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Electrochemical construction of 2,5-diaryloxazoles *via* N–H and C(sp^3)-H functionalization

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ABSTRACT

An efficient N–H and C(sp^3)-H functionalization of aryl ketones with benzylamines/amino acids was developed under mild conditions by virtue of anodic oxidation. A variety of functionalized 2,5-diaryloxazoles were obtained with good to excellent yields. Moreover, some important natural products can be prepared by this method. The reaction features a broad substrate scope, scalability, metal-free and chemical oxidant-free.

The 2,5-diaryl substituted oxazoles is one of the most abundant and significant structure in pharmaceuticals and natural products [1–8], such as antiproliferative natural product *O*-methylhalfordinol, antimycobaterial natural product Texamine, Balsoxin and Texaline (Fig. 1) [9,10]. As a consequence of the extraordinary abundance of 2,5-diaryloxazoles in biologically active compounds, various methods have been developed for construction of 2,5-diaryloxazoles and are mainly divided into two types: (1) transition metal-catalyzed reaction [11–18] and (2) chemical oxidants under metal-free conditions [19–21]. Recently, Ackermann's group successfully developed a direct C–H arylation of oxazoles with arylhalides catalyzed by copper(I) to give 2,5-diaryloxazoles (Scheme 1a) [22]. Jiang's group also reported a method of synthesis of 2,5-diaryloxazoles with TBHP/I_2 [23]. However, the use of chemical oxidants, metal catalysts can lead to the generation of metal residues and environmental pollution. It is well known that organic electrochemistry, by using the transportation of electrons to realize the redox process, can effectively avoid the involvement of metals and oxidants, which has been widely applied in the construction of nitrogen-containing heterocycles [24–30]. In 2019, Waldvogel's group used direct electrochemical oxidation of iodoarene ArI in $Et_3N{\cdot}5HF$ and mediates the fluorocyclization of *N*-propargylamides to 5-fluoromethyl-2-oxazoles (Scheme 1b) [31]. However, due to the inertness of the C(sp^3)-H bond, direct construction of 2,5-diaryloxazoles *via* C(sp^3)-H and N–H under electrochemical conditions has not been explored yet.

Hence, based on previous studies in our group [32–36], we report an electrochemical synthesis of 2,5-diaryloxazole derivatives from readily available aryl ketones and aromatic benzylamines, in which the use of metal and chemical oxidants was avoided. Moreover, the natural α-amino acids can be employed as the coupling partners in this electrochemical reaction. More importantly, the preparation of four known 2,5-diaryloxazole alkaloids can be scaled up easily by virtue of this developed method.

As a model reaction, the reaction of acetophenone **1a** with benzylamine **2a** was performed in an undivided cell at a constant current of 10 mA in the presence of NaI in DMF at 90 °C. To our delight, the desired product was obtained in 60% isolated yield (entry 1, Table S1 in Supporting information), which encouraged us to optimize the reaction conditions further. First of all, the solvent effect was investigated, and DMF was determined to be the best solvent (entries 1–4, Table S1). Considering the poor solubility and conductivity of NaI in DMF, other solvents were added to DMF to increase the solubility and conductivity of the electrolyte (entries 5–9, Table S1). H_2O was found to be the best choice. The co-solvent DMF/H_2O (10/1) gave the desired product with 77% isolated yield.

Then, various electrolytes were investigated. The experimental results showed that the iodide ion was necessary for the reac-

