Electrosynthesis Hot Paper

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Nickela-electrocatalyzed Mild C–H Alkylations at Room Temperature

*Ramesh C. Samanta, Julia Struwe, and Lutz Ackermann**

Abstract: *Direct alkylations of carboxylic acid derivatives are challenging and particularly nickel catalysis commonly requires high reaction temperatures and strong bases, translating into limited substrate scope. Herein, nickel-catalyzed C–H alkylations of unactivated 8-aminoquinoline amides have been realized under exceedingly mild conditions, namely at room temperature, with a mild base and a user-friendly electrochemical setup. This electrocatalyzed C–H alkylation displays high functional group tolerance and is applicable to both the primary and secondary alkylation. Based on detailed mechanistic studies, a nickel(II/III/I) catalytic manifold has been proposed.*

In recent years, C–H activation has been recognized as a transformative tool in molecular syntheses.[1] Although the vast majority of C–H functionalizations was predominantly realized by precious 4d and 5d transition metals, recent focus has shifted to the less toxic Earth-abundant 3d transition metals.[2] While increasing advances have been accomplished in site-selective C–H activation via chelation assistance, a direct C–H alkylation of arenes remains challenging due to undesirable competitive β-hydride elimination. These approaches rely heavily on the precious and rather toxic 4d metals ruthenium[3] and palladium.[4,5] Among the 3d transition metals, cobalt,[6] iron,[7] and manganese-catalyzed[8] reactions have been developed. However, their applications to functionalized substrates are severely limited due to the use of an excess amount of highly reactive Grignard reagents. To meet the continuous demand for suitable C–H alkylations, nickel catalysis was largely explored by Chatani,[9] Ackermann,[10] and Punji,[11] among others.[12] The *N,N'*-bidentate 8-aminoquinoline,[13] which was previously introduced by Daugulis,[14] enabled particularly efficient nickel catalysis. Major issues associated with and beyond known nickel-catalyzed C–H alkylations are the requirement of high reaction temperatures and the use of strong bases, such as lithium *tert*-butoxide (LiO*t*Bu) and lithium bis(trimethyl)silylamide (LiHMDS), thereby limiting applications to substrates with sensitive functional groups. Therefore, strategies for mild C–H alkylations by nickel catalysis continue to be highly desirable.

Recently electrosynthesis[15] has gained considerable momentum due to the use of electricity as a sustainable alternative for toxic chemical redox equivalents, thereby avoiding stoichiometric formation of waste products. In this regard, electrochemical C–H activation[16] has resulted in a renaissance in this field with notable contributions by Mei,[17] Ackermann,[18] Lei,[19] and Xu.[20]

Despite the undisputable advances in metalla-electro-oxidative C–H activation, net redox-neutral transformations under electrochemical conditions have barely been explored, while the effect of electricity was shown to be beneficial for net redox-neutral nickel-catalyzed Ullmann-type C–N bond-forming reactions.[21] Moreover, recently disclosed electrochemical net redox-neutral C–C coupling by Sevov[22] and C–S couplings by Mei[23] and Wang[24] represent key contributions for electrochemical cross-coupling reactions.

As part of our program on sustainable C–H activation,[25] we report herein a nickel-catalyzed C–H alkylation using both primary and more challenging secondary alkyl halides under particularly mild electrochemical conditions. The key findings include a) nickela-electrocatalyzed C–H activations at room temperature, b) tolerance of sensitive functionalities, c) absence of additional phosphine or amine ligands, d) mild bases for nickel-catalyzed C–H activation, and e) detailed mechanistic insights.

We commenced our studies by probing various reaction conditions to enable the nickel-catalyzed electrochemical C–H alkylation of benzamide **1a** with the *n*-octyl iodide **2a** in an undivided cell setup.[26] Zinc as the anode material and nickel foam as the cathode delivered the desired alkylation product **3aa** in 76 % yield at room temperature, notably with Et_3N as a mild base (Table 1, entry 1). Slow addition of the alkyl

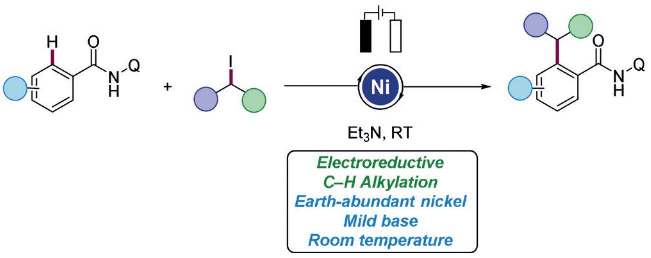

Figure 1. Nickel-catalyzed electrochemical C–H alkylations at room temperature.

