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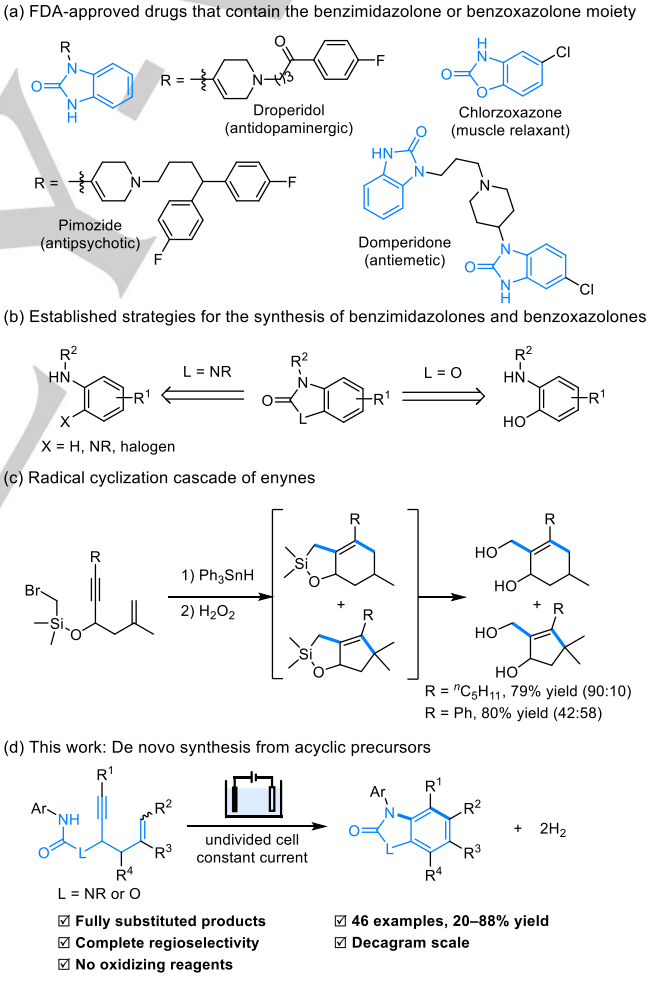
De Novo Synthesis of Highly Functionalized Benzimidazolones and Benzoxazolones by an Electrochemical Dehydrogenative Cyclization Cascade

Fan Xu,[a,+] Hao Long,[a,+] Jinshuai Song,[b] and Hai-Chao Xu[a,*]

Abstract: Benzimidazolone and benzoxazolone moieties are important scaffolds in a variety of pharmaceutical molecules. These bicyclic heterocycles are usually prepared from a benzene derivative through the construction of an additional five-membered heterocyclic ring. We report herein a methodology that enables the efficient synthesis of highly substituted benzimidazolone and benzoxazolone derivatives by building both the benzene and the heterocyclic rings via a dehydrogenative cyclization cascade. Readily available arylamine-tethered 1,5-enynes undergo biscyclization/dehydrogenation cascade to afford functionalized benzanellated heterocycles in a single step with complete control of regioselectivity. These electricity-powered oxidative transformations proceed via H_2 evolution, obviating the need for transition metal-based catalysts and oxidizing reagents.

Many FDA drugs, including droperidol, pimozide, domperidone and chlorzoxazone, contain a benzimidazolone or benzoxazolone scaffold (Scheme 1a).[1] The construction of these structural cores generally relies on the functionalization of benzene derivatives such as carbonylation of *o*-phenylenediamine[2] or 2-aminophenol[3] and cyclization of a functionalized aniline derivative (Scheme 1b).[4] An obvious limitation is that the structural diversity of the synthesized benzimidazolone and benzoxazolone derivatives is limited due to the narrow range of starting substrates that can be used.

