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Catalyst-free electrochemical decarboxylative cross-coupling of *N*-hydroxyphthalimide esters and N-heteroarenes towards C(sp^3)–C(sp^2) bond formation†

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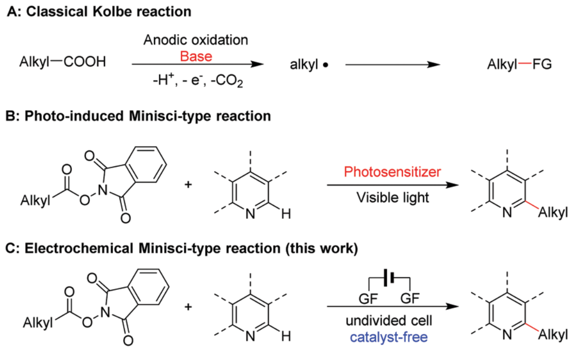
Cheap and widely available carboxylic acids are a class of ideal substrates to construct valuable compounds. As a candidate of decarboxylative reactions, the acid-based neutral *N*-hydroxyphthalimide ester undergoes a reductive decarboxylative process rather than a common oxidative decarboxylative process, which is a potential transformation mode for new reactions. In this work, we developed an electrochemical C(sp^3)–C(sp^2) coupling of *N*-hydroxyphthalimide esters and N-heteroarenes without any catalysts. Remarkably, this electrochemical protocol can not only be directly realised by carboxylic acids in a one-pot fashion, but also be scaled up using a continuous-flow reactor.



Scheme 1 Decarboxylative reaction.

Alkyl carboxylic acids are widely present in natural products, pharmaceuticals and agrochemicals. The decarboxylative reaction of alkyl carboxylic acids is an efficient method to produce alkyl radicals due to the good site selectivity with CO_2 release.[1] This process has been performed well in transition-metal catalysis,[2] photochemistry[3] and electrochemistry.[4] The famous Kolbe reaction is a classic case of electrochemical oxidative decarboxylative reaction[4c,5] (Scheme 1A). However, this type of reaction usually needs base, which can react with carboxylic acids to afford the corresponding carboxylates. The carboxylates could lose an electron more easily at the anode. So, the Kolbe pathway might be inappropriate in some systems requiring strong acid, such as Minisci-type reactions.[6] Moreover, strong proton acceptors are not compatible with systems involving carboxylic acids.[7]

In order to solve the above problems, chemists made many efforts towards exploring new strategies. For example, the acid–base neutral *N*-hydroxyphthalimide (NHP) ester can undergo a reductive decarboxylative protocol to generate the corresponding carbon radical.[8] During the past few years, NHP esters have been widely applied in photochemical synthesis.[9] For Minisci-type arylation, Fu,[10] Wang,[11] Opatz[12] and Noël[13] have achieved photo-induced C(sp^3)–C(sp^2) bond formation. In most reports, precious or complicated photosensitizers, such as iridium complexes[10b] or copper complexes,[11] were generally essential (Scheme 1B).

Recently, electrochemical synthesis has attracted more and more attention, avoiding the use of catalysts and oxidants, which meet with the requirement of green and sustainable chemistry.[14] However, reductive decarboxylation of NHP esters at the cathode remains less developed.[15] As a complement of the Kolbe reaction, obtaining radicals at the cathode may provide opportunities to achieve new reactions. In this work, we introduced a simple and efficient electrochemical protocol of NHP esters and quinoline derivatives to construct C–C bonds without any catalysts (Scheme 1C).

We started our investigation by using the NHP ester (**1d**) and 4-methylquinoline (**2a**) as the model substrates. By using *p*-toluenesulfonic acid (*p*-TsOH) as the additive, ^{n}Bu$_4$NBF$_4$ as the electrolyte and dimethylacetamide (DMA) as the solvent, the desired product could be obtained in 87% GC yield and 91% isolated yield under 7.5 mA constant current for 150 min (Table 1, entry 1).