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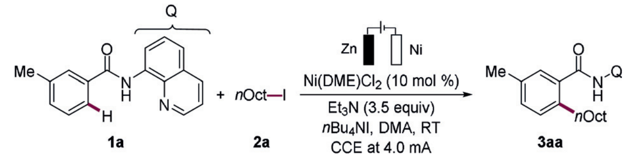
[*] Dr. R. C. Samanta, J. Struwe, Prof. Dr. L. Ackermann
Institut für Organische und Biomolekulare Chemie
Georg-August-Universität Göttingen
Tammannstrasse 2, 37077 Göttingen (Germany)
E-mail: Lutz.Ackermann@chemie.uni-goettingen.de
Homepage: http://www.ackermann.chemie.uni-goettingen.de
Prof. Dr. L. Ackermann
Woehler Research Institute for Sustainable Chemistry (WISCh),
Georg-August-Universität Göttingen
Tammannstrasse 2, 37077 Göttingen (Germany)

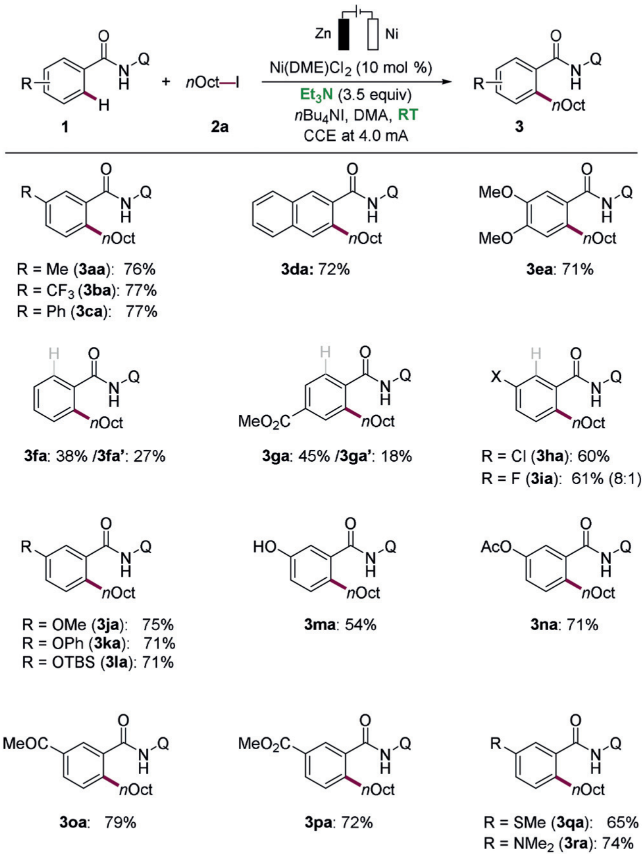
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/anie.202004958.

Table 1: Optimization of the nickel-catalyzed electrochemical C–H alkylation.[a]



Entry	Deviation from standard conditions	Yield [%][b]
1	none	76
2	direct addition of **2a**	41
3	graphite felt anode	–
4	Mg anode	6
5	with nickel catalyst but no current	–
6	without current or nickel catalyst	–
7	Zn dust instead of current	8
8	DMF instead of DMA	67
9	MeOH instead of DMA	27[c]
10	without Et_3N	55

[a] Reaction conditions: Undivided cell, **1a** (0.30 mmol), **2a** (1.05 mmol), [Ni] (10 mol%), Et_3N (3.5 equiv), $n$$Bu_4NI$ (2.0 equiv), solvent (3.2 mL), RT, constant current at 4.0 mA, 8 h, zinc anode, nickel-foam cathode and **2a** was added slowly over 7 h. [b] Yield of isolated product. [c] No conducting salt was added. DMA = *N*,*N*-dimethylacetamide. DMF = *N*,*N*-dimethylformamide.

