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Electrochemical Dehydrogenative C–H Aminomethylation of Imidazopyridines and Related Heterocycles

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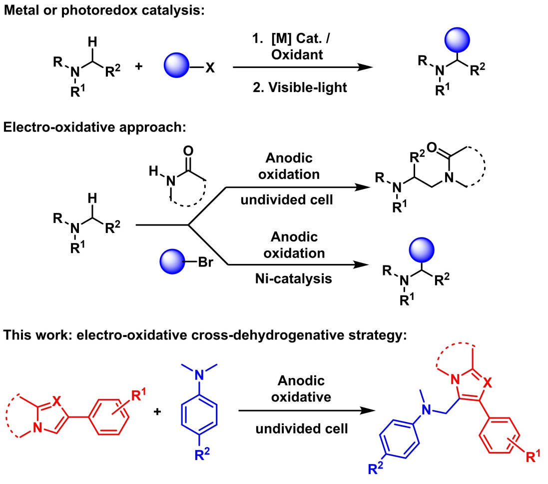
Abstract: A facile and environmentally friendly electrochemical protocol is herein reported for the $C(sp^2)$–$C(sp^3)$ cross dehydrogenative coupling between imidazopyridines and N,N-dimethylanilines. The broad functional group compatibility includes halogens, ester, alcohol, sulfone as well as thiophene. This methodology is also suitable for benzo[d]imidazo[2,1-b]thiazole, thiazoimidazole and tetrahydroisoquinoline, and can be scaled up to 5 mmol. Mechanistic insights are discussed.

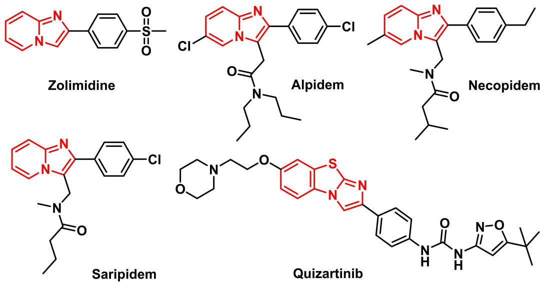
Introduction

N-containing molecules are important scaffolds for pharmaceuticals because of their excellent biological and medicinal activity.[1–4] In this context, the direct α-C–H functionalization of amines is of great interest in organic synthesis.[5–9] In the past decades, many efforts have been made for the direct functionalization of α-amino C–H bonds with transition-metal catalysts.[10–14] However, those often require external oxidants, such as for example stoichiometric hypervalent iodides, and harsh reaction conditions. Moreover, their scope is usually limited in terms of functional group and heterocyclic tolerance. Recently, some photocatalytic techniques have enabled remarkable methods for the direct functionalization of α-amino C–H bonds.[15,16] In addition, several research groups have also reported electrochemical solutions.[17–19] For example, Lei and co-authors reported an electrochemical oxidative method for the N–H aminomethylation of amides, while Ye's group developed an electrochemical Ni-catalyzed aminomethylation method of aryl bromides (Scheme 1).



Scheme 1. Selected α-amino C–H bond functionalization methods.

Meanwhile, the imidazo[1,2-*a*]pyridine core is a fused N-containing heterocycle associated to a wide range of pharmacological activities.[20] Related commercially available drugs[21–24] include Zolimidine, Alpidem, Necopidem, Saripidem, Zolpidem, Olprinone, and benzo[*d*]imidazo[2,1-*b*]thiazole[25] (Scheme 2). Therefore, the direct functionalization of Imidazo[1,2-*a*]pyridine[26] and its derivatives constitutes a valuable research objective for drug diversification. Herein, we report the mild and environmentally friendly $C(sp^3)$–H/$C(sp^2)$–H cross-coupling between imidazo[1,2-*a*]pyridines and N,N-dimethylanilines via electrochemical anodic oxidation.[27–34]



Scheme 2. Selected imidazopyridine containing and related drugs.

