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Chemistry with Electrochemically Generated N-Centered Radicals

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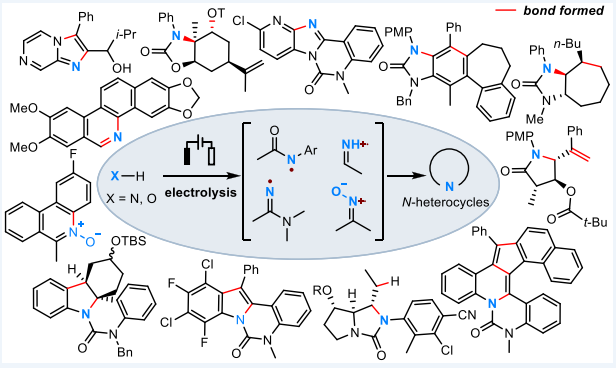
Peng Xiong and Hai-Chao Xu*

State Key Laboratory of Physical Chemistry of Solid Surfaces, Key Laboratory of Chemical Biology of Fujian Province, Innovative Collaboration Center of Chemistry for Energy Materials, and College of Chemistry and Chemical Engineering, Xiamen University, Xiamen 361005, P. R. China

CONSPECTUS: N-centered radicals are versatile reaction intermediates that can react with various π systems to construct C−N bonds. Current methods for generating N-centered radicals usually involve the cleavage of an N−heteroatom bond; however, similar strategies that are applicable to N−H bonds prove to be more challenging to develop and therefore are attracting increasing attention.

In this Account, we summarize our recent efforts in the development of electrochemical methods for the generation and synthetic utilization of N-centered radicals. In our studies, N-aryl amidyl radical, amidinyl radical and iminyl radical cation intermediates are generated from N−H precursors through direct electrolysis or indirect electrolysis assisted by a redox catalyst. In addition, an electrocatalytic method that converts oximes to iminoxyl radicals has also been developed. The electrophilic amidyl radical intermediates can participate in 5-*exo* or 6-*exo* cyclization with alkenes and alkynes to afford C-centered radicals, which can then undergo various transformations such as H atom abstraction, single-electron transfer oxidation to a carbocation, cyclization, or aromatic substitution, leading to a diverse range of N-heterocyclic products. Furthermore, amidinyl radicals, iminyl radical cations, and iminoxyl radicals can undergo intramolecular aromatic substitution to afford various N-heteroaromatic compounds. Importantly, the electrochemical reaction can be channeled toward a specific product despite the presence of other competing pathways. For a successful electrosynthesis, it is important to take into consideration of both the electron transfer steps associated with the electrode and the nonelectrode related processes.



A unique feature of electrochemistry is the simultaneous occurrence of anodic oxidation and cathodic reduction, which, as this Account demonstrates, allows the dehydrogenative transformations to proceed through H_2 evolution without the need for chemical oxidants. In addition, cathodic solvent reduction can continuously generate a low concentration of base, which facilitates anodic substrate oxidation. Such a mechanistic paradigm obviates the need for stoichiometric strong bases and avoids base-promoted decomposition of sensitive substrates or products. Furthermore, electrode materials can also be adjusted to control the reaction outcome, as demonstrated by the synthesis of N-heteroaromatics and the corresponding N-oxides from biaryl ketoximes.

1. INTRODUCTION

The prevalence of nitrogen-containing natural products, pharmaceuticals, and functional materials has simulated continued interest in the development of efficient C−N bond forming reactions. To this end, a wide variety of ionic substitution and transition metal-catalyzed cross-coupling reactions have been reported, whereas radical-based methods remain underdeveloped.[1−5] The high reactivity of several types of N-centered radicals provides excellent opportunities for forging C−N bonds that are difficult to access through alternative methods. N-centered radicals are usually generated through the cleavage of a relatively weak N−heteroatom bond or, more desirably, a N−H bond.[1−5] In the latter case, the N−H precursor can be converted to an N-centered radical either through a two-step process involving proton/electron transfer or electron/proton transfer or in a single step through proton-coupled electron transfer (PCET).[6] In the past decade, advances in single electron transfer (SET)-based methods, especially photoredox catalysis, have facilitated the rapid development of the chemistry of N-centered radicals.[3−5] However, these photochemical methods based on N−H cleavage frequently require the use of noble metal-based catalysts or stoichiometric chemical oxidants. In addition, there is a dearth of oxidative transformations.

Organic electrochemistry, which promotes chemical transformations with electricity, has been attracting increasing interest in the past few years.[7−17] Electrochemically driven

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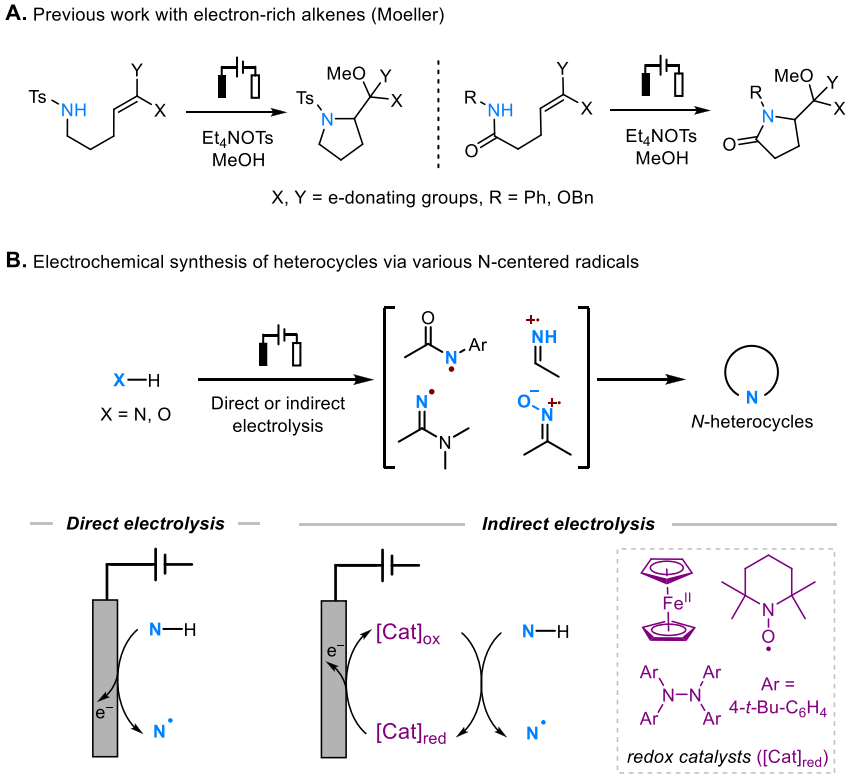

Figure 1. Electrosynthesis of N-heterocycles via N-centered radicals. Ts = *p*-toluenesulfonyl.

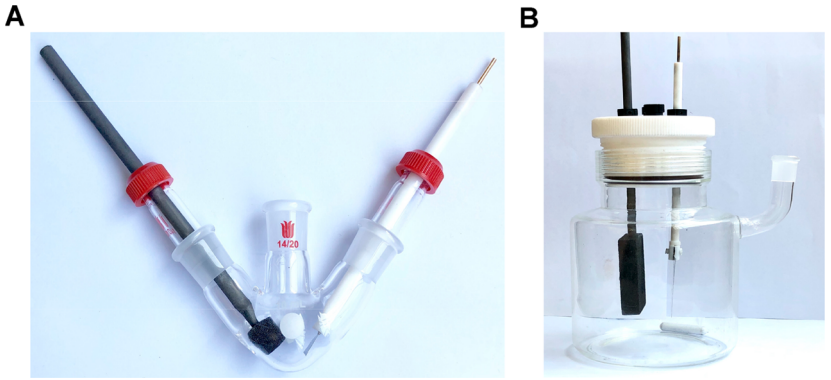

Figure 2. Electrolytic cells for milligram (A) and gram (B) scale reactions.

radical reactions would combine the benefits of environmental sustainability and tunable selectivity. Early studies by Moeller and co-workers showed that anodic oxidation of a sulfonamide or acidic amide moiety, followed by cyclization of the resultant N-centered radical, would afford a C-centered radical that can be further converted to an N-heterocyclic product (Figure 1A).[18−20] We have demonstrated that electrochemical methods provide an efficient tool for the generation of various N-centered radicals from N−H precursors through direct electrolysis or indirect electrolysis employing a redox catalyst (Figure 1B). This Account intends to summarize the results of our previous studies on the electrosynthesis of heterocycles via N-centered radicals.