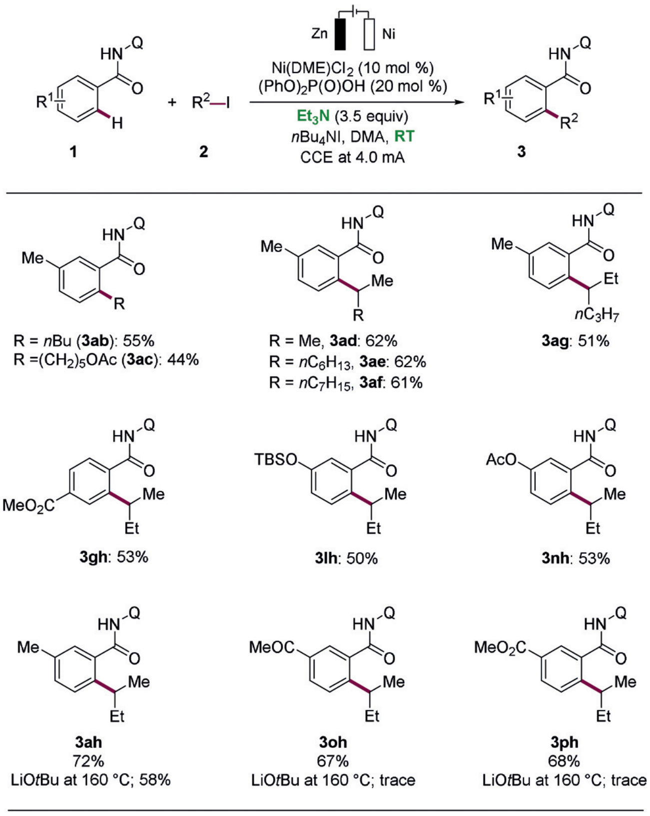


Scheme 1. Nickela-electrocatalyzed C–H alkylation of amides **1**. [a] Bisalkylation product (7%).

iodide **2a** was required to suppress its homocoupling, otherwise **3aa** was obtained in a lower yield of 41% (entry 2). Previous studies on nickela-electrooxidative C–H activation have used graphite felt and nickel foam as anode and cathode, respectively;[27] however, this was not suitable here (entry 3). The combination of zinc anode with electricity was beneficial, and the nickel catalyst was essential for this transformation (entries 4–6). The reaction was sluggish when performed with stoichiometric amounts of zinc as the chemical reductant (entry 7). DMF was also found to be a potent solvent for this transformation with a slightly lower efficacy (entry 8). The use of methanol in lieu of DMA and TBAI was found less efficient (entry 9). It is noteworthy that a yield of 55% of product **3aa** was obtained in the absence of an additional base (entry 10). Notably, no desired product was obtained when the reaction was performed under air instead of N_2 atmosphere.

Having the optimized reaction conditions in hand, we examined the versatility of the nickel-catalyzed electrochemical C–H alkylation manifold for differently substituted benzamides **1** using *n*-octyl iodide as the alkylation reagent (Scheme 1). Both electron-donating as well as electron-withdrawing substituents at the benzamides **3aa**–**3ca** were well suited. 3,4-Disubstituted amides **1d** and **1e** were also alkylated in good yield. In the case of unsubstituted **1f** and *para*-substituted benzamides **1g**, bis-alkylation was also observed. Halogen-containing amides were alkylated to **3ha** and **3ia** with excellent chemoselectivity. Aryl ethers and silyl ether were smoothly converted to the products **3ja**–**3la**. A free phenolic hydroxyl group was well tolerated and product **3ma** was obtained in good yield, bypassing the inherent preference for O-alkylation. Electrophilic functional groups that are prone to nucleophiles or bases, such as acetate, ketone, and ester groups in **3na**–**3pa**, were also well tolerated. Oxidation-labile thioether **3qa** and arylamine **3ra** were viable under the nickela-electrocatalysis. 3-Substituted amides **1a**–**1e** and **1h**–**1r** delivered only monoalkylation products and the selectivity was governed by the steric hindrance.

