Evolution of High-Valent Nickel-Electrocatalyzed C–H Activation: From Cross(-Electrophile)-Couplings to Electrooxidative C–H Transformations

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Abstract: C–H activation has emerged as one of the most efficient tools for the formation of carbon–carbon and carbon–heteroatom bonds, avoiding the use of prefunctionalized materials. In spite of tremendous progress in the field, stoichiometric quantities of toxic and/or costly chemical reagents, such as silver(II) or copper(II) salts, are largely required for oxidative C–H activations. Recently, electrosynthesis has experienced a remarkable renaissance that enables the use of storable, safe and waste-free electric current as a redox equivalent. While major recent momentum was gained in electrocatalyzed C–H activations by 4d and 5d metals, user-friendly and inexpensive nickel-electrocatalysis has until recently proven elusive for oxidative C–H activations. Herein, the early developments of nickel-electrocatalyzed reductive cross-electrophile couplings as well as net-redox-neutral cross-couplings are first introduced. The focus of this Minireview is, however, the recent emergence of nickel-catalyzed electrooxidative C–H activations until April 2020.

Introduction

During the past decades, transition-metal-catalysis has been established as one of the most reliable tools for C–C and C–Het formations.[1] Particularly, palladium-catalyzed cross-couplings have thus revolutionized molecular syntheses, with transformative applications, to medicinal chemistry, crop protection, material sciences and pharmaceutical industries.[2] While inter alia Mizoroki–Heck,[3] Suzuki–Miyaura,[4] Negishi[5] cross-couplings have largely benefited from the power of versatile palladium catalysts,[6] early findings by inter alia Corriu, Kumada[7] and Kochi[8] have indicated the until recently largely untapped potential of Earth-abundant and less toxic nickel catalysis.[9] Generally speaking, cross-coupling reactions require two prefunctionalized starting materials, namely an electrophilic organic (pseudo)halide and a nucleophilic organometallic or main group element species.[2] The synthesis of the organic nucleophile is predominantly accomplished by the oxidative addition or halogen/metal-exchange of an organic electrophile.[11] As a consequence, cross-electrophile couplings directly between two different organic (pseudo)halides have been recognized as a more step economical approach.[12] An even more efficient alternative to conventional cross-couplings is represented by the direct oxidative transformation of two otherwise inert C–H bonds, by fully avoiding any substrate prefunctionalization.[13] Oxidative C–H activations require terminal oxidants,[14] typically stoichiometric amounts of often expensive and/or toxic transition metal salts. Early contributions by Volta,[15] Kolbe,[16] and Faraday[17] have indicated the potential of electrochemistry. Within a remarkable renaissance of organic electrosynthesis,[18] inexpensive electricity has very recently been identified as a viable redox equivalent in electrooxidative C–H activations.[19] This emergence of first electrooxidative C–H activations by versatile nickel catalysis is described herein, covering the literature until April 2020. Likewise, we summarize the key findings on electrochemical cross-electrophile and redox-neutral cross-coupling reactions enabled by nickel electrocatalysis.

Reactive cross-electrophile coupling

In 1976, Jennings and co-workers[20] described the first electrochemical synthesis enabled by nickel catalysis to generate the homo-coupling product 2a of phenyl or benzyli bromides 1a with copper as the sacrificial anode material (Scheme 1a). Later, for electroreductive homo-coupling reactions of alkynyl and aliphatic halides, 1b and 1c proved to be viable substrates with a nickel/bipyridine catalyst as reported by Tuck and Périchon, suggesting a nickel(0) intermediate as the active species (Scheme 1b and 1d).[21] A practical application of the nickel catalysis by the Fauvarque group was represented by the synthesis of poly(1,4-phenylene) 2d from 1,4-dibromoarene 1d (Scheme 1d).[22] Subsequently, alternative dihalo(hetero)arenes and even 1,2-diiodoethyne were successfully employed for nickela-electroreductive coupling reactions to synthesize different films and polymers.[23]