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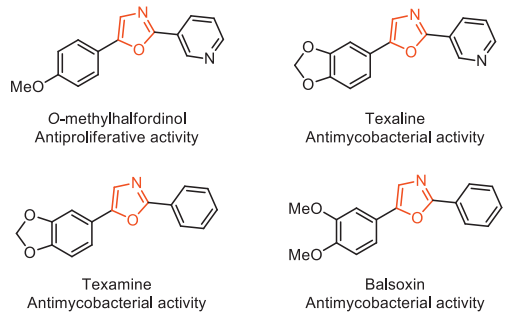
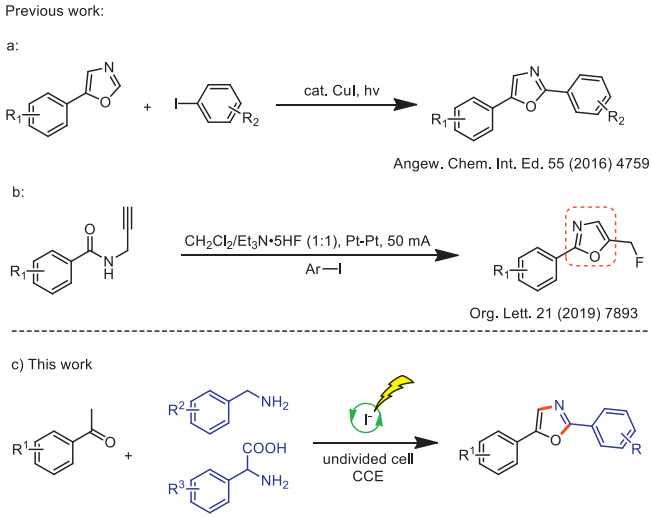
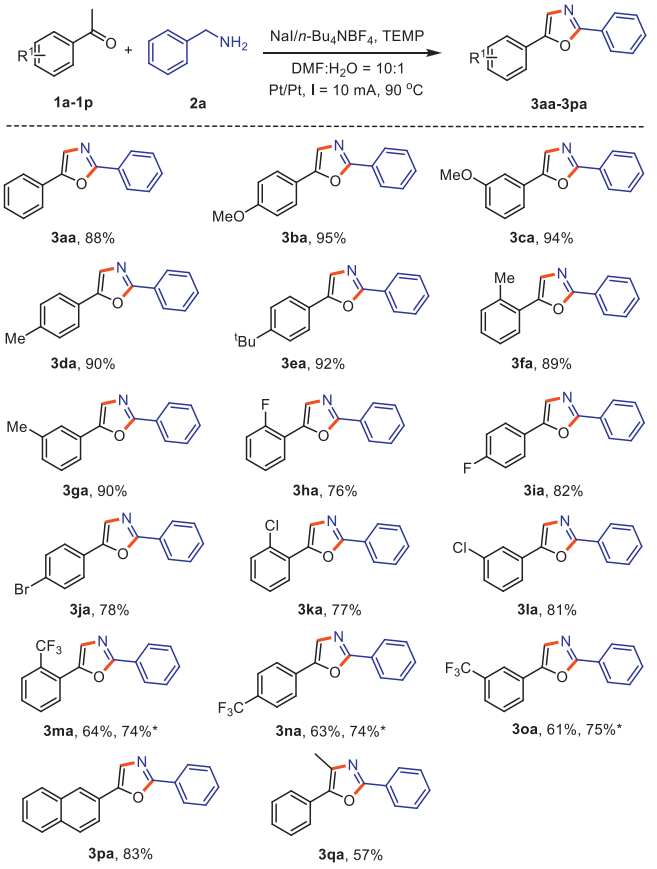


Fig. 1. Selected examples of 2,5-diaryl substituted oxazoles compounds.



Scheme 1. Previous work and this work.



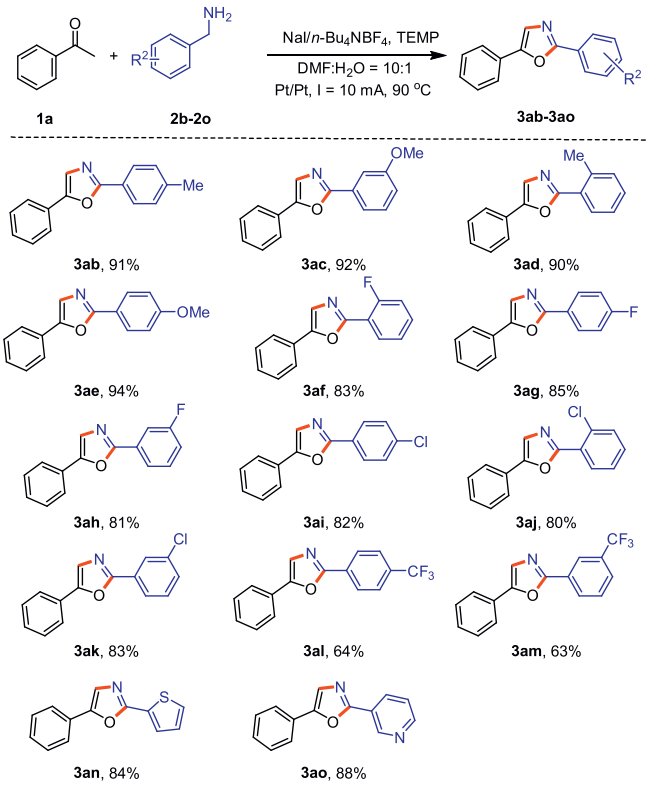
Scheme 2. Scope of substrates. Unless otherwise noted, all reactions were performed with **1a-1q** (0.3 mmol), **2a** (0.7 mmol), NaI (0.06 mmol), *n*-Bu_4NBF_4 (0.4 mmol), TEMP (0.3 mmol), DMF (3.0 mL). The reaction was carried out at 90 °C for 12 h. * Reaction conditions: **1m**, **1n**, **1o** (0.3 mmol), **2a** (0.9 mmol), NaI (0.3 mmol), TEMP (0.3 mmol), DMF (3 mL); the electrolysis was conducted in an undivided cell at 90 °C. TEMP = 2,2,6,6-Tetramethylpiperidine.