2. GENERAL ASPECTS OF PREPARATIVE ELECTROSYNTHESIS

In our studies, the reactions are generally conducted in undivided cells employing a controlled current, which is the most convenient approach for preparative electrolysis. The electrolytic cell adopts a two-electrode configuration and is constructed using a three-necked round-bottomed flask or a beaker-type glass flask depending on the scale of the reaction (Figure 2). Reticulated vitreous carbon (RVC), which combines good chemical resistance and high surface area, is chosen as anode material, and Pt, a metal with excellent electrocatalytic reactivity for H_2 evolution, is usually employed as cathode material. Because current density often affects the efficiency of preparative electrolysis, the gram scale reaction is usually conducted with the same anodic current density as the milligram scale reaction. To increase productivity, the gram scale reactions employ larger electrodes to allow the use of higher current.

Electrosynthesis can be conducted using direct electrolysis or indirect electrolysis employing a redox catalyst. Direct electrolysis is relatively simple and eliminates the cost of catalysts and the need for separating the catalysts from

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products. This approach requires redox active substrates and an increase in potential (for oxidation) from substrate to product to avoid overoxidation. Additionally, the reactive radical intermediates generated heterogeneously on the electrode surface through direct electrolysis can suffer from several side reactions such as dimerization, overoxidation to cationic species, and reaction with electrode to cause electrode passivation.[17] The use of a redox catalyst allows the generation of radical species away from the electrode in the bulk solution and can thus avoid some of the above-mentioned problems associated with direct electrolysis. In addition, indirect electrolysis allows the reaction to proceed at potentials lower than those of substrates, which reduces undesirable redox processes and increases functional group tolerance. Notwithstanding these promising features of indirect electrolysis, the lack of versatile catalysts and catalytic systems hinders the development of electrocatalytic radical reactions.

3. ELECTROCHEMICAL GENERATION AND REACTIONS OF AMIDYL RADICALS

Since SET oxidation of *N*-alkyl amides requires high redox potentials and often leads to undesirable functionalization at the α carbon of the amidyl nitrogen,[21] anilides, which are more easily oxidized, are generally chosen as the radical precursors in our studies. In addition, *N*-aryl amidyl radicals are less prone to undergo H atom abstractions compared with *N*-alkyl amidyl radicals.[22] Based on these considerations, we explored different electrolysis conditions for the cyclization of alkene- and alkyne-tethered anilides (Figure 3). The anilide N−H is converted to N-centered radical through proton/electron transfer with indirect electrolysis or electron/proton transfer with direct electrolysis.

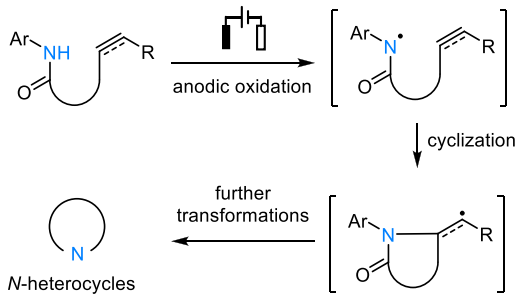

Figure 3. Electrochemical generation and cyclization of amidyl radicals.

Initial studies found that (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) could serve as an efficient redox mediator for the electrochemical amino-oxygenation of unactivated alkenes (Figure 4).[23] After the electrochemical cyclization of **1e**, the TEMPO-derived alkoxyamine group in the product **2e** can be reduced to a hydroxyl (**3a**) or eliminated altogether to form an alkene moiety (**3b**). Mechanistic studies showed TEMPO to both mediate the formation of the amidyl radical intermediate and trap the C-radical generated after the cyclization. The reaction starts with the anodic oxidation of TEMPO to generate $TEMPO^+$ and the cathodic reduction of H_2O to H_2 and HO^-. Deprotonation of substrate **1b** by HO^- leads to its conjugate base $\mathbf{1b}^-$, which can be oxidized at a much lower potential than **1b**. Therefore, SET oxidation of $\mathbf{1b}^-$ with $TEMPO^+$ furnishes an amidyl radical **4**, which subsequently cyclizes to a C-centered radical **5**. Trapping of **5** with TEMPO results in the formation of the final product **2b**.

The basic additive Na_2CO_3 is not critical for success, but its absence results in lower current efficiency and yield. For example, the yield of **2b** is reduced from 90% (1.5 F mol^{-1}) under the optimal conditions to 70% (2.5 F mol^{-1}) when Na_2CO_3 is not added to the reaction mixture. Since Na_2CO_3 is barely soluble in H_2O/MeCN (1:19) and does not affect the cyclic voltammogram of **1b**, this base is unlikely to play a major role in promoting substrate oxidation. Instead, the continuous generation of HO^- at the cathode is instrumental in facilitating amidyl radical formation and in eliminating the stoichiometric addition of a strong base.

One glaring drawback of TEMPO is its overly fast trapping of the cyclization-derived C-radical intermediate, which precludes other transformations for the cyclization-derived C-radical. Subsequent search for a noninterfering redox catalyst culminated in the discovery that ferrocene (Cp_2Fe), an easily available organometallic compound, could substitute for TEMPO to mediate the electrochemical generation of amidyl radicals from anilides.[24] Figure 5A summarizes the scheme for ferrocene-catalyzed electrochemical hydroamidation of alkene-tethered anilides, including carbamates, ureas, and amides, with 1,4-cyclohexadiene (1,4-CHD) as a H atom donor.[24] The relatively low oxidation potential of ferrocene makes it a very selective redox catalyst that is compatible with a wide array of functional groups. Notably, it is possible to selectively oxidize a PMP-substituted carbamate in the presence of a Ph-substituted one (**7c**) or a sulfonamide (**7d**). The reaction mechanism is similar to that of the aforementioned amino-oxygenation process, but with H atom transfer as the termination step. Specifically, anodic oxidation and cathodic reduction provide the requisite oxidant ferrocenium and base MeO^-, respectively, which then coordinate to convert anilide **6a** to amidyl radical **8**. Deprotonation of NH group reduces significantly the potential difference between substrates and allows anilides of diverse electronic properties to participate in the hydroamidation reaction. Subsequent cyclization of **8** affords C-radical **9**, which abstracts a H atom from 1,4-CHD or a solvent molecule to generate the hydroamidation product **7a**. The cyclohexadienyl radical derived from the H-transfer reaction of 1,4-CHD likely forms benzene after further electron and proton elimination.

