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Decarboxylative C_{sp^3}−N Bond Formation by Electrochemical Oxidation of Amino Acids

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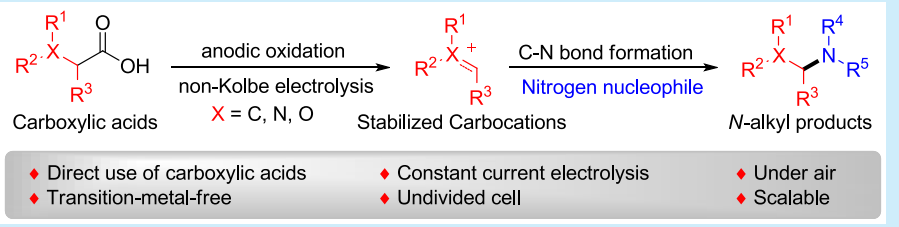
Supporting Information



ABSTRACT: Decarboxylative C_{sp^3}−N coupling reactions have been developed through electrochemical oxidation of amino acids. The reaction proceeds via anodic oxidative decarboxylation of carboxylic acids to form stabilized carbocations, which are trapped by azoles or amides to construct C−N bonds. This method avoids the preactivation of carboxylic acids and the use of expensive transition-metals and external chemical oxidants.

Carbon-nitrogen bond formation is one of the most important transformations in organic chemistry owing to the prevalence of nitrogen-containing motifs in natural products, pharmaceuticals, agrochemicals, and functional materials.[1] Transition-metal-catalyzed C_{sp^2}−N coupling procedures with prefunctionalized reagents, such as C−halide and C−metal have been developed as a powerful tool to construct C−N bonds, under basic or oxidative conditions.[2] Among them, Buchwald−Hartwig coupling,[3] Ullmann-type reactions,[4] and Chan−Lam oxidative amination[5] are notable methods for C_{sp^2}−N cross-couplings. However, broad-scope C_{sp^3}−N cross-couplings are very scarce, and classical methods, such as nucleophilic substitution with alkyl halides,[6] reductive amination with carbonyls,[7] Curtius rearrangement,[8] and Mitsunobu reaction with alcohols,[9] are still commonly used for C_{sp^3}−N bond formation. Therefore, new methods and strategies for efficient C_{sp^3}−N bond formation with easily available starting materials under mild conditions are greatly demanded. For example, the recent development of cross dehydrogenative couplings of N−H and C_{sp^3}−H bonds[10] and transition-metal-catalyzed alkylation of nitrogen nucleophiles with aliphatic halides[11] have attracted much attentions.

Due to the characteristics of carboxylic acids, including great availability, high stability, low-cost, and nontoxic nature, this class of compounds is one ideal reactant for organic synthesis. Decarboxylative reactions have been demonstrated to be applicable to the formation of C−C and C−X bonds.[12] Although several precedents of decarboxylative C_{sp^3}−N couplings have been reported, they are limited to special substrates or intramolecular reactions.[13] Very recently, the decarboxylative C−N cross-coupling was reported by Fu,[14] Hu,[15] and Macmillan[16] via photoredox and copper catalysis (Scheme 1A). In these processes, alkyl carboxylic acids were first converted into the corresponding redox active esters, *N*-hydroxyphthalimide (NHPI) esters or iodomesitylene dicarboxylates (IMDC), thus enabling CO_2 extrusion in the presence of a photocatalyst to generate the required alkyl radicals for copper-catalyzed C−N cross-coupling. Despite the ground-breaking nature of these transformations, the preactivation of carboxylic acids is still necessary for the decarboxylation event.

The direct use of carboxylic acids as reactants would be ideal for a broad-scope C−N cross-coupling. Carboxylic acids can be decarboxylated by anodic oxidation to radicals,[17] which normally undergo addition to double bonds or can combine to form symmetrical dimers in the Kolbe electrolysis.[18] Radical intermediates formed under Kolbe conditions can be further oxidized to generate the corresponding carbocations, in a process referred to as non-Kolbe electrolysis or Hofer−Moest reaction (Scheme 1B).[19] Recently, the group of Baran applied

