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Electrochemical Synthesis of Imidazo-Fused N-Heteroaromatics via C–N Bond Forming Radical Cascade

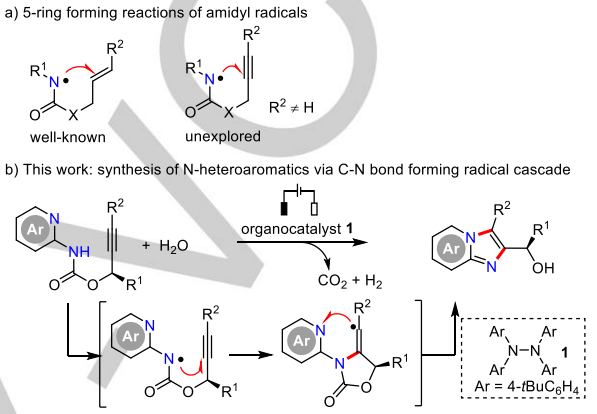
Zhong-Wei Hou,[+] Zhong-Yi Mao,[+] Yared Yohannes Melcamu, Xin Lu* and Hai-Chao Xu*

Abstract: We have developed a unified strategy for preparing a variety of imidazo-fused *N*-heteroaromatics through regiospecific electrochemical (3+2) annulation reaction of heteroarylamines with tethered internal alkynes. The electrosynthesis employs a novel tetraarylhydrazine as the catalyst, has a broad substrate scope, and obviates the need for transition-metal catalysts and oxidizing reagents.

The development of more efficient and sustainable methods for constructing C–N bonds has always been a major focus of synthetic organic chemistry due to the critical roles of N-containing compounds in pharmaceutical, agrochemical and material industries.[1] Despite the recent resurgence of interests in organic radical chemistry, radical C–N bond formation reactions remain underdeveloped.[2] Lately, many research groups including us have succeeded in creating C–N bonds by cyclizing N-centered radicals with alkenes (Scheme 1a).[3] In comparison, there have only been a few studies on the cyclization of N-centered radicals with alkynes,[4] probably due to the lack of versatile radical initiation methods and the competing ionic cyclization reaction[5] when using a N–H based radical precursor. On the other hand, there is also a lack of C–N bond forming cyclization reactions employing C-centered radicals,[6] which show a strong preference for reaction with the carbon instead of the nitrogen in N-containing π-systems.[7]

Imidazo-fused heteroaromatics are important scaffolds as they are featured in numerous bioactive compounds including commercialized drugs such as Zolpidem, Olprinone and Cefozopran.[8] The oxidative (3+2) annulation of arylamines with alkynes is one of the most attractive strategies to access these structures because of the easy availability of starting materials and the inherent atom- and step-economical features. However, the reported methods employ only terminal alkynes or alkynes substituted with halogen or electron-withdrawing groups to provide sufficient reactivity and regioselectivity.[9]

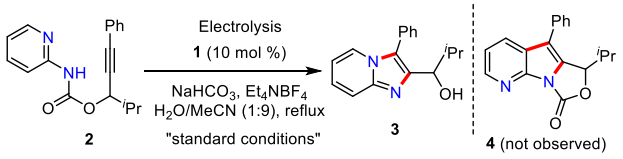
Organic electrochemistry is a powerful and attractive tool for organic synthesis because it employs electrons as “reagents” and is tunable in the activation of small molecules to generate reactive intermediates.[10,11] In this context, few methods have been developed for preparing amidyl radicals via direct[12] or indirect[3g,4b,4c] electrolysis of N–H bearing precursors. Here we report an electrochemical synthesis of imidazo-fused *N*-heteroaromatics through an unprecedented radical C–N bond-forming cyclization cascade (Scheme 1b). Our electrolytic approach employs a traceless linker to enable the regiospecific (3+2) annulation of internal alkynes.



Scheme 1. Design of radical cyclization cascade for the synthesis of imidazo-fused N-heteroaromatics.