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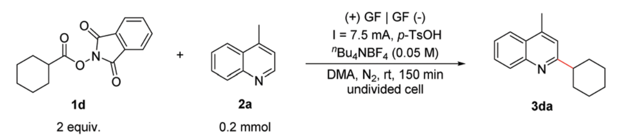
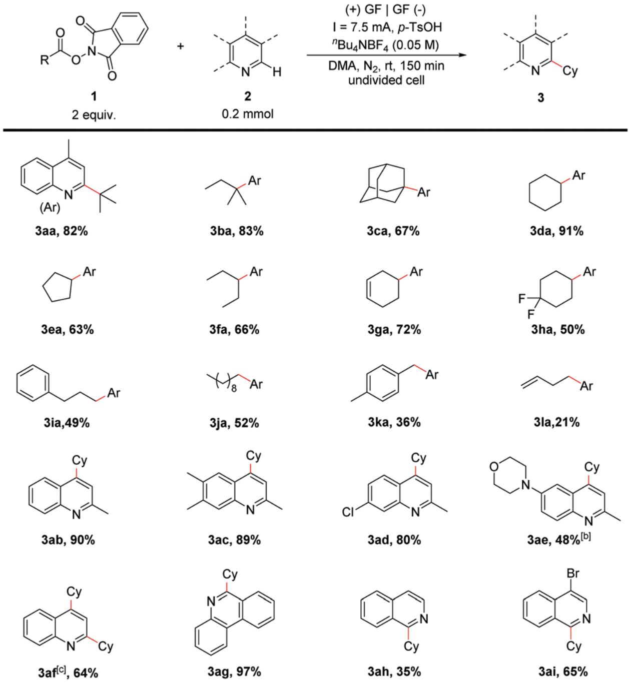
Table 1 Effects of reaction parameters[a]



Entry	Variation(s) from the standard conditions	Yield[b] (%)
1	None	87 (91)[c]
2	5 mA instead of 7.5 mA, 225 min	71
3	12.5 mA instead of 7.5 mA, 90 min	77
4	CH_3SO_2H instead of *p*-TsOH	84
5	TFA instead of *p*-TsOH	80
6	CF_3SO_2H instead of *p*-TsOH	70
7	DMSO instead of DMA	86
8	DMF instead of DMA	84
9	MeCN instead of DMA	80
10	(+) C rod|C rod (−)	55
11	(+) GF|C rod (−)	77
12	(+) GF|Pt (−)	9
13	In air	88
14	Without electric current	n.d.
15	Cyclohexanecarboxylic acid instead of **1d**	n.d.

[a] Reaction conditions: graphite felt anode (15 mm × 10 mm × 3 mm), graphite felt cathode (15 mm × 10 mm × 3 mm), constant current = 7.5 mA, **1d** (2 equiv., 0.4 mmol), **2a** (1.0 equiv., 0.20 mmol), *p*-TsOH (1.5 equiv., 0.3 mmol), $^{n}Bu_4NBF_4$ (0.05 M, 0.25 mmol), DMA (5 mL), room temperature, N_2, 150 min (3.5 F). [b] The yields were determined by GC analysis with biphenyl as the internal standard. [c] Isolated yield. n.d. = not detected.

When we decreased or increased the current, the yield decreased (Table 1, entries 2 and 3). When other strong acids such as methane sulfonic acid and trifluoroacetic acid (TFA) were used, the yield decreased slightly (Table 1, entries 4 and 5). The trifluoromethanesulfonic acid seemed to be worse (Table 1, entry 6). For the solvent, polar solvents such as *N*,*N*-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), and MeCN demonstrated similar reactivity to DMA (Table 1, entries 7–9). The variation of electrodes had the biggest influence on this reaction. Carbon-based materials showed good activity at both the anode and cathode. And graphite felt was better than carbon rods (Table 1, entries 10–12). This reaction could proceed smoothly in air (Table 1, entry 13). In summary, multiple solvent/acid choices and air can provide more potential application opportunities. Finally, the product cannot be detected without electric current (Table 1, entry 14). In addition, cyclohexanecarboxylic acid cannot replace the NHP ester under these conditions (Table 1, entry 15).

