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Electrochemically mediated decarboxylative acylation of *N*-nitrosoanilines with α-oxocarboxylic acids

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ABSTRACT

An efficient palladium-catalyzed electrooxidation C–H acylation reaction of *N*-nitrosoanilines with α-oxocarboxylic acids was developed. The anodic oxidation of the Pd(II) intermediate was found to be the key to complete the reaction. In this case, the *N*-nitroso group was observed to be an effective directing group for C–H activation reaction. Moreover, the synthetic transformation of derivatives of natural products (L-menthol, dehydroepiandrosterone, and pregnenolone) was successfully realized. Finally, flow electrochemical synthesis of some substrates was achieved.

As the "holy grail" of organic synthesis, C–H functionalization has attracted wide attention from synthetic chemists [1]. Transition metal-catalyzed oxidative C–H functionalization provides a straightforward synthetic approach for the construction of carbon–carbon and carbon–heteroatom bonds [2,3]. Especially, C–H functionalization of arenes can simplify the access to important biologically active small molecules [4,5]. In recent years, direct functionalization of inert aryl C–H bonds under the catalysis of transition-metal catalysts has attracted extensive attention owing to their excellent step economy and atom efficiency [6–8], and aryl C–H activation methods with different directing groups have been successively developed [9]. Despite these achievements, many efficient directing groups have not yet been involved in C(sp^2)–H functionalization. *N*-Nitroso compounds are a very useful class of medicinal compounds and synthetic materials [10,11], and they are also important precursors for the synthesis of various nitrogen-containing compounds, such as hydrazine and octanone [12,13]. Moreover, they are a potential directing group that can be applied to C–H activation [14,15]. Therefore, the modification of *N*-nitroso compounds *via* C–H activation must be realized.

Electrochemistry has attracted increased attention in recent years because of its coincidence with the current development of green chemistry [16–21]. As a reliable alternative to redox reagents, electrochemistry can achieve redox conversions without exogenous oxidants, such as copper salts, silver salts, and persulfate salts [22–26]. In recent years, various electrooxidative transition metal catalytic systems that offer an efficient way to construct important chemical bonds have been developed (Fig. 1a) [27–31]. In these electrochemical reactions, pyridine, quinoline, oxime, and amide are used as C–H-activated directing groups. However, *N*-nitroso, a very active and plastic functional group, has not yet been studied by electrochemists. In this study, under electrochemical conditions, C–H acylation reaction was realized by taking it as a directing group. Hence, not only the traditional electrochemical synthesis of *N*-nitroso-2-aminobenzophenones under palladium catalysis and nonoxidation (Fig. 1b), but also flow electrochemical synthesis were achieved.

Phenylglyoxylic acid **1a** and *N*-methyl-*N*-nitrosoaniline **2a** were used as substrates. The reaction conditions were screened (Table 1). The specific information on the other conditions is provided in Table S1 (Supporting information). The results of electrolysis were optimal when $^{n}Bu_4NOAc$ (1.0 equiv.) was used with $Pd(OAc)_2$ (10 mol%) as the catalyst, HFIP/TFE (3:3) as a solvent, Pt as an anode, and stainless steel as a cathode at a constant current of 5 mA and a reaction temperature of 60 °C in an undivided cell. The yield decreased to 63% when HFIP was used as a solvent (entry 2). Platinum plates and stainless steel or graphite rods were applied to both electrodes to test the electrode effect. The anode and the cathode were also changed, but none of the tested materials could

