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Nickel-catalyzed electrochemical reductive decarboxylative coupling of *N*-hydroxyphthalimide esters with quinoxalinones†

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Herein the first example of electrochemically enabled, $NiCl_2$-catalyzed reductive decarboxylative coupling of *N*-hydroxyphthalimide (NHP) esters with quinoxalinones is reported. A range of primary, secondary, tertiary aliphatic carboxylic acids and amino acid-derived esters were tolerated well. This decarboxylative coupling allows access to structurally diverse 3-alkylated quinoxalinones in up to 91% yields.

Electrochemical metal catalysis significantly expanded the scope of electrosynthesis by integrating sustainable electrosynthesis and powerful metal catalysis.[1] This strategy arguably represents an attractive means for enabling cross-coupling,[2] C–H and C=C functionalization reactions.[3] In contrast to precious 4d transition metals, nickel catalysis provides a unique single-electron-transfer catalytic cycle.[4] The combination of electrosynthesis with a nickel catalytic system would provide opportunities with great synthetic potential. Indeed, some seminal studies have demonstrated the synthetic utility of electrochemically driven nickel catalysis in reductive cyclizations.[5] In 2017, Baran and co-workers elegantly established an electrochemical nickel-catalyzed amination reaction.[6] Recently, groups of Hasen,[7] Bio,[8] Loren,[9] Wang,[10] Mei,[11] Meggers,[12] and Guo[13] have independently broadened the viable scope of electrochemical nickel catalysis in nonchiral and chiral transformations. Despite these significant advances, synthetic applications of electrochemical nickel catalysis are still desired.

3-Alkylated quinoxalinones are unique structural motifs existing widely in biologically active molecules (Fig. 1a).[14] The reported methodologies for the construction of 3-alkylated quinoxalinones mainly relied on the oxidative coupling of alkyl radical precursors with quinoxalinones.[15] To achieve efficient alkyl radical formation, chemical oxidants such as TBHP and $K_2S_2O_8$ are always needed. Besides, the functional group tolerance for the alkyl radical precursors is not always good. NHP esters are versatile C_{sp^3} radical precursors with flexible functional group variations.[16] The electrochemical reductive decarboxylative coupling of NHP esters may provide diverse 3-alkylated quinoxalinones under mild conditions. Encouraged by previous studies on nickel-catalyzed decarboxylative coupling of NHP esters with radical acceptors,[17] and in continuation of our research interest in electrochemical C–H functionalizations of quinoxalinones,[18] we herein report the first example of electrochemically enabled, nickel-catalyzed reductive decarboxylative coupling of NHP esters with quinoxalinones (Fig. 1b). The reaction tolerated a range of primary, secondary, and tertiary aliphatic carboxylic acids and especially amino acid-derived NHP esters, providing diverse 3-alkylated quinoxalinones in good to excellent yields.

Using 2-quinoxalinone **1a** and NHP ester **2e** as the model substrates, we began our investigation into the optimal reaction conditions (Table 1). When decarboxylative coupling of **1a** and **2e** was performed in CH_3CN with graphite felt as the anode and nickel foam as the cathode under constant current electrolysis

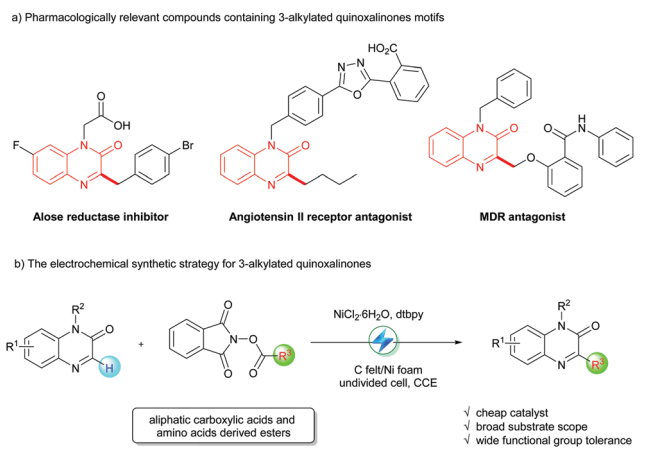

Fig. 1 Electrochemically enabled, nickel-catalyzed 3-alkylated quinoxalinone synthesis.