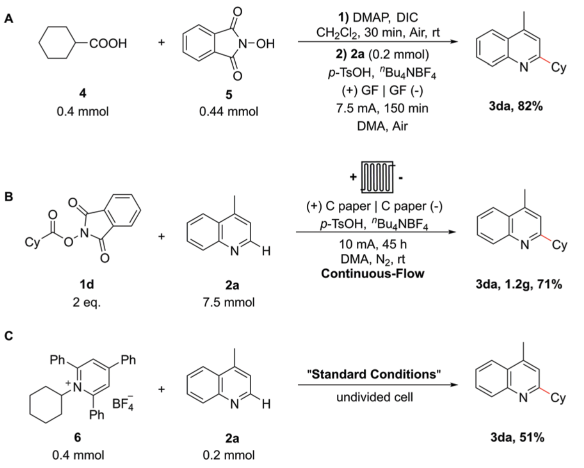


Scheme 2 Substrate scope of the reaction.[a] [a] Reaction conditions: graphite felt anode (15 mm × 10 mm × 3 mm), graphite felt cathode (15 mm × 10 mm × 3 mm), constant current = 7.5 mA, **1** (2 equiv., 0.4 mmol), **2** (1.0 equiv., 0.20 mmol), *p*-TsOH (1.5 equiv., 0.3 mmol), $^{n}Bu_4NBF_4$ (0.05 M, 0.25 mmol), DMA (5 mL), room temperature, N_2, 150 min (3.5 F), isolated yield. [b] NMR yield with CH_2Br_2 as the internal standard. [c] **1** (4 equiv., 0.8 mmol) was used and the time was extended to 300 min.

With the best optimized reaction conditions in hand, we focused on exploring the substrate scope. Firstly, both chain and cyclic tertiary carboxylic esters could afford the corresponding products in moderate to good yield (**3aa**, **3ba** and **3ca**). For secondary aliphatic carboxylic esters, the yields decreased to moderate values except for the cyclohexyl ester (**3da**, **3ea** and **3fa**). Meanwhile, the alkenyl group can be retained under this system (**3ga**). A difluoro-substituted carboxylic ester could also afford 50% yield (**3ha**). With regard to primary acids, high site selectivity was shown and a moderate yield could be generated, without rearrangement (**3ia** and **3ja**). The benzyl product was isolated in a low yield (**3ka**). And the terminal alkenyl groups were tolerated, which provided a chance for further functionalization (**3la**). On the other hand, other quinolines substituted with methyl could also afford good yields (**3ab** and **3ac**). The chlorine atom was compatible with this system (**3ad**). The electron-rich 6-(morpholinyl)-2-methylquinoline led to a moderate isolated yield (**3ae**). When doubling the amount of ester and time, the unsubstituted quinoline could give the disubstituted product selectively (**3af**). For other N-heteroarenes, the phenanthridine furnished the corresponding product in 97% yield (**3ag**). The isoquinoline only afforded 35% product due to the complicated side reaction (**3ah**). But, with C4 being substituted with the bromo atom, the yield improved to 65% (**3ai**) (Scheme 2).

In order to make this protocol more convenient, we tried to achieve this transformation in a one-pot fashion. Without separation of the ester, the following electrochemical reaction would not be influenced (Scheme 3A). Remarkably, we scaled up this reaction on a gram-scale under a continuous-flow system (for more details please check the ESI,† S11). In this system, we tried to decrease the reaction time. The flow system had a higher faradaic efficiency and a good isolated yield (Scheme 3B). To our delight, the Katritzky *N*-cyclohexylpyridinium salt (Scheme 3, **6**) can also be tolerated under the standard conditions (Scheme 3C). This electrochemical approach can build C–C bonds through not only carboxylic acids, but also pyridinium salts, which came from aliphatic amines.

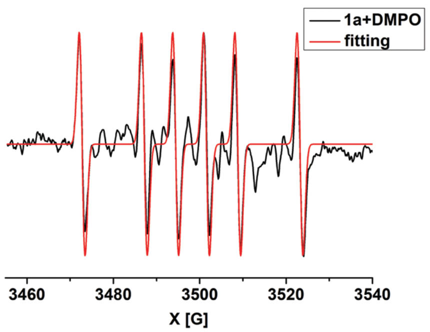
Next, we tried to explore the mechanism of this system, and did some control experiments. When removing the quinoline, the bicyclohexyl can be detected by GC-MS, which may form by



