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Letter

C- to N-Center Remote Heteroaryl Migration via Electrochemical Initiation of N Radical by Organic Catalyst

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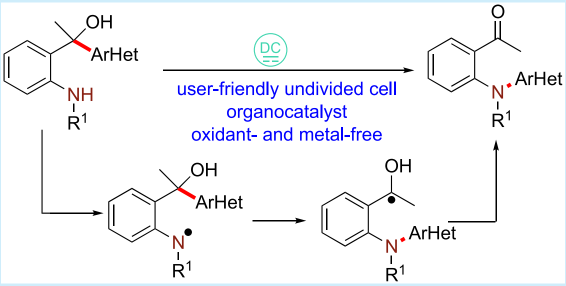
ABSTRACT: Herein an exogenous oxidant- and metal-free electrochemical heteroaryl migration triggered by N radicals to construct new N−C bonds was developed. This methodology features a high atom economy and utilization rate of energy, and it is insensitive to water and air. Moreover, a user-friendly undivided cell was employed. The use of an organic catalyst makes it more efficient, green, and practical.

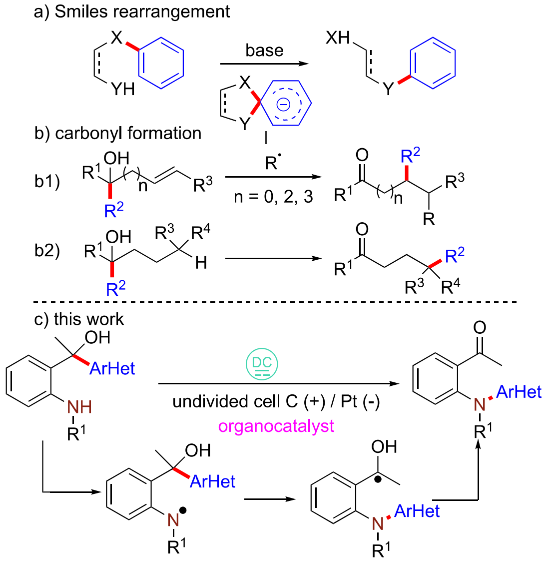


The intramolecular migration reaction, a powerful tool for the construction of unexpected and highly complex molecular scaffolds with abundant bioactivities, has attracted increasing attention.[1] The classical Smiles rearrangement supplied a particularly appealing methodology to construct a new C−C or C-hetero bond via an intramolecular nucleophilic substitution reaction featuring a key spirocyclic intermediate I (Scheme 1a,[2] **I**). On the basis of the mechanism of the spirocyclic intermediate and the resurgence of interests in radical chemistry, many radical-based rearrangement reactions have been developed and have gained increased attention.[3,4] Radical reactions usually exhibit higher selectivity and better functional-group compatibility under neutral and mild conditions.[3] Lately, Zhu[5] and many other research groups[6] have succeeded in the heteroarylation of unactivated alkenes via heteroaryl ipso-migration with the formation of a carbonyl group (Scheme 1, **b1**). The radical addition of a C−C triple bond or double bond initiates the reactions above. Moreover, Zhu developed a $C_{(sp^3)}$−H bond heteroarylation through heteroaryl migration based on the 1,5-HAT (HAT = hydrogen atom transfer) mediated by alkoxyl radicals (Scheme 1, **b2**[7]).

Nevertheless, to the best of our knowledge, the remote heteroaryl migration initiated by N-centered radical is rare. It leads to C−N bond formation to construct abundant N-containing compounds, which are prevalent in marketed drugs, material industries, and natural products.[8]

Therefore, the development of novel, sustainable, and efficient methodologies to assemble unprecedented N-containing compounds is still in high demand. However, attributing to the difficulty in homolysis of the N−H bond, the lack of practical and green radical initiation methods makes N radical chemistry still underexplored. Traditionally, the N-centered radical can be obtained under the costly oxidant of hypervalent iodine reagents[9] by the direct homolysis of the N−

Scheme 1. Remote (Hetero)aryl Migrations[a]



[a](a) Classical Smiles rearrangement, X = S, SO, SO_2, O, CO_2, YH = OH, NHR, SH, CH_2R, CONHR. (b) Radical (hetero)aryl migration driven by the formation of carbonyl. (c) Heteroaryl migration via electrochemical initiation of N-centered radicals by organic catalyst (this work).

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H bond. Furthermore, the homolysis of the N−O,[10] N−N,[11] N−X,[12] or N−S[13] smoothly leads to the corresponding N radical. However, employing the expensive oxidants or the preactivated amino precursors restricts the wide application of these methods. Recently, the groundbreaking development of photoredox catalysis has supplied new strategies for the generation of the N radical from direct N−H compounds.[14] Nevertheless, a complex and costly photocatalyst is necessary under the photoredox-initiated radical reaction.