While homo-coupling reactions have gained significant momentum, cross-electrophile couplings are more attractive, but at the same time significantly more challenging due to the full chemoselectivity control. In this context, the Périchon group[24] described an early strategy for nickel-catalyzed electro-reductive cross-electrophile coupling between electron-donating arenes 3a and electron-deficient arenes 4a (Scheme 2a). Furthermore, Jutand and Périchon demonstrated the robustness of the nickel catalysis for the reductive cross-coupling of α-hal-
with aryl and alkenyl halides, in which the electro-mediated formation of the nickel(II)-aryl or nickel(II)-alkenyl moiety occurred as the initial step (Scheme 2b and 2c). The selectivity towards the desired cross-electrophile coupling was achieved by the judicious choice of the two substrates. Very recently, Mei and Rueping independently devised reaction conditions for nickel-electroreductive relay cross-couplings between aryl (3d) and alkyl (4d) halides (Scheme 2d).

Achieving full selectivity control in terms of asymmetric electrosynthesis continues to be challenging. In 1997, an asymmetric electrochemical reductive cross-coupling was accomplished by Durandetti/Périchon for the first time by means of a chiral auxiliary for nickel catalysis (Scheme 3a). As a result, chiral arylpropionic acid derivatives 8a were obtained from aryl halide 6a and the chiral urea 7a. In 2019, Reisman accomplished a catalytic asymmetric reductive electro-coupling, extending the viable substrate scope to vinyl bromides 6b and benzyl halides 7b by the action of Ni(DME)Cl₂ as the precatalyst along with the indanyl-substituted bis(oxazoline) ligand L2 (Scheme 3b).

A general catalytic cycle of nickel-electroreductive cross-electrophile couplings is depicted in Scheme 4. The active species LₙNi⁺ (9b) is reductively formed at the cathode from the precursor LₙNi⁻X (9a), which is stabilized by ligands, such as PPh₃ or bipyridine. Then, the intermediate LₙR¹Ni⁺X (9c) is formed through an inherently faster oxidative addition of R¹X onto the nickel(0) species 9b with the reactivity order being ArBr > ArCl > ArBr > PyCl > ArI > α-chloroester. Subsequently, a

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cathodic reduction gives the nickel(I) intermediate 9d. The sacrificial anodic oxidation prevents the further oxidation of low-valent nickel(I) species. Next, the nickel(I) intermediate 9d undergoes an oxidative addition with R₂Y to obtain the nickel(III) species 9e, followed by reductive elimination to deliver the desired crosselectrophile coupling product, while yielding the reduced nickel(I) complex 9f through cathodic reduction.

Net redox-neutral cross-couplings for C–C formation

In contrast to reductive cross-electrophile couplings, net redox-neutral transformations can require only one prefunctionalized substrate. Even though there is overall no need for an oxidant or a reductant for net redox-neutral transformation electrochemistry can facilitate the formation of the corresponding coupling products with a non-prefunctionalized substrate. Hence, in 1996, Ozaki reported a radical cyclodition for the preparation of pyrrolopyridine and pyrrolopyrrole under nickel-catalyzed electroreductive conditions (Scheme 5a). The electrolysis was conducted with graphite plate as the cathode and a zinc plate as the anode at ambient temperature. Thereafter, nickel-catalyzed perfluoroalkylations were electrochemically achieved using homogeneous as well as on silica supported catalyst (Scheme 5b and 5c).

Scheme 3. Stereoselective cross-electrophile-couplings.

Scheme 4. General mechanism for nickel-a-electroreductive cross-electrophile coupling.

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The alkylation of quinoxalinones was accomplished using N-hydroxyphthalimide esters via a decarboxylative radical formation under nickel-catalyzed electroreductive conditions. In case of the acylations, the acyl radical was generated from the corresponding α-keto acids by anodic oxidation. Very recently, Seov disclosed a related Mizoroki-Heck reaction that was electrochemically promoted under mild conditions with the aid of an iron anode and a nickel cathode (Scheme 5f). These studies revealed that low-valent nickel complexes effectively catalyze the conversion of unactivated olefins under electroreductive conditions. The reactions reported thus far mostly took advantage of the reductive half-reaction, and consequently requires either a sacrificial anode or amine bases as the terminal reductant.

