Letter

Electrochemical Oxidation Induced Site-Selective Intramolecular C(sp3)-H Amination

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Electrochemical Oxidation Induced Site-Selective Intramolecular C(sp^3)-H Amination

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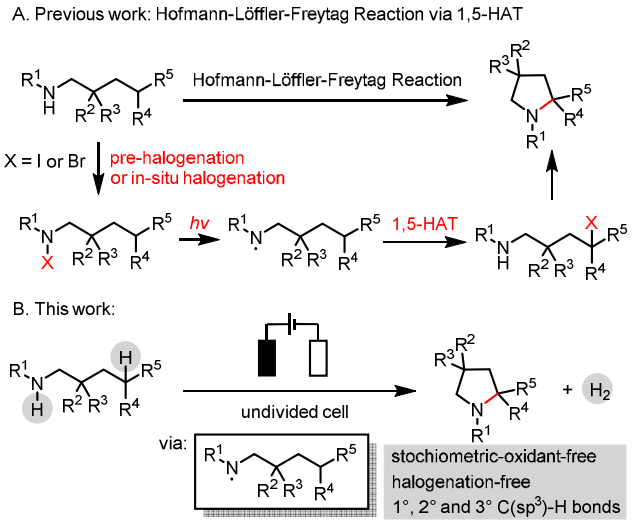
Dedicated to Professor Xiyan Lu on the occasion of his 90th birthday

ABSTRACT: The cross-coupling of C(sp^3)-H and N-H represents one of the most straightforward approaches to construct saturated nitrogen-containing compounds. The additional oxidants or halogenated reagents are generally required in such processes. Herein, we developed an electrochemical oxidative intramolecular C(sp^3)-H bonds amination of amides by employing carbon rod anode, platinum plate cathode in an undivided cell under contant-current electrolysis conditions. Tetrabutylammonium acetate was not only employed as an electrolyte, but also can form the intermolecular hydrogen bond with amide and promote the cleavege of N-H bond. The additional oxidants and *N*-halogenation step can be obviated in this methodology. A variety of benzylic and non-activated tertiary, secondary, primary C(sp^3)-H amination can be achieved with good yields.

KEYWORDS electrosynthesis, oxidative coupling, amination, radical, annulation, heterocyles

The direct C(sp^3)-H functionalization represents a powerful and straightforward protocol for constructing carbon-carbon or carbon-heteroatom bonds.[1] In particular, the selective C(sp^3)-H amination enables the efficient synthesis of saturated nitrogen-containing heterocycles,[2] which are important structural motifs in various biologically active compounds.[3] Due to the high C-H bond-energy, chemo- and regio-selectivity of non-activated C(sp^3)-H functionalization are significantly challenging.[4] After years of efforts, the great achievement has been made in transition-metal-catalyzed C(sp^3)-H amination with the assistance of directing groups.[5]

Besides, radical C-H activation provides another complementary approach to enable remote C(sp^3)-H amination.[6] A well-known process is the Hofmann–Löffler–Freytag (HLF) reaction, which converts *N*-haloamines into pyrrolidines through 1,5-hydrogen-atom-trasfer (HAT) process (Scheme 1A).[7] Unlike transition-metal-catalyzed C-H amination reactions, the additional steps for the installation and removal of directing group can be avoided. A significant breakthrough in the modification of HLF reaction has been discovered by Suarez and co-workers.[8] The preparation of *N*-haloamines can be avoided. Because the harsh reaction conditions are required for the generation of *N*-centered radical, seeking for more mild strategy for producing radicals would be very meaningful.[9] Since the iodine and the *in-situ* generated acetyl hypoiodite (such as AcOI) would lead to undesired oxidations of weaker C- H bonds[9a], decreasing the reaction concentration of iodine can be regarded as a good way to expand the substrate applicability and solve the chemoselectivity issues. Recently, Muñiz,[9e, 10] Nagib[9a] and Herrera[11] have achieved the iodide catalyzed δ C-H amination. According to these great progress, the directly breaking the N–H bonds to generate *N*-centered radical would provide a more desirable strategy to achieve HLF reactions under halogenated reagent-free conditions. Traditional methods for the generation of *N*-centered radical are harsh and mostly through the cleavage of N-X bonds (X = oxygen, nitrogen or halogen atom).[12] Despite the photoredox catalyzed proton-coupled electron transfer process has been proven as a powerful pathway to offer the amidyl radical from amides,[13] the HLF reaction through directly breaking the N-H bond pathway remains undeveloped.