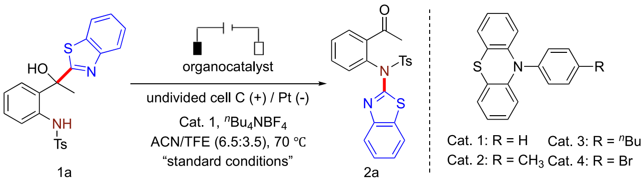
Electrochemistry, an environment-friendly and practical synthesis tool employing traceless electrons as “reagents” to activate numerous small molecules by a redox process avoiding exogenous oxidants, has attracted increasing attention.[15]

Lately, Xu and have Lei developed several electrochemical cyclization reactions initiated by N-centered radical via the homolysis of the N−H bond of amides without any additional oxidants.[16] However, to date, N−C bond formation reactions promoted by a N-centered radical initiated by electrochemistry remain underdeveloped due to lack of applicative reaction types. Herein we reported a remote heteroaryl migration to access to 2-aminophenyl benzothiazoles via the electrochemical initiation of N-centered radicals under metal-free and oxidant-free conditions with good H_2O and air tolerance (Scheme 1c), and an organic catalyst was employed to give higher productivity.

Initially, *N*-(2-(1-(benzo[*d*]thiazol-2-yl)-1-hydroxyethyl)phenyl)-4-methylbenzenesulfonamide **1a** was chosen as the model substrate to explore the reaction conditions for the envisioned remote heteroaryl migration via the electrochemical initiation of N-centered radical (Table 1). After considerable screening of the reaction parameters, the desired migration product **2a** was generated in excellent yield (93%) after the consumption of 1.990 F/mol of charge in a user-friendly undivided cell equipped with a carbon cloth anode and a platinum plate cathode using a mixed solvent of ACN/TFE ((6.5:3.5) mL) under a constant current of 8 mA at 70 °C (entry 1), and the organic catalyst **1** was essential for this reaction. In theory, 1.996 F/mol of electric energy is necessary. Thus this proposal features an extremely high utilization rate of energy. When TEMPO was used as the catalyst, only a trace amount of the desired product was detected (entry 2), and using commercially available ferrocene or substituted ferrocene led to a dramatic decrease in the yield (entries 3−6). Interestingly, poor catalytic performance was observed when 10-(substituted phenyl)-10*H*-phenothiazine was used as the redox catalyst (entry 7). A dramatic yield reduction was obtained when TFE was replaced by TCE, EtOH, or HFIP (entry 8), and ^{n}Bu$_4$NBF$_4$ was the best choice compared with ^{n}Bu$_4$NPF$_6$, ^{n}Bu$_4$NOAc, and ^{n}Bu$_4$NI (entry 9). Only 35% of the desired product was obtained in the absence of an electrolyte (entry 10). Replacing carbon cloth with Pt, RVC, or C rod led to nearly no corresponding product generated (entries 11−13). Using C fiber instead of carbon cloth resulted in a slight decrease in the yield, with 84% yield obtained (entry 14)

When carbon cloths were used as the anode and cathode, only 42% product yield was produced (entry 15). The decrease in temperature led to a dramatic yield reduction (entry 16). No dramatic yield reduction was observed when this reaction was performed under a constant voltage (entry 17). The control experiment indicated that the electric current was indispensable in this transformation (entry 18). Only 35% yield was produced in the absence of a catalyst (entry 19). Interestingly, the yield could be boosted to 87% by increasing the electrolysis time to 3.5 h with 3.482 F/mol electricity consumed (entry 19).

Table 1. Optimization of Reaction Conditions[a]