Net redox-neutral C–Het cross-couplings

In contrast to carbon-prenucleophiles, the stronger coordinating properties of heteroatoms can significantly alter the catalytic efficacy. In 2017, electrocatalyzed aminations and alkoxyations of prefunctionalized aryl electrophiles with aliphatic amines and alcohols were realized at room temperature by Baran (Scheme 5g and 5h). Later, amino acid esters, nucleosides and oligopeptides were addressed employing Ni(bpy)$_3$Br$_2$ as the catalyst along with DBU as an external base (Scheme 5i). In 2018, Léonel developed the phosphorylation of aryl halides with dialkyl phosphites by nickel-electrocatalysis using a sacrificial iron-nickel alloy anode (Scheme 5j). Subsequently, an improved method that avoided a sacrificial anode for electrochemically nickel-catalyzed C–P formation with ample scope was presented by Cui and Xiang, enabling the use of dialkyl phosphites, ethyl phenylphosphinate, and diphenylphosphate oxide (Scheme 5k). In 2019, a nickel-electrocatalysis furthermore enabled Ullmann-type thiolations of aryl iodides with both aryl and alkyl thiols within a non-sacrificial anode approach, as achieved by Wang and Pan (Scheme 5l). In the meantime, Mei independently developed the nickel-electrocatalyzed C–S coupling of more challenging aryl bromides and chlorides with aryl thiols in the absence of an external base (Scheme 5m). A proposed mechanism for nickel-electrocatalyzed cross-coupling reactions was suggested based on related nickel-photoredox-catalyzed cross-couplings (Scheme 6). The L$_3$Ni$^+$ complex 13b is generated from the precursor L$_3$NiX 13a at the cathode, and reacts with the organic halide via an oxidative addition to give the nickel(II) intermediate 13c. At the same time, the radical 13f is formed through a base-mediated anodic oxidation, hence avoiding the use of a sacrificial anode. The organic radical 13f next provides the nickel(III) species 13d, which then undergoes reductive elimination to furnish the desired product and the nickel(II) species 13e. Finally, complex 13e undergoes cathodic reduction to regenerate the catalytically competent nickel(0) species 13b. As a by-product, the radical 13f can lead to the homocoupling dimer.
Nickela-Electrocatalyzed Oxidative Transformations

In comparison to transition-metal-catalyzed cross-couplings, direct dehydrogenative C–H activations represent a more attractive and effective strategy to reduce the footprint of organic syntheses, avoiding the prefunctionalization of all substrates.[13, 42] Despite the indisputable progress in this area, stoichiometric quantities of toxic and costly chemical redox reagents such as silver(I) and copper(II) salts, are usually required. However, electricity has been identified as a clean redox agent for C–H activations.[43] While electrocatalyzed C–H activation witnessed considerable advances with the aid of 4d and 5d metals, such as palladium,[44] ruthenium,[45] rhodium[46] and iridium complexes,[47] the development of cost-effective and less toxic 3d metals,[19a, 48] cobalt,[49] iron,[50] manganese,[50] copper[51] and nickel continue to be scarce, but bear unique potential towards ideal resource-economy.

Asymmetric functionalization of enolates

In 2019, nickel-catalyzed electrochemical asymmetric C(sp³)–H functionalization was reported by Guo (Scheme 7).[52] Thus, an enantioselective α-benzylation of 2-acyl imidazoles 14 was realized with p-methylphenol derivatives 15 as the benzylation reagents under electrochemical conditions. The combination of Ni(OAc)₂ and a chiral diamine ligand L3 served as a typical Lewis-acid to deliver the benzylation products 16a–16i in good yields and enantioselectivities. The tailored design of substrates 14 called for α-aryl substituents at the ketones to enhance its acidity (pKₐC–H 15–18 in DMSO) and activated tolune derivatives 15 with a bond dissociation energy (BDEC–H) of ∼80 kcal mol⁻¹ to guarantee high efficacy.[53]

Based on among others cyclic voltammetry experiments, a radical mechanism was proposed (Scheme 8). Hence, substrate 14 binds to the chiral nickel complex, followed by deprotonation of intermediate 17a to generate the enolate 17b, which is then in turn oxidized at the anode to produce the stabilized radical intermediate 17c. Additionally, p-methylphenol derivatives 15 are also oxidized with hydrogen evolution at the anode to produce the benzylic radical 17d, which combines with radical 17c, delivering the complex 17e. Finally, the desired product 16 is formed, while the catalytically active intermediate 17a is regenerated.