tion (entries 10–12, Table S1). Among the various iodide salts, NaI proved to be the optimal electrolyte for the reaction (entries 9, 13–15, Table S1). In order to make it more practical, various auxiliary electrolytes, such as *n*-Bu_4NBr, *n*-Bu_4NBF_4, *n*-Bu_4NPF_6, *n*-Bu_4NClO_4, were examined in the reaction. It was found that *n*-Bu_4NBF_4 favored this reaction, enhancing the reaction yield to 88% (entries 16–19, Table S1). Changing the platinum electrode to a carbon anode or carbon cathode led to a decrease in the yield. Further optimizing the current density showed that 10 mA/cm^2 was the optimal value. It was worth noting that no desired product was detected without electricity under the standard reaction conditions (entry 20, Table S1), which suggested that the reaction driving force should be the employment of electric energy.

With the optimal reaction conditions in hand, we next explored the scope of substrates of this reaction. Firstly, various aryl ketones were employed in the reaction to investigate the scope of aryl ketones (Scheme 2). When the phenyl ring of acetophenone bore electron-donating groups, the desired product can be obtained with 89%–95% yields (**3ba-3ga**). On the contrary, when the phenyl ring bore electron-withdrawing groups, such as various halogens, the reaction can provide corresponding products with the yields of 76%–82% (**3ha-3la**). This meant that the electron-withdrawing group had an influence on this reaction. Especially, the strong electron-withdrawing group, such as trifluoromethyl, disfavored this reaction (**3ma-3oa**). When 2-acetonaphthone was employed, the corresponding product can be obtained with 83% yield (**3pa**). When propiophenone was employed, the corresponding product can be obtained with 57% yield (**3qa**). This showed that the reaction had greater compatibility with aryl ketones.

Subsequently, various benzylamines were employed to examine the scope of the reaction substrates. As shown in Scheme 3, high yields of 90%–94% were obtained with electron-donating substituents on the phenyl ring (**3ab-3ae**). When the benzylamines bearing electron-withdrawing group were employed as the reaction substrates, the desired product can be obtained with the yields of 80%–85% (**3af-3ak**). This meant that this reaction can be carried out smoothly regardless of the electronic effect although the electron-withdrawing had a little influence on the yields. When the benzylamine bore a strong electron-withdrawing group, nevertheless, the yields were decreased obviously to 60%–65% (**3al** and **3am**). Moreover, excellent yields were also obtained when the phenyl ring of benzylamines was replaced by the heterocyclic rings (**3an** and **3ao**). Similarly, the experimental results showed there was a great compatibility for the aromatic benzylamine substrate.

In order to make the protocol more practical, the natural α-amino acids were examined as the coupling partners in this electrochemical reaction since these natural α-amino acids are low cost and readily available. However, under the same condition of Scheme 2, only low reaction yield was obtained. After solvent screening, we found that reaction solvent had a great influence on the reaction. Gratifyingly, we found that the mixed solvent of DMF and DMSO favored this reaction and the ratio of 30:1 (DMF:DMSO) was the best co-solvent in this reaction (entries 1–9, Table S2 in Supporting information). Meanwhile, iodine ion was necessary for this reaction. Without iodide ions, this reaction did not occur (entries 10–12, Table S2). Then, different iodide salts were optimized

