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Electrochemical C–H Amidation of Heteroarenes with *N*-Alkyl Sulfonamides in Aqueous Medium

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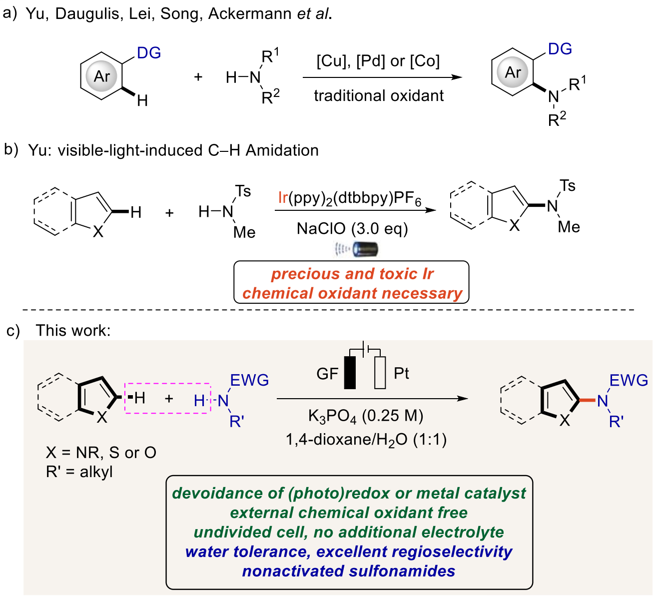
Abstract: The construction of C–N bonds by free radical reactions represents a powerful synthetic approach for direct C–H amidations of arenes or heteroarenes. Developing efficient and more environmentally-friendly synthetic methods for C–H amidation reactions remains highly desirable. Herein, metal-free electrochemical oxidative dehydrogenative C–H amidations of heteroarenes with *N*-alkylsulfonamides have been accomplished. The catalyst- and chemical oxidant-free C–H amidation features an ample scope, and employs electricity as the green and sole oxidant. A variety of heteroarenes, including indoles, pyrroles, benzofuran and benzothiophene, thereby underwent this C(sp^2)–H nitrogenation. Cyclic voltammetry studies and control experiments provided evidence for nitrogen-centered radicals being directly generated under metal-free electrocatalysis.

The construction of C–N bonds is one of the most vibrant areas in organic synthesis. Among several approaches, the development of methods for direct C–H amidations of arenes or heteroarenes is critically important, due to the prevalence of aromatic amines in both pharmaceuticals and materials.[1,2] Although copper-catalyzed Ullman couplings[3] and palladium-catalyzed Buchwald-Hartwig amidations[4] with aryl halides have proven to be powerful, direct amidations of aromatic C–H bonds without pre-functionalization have been pursued as more step-economical routes. Thus, significant contributions have been reported on transition metal-catalyzed C–H amidations of arenes (Scheme 1a).[5] However, the need for nonremovable directing groups, high reaction temperatures and waste-generating stoichiometric oxidants continue to be their insurmountable limitation.[6-8]

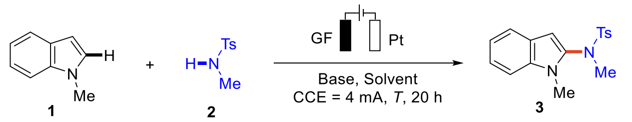
In contrast, the construction of C–N bonds by free radical reactions represents a powerful class of chemical transformations and has attracted considerable attention.[9] In particular, nitrogen-centered radicals have received increasing attention.[10] The well-established synthetic approaches to form *N*-radicals include the proton-coupled electron transfer (PCET) or oxidative deprotonation electron transfer (ODET) developed by Knowles[11] and Xiao[12] in the presence of iridium or ruthenium photocatalysts. Inspired by these work, Yu recently developed a visible-light-promoted direct oxidative C–H amidation of heteroarenes with nonactivated sulfonamides (Scheme 1b).[13] At the beginning of this reaction, stoichiometric NaClO is needed to oxidatively quench the iridium^{III} catalyst to generate iridium^{IV}. Thus, the development of efficient and more environmentally-friendly synthetic methods is still highly desirable and valuable,[9d] particularly by means of electrosynthesis. In connection with our continued interest in electrochemical syntheses[14,15] and C–N bond formation using electricity as the sole oxidant,[16] we questioned whether the efficiency and mildness noted in the *N*-radical formation could be translated into an electro-oxidative heteroarene amidation strategy. We have now devised an unprecedented C–H amidation of heteroarenes that can be performed with commercially available, inexpensive reagents under green and operationally-simple electrochemical conditions (Scheme 1c). Compared to previously disclosed methods, salient features of our strategy comprise (a) the absence of external chemical oxidants, (b) (photo)redox and metal catalyst-free condition, (c) the use of a user-friendly undivided cell setup without additional electrolyte, (d) high regioselectivity, and (e) full water tolerance.