Organic electrochemistry is an enabling and inherently green synthetic technology that employs traceless electric current to promote redox reactions[5] Compared to conventional synthetic methods, electrosynthesis obviates the use of potentially hazardous redox reagents, and demonstrates remarkable reaction versatility toward a wide range of organic substrates thanks to tunable electrode potentials.[6] We[7] have previously reported the electrochemical synthesis of N-heterocycles through amidyl radical[8] cyclization reactions. These results prompted us to boldly speculate that an electrochemically enabled radical cyclization cascade could be employed to prepare benzoheterocycles through de novo construction of the bicyclic scaffold. Despite that it is difficult to obtain the 6,5-fused ring system through radical cyclization of enynes under reductive conditions (Scheme 1c),[9] we have successfully implemented the strategy under electrochemical conditions. Herein, we report the electrochemical synthesis of benzimidazolones and benzoxazolones by constructing both the benzene ring and the five-membered heterocyclic ring in a single step from arylamine-tethered 1,5-enynes (Scheme 1d). Our synthetic strategy provides facile access to highly functionalized benzoheterocycles with diverse substitution patterns with complete regiocontrol. In addition, the electrochemical dehydrogenative reactions proceed via H_2 evolution, which obviates the need for sacrificial oxidizing reagents and proton acceptors.



Scheme 1. Synthesis of benzimidazolones and benzoxazolones.

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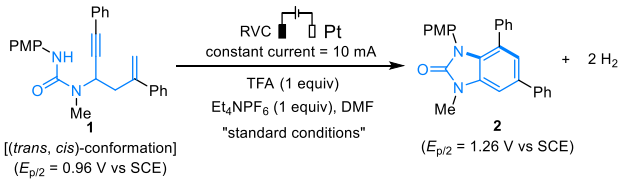
Table 1. Optimization of reaction conditions.[a]



[(*trans*, *cis*)-conformation] ($E_{p/2}$ = 0.96 V vs SCE)

($E_{p/2}$ = 1.26 V vs SCE)

Entry	Deviation from standard conditions	Yield [%][b]
1	none	83[c]
2	No TFA	65[c]
3	Reaction at 50 °C	26 (27)
4	DMA as solvent	54 (9)
5	DMSO as solvent	51
6	TFE as solvent	68
7	Pt plate (1 cm x 1 cm) as anode	39 (13)
8	Graphite plate (1 cm x 1 cm) as anode	36 (5)
9	Ni plate (1 cm x 1 cm) as cathode	66 (8)
10	Stainless steel plate (1 cm x 1 cm) as cathode	51
11	RVC (1 cm x 1 cm x 1.2 cm) as cathode	14 (42)

[a] Reaction conditions: reactions run on a 0.2 mmol scale (j_{anode} = 0.15 mA cm^{-2} for entry 1), RVC (1 cm x 1 cm x 1.2 cm), Pt plate (1 cm x 1 cm), solvent (6 mL), argon, 2.7 h (5.0 F mol^{-1}). [b] Determined by ^1H NMR analysis using 1,3,5-trimethoxybenzene as the internal standard. Unreacted **1** in parenthesis. [c] Yield of isolated **2**. PMP, *p*-methoxyphenyl; DMF, dimethylformamide; DMA, dimethylacetamide; TFE, 2,2,2-trifluoroethanol.