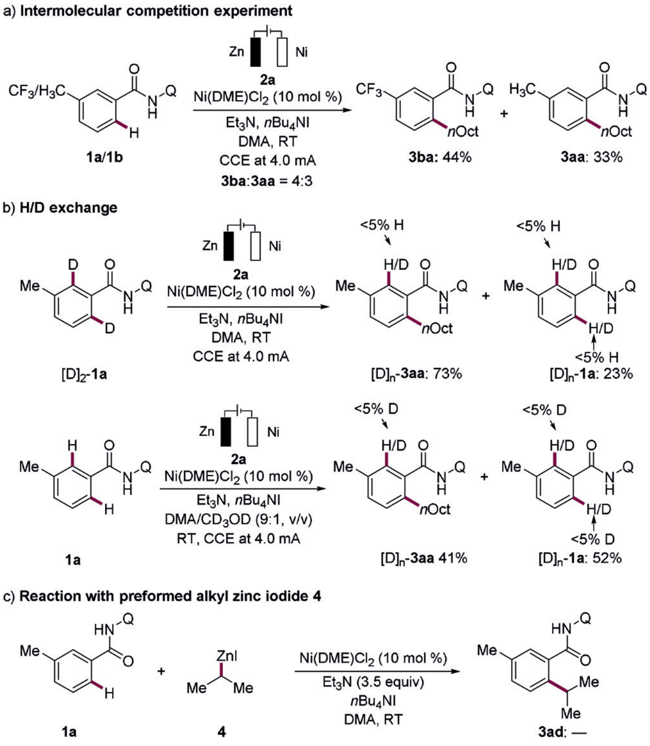
The scope of viable alkyl iodides **2** was next explored, and slightly modified conditions were equally applicable for alkylation using secondary alkyl iodides (Scheme 2). In contrast to known procedures under harsh reaction conditions (160 °C, LiO*t*Bu), benzamide **1a** was selectively C–H alkylated with various secondary alkyl iodides **2** with this nickel-catalyzed electrochemical manifold under extremely mild conditions with Et_3N as the base. Importantly, acyclic secondary alkyl iodides **2d**–**2h** reacted efficiently to deliver the products **3ad**–**3ah** in good yields without chain-walking,[28] thereby avoiding the formation of isomerization products. Benzamides containing sensitive functional groups, such as OTBS, OAc, CO_2Me, and COMe were well tolerated under the nickela-electrocatalyzed C–H alkylation reaction conditions to furnish the products **3gh**, **3lh**, **3nh,** **3oh**, and **3ph** in moderate to good yields. Interestingly, the electrochemical secondary alkylation method resulted in a better selectively and the desired monoalkylation product **3gh** was obtained in 53% yield, with only trace of bisalkylation was detected. However, it is noteworthy that previously reported methods for direct C–H alkylation of benzamide **1a** using a secondary alkyl bromide delivered the product **3ah**



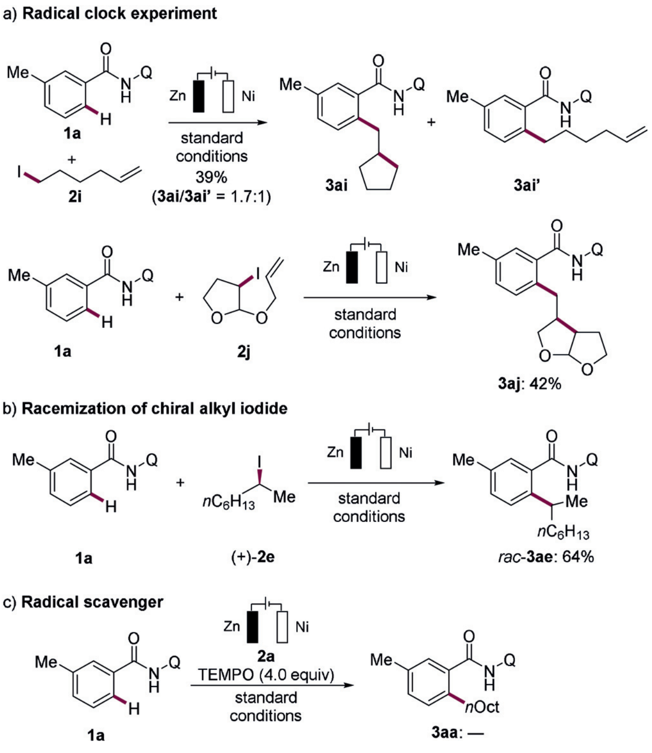
Scheme 2. Nickel-catalyzed electrochemical C–H activation with alkyl iodides **2**. For comparison, the following with chemical method was applied: benzamide **1** (0.5 mmol), 2-bromobutane (1.0 mmol), Ni(DME)Cl$_2$ (10 mol%), bis[2-(*N*,*N*-dimethylamino)ethyl] ether (BDMAE) (40 mol%), LiO*t*Bu (2.0 equiv) in toluene at 160 °C for 20 h.