Scheme 1. Strategies for direct C–H amidation of heteroarenes.

We initiated our studies by probing various reaction conditions for the envisioned metal-free electrochemical C–H amidation reaction of indole **1a** in a most user-friendly undivided cell set-up with a platinum plate cathode and graphite felt (GF) anode (Table 1 and Table S2 in the SI). After considerable preliminary experimentation, we observed that the desired amidation with amide **2a** was best accomplished with a mixed solvent consisting of 1,4-dioxane/H_2O (1:1) and K_3PO_4 as both the key base and electrolyte (entries 1-12). The efficacy of the electro-oxidation was reflected by efficient C–H amidations occurring at a temperature of 80 °C (entries 13 and 14). Attempts to reduce the amount of K_3PO_4 or coupling parter **2a** loading led to a decreased yields (entry 15). A significant decline of yield was observed when a Pt anode or Fe cathode was used. It is noteworthy that when Ni-foam was used as the cathode, the amidation product **3aa** was isolated in 64% yield (entry 16). Control experiments confirmed the essential role of electricity for the electrooxidative amidation (entries 17).

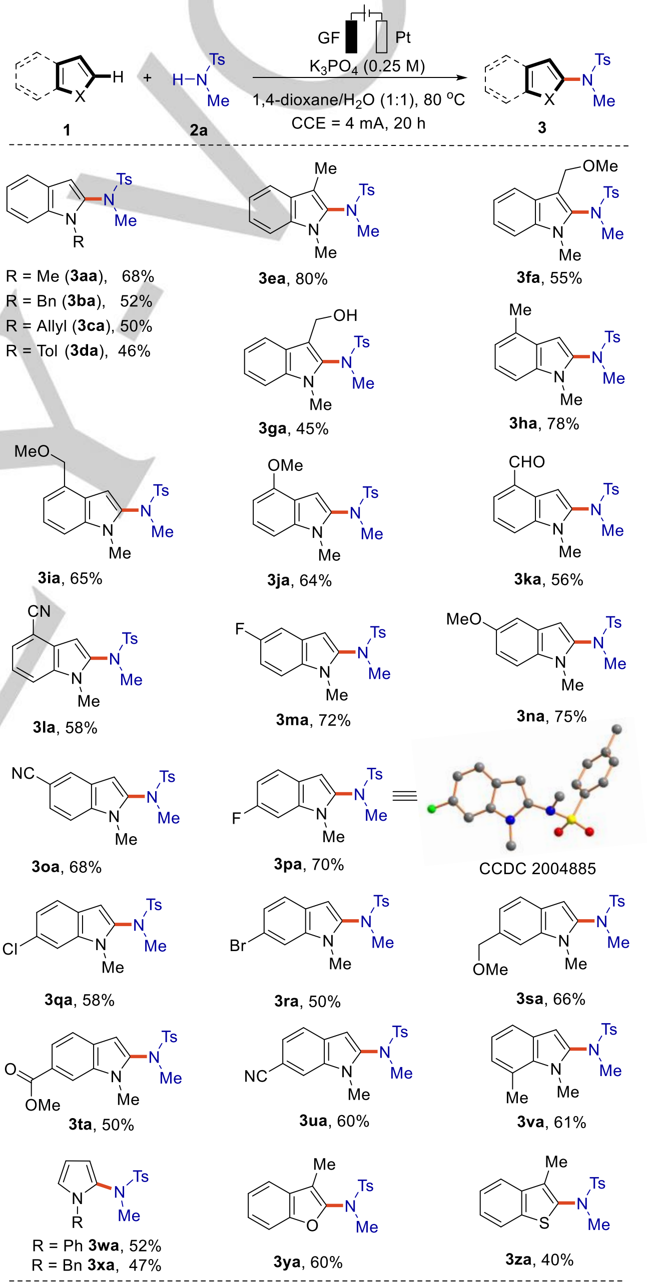
Table 1. Electrochemical C–H Amidation of Heteroarenes with Sulfonamides.[a]