We first investigated the electrochemical dehydrogenative cyclization of an easily available urea substrate **1** in a three-necked round-bottomed flask equipped with two electrodes (Table 1). Base additives were specifically avoided due to the susceptibility of **1** to base-promoted ionic hydroamidation (Figure S1). On the other hand, the substrate is stable under acid conditions. After reaction optimization, we obtained the target benzimidazolone product **2** in 83% yield by performing the electrolysis at 100 °C and a constant current of 10 mA, with a reticulated vitreous carbon (RVC) anode, a platinum plate cathode, 1 equiv of trifluoroacetic acid (TFA) as acid additive, and DMF as solvent (entry 1). The oxidation potential of the product **2** ($E_{p/2}$ = 1.26 V vs SCE) was higher than that of starting material **1** ($E_{p/2}$ = 0.96 V vs SCE), which prevented the oxidative decomposition of **2** during the electrolysis. The inclusion of TFA was found to significantly improve the yield of **2** (entry 2), likely by facilitating cathodic proton reduction[27] and avoiding base-promoted side reactions mentioned above. Lowering the reaction temperature to 50 °C (entry 3) or replacing DMF with another solvent such as DMA (entry 4), DMSO (entry 5) or TFE (entry 6), all resulted decreased product formation. We speculated that heating was necessary for the urea substrate **1** to overcome the energy barrier of a conformational change from its preferred (*trans*, *trans*)-conformation to the (*trans*, *cis*)-conformation required for its cyclization (Figure S2).[10] Alternative anode materials, such as Pt (entry 7) and graphite (entry 8), as well as cathode materials with greater overpotential for proton reduction, such as Ni (entry 9), stainless steel (entry 10) and RVC (entry 11), were all less effective in promoting the product formation compared to the original choice of RVC and Pt.

The scope of the electrochemical synthesis of benzimidazolones was explored by varying the substituents of the urea substrate (Scheme 2, Ar and R^1–R^5). In addition to the electron-rich PMP substituent, the reaction was shown to tolerate not only unsubstituted benzene (**3**), but also a broad range of functionalized phenyl moieties with diverse electronic properties, including those bearing a Me (**4**), F (**5**) or CN group (**6**) on the terminal urea nitrogen. On the other hand, the Me group on the linking nitrogen could be replaced with a removable Bn (**6**–**8**), ^{n}Bu (**9**) or Ph (**10**). The terminal alkynyl position (R^2) could be functionalized with a 2-thiophenyl (**13**) or cyclohexenyl (**18**) substituent. Alternatively, R^2 could also be installed with a primary (**14**, **15**, and **19**–**21**), secondary (**22**), or tertiary (**23**) alkyl group. It is worth noting that a terminal alkyne (R^2 = H) led to the formation of the desired product (**16**), albeit in a low yield (20%). The electrochemical reaction also demonstrated broad compatibility with different substituents on the alkenyl positions (R^3, R^4). For example, 1,1-disubstituted alkenes bearing a sterically bulky ^{t}Bu substituent (**11**) or an alkynyl group (**12**) could be converted to the corresponding benzimidazolone products in moderate yields. Similarly, trisubstituted alkenes were shown to be excellent substrates for the synthesis of benzimidazolone derivatives bearing a penta-substituted benzene ring (**17**–**23**). In addition to acyclic olefins, alkenes embedded in a 5- (**24**), 6- (**25**–**28**) or 7- (**29**) membered ring were also well tolerated. Remarkably, our method could be used to efficiently synthesize a panel of fully substituted benzimidazolones (**30**–**35**). Finally, the alkenyl moiety could be replaced with an aryl group such as a phenyl (**36**) or a naphthyl ring (**37**), providing facile access to naphthyl- and phenanthryl-fused imidazolidinones.

We next investigated whether our electrochemical cyclization cascade could be used to prepare functionalized benzoxazolones from propargylic carbamates (Scheme 3). We first tested the same reaction conditions that we used earlier for benzimidazolone synthesis, which unfortunately resulted in poor yield (18% for **38**) probably due to acid induced decomposition of the propargylic carbamate substrate. However, conducting the electrolysis in refluxing TFE (80 °C) with AcOH (5 equiv) as the acid additive led to significant yield improvement. Subsequent studies found the reaction to be compatible with a variety of 1,1-substituted alkenes carrying alkyl groups with different steric properties and aryl groups， such as Me (**38** and **39**), cyclohexyl (**40**), ^{t}Bu (**41**) and *p*-chlorophenyl (**42**). Fully substituted benzoxazolones, such as **43**, could also be synthesized in satisfactory yield. Similar to what was observed in the benzimidazolone synthesis, substitution of the alkene moiety with an aryl group afforded naphthyl- and even phenanthrenyl-fused oxazolidones efficiently (**44**–**47**).