(58%) in diminished yield. More importantly, for benzamides **1o** and **1p** bearing COMe and CO$_2$Me functional groups, respectively, only traces of the desired alkylation products **3oh** and **3ph** were detected.[10d]

To gain insight into the reaction mechanism, an intermolecular competition experiment between substrates **1a** and **1b** revealed that the electron-deficient amide **1b** reacted faster than the electron-rich substrate **1a** (Scheme 3a). No significant deuterium scrambling was observed in either the product or the unreacted starting material when the reaction was performed with [D]$_4$-MeOD as additive, which excludes reversibility in the C–H cleavage step (Scheme 3b). When the reaction was performed with alkylzinc iodide **4**, product formation was not observed. Hence, the in situ generation of alkylzinc halides in the reaction mechanism can be ruled out (Scheme 3c). In radical clock experiments, both substrates **2i** and **2j** provided the cyclization products **3ai** and **3aj**, respectively, which is suggestive of a homolytic C–I bond cleavage for the nickela-electrocatalyzed C–H alkylation (Scheme 4a). The chiral alkyl iodide (+)-**2e** underwent racemization under the developed reaction conditions to yield the product *rac*-**3ae** (Scheme 4b). Moreover, the desired alkylation reaction did not proceed in the presence of the radical scavenger TEMPO, providing further support for a single-electron-transfer (SET) regime (Scheme 4c).

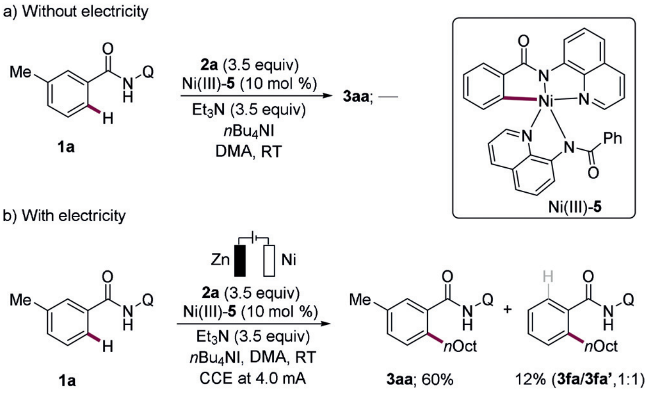


Scheme 3. Mechanistic investigations. a) Intermolecular competition experiment. b) H/D exchange studies. c) Attempted use of organozinc halide as alkylation reagent.



Scheme 4. Mechanistic control experiments towards single-electron transfer.