Ferrocene is essential for the success of the electrocatalytic hydroamidation reaction. For instance, the omission of ferrocene from the reaction mixture resulted in no formation of **7a** when **6a** was electrolyzed under otherwise the same conditions. The oxidation potential of ferrocene is lower than that of TEMPO. For ferrocene to be an effective redox catalyst for amidyl radical formation, it is critical to use a nonpolar solvent, such as THF, to reduce the potential gap between the substrate-derived anion and ferrocene. For instance, the difference in oxidation potential between ferrocene and $\mathbf{6a}^-$ was measured to be only 60 mV in THF/MeOH (5:1) but increases to 460 mV in MeOH. With MeOH as a solvent, the hydroamidation was abolished due to a lack of effective SET between ferrocenium and $\mathbf{6a}^-$. It should be stressed that the mechanistic principle shown in Figure 4A for the amidyl radical formation is also applicable to the generation of C-centered radicals.[25−28]

Building on our success with alkene hydroamidation, we next achieved ferrocene-catalyzed stereoselective synthesis of 7-membered carbocycles through a 5-*exo*-*trig*/7-*endo*-*trig*

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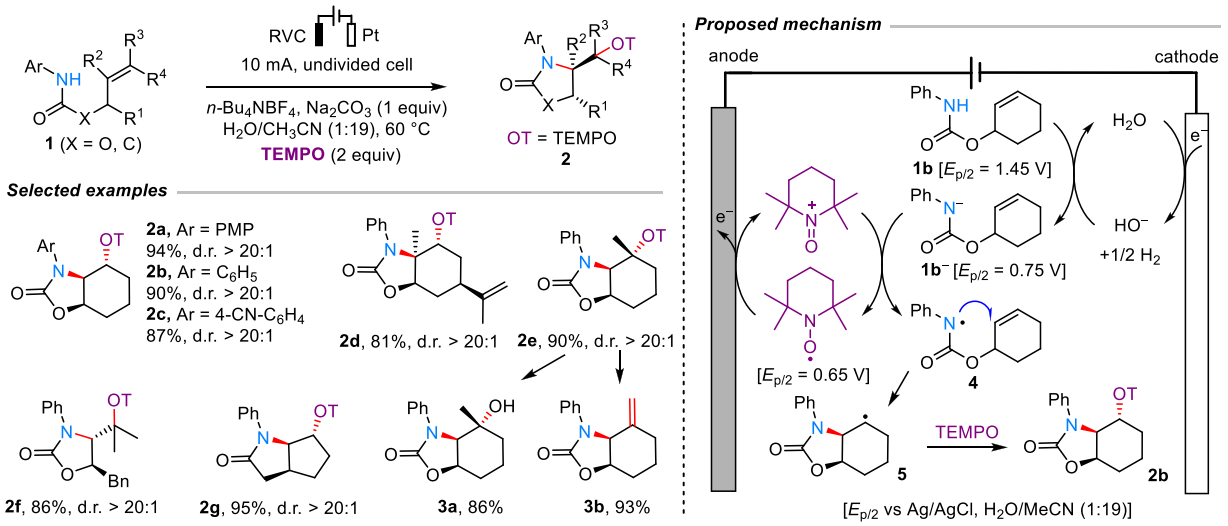

Figure 4. TEMPO-mediated electrochemical amino-oxygenation of alkenes. PMP = *p*-methoxyphenyl.

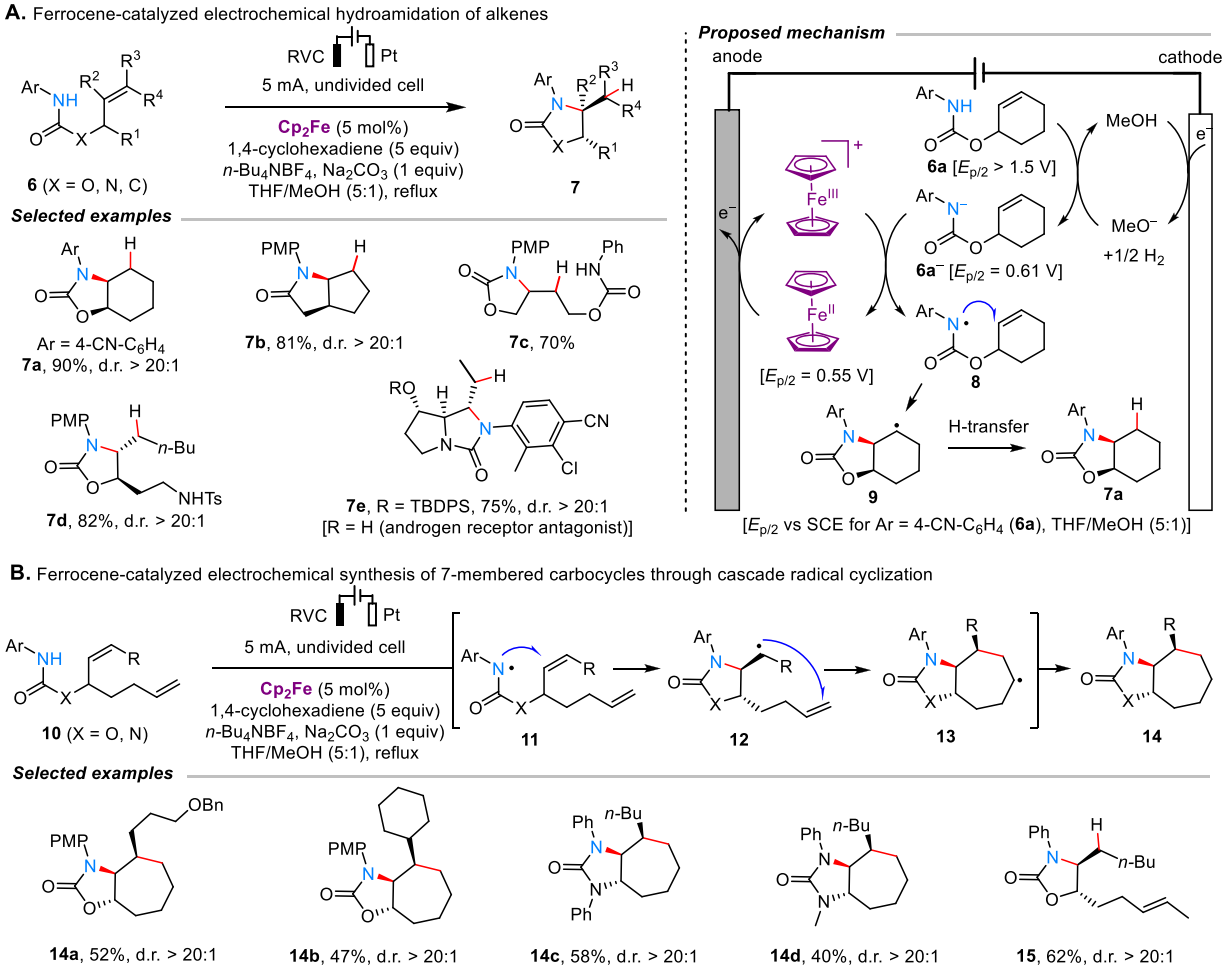

Figure 5. Ferrocene-catalyzed electrochemical generation of amidyl radicals and its application in redox neutral alkene functionalization reactions.

cyclization cascade using essentially the same reaction conditions (Figure 5B).[29] In this reaction, the cyclization-derived C-radical intermediate **12** is trapped intramolecularly by a tethered terminal alkene to form a 7-membered C-radical **13**. The latter C-radical is reduced by 1,4-CHD or the solvent to give the final product **14**. The *trans* disposition of the C-centered radical to the remaining alkene double bond in **12** likely contributes to the observed preference for 7-*endo-trig* cyclization over the 6-*exo-trig* alternative. A notable side reaction of **12** involves it undergoing intermolecular H atom abstraction. This can be triggered when the terminal alkene in **10** is replaced with an internal alkene, which would reroute C-radical intermediate **12** to form the monocyclic **15** instead of the desired bicyclic product.