Nickela-electrocatalyzed C–H amination

In spite of indisputable advances in the field, electrooxidative C(sp³)–H activations by nickel catalysis remain elusive until recently. In 2018, Ackermann reported on the first nickel-electrocatalytic C–H activation of benzamides 18 and secondary amines 19 (Scheme 9).[54] The reaction was realized with NiDMECl₂ as the catalyst and NaOIPiv as the base in an operationally simple undivided cell. The Authors. Published by Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Scheme 6. The general mechanism of nickel-electrocatalyzed redox-neutral cross-coupling.

Scheme 7. Asymmetric electrochemical benzylation of activated ketones 12.

Scheme 8. Proposed catalytic cycle for asymmetric benzylation.
noline (AQ) displayed best results over N,O-chelation, thus far mostly used for complementary cobalta-electrocatalyzed C=H activations. Within the redox-mediator-free reaction conditions, the robustness of the nickela-electrochemical C=Haminations of decorated arenes 18 with cyclic and acyclic secondary amines 19 were established. A broad range of valuable functional groups, including ester, halo, cyano, thio, and thioester, were well tolerated as were heteroarenes (20a–20m). Noteworthily, thiazine and challenging acyclic amines gave the corresponding products (20n–20o) with satisfactory yields, as compared to the cobalta-electrocatalysis.

To gain insights into the mechanism, the modus operandi was also interrogated. Compared with the ruthenium-, rhodium-, iridium-, cobalt- or iron-catalyzed electrochemical C=H activations, intermolecular competition experiments showed that electron-poor arenes 18j reacted preferentially over the electron-rich analogs 18i, suggesting rather a base-assisted concerted-metalation-deprotonation (CMD) mechanism (Scheme 10a). In addition, a kinetic isotope effect (KIE) of $k_D/k_H = 1.1$ performed by an in operando approach indicated that the C=H activation is not kinetically relevant (Scheme 10b and c).

Furthermore, a kinetic profile was established by means of in operando React-IR, which revealed the absence of a major initiation period (Figure 1a). In addition, the Ackermann group performed head-space gas-chromatographic analysis, which showed the generation of molecular hydrogen as the sole byproduct. Finally, a series of cyclic voltammetry studies was conducted. The addition of both the substrate and NaOPiv displayed a strong influence on the electrode potential for the nickel(II/III) event, which was observed at $E_p = +0.26 \text{ V vs. Fc}$. Moreover, at a higher temperature, the reversible oxidation wave of nickel(II/III) event was significantly shifted to $E_p = +0.18 \text{ V vs. Fc}^{-1}$, which could be rationalized the generation of a cyclometalated nickel(III) intermediate (Figure 1b). Furthermore, an additional reversible oxidation wave was observed at $E_p = +0.49 \text{ V vs. Fc}^{-1}$ (Figure 1c).

According to these mechanistic findings, a plausible catalytic cycle was proposed to start with a carboxylate-assisted C=H nickelation to generate the nickel(III) species Ni(III)21b
Thus, C–H activation, coordination of the coordinated amine 19 and anodic oxidation deliver nickel(III)-amide complex \( \text{Ni}^\text{III}-21 \), which undergoes an electrochemical single electron transfer (SET) for an oxidation-induced reductiveelimination from the \( \text{Ni}^\text{IV} \) species \( \text{Ni}^\text{IV}-21 \). Thereby, the catalytically competent complex \( \text{Ni}^\text{II}-21 \) is regenerated upon the coordination by substrate 18, releasing the desired product 20.

