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Nickellaelectro-Catalyzed C–H Alkoxylation with Secondary Alcohols: Oxidation-Induced Reductive Elimination at Nickel(III)

Shou-Kun Zhang, Julia Struwe, Lianrui Hu and Lutz Ackermann*[a]

Abstract: Nickellaelectro-oxidative C–H alkoxylations with challenging secondary alcohols were accomplished in a fully dehydrogenative fashion, thus avoiding stoichiometric chemical oxidants with H_2 as the only stoichiometric byproduct. The nickellaelectro-catalyzed oxygenation proved viable with various (hetero)arenes, including naturally occurring secondary alcohols without racemization. Detailed mechanistic insights, including DFT computation, and cyclovoltammetric studies of a well-defined C–H activated nickel(III) intermediate, render an oxidation-induced reductive elimination at nickel(III) likely to be operative.

C−O forming transformations[1] are of utmost importance to the synthesis of bioactive pharmaceuticals,[2] natural products[3] and functional materials.[4] Classical approaches for the synthesis of aryl ethers, such as the palladium-catalyzed Buchwald−Hartwig cross-couplings[5] and copper-catalyzed Ullmann−Goldberg[6] or Chan−Evans−Lam reactions[7] rely on prefunctionalized substrates, the preparation and use of which result in undesired byproducts and solvent waste. In contrast, dehydrogenative functionalizations of otherwise inert C–H bonds constitute more sustainable strategies, which significantly reduce the footprint of organic syntheses.[8] Despite of major advances in C–H activation, C–H alkoxylations are less developed than typical hydroxylations,[9] acetoxylations,[10] and phenoxylations,[11] because competing *β*-hydride elimination or overoxidation represent undesired side reactions. Specifically, C–H alkoxylations with sterically encumbered secondary alcohols continue to be difficult, which contrast the wealth of viable methods for the use of primary alcohols.[12]

In recent years, electrosynthesis[13] has gained significant attention through the use of waste-free and inexpensive electric current as redox equivalent, thereby avoiding stoichiometric amounts of toxic and costly chemical redox reagents. Electrochemical C–H activations[14] have until recently largely required expensive 5d and 4d metals, such as palladium,[15] ruthenium,[16] rhodium,[17] and iridium.[18] In sharp contrast, major recent momentum was gained by the use of earth-abundant, less toxic 3d metals,[19] such as cobalt[20] and copper,[21] as reported by Ackermann, Lei, and Mei, among others. In spite of the indisputable progress, such cost-effective nickel electrocatalysis has, until very recently proven, elusive, when we established the nickellaelectro-catalyzed C–H aminations, which were however restricted to morpholine−type amines.[22] In contrast, we have now found that versatile nickel catalysts are uniquely effective for challenging C–H electro-alkoxylations with sterically encumbered secondary alcohols, on which we report herein. It is noteworthy that complexes of cobalt, copper, and even precious palladium, iridium, ruthenium and rhodium did not catalyze the difficult secondary C–H alkoxylations. In addition, we disclose mechanistic support for an oxidation-induced reductive elimination nickel(III/IV) regime.

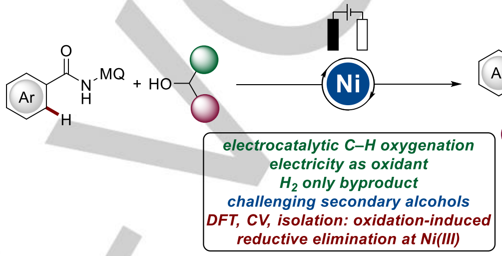
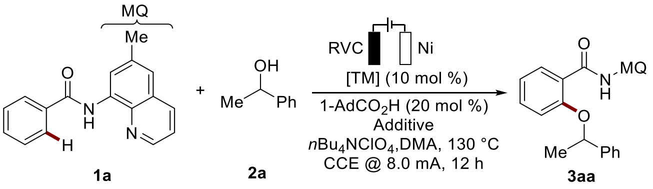


Figure 1. Nickellaelectro-catalyzed C–H alkoxylation with secondary alcohols: Mechanistic insights by isolation, CV and DFT studies.

