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Electrochemically promoted diamidation of alkenes to dihydroimidazole skeleton†

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The dihydroimidazole framework is a valuable heterocyclic compound widely found in natural products, ligands, molecular catalysts, pesticides, *etc*. The construction of a dihydroimidazole framework from alkenes is an attractive synthesis approach. Herein, we report a simple and environmentally friendly electrocatalytic diamination reaction of alkenes. The reaction involves constructing a dihydroimidazole framework from readily available alkenes, CH_3CN, and H_2O. CH_3CN serves as a solvent and a nitrogen source, whereas H_2O provides an oxygen source without the need for catalysts and oxidants. The synthesized 3,4-dihydroimidazole compound can be further hydrolyzed into vicinal diamines. As far as we know, the synthesis of dihydroimidazole frameworks through electrochemical Ritter-type diamination of alkenes has not been reported yet.

Introduction

The 1,2-diamine motif is widely present in natural products, pharmaceutical compounds, and molecular catalysts (Fig. 1).[1] Difunctionalization of alkenes[2] with amination reagents, which is one of the most straightforward and practical strategies[3] for assembling scaffolds, has achieved remarkable progress[4] in the past few decades. However, these reported methods often require the utilization of transition metal reagents and even stoichiometric amounts of osmium or cobalt.[4a,5] Moreover, the use of stoichiometric amounts of chemical oxidants (*e.g.*, iodine(III) reagents or organic peroxides)[4d,6] or azide reagents[4b,c,7] raises costs and environmental and safety issues, whereas the use of strong oxidizers may produce environmentally hazardous by-products and pose an explosion hazard when used with azide sources, particularly for large-scale applications.[8] In addition, they are often limited in substrate scope and sometimes require special amination reagents (*e.g.*, diaziridinone and its analogs[4e,9] or azido-iodine compounds).[4c] Therefore, developing highly efficient, mild, and green synthetic strategies is still desirable, and an additional substrate combination for the 1,2-diamine motif should be found to address the aforementioned drawbacks.

Electrochemistry offers an environmentally friendly, gentle, and efficient alternative to traditional chemical methods of redox conversion.[10] In the alternative method, common organic starting materials can lose or gain electrons at the electrode surface without the need for an external redox agent; thus, highly reactive intermediates are readily produced. Electrochemistry allows the precise external control of chemoselectivity and flux of reactive intermediates by regulating the applied current or potential. Compared with the energy efficiency in traditional chemical methods, that in the alternative method is maximized because of the latter's precise external control. Recently, electrochemical anodic oxidation has

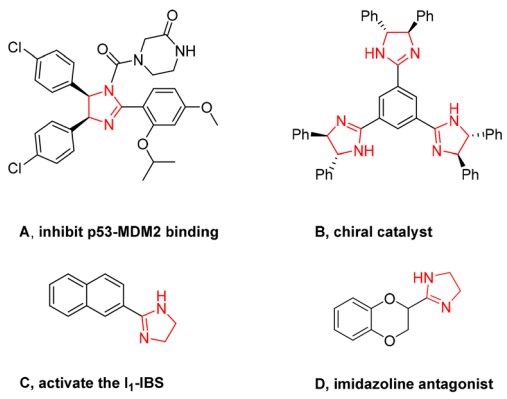

Fig. 1 Dihydroimidazole-based drugs and bioactive molecules.

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shown great potential in the construction of a 1,2-diamine motif.

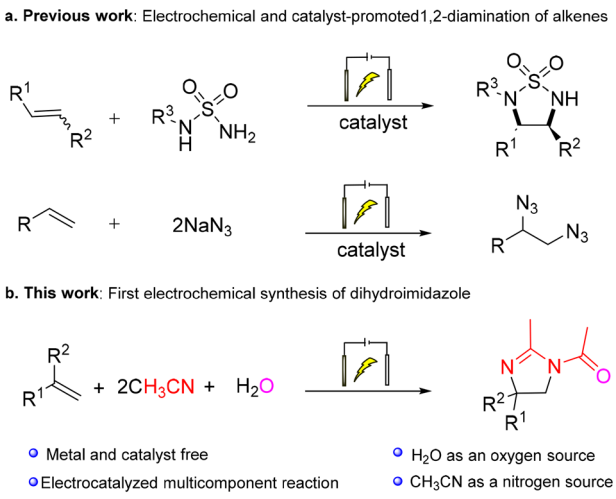
For instance, Xu and his colleagues[11] reported an electrochemical reaction of synthesizing 1,2-diamine compounds with diastereoselectivity using aryl alkenes and sulfonamides mediated by tris (2,4-dibromophenyl) amine. Lin's group[7b] has also made remarkable progress in the electrocatalytic diazidation of alkenes (Scheme 1). Despite the remarkable progress made above, issues such as limited types of nitrogen sources and 1,2-diamine structures may exist. Dihydroimidazole frameworks are a class of important nitrogen-containing heterocyclic compounds[12] with the structural characteristics of two nitrogen atoms and two sp^3 C–H bonds, which can be easily synthesized by 1,2-diamination of alkenes in theory. However, electrochemical synthesis of dihydroimidazole has not been reported because of the lack of well-matched nitrogen sources, alkenes, and electrochemical conditions.