The cyclometalated nickel(III)-**5**[27a] complex was synthesized and used as a catalyst for the electrocatalytic alkylation reaction. Interestingly, it was found to be catalytically



Scheme 5. Catalytic activity of Ni^{III}-**5** complex.

incompetent in the absence of electricity, although the desired C–H alkylation took place in the presence of electricity (Scheme 5). This finding indicates that cathodic reduction is necessary to generate the active catalyst. Cyclic voltammetry studies of the nickel(III)-**5** complex revealed the following reduction potentials in DMA: Ni^{III}/Ni^{II} at −1.01 V, Ni^{II}/Ni^{I} at −1.52 V, and Ni^{I}/Ni^{0} at −2.40 V vs. $Fc^{0/+}$.[26] A fast coordination of amide **1a** with $Ni(DME)Cl_2$ shifted the potentials to Ni^{II}/Ni^{I} at −1.51 V and Ni^{I}/Ni^{0} at −2.28 V compared to the free $Ni(DME)Cl_2$. A sharp increase in the reductive current was observed upon addition of **2a** to $Ni(DME)Cl_2$ with an onset potential of −1.0 V and the peak potential of −2.21 V vs. $Fc^{0/+}$. A similar phenomenon was observed with the mixture of $Ni(DME)Cl_2$, **1a**, and **2a**.[26]

Based on our mechanistic studies we propose a nickel(II/III/I) manifold for the electrocatalysis. The catalytic cycle is initiated by a cathodic reduction to deliver intermediate **[Ni^{I}-A]**, which in turn reacts with alkyl iodide **2** and upon C–H cleavage forms the cyclometalated intermediate **[Ni^{III}-B]**. Note that **[Ni^{III}-B]** (Ni^{III}-**5**) was shown to be catalytically competent under the electrochemical reaction conditions (vide supra). Subsequent cathodic reduction initially generates **[Ni^{II}-C]** intermediate. Next, a single-electron transfer (SET) generates the intermediate **[Ni^{III}-D]**, which next forms **[Ni^{III}-E]** and subsequently delivers the desired product **3**. At the same time, coordination of substrate **1** regenerates the catalytically competent species **[Ni^{I}-A]**. To compensate for the cathodic reduction, anodic zinc oxidation takes place, while the role of zinc as a redox mediator is unlikely.[29]

In conclusion, we have developed a nickel-catalyzed electrochemical direct C–H alkylation of quinoline amides under unprecedentedly mild reaction conditions, namely at room temperature with the mild base Et_3N. This strategy enabled the conversion of a wide range of primary and secondary alkyl iodides, while various sensitive functional groups are tolerated. Detailed mechanistic studies provided strong support for a Ni(II/III/I) catalytic cycle through SET processes. We believe that our findings overcome the difficulties in typical nickel-catalyzed C–H alkylations, for which harsh reaction conditions of 160 °C temperature and LiO*t*Bu have been prevalent.

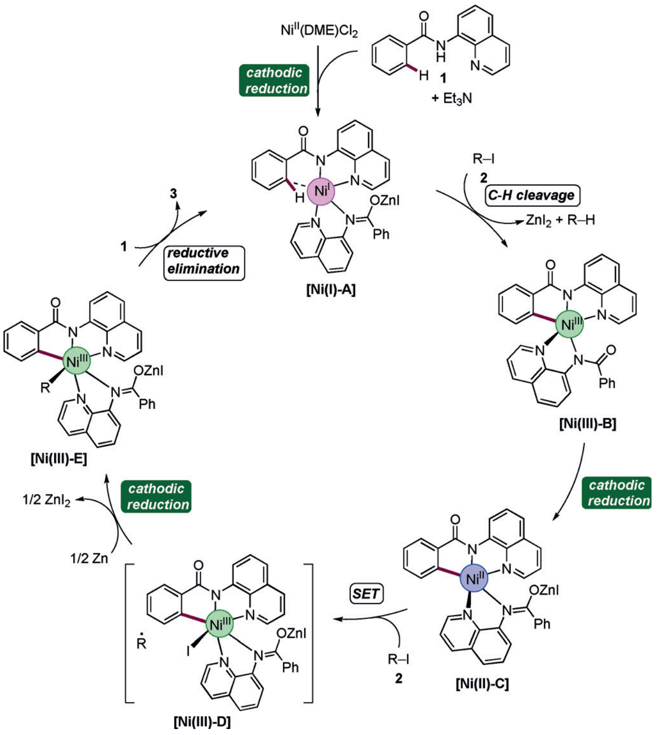


Figure 2. Proposed catalytic cycle for nickela-electrocatalyzed C–H alkylation.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: C–H alkylation · electrosynthesis · homogeneous catalysis · nickel · redox-neutral reactions

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