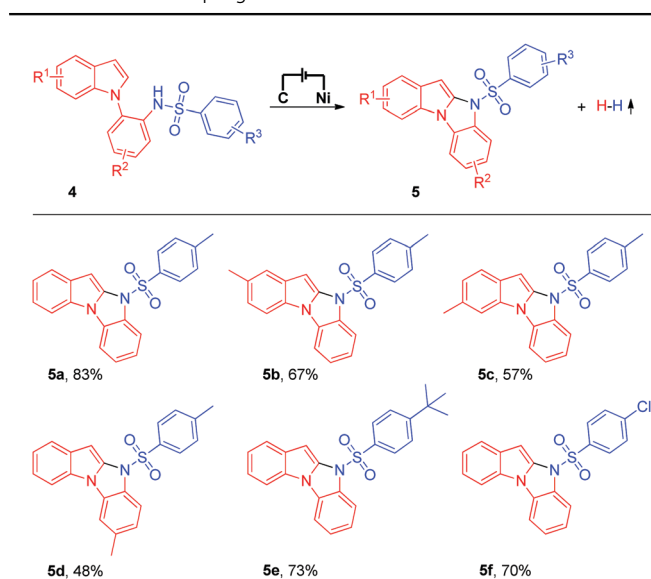
Table 2 Substrate scope of the electrochemical intermolecular oxidative C-H/N-H cross-coupling reaction<sup>a</sup>


|                             |                              |                              |
|-----------------------------|------------------------------|------------------------------|
| <b>3a</b> , 75%             | <b>3b</b> , 58%              | <b>3c</b> , 85% <sup>b</sup> |
| <b>3d</b> , 57%             | <b>3e</b> , 63%              | <b>3f</b> , 59%              |
| <b>3g</b> , 64%             | <b>3h</b> , 84% <sup>b</sup> | <b>3i</b> , 51%              |
| <b>3j</b> , 82 <sup>c</sup> | <b>3k</b> , 59%              | <b>3l</b> , 52% <sup>c</sup> |
| <b>3m</b> , 40%             | <b>3n</b> , 50%              | <b>3o</b> , 64%              |
| <b>3p</b> , 50%             | <b>3q</b> , 53%              | <b>3r</b> , 0%               |

<sup>a</sup> Standard conditions: graphite rod anode, nickel plate cathode, constant current = 8 mA, **1** (0.3 mmol), **2** (2.0 equiv.), NaNO<sub>3</sub> (0.3 mmol), MeCN (4.8 mL), H<sub>2</sub>O (1.0 mL), EtOH (1.2 mL), 50 °C, 5 h (5.0 F mol<sup>-1</sup>), undivided cell. <sup>b</sup> 4.5 h (4.5 F mol<sup>-1</sup>). <sup>c</sup> **2a** (3.0 equiv.).

the current electrochemical conditions, the intramolecular oxidative C-H/N-H cross-coupling products could not be obtained. Next, we tried to modify the reaction conditions to obtain the target products (for details about the optimization of reaction conditions, see the ESI†). To our delight, when a catalytic amount of ferrocene (Cp<sub>2</sub>Fe) was added as the mediator, the intramolecular oxidative C-H/N-H cross-coupling reaction proceeded well and the corresponding 10*H*-benzo[4,5]imidazo[1,2-*a*]indole derivative could be isolated in 83% yield (Table 3, **5a**). The substrate scope of the electrochemical intramolecular oxidative C-H/N-H cross-coupling reaction was then investigated. Various *N*-(2-(1*H*-indol-1-yl)phenyl)benzenesulfonamide derivatives were all suitable substrates in this transformation (Table 3, **5b** to **5f**).

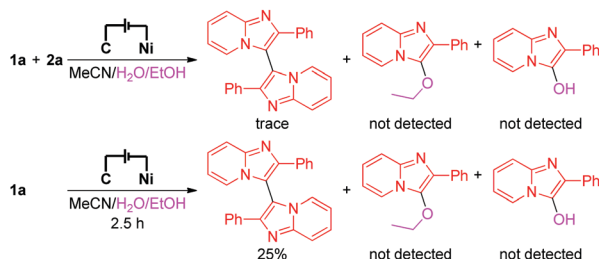
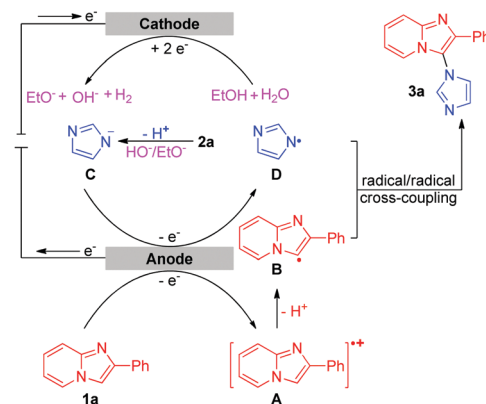
To investigate the details of the mechanism for this electrochemical oxidative C-H/N-H cross-coupling reaction, several control experiments were carried out. First, cyclic voltammetry