The first aim of our study was to develop an electrochemical process that could be used to efficiently generate amidyl radicals from N–H precursors without the need for transition-metal catalysts. To this end, we chose the readily accessible carbamate **2** as a model substrate and screened a variety of different electrolysis conditions employing an undivided cell equipped with a reticulated vitreous carbon (RVC) anode and a platinum cathode (Table 1 and Table S1). The optimal results were obtained when **2** was electrolyzed at a constant current in a mixed solvent of MeCN/H_2O (9:1) under reflux in the presence of 10 mol % of tetraarylhydrazine **1** as catalyst. Despite their easy availability, the use of tetraarylhydrazines as redox catalyst has not been reported.[13] Under these conditions, the desired imidazopyridine **3** was isolated in 89% yield (entry 1).

Table 1. Optimization of reaction conditions.[a]



Entry	Deviation from standard conditions	Yield [%][b]

[*] Z.-W. H,[+] Z.-Y. Mao,[+] Y. Y. Melcamu, Prof. Dr. X. Lu, Prof. Dr. H.-C. Xu
State Key Laboratory of Physical Chemistry of Solid Surfaces, *i*ChEM, and College of Chemistry and Chemical Engineering, Xiamen University
Xiamen 361005 (P. R. China)
E-mail: xinlu@xmu.edu.cn; haichao.xu@xmu.edu.cn
Homepage: http://chem.xmu.edu.cn/groupweb/hcxu/

[+] These authors contributed equally to this work.

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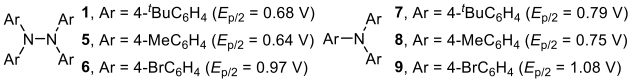
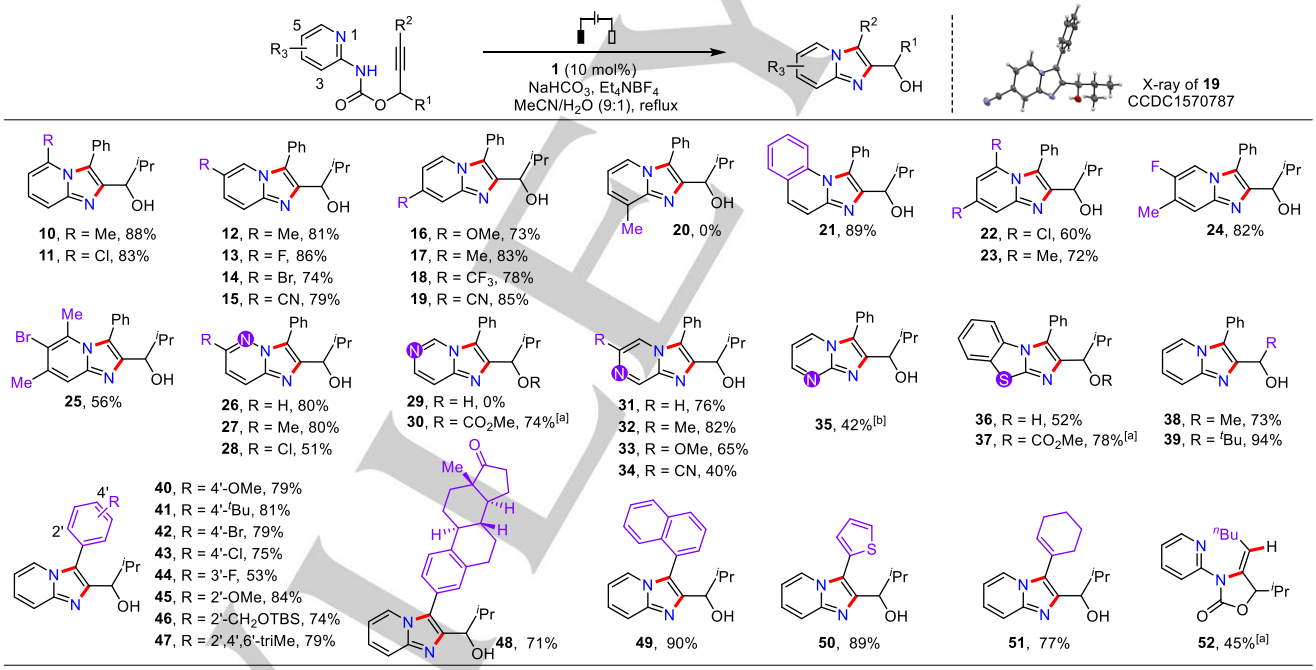
1	None	89[c]
2	no **1**	9 (70)
3	no $NaHCO_3$	60
4	at RT	30 (52)
5	with **5** as the catalyst	69 (15)
6	with **6** as the catalyst	32 (50)
7	with **7**, **8** or **9** as the catalyst	11–39
8	with ferrocene as the catalyst	5 (68)
9	under air	75