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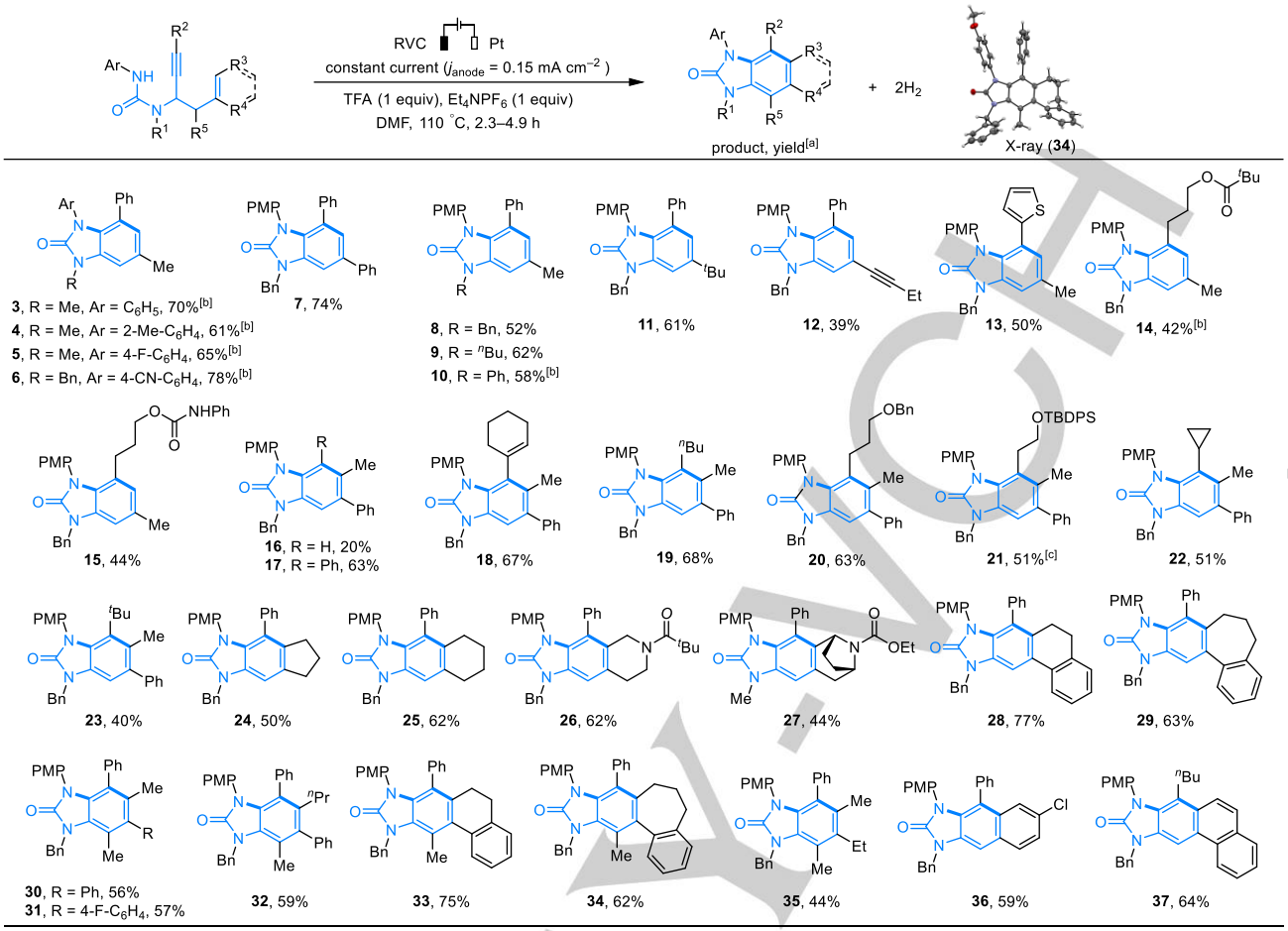
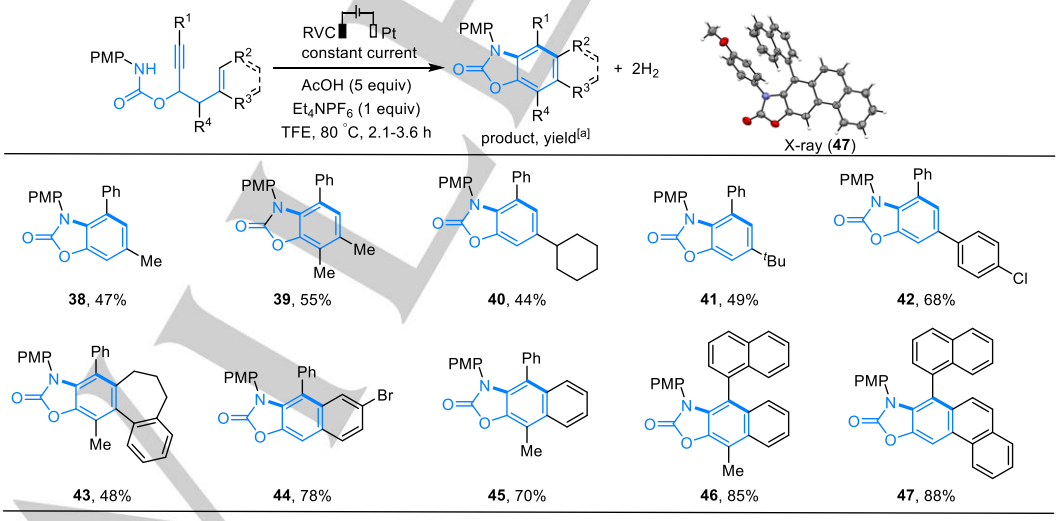