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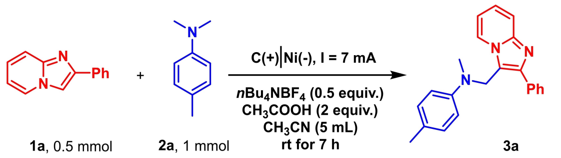
Results and Discussion

To this end, optimization experiments for the step and atom efficient cross dehydrogenative C–C coupling[35–40] reaction between model substrates 2-phenylimidazo[1,2-a]pyridine and 4,N,N-trimethylaniline were performed. The reaction was carried out in an undivided cell equipped with a graphite anode and a nickel cathode while utilizing CH_3CN as solvent at constant current. An isolated yield of 94% was obtained when the reaction was performed at room temperature with 0.5 equiv. nBu$_4$NBF$_4$ as the electrolyte and a small amount of CH_3COOH (2 equiv., entry 1, Table 1). Importantly, no desired product could be obtained without electricity (entry 2). Moreover, only 27% of the product could be obtained without acetic acid (entry 3, see the Supporting Information for an acid screening). The effect of the solvent was then investigated. No desired product could be detected when MeOH or HFIP were utilized (entries 4 and 5). In addition, other electrolytes generally delivered lower yields (entries 6–8). Reducing or increasing the operating current likewise led to inferior results (entries 9–10). Finally, utilizing a silver or magnesium plate as cathode proved detrimental to the yield (entries 11–12).

With the optimized reaction conditions established, we then explored the scope of this electro-oxidative C(sp^3)–H/C(sp^2)–H cross-coupling. First, a series of N,N-dimethylanilines were engaged in this transformation and the results are shown in Scheme 3. The model substrate 2-phenylimidazo[1,2-a]pyridine reacted smoothly with various N,N-dimethylanilines to afford good to excellent yields of the corresponding dehydrogenative coupling products. N,N-dimethylanilines bearing electron-donating substituents such as methyl, *t*Bu, or methoxy groups could afford the desired products (**3 a**–**3 c**). Moreover, electron-withdrawing substituents such as cyano, trifluoromethyl and ester groups were also suitable for this reaction (**3 d, 3 i, 3 j**).

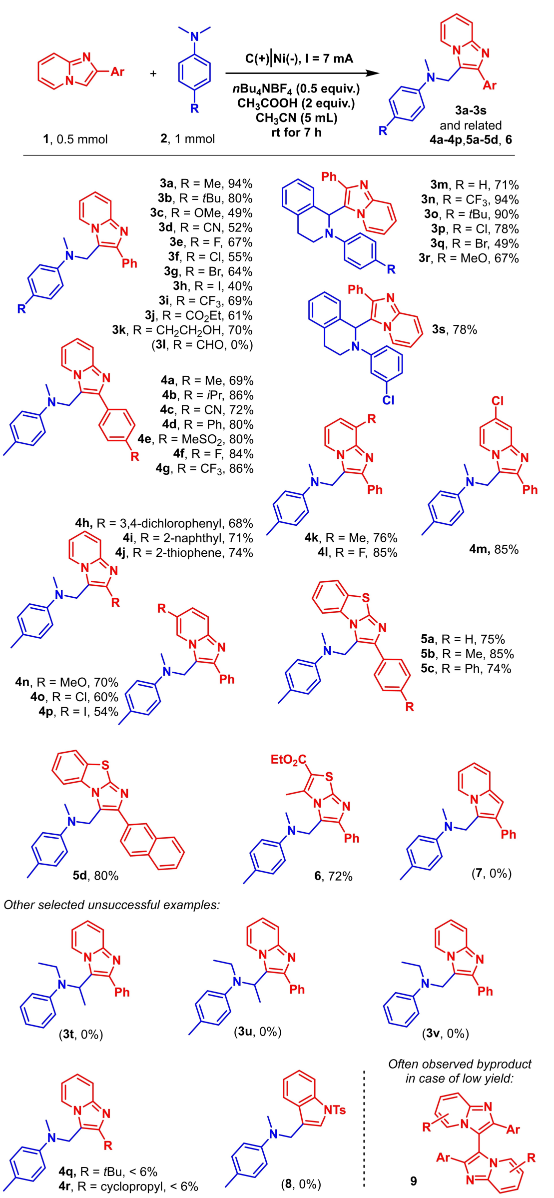
The variations in coupling efficiency depending on the *para* substituent of the aniline may relate to some extend to the fine differences expected upon aniline oxidation (see mechanistic investigations beneath). Importantly, halide substituents including fluoro, chloro, bromo and even iodo, were well tolerated to afford the corresponding products in promising to good yields (**3 e**–**3 h**). Impressively, an unprotected primary alcohol functional group was also found to be well tolerated (**3 k**). Unfortunately, however, a formyl group was not tolerated, as product **3 l** could not be observed (for other unsuccessful substrates, see the Supporting Information). Instead, aldehyde

Table 1. Optimization of reaction conditions.[a]



