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Selective 1,2-addition of acetonitrile/acetone to α,β-unsaturated aldehydes at room temperature: access to cinnamyl alcohol derivatives with potential protective effects against exercise-induced skeletal muscle injury

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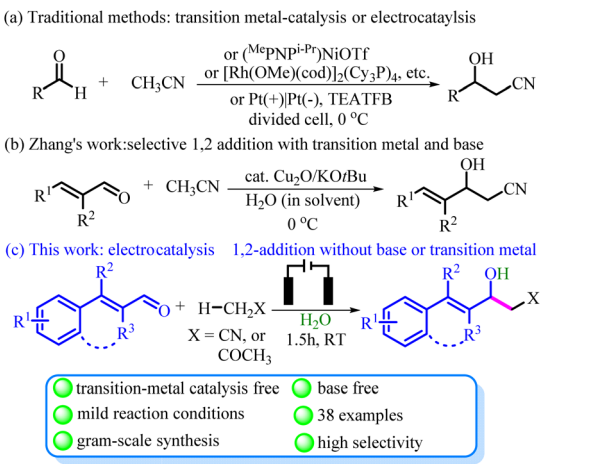
In this work, we developed an electrocatalytic selective 1,2-addition of acetonitrile/acetone to α,β-unsaturated aldehydes at room temperature to give 38 cinnamyl alcohol derivatives in mild reaction conditions. Kinetic isotope effect (KIE) experiments and DFT calculations have been performed to shine light on the transformation mechanism. Further molecular docking results suggest that the obtained products containing the nitrile group give potential protective effects against exercise-induced skeletal muscle injury.

Eccentric training, such as downhill running or slow-descent squats, is a critically important training method, as it can effectively enhance the dynamic and static stability of muscle and tendon tissue. However, acute eccentric contractions are known to induce skeletal muscle damage that causes infiltration of neutrophils to the site of injury within several hours.[1–4] Methyl cinnamate, as a natural ester compound found in peppercorn, has been shown to have a protective effect on exercise-induced skeletal muscle damage by activating the AMPK pathway. Thus, the synthesis of cinnamic acid derivatives holds great significance for the development of drugs aimed at protecting skeletal muscle damage.

The nitrile is an essential functional group for drug activity, and versatile transformations.[5–8] For example, it can be easily converted into an amide or carboxylic acid by hydrolysis reaction under different conditions. An attractive method for the incorporation of the nitrile group is based on direct transformations of α C(sp^3)–H bonds of simple alkyl nitriles (such as acetonitrile) into C–C bonds, which generally saves them from prefunctionalization,[9–16] while showing higher atom/step-economy.[17–24]

Due to their poor acidity, high bond energy, and unreactive molecular orbital profile, the activation of α-C(sp^3)–H bond adjacent to the nitrile group remains rather rudimentary, and peroxide and strong base reagents are usually used, which cannot avoid causing undesired side reactions and environmental pollution.[25,26] To address these issues, Lewis acidic transition metals with the ligand are used to improve the acidity of α-C(sp^3)–H bonds, such as Rh or Ni complexes (Scheme 1a).[17,18,24,27–29] At the same time, Rossi and coworkers reported an electrochemical activation of α-C(sp^3)–H bond by electrogenerated base under galvanostatic control in a divided cell equipped with Pt electrodes at 0 °C (Scheme 1a).[30] This electrogenerated cyanomethyl anion reacted with carbonyl compounds by nucleophilic addition.

To date, most of these reactions can only use aldehydes as the other aldol reaction partners, and α,β-unsaturated aldehydes have been barely explored. Recently, Zhang and coworkers have reported the Cu_2O-catalyzed activation of the α-C(sp^3)–H bond of alkyl nitriles to obtain the α-cyano carbanion, and a large number of δ,γ-unsaturated-β-hydroxyl nitriles are obtained in good to high yields (Scheme 1b).[31] However, the



Scheme 1 The activation strategy of the α-C–H bond.