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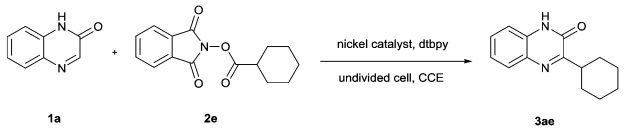
Table 1 Optimization of reaction conditions[a]



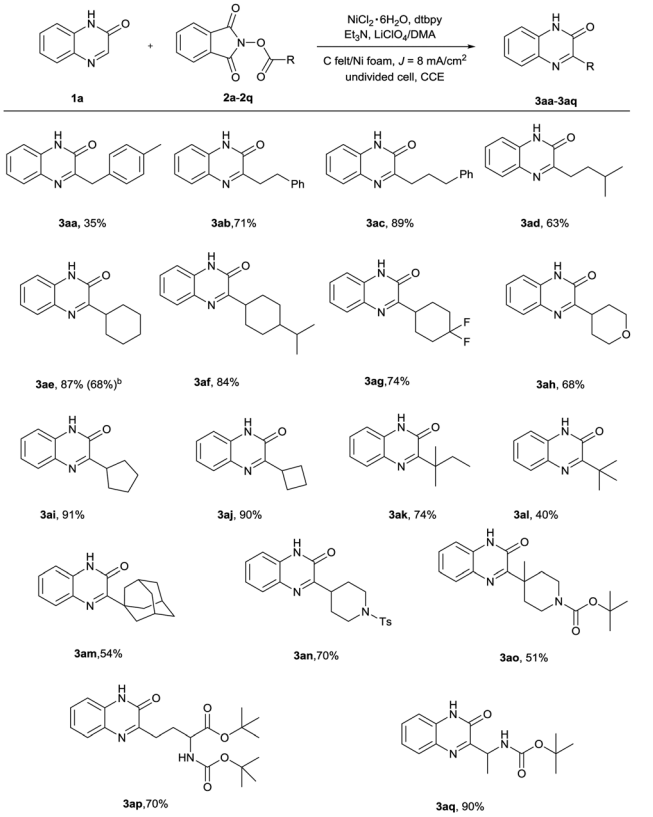
Entry	Catalyst	*I*/mA	Anode/cathode	Yield[b] (%)
1[c]	$NiBr_2$·glyme	4	C felt/Ni foam	26
2	$NiBr_2$·glyme	4	C felt/Ni foam	38
3	$NiBr_2$·glyme	6	C felt/Ni foam	82
4	$NiBr_2$·glyme	8	C felt/Ni foam	85
5	$NiBr_2$·glyme	8	C felt/C felt	82
6	$NiBr_2$·glyme	8	C felt/Pt	13
7	$NiBr_2$·glyme	8	Mg/Ni foam	14
8	$NiBr_2$	8	C felt/Ni foam	72
9	$Ni(acac)_2$	8	C felt/Ni foam	84
10	$NiCl_2$·glyme	8	C felt/Ni foam	37
11	$NiCl_2(pph_3)_2$	8	C felt/Ni foam	73
12	$NiCl_2$(dppe)	8	C felt/Ni foam	73
13	$NiCl_2(Cy)_2$	8	C felt/Ni foam	80
14	**$NiCl_2·6H_2O$**	**8**	**C felt/Ni foam**	**87**
15	$NiCl_2·6H_2O$	8	C felt/Ni plate	48
16	—	8	C felt/Ni foam	27

[a] Reaction conditions: **1a** (0.3 mmol), **2e** (0.6 mmol), $LiClO_4$ (1.0 mmol), nickel catalyst (0.06 mmol), 4,4′-di-*tert*-butyl-2,2′-bipyridine (dtbpy, 0.06 mmol), triethylamine (0.25 mL), anhydrous DMA (4 mL), graphite felt ($10 \times 10 \times 1$ mm^3) as the anode, nickel foam ($10 \times 10 \times 1$ mm^3) as the cathode, undivided cell, 8 mA, 60 °C, 3 h, Ar. [b] Isolated yield. [c] CH_3CN as the solvent.

(CCE) conditions, the desired product **3ae** was isolated in 26% yield (entry 1). When anhydrous *N*,*N*-dimethylacetamide (DMA) was used as the solvent, the yield of **3ae** increased to 38% (entry 2). Further optimization showed that **3ae** could be obtained in 85% yield when the current was increased to 8 mA, while decreased current density led to lower yields (entries 4 *vs.* 2 and 3). To improve the chemical yield of **3ae**, a series of electrode materials were screened. The results showed that graphite felt and nickel foam were the optimal electrode materials. Next, a series of nickel catalysts were screened (entries 7–14). The results revealed that readily available $NiCl_2·6H_2O$ could give the best yield of 87% (entry 14). The replacement of the Ni foam with a Ni plate decreased the yield to 48% (entry 15). Control experiments showed that only 27% yield was obtained in the absence of a $NiCl_2$ catalyst (entry 16).