Entry	Solvent	Base	T / °C	Yield / %
1	MeCN/H_2O (3:1)	Na_2CO_3	50	15
2	*t*-AmylOH/H_2O (3:1)	Na_2CO_3	50	n.r.
3	*i*-PrOH/H_2O (1:1)	Na_2CO_3	50	n.r.
4	DMSO/H_2O (2:1)	Na_2CO_3	50	13
5	1,4-Dioxane/H_2O (1:1)	Na_2CO_3	50	27
6	1,4-Dioxane/H_2O (1:1)	–	50	n.r.
7	1,4-Dioxane/H_2O (1:1)	K_2CO_3	50	24
8	1,4-Dioxane/H_2O (1:1)	NaOH	50	37
9	1,4-Dioxane/H_2O (1:1)	NaOPiv	50	20
10	1,4-Dioxane/H_2O (1:1)	NaOAc	50	32
11	1,4-Dioxane/H_2O (1:1)	K_3PO_4	50	55
12	1,4-Dioxane/H_2O (2:1)	K_3PO_4	50	50
13	1,4-Dioxane/H_2O (1:1)	K_3PO_4	30	21
14	**1,4-Dioxane/H_2O (1:1)**	**K_3PO_4**	**80**	**68**
15[b]	1,4-Dioxane/H_2O (1:1)	K_3PO_4	80	54
16[c]	1,4-Dioxane/H_2O (1:1)	K_3PO_4	80	64
17[d]	1,4-Dioxane/H_2O (1:1)	K_3PO_4	80	n.r.

[a] Undivided cell, GF anode, Pt cathode, constant current = 4 mA, **1** (0.5 mmol), **2a** (1.0 mmol, 2.0 equiv), base (0.25 M, 1.0 mmol, 2.0 equiv), solvent (4.0 mL), under air, 20 h. Yield of isolated products. [b] With K_3PO_4 1.0 equiv. [c] GF(+)|Ni(−) instead of GF(+)|Pt(−). [d] No electricity.

With the optimized reaction conditions in hand, we explored the scope of the electrochemical C–H amidation with a variety of heteroarenes **1** (Scheme 2). Several substituents on the indole N were explored. Methyl (Me), benzyl (Bn), allyl and *para*-methylphenyl (Tol) indoles performed well to give the desired products **3aa**-**3da** in moderate to good yields. However, we found that 1*H*-indole and *N*-Ac indole could not be amidated in this transformation. We were pleased to find that C3-substituted indoles underwent this transformation efficiently despite a possible existing steric hindrance. 3-methyl and 3-methoxymethyl (MOM) indole derivatives furnished the 2-aminated products **3ea** and **3fa**. The more sensitive hydroxymethyl group was likewise tolerated, albeit with lower yield. We then examined various substituents at the C4-C7 positions and 2-aminated indole derivatives **3ha**-**3va** were obtained in reasonable yields (50-78%). The structure of the product **3pa** was unambiguously confirmed by single-crystal X-ray analysis.[17] Additionally, other heteroarenes, such as pyrrole, benzofuran and thiophene derivatives, were also accessible to site-selectively give the corresponding products **3wa**-**3za**.