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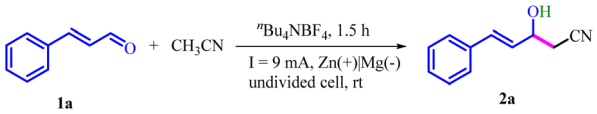
strong base KO*t*Bu and transition metal Cu_2O are needed for this transformation. Thus, developing mild and green tactics that consist of activating the α-C(sp^3)–H bond, especially avoiding extra transition-metal catalysts and strong base reagents, is still in demand.

Using electrons as mass-free reagents, organic electrosynthesis is emerging as a uniquely attractive method for the activation of relatively inert chemical bonds due to their environmentally friendly nature, sustainability, and mild reaction conditions.[32–38] In the past few years, many applications of the electrochemical activation of α-C(sp^3)–H bond toward the construction of C–X (X = C, heteroatom) have been reported.[39–51] An electrochemical activation of the α-C(sp^3)–H bond adjacent to the nitrile group used for the electrogeneration of cyanomethyl anion, which reacted with carbonyl compounds by nucleophilic addition.[30] However, the selective 1,2-addition of acetonitrile to α,β-unsaturated aldehydes *via* electrocatalytic α-C(sp^3)–H bond activation has not been reported to date. In continuation of our research interest for developing the eco-friendly synthetic strategies.[52–55] Herein, we report the successful discovery of the selective 1,2-addition of acetonitrile/acetone to α,β-unsaturated aldehydes *via* an electrochemical activation of the α-C(sp^3)–H bond, to provide a series of δ,γ-unsaturated-β-hydroxyl nitriles without transition metal catalysis and base (Scheme 1c).

We began this study by using the cinnamaldehyde **1a** as the model substrate, ^{n}Bu$_4$NBF$_4$ as the supporting electrolyte, and a mixture of these compounds in 10 mL CH_3CN was then electrized in an undivided cell (a three-necked round-bottomed flask) equipped with a Zn plate anode and a magnesium rod cathode, at room temperature (Table 1). To our great joy, the electrochemical process performed very well under the original electrized conditions, to give the desired product **2a** with a 90% yield in 1.5 hours (entry 1). Changing the supporting electrolyte from ^{n}Bu$_4$NBF$_4$ to ^{n}Bu$_4$NI, ^{n}Bu$_4$NPF$_6$, or ^{n}Bu$_4$NBr provided a lower yield (entries 2–4). When using DMF or DMSO as the solvent, the transformation performed poorly (entries 5 and 6). Changing the electrolytic time or current can't afford the higher product yield (entries 7–10). Replacing the electrode with others led to poor reaction efficiency (entries 11–15). As for the reaction temperature, neither a higher nor a lower value improved the reactivity (entries 16 and 17). The N_2 atmosphere was proven not to be needed (entry 18). Finally, the control experiment suggested that electricity was essential for the electrochemical reaction (entry 19). The scalability of this electrochemical transformation was confirmed by the facile manufacture of 0.39 g of product **2a** (entry 20). Thus, this electrochemical protocol could serve as a practical method to prepare δ,γ-unsaturated-β-hydroxyl nitriles.

With the optimum conditions in hand, we researched the scope of the electrolytic selective 1,2-addition protocol regarding the scope of the α,β-unsaturated aldehydes starting material (Table 2). Firstly, a variety of β-aryl-substituted α,β-unsaturated aldehydes were used to demonstrate the reaction's generality. Electron-donating (–Me, –OMe, and –NMe_2) substituent groups at the *para*-, *meta*-, or *ortho*-positions of the β-aryl group of α,β-unsaturated aldehydes showed good

Table 1 Optimization of the reaction conditions[a]