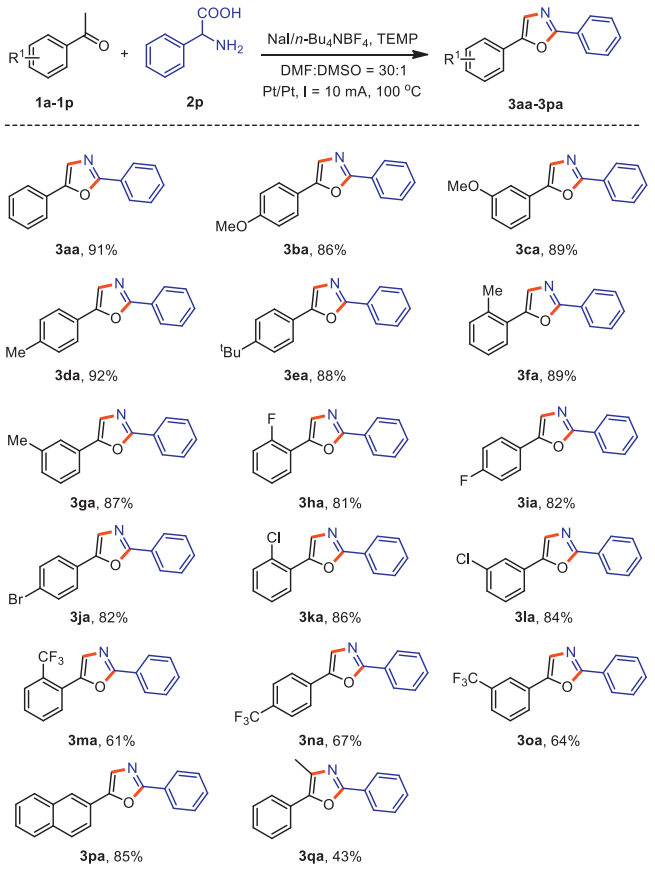


Scheme 3. Scope of substrates. Unless otherwise noted, all reactions were performed with **1a** (0.3 mmol), **2b-2o** (0.7 mmol), NaI (0.06 mmol), *n*-Bu_4NBF_4 (0.4 mmol), TEMP (0.3 mmol), DMF (3.0 mL). The reaction was carried out at 90 °C for 12 h.

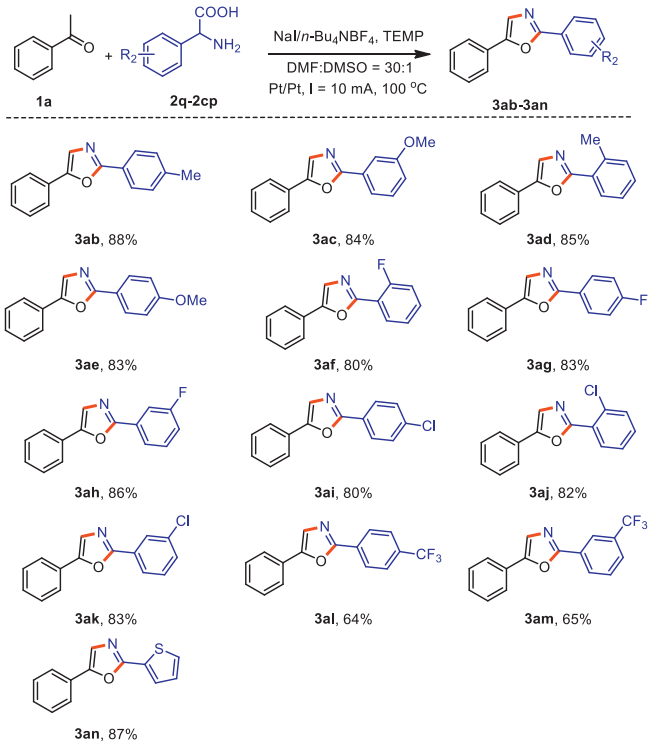
and the experimental results indicated that NaI should be the most favorable for the reaction (entries 9, 13–15, Table S2). Afterwards some auxiliary electrolytes were added to further enhance the reaction yield and practicality. It was found that *n*-Bu_4NBF_4 gave the best result (entries 16–19, Table S2). Finally, we found that increasing the reaction temperature favored this reaction, perhaps due to higher temperature assistance on the decarboxylation. Therefore, the optimal temperature can be determined at 100 °C. It was worth noting that no desired product was observed without electricity, (entry 20, Table S2), which suggested that the reaction driving force should be the electric energy.