Our studies were initiated by optimizing reaction conditions for the envisioned nickellaelectro-catalyzed C–H oxygenation of amide **1a** with the challenging secondary alcohol **2a** in an undivided cell set-up (Table 1 and Table S1–S7 in the Supporting Information). After considerable experimentation, the desired product **3aa** was obtained with $Ni(DME)Cl_2$ as the catalyst and bulky carboxylate NaO_2CAd as the additive, whilst RVC and nickel foam electrodes were found to be beneficial (entries 1–4). Here, C–H acetoxylations were not observed. The catalysts' performance was improved by adjusting the alcohol concentration (Table S4). Control experiments confirmed that the eletrooxidative C–H transformation could not be realized in the absence of the electricity, the nickel complex or the additive (entries 7–9). Other nickel compounds, such as $Ni(COD)_2$, $Ni(acac)_2$ or $Ni(OAc)_2$ furnished the desired product **3aa** (entry 10, and Table S3). It is particularly noteworthy that nickel catalysts featured proved uniquely effective for the challenging C–H activation with secondary alcohols, while other transition metals, including cobalt, copper, and even precious palladium, iridium, ruthenium or rhodium, fell short under otherwise identical reaction conditions (entries 11–17 and Table S7). Indeed, while palladium, copper and cobalt catalysts were highly effective for primary alcohols, no or very minor catalytic turnover was accomplished with the secondary alcohol **2a** (Table S9).

Table 1. Optimization of the nickellaelectro-catalyzed secondary alkoxylation.[a]



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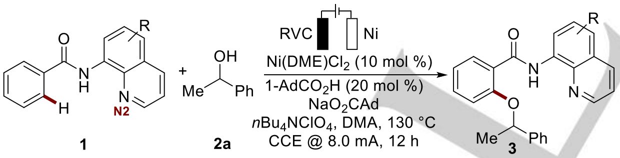
Entry	[TM]	Additive	**3aa** [%]
1	Ni(DME)Cl$_2$	NaOPiv	45[b]
2	Ni(DME)Cl$_2$	NaO$_2$CAd	55[b]
3	Ni(DME)Cl$_2$	KOAc	24[b]
4	Ni(DME)Cl$_2$	K$_2$HPO$_4$	---[b]
5	Ni(DME)Cl$_2$	NaO$_2$CAd	74
6	Ni(DME)Cl$_2$	NaO$_2$CAd	69[c]
7	---	NaO$_2$CAd	---
8	Ni(DME)Cl$_2$	---	---
9	Ni(DME)Cl$_2$	NaO$_2$CAd	---[d]
10	Ni(COD)$_2$	NaO$_2$CAd	67
11	Co(OAc)$_2$·4H$_2$O	NaO$_2$CAd	---
12	Mn(OAc)$_2$	NaO$_2$CAd	---
13	Cu(OAc)$_2$·H$_2$O	NaO$_2$CAd	---
14	Ru(OAc)$_2$(PPh$_3$)$_2$	NaO$_2$CAd	---
15	[Cp*RhCl$_2$]$_2$	NaO$_2$CAd	---[e]
16	Pd(OAc)$_2$	NaO$_2$CAd	---
17	[Cp*IrCl$_2$]$_2$	NaO$_2$CAd	---[e]

[a] Reaction conditions: **1a** (0.25 mmol), **2a** (2.5 mmol), 1-AdCO$_2$H (20 mol %), [TM] (10 mol %), additive (1.0 equiv), *n*Bu$_4$NClO$_4$ (0.5 mmol), DMA (3.0 mL), CCE = 8.0 mA, 12 h, N$_2$, RVC anode and Ni foam cathode, isolated yield. [b] **2a** (1.25 mmol). [c] DMPU as solvent. [d] No current. [e] [TM] (5.0 mol %).