1a 2a

Entry	Variation from the standard conditions	Yield (%)
1	None	90
2	^{n}Bu$_4$NI instead of ^{n}Bu$_4$NBF$_4$	73
3	^{n}Bu$_4$NPF$_6$ instead of ^{n}Bu$_4$NBF$_4$	75
4	^{n}Bu$_4$NBr instead of ^{n}Bu$_4$NBF$_4$	70
5	DMF as solvent[b]	76
6	DMSO as solvent[b]	65
7	1 h instead of 1.5 h	73
8	2 h instead of 1.5 h	64
9	6 mA instead of 9 mA	85
10	12 mA instead of 9 mA	88
11	Graphite instead of Mg as the cathode	60
12	Pt instead of Mg as the cathode	65
13	Graphite instead of Zn as the anode	Trace
14	Pt instead of Zn as the anode	Trace
15	Mg instead of Zn as the anode	34
16	60 °C instead of rt	84
17	0 °C instead of rt	80
18	N_2 instead of air	88
19	No current	n.d.
20[c]	Large-scale reaction	76

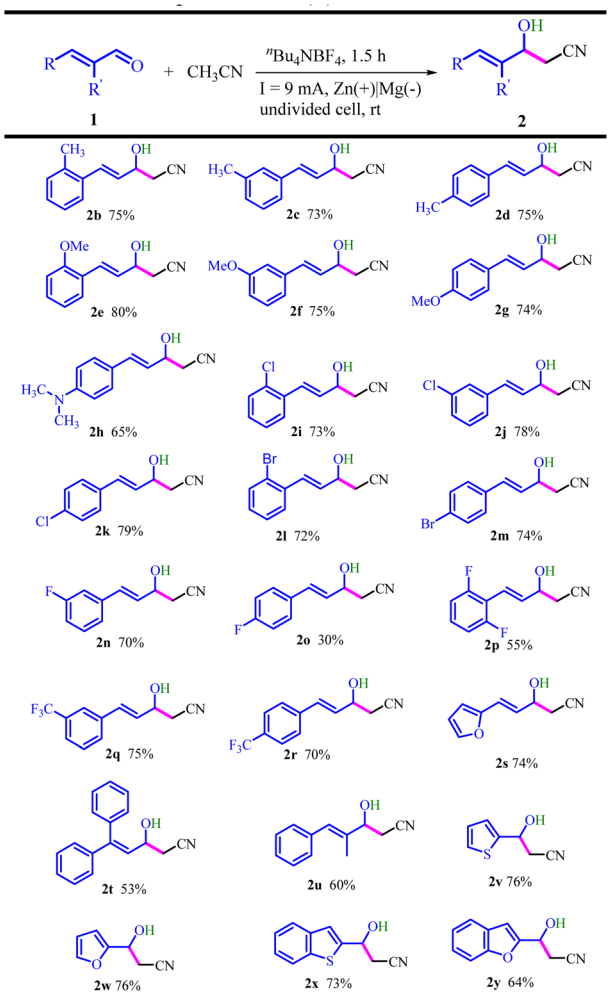
[a] Reaction conditions: Zn plate anode (10 mm × 10 mm × 0.2 mm), magnesium rod cathode (*Φ* 5 mm), constant current = 9 mA, **1a** (0.3 mmol), ^{n}Bu$_4$NBF$_4$ (1 mmol), MeCN (10 mL), 1.5 h, air, room temperature, undivided cell. [b] MeCN (1 mL), DMF, or DMSO (9 mL). [c] Reaction conditions: Zn plate anode (10 mm × 10 mm × 0.2 mm), magnesium rod cathode (*Φ* 5 mm), constant current = 9 mA, **1a** (3 mmol), MeCN (50 mL), 10 h, air, room temperature, undivided cell. Isolated yields are shown.

tolerance, yielding the desired products (**2b–2h**) in 74–80% yields. Enals possessing electron-withdrawing groups (F, Cl, Br) at the *para*-, *meta*-, or *ortho*-positions were also well tolerated, affording the corresponding products **2i–2n** in good yields, except the yield for the F at *para*-position (**2o**) was not high. Thus, these substituents facilitate additional modification at the halogenated positions. Multi-substituted α,β-unsaturated aldehydes at the β-phenyl ring were also compatible with the reaction (**2p**).