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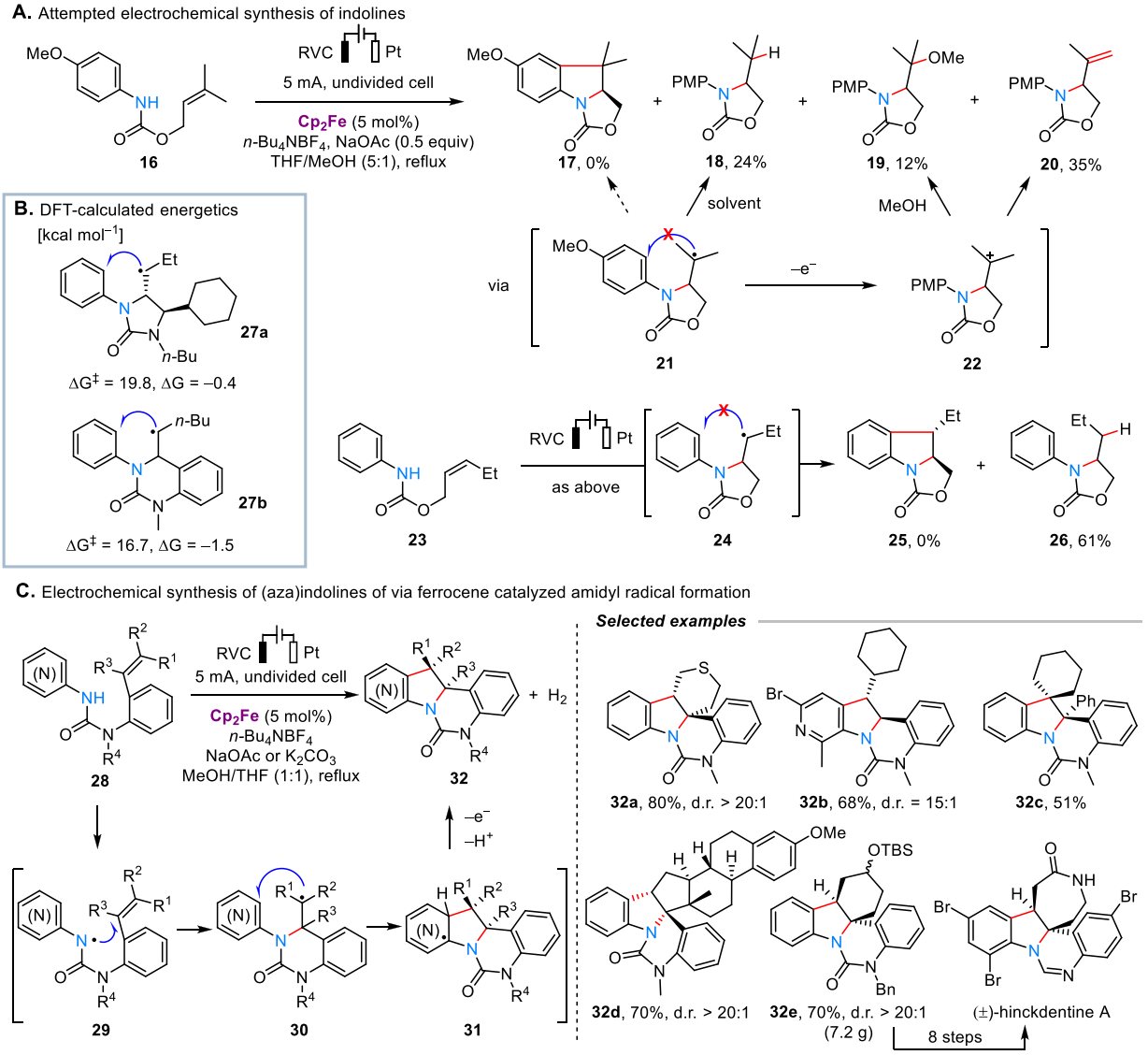

Figure 6. Electrochemical synthesis of indolines through amidyl radical-mediated intramolecular [3 + 2] annulation.

The combination of anodic oxidation and cathodic proton reduction allows dehydrogenative transformations to proceed through H_2 evolution without the need for stoichiometric chemical oxidants. Initial attempts to cyclize carbamates **16** and **23** to form indoline products **17** and **25** through intramolecular dehydrogenative annulation failed even in the absence of 1,4-CHD (Figure 6A).[30] The failure is caused by the relatively slow cyclization of the radical intermediate **21**, generated from the cyclization of the electrocatalytically derived amidyl radical intermediate, compared with H atom abstraction (**18**) or further oxidation (**22**). The same side reaction was also observed for **23**. In radical cascade cyclizations, the formation of the first ring would affect the subsequent cyclization because of reduced conformational flexibility. DFT-calculations suggested that the cyclization of radical **27b**, in which the reacting partners (C-radical and *N*-phenyl group) was placed on a six-membered ring, was kinetically and thermodynamically more favorable than radical **27a** that contained a five-membered ring linkage (Figure 6B). Consistently, the cyclization of urea **28** proceeded efficiently regardless of the substitution pattern of the alkene moiety, leading to highly functionalized indoline and azaindoline products (Figure 6C).[30] These reactions proceed through the cascade cyclization of amidyl radical **28** to give **31**, which undergoes electron and proton loss to afford the final product **32**. Compound **32e**, prepared on a gram scale, can be further converted in 8 steps to hinckdentine A, a natural product derived from *Hincksinoflustra denticulata*.

There have been substantially fewer published studies on the cyclization of N-centered radicals with alkynes than with alkenes, probably due to the high propensity of N−H-based precursors to undergo ionic reactions.[31,32] For example, alkyne **33** can easily undergo intramolecular hydroamidation in the presence of a catalytic amount of MeO^-. Fortunately, the use of ferrocene enables efficient dehydrogenative annulation of **33** to furnish highly functionalized indole and azaindole derivatives (Figure 7A).[33] These results highlighted the unique ability of our electrochemical method to effect radical reactions of base-sensitive substrates. Following annulation, indole derivative **35f** can be further converted to isocryptolepine (**36**) in one step. The same synthetic strategy can also be applied to the cyclization of diyne substrates to generate polycyclic N-heteroaromatic compounds (Figure 7B).[34] Note that the use of a redox catalyst with relatively low oxidation