Herein, we report a simple and environmentally friendly electrocatalytic diamination reaction of alkenes. The reaction involves constructing a dihydroimidazole framework from readily available alkenes, CH_3CN, and H_2O. CH_3CN serves as a solvent and a nitrogen source,[13] whereas H_2O provides an oxygen source without the need for catalysts and oxidants. The synthesized 3,4-dihydroimidazole compound can be further hydrolyzed into vicinal diamines. As far as we know, the synthesis of dihydroimidazole frameworks through electrochemical Ritter-type diamination of alkenes has not been reported yet.

Results and discussion

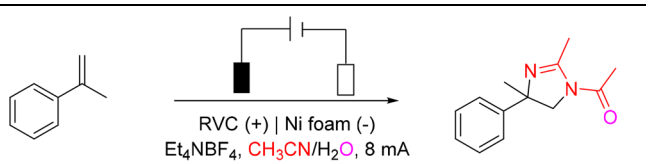
We used 2-phenyl-1-propene (**1a**) as the model substrate to establish the optimal conditions for this reaction by optimizing the reaction conditions. Under the constant current condition of 8 mA, the reaction proceeded smoothly in a three-necked flask with Et_4NBF_4 as the electrolyte, reticulated vitreous carbon (RVC) electrode as the anode, and Ni foam electrode as the cathode. The required product **2a** (Table 1, entry 1) was obtained with an 82% yield. The yield decreased when the cathode was replaced with platinum or nickel sheets (Table 1, entries 2 and 3), whereas the yield of **2a** was 59% when the cathode and anode were replaced with platinum sheets (Table 1, entry 4). However, the yield of **2a** was only 35% when the cathode and anode were replaced with carbon rods (Table 1, entry 5). Increasing or decreasing the current would decrease the reaction activity (Table 1, entries 6 and 7). Only trace amounts of product **2a** were detected when Et_4NCl, Et_4NBr, and Et_4NI were used as electrolytes (Table 1, entry 8). The reaction could not proceed without current (Table 1, entry 9). In summary, the optimal conditions established are as follows: RVC as anode, foam nickel electrode as cathode, Et_4NBF_4 (4 equiv.) as electrolyte, extra dry CH_3CN and H_2O as solvent (extra dry CH_3CN = 6 mL; H_2O = 5 μL), and reaction at room temperature with a constant current of 8 mA for 3–6 h.

Under optimal conditions, the substrate range was explored. The results are shown in Schemes 2 and 3. First, the model substrate 2-phenyl-1-propene (**1a**) presented the target product in 82% yield, and it could obtain the target product with 76% (**2b**), 71% (**2c**), 73% (**2d**), 72% (**2e**), and 61% (**2f**) yields when the benzene ring was *para*-carried with groups such as fluorine, chlorine, bromine, trifluoromethyl, and nitro groups. When halogen groups such as fluorine and bromine groups exist in the *meta* position of the aromatic ring, the target product can be obtained with yields of 83% (**2g**) and 66% (**2h**), respectively. When a methyl group exists in the *meta* position of the aromatic ring, the target product can be obtained with a yield of 55% (**2j**). However, when the CH_3CN



Scheme 1 1,2-Diamination of alkenes.