Meanwhile, trifluoromethyl substitution on the β-phenyl ring was tolerated (**2q** and **2r**). The β-phenyl ring could be replaced with another aromatic group, such as furyl (**2s**). Moreover, α-branched enals with a methyl group and β-branched enals with a phenyl group could afford the corresponding product in acceptable yield (**2t** and **2u**). Interestingly, furan-2-carbaldehyde, thiophene-2-carbaldehyde, benzofuran-2-carbaldehyde, and benzo[*b*]thiophene-2-carbaldehyde were well tolerated due to the unsaturated compounds' properties of these heterocycles (**2v–2y**).

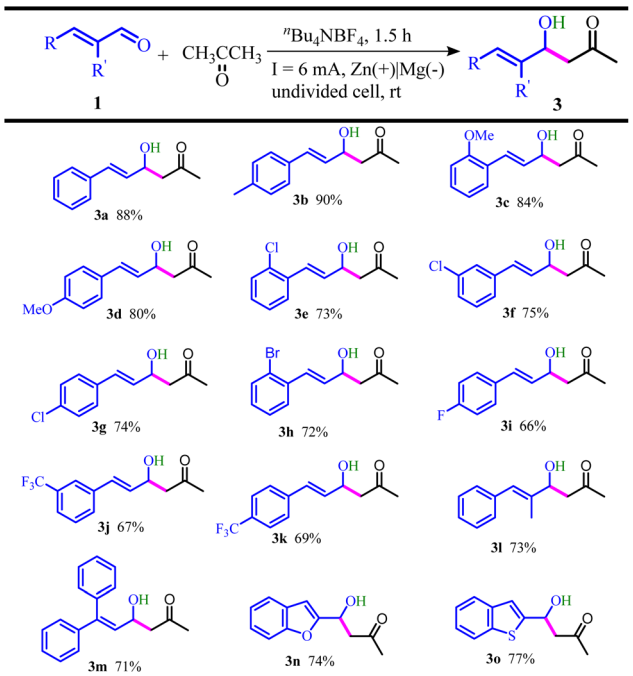
To highlight the utility of this electrochemical activation of α-C(sp^3)–H bond, acetone was subjected to the standard reaction conditions (Table 3). The corresponding product **3a** was obtained in good yield (88%). Then, we use a variety of β-aryl

Table 2 Scope of enals (1) used in the reaction[a]

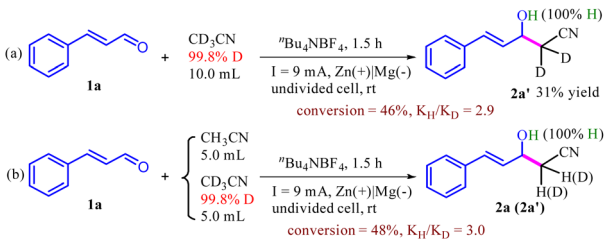


[a] Reaction conditions: Zn plate anode (10 mm × 10 mm × 0.2 mm), magnesium rod cathode (Φ 5 mm), constant current = 9 mA, **1a** (0.3 mmol), $^{n}Bu_4NBF_4$ (1 mmol), MeCN (10 mL), 1.5 h, air, room temperature, undivided cell. Isolated yields are shown.

Table 3 Scope of enals (1) used in the reaction[a]



[a] Reaction conditions: Zn plate anode (10 mm × 10 mm × 0.2 mm), magnesium rod cathode (Φ 5 mm), constant current = 6 mA, **1a** (0.3 mmol), $^{n}Bu_4NBF_4$ (1 mmol), CH_3COCH_3 (10 mL), 1.5 h, air, room temperature, undivided cell. Isolated yields are shown.