Under the optimized reaction conditions, we turned our attention to the scope of the substrates (Scheme 4). First of all, the electronic effect was investigated. When the acetophenones bore electron-donating group on the phenyl ring, the reaction yields were above 85% (**3ba-3ga**). When the phenyl ring bore electron-withdrawing groups, such as halogens, the reaction can provide the corresponding products with above 80% yields (**3ha-3la**). When the acetophenone bore a strong electron-withdrawing group, such as trifluoromethyl, the product yield was decreased to less than 70% (**3ma-3oa**). This meant that this reaction was not sensitive to the electronic effect although the electron-withdrawing had a slight influence on the reaction yield. On the other hand, it was found that the *ortho*-substitution had little influence on the reaction (**3da** *vs.* **3fa**, **3ha** *vs.* **3ia**), which implied that steric effect had little influence on the reaction. When 2-acetonaphthone was employed, the corresponding product can be obtained with 85% yield (**3pa**). When propiophenone was employed, the corresponding product can be obtained with 43% yield (**3qa**). As a result, the reaction has a great compatibility with the acetophenone substrates.

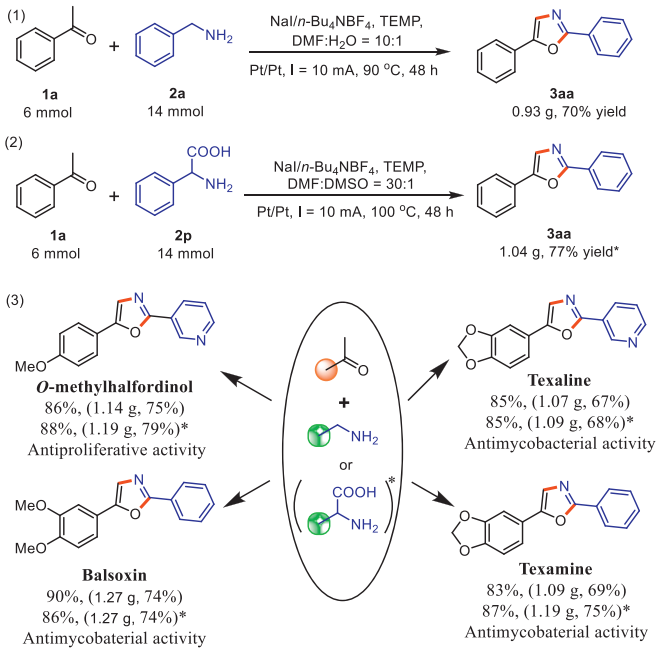
Next, the scope of phenylglycines were extended, as shown in Scheme 5. It was found that the electron-donating substituents on



Scheme 4. Scope of substrates. Unless otherwise noted, all reactions were performed with **1a-1q** (0.3 mmol), **2p** (0.65 mmol), NaI (0.06 mmol), *n*-Bu_4NBF_4 (0.4 mmol), TEMP (0.3 mmol), DMF (3.0 mL). The reaction was carried out at 100 °C for 14 h.



Scheme 5. Scope of substrates. Unless otherwise noted, all reactions were performed with **1a** (0.3 mmol), **2q-2cq** (0.65 mmol), NaI (0.06 mmol), *n*-Bu_4NBF_4 (0.4 mmol), TEMP (0.3 mmol), DMF (3.0 mL). The reaction was carried out at 100 °C for 14 h.



Scheme 6. Gram-scale experiments and the employment in the preparation of the natural products. * Phenylglycine was employed as the substrate.