Entry	Variations from the optimal conditions	Yield [%]
1	**None**	**94 (94)**[b]
2	No current	0
3	No acid	27
4	MeOH as solvent[c]	0
5	HFIP as solvent[c]	0
6	nBu$_4$NPF$_6$ as electrolyte[c]	76
7	nBu$_4$NClO$_4$ as electrolyte[c]	81
8	nBu$_4$PBF$_4$ as electrolyte[c]	68
9	6 mA[c]	70
10	10 mA[c]	66
11	Ag as cathode	83
12	Mg as cathode	43

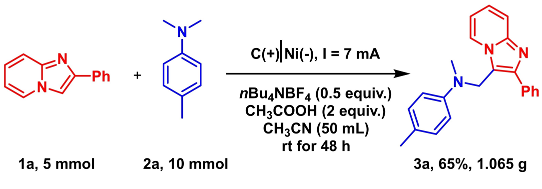
[a] Standard conditions: an undivided cell was utilized, anode: graphite: 52×8×2 mm, of which 20×8×2 mm immersed, cathode: nickel, same dimensions. The yields were determined by ^{1}H NMR analysis utilizing CH_2Br_2 as the internal standard (0.5 mmol) added at the end of the reaction. [b] Isolated yield of product in parentheses. [c] The reaction time is 8 h, 1 equiv. of electrolyte was used.



Scheme 3. Substrate scope, isolate yields. Reaction conditions: anode: graphite: 52×8 ×2 mm, of which 20×8 ×2 mm immersed, cathode: nickel, same dimensions. **1** (0.5 mmol), **2** (1 mmol), nBu$_4$NBF$_4$ (0.25 mmol), CH_3COOH (1 mmol), CH_3CN (5 mL), rt, 7 mA, 7 h.

starting material **2l** (4-(dimethylamino)benzaldehyde) was recovered in only 46% yield, indicating some oxidative decay. A *homo* coupling product of 2-phenylimidazo[1,2-a]pyridine was also found (**9**, 40%), which is well-known[41–44] and an often observed byproduct when the yield of expected *hetero* coupling is low. Some remaining unreacted 2-phenylimidazo[1,2-a]pyridine **1a** (24%) was also recovered. Next, we screened the reaction with various N-aryl tetrahydroisoquinolines. Thus, electron-donating, electron-withdrawing, and halogen substituents on the phenyl ring were found to afford the corresponding desired products in good to excellent yields (**3m**–**3s**). It should be noted that the scope of this reaction is otherwise limited to N,N-dimethylanilines. For example, N,N-diethylanilines, or an N-ethyl-N-methylaniline did not deliver any of the expected coupling products (**3t**–**3v**), and were recovered mostly unreacted, presumably due to steric factors. Also in these cases, some *homo* coupling product **9** could be identified, together with some unreacted starting materials. We then screened variously arylated imidazo[1,2-*a*]pyridines (**4a**–**4p**). There too, the substrate scope was found to be broad in terms of electron-donating or withdrawing groups (**4a**–**4h**). The substrates with 2-naphthyl and 2-thienyl groups on the imidazo[1,2-*a*]pyridines afforded the corresponding desired products **4i** and **4j** in 71% and 74% yield, respectively. Diverse imidazo[1,2-*a*]pyridine backbones were also successfully tested (54-85% yields, **4k**–**4p**). Surprisingly however, 2-tertbutyl-imidazo[1,2-a]pyridine and 2-cyclopropyl-imidazo[1,2-a]pyridine delivered only traces of the corresponding coupling products (**4q**–**4r**), together with some noted decomposition. Next, the method was tested on other imidazoheterocycles, such as benzo[*d*]imidazo[2,1-*b*]thiazole, thiazoimidazole and indolizine (Scheme 3). We observed that electron-neutral and electron-donating substrates afforded the corresponding desired products in good yields (**5a**–**5d**). Subsequently, the coupling product of a thiazoimidazole was obtained in 72% yield (**6**). Unfortunately, indolizine is not a competent substrate in this reaction (**7**), nor is N-tosyl-indole (**8**), whether at the C2 or C3 position.

To further explore the applicability of this method, we adapted the reaction conditions for a gram scale batch (Scheme 4). When 5 mmol of **1a** was applied under standard conditions, and the reaction was carried out under 7 mA constant current for 48 h because the electrode size was not enlarged for the large-scale reaction, thus requiring a longer reaction time, the desired product **3a** was obtained in 65% isolated yield.



Scheme 4. Gram-scale synthesis.