Scheme 2. Scope of benzimidazolone synthesis. [a] Yield refers to isolated yield of purified product (0.2 mmol scale), 4.2–9.2 F mol^{-1}. [b] No TFA. [c] AcOH (5 equiv) instead of TFA. Bn, benzyl; TBDPS, *tert*-butyldiphenylsily.



Scheme 3. Scope of benzoxazolone synthesis. [a] Yield refers to isolated yield of purified product (0.2 mmol scale), 4.0–6.7 F mol^{-1}.

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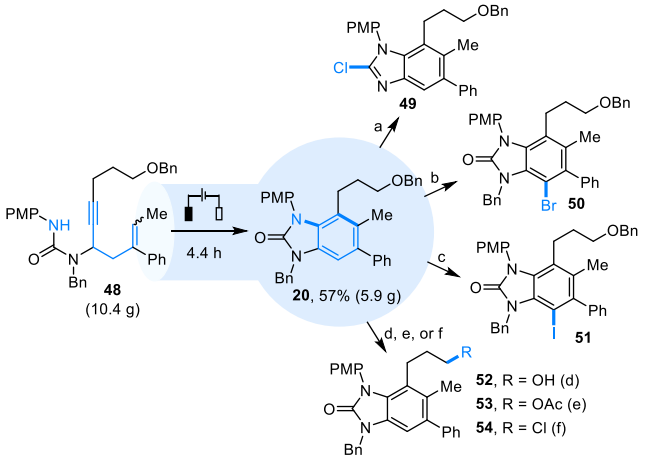