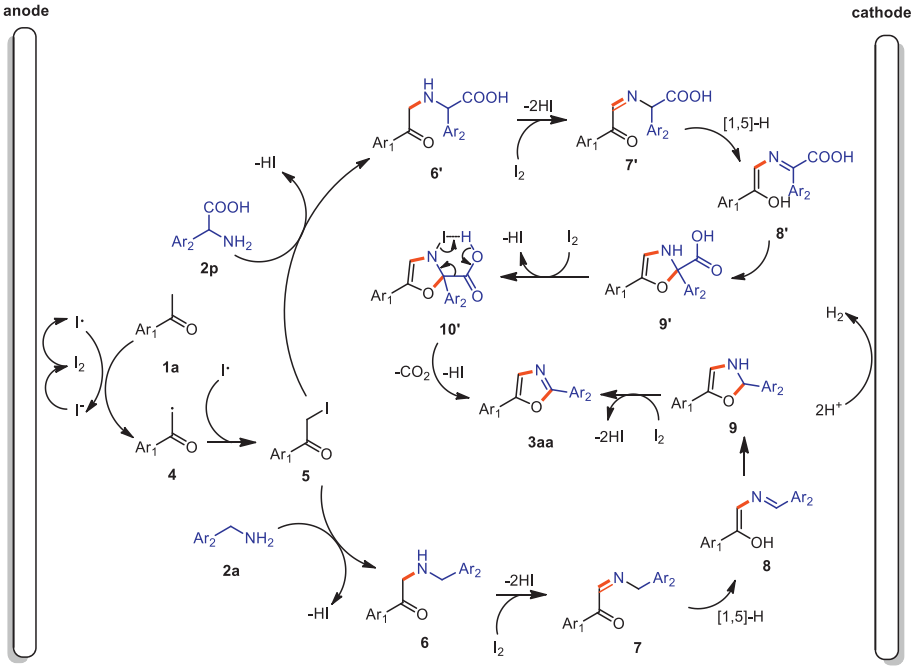
the phenyl rings favored this reaction to give the desired products with the yields of more than 80% (**3ab**-**3ae**). When the electron-withdrawing group was installed on the phenyl ring, the reaction yields were decreased a little, range of 64%–71% (**3af**-**3am**). When the phenyl ring was replaced by heterocyclic ring, the desired product can be still obtained with high yield (**3an**). Therefore the reaction had a good extensibility to phenylglycines.

To evaluate the practicability of this electrochemical synthesis, some gram scale of experiments were performed under the standard condition. As shown in Scheme 6, when the benzylamine was employed as a substrate, 0.93 g of the desired product can be obtained with 70% yield (reaction 1). When the phenylglycine was employed, 1.04 g of the desired product could be obtained with 77% yield (reaction 2). In addition, several natural products can be synthesized by virtue of this method. As shown in reaction 3 (Scheme 6), Balsoxin, *O*-methylhalfordinol, Texaline and Texamine, which have great biological activities, can be obtained by this method.

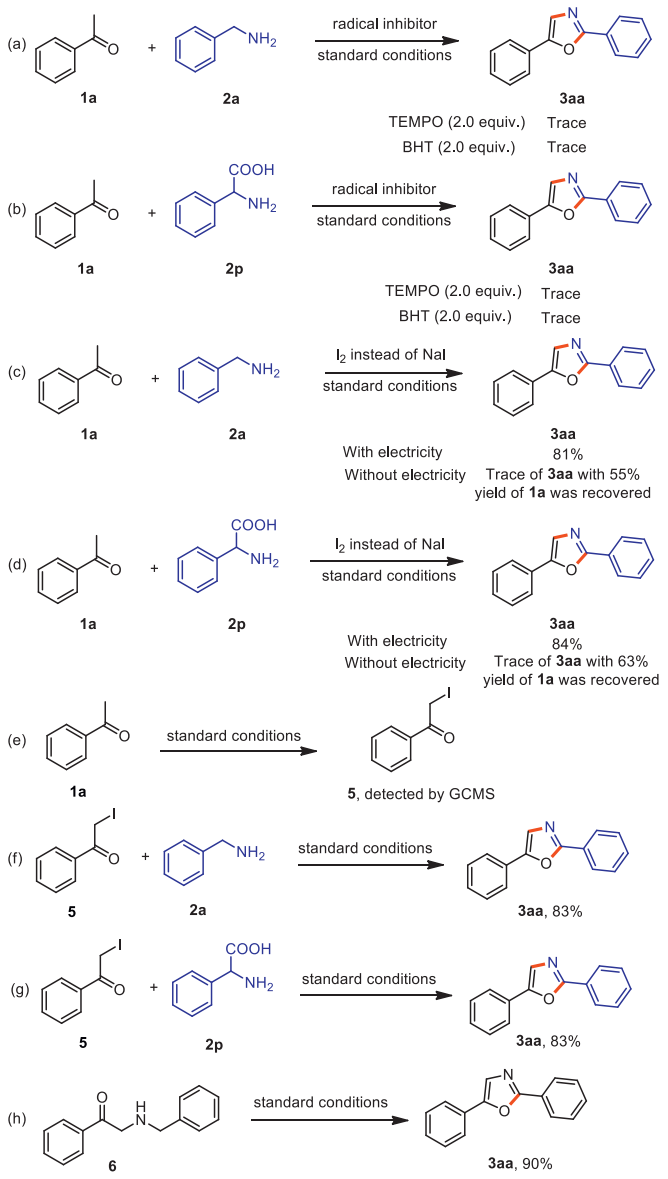
In order to understand the reaction process more clearly, we also performed cyclic voltammetric experiments. In the range of 0-2.0 V *vs.* Ag/AgCl, no obvious oxidation wave of acetophenone **1a** was observed (curve c in Fig. 2), perhaps due to the inertness of the C(sp^3)-H bond. No obvious oxidation wave of benzylamine **2a** was observed, while NaI showed two oxidation waves at 0.66 V and at 1.54 V, respectively (curves b and d in Fig. 2). This indicated that iodide anions should be oxidized firstly, and the following transformation can be initiated from this oxidized iodide ion, which should be the intermediate of this reaction.