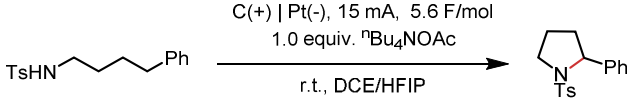


Scheme 1. Hofmann–Löffler–Freytag reactions for the formation of pyrrolidines.

We speculated that the electrochemical oxidation can achieve this goal. Over the past decades, electrochemical oxidation offers a mild and efficient strategy for the external oxidant-free dehydrogenative cross-coupling reactions.[14] In electrochemical dehydrogenative cross-coupling reactions, the protons releasing from the substrates can be *in-situ* reduced on the cathode to form H_2. Particularly, anodic oxidation can provide a convenient approach to generate *N*-centered radicals by cleavage the strong nitrogen–hydrogen (N-H) bonds of amines and amides.[15] Several advances on the C-N bonds cyclization reactions have been achieved through the radical addition of

N-centered radical to unsaturated bonds.[16] By using stoichiometric amount of halogen anion as a mediator, an electro-oxidative intramolecular C(sp^3)-H amination reaction has been reported.[17] Herein, we reported an electrochemical oxidation induced Hofmann–Löffler–Freytag reaction that can achieve the remote C(sp^3)-H amination of amides without the use of halogenated reagents under very mild conditions (Scheme 1B).[18] Not only benzylic, but the non-activated tertiary, secondary, primary C(sp^3)-H bonds were also compatible in the reaction system. The metal catalyst, halogenated reagents and stoichiometric additional oxidants were not required in this procedure.

Table 1. Optimization of the reaction conditions.[a]



1aa **2aa**

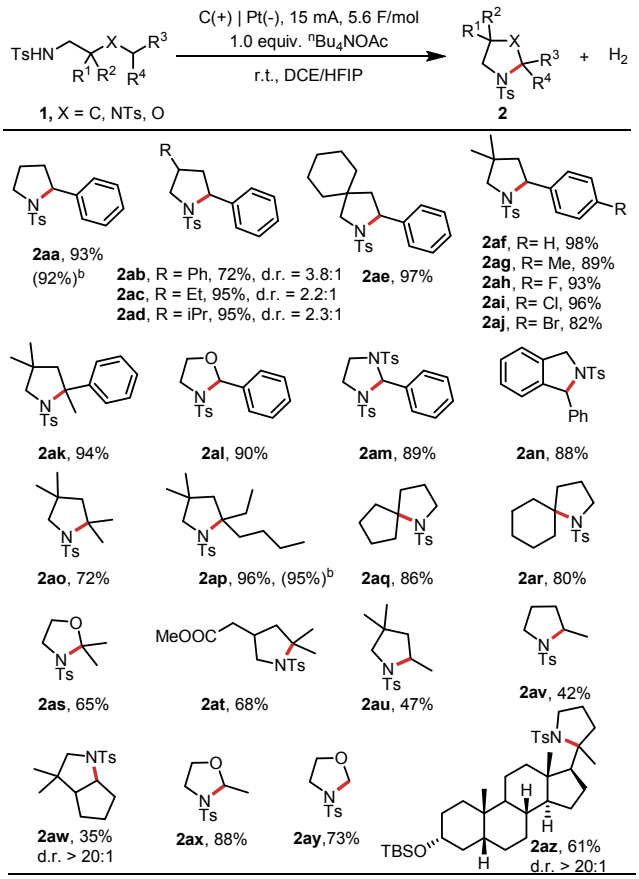
Entry	Variation form standard conditions	**2aa** (%)[b]
1	Standard conditions	96 (93[c])
2	Without current	n.d.
3	Pt(+) | Pt(-) instead of C(+) | Pt(-)	30
4	0.5 equiv. ^{n}Bu$_4$NOAc	86
5	MeCN/HFIP= 8mL/4mL as solvent	69
6[d]	NaOAc instesd of ^{n}Bu$_4$NOAc	85
7	^{n}Bu$_4$NBF$_4$ or ^{n}Bu$_4$NPF$_6$ instead of ^{n}Bu$_4$NOAc	n.d.

[a]Reaction conditions: carbon rod anode (Φ 6mm), platinum plate cathode (15 mm* 15 mm* 0.3 mm), constant current = 15 mA, **1aa** (0.40 mmol), ^{n}Bu$_4$NOAc (0.40 mmol), solvent (DCE/HFIP= 8 mL/4 mL),undivided cell, N_2, 5.6 mol/F. [b]Yields of **2aa** were determined by GC analysis by using biphenyl as the internal standard. [c]Isolated yield was shown in the parentheses. [d]Adding 1.0 equiv. ^{n}Bu$_4$NBF$_4$ as electrolyte. n.d. = no determined.