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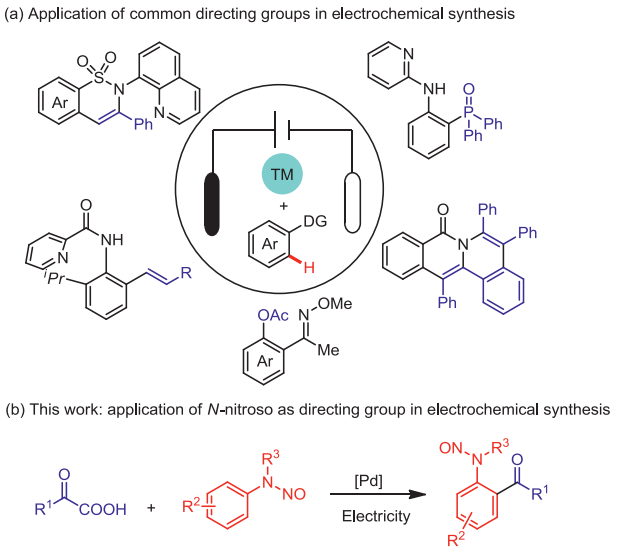
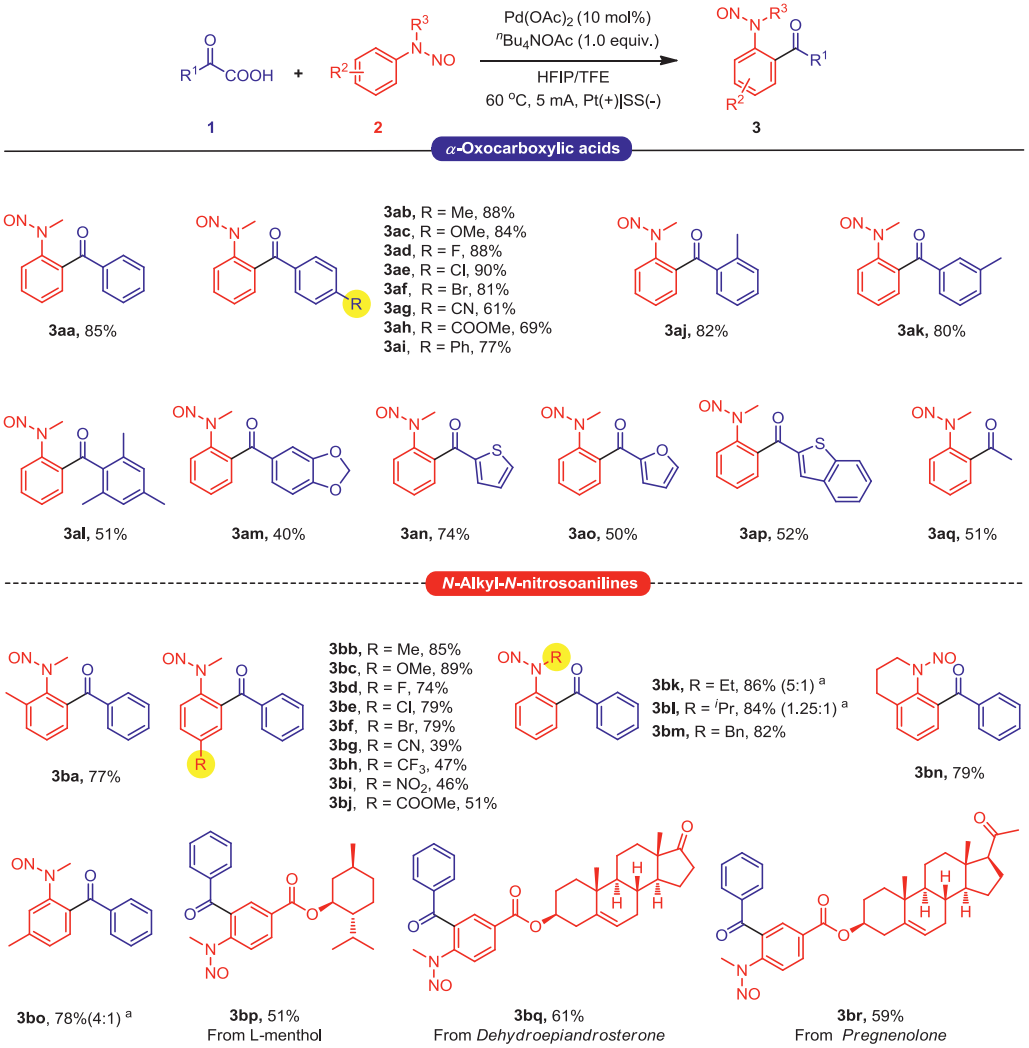


Fig. 1. Site-selective C–H activation *via* the use of a directing group of electrochemistry and transition-metal catalysis.

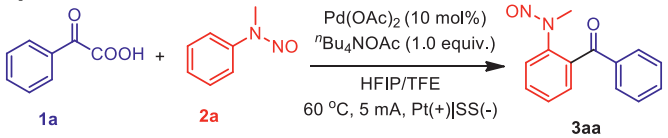
increase the yield of **3aa** (entries 3 and 4). When the temperature was changed to room temperature (entry 5), the yield of **3aa** was 70%. Among the Pd catalysts tested, $Pd(OAc)_2$ was found to be optimal (entries 6 and 7). When the amount of $Pd(OAc)_2$ was reduced to 5 mol%, **3aa** was afforded in 77% yield (entry 8). Control experiments showed that in the absence of electricity or $Pd(OAc)_2$, no desired product was obtained (entries 9 and 10). The change in yield was also tested under divided cell conditions (entry 11). Considering whether the presence of acetate can promote the reaction, we tried to use HOAc as the additive. Unfortunately, the yield of the target product could not be improved (Table S1 in Supporting information).