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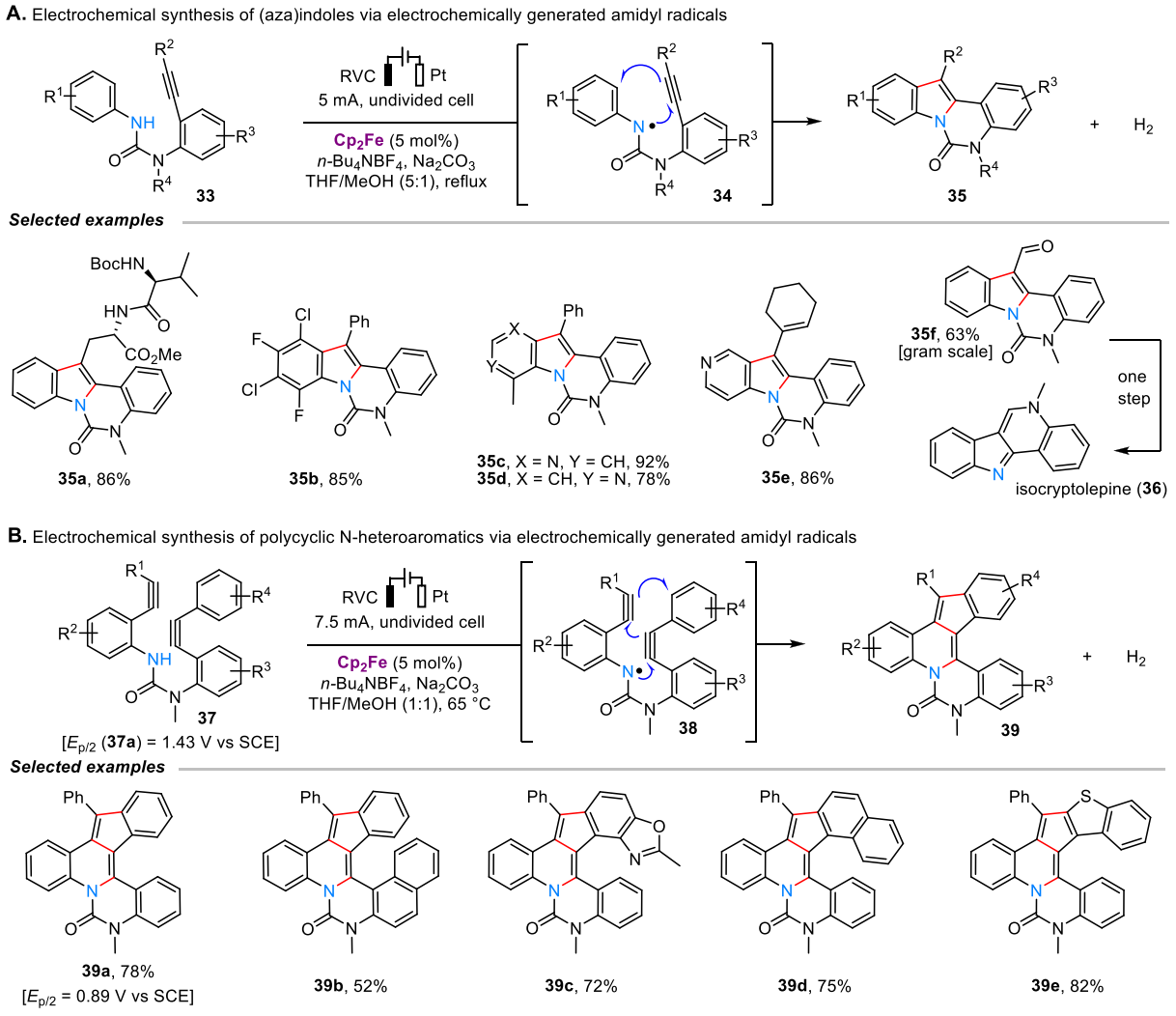

Figure 7. Electrochemical synthesis of N-heteroaromatics via amidyl radical mediated dehydrogenative cyclization cascades.

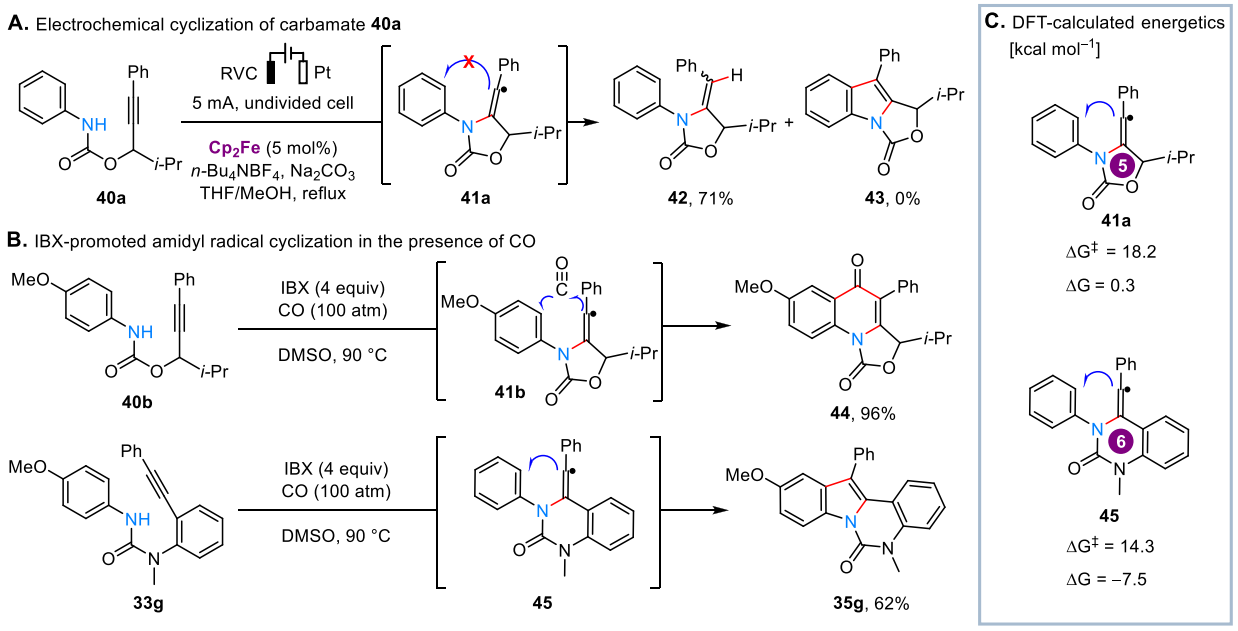

Figure 8. Effect of fused rings on vinyl radical cyclizations. IBX = 2-iodoxybenzoic acid.

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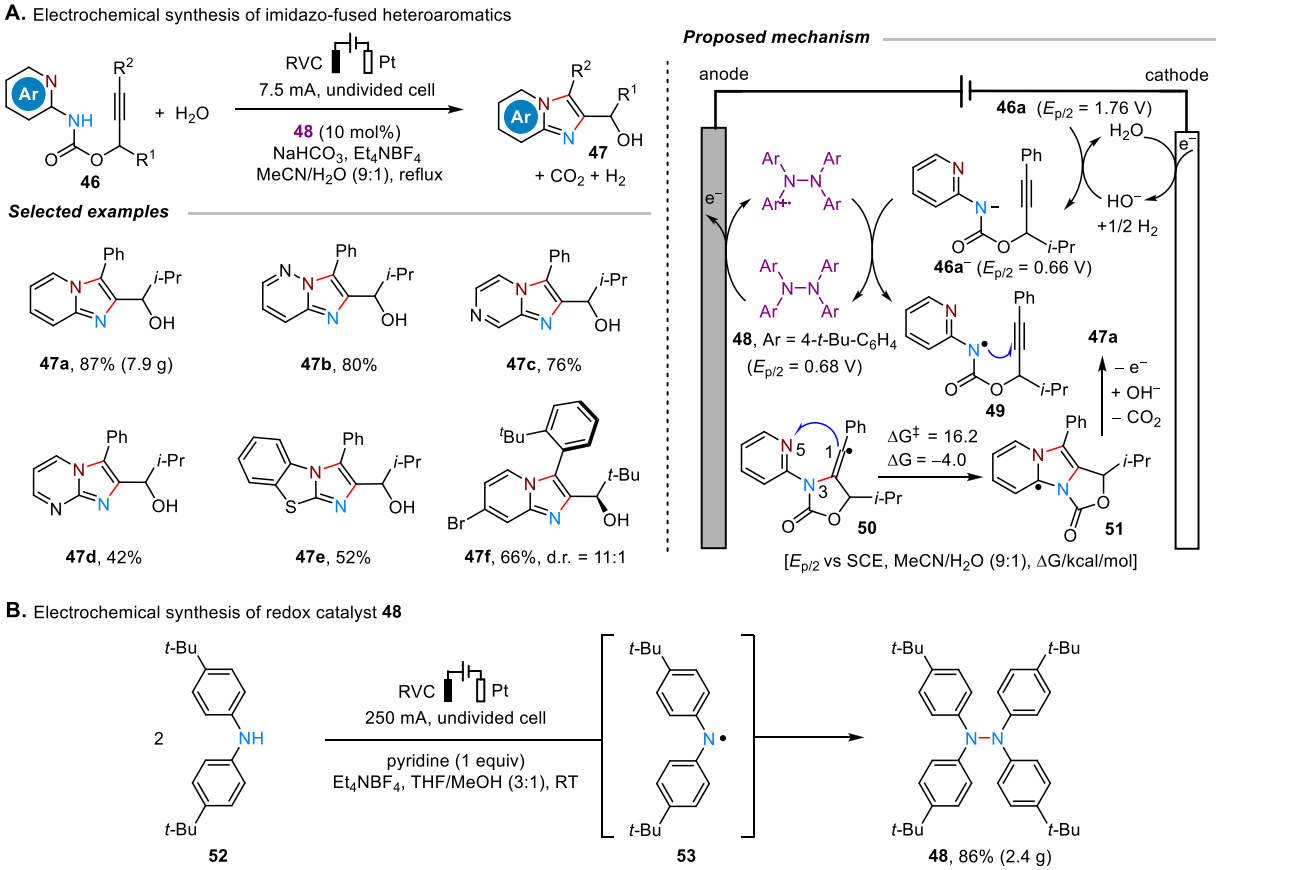