[a] Reaction conditions: undivided cell, RVC anode, Pt cathode, **2** (0.3 mmol), H_2O (1 mL), MeCN (9 mL), Et_4NBF_4 (0.3 mmol), $NaHCO_3$ (0.6 mmol), 7.5 mA (j_{anode} = 0.1 mA cm^{-2}), 3.7 h (3.5 F mol^{-1}). [b] determined by ^1H NMR analysis, unreacted **1** in parenthesis. [c] Yield of isolated **3**.



The organic catalyst (entry 2), $NaHCO_3$ (entry 3) and heating (entry 4) were all found to be essential for the reaction to achieve the optimal yield. Other tetraarylhydrazines with similar (entry 5) or higher oxidation potentials (entry 6), common triarylamines (entry 7) and ferrocene[3g,4b,4c] (entry 8) all showed poor catalytic performance. Stringent removal of oxygen from the reaction system was not needed as performing the electrolysis under atmospheric conditions also produced the desired **3** in 75% yield (entry 9). Note that we did not observe the generation of **4**, which would indicate the occurrence of carbophilic cyclization, under any circumstances.

We investigated the substrate scope first by testing different aminoheteroarene moieties (Scheme 2). Generally, annulation of a 2-aminopyridine derivative demonstrated broad tolerance toward a wide range of substituents with diverse electronic properties at the C6 (**10**, **11**), C5 (**12**–**15**), C4 (**16**–**19**) but not the C3 (**20**) position of the pyridyl ring. Substrates with multiple substituents afforded densely functionalized imidazopyridines (**21**–**25**). Furthermore, replacement of the 2-aminopyridine moiety with a host of aminodiazine structures was also shown to be possible. The reaction proceeded smoothly in all instances regardless of the nitrogen positions, leading to the formation of imidazo[1,2-*b*]pyridazines (**26**–**28**), imidazo[1,2-*c*]pyrimidine (**30**), imidazo[1,2-*a*]pyrazines (**31**–**34**) and imidazo[1,2-*a*]pyrimidine (**35**). The synthesis of imidazo[1,2-*c*]pyrimidine **30** required the use of Na_2CO_3 as the base and MeOH/THF (1:3) as the solvent (See Table S2 for details). Medicinally important imidazo[2,1-*b*]benzothiazoles (**36**, **37**) could also be prepared by the electrolytic method.



Scheme 2. Substrate scope using a carbamate linkage. Reaction conditions: Table 1, entry 1, substrate (0.3 mmol), 3.7 h (3.5 F mol^{-1}). All yields are isolated yields. [a] Reaction run with **1** (5 mol %) and Na_2CO_3 (0.3 mmol) in refluxing MeOH/THF (1:3, 9 mL). [b] 0.5 equiv of $NaHCO_3$.