Under the optimized reaction conditions, substrate suitability studies were conducted using α-oxocarboxylic acid compounds with various substituents (Scheme 1). First, an α-oxocarboxylic acid with a substituent in the *ortho*-, *meta*-, or *para*-position of the phenyl ring exhibited a good yield (**3ab**, **3aj** and **3ak**). Both electron-donating (OMe) and electron-withdrawing groups (F, Cl, Br, CN, COOMe and Ph) were also well tolerated, providing the corresponding products in 61%–88% yields (**3ac–3ai**). Furthermore, bearing a bis- or a tri-substituted phenyl unit was suitable for this reaction to afford **3al–3am** in moderate yields. Moreover, 2-oxo-2-(thiophen-2-yl)acetic acid, 2-(furan-2-yl)-2-oxoacetic acid, and 2-(benzo[*b*]thiophen-2-yl)-2-oxoacetic acid smoothly participated in



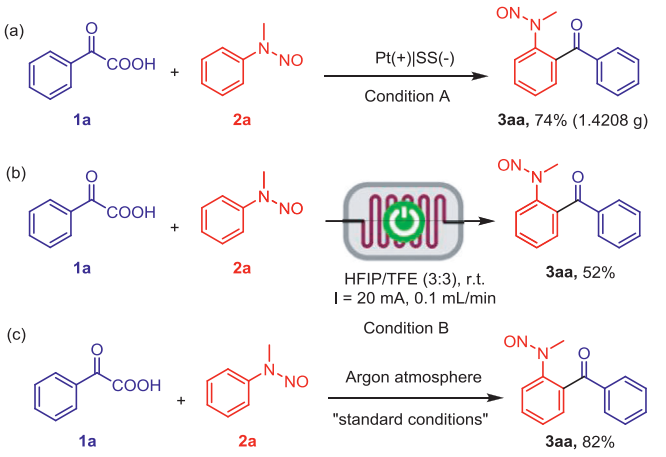
Scheme 1. Substrate scope. Reaction conditions: Pt plate anode (1 cm × 1 cm), stainless steel cathode (1 cm × 1 cm), undivided cell, **1** (0.3 mmol), **2** (0.2 mmol), HFIP (3 mL), TFE (3 mL), $^{n}Bu_4NOAc$ (0.2 mmol), $Pd(OAc)_2$ (0.02 mmol), 5.0 mA, 60 °C, 3.5 h. Isolated yield. [a] Ratio of isomers, determined by the ^1H NMR spectra.

Table 1
Optimization of the reaction conditions.[a]

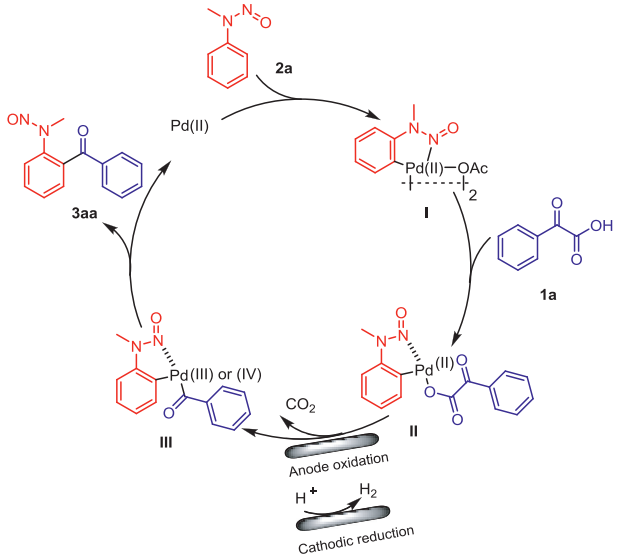


Entry	Variation from standard conditions	Yield (%) [b]
1	None	85
2	HFIP	63
3	Pt(+)|Pt(−) instead of Pt(+)|SS(−)	75
4	C(+)|SS(−) instead of Pt(+)|SS(−)	76
5	Room temperature instead of 60 °C	70
6	$PdCl_2$ instead of $Pd(OAc)_2$	42
7	$Pd(TFA)_2$ instead of $Pd(OAc)_2$	45
8	$Pd(OAc)_2$ (5 mol%) instead of $Pd(OAc)_2$ (10 mol%)	77
9	No $Pd(OAc)_2$	NR
10	No electric current	NR
11	Divided cell	40

[a] Reaction conditions: Pt plate anode (1 cm × 1 cm), stainless steel cathode (1 cm × 1 cm), undivided cell, **1a** (0.3 mmol), **2a** (0.2 mmol), HFIP (3 mL), TFE (3 mL), *n*-Bu_4NOAc (0.2 mmol), $Pd(OAc)_2$ (0.02 mmol), 5.0 mA, 60 °C, 3.5 h. NR = no reaction.
[b] Yield of isolate.