Figure 9. Electrochemical synthesis of imidazo-fused heteroaromatics employing an organic redox catalyst.

potential instead of direct electrolysis is critical for success because the heteroaromatic products formed during the electrolysis are oxidized at close or even lower potentials than the starting materials.

Similar to the reaction of allylic alcohol-derived anilide **23**, the electrolysis of carbamate **40a**, prepared from a propargylic alcohol, affords only the monocyclized hydroamidation product **42** in 71% yield (Figure 8A). Apparently, the cyclization of the vinyl radical intermediate **41a** onto the *N*-phenyl ring cannot compete with H atom abstraction from solvent molecules. In another amidyl radical reaction with carbamate **40b** as substrate, the addition of the corresponding vinyl radical **41b** onto the N-PMP group is slow enough that the intermediate can be trapped with CO prior to the cyclization to give rise to 2-quinolone products (Figure 8B).[35] It should be noted that IBX, an oxidant known to promote the formation of amidyl radicals from anilides, needs to be employed,[36] but its competitive oxidation of solvent molecules (DMSO) restricts the reaction scope to electron-rich substrates. In contrast, the reaction of **33g** under the same conditions affords indole **35g** without CO incorporation,[35] which can be attributed to the kinetic preference for the cyclization of **45**. This was also confirmed by DFT calculations (Figure 8C).[33]

Replacing the *N*-phenyl group in **40a** (Figure 8A) with an N-heteroaryl moiety (**46**) greatly improves the efficiency of cascade cyclization, providing convenient access to a variety of imidazo-fused N-heteroaromatic products **47** (Figure 9A).[37] In this reaction, ferrocene is replaced with tetraarylhydrazine **48**, which is a more powerful oxidant in the employed solvent system [$E_{p/2}$(**48**) = 0.68 V vs SCE, $E_{p/2}(Cp_2Fe)$ = 0.34 V vs SCE, MeCN/H_2O (9:1)]. Annulation of **46f**, which carries a sterically demanding *t*-Bu at both alkynyl and propargylic positions is shown to afford axially chiral biaryl **47f** with good diastereoselectivity.[38] A possible mechanism is illustrated in Figure 9A (right panel), in which electrocatalytically generated amidyl radical **49** undergoes cascade cyclization to form a tricyclic radical intermediate **51**. SET oxidation of **51**, followed by hydrolysis of the carbonyl moiety, furnishes the final product **47a**. DFT calculations suggested that the regioselective C−N bond formation between the vinyl radical (C1) and the pyridyl nitrogen (N5) is likely driven by an energetically more favorable n(pyridine) → p(C1) interaction over p(pyridine) → p(C1).[37]

An electrochemical method has also been developed for synthesizing redox catalyst **48** through the dimerization of diarylamine **52**, likely via aminyl radical intermediate **53** (Figure 9B).[33,39]

The formation of alkene **20** through the electrolysis of **16** (see Figure 6A) encouraged us to develop a metal- and oxidant-free intramolecular oxidative amination reaction.[40,41] A noticeable challenge is that protic solvents such as MeOH and H_2O, which are preferred under the electrocatalytic conditions for generating the requisite amidyl radical intermediates, are often nucleophilic and thus readily react with the carbocation intermediates. To address this problem, we employed a direct electrolysis approach with a non-nucleophilic solvent, $AcNMe_2$ (Figure 10A).[42] Dehydrogenative amination of N-aryl amides, carbamates, or ureas (**54**) tethered to tri- or tetra-substituted alkenes yields heterocycles (**55**) bearing an alkenyl moiety that can be further derivatized. Unlike the aforementioned electrocatalytic methods, this direct electrolysis approach is

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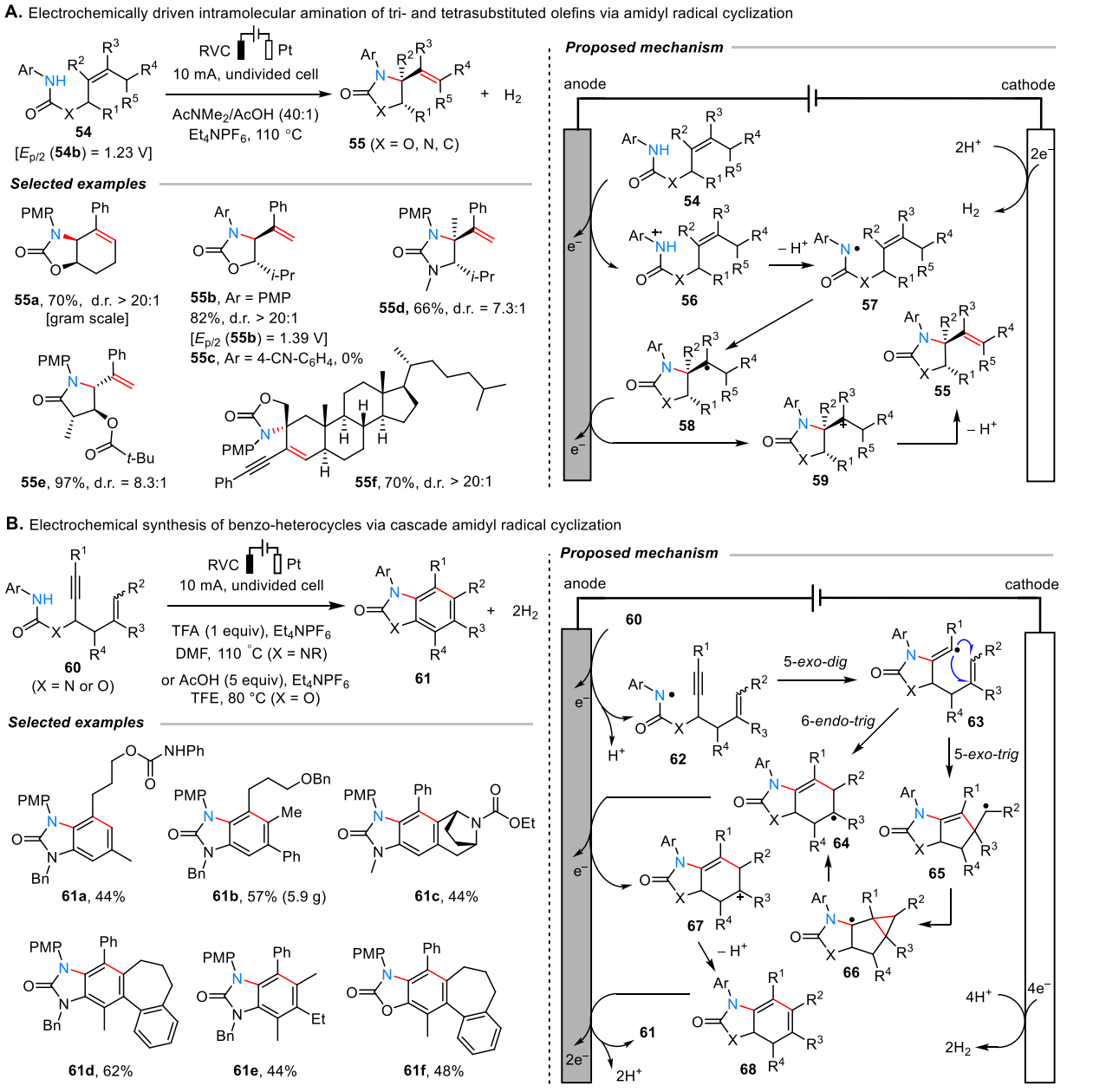