We next varied the propargyl group in the starting substrate (Scheme 2). The reaction was shown to be compatible with methyl (**38**) and *tert*-butyl (**39**) on the propargylic position. On the other hand, the benzene ring at the terminus of the alkyne could be functionalized with a variety of substituents with diverse electronic and steric properties (**40**–**48**). While the alkyne could also be terminally substituted with 1-naphthyl (**49**), 2-thiophenyl (**50**) or cyclohexenyl group (**51**), the installation of an alkyl group did not result in the generation of the corresponding imidazopyridine product in $MeCN/H_2O$; alternatively, the hydroamidation product **52** was isolated when the reaction was

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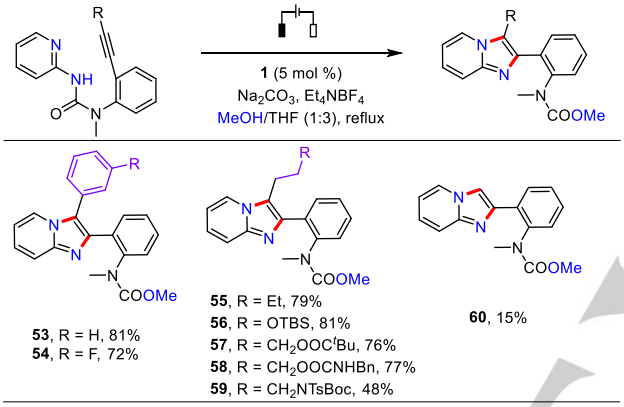
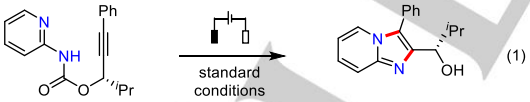
conducted in MeOH/THF, a solvent system with better H-atom donating ability.

We speculated that the terminal alkyl substituent caused the intermediate vinyl radical to favor H-atom abstraction from the solvent over the azaphilic cyclization. To address this problem, we drew inspiration from our recent findings that the formation of a six-membered ring in the first step of the amidyl radical cyclization cascade could greatly facilitate the subsequent construction of the five-membered ring.[4b] To our delight, the urea-linked substrates, especially those carrying an alkyl-capped alkyne, exhibited significantly improved reaction compatibility and furnished imidazopyridines **53**–**60** even when only 5 mol % of **1** was added (Scheme 3). In all cases, the starting compound was electrolyzed in MeOH, which installed a methoxycarbonyl substituent on the amino group of the corresponding product to protect it from oxidative decomposition.

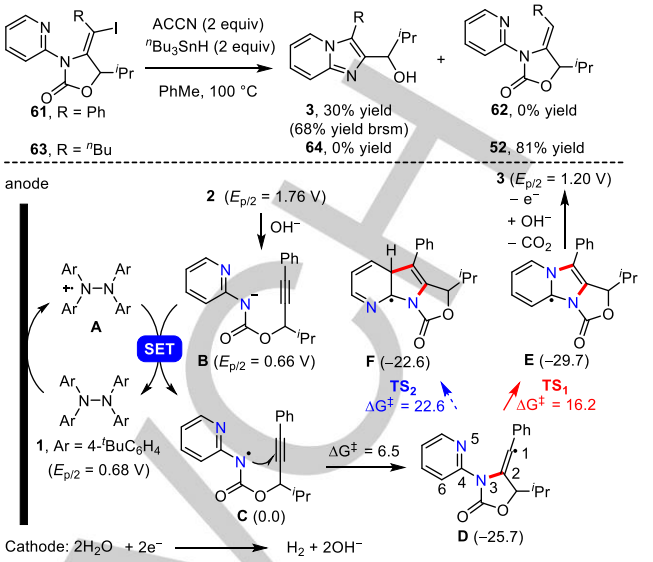


Scheme 3. Substrate scope using a urea linkage. Reaction conditions, urea substrate (0.3 mmol), **1** (0.015 mmol), Et_4NBF_4 (0.3 mmol), Na_2CO_3 (0.3 mmol), MeOH/THF (1:3, 9 mL), reflux, 7.5 mA, 4–8.5 h (3.7–8 F mol^{-1}).

As further evidence for the application potential of our method, we first demonstrated that the synthesis of **3** could be performed on a decagram scale with similarly high yield as that of the small-scale reaction (Eq. 1). Furthermore, enantioenriched (−)-**2** was shown to afford (−)-**3** without racemization (Eq. 1).