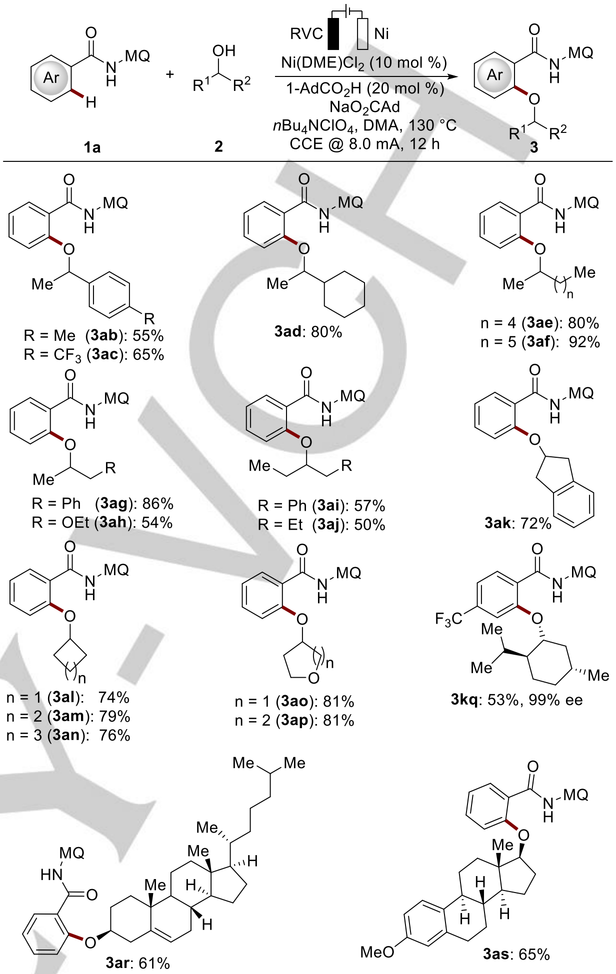
The efficacy of the nickellaelectro-oxidation was considerably affected by the substitution pattern of the quinoline moiety (Scheme 1). Analysis by computation at the PEB0/Def2TZVP level of theory[23] unraveled the key importance of increased electron-density at the quinolinyl nitrogen, while decreased electron-density at the amide nitrogen was beneficial (Figure S16 in the Supporting Information). These findings indicate the importance of increased σ-donation at the sp^2-hybridized quinolinyl nitrogen in concert with an anionic amide nitrogen.



1	6-Me (**1a**)	6-OMe (**1q**)	5-Me (**1r**)	H (**1s**)	5-OMe (**1t**)
N2	-0.33113	-0.33106	-0.32977	-0.32840	-0.32737
3	**3aa** 74% (15%)[a]	**3qa** 67% (19%)[a]	**3ra** 61% (21%)[a]	**3sa** 53% (37%)[a]	**3ta** 28% (64%)[a]

Scheme 1. Directing group power for nickellaelectro-oxidative alkoxylation. [a] Yields of recovered starting materials in parenthesis.

With the optimized reaction conditions in hand, we probed the versatility of the nickellaelectro-catalyzed C–H alkoxylation with various secondary alcohols **2** (Scheme 2). Not only benzylic alcohols **2b** and **2c** were well accepted, but also alicyclic, cyclic and heterocyclic alcohols were successfully converted with moderate to excellent yields (**3ab**–**3ap**). Remarkably, the naturally-occurring alcohols menthol, cholesterol and *β*-estradiol **2q**–**2s** were identified as viable substrates, notably without racemization at the stereogenic centers (Figure S1 and S2).



Scheme 2. Electrooxidative C–H alkoxylation of arenes with secondary alcohols.

Moreover, we evaluated the robustness of the nickellaelectro-catalyzed C–H alkoxylation with a variety of functionalized benzamides **1** (Scheme 3). Thus, the reactions proceeded efficiently with arenes **1** bearing valuable functional groups, such as halo, sulfido, and cyano substituents. For the *meta*-substituted substrates **1b** and **1c** the reaction occurred with high position-selectivity by repulsive steric interactions. The nickellaelectrocatalysis was not limited to arenes, but the heteroarene **1o** was also selectively transformed. It is noteworthy that the strongly-coordinating pyridine was fully tolerated to give bidentate amide-guided C–H functionalization (**3pa**). Likewise, the gram-scale synthesis was realized without compromising the efficacy on scale (**3ba**).