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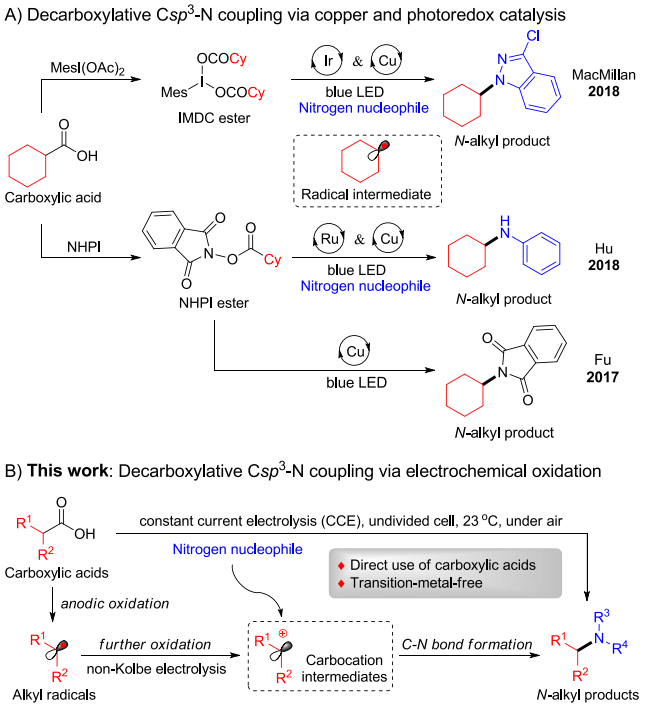
Scheme 1. Decarboxylative C−N Cross-Couplings

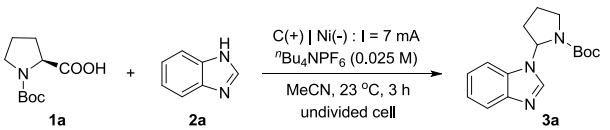


these electrogenerated carbocations to synthesize hindered dialkyl ethers from carboxylic acids, demonstrating the power of electrochemical decarboxylation for C−O bond formation.[20] In contrast, although intramolecular C−N bond coupling by electrochemical decarboxylation is known,[21] intermolecular reactions are restricted to solvolysis with MeCN[18] or *N*-formylation of amines via decarboxylation of glyoxylic acid.[22] We envisioned that the C−N coupling could take place if the appropriate nitrogen nucleophiles would trap the carbocations generated by anodic oxidative decarboxylation (Scheme 1B). This anticipated C−N bond formation by electrochemical method would exhibit several advantages: 1) no need to preactivate carboxylic acids; 2) transition-metal- and expensive photocatalyst-free; 3) no external oxidant. However, the carbocations generated at the anode are usually very reactive species, referred to as "hot carbocations",[18] and easily undergo reactions with mild nucleophilic solvents (e.g., MeCN, MeOH, etc.), rearrangement, or elimination to form alkenes. Accordingly, in order to facilitate the formation of C−N bonds, the carbocation intermediates should be sufficiently long-lived to undergo disengagement from the electrode surface, therefore allowing the effective molecular collision with nitrogen nucleophile. For example, neighboring heteroatoms, such as N and O, are expected to stabilize the carbocations generated by electrochemical oxidation[23] of abundant biomass resources, such as α-amino acids and α-hydroxy acids.[24] Therefore, this efficient electrochemical decarboxylative C−N cross-coupling could enable the direct conversion of inexpensive α-amino acids into complex and medicinally relevant pharmacophores under mild and green conditions. We report herein the successful transition-metal-free decarboxylative C_{sp^3}−N cross-coupling via electrochemical oxidation of amino acids with a broad-range of *N*-nucleophiles.

In order to efficiently trap the relatively stable iminium cations generated by anodic oxidation of amino acids, *N*-based nucleophiles should be reactive enough and, at the same time, should display good stabilities under electrolysis. Since azoles are important moieties in organic chemistry[25] and normally serve as good nucleophiles,[26] we decided to start our study with azoles to construct C−N bonds by electrochemical decarboxylation.

The optimization of the reaction conditions for the decarboxylative C−N bond coupling was performed using Boc-L-proline (**1a**) as the carboxylic acid and benzimidazole (**2a**) as the nucleophile (Table 1). The best results were

Table 1. Optimization of Reaction Conditions[a]



entry	deviation from standard conditions	yield (%)[b]
1	none	99
2	reaction time: 2 h	85
3	^{n}Bu$_4$NBF$_4$ as supporting electrolyte	82
4	LiClO$_4$ as supporting electrolyte	65
5	^{n}Bu$_4$NClO$_4$ as supporting electrolyte	20
6	^{n}Bu$_4$NI as supporting electrolyte	-
7	graphite as cathode	24
8	no electricity	-