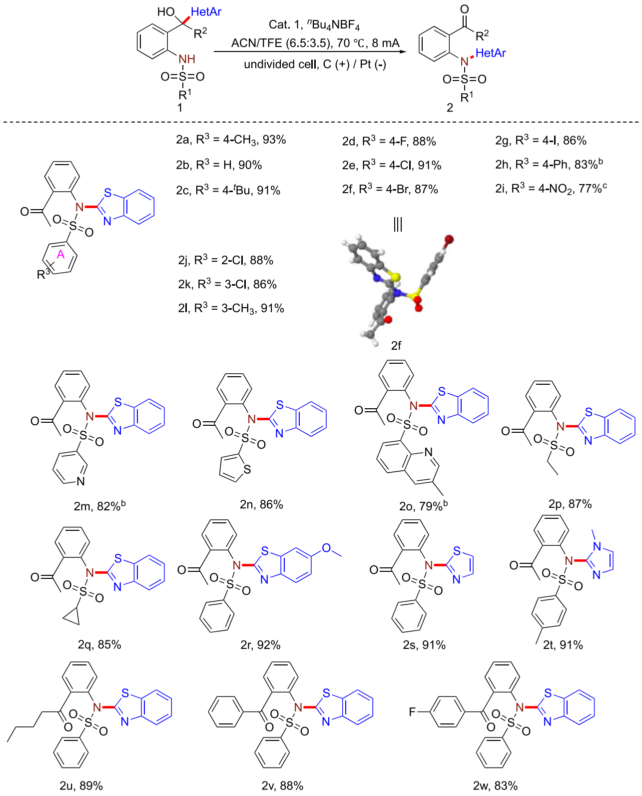
entry	variation from “standard conditions”	yield (%)[b]
1	none	93
2	with TEMPO as catalyst	trace
3	with ferrocene as catalyst	28
4	with 1,1′-dimethylferrocene as catalyst	16
5	with cyanoferrocene as catalyst	27
6	with ethylferrocene as catalyst	18
7	2-4 as catalyst	44; 42; 86
8	TCE or EtOH or HFIP instead of TFE	42; 47; 51
9	^{n}Bu$_4$NPF$_6$ or ^{n}Bu$_4$NOAc or ^{n}Bu$_4$NI as electrolyte	55; 14; 17
10	no electrolyte	35
11	Pt (+)/Pt (−)	0
12	RVC (+)/Pt (−)	trace
13	C rod (+)/Pt (−)	trace
14	C fiber (+)/Pt (−)	84
15	carbon cloth (+)/carbon cloth (−)	42
16	30 or 50 °C	18; 39
17	2 V; 3 V; 4 V	89; 87; 82[c]
	Control Experiments	
18	no current	0
19	no catalyst	35, 87[d]

[a] Reaction conditions: **1a** (0.3 mmol), catalyst (0.015 mmol, 5 mol %), ^{n}Bu$_4$NBF$_4$ (0.3 mmol), solvent (ACN/TFE = 6.5 mL/3.5 mL), 70 °C, 2 h, 1.990 F/mol, undivided cell, carbon cloth anode (40 mm × 20 mm), platinum plate cathode (20 mm × 20 mm), constant current = 8 mA. ACN: acetonitrile, TFE: 2,2,2-trifluoroethanol, TEMPO: 2,2,6,6-tetramethylpiperidino-oxy, TCE: trichloroethanol, HFIP: 1,1,1,3,3,3-hexafluoro-2-propanol. [b] Isolated yield. [c] 1.5 h. [d] 3.5 h.

With the optimized electrochemical remote heteroaryl migration to construct a new C−N bond obtained, a series of experiments were carried out to investigate the reaction scope by varying **R^1**, **HetAr**, and **R^2** (Scheme 2). To our delight, an excellent yield could be obtained when the phenyl ring **A** was substituted with an electron-rich or an electron-deficient group (**2a**−**l**).

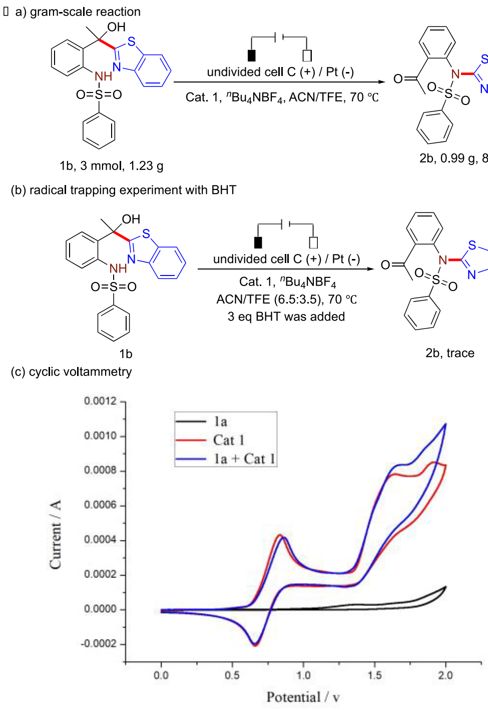
This methodology was compatible with halogens including F, Cl, Br, and I, which could be used to further the functionalization (**2d**−**2g**, **2j**, **2k**), and the structure of **2f** was confirmed by X-ray crystallographic analysis (Figure S3, CCDC = 1955548). Moreover, this reaction did not seem to be affected by the positions of the substituents on the **A** ring (**2e**, **2j**, **2k**). When **A** rings were replaced by heteroaryl or alkyl groups, no detrimental effect on the yield was observed (**2m**−**q**). Although electron-deficient **R^1** led to lower reactivity, complete substrate conversion could be achieved by extending the electrolysis time, with good yield obtained (**2i**, **2m**, **2o**). Excellent yields were produced when the benzothiazole ring was replaced by 6-methoxy-1,3-benzothiazole, thiazole, or imidazole (**2r**−**t**). Furthermore, replacing **R^2** with a linear alkyl, unsubstituted, or substituted phenyl group did not blunt this reaction (**2u**−**w**). To our delight, 81% isolated yield was obtained when the reaction was scaled up to the gram scale in a user-friendly undivided cell (Scheme 3a).