We began the investigation of electro-oxidative intramolecular C(sp^3)-H amination reaction (Table 1) by contant-current electrolysis of *N*-tosyl-4-phenylbutan-1-amine (**1aa**). To our delight, the formation of pyrrolidine **2aa** was observed by using a carbon rod anode and a platinum plate cathode in an undivided cell containing an electrolyte solution of ^{n}Bu$_4$NOAc in the DCE and HFIP (2:1). Under the conditions, 96% GC yield and 93% isolated yield of product can be obtained at room temperature (Table 1, Entry 1). As expected, no conversion can be observed without current (Table 1, Entry 2). In comparison, when a Pt anode was used instead of carbon rod, the significant decline of yield was obtained (Table 1, Entry 3). Decreasing the loading of ^{n}Bu$_4$NOAc into 0.5 equivalent, provided a reduced yield (85%, Table 1, Entry 4). When the MeCN/HFIP (2:1) was used as solvent, the transformation can also proceed in 69% yield (Table 1, Entry 5). Using NaOAc instead of ^{n}Bu$_4$NOAc, 85% yield of pyrrolidine can be formed (Table 1, Entry 6). However, change the eletrolyte into ^{n}Bu$_4$BF$_4$ or ^{n}Bu$_4$NPF$_6$, no reaction can be observed (Table 1, Entry 7). We proposed that ^{n}Bu$_4$NOAc was not only act as an electrolyte, but also as a base.

With the optimized conditions in hand, we investigated the substrate scope of this transformation (Table 2). Various 2-arylpyrrolidines can be synthesized in good to excellent yields. The different mono- or di-substitution on the beta-position of the sulfonamide can be well tolerated (**2ab-2af**, 72%-98%), which demonstrated a little influence of a possible gem-dimethyl effect. Several substituents in the para-position of the aryl group were compatible in the electro-chemical system (**2ag-2aj**). The tertiary benzylic C-H amination can also be achieved by using this transformation (**2ak**, 94%). To our delight, the oxygen atoms and nitrogen atoms adjacent to the benzylic C-H bond can participate well in the reaction to give oxazolidine and imidazolidine derivatives (**2al** and **2am**), respectively. The substrate with a phenyl backbone provided the corresponding isoindoline derivative with an excellent yield under the constant current electrolysis conditions (**2an**, 88%).

Table 2. Scope of the electrochemical oxidation induced site-selective intramolecular C(sp^3)-H amination.[a]

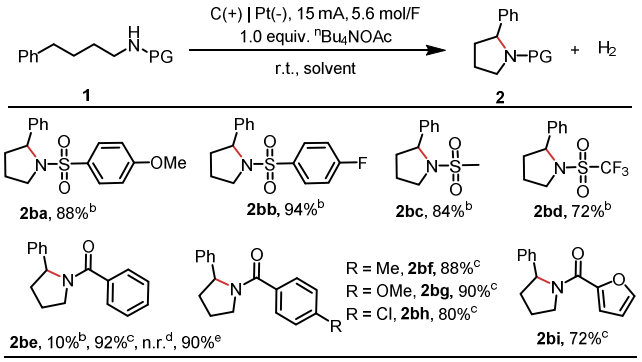


[a]Reaction conditions: carbon rod anode (Φ 6mm), platinum plate cathode (15 mm*15 mm*0.3 mm), constant current = 15 mA, **1** (0.40 mmol), ^{n}Bu$_4$NOAc (0.40 mmol), solvent (DCE/HFIP = 8 mL/4 mL), undivided cell, N_2, 5.6 F/mol. Isolated yields were shown. The d.r. values were determined by ^{1}H NMR. [b]5 mmol scale, DCE/HFIP= 50 mL/25 mL, 48 h.