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (0.3 mmol), ^{n}Bu$_4$NPF$_6$ (0.025 M), 8 mL of MeCN, 23 °C, under air. [b]Yield determined by ^{1}H NMR analysis of the crude reaction mixture using (*E*)-1,2-diphenylethene as an internal standard.

obtained by conducting the electrolysis for 3 h under a constant current of 7 mA in an undivided cell equipped with a graphite anode and a nickel cathode at room temperature in acetonitrile. Under these conditions, the C−N coupled product **3a** was obtained in almost quantitative yield (Table 1, entry 1). Shortening the reaction time and replacing supporting electrolyte or electrode led to lower yields (Table 1, entries 2−7). A control experiment showed that electricity is crucial for the success of the desired reaction (Table 1, entry 8).

With the optimized conditions established to obtain product **3a**, the scope of the reaction was then explored by first varying the carboxylic acids (Scheme 2). Commercially available cyclic *N*-protected α-amino acids, such as proline, azetidinecarboxylic acid, and six-membered α-amino acids reacted well with benzimidazole (**2a**) to give the desired C−N coupled products (**3a**−**3e**) in good yields. Similarly, acyclic amino acid derivatives, including alanine (**3f**, **3m**), valine (**3g**), leucine (**3h**), phenylalanine (**3i**, **3n**), lysine (**3j**), methionine (**3k**), and glycine (**3l**), were all found to be suitable substrates for decarboxylation, leading to products with a free N−H bond during electrolysis. Moreover, dipeptide derivative (Gly-Pro) also underwent decarboxylative C−N bond formation with benzimidazole to provide **3s** in 50% yield. In addition, tetrahydrofuroic acid, 4-methoxyphenylacetic acid, and 2,2-diphenylacetic acid were successfully applied in this reaction, affording **3o**, **3p**, and **3q**, respectively, although with lower yields. Furthermore, γ-lactam moiety was also tolerated in the formation of product **3r**.

We next tested a variety of *N*-based nucleophiles (Scheme 2). Pyrazole, 1,2,3- and 1,2,4-triazole, benzotriazole, and tetrazole derivatives were found to be efficient nucleophiles

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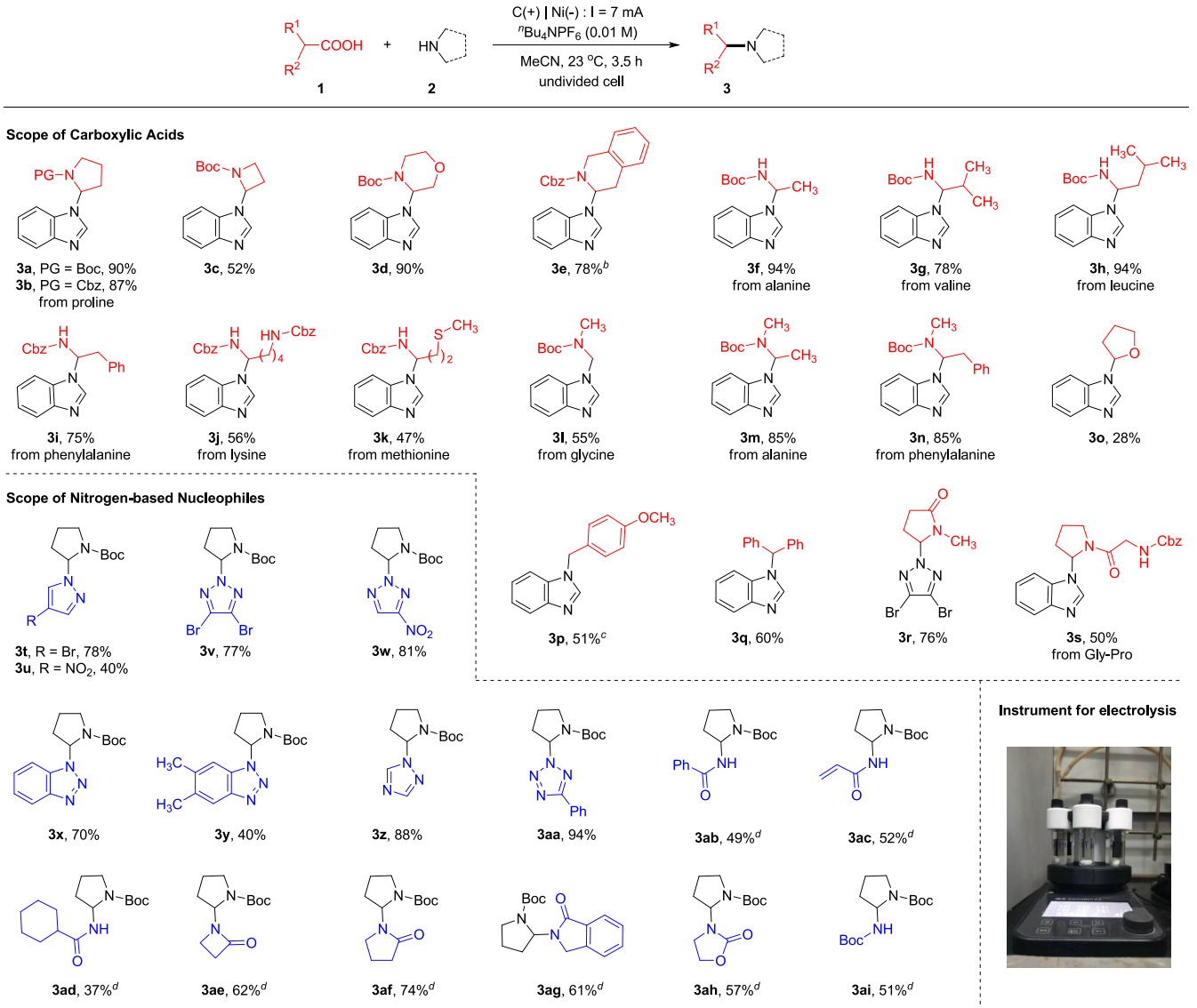
Scheme 2. Scope of Decarboxylative C−N Bond Formation by Electrochemical Oxidation[a]