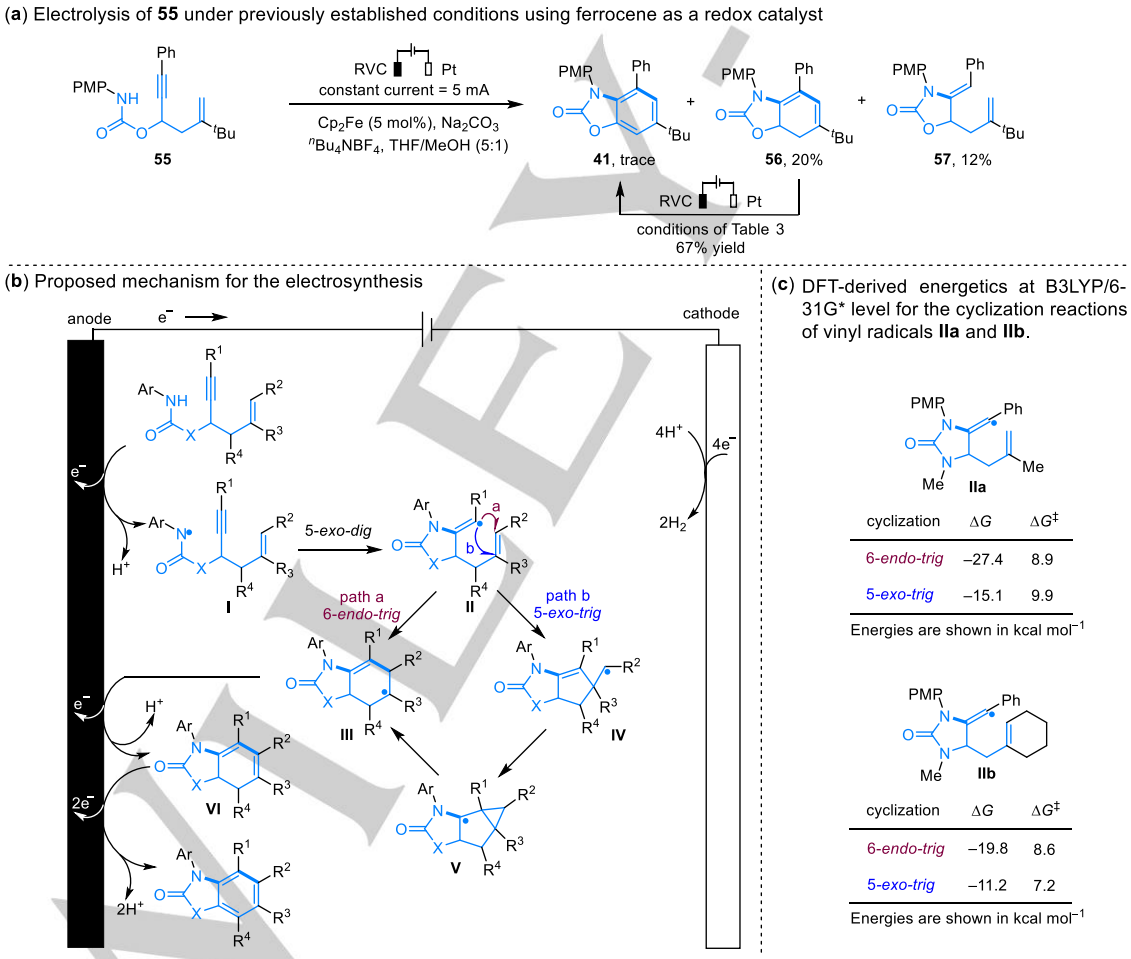


Scheme 4. Gram-scale synthesis and chemoselective derivatization of benzimidazolone **20**. Reaction conditions: a. i) ^{t}BuOK, O_2, DMSO, rt, 72%; ii) $POCl_3$, 110 °C, 52%. b. NBS, HBr, CH_3CN, rt, 82%. c. I_2, Ag_2SO_4, EtOH, 85 °C, 53%. d. $Pd(OH)_2/C$, H_2, MeOH, rt, 88%. e. AcCl, $AlCl_3$, CH_2Cl_2, 0 °C, 65%. f. $POCl_3$, DMF, 80 °C, 99%.