In addition, we carried out electricity on/off experiments to probe a radical chain scenario (Scheme 4a). Hence, the reaction was haltered without electrochemistry. Yet, the C–H alkoxylation continued when switching the electric current back on, ruling out a radical chain process.

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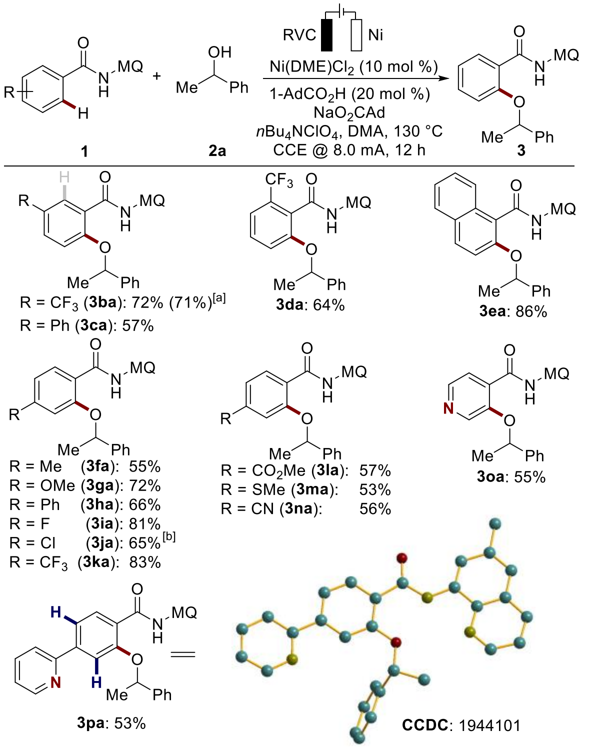
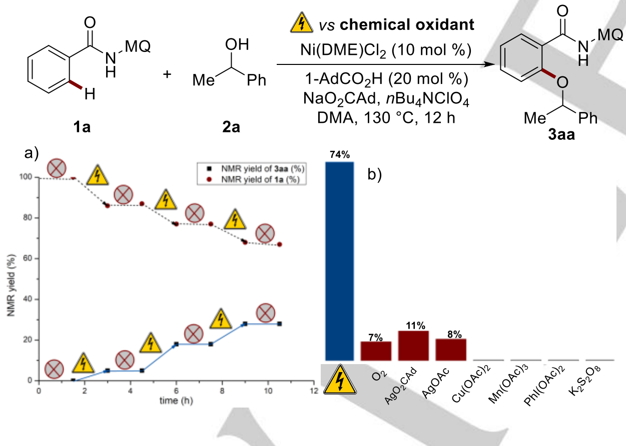


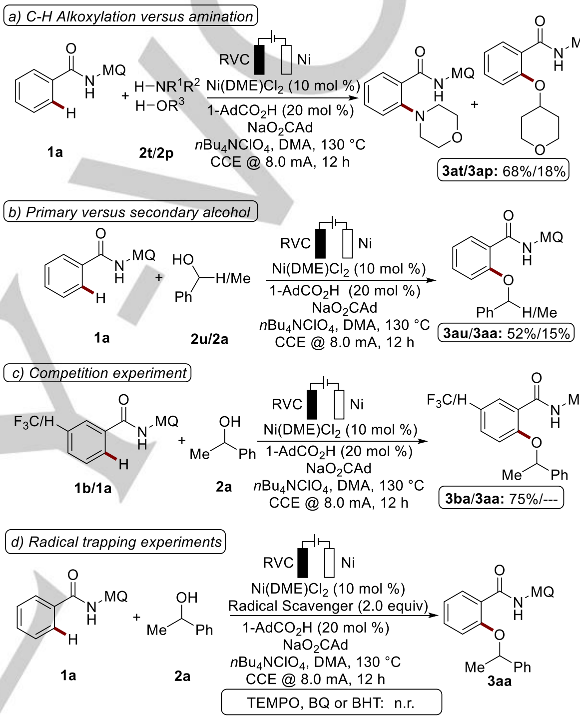
Scheme 3. Electrooxidative C–H alkoxylation of arenes. [a] Gram-scale testing with **1b** (4.0 mmol,1.32 g). [b] 3.0 mA, 32 h.