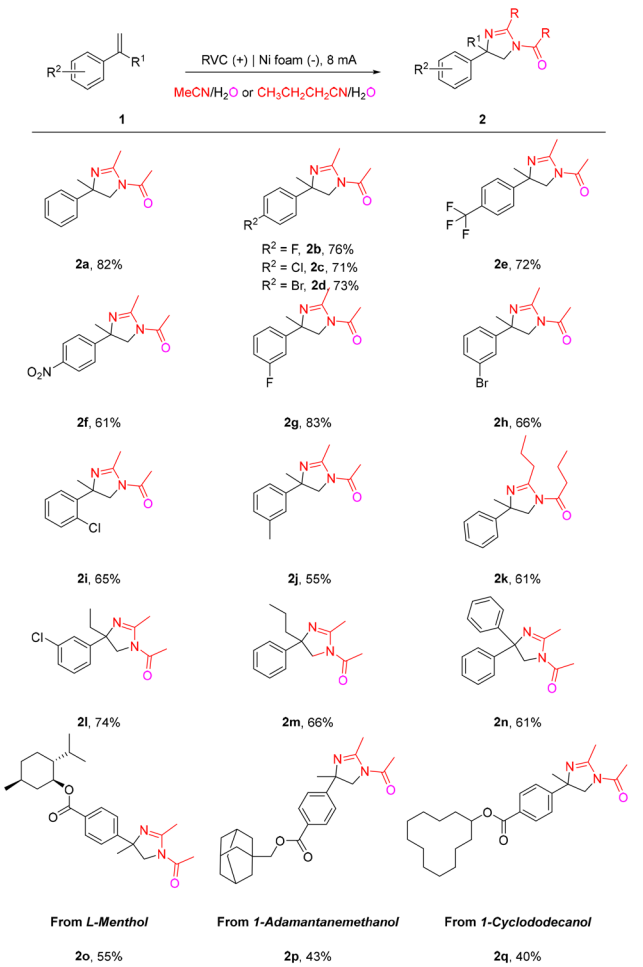
Table 1 Optimization of the reaction conditions[a]



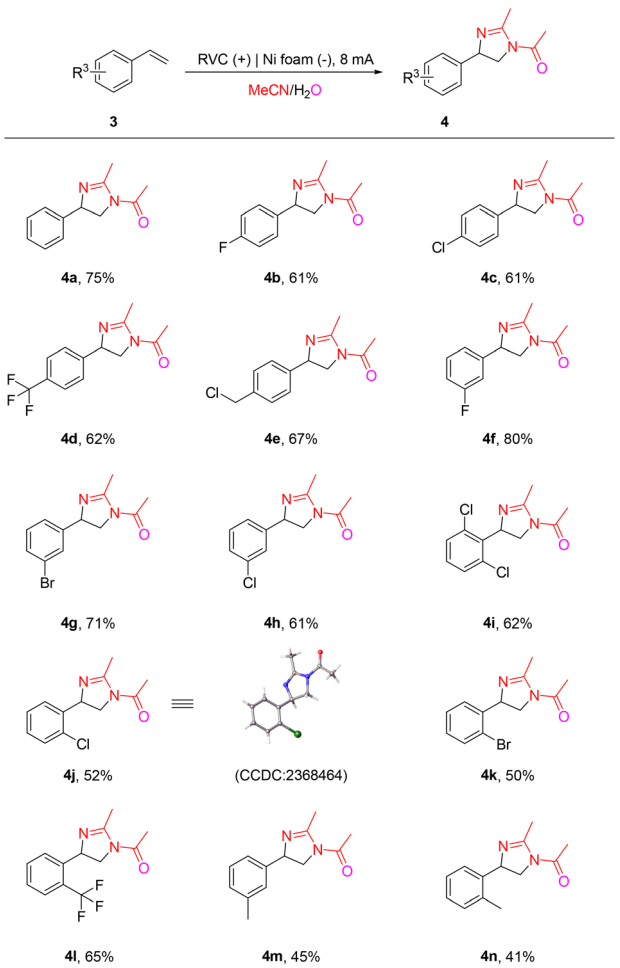
1a **2a**

Entry	Variation from standard conditions	Yield[b,c] (%)
1	None	82
2	RVC (+)|Pt (−) instead of RVC (+)|Ni foam (−)	68
3	RVC (+)|Ni (−) instead of RVC (+)|Ni foam (−)	61
4	Pt (+)|Pt (−) instead of RVC (+)|Ni foam (−)	59
5	C (+)|C (−) instead of RVC (+)|Ni foam (−)	35
6	10 mA instead of 8 mA	64
7	6 mA instead of 8 mA	62
8	Et_4NCl, Et_4NBr, and Et_4NI instead of Et_4NBF_4	Trace
9	No electricity	0

[a] Standard conditions: RVC (100 PPI, 1 cm × 1 cm × 1.2 cm) anode, Ni foam (1 cm × 2 cm × 0.5 cm) cathode, extra dry CH_3CN and H_2O as solvent (extra dry CH_3CN = 6 mL, H_2O = 5 μL), undivided cell, constant current = 8 mA, **1a** (0.2 mmol, 1 equiv.), Et_4NBF_4 (0.8 mmol, 4 equiv.), and room temperature. [b] Isolated yields. [c] Unless otherwise specified, extra dry CH_3CN with a water content of ≤10 ppm was used.