The electrochemical cyclization reaction could be applied on a decagram scale (Scheme 4), as demonstrated by the successful synthesis of 5.9 g of benzimidazolone **20** from 10.4 g of **48** (57% yield). In addition, **20** could subsequently be converted to chlorobenzimidazole **49** by chemoselectively removing its N-Bn group and then reacting with $POCl_3$. The remaining hydrogen on the penta-substituted benzene ring of **20** could be substituted by a bromine (**50**) or an iodine (**51**) to provide a functional group handle for further derivatization. The side chains could also be chemoselectively functionalized. For example, the OBn group on the alkyl chain could be orthogonally deprotected (**52**), or converted to an acetoxy (**53**) or chloro **(54)** group.

We have previously reported the electrocatalytic formation of amidyl radicals using ferrocene as a mild redox catalyst.[7a] Under these conditions, the carbamate substrate **55** could be converted to cyclohexadiene **56** (20%) and monocyclized 1,5-diene **57** (12%), together with a trace amount of benzoxazolone **41** (Scheme 5a). Importantly, electrochemical dehydrogenation of **56** in TFE afforded **41** in 67% yield. Overall, these results strongly supported



Scheme 5. Mechanistic investigations and proposal.

the occurrence of a radical cyclization cascade leading to the formation of the bicyclic scaffold of the benzoheterocycle product, which was illustrated by the proposed mechanistic pathway in Scheme 5b. First, the arylamine moiety in the starting material is anodically oxidized and deprotonated to furnish an amidyl radical **I**,[7b] which then undergoes 5-*exo*-*dig* cyclization to produce a vinyl radical **II**.[7a,11] Intramolecular 6-*endo*-*trig* cyclization of **II** results in the formation of a cyclic carbon radical **III**. Alternatively, **II** can undergo 5-*exo*-*trig* cyclization to generate an exocylic C-radical **IV**, which can subsequently be converted to **III** via a tricyclic radical intermediate **V**.[9,12,13] The vinyl radical cyclization usually affords a mixture of 5-*exo* and 6-*endo* products.[9,12,13] Computational studies suggested that the substitution pattern of the acceptor alkene moiety plays a critical role in the mechanistic pathway through which the second cyclization step would proceed kinetically (Scheme 5c). The tertiary C-radical **III** next undergoes SET oxidation, followed by deprotonation, to afford a cyclohexadiene intermediate **VI**, which is eventually dehydrogenated through the sequential loss of two electrons and two protons to generate the final benzo-fused heterocyclic product. The electrons gathered at the anode travel to the cathode and combine with protons to produce H_2. As a result, no electron and proton acceptors are needed.

In summary, we have achieved the synthesis of benzimidazolones and benzoxazolones through de novo construction of the benzoheterocyclic scaffold via electrochemical dehydrogenative radical cyclization of acyclic precursors. These reactions allow efficient access to highly functionalized benzimidazolones and benzoxazolones, including fully substituted benzoheterocycles, with complete control of regioselectivity.

Acknowledgements

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Keywords: electrochemistry • benzimidazolones • benzoxazolones • dehydrogenative cyclization cascade • radical

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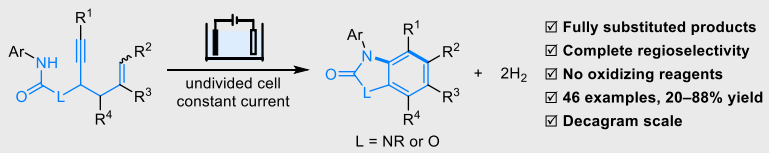

Report herein is an electricity-powered synthesis of highly substituted benzimidazolone and benzoxazolone derivatives by de novo construction of the benzene and the heterocyclic ring via a dehydrogenative cyclization cascade. The electrosynthesis method proceeds via H_2 evolution, obviating the need for oxidizing reagents and proton acceptors.

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