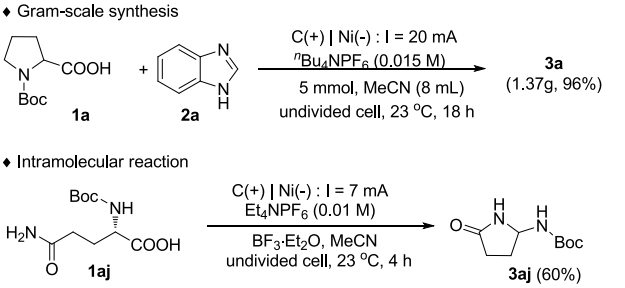


[a]Reaction conditions: **1** (0.5 mmol), **2** (0.3 mmol), $^{n}Bu_4NPF_6$ (0.01 M), 8 mL of MeCN, 23 °C, under air, constant current (7 mA), 3.5 h. Isolated yields after column chromatography. [b]The reaction was performed in MeCN/DMSO = 8 mL/0.2 mL. [c]2,6-Lutidine (0.26 mmol) was added, and the reaction was performed for 4 h. [d]Et_4NPF_6 (0.01 M), $BF_3{\cdot}OEt_2$ (0.02 mmol), 8 mL of MeCN, 23 °C.

to trap the iminium cation generated by decarboxylation of Boc-L-proline (**1a**) to give products **3t**−**3aa** in good yields with excellent regioselectivities, which were determined by NMR analysis. Further studies revealed that, under slightly modified conditions, primary amides as well as *β*- and *γ*-lactams and oxazolidin-2-one can also be used as the *N*-based nucleophiles to form the desired C−N coupled products **3ab**−**3ai** in moderate to good yields.

Importantly, the reaction is scalable (Scheme 3). For example, the desired product **3a** can be produced in excellent yield (96%, 1.37 g) under high concentration conditions (5 mmol, 8 mL MeCN). 5-Amino-2-pyrrolidinones would be expected to have pharmacological activities and previously require multistep synthesis.[27] By electrolysis, the intramolecular reaction of Boc-L-glutamine (**1aj**) was also successful to give the cyclized product **3aj** in 60% yield (Scheme 3).