With the optimized reaction conditions identified, we began to survey the scope and the generality of the protocol by examining the reactions of 2-quinoxalinone **1a** with a variety of NHP esters **2**. As shown in Table 2, redox active esters derived from primary, secondary, tertiary carboxylic acids and also amino acids with a broad scope are all suitable substrates, giving **3aa–3aq** with up to 91% yield. First, a series of primary carboxylic acid derived NHP esters were tested under the optimal conditions. The results showed that the decarboxylative coupling reactions underwent smoothly, giving the corresponding products **3aa–3ad** with up to 89% yields. The secondary carboxylic acid derived NHP esters were also suitable substrates, yielding **3ae–3aj** in 68–91% yields. It is noteworthy that tetrahydro-2*H*-pyran-4-carboxylic acid derived NHP ester could give the corresponding product **3ah** in 68% yield. Next, the tertiary carboxylic acid

Table 2 Substrate scope with respect to NHP esters[a]

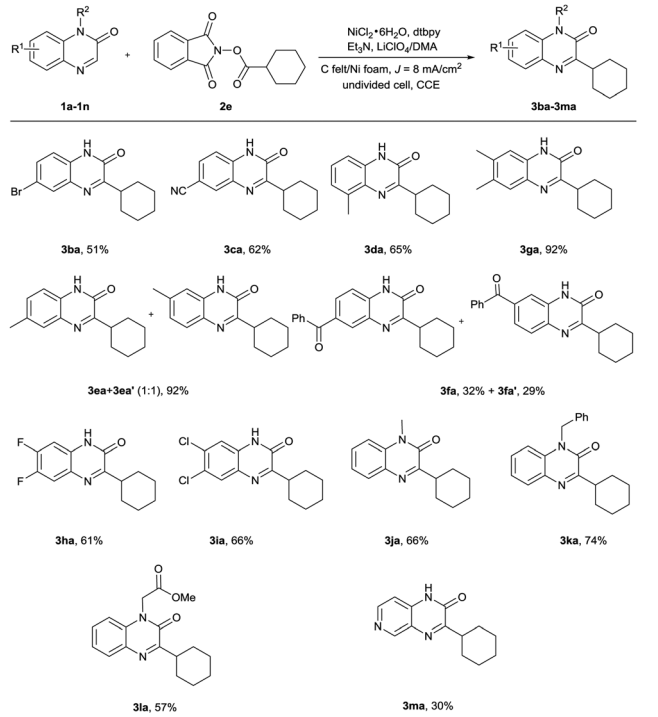


[a] Reaction conditions: **1a** (0.3 mmol), **2** (0.6 mmol), $LiClO_4$ (1.0 mmol), $NiCl_2·6H_2O$ (0.06 mmol), dtbpy (0.06 mmol), triethylamine (0.25 mL), anhydrous DMA (4 mL), graphite felt ($10 \times 10 \times 1$ mm^3) as the anode, nickel foam ($10 \times 10 \times 1$ mm^3) as the cathode, undivided cell, 8 mA, 60 °C, 3 h, Ar; isolated yield. [b] The yield in parentheses was the result for a 3 mmol scale synthesis.

derived NHP esters were also tolerated well to give **3ak–3am** in 40–74% yields. Moreover, amino acid derived NHP esters underwent the decarboxylative coupling with 2-quinoxalinone **1a** smoothly, affording the corresponding products **3an–3aq** in 51–90% yields. To demonstrate the synthetic utility of this electrochemical protocol, a scale-up reaction of **1a** with **2e** was carried out. To our delight, the desired product **3ae** was obtained in 68% yield (see the ESI† for details).

To further explore the synthetic potential of this electrochemical methodology, the reaction of NHP ester **2e** with a variety of 2-quinoxalinones **1** was investigated (Table 3). First, monosubstituted 2-quinoxalinones were investigated under the optimal conditions. Methyl, bromide, and cyano substituents were well tolerated, giving the corresponding products **3ba–3da** in 51–65% yields. When methyl substituted 2-quinoxalinones with a 1 : 1 regioisomer ratio were employed as the substrates, the corresponding products **3ea** and **3ea′** were obtained in 92% total yield. Similarly, with the regiomers of benzoyl substituted quinoxalinone (1 : 1 ratio) as the substrates, **3fa** and **3fa′** were obtained in 32% and 29% yields, respectively. Then, disubstituted 2-quinoxalinones were tested under the standard conditions, and the corresponding products **3ga–3ia** were obtained in 61–92%