In order to collect some mechanistic insights, we then performed selected cyclic voltammetry (CV) experiments (Figure 1). Interestingly, substrates **1a** and **2a** have similar oxidation potentials in CH_3CN. However, on closer inspection, the addition of AcOH seems to slightly increase the oxidation potential of **1a**, while it slightly decreases that of **2a**. Thus, under optimized conditions, the initiation of the reaction through the oxidation of aniline **2a** seems plausible, even if early oxidation of substrate **1a** cannot be excluded.

Based on the above-mentioned results and literature reports,[15–19] a plausible mechanistic pathway is outlined in Scheme 5. First, one electron anodic oxidation of N,N,4-trimethylaniline **2a** would lead to the radical cation **I**. Next, the deprotonation of the radical cation would afford the tertiary α-amino carbon radical **II**, followed by further one electron oxidation to generate the iminium cation **III**. Consequently, electrophilic addition of the iminium cation to 2-phenylimidazo[1,2-*a*]pyridine **1a** would afford product **3a**, associated to another proton release from intermediate **IV**. Alternatively, a radical recombination scenario between the α-

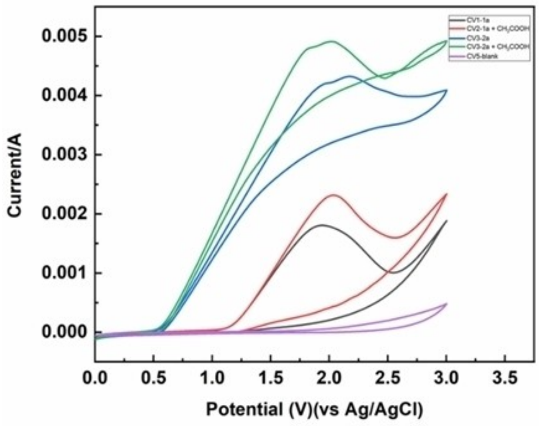
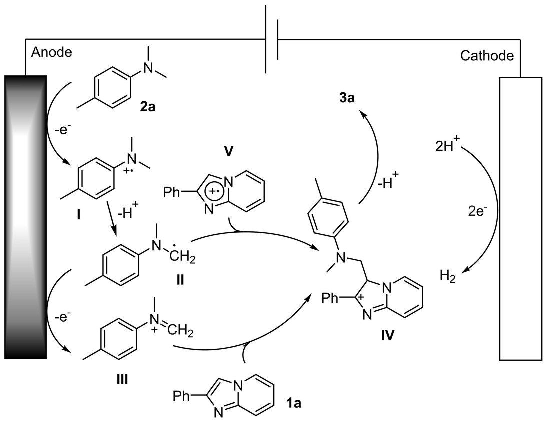


Figure 1. Cyclic voltammetry of **1a** and **2a** in 0.02 M nBu_4NBF_4 in MeCN, using Pt wire working electrode, Pt wire as counter electrode, and Ag/AgCl as reference electrode at 100 mV/s scan rate. Top green line (**2a** + AcOH), blue line (**2a**), red line (**1a** + AcOH), black line (**1a**), purple line (blank).



Scheme 5. Proposed mechanism.

amino carbon radical **II** and the radical cation **V** that would arise from **1 a** oxidation[41–44] would also be accommodated by the CV experiments (Figure 1).

Conclusion

In conclusion, we developed a new electro-chemical protocol for the oxidative C(sp^3)–H/C(sp^2)–H cross-coupling between imidazo[1,2-*a*]pyridines and N,N-dimethylanilines. This methodology is also suitable for related heterocycles such as benzo[*d*]imidazo[2,1-*b*]thiazole and thiazoimidazole. A wide variety of functional groups were found to be tolerated. This metal-free, facile and environmentally friendly method is moreover amenable to gram-scale. The present study should therefore have a lasting impact on the field of sustainable synthesis, in particular in the context of cross dehydrogenative couplings.

Experimental Section

General procedure: The imidazo[1,2-*a*]pyridines **1** (0.5 mmol, 1 equiv.), N,N-dimethyl-p-toluidine **2** (1 mmol, 2 equiv.), *n*Bu_4NBF_4 (0.25 mmol, 0.5 equiv.), CH_3COOH (1 mmol, 2 equiv.), CH_3CN (5 mL) are added into a reaction vial. Then the reaction vial is equipped with a graphite anode and nickel cathode (see Supporting Information for pictures). The current is set to 7 mA while stirring at room temperature for 7 h. The solvent is then removed under reduced pressure and the desired product is purified through silica gel chromatography.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: anodic oxidation · C–H aminomethylation · cross dehydrogenative coupling · electrochemical coupling · imidazopyridines

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