Figure 10. Cyclization reactions of amidyl radicals generated through direct electrolysis. TFA = trifluoroacetic acid. TFE = 2,2,2-trifluoroethanol.

not compatible with substrates bearing electron-deficient N-aryl groups because of competitive oxidation of solvent. For example, the electrolysis of compound **54c** bearing an electron deficient aryl group (4-CN-C_6H_4) failed to afford any of the desired **55c** and left most of the starting material intact. Mechanistically, **54** undergoes anodic oxidization to give radical cation **56**, which loses a proton to furnish amidyl radical **57**. Cyclization of **57**, followed by anodic oxidation of the resultant tertiary C-radical **58**, leads to carbocation **59**, which then regioselectively eliminates a proton to form the final product **55**. Importantly, the oxidation potential of **55** is greater than that of **54** [e.g., $E_{p/2}$(**54b**) = 1.23 V vs $E_{p/2}$(**55b**) = 1.39 V], which ensures that the product is not overoxidized. Furthermore, the addition of AcOH facilitates H_2 generation at the cathode. It should be noted that 1,2-disubstituted alkenes are poor substrates due to the lower stability of secondary carbocations.

Building on our experience with amidyl radical cascades, we designed an array of enyne substrates (**60**) for the regiospecific synthesis of highly substituted benzimidazolones and benzoxazolones (Figure 10B).[43] Like the reaction of **54**, the dehydrogenative cyclization of **60** is achieved through direct electrolysis under acidic conditions in a non-nucleophilic solvent such as DMF or TFE. Mechanistically, *5-exo-dig* cyclization of the amidyl radical **62** generated on the anode from **60** affords a vinyl radical **63**, which then gives rise to a tertiary C-radical **64** either directly via *6-endo-trig* cyclization or indirectly via a two-step process of *5-exo-trig* cyclization and ring expansion that involves the formation of intermediates **65** and **66**. Anodic oxidation of **64** affords the carbocation **67**, which loses a proton to give diene **68**. The latter eventually undergoes further dehydrogenation on the anode to afford the final product **61**. Again, the higher redox potential of **61** compared to that of **60** ensures that it is not further oxidized under the employed electrochemical conditions.

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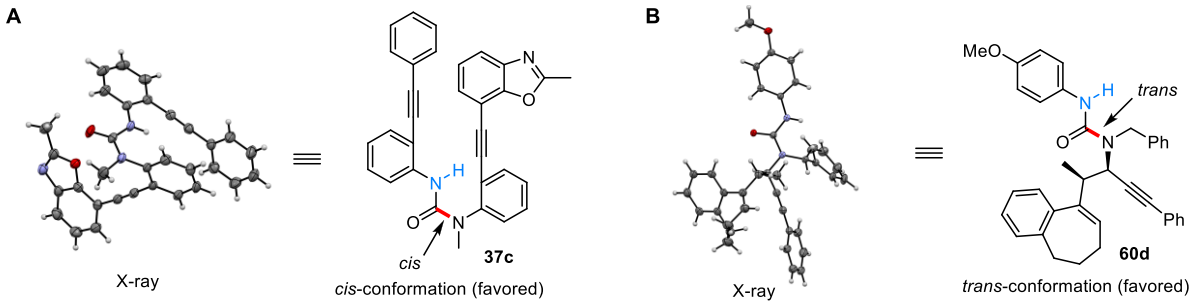

Figure 11. ORTEP drawings of urea substrates **37c** (A) and **60d** (B).

In the above discussions, all the urea-derived amidyl radicals are drawn as the *cis*-conformation, the one that can cyclize. However, the preferred conformation of a urea is structurally dependent. For example, while urea **37c** preferred the *cis*-conformation,[34] compound **60d** adopts the *trans*-conformation as revealed by X-ray crystal structural analysis (Figure 11).[43] Since the barrier for conformational change of ureas from *trans* to *cis* is predicted to be higher than that of the amidyl radical 5-*exo* cyclizations, heating, which helps speed up the conformational change, is found to be critical for the electrochemical cyclization reactions of urea **60**.[43]

4. ELECTROCHEMICAL GENERATION AND REACTIONS OF σ-TYPE N-CENTERED RADICALS

σ-Type N-centered radicals, such as iminyl radicals, are generally produced through the cleavage of a relatively weak N−X (X = O, N, etc.) bond.[44] In our studies, it was found that the electrolysis of amidines **69** in refluxing MeOH afforded 2-aryl benzimidazole and pyridoimidazole products (**72**) (Figure 12A).[45] While substrates derived from meta-substituted anilines result in a mixture of regioisomers (e.g., **72b**), 3-aminopyridine-derived substrates can react in a regioselective manner at the position ortho to the pyridyl nitrogen (e.g., **72d**). Note that overoxidation of the benzimidazole product was observed in cases where the amidine contained an electron-rich N-aryl ring because of the close oxidation potential of the product with the starting amidine. Mechanistic studies suggested that the C−N bond formation involves the cyclization of amidinyl radical **70** onto the N-aryl ring.

Encouraged by the success with the cyclization of amidines, we envisioned that the electrolysis of biaryl imines could provide a simple approach to synthesize phenanthridines and the structurally related pyridine-fused N-heteroaromatic compounds. Indeed, the electrolysis of aldehydes **73** in the presence of NH_3 in a mixed solvent of HFIP/MeOH at RT proved successful in generating a variety of polycyclic N-heteroaromatic compounds (**76**) (Figure 12B).[46] When meta-substituted substrates are used, the N-radical intermediate adds to the phenyl ring regioselectively at the position para to the substituent (e.g., **76b**). In contrast, previously reported iminyl radical cyclization reactions for synthesizing phenanthridines were much less selective and favored ortho cyclization.[47] The experimental observations, together with DFT calculations, suggested that the C−N bond formation during the electrolysis of biaryl imines formed in situ proceeded most likely through cyclization of radical cation intermediate **74** instead of a deprotonated neutral iminyl radical. Additionally, HFIP also plays a crucial role in stabilizing the radical cation intermediates. In the synthesis of nornitidine (**76e**), controlled-potential electrolysis (1.50 V vs SCE) is required to avoid product overoxidation ($E_{p/2}$ = 1.57 V vs SCE).[46]