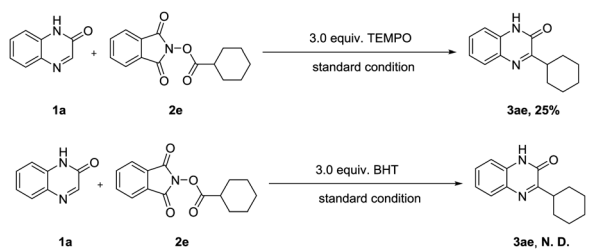
Table 3 Substrate scope with respect to 2-quinoxalinones[a,b]



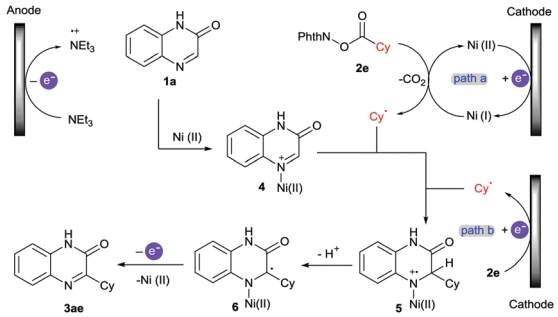
[a] Reaction conditions: **1** (0.3 mmol), **2e** (0.6 mmol), $LiClO_4$ (1.0 mmol), $NiCl_2{\cdot}6H_2O$ (0.06 mmol), dtbpy (0.06 mmol), triethylamine (0.25 mL), anhydrous DMA (4 mL), graphite felt (10 × 10 × 1 mm^3) as the anode, nickel foam (10 × 10 × 1 mm^3) as the cathode, undivided cell, 8 mA, 60 °C, 3 h, Ar. [b] Isolated yield.

yields. The *N*-protected 2-quinoxalinones were also suitable coupling partners, giving **3ja**–**3la** in 57–74% yields. Notably, when pyrido[3,4-*b*]pyrazin-2(1*H*)-one was employed as the substrate, the coupling product **3ma** was obtained in 30% yield.

To explore the mechanism for the decarboxylative coupling of quinoxalinones with NHP esters, a series of control experiments were performed. As shown in Scheme 1, the yield of target product **3ae** was reduced to 25% by including 3.0 equiv 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) to the standard conditions. When 3.0 equiv. butylated hydroxytoluene (BHT) was used as the radical inhibitor, no **3ae** was observed. These results indicate that this reaction involves radical species. To gain more insight into the mechanism, cyclic voltammetry (CV) experiments were carried out (see the ESI† for details). The results showed that there is an obvious reduction peak



Scheme 1 Control experiments.



Scheme 2 Proposed mechanism for the formation of **3ae**.

at −1.3 V *vs.* Ag/$AgNO_3$ (0.1 M in CH_3CN) for substrate **2e**. In addition, the reductive potential of the complex of $NiCl_2{\cdot}6H_2O$ with dtbpy was observed at −1.1 V *vs.* Ag/$AgNO_3$ (0.1 M in CH_3CN). These results suggest that the Ni(II) complex is easier to be reduced than substrate **2e**.

Based on the above experimental studies and related literature reports,[9] the reaction mechanism for the decarboxylative coupling of quinoxalinone **1a** with NHP ester **2e** was proposed. As depicted in Scheme 2, Ni(II) is first reduced to Ni(I) at the cathode. The resulting Ni(I) species undergoes a single-electron-transfer with NHP ester **2e** to give Ni(II) species and a cyclohexyl radical (path a). Meanwhile, the direct reduction of NHP ester **2e** at the cathode to generate a cyclohexyl radical can't be ruled out (path b).[8] Then, the cyclohexyl radical undergoes an addition reaction with complex **4** to give radical cation **5**, which then loses one molecule of H^+ to afford radical **6**. Finally, radical **6** undergoes further oxidation and then loses one molecule of Ni(II)) to give the desired product **3ae**. Meanwhile, NEt_3 is oxidized at the anode to give a triethylamine radical cation.

In conclusion, we have developed the first example of $NiCl_2$-catalyzed electrochemical reductive coupling of NHP esters with quinoxalinones. By integrating electrochemistry with nickel catalysis, biologically important 3-alkylated quinoxalinones were obtained in good to excellent yields. The present method features mild conditions, cheap catalysts, a broad substrate scope, and excellent functional group tolerance.

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Conflicts of interest

There are no conflicts to declare.

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