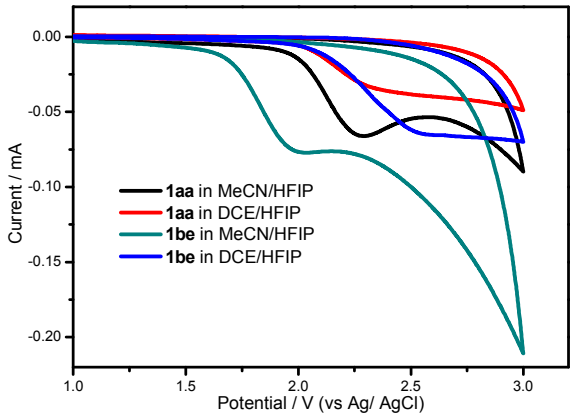
It is worth noting that the involvement of the benzylic position is not necessary for the transformation. The reaction is also applicable to the δ-selective C-H amination of non-activated C-H bonds (**2ao-2az**). The amination of dimethyl substituted inert tertiary C-H bond would react efficiently to give the corresponding product (**2ao**, 72%). Variation of the steric environment around the inert C-H bond had effect on the outcome of the reaction, the **2ap** was obtained in excellent yield. Related substrates, wherein the non-activated C-H bonds from carbocycles of various sizes, also reacted efficiently to form spiro compounds **2aq** and **2ar**.α-Oxy tertiary C-H bond was reactive for amination, as shown by the formation of oxazolidine product **2as**. A pregabalin deriveative were also viable in this reaction, as demonstrated by the generation of **2at**. This strategy is not limited to the amination of tertiary C(sp^3)-H bonds, secondary and primary C(sp^3)-H bonds could also be tolerated (**2au-2ay**). Significantly increased yields are

observed when the secondary or primary C-H bond adjacent to oxygen atoms (**2ax**, **2ay**). Additionally, a steroid-derived *p*-toluenesulfonamide **1az** that contain several distinct tertary C-H bonds and the activated C-H bonds adjacent to heteroatoms can also be selectively functionalized at the single position to provide the pyrrolidine derivatives (**2az**, 61%).

Table 3. Scope of *N*-protecting group.[a]

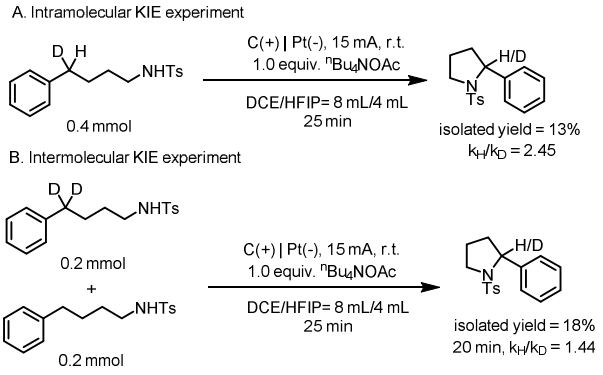


[a]Reaction conditions: carbon rod anode(Φ 6mm), platinum plate cathode (15 mm*15 mm*0.3 mm), constant current = 15 mA, **1** (0.40 mmol), $^{n}Bu_4NOAc$ (0.40 mmol), undivided cell, N_2, 5.6 F/mol. Isolated yields were shown. [b]DCE/ HFIP (8 mL/4 mL), [c]CH_3CN/HFIP (8 mL/4 mL). [d]Shono's system: platinum plate anode, platinum plate cathode, constant current (100 mA/cm^2), KBr (0.5 equiv.), NaOMe (0.5 equiv.), methanol, reflux; n. r.= no reaction. [e]5 mmol scale, DCE/HFIP= 50 mL/25 mL, 48 h.



Scheme 2. Cyclic voltammetry of 1aa and 1be in MeCN/HFIP= 2/1 or DCE/HFIP = 2/1.

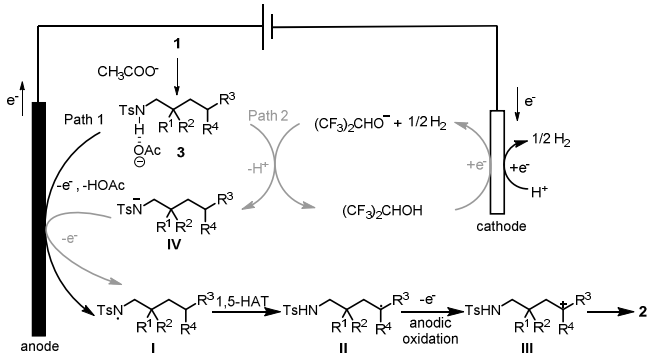
Besides the tosylated substrate, other sulfonyl groups such as (4-methoxyphenyl)sulfonyl (**2ba**), (4-fluorophenyl)sulfonyl (**2bb**), methanesulfonyl (**2bc**), and trifluoromethanesulfonyl (**2bd**) are well tolerated (Table 3). However, the *N*-(4-phenylbutyl)benzamide would obtained the desired products in only 10% yield under above reaction conditions. And this result might be attributed to that the *N*-(4-phenylbutyl)benzamide ($E_{1/2}$ = 2.30 V vs Ag/AgCl) is more difficult to be oxidized than *N*-tosyl-4-phenylbutan-1-amine ($E_{1/2}$ = 2.13 V vs Ag/AgCl) in a mixed solvent of DCE/HFIP(2:1). At the same time, we found that the adoption of a mixed solvent of MeCN/HFIP (2:1) lowered the oxidation potential of **1be** slightly ($E_{1/2}$ = 1.83 V vs Ag/AgCl) (Scheme 2). The cyclic voltammetry studies suggested the possibility of benzamide derivatives might be tolerated in this transformation when acetonitrile was used instead of DCE. As expected, phenyl(2-phenylpyrrolidin-1-yl)methanone **2be** can be formed in 92% yield when MeCN/HFIP (2:1) was used as solvent. In contrast, the benzoyl protected amides can not be compatible in Shono's system.[17] Several substituents in the para-position of the benzoyl were compatible in the electrochemical system (**2be-2bh**). *N*-(4-phenylbutyl)furan-2-carboxamide would give the desired product in 72% yield (**2bi**). Using the described conditions, we demonstrate the feasibility of performing this transformation in the gram-scale. The constant current electrolysis of 5 mmol of **1aa**, **1ap**, **1be** can be conducted to produce the desired pyrrolidines (**2aa**, **2ap**, **2be**) in 92%, 95% and 90% isolated yield respectively.