To shine light on the reaction mechanism, cyclic carbamate **61** containing a C(sp^2)–I bond was employed as the vinyl radical precursor and reacted to produce the imidazopyridine product **3** in 30% yield when treated with ACCN and nBu_3SnH (Scheme 4). These results lent support to the hypothesis that **3** was generated from the azaphilic cyclization of a vinyl radical intermediate. In comparison, the reaction of the alkyl-substituted **63** afforded only the reduced product **52**, suggesting that the alkyl-substituted vinyl radical favored H-atom abstraction over cyclization.



Scheme 4. Mechanistic studies and rationale. DFT (UB3LYP/6-31G*) calculated energetics (kcal mol^{-1}) are Gibbs free energies in the gas phase. Energies of **C**–**F** are relative to **C**. ACCN, 1,1′-azobis(cyclohexanecarbonitrile).

Based on the studies above, a possible mechanism for the electrolytic (3+2) annulation reaction was proposed using model substrate **2** (Scheme 4). The reaction begins with the anodic oxidation of tetraarylhydrazine **1** ($E_{p/2}$ = 0.68 V vs SCE), which produces a stable radical-cation intermediate **A**. Meanwhile, hydroxide is generated from the reduction of H_2O at the cathode and it deprotonates **2** to afford the anion **B**, whose oxidation potential is significantly lower than that of **2** ($E_{p/2}$ = 1.76 V for **2**, 0.66 V for **B**, vs SCE). Because of the continuous generation of the requisite base at low concentration, base-promoted ionic cyclization[5] of **2** is avoided (Scheme S1). A single electron transfer then occur from **B** to **A**, which results in the formation of amidyl radical **C** and the regeneration of **1**. The 5-*exo*-*dig* cyclization of **C** affords vinyl radical **D**, which then reacts regioselectively with the pyridyl nitrogen to generate a tricyclic radical intermediate **E**. The ensuing one-electron oxidation of **E**, followed by the hydrolysis of its carbonyl linker, forms the imidazopyridine product **3** ($E_{p/2}$ = 1.20 V), which has an oxidation potential lower than that of the starting carbamate **2**. The use of a redox catalyst instead of direct electrolysis protects the product from oxidative decomposition.

The cascade radical cyclization was further examined by DFT (density functional theory) calculations (Scheme 4). The formation of **E** via the C–N bond-forming pathway is thermodynamically and kinetically favored over the alternative C–C bond-forming pathway to give **F**. Detailed NBO (natural bonding orbital) analyses (Schemes S2 and S3) revealed that the regioselectivity of the cyclization reaction toward C–N bond formation was due to the *n*(pyridine)→*p*(C1) interaction being much more energetically favorable than that of π(pyridine)→*p*(C1). This was consistent with the observation that the dihedral angle N5–C4–N3–C2 (20.3°) in **TS₁** is much smaller than C6–C4–N3–C2 (30.1°) in **TS₂**.

In summary, we have reported a regiospecific electrochemical [3+2] annulation reaction of heteroarylamines with internal

alkynes that is applicable to the synthesis of a host of imidazo-fused *N*-heteroaromatics. This electrosynthesis is enabled by the development of a tetraarylhydrazine as the catalyst to generate the amidyl radicals and by uncovering novel reactivities of N- and C-centered radicals for C–N bond formation.

Acknowledgements

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Keywords: electrochemistry • heterocycles • radical • annulation • alkyne

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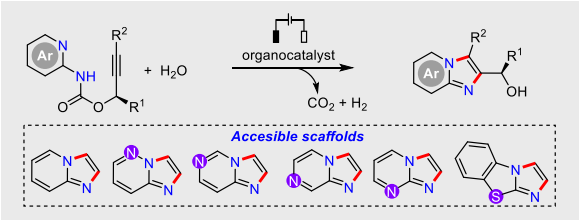

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