Scheme 2. Electrochemical C–H amidation of different heteroarenes **1**.

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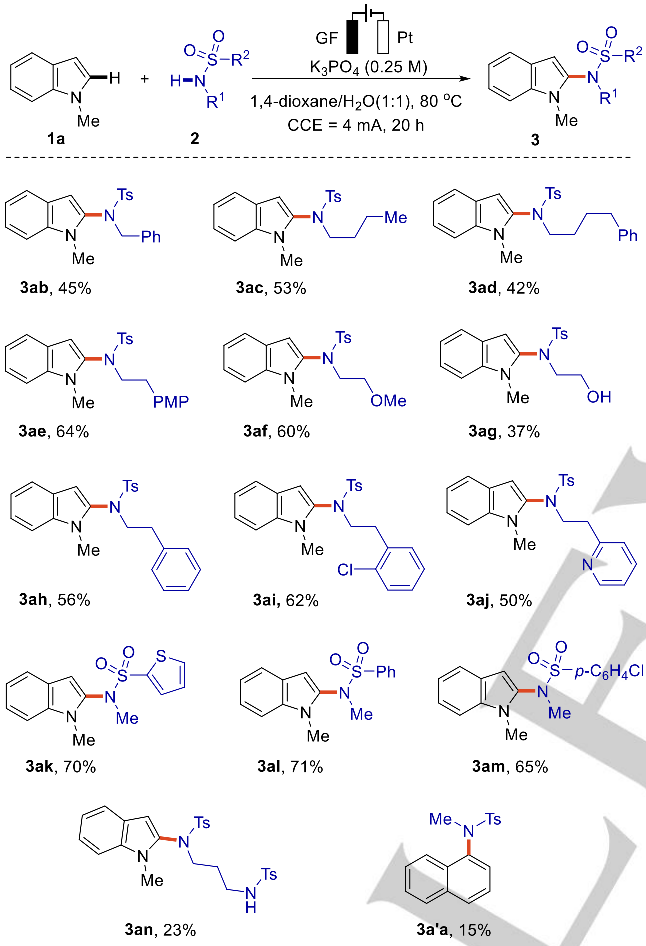
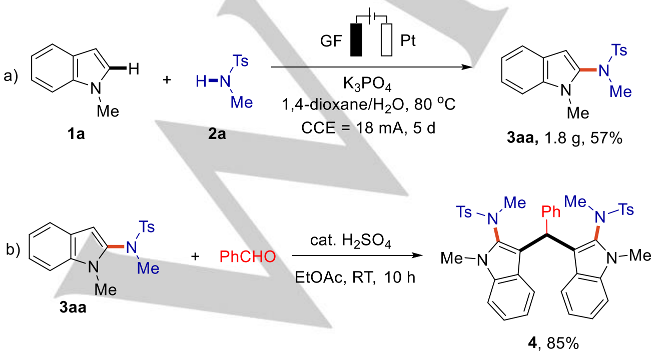
The scope of the amidation reaction was further examined with various substituted sulfonamides **2** (Scheme 3). Generally, the alkyl part of the sulfonamide **2** did not significantly alter the reaction efficiency and the amidated products **3** were smoothly obtained in low to moderate yields (**3ab**-**3ao**). As depicted in Schemes 2 and 3, amidation approach was compatible with several sensitive functional groups, such as chloro, bromo, nitrile, hydroxyl, formyl, ester and amino. It's noteworthy that naphthalene **1a'** underwent the electro-oxidative C–H amidation with *N*-methyl-*para*-toluenesulfonamide **2a**, giving a minor amount of product **3a'a**.



Scheme 3. Electrochemical C-H amidation with *N*-alkyl sulfonamides **2**.



Scheme 4. a) Gram-scale reaction and b) derivatization of compound **3aa**.