Scheme 2 The range of alkenes with substituents at the α-position. Reaction conditions: RVC (100 PPI, 1 cm × 1 cm × 1.2 cm) anode, Ni foam (1 cm × 2 cm × 0.5 cm) cathode, undivided cell, constant current = 8 mA, **1a** (0.2 mmol, 1 equiv.), Et_4NBF_4 (0.8 mmol, 4 equiv.), extra dry CH_3CN and H_2O as solvent (extra dry CH_3CN = 6 mL, H_2O = 5 μL); electrolysis was carried out at room temperature under air atmosphere.

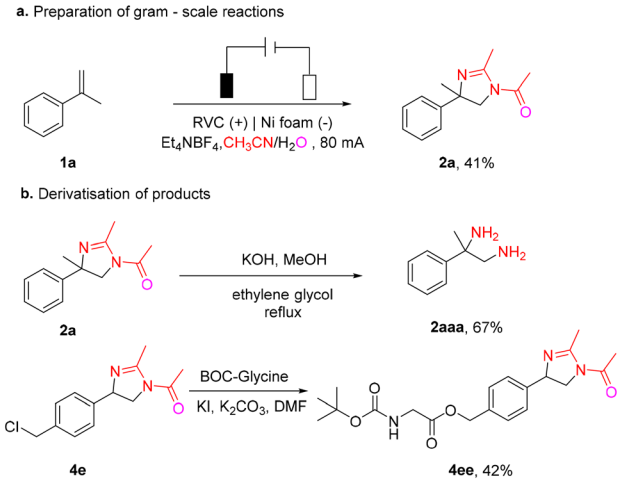


Scheme 3 The range of alkenes without substituents at the α-position. Reaction conditions: RVC (100 PPI, 1 cm × 1 cm × 1.2 cm) anode, Ni foam (1 cm × 2 cm × 0.5 cm) cathode, undivided cell, constant current = 8 mA, **3a** (0.2 mmol, 1 equiv.), Et_4NBF_4 (0.8 mmol, 4 equiv.), extra dry CH_3CN and H_2O as solvent (extra dry CH_3CN = 6 mL, H_2O = 5 μL); electrolysis was carried out at room temperature under air atmosphere.

was replaced with butyronitrile, the target product (**2k**) could be obtained in 61% yield. When halogen groups such as chlorine are found in the adjacent position of the aromatic ring, the target product can be obtained with a yield of 65% (**2i**). When the R^1 group is replaced with ethyl, propyl, or phenyl, the yield of the target product gradually decreases as the steric hindrance increases. The target product can be obtained with yields of 74% (**2l**), 66% (**2m**), and 61% (**2n**). In addition, electrochemical methods can be used to modify natural products, such as L-menthol, 1-adamantane methanol, and 1-cyclododecanol, affording the corresponding derivatives (**2o–2q**) in 40%–55% yields.

When we replace 2-phenyl-1-propene (**1a**) with styrene (**3a**), the target product can still be obtained with a 75% (**4a**) yield. On the benzene ring of styrene, a series of different substitutions can be successfully carried out for electrochemical 1,2-diamination reactions, including fluorine, chlorine, bromine, trifluoromethyl, and methyl. Alkenes with 2,6-disubstituted benzene rings are also suitable substrates (**4i**). We also confirmed the structure of (**4j**) through X-ray diffraction analysis. In addition, the electrochemical reaction of 1,2-diamination is compatible with chloromethyl groups (**4e**). After switching to styrene, the yield is generally slightly lower than that of alkenes with substituents at the α-position. The possible reason is that when substituents exist at the α-position, stabilizing carbocations is easy, resulting in a high electrochemical reaction activity for 1,2-diamination. This finding is consistent with our speculated mechanism.

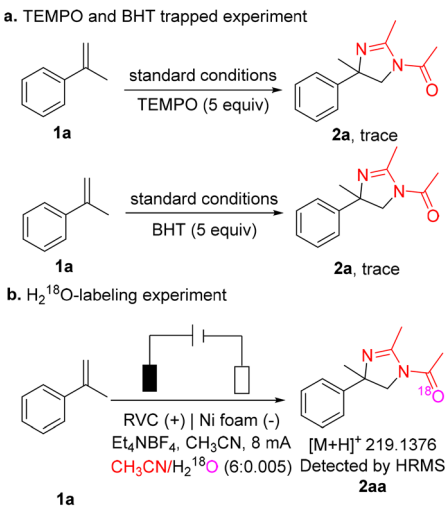
We conducted a gram-scale conversion of the electrocatalytic diamination reaction of alkenes under constant current conditions of 80 mA to demonstrate further the synthetic application of this electrochemical method. The reaction of alkene **1a** with CH_3CN and H_2O was completed at a scale of grams, and the target product **2a** (0.71 g) was obtained with a 41% yield (Scheme 4a). In addition, 1,2-diamine compounds are important synthetic units, such as drug intermediates, cat-



