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Electrooxidative C(sp3)–H Amination of Azoles via Intermolecular Oxidative C(sp3)–H/N–H Cross-Coupling

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ABSTRACT: A method for electrooxidative C(sp3)-H amination via intermolecular oxidative C(sp3)-H/N-H cross-coupling has been developed under metal- and oxidant-free conditions. The C(sp3)-H bonds adjacent to oxygen, nitrogen and sulfur atom could all react smoothly with various amines to give corresponding products with moderate to good yields (30-93%). In addition, the C(sp3)-H bonds of benzylic and allylic are also tolerated in this reaction. A preliminary mechanistic study indicates that the C-H cleavage of tetrahydrofuran is probably not involved in the rate-determining step.

KEYWORDS: Electrooxidative, C(sp3)–H Amination, C(sp3)–H/N–H Cross-Coupling, dehydrogenation, External oxidant-free, Azoles

Nitrogen-containing compounds as an important class of compounds have been widely found in pharmaceutical agents, natural products and functional materials.¹ Consequently, seeking efficient strategies for the facile construction of carbon-nitrogen bonds has been one of the major research topics in synthetic chemistry.² Over the past few years, direct catalytic C-H amination as one of the most efficient, atom- and stepeconomical ways to construct C-N has gained more and more attention in this field.³ Although, great progress has been made in direct C(sp2)-H amination,⁴ the methods for direct C(sp3)-H amination⁵ were still rare and of great challenges due to the relatively inert properties of C(sp3)-H bonds. In recent years, our group and other groups have reported some methods for C(sp3)-H/N-H amination under transition-metal-catalyzed such as Cu,⁶ Ni,⁷ Fe⁸ and Ru⁹ etc. or metal-free conditions.¹⁰ Despite the advances achieved, some limitations still exist such as tedious work-up procedures, poor selectivity, harsh reaction conditions and the use of excess external oxidants.

In recent years, electrochemical oxidation¹¹ as a versatile and environmentally friendly synthetic method has been used as an alternative tool for construct new chemical bonds via direct C–H bond activation.¹² Recently, electrochemical oxidation direct C-H amination¹³ has been studied. However, there is no precedent for electrooxidative inert C(sp3)-H/N-H crosscoupling.

(a)
$$R-H + HN$$
 $\xrightarrow{\text{metal}}$ $\begin{bmatrix} M_{cat}, \\ H \end{bmatrix}$ $\xrightarrow{R-N}$ $+ H_2[O]$

(b)
$$R-H + HN$$
 $\xrightarrow{\text{oxidation}}_{e^- + H^+} \left[\cdot N \right] \longrightarrow R-N + H_2 \uparrow$

Scheme 1. Amine functionalization.

Although several approaches for construct C(sp3)-N by transition-metal-catalyzed have been achieved,⁶⁻⁹ there is still a common problem that metal catalysts are easily coordinated with amines (Scheme 1, a). As a result, the metal catalysts

Table 1. Optimization of the reaction conditions.^a



Entry	Variation from the standard conditions	Yield of		
		$3a(\%)^{\circ}$		
1	none	92		
2	2.5 h instead of 3 h	82		
3	LiClO ₄ instead of ⁿ Bu ₄ NBF ₄	77		
4	ⁿ Bu ₄ NPF ₆ instead of ⁿ Bu ₄ NBF ₄	83		
5	60 °C instead of 80 °C	74		
6	RT instead of 80 °C	49		
7	1 mL 2a instead of 2 mL	80		
8	lequiv. 2a instead of 2 mL	41		
9	0.2 mmol ⁿ Bu ₄ NBF ₄ instead of 2 mmol	92		
10	0.1 mmol ⁿ Bu ₄ NBF ₄ instead of 2 mmol	86		
11	air instead of N_2	79		
12	no electric current	n.d.		