The scalability of the electrochemical C–H amidation was probed next and a 10 mmol scale reaction of **1a** and **2a** yielded 1.8 g of product **3aa** (Scheme 4a). Derivation of this product was performed to access the privileged indole derivative **4** with a diverse range of pharmacological activities[18] (Scheme 4b).

To investigate the interaction between base and sulfonamide **2**, thus understanding the pathway for the generation of the *N*-centered amide radical, cyclic voltammetry studies were performed (Figure 1 and Figure S1 in the SI). We found that the oxidation potential of sulfonamide alone is relatively high with $E_{1/2}$ = +2.5 V *vs* Ag/AgCl in acetonitrile. We then carried out cyclic voltammetry studies of sulfonamide **2a** in acetonitrile/water (10:1) containing 0.2 M K_3PO_4, which acts as a base as well as an electrolyte. The mixture of the sulfonamide and K_3PO_4 resulted in a new oxidation wave at around +1.0 V *vs* Ag/AgCl. Compared to sulfonamide, the oxidation potential and onset potential of the new peak were shifted to lower potentials. This outcome is consistent with the formation of a *N*-centered amide anion from sulfonamide and K_3PO_4, and the *N*-anion is electron-rich and much more easily oxidized to a *N*-centered amide radical.

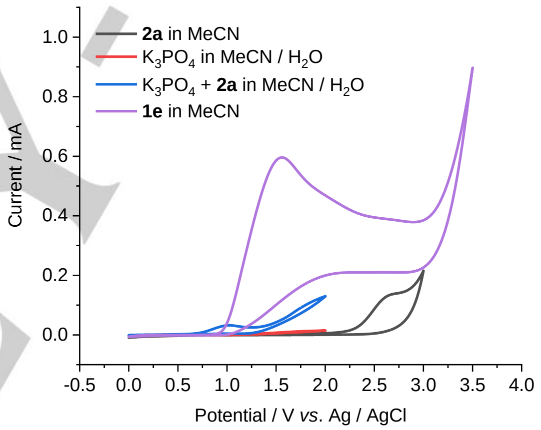
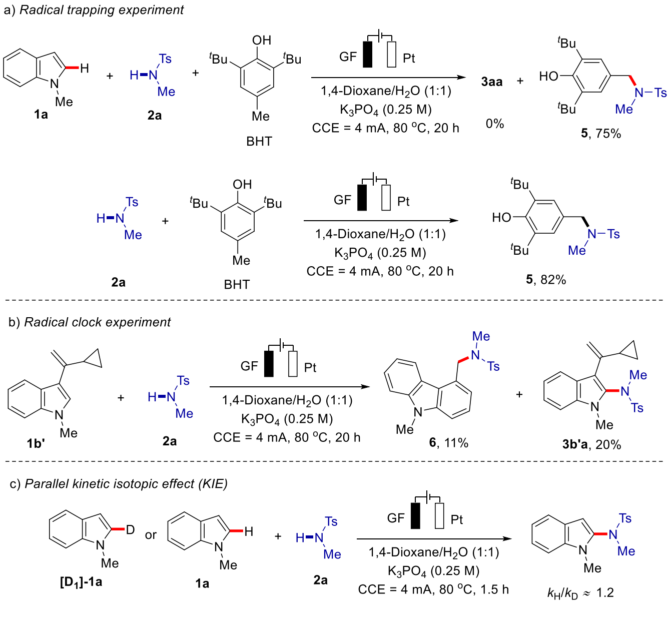