Scheme 2. Applied and control experiments. Conditions A: Pt plate anode, stainless steel cathode, undivided cell, **1a** (12 mmol, 1.8016 g), **2a** (8 mmol, 1.0892 g), HFIP (45 mL), TFE (45 mL), $^nBu_4NOAc$ (6 mmol), $Pd(OAc)_2$ (0.8 mmol), 40 mA, 60 °C, 20 h. Isolated yield. Conditions B (Electrolysis conditions): Graphite anode, stainless steel cathode, electrode surface (8 cm × 6 cm), **1a** (0.3 mmol), **2a** (0.2 mmol), solvent (6 mL), tr = 75 s (calculated), 60 min (3.7 F/mol). Isolated yield.



Scheme 3. Proposed mechanism.

this reaction to give heteroaromatic ketones **3an**, **3ao** and **3ap** in yields of 74%, 50% and 52%, respectively. Pyruvic acid could also be involved in the reaction and afforded the desired product in 51% yield (**3aq**). Additionally, we also tried 2-oxo-2-(pyridin-4-yl) acetic acid and other types of carboxylic acids (benzoic acid, phenylaceticacid, *trans*-cinnamic acid), but failed to get the target product (Scheme S1 in Supporting information).

Subsequently, a substrate scope study of *N*-alkyl-*N*-nitrosoanilines compounds was conducted. As shown in Scheme 1, various *N*-alkyl-*N*-nitrosoaniline compounds afforded moderate to good yields under the electrochemical conditions. According to all the presented examples, the electronic properties of the substituents on the *N*-alkyl-*N*-nitrosoanilines slightly affected the yield of the product. For various *N*-alkyl-*N*-nitrosoanilines, the Me (**3ba-3bb**), MeO (**3bc**), F (**3bd**), Cl (**3be**), Br (**3bf**), CN (**3bg**), CF_3 (**3bh**), NO_2 (**3bi**), and COOMe (**3bj**) substituted *N*-alkyl-*N*-nitrosoanilines were suitable for this conversion, a result that also demonstrated the potential of this electroorganic synthesis method in organic synthesis. Different alkyl-substituted *N*-nitrosoanilines were also reacted with α-oxocarboxylic acids to obtain the target products in good yields (**3bk–3bm**). When the nitrogen atom has an ethyl or isopropyl group, the steric hindrance of the two groups on the nitrogen atom may be equal, resulting in *cis* and *trans* isomers (**3bk-3bl**) [15]. The *N*-nitrosoaniline corresponding to tetrahydroquinoline, the target product, could also be obtained in 79% yield (**3bn**). In addition to the ortho and para alkane groups, when alkane groups were in the *meta*-position, good selectivity could be obtained, that is, greater than 4:1 (**3bo**:**3bo'**).

Afterward, the substrate scope of natural product derivatives was investigated. The three natural product derivatives L -menthol, dehydroepiandrosterone, and pregnenolone gave the target product in moderate yields (**3bp–3br**), another result that demonstrated the potential of this electroorganic synthesis method in functional group tolerance.

The utility of this reaction (Scheme 2) was further investigated by performing gram-scale-up experiments. The target product was obtained in moderate yields. Under standard conditions in the gram-scale experiments, the target product was obtained in good yield. However, the limitations of traditional electrochemistry, such as large electrode gap, limited mass transfer, and difficulty in scaling up, limit the industrial application of these complex organic chemical reactions. Electrochemical microreactors can satisfactorily solve these problems because of their extremely large surface-to-volume ratio, which enhances mass and heat transfer and provides more reaction sites compared with classical batch-type reactors [32]. Thus, this reaction was tested using a flow electrochemical reactor. Surprisingly, the target product was obtained in 52% yield. The reaction mechanism was further clarified by performing a series of control experiments (Scheme 2c). Additionally, 82% yield was obtained when the reaction was performed under Ar conditions. Therefore, this process was confirmed to be an electrooxidation process.

On the basis of the abovementioned results and the reports in the literature [15], a possible mechanism for the electrochemical oxidation is presented in Scheme 3. First, this transformation is believed to start with the ortho-palladation of **2a** with $Pd(OAc)_2$ to provide the five-membered palladacycle **I**, which subsequently undergoes anion exchange with **1a** to afford intermediate **II**, followed by electrooxidation and concurrent decarboxylation to furnish the Pd(III) or Pd(IV) intermediate **III**. Finally, product **3aa** is generated by reductive elimination with the simultaneous release of a Pd(II) species to complete the catalytic cycle. At the same time, protons were reduced at the cathode to produce H_2.

In summary, we developed an economical and practical method for the synthesis of *N*-nitroso-2-aminobenzophenones through electrochemical oxidation. A wide range of *N*-nitroso-2-aminobenzophenones were obtained in moderate to high yields. The three natural product derivatives L-menthol, dehydroepiandrosterone, and pregnenolone gave the target product in moderate yields. We contend that this electrochemical strategy for accessing *N*-nitroso-2-amino benzophenones will facilitate the synthesis of various natural product compounds.

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.2022.05.051.

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