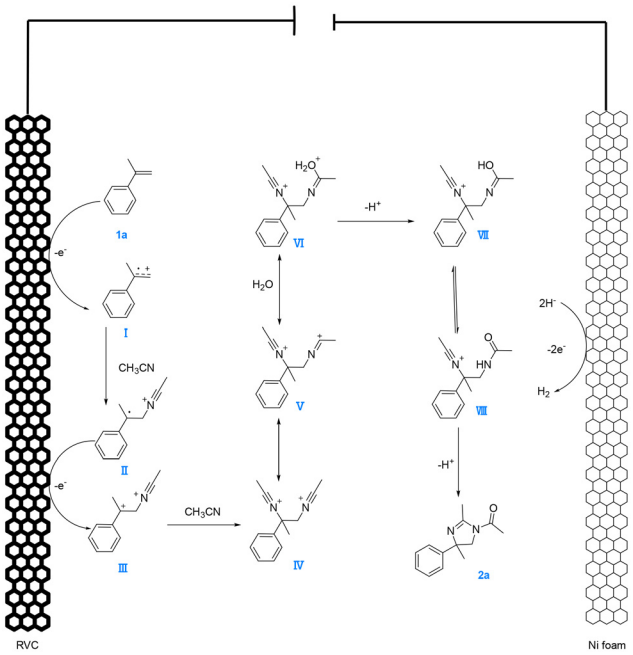
Scheme 4 Electrochemical applications.

alysts, and ligands. Therefore, synthesizing 1,2-diamine compounds from readily available alkenes is important. We dissolved 0.2 mmol **2a** in potassium hydroxide, methanol, and ethylene glycol, and it was heated under reflux. After the reaction was completed, the diamine compound **2aaa** was obtained with a 67% yield. In addition, **4e** can be used to modify BOC Glycine, providing the corresponding derivative with a yield of 45% (**4ee**).

We conducted several control experiments to gain a deep understanding of the reaction mechanism (Scheme 5). When 5 equiv. BHT and TEMPO are added to the reaction, only trace amounts of product **2a** are detected, indicating that the reaction may involve the free radical pathway (Scheme 5a). We conducted an $H_2{}^{18}O$ labeling experiment to verify the source of oxygen in product **2a**. When $H_2{}^{18}O$ (5 μL) is added to the reaction, the results show that the ^{18}O labeled product **2aa** can be detected by HRMS analysis (Scheme 5b and Fig. S2†). The



Scheme 5 Control experiments.



Scheme 6 Possible reaction mechanism.

results indicate that H_2O may provide oxygen atoms for the formation of the target product **2a**. Finally, we conducted radical clock experiments using compounds **5a** and **6a**. Products **5aa** and **6aa** can be detected by HRMS analysis, indicating that the reaction is undergoing a free radical pathway (see ESI† for additional details).

We also conducted cyclic voltammetry analysis on compound **1a**. The test results show that an irreversible oxidation peak is observed at 2.45 V (relative to Ag/AgCl) in the cyclic voltammogram of **1a**, indicating that **1a** may be oxidized at the anode (RVC).

On the basis of the above experimental results and previous literature reports,[14] we proposed a possible mechanism (Scheme 6). 2-Phenyl-1-propene **1a** is oxidized at the anode (RVC) to form alkene radical cation **I**, which is captured by the CH_3CN to form intermediate **II**. Then, intermediate **II** loses an electron to intermediate **III**. Intermediate **III** is captured by a molecular CH_3CN to form intermediate **IV**, which then forms a carbocation intermediate. After hydrolysis, it forms amide product **VIII**, which is then cyclized to obtain the target product **2a**. This process is essentially a Ritter reaction,[15] with the difference being the methods and synthetic precursors for generating carbocations.

Conclusions

We have developed a simple and environmentally friendly electrochemically driven 1,2-diamination reaction of alkenes, which is an effective method for constructing 1,2-diamine framework compounds from readily available alkenes, CH_3CN, and H_2O. The reaction does not require additional catalysts

and oxidants, and the raw materials are readily available. We hope that this protocol can provide a complementary way for dihydroimidazole compounds and be widely applied in modern synthetic chemistry and pharmaceutical research.

Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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