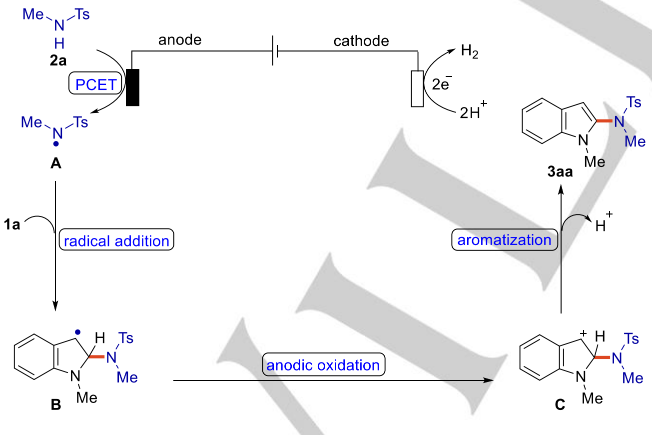
Figure 1. Cyclic voltammetry studies. Conditions: Cyclic voltammograms of sulphonamide **2a** (5.0 mM) in MeCN containing 0.1 M *n*-Bu_4NPF_6 (black), K_3PO_4 (0.2 M) (red), and the mixture of **2a** (0.2 M) and K_3PO_4 (0.2 M) (blue) in acetonitrile/H_2O (10:1), cyclic voltammogram of indole **1e** (5.0 mM) in MeCN containing 0.1 M *n*-Bu_4NBF_4 (purple), at ambient temperature. The scan rates were 100 mV/s.

Considering that this conversion process includes a radical addition step, a number of control experiments was thereafter conducted. *N*-centered radical **A** could be trapped by 2,6-di-*tert*-butyl-4-methylphenol (BHT). When a mixture of sulfonamide **2a** and BHT was subjected to the standard electrochemical conditions, and the trapping product **5** was isolated through an intramolecular radical transfer,[19] independent of the presence of indole **1a** (Scheme 5a). The radical clock reaction with 3-(1-cyclopropylvinyl)-1-methyl-1*H*-indole **1b'** as a radical trapping reagent provided the radical cyclization product **6** in 11% yield, along with the otherwise typical product **3b'a** (Scheme 5b). Furthermore, we synthesized deuterated substrate [D_1]-**1a** (95% D) and an kinetic isotope effect (KIE) experiment was undertaken by parallel independent reactions, giving a KIE value of $k_H/k_D \approx$ 1.2 (Scheme 5c). These results suggest a fast and facile C–H cleavage.



Scheme 5. Summary of key mechanistic findings.

Based on our mechanistic studies, a radical mechanism is proposed in Scheme 6 for this electrocatalyzed C(sp^2)–H amidation reaction. First, *N*-alkylsulfonamide **2a** undergoes a concerted proton-coupled electron transfer event at the anode to give the key *N*-radical **A**.[11] The subsequent radical addition to indole **1a** furnishes the new C–N bond and the thermodynamically more stable carbon-centered radical **B**. Then, radical **B** undergoes further SET oxidation to form the cation intermediate **C**. Finally, **C** generates the final amidation products **3aa** through proton elimination/aromatization, generating molecular hydrogen as a byproduct at the cathode.



Scheme 6. Proposed mechanism.

In conclusion, we have developed an efficient approach for electrochemical C–H amidations of unactivated heteroarenes via oxidative cleavage of N–H bonds under metal catalyst- and chemical oxidant-free conditions. A variety of heteroarenes, including indoles, pyrroles, benzofurans and benzothiophenes, proved applicable to the electro-C–H-amidation. The robust catalyst-free C–H amidation was broadly applicable to *N*-alkylsulfonamides under green and mild reaction conditions. Control experiments and cyclic voltammetry studies were indicative of the generation of a nitrogen radical via an anodic oxidation.

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Keywords: heterocycles • amidation • electrochemistry • radicals

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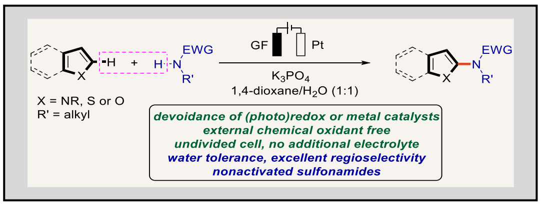

Metal-free electrochemical dehydrogenative C–H amidation of heteroarenes with *N*-alkylsulfonamides have been accomplished. The catalyst- and chemical oxidant-free C–H amidation featured ample substrate scope and employed electricity as the sole oxidant.