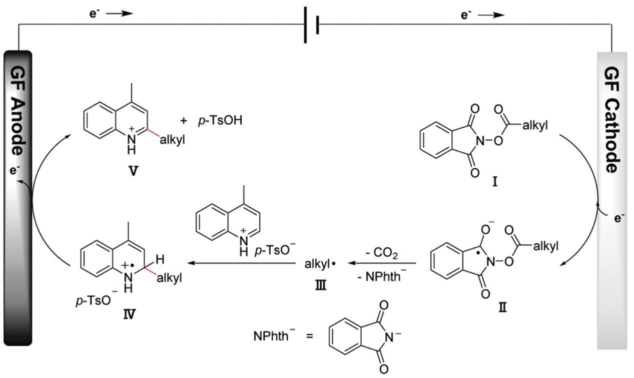
Scheme 3 Other extensions of the reaction.[a] [a] Reaction conditions: (A) **4** (2 equiv., 0.4 mmol), **5** (0.44 equiv., 0.44 mmol), DMAP = 4-dimethylaminopyridine (0.2 equiv., 0.04 mmol), DIC = *N*,*N*′-diisopropylcarbodiimide (2.4 equiv., 0.48 mmol), CH_2Cl_2 (1 mL), room temperature, air, 30 min. Then, adding **2a** (1.0 equiv., 0.20 mmol), *p*-TsOH (1.5 equiv., 0.3 mmol), ^{n}Bu$_4$NBF$_4$ (0.05 M, 0.25 mmol), DMA (4 mL), graphite felt anode (15 mm × 10 mm × 3 mm), graphite felt cathode (15 mm × 10 mm × 3 mm), constant current = 7.5 mA, room temperature, N_2, 150 min (3.5 F). (B) In a continuous-flow system, carbon paper (93 mm × 93 mm × 0.2 mm), carbon paper (93 mm × 93 mm × 0.2 mm), constant current = 10 mA, **1d** (2 equiv., 15 mmol), **2a** (1.0 equiv., 7.5 mmol), *p*-TsOH (1.5 equiv., 11.25 mmol), ^{n}Bu$_4$NBF$_4$ (0.05 M, 5 mmol), DMA (100 mL), room temperature, N_2, 45 h (2.2 F). (C) Graphite felt anode (15 mm × 10 mm × 3 mm), graphite felt cathode (15 mm × 10 mm × 3 mm), constant current = 7.5 mA, **6** (2 equiv., 0.4 mmol), **2a** (1.0 equiv., 0.20 mmol), *p*-TsOH (1.5 equiv., 0.3 mmol), ^{n}Bu$_4$NBF$_4$ (0.05 M, 0.25 mmol), DMA (5 mL), room temperature, N_2, 150 min (3.5 F).

the homo-coupling of cyclohexyl radicals (see the ESI,† S12). Moreover, radical-trapping experiments were conducted. When 2,6-di-*tert*-butyl-4-methylphenol (BHT) was used as the radical-trapping reagent, the coupling products with a cyclohexyl radical and BHT were detected by GC-MS (see the ESI,† S13). The above results indicated that the cyclohexyl radical was probably involved in this transformation.

Besides, EPR results are shown in Scheme 4. In the absence of quinoline and acid, a carbon centre radical trapped by 5,5-dimethyl-1-pyrroline *N*-oxide (DMPO) was detected (g = 2.0065, A_N = 14.4 G, A_H = 21.65 G). We proposed that the NHP ester can lose one electron and produce a carbon radical after the decarboxylation.



Scheme 4 EPR results.[a] [a] Reaction conditions: graphite felt anode (15 mm × 10 mm × 3 mm), graphite felt cathode (15 mm × 10 mm × 3 mm), constant current = 7.5 mA, **1d** (0.4 mmol), ^{n}Bu$_4$NBF$_4$ (0.05 M, 0.25 mmol), DMA (5 mL), room temperature, N_2, 40 min. And then, DMPO (0.3 mmol) was added in the system, for another 1 min electrolysis.



Scheme 5 Proposed mechanism.

To further investigate the electrochemical properties of each substrate, we performed cyclic voltammetry (CV) tests. We can observe a reduction peak at −1.25 V (*vs.* AgCl/Ag, the same below), which belonged to the ester (see the ESI,† S14). And, for the quinoline, no extra significant reduction peak can be observed relative to the blank control.

Based on the above experimental results, the possible mechanism for the electrochemical decarboxylative cross-coupling reaction is shown in Scheme 5. At first, the NHP ester (Scheme 5, **I**) could get one electron from the cathode to give a radical anion (Scheme 5, **II**), which further underwent decarboxylation to form the corresponding alkyl radical (Scheme 5, **III**). Then, the alkyl radical could attack protonated quinoline to form a new C–C bond (Scheme 5, **IV**). Finally, the generated radical lost an electron on the anode, and subsequently lost a proton to give the target product (Scheme 5, **V**).

In conclusion, we developed a catalyst-free electrochemical protocol for the Minisci-type arylation by using NHP esters and N-heteroarenes. This method used the cathode reduction process to convert the ester into the corresponding carbon radical directly. Our approach is a complement to the Kolbe oxidative decarboxylation reaction and a promising strategy for finding more new reactions.

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Conflicts of interest

There are no conflicts to declare.

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