Scheme 3. Kinetic isotope effect experiments

To gain a deeper insight into the mechanism of the transformation, the kinetic isotope effect experiments were carried out. And intramolecular and intermolecular kinetic isotopic effect values was obtained as 2.45 and 1.44, respectively (Scheme 3), which indicated that the breaking of C-H bonds might be involved in the rate-determining step of the transformation.

To investigate the interaction between acetate anion and amide, the ^{1}H NMR study was performed. The signal of the N-H bond of sulfonamide was obviously shifted downfield when tetrabutylammonium acetate was added (Figure S6 in supporting information). The reason for this result is the intermolecular H-bonding of N-H group to acetate anion.[19] We proposed that the intermolecular H-bonding would assist the oxidation and deprotonation of the sulfonamide to generate the amidyl radical. The cyclic voltammetry studies showed that the half-peak potential of **1aa** would slightly decrease in the presence of acetate anion (Figure S10 in supporting information).



Scheme 4. Proposed mechanism.

A plausible mechanism for the electro-oxidative intramolecular Csp^3-H amination reaction was outlined in Scheme 4. We proposed that the process began with the formation of a bonding complexes **3** between sulfonamide **1** and acetate. The single electron oxidation on the anode lead the generation of the *N*-centered radical intermediate **I** (Path 1). The subsequent 1,5-HAT of the δ-C-H bond by aminyl radical provided a C-centered radical **II**. Then the radical species underwent further oxidation to furnish a carbon cation intermediate **III**. Followed

by the nucleophilic attack of the sulfonamide and the proton eliminations, cyclization product would be formed. Concomitant cathodic reduction of generated protons would generate H_2 during the reaction process, which avoids the use of stoichiometric external oxidant in the transformation. The generated alkoxide might deprotonate the substrate to afford N-anion **IV**, which can be rapidly oxidized on the anode to give the *N*-centered radical intermediate **I** (Path 2).

In summary, we have successfully developed an electro-oxidative Hofmann–Löffler–Freytag reactions. The intramolecular remote inert δ-C(sp^3)-H amination reactions can be achieved through a 1,5-HAT process. The requirement of metal catalyst, halogenated reagents and stoichiometric additional oxidant can be avoided. Our electrosynthetic method is broadly compatible with a wide benzylic C(sp^3)-H bonds and inert tertiary, secondary as well as primary C(sp^3)-H bonds, which can provide access to various functionalized nitrogen-containing heterocycles with great synthetic values. The reaction can be easily scaled up. The transformation holds significant potential for the applications to other remote C(sp^3)-H functionalization reactions.

ASSOCIATED CONTENT

Supporting Information.
The Supporting Information is available free of charge via the Internet at http://pubs.acs.org, which included NMR data and characterization (PDF)

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Notes

The authors declare no competing financial interest.

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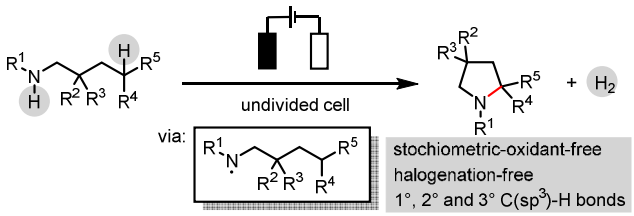
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