Scheme 2. Substrate Scope of Electrochemical Remote Heteroaryl Migration Initiated by N-Centered Radicals[a]



[a] Reaction conditions: Table 1, entry 1; isolated yields are shown. [b] 3.5 h. [c] 4 h.

Scheme 3. Gram-Scale Experiment and Mechanistic Studies

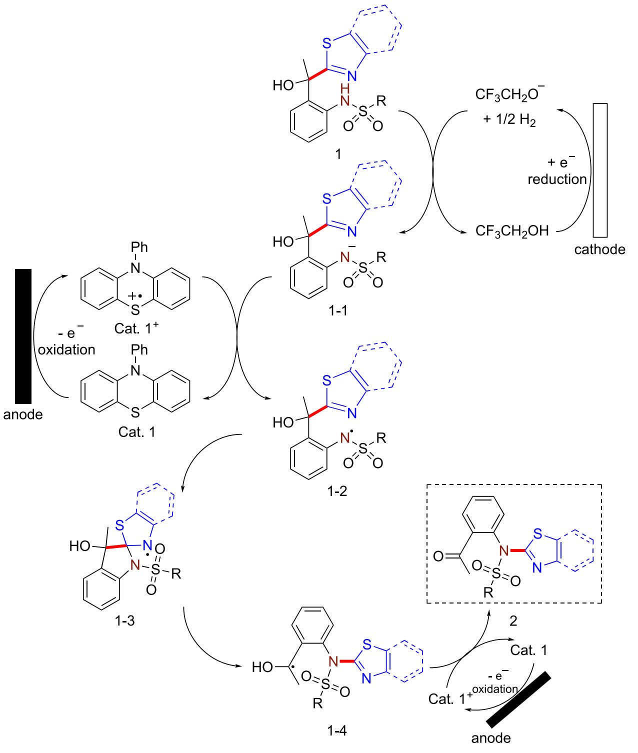


To gain insight into the reaction mechanism, radical trapping and cyclic voltammetry experiments were carried out (Scheme 3b,c). Only a trace amount of the desired product was detected in the presence of BHT (butylated hydroxytoluene, Scheme 3b), and the corresponding **1b** radical was trapped, which was confirmed by **MS** (Figure S1). Moreover, cyclic voltammetry (CV) experiments were investigated to get more information (Scheme 3c). No obvious oxidation peak of **1a** was observed (black, Scheme 3c). It was noteworthy that **Cat. 1** featured two obvious oxidation peaks at 0.84 and 1.65 V (red, Scheme 3c).

Similar oxidation peaks can be found in the presence of **1a** and **Cat. 1** (blue, Scheme 3c). The results above indicated that **Cat. 1** was oxidized first at the anode, which was likely to conduce to the single electron oxidation of **1a**.

On the basis of the results above and previous reports,[17] a possible reaction process of electrochemical C- to N-center remote heteroaryl migration was proposed, as shown in Scheme 4.

Scheme 4. Proposed Mechanism



The **TFE** anion was produced at the cathode, which led to the generation of the N-anion intermediate **1-1**. Meanwhile, **Cat. 1** was oxidized at the anode to a stable radical cation intermediate **Cat. 1^+**,[18] and the corresponding N-radical intermediate **1-2** was obtained via a single-electron oxidation by **Cat. 1^+**, which was transformed into spiro radical intermediate **1-3**.[16b] Then, C-radical intermediate **1-4** was formed via a carbon-to-nitrogen heteroaryl migration with $C_{(sp^3)}$−$C_{(sp^2)}$ cleavage, which was oxidized by **Cat. 1^+** to form the desired product.

In summary, an electrochemical heteroaryl migration triggered by N radicals was demonstrated, which supplied an alternative strategy to construct new N−C bonds besides Ullmann coupling. An organocatalyst was used to avoid the transition-metal complex, and exogenous oxidants, which might lead to potential danger, environmental pollution, and undesired byproducts, were avoided. Moreover, this method featured a high atom economy and utilization rate of energy and good water and air tolerance. Moreover, on the basis of the control experiments, we proposed a possible mechanism.

■ ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04141.

General experimental procedures, characterization, and copies of NMR spectra (PDF)

Accession Codes

CCDC 1955548 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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