The clear benefits of electricity were not restricted to being a green and inexpensive oxidant. Indeed, the electrocatalysis was characterized by significantly improved levels of performance as compared to the chemical oxidants AgOAc, $Cu(OAc)_2$, molecular oxygen, $PhI(OAc)_2$ or $K_2S_2O_8$ (Scheme 4b).



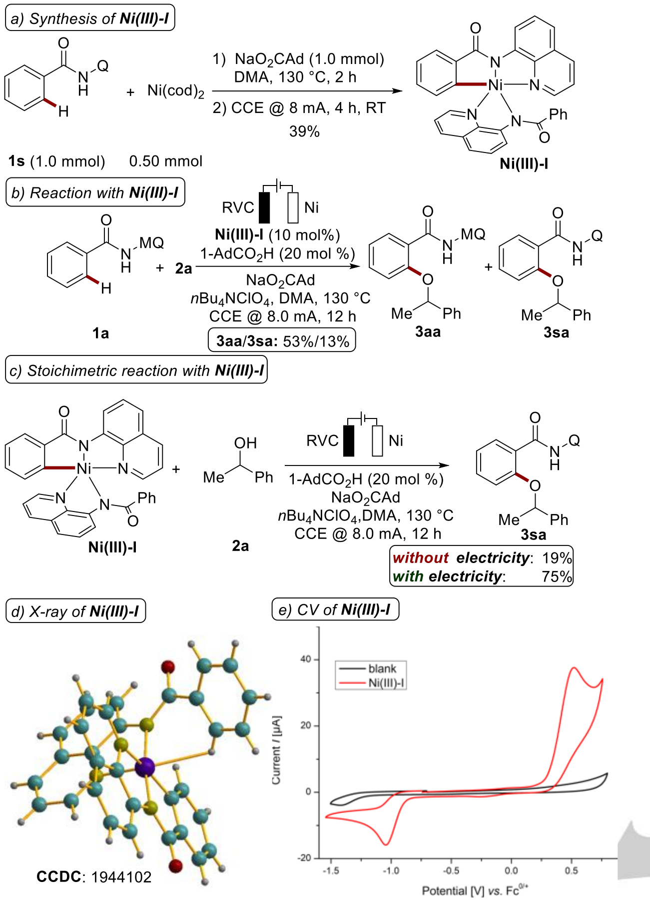
Scheme 4. a) On/off experiment. b) Electrochemical *vs.* chemical oxidants.

Given the unique performance of the nickellaelectro-catalyzed C–H activation, a series of experiments were conducted to gain insights into the reaction mechanism. Intermolecular competition experiments between secondary alcohol **2p** and amine **2t**, or with primary alcohol **2u** highlighted the particular challenge of the nickellaeletrooxidative secondary C–H alkoxylations (Scheme 5a and 5b). In contrast to cobaltaelectro-catalysis by a BIES mechanism, an intermolecular competition experiment showed electron-deficient arenes **1** to be inherently more reactive (Scheme 5c). This finding is indicative of a concerted-metalation-deprotonation (CMD) mechanism for the C–H activation.[24] Head-space gas-chromatographic analysis identified H_2 as the only stoichiometric byproduct (Figure S14). The electrocatalysis was inhibited by the typical radical scavengers TEMPO, BHT and BQ, being indicative of single-electron-transfer (SET) steps (Scheme 5d). A minor kinetic isotope effect of $k_H/k_D \approx 1.4$ by independent experiments gave support for a facile C–H scission (Figure S13). H/D exchange was not found when using isotopically labeled *t*BuOD as the additive (Figure S11). An irreversible nickelation[25] was further found by DFT calculations to generate the substrate-coordinated nickel(II) intermediate **Ni(II)-II** (Figure S20). Thus, the combined analysis by DFT and CV studies provided strong support for a viable nickel(II/III) oxidation (purple, Figure S22).