**Table 3** Substrate scope of the electrochemical intramolecular oxidative C–H/N–H cross-coupling reaction<sup>a</sup>

<sup>a</sup> Standard conditions: graphite rod anode, nickel plate cathode, constant current = 8 mA, **4** (0.3 mmol), Cp<sub>2</sub>Fe (20 mol%), <sup>n</sup>Bu<sub>4</sub>NBF<sub>4</sub> (0.3 mmol), MeCN (3.5 mL), EtOH (3.5 mL), 70 °C, 4 h (4.0 F mol<sup>−1</sup>), undivided cell.

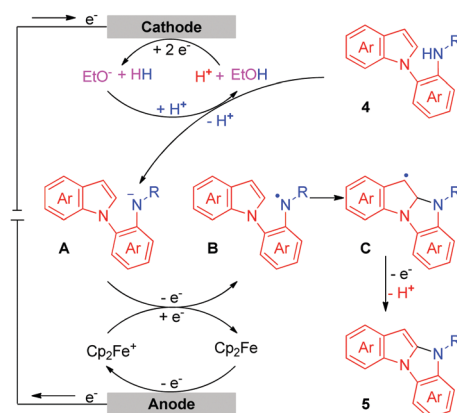
experiments on model substrates were carried out. **1a** and **2a** have very similar redox potentials. **1a** could be oxidized when the oxidation potential exceeded 0.94 V, while **2a** started to get oxidized from 0.93 V (for more details about the cyclic voltammetry experiments, see the ESI<sup>†</sup>). This result showed that **1a** and **2a** could be synchronously oxidized at the anode under our electrochemical conditions. Second, the model reaction and the electrolysis of **1a** in the absence of **2a** were investigated, respectively (Scheme 2). Homo-coupling products of **1a** were detected in both reactions, while the capture product of **A** (see Scheme 3 for the structure of **A**) by H<sub>2</sub>O or EtOH was not detected. These results indicated that **1a** could be converted to the corresponding radical under our electrochemical conditions and the pathway of radical cation intermediate **A** captured by a nucleophile might be ruled out.

Based on the results of the above experiments and previous reports,<sup>5c,10</sup> a possible mechanism for the intermolecular oxidative C–H/N–H cross-coupling reaction is shown in Scheme 3. The anodic oxidation and deprotonation of **1a** produce radical **B**. The cathodic reduction of H<sub>2</sub>O or EtOH produces H<sub>2</sub> and HO<sup>−</sup> or EtO<sup>−</sup>.

**Scheme 2** Control experiments.**Scheme 3** Proposed mechanism of the intermolecular oxidative C–H/N–H cross-coupling reaction.

The generated HO<sup>−</sup> or EtO<sup>−</sup> then deprotonates substrate **2a** to afford its conjugate base **C**. **C** is further oxidized at the anode, forming the nitrogen radical **D**. Next, radical/radical cross-coupling affords the C–H/N–H cross-coupling product **3a**. Note that the pathway of radical addition of nitrogen radical **D** to **1a** could not be fully ruled out. In addition, for some alkyl amines, the corresponding nitrogen radicals are unstable, which may be the reason why **3r** was not obtained. As for the intramolecular oxidative C–H/N–H cross-coupling reaction (Scheme 4), the reaction begins with the anodic oxidation of Cp<sub>2</sub>Fe to afford Cp<sub>2</sub>Fe<sup>+</sup>,<sup>11</sup> and Cp<sub>2</sub>Fe<sup>+</sup> then oxidizes the deprotonated **4** (**A**) to regenerate Cp<sub>2</sub>Fe and form nitrogen radical intermediate **B**. Sequential radical addition, single electron oxidation, and deprotonation finally afford the C–H/N–H cross-coupling product **5**.

In summary, we have developed an electrochemical oxidative C–H/N–H cross-coupling reaction. Under metal catalyst-free and exogenous-oxidant-free conditions as well as using cheap and commercially available sodium nitrate as the electrolyte, a series of C-3 aminated imidazo[1,2-*a*]pyridines were synthesized with hydrogen evolution. Furthermore, by using a catalytic amount of ferrocene as the mediator, electrochemical intramolecular oxidative C–H/N–H cross-coupling for the synthesis of significant 10*H*-benzo[4,5]-imidazo[1,2-*a*]indole derivatives has also been reported.

**Scheme 4** Proposed mechanism of the intramolecular oxidative C–H/N–H cross-coupling reaction.

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## Conflicts of interest

There are no conflicts to declare.

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