More importantly, EPR experiments detected a mixed signal of 5,5-dimethyl-1-proline-*N*-oxide (DMPO) trapping carbon radical **4** (Fig. 3a). This should be the direct evidence for the presence of phenacyl carbon radical **4** in the reaction. Moreover, a mixed signal of DMPO trapping carbon radical **4** and the oxidized DMSO was identified in the electrolysis of the mixture of acetophenone **1a** and NaI (Fig. 3b).

On the other hand, a series of control experiments were carried out to investigate the mechanism (Scheme 7). Initially, when 2 equiv. of 2,2,6,6-tetramethylpiperidinooxy (TEMPO) and butylated hydroxytoluene (BHT) were used as free radical traps, no product was obtained from this reaction (Schemes 7a and b). Then we added 0.2 equiv. of I_2 in place of sodium iodide to the reaction mixture, when benzylamine/phenylglycine was employed, the corresponding product could be obtained with 81%/84% yield, and only trace amounts of product were obtained without electrolysis while 55%/63% acetophenone was recovered (Schemes 7c and d). Gratifyingly, a small amount of iodoacetophenone **5** was detected by GC-MS in the absence of **2a**/**2p** under standard conditions (Scheme 7e). The iodoacetophenone **5** can afford the desired product **3aa** with a yield of 83% (Schemes 7f and g). This suggested



Scheme 8. Proposed possible reaction mechanism.



Scheme 7. Control experiments.

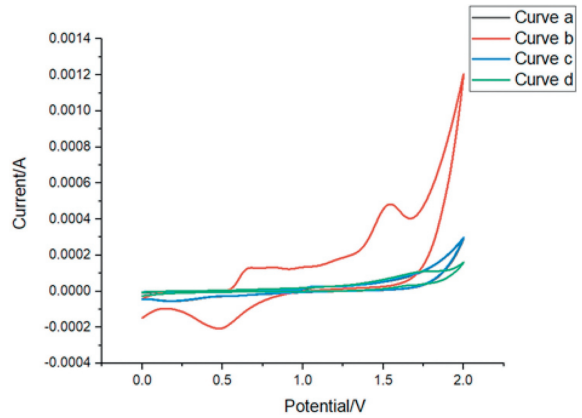


Fig. 2. Cyclic voltammograms of **1a**, **2a** and NaI in 0.1 mol/L n-Bu_4NBF_4/DMF&H_2O using Pt disk as the working electrode, and Pt wire and Ag/AgCl as the counter and reference electrodes, respectively, at a scan rate of 100 mV/s. Background (curve a), NaI (2 mmol/L) (curve b), and **1a** (5 mmol/L) (curve c) and **2a** (5 mmol/L) (curve d).