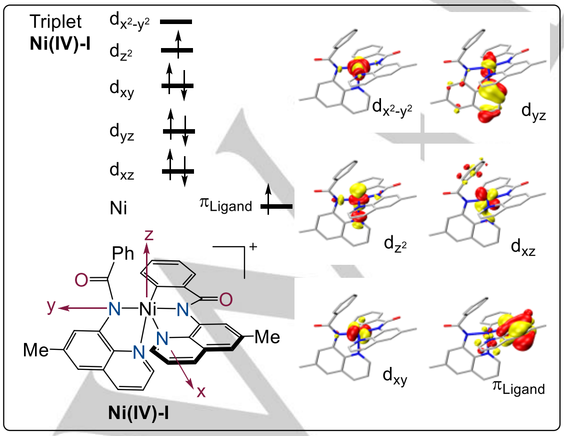
Scheme 5. Summary of selected mechanistic findings. Conversions determined by ^1H-NMR analysis with 1,3,5-$(MeO)_3C_6H_3$ as the internal standard.

To rationalize the elementary process of C–O formation, the well-defined nickel(III) complex **Ni(III)-I** was independently synthesized, and fully characterized, including X-ray diffraction analysis (Scheme 6a).[26] The well-defined nickel(III) complex **Ni(III)-I** was competent in a catalytic and stoichiometric setting, provided that electricity was applied (Scheme 6b and 6c). Cyclic voltammetric studies of **Ni(III)-I** showed a facile oxidation at a potential of 0.50 V *vs.* $Fc^{0/+}$ (red, Scheme 6e), suggesting the formation of a formal nickel(IV) complex.



Scheme 6. a) Synthesis of **Ni(III)-I**; b), c) Catalytic and stoichiometric reactions with **Ni(III)-I**, conversions determined by ^{1}H-NMR analysis with 1,3,5-(MeO)$_3$C$_6$H$_3$ as the internal standard; d) X-ray diffraction analysis of **Ni(III)-I**; e) CV data of **Ni(III)-I** (DMA, 0.1 M [nBu$_4$NPF$_6$], 100 mV/s).

In good agreement with these results, DFT calculations indicate a non-innocent ligand phenomena in the oxidation process to generate a formal nickel(IV) species (Scheme 7). The oxidation is hence best described as a ligand centered process. Finally, high-valent intermediate **Ni(IV)-I** will be coordinated by the alcohol **2**, along with subsequent deprotonation and reductive elimination to furnish the alkoxylated products **3** (Figure S19).[26]



Scheme 7. Calculated electronic configuration of **Ni(IV)-I** ground triplet state.

As to the synthetic utility, it is noteworthy that the 6-methylquinuoline was easily removed in a traceless fashion to provide efficient access to benzamide **4**, benzoic acid **5**, or aromatic aldehyde **6** (Scheme S15–S17).

In summary, we have reported on a carboxylate-enabled nickellaelectro-catalyzed alkoxylations with challenging secondary alcohols. The robust electrochemical C–H activation was accomplished with broad substrate scope through traceless removable quinoline amides. The most user-friendly nickel electrocatalyst ensured high levels of chemo- and position-selectivities. The C–H oxygenation was more effective with electricity than with any other chemical oxidant. Detailed mechanistic studies by experiment, cyclovoltammetry and computation provided strong support for an oxidation-induced reductive elimination nickel(III/IV) manifold.

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Keywords: Electrochemistry • C–H Alkoxylation • Mechanism • Nickel • Oxygenation • Electrocatalysis

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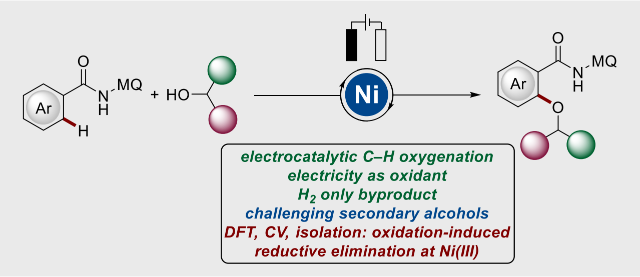

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II, III or IV: Challenging secondary C–H alkoxygenations were accomplished by a versatile nickel electrocatalyst. Mechanistic studies by experiment and computation provide support for an oxidation-induced reductive elimination regime.