^a Reaction conditions: Pt anode, Pt cathode, constant current = 12 mA, **1a** (0.3 mmol), **2a** (2.0 mL), ⁿBu₄NBF₄ (2 mmol), in 8.0 mL CH₃CN at 80 °C under N₂ for 3 h. ^b Yields shown are of isolated products. RT = room temperature. n.d. = not detected.





 a Reaction conditions: Pt anode, Pt cathode, constant current = 12 mA, 1 (0.3 mmol), **2a** (2.0 mL), nBu_4NBF_4 (0.2 mmol), in 8.0 mL CH₃CN at 80 o C under N₂ for 3 h. Yields shown are of isolated products. b 4 h. c 5 h.

deactivation that dramatically limit the scope of these reactions. However, electrochemical oxidation can provide convenient access to reactive radical species via single electron transfer and subsequent hydrogen transfer process on the surface of the electrode (Scheme 1, b).^{12g,13d,14} This provides a new choice for amine functionalization. Therefore, we envisioned the goal of construction of C(sp3)-N bond via electrochemical oxidation process could be achieved. Herein, we disclose a new strategy for the formation of C-N bond through electrooxidative dehydrogenative C(sp3)-H/N-H cross coupling under metal- and oxidant-free conditions.

We initially chose 1H-benzotriazole (1a) and tetrahydrofuran (2a) as the model substrates to test the reaction and selected data are listed in Table 1 and Table S1. To our delight, 1a and 2a reacted efficiently to afford the desired product (3a) in 92% yield by using a constant current of 12 mA in an undivided three-necked bottle, at 80 °C, for 3 h (Table 1, entry 1). Notably, 4a, which was produced in previous works,^{9, 10d, 10e} was not observed in our reaction. Encouraged by the excellent selectivity, we further optimized the reaction conditions. The yield of 3a reduced when the reaction time was 2.5 h (Table 1, entry 2). The influence of the electrolyte was also studied. When other electrolytes, such as LiCIO₄ and ⁿBu₄NPF₆ were used instead of ⁿBu₄NBF₄, the yield of desired product was reduced (Table 1, entries 3-4). Then the reaction temperature was studied and results showed that the yield of the target Table 3. Substrate scope of electrooxidative C(sp3)-H amination of 1H-benzotriazole with other C(sp3)-H sources.^a



^a Reaction conditions: Pt anode, Pt cathode, constant current = 12 mA, **1a** (0.3 mmol), **2** (10 equiv.), ⁿBu₄NBF₄ (0.2 mmol), in 10.0 mL CH₃CN at 80 °C under N₂ for 3 h. Yields shown are of isolated products. ^b **2v** (2 equiv.). ^c **2w** (6 equiv.), CH₃CN/CF₃CH₂OH = 8/2 mL.

product reduced when the temperature decreased to 60 $^{\circ}$ C or room temperature (Table 1, entries 5-6). However, a good yield of **3a** was still observed when equivalent of **2a** was used (Table 1, entries 7-8). Through an investigation of the amount of electrolyte we found that the yield of the target product didn't reduce even the amount of electrolyte decreased to 0.2 mmol (Table 1, entries 9-10). Notably, a 79% yield of **3a** was still observed under atmospheric conditions (Table 1, entry 11). No desired product could be obtained without an electric current in this reaction (Table 1, entry 12).

With the optimal reaction conditions established, reactions of various azoles (1) combined with tetrahydrofuran (2a) were explored and results are summarized in table 2. Initially, we tested the reactivity of substituted 1H-benzotriazole. In general, both electron-donating and electron-withdrawing substituents on the benzene ring of 1H-benzotriazole were well-tolerated in this reaction (Table 2, 3b-3e). 5-Phenyl-2H-tetrazole could also successfully react with THF to give the desired product in good yield (Table 2, 3f). For 4-phenyl-1H-1,2,3-triazole, reactions also proceeded smoothly with THF to deliver the desired products in good to excellent yields, in which p-OMe (3h) and p-Cl (3i) groups on the benzene ring of 4-phenyl-1H-1,2,3triazole could be well tolerated. 3-Phenyl-1H-pyrazoles were also suitable substrates, although longer reaction time (4-5 h) was required to give good yields (Table 2, 3j-3l). Notably, 3,5diphenyl-1H-pyrazole (Table 2, 3m) proved to be good substrates under the current conditions. In addition, a 73% yield was obtained by employing 1H-indazole as the reactant (Table 2, **3n**).

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Scheme 2. Gram scale synthesis.

(a) Radical-trapping experiment



(b) KIE Determined with Two Parallel Reactions



(c) Intermolecular Kinetic Isotopic Effect (KIE)

1a	+	2a +	2a ^l -	as above	-	3a	÷	3a ^l
		1 mL	1 mL	<i>K_H/K_D</i> = 1.22		27%		6

Scheme 3. Additional experiments.