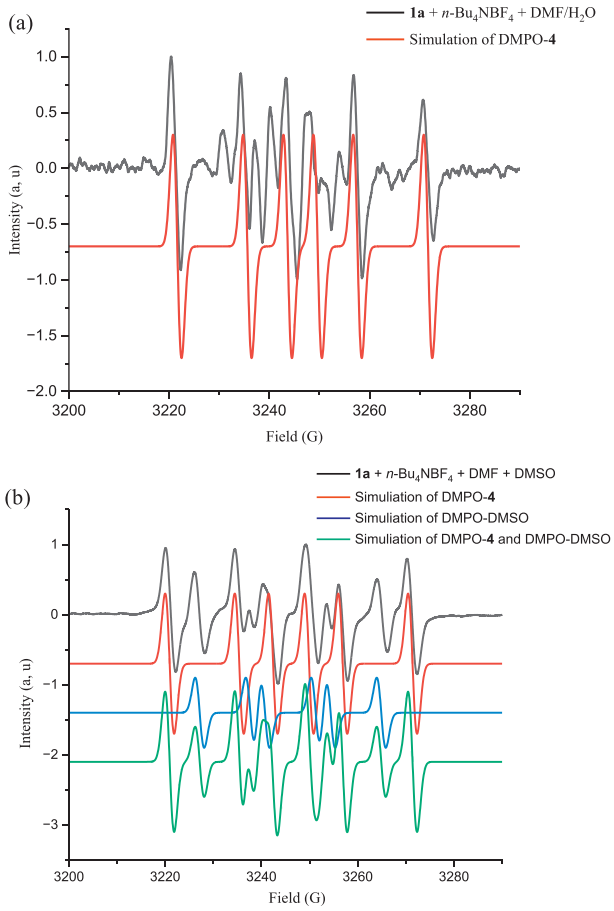


Fig. 3. Electron paramagnetic resonance (EPR) spectra for reaction mixtures in the presence of the radical trapper DMPO and their simulations. (a) After electrolysis of **1a** in 0.1 mol/L n-Bu_4NBF_4/(DMF:H_2O=10:1) for 1.5 h: experimental spectrum (black line), simulation of DMPO-**4** (A_N = 14.5 G, A_H = 21.5 G, g = 2.0060) (red line). (b) After electrolysis of **1a** in 0.1 mol/L n-Bu_4NBF_4/(DMF:DMSO = 30:1) for 1.5 h: experimental spectrum (black line), simulation of DMPO-**4** (A_N = 14.5 G, A_H = 21.5 G, g = 2.0060) (red line), simulation of DMPO-DMSO (A_N = 13.6 G, A_H = 10.5 G, g = 2.0060) (blue line), simulation of DMPO-4 and DMPO-DMSO (green line).

that iodoacetophenone **5** should be an intermediate in the reaction. Therefore, we assumed that the reaction might undergo nucleophilic substitution to afford compound **6** firstly. Actually, compound **6** could afford the target product **3aa** with a yield of 90%, which confirmed our speculation (Scheme 7h).

On the basis of the above-mentioned experimental results and previous literature reports [37–42], a plausible reaction mechanism is proposed as shown in Scheme 8. Firstly, under high temperature conditions, NaI is oxidized to I_2 at the anode and then further oxidized to iodine radical. Subsequently, on the anode surface, iodine radical reacts with substrate **1a** to produce intermediate **4**, which coupled with iodine radical to generate intermediate **5**. Then, **5** is easily nucleophilically substituted by benzylamine **2a** to generate intermediate **6**, which is oxidized to intermediate **7** at the anode. Finally, intermediate **7** is nucleophilic cyclized to generate **9**, which is further oxidized to generate the desired product **3aa**. Meanwhile, the proton is reduced to hydrogen evolution at the cathode.

When **2a** was replaced by phenylglycine **2p**, the mechanism can be described as below. After the formation of intermediate **5** on the anode surface, nucleophilic substitution of **5** by phenylglycine readily produces **6′**, which is oxidized to intermediate **7′** on the anode surface. For the cyclization step, **7′** is isomerized *via* a [1,5]-H shift to compound **8′**. Then intermediate **8′** is nucleophilic cyclized

to generate **9′**, which is subjected to further oxidative decarboxylation to generate the desired product **3aa**. Meanwhile, the proton is reduced to hydrogen evolution at the cathode.

In summary, we developed an electrochemical approach to synthesize 2,5-diaryloxazoles from the facile starting materials of aryl ketones and benzylamines/amino acids. The reaction features a broad scope of substrates, scalability, and mild conditions. Additionally, the four natural products can be prepared easily by this method, which provides a facile route to synthesize natural products.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2023.108897.

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