Iminoxyl radicals, which are σ-radicals with both a reactive oxygen and nitrogen, have been shown to be able to cyclize with alkenes and alkynes.[48,49] We have demonstrated that this synthetic strategy can be applied to the preparation of N-heteroaromatics, with arenes as substrates (Figure 12C).[50] N-Heteroaromatic N-oxides **78** can be synthesized from easily available biaryl ketoximes **77**, by performing electrolysis in an aqueous solution with TEMPO as redox catalyst and a Pt-based cathode. Interestingly, switching to a Pb cathode leads to deoxygenated N-heteroaromatics **79** instead. Both types of products can be obtained with high regioselectivity when meta-substituted ketoximes are employed (e.g., **78b** and **79b**). In fact, electrochemical cyclization of these ketoximes is found to be even more selective than that of biaryl aldimines described above, probably due to their increased steric hindrance. Unlike the reactions shown in Figure 11A,B, the redox catalyst is essential for the cyclization of ketoximes. As an example, the reaction of **77a** in the absence of TEMPO afforded **78a** in only 14% yield. Mechanistically, an iminoxyl radical (resonance structures **80a** and **80b**) is first generated through TEMPO-catalyzed anodic oxidation and undergoes selective N-cyclization to furnish intermediate **81**, which is subsequently converted to N-oxide **78** via TEMPO-assisted rearomatization. When the reaction is performed with a Pt cathode, H_2O is reduced to generate H_2 and HO^-, whereas the use of a Pb cathode, which has a higher overpotential for H_2 evolution, leads to the reduction of **78** and the concomitant formation of **79** as the final product.[51,52]

5. CONCLUSIONS AND OUTLOOK

SET oxidation provides a straightforward approach for the generation of synthetically useful radical intermediates from easily available and stable materials. In this context, electrochemistry is an attractive synthetic tool for effecting SET processes due to its inherent sustainability and tunability. As summarized in this Account, various N-centered radicals, such as N-aryl amidyl radicals, amidinyl radicals, iminyl radical cations, and iminoxyl radicals, can all be efficiently generated from easily available precursors through electrochemical SET oxidation. The ensuing cyclization of these reactive intermediates with various π-systems results in a host of structurally diverse N-heterocycles. A notable advantage of our method is that anodic oxidation and cathodic proton reduction occur simultaneously, which allows the dehydrogenative reactions to proceed through H_2 evolution and thus obviates the need for electron and proton acceptors and stoichiometric strong bases.

Future research will aim at expanding the application scope of our electrochemical methods so that a wider variety of N-

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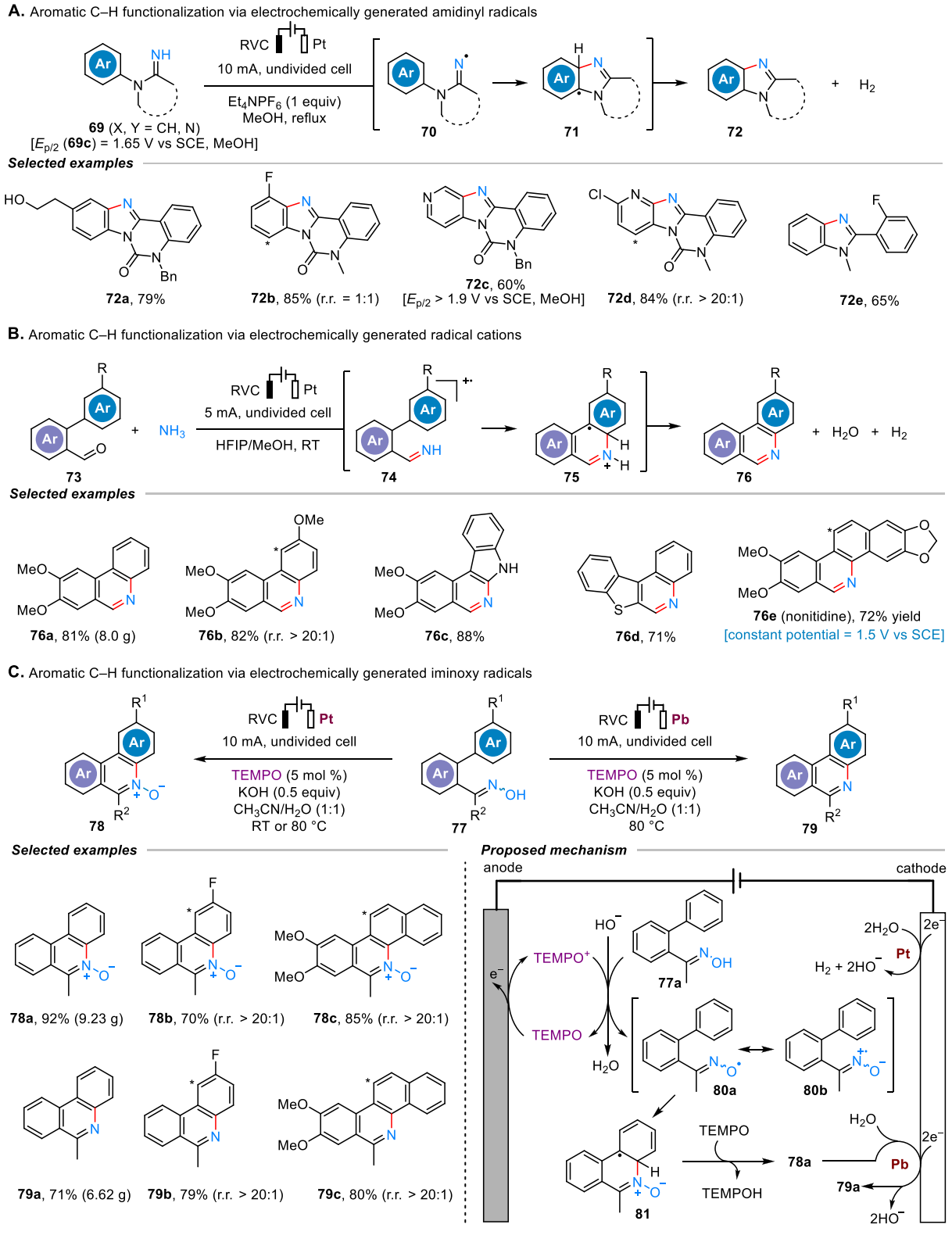

Figure 12. Electrochemical synthesis of N-heteroaromatics via σ-type N-centered radicals. HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol.

centered radicals can be accessed. In addition, established transformations rely mainly on the innate reactivities of the radical intermediates. Merger of electrochemistry with other catalytic technologies such as transition metal catalysis to modulate the reactivities of radicals will allow them to participate in new transformations. These efforts will further enhance the synthetic utilities of electrochemically generated N-centered radicals.

AUTHOR INFORMATION

Corresponding Author

*Email: haichao.xu@xmu.edu.cn.

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ORCID

Hai-Chao Xu: 0000-0002-3008-5143

Notes

The authors declare no competing financial interest.

Biographies

Peng Xiong was born in 1992 in Jiangxi, China. He earned a B.S. degree in Chemistry from Nanchang University in 2014 and a M.S. degree in Chemistry from Xiamen University in 2017. He is currently a third-year Ph.D. student at Xiamen University under the supervision of Professor Hai-Chao Xu. His thesis research centers on the chemistry of electrochemically generated radical intermediates.

Hai-Chao Xu was born in 1983 in Hunan, China. He joined Xiamen University, China, in 2013 and has been a Professor of Chemistry since 2014. He obtained a B.S. in Chemistry in 2006 from Xiamen University. After graduation, he moved across the Pacific to continue his education at Washington University in St. Louis, USA, where he obtained his Ph.D. in Chemistry with Professor Kevin. D. Moeller in 2010. From 2011 to 2013, he worked as a postdoctoral associate in the laboratory of Professor Jonathan A. Ellman at Yale University, USA. His research focuses on organic electrochemistry and radical chemistry.

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