Furthermore, we examined the scope of functionalized ether substrates and other C(sp3)-H sources 2 using 1a as the coupling partner and the results are listed in table 3. Initially, functionalized ether substrates such as tetrahydropyran, isochroman and butyl ether were employed to react with 1Hbenzotriazole under standard conditions. Although the amount of ethers was reduced to 10 equiv., the corresponding products were obtained in moderate to excellent yields (Table 3, **30-3q**). Then other C(sp3)-H sources were examined in this reaction. To our delight, N-Methyl pyrrolidone showed a high reactivity and 3r as the only product was obtained in 85% yield. Furthermore, the C(sp3)-H bonds adjacent to sulfur could also be reacted with 1H-benzotriazole smoothly (Table 3, 3s). Delightfully, 1,4-thioxane reacted smoothly with 1H-benzotriazole to give the 3t as the only product. Notably, N-formylmorpholine could also react with the 1H-benzotriazole to form the target products (Table 3, 3u) in good yields but with poor selectivity. It is noteworthy to emphasize that the benzylic C(sp3)-H and allylic C(sp3)-H bonds could be also tolerated in this reaction give the corresponding products in moderate yields (Table 3, **3v** and **3w**).

Notably, when this reaction run on gram scale, the desired product 3a could still be obtained in 64% yield, highlighting the potential application of this method (Scheme 2).

In order to elucidate the reaction mechanism, some additional experiments were carried out. First, the cyclic voltammetry (CV) experiments on both reactants have been carried out and showed that the oxidation peaks of 1a and 2a in acetonitrile were 2.00 V and 2.54 V (Figure S1.)¹⁵ respectively. Since the operating voltage ranged from 1.90 to 2.23 V, only 1a was possible oxidated under the standard conditions. Second. radical-trapping experiment was conducted to clarify whether this reaction involved radical process (Scheme 3, a). When, 2 equiv. of TEMPO (2, 2, 6, 6-tetramethyl-1piperidinyloxy) or BHT (2,4-di-tert-butyl-4-methylphenol) was added into the reaction system, the desired product **3a** was totally suppressed. Additionally, 5a was observed in 76% vield. These mechanistic observations implicated that this reaction probably proceeds by a radical pathway. Then the kinetic isotopic effect (KIE) was studied. When two parallel reactions were carried out with tetrahydrofuran and d8tetrahydrofuran as the substrates respectively to determine the kinetic isotopic effect, a kH/kD = 1.07 was obtained (Scheme 3, b). We further did an intermolecular competitive reaction of tetrahydrofuran and d_8 -tetrahydrofuran with **1a** and a KIE value of kH/kD = 1.22 was observed (Scheme 3, c)¹⁶. These results suggest that the C-H cleavage of tetrahydrofuran was probably not involved in the rate-determining step. Last but not least, H₂ gas bubbles were clearly observed and detected by GC at cathode in the scare-up reaction.

On the basis of the above results and literature reports, 12g,13d,14 a tentative mechanism was proposed as shown in scheme S1¹⁷. First, nitrogen radical **A** was formed by the anode oxidant through single electron transfer and subsequent hydrogen transfer process. Then nitrogen radical **A** reacts with **2a** to afford the cross-coupling product **3a**. Meanwhile, cathodic reduction of proton-hydrogen leads to the formation of hydrogen gas.

In conclusion, we have developed a simple and efficient method for electrooxidative C(sp3)–H amination of azoles via intermolecular oxidative C(sp3)–H/N–H cross-coupling under metal- and oxidant-free conditions. The C(sp3)-H bonds adjacent to oxygen, nitrogen and sulfur atom can all react smoothly with various amines to give corresponding products with moderate to good yields (30-93%). In addition, the C(sp3)-H bonds of benzylic and allylic are also tolerated in this reaction. Notably, this reaction can be run on gram scale, giving the desired product in 64% yield. The reaction features mild reaction conditions, wide range of substrates, good to excellent yields and an easy work-up procedure, which demonstrate the potential application of this protocol in synthetic chemistry. Detailed mechanistic studies of this methodology are currently ongoing in our laboratory.

ASSOCIATED CONTENT

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

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The authors declare no competing financial interest.

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(15) For a comprehensive description of the cyclic voltammetry (CV) experiments please refer to the Supporting Information.

(16) The detailed description of the kinetic isotopic effect (KIE) experiments are provided in the Supporting Information.

(17) The mechanism of this reaction is shown in the Supporting Information.

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