Scheme 3. Gram-Scale Synthesis and Intramolecular Reaction



In order to understand the oxidation/reduction potentials for the substrates, cyclic voltammetry (CV) experiments were carried out with Boc-L-proline (**1a**) and benzimidazole (**2a**) in acetonitrile (Figure 1). For benzimidazole (**2a**), no obvious oxidation peak was observed.[28] Boc-L-proline (**1a**) showed an

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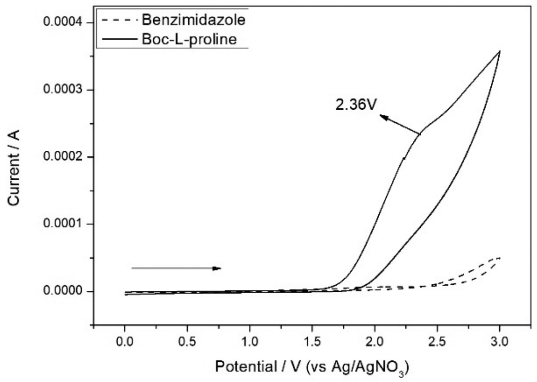
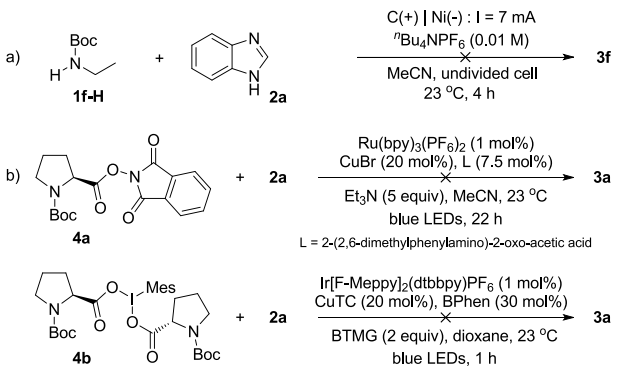


Figure 1. CV of Boc-L-proline (**1a**) and benzimidazole (**2a**). Cyclic voltammograms recorded in 0.01 M $^{n}Bu_4NPF_6$-MeCN solution: scan rate, 50 mV s^{-1}; starting potential, 0 V; glass carbon (3 mm diameter, Working Electrode); platinum plate (Counter Electrode); $Ag/AgNO_3$ (0.01 M $AgNO_3$in MeCN, Reference Electrode). Concentrations: benzimidazole (0.06 mmol, 8 mL MeCN) and Boc-L-proline (0.1 mmol, 8 mL MeCN).

oxidative potential around 2.36 V in its CV. These results and the literature[20,23] indicate that carboxylic acids most likely undergo oxidation to their respective cations at the anode in our electrochemical reactions. To further confirm that the reactive intermediates are generated at the anode, we performed control experiments using H-type divided cell separated by an AMI-7001 membrane, expecting that the final product would be obtained in the anodic chamber.[28] The reactions were conducted under the standard conditions, and both the divided anodic chamber and cathodic chamber contained the same solution, including substrates, solvent, and supporting electrolyte. Indeed, in the case of Boc-L-proline (**1a**) and benzimidazole (**2a**), the desired product **3a** was exclusively produced in the anodic chamber. Compound **3a** was obtained in 12% yield in this experiment due to the lower efficiency of the electrolysis in the divided cell.

In addition, although electrochemical oxidation on cyclic amine derivatives can also generate iminium cations,[23] this process does not compete under our reaction conditions as shown, for example, in the successful formation of tetrahydroisoquinoline derivative **3e**, which bears a potentially oxidizable benzylic amine (Scheme 2). Moreover, when Boc-ethylamine (**1f-H**) was used instead of Boc-alanine (**1f**), product **3f** was not detected at all (Scheme 4a). Furthermore,

Scheme 4. Control Experiments: (a) Decarboxylation vs Dehydrogenation and (b) Comparison Experiments with Photoredox Catalysis



in order to compare our results with those obtained under photoredox catalysis, two redox active esters of Boc-L-proline, **4a** and **4b**, were synthesized and subjected to the reported photoredox conditions[15,16] with benzimidazole (**2a**) as the *N*-nucleophile (Scheme 4b). However, no desired product **3a** was detected.[28] These results show that our decarboxylative C−N coupling reaction via electrochemical oxidation is a complementary method to photoredox catalysis, especially in the case of α-amino acids as the substrates.

In summary, we have achieved the decarboxylative C_{sp^3}−N coupling by electrochemical oxidation with readily available α-amino acids as substrates and a wide variety of azoles and carboxamides as the *N*-nucleophiles. In this protocol, carboxylic acids are directly used without any preactivation under transition-metal- and external-oxidant-free conditions. We expect that this efficient C−N bond formation reaction that proceeds under green conditions will find wide applications in organic synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03696.

Data and spectral copies of ^{1}H, ^{13}C NMR, and HRMS for starting materials and target compounds (PDF)

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Notes

The authors declare no competing financial interest.

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