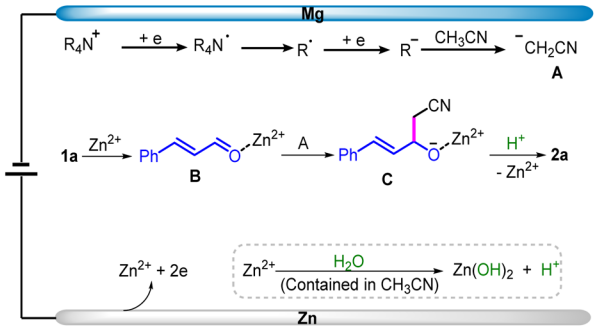


Scheme 2 The KIE experiments.

substituted α,β-unsaturated aldehydes to react with acetone. Electron-donating (Me, OMe) substituent groups at the *para*-, *meta*-, or *ortho*-positions of the β-aryl group of α,β-unsaturated aldehydes showed good tolerance, yielding the desired products (**3b–3d**) in excellent yields. Enals possessing electron-withdrawing groups (F, Cl, Br, or CF_3) were also well tolerated (**3e–3k**). Moreover, α-branched enals with a methyl group and β-branched enals with a phenyl group could afford the corresponding product in acceptable yield (**3l** and **3m**). Benzofuran-2-carbaldehyde, and benzo[*b*]thiophene-2-carbaldehyde were well tolerated (**3n** and **3o**).

To shed light on the reaction mechanism, several intermolecular competing kinetic isotope effect (KIE) experiments were conducted, as shown in Scheme 2. The transformations with CH_3CN and CD_3CN (99.8% D) disclosed a K_H/K_D of 2.9 under the classic reaction conditions (Scheme 2). This value concurred with the result (K_H/K_D of 3.0) from the treatment with the mixture of CH_3CN and CD_3CN at the ratio 1 : 1. This result implied that the cleavage of the C–H bond of CH_3CN could be related to the rate-limiting step. Of note, no deuterium was detected in the hydroxyl group of **2a′**, indicating that the proton of the hydroxyl group in the corresponding product might originate from H_2O contained in the used solvent.

Based on the above findings, DFT calculations (shown in SI) and the relevant reports,[30] a plausible reaction mechanism was proposed and shown in Scheme 3. Initially, a tetraalkylammonium cation R_4N^+ accepts one electron from the cathode to give a neutral radical $R_4N^{\bullet}$, which undergoes rupture of a C–N bond to form an alkyl radical $R^{\bullet}$. The alkyl radical $R^{\bullet}$ quickly accepts another electron to yield an alkyl carbanion R^-, which undergoes protonation by CH_3CN to afford a cyanomethyl anion **A**. Subsequently, the substrate **1a** was activated by the Zn^{2+} to give the intermediate **B**, which captured the intermediate **A** to give **C**, which undergoes a protonation and



Scheme 3 Plausible mechanism for the reaction.

subsequent Zn^{2+} abstraction to give the final product **2a**. Meanwhile, Zn was oxidized at the anode to form Zn^{2+}, which reacts with H_2O to release a proton.

Due to the good biological activity of cinnamyl alcohols, we have performed binding constant research of the synthetic products in this work. Among the synthetic cinnamyl alcohols, 10 compounds containing the nitrile group exhibit high binding affinity like that of cinnamaldehyde methyl ester with AMP-activated protein kinase (Table S1). This result suggests that the nitrile group is important in the binding model. This method offers a novel approach for developing a drug to treat skeletal muscle injury.

In summary, we have successfully developed an efficient electrochemical selective 1,2-addition reaction of acetonitrile/acetone to cinnamaldehydes used for the synthesis of cinnamyl alcohol derivatives. Our electrochemical synthetic strategy is compatible with a wide range of α,β-unsaturated aldehydes. Notably, the obtained products exhibit potential protective effects against skeletal muscle injury.

Conflicts of interest

The authors declare no conflict of interest, financial or otherwise.

Data availability

The data supporting this article are provided within the main article and supplementary information (SI). Supplementary information is available. See DOI: https://doi.org/10.1039/d6ra01217e.

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