**Nickel-electrocatalyzed C–H alkoxylation**

Transition-metal-catalyzed C–O formations via C–H hydroxylation, acetoxilation, and phenoxylation have experienced significant advances. In contrast, C–H alkoxylation has remained underdeveloped, which is largely due to alcohols undergoing competitive β-hydride elimination or overoxidation. In 2017, Ackermann reported the first anodic oxidative C–H alkoxylation of arenes with various primary alcohols by cobalt catalysis. Subsequently, palladium-catalyzed electrooxidative C(sp\(^3\))-H oxygenation with carboxylic acids and menthols was accomplished by Mei. In comparison with the transition-metal-catalyzed chemical or electro-oxidative C–H alkoxylation of arenes using primary alcohols and some simple secondary alcohols as reagent solvent, the nickel-electrooxidative C–H oxygenation of arenes provided the desired products in high yields even with sterically encumbered secondary alcohols. Notably, naturally occurring alcohols, such as menthol, cholesterol and β-estradiol (23p–23r), could be also successfully transformed, maintaining the integrity of the stereogenic centers. Additionally, the gram-scale electrocatalytic oxidation very recently made viable for electrooxidative C–H alkoxylation.

In 2020, the Ackermann group achieved the nickel-electrooxidative C–H alkoxylation of both electron-poor and electron-rich arenes 22 with secondary alcohols 23 using Ni(DME)Cl\(_2\) as the catalyst and bulky NaOAd as the additive in an user-friendly undivided cell set-up (Scheme 12). Under the optimized reaction conditions, the substitution pattern on the quinoline moiety had a strong impact on the efficacy of the nickel-electrochemical oxidation. Computational studies at the PBE0/Def2TZVP level of theory illustrated that the increased electron-density at the quinolyl nitrogen and the decreased electron-density at the free amide nitrogen were found to be critical for the electrochemical C–O formation.

A variety of (hetero)arenes 22f–22p were employed to probe the versatility of nickel-electrooxidative C–H transformations, uncovering a broad scope of valuable electrophilic functional groups were fully accepted, such as halide, ester, thioether, nitrile, and even the strongly coordinating pyridine.

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**Scheme 11.** Plausible catalytic cycle.

**Scheme 12.** The impact of substitution pattern on nickel-electrooxidative alkoxylation. Yields of recovered starting materials are in parenthesis. N2 = net atomic charges of the N2 atom.

**Scheme 13.** Nickel-electrooxidative C–H alkoxylation. [a] Gram-scale testing with 22j (4.0 mmol, 1.32 g).
was achieved without compromising the catalysts’ efficacy on scale (24 j).

Competition experiments between amines 19a and alcohols 23o showed nickel-electrocatalyzed C–H oxygenation to be more challenging than the C–N transformation (Scheme 14a). Moreover, primary and secondary alcohols 23 reflected the particular challenge of secondary C–H alkoxylations (Scheme 14b).

To gain insights into the nickel catalyst’s mode of action, a series of detailed mechanistic studies was conducted. In contrast to cobalt-electrocatalysis[49], intermolecular competitive reaction showed the more electron-deficient amines to react inherently faster, being as suggestive of CMD mechanism.[56] In good agreement with this observation, no H/D exchange was observed with [D₄]-MeOH as the cosolvent and a kinetic isotope effect of kH/kD ≈ 1.4 by independent experiments provided support for a fast C–H scission. No products could be detected after the addition of the typical radical scavengers 2,2,6,6-tetramethylpiperidinylxoyl (TEMPO), butylhydroxytoluol (BHT) or 1,4-benzoquinone (BQ), showing a possible single-electron-transfer (SET) step. Moreover, electricity off-on experiments were performed under standard conditions to investigate a radical chain scenario (Scheme 15). However, the C–H activation was stopped in the absence of the current and continued after switching the electricity back on, rendering a radical-chain process unlikely to be operative.

Importantly, the well-defined nickel(III) complex NiIII-I could be independently synthesized by electrooxidation (Scheme 16). CV analysis displayed a facile oxidation wave at the potential of 0.50 V vs. Fc⁰/⁺, indicating the formation of a formal nickel(IV) complex (Scheme 16). Moreover, stoichiometric reactions of NiIII-I illustrated high efficiency in the presence of electricity while offering lower yields without current, providing strong evidence for a nickel(IV) intermediate.

A further support was obtained by DFT calculations that showed the coordinated ligand to participate in the redox event in a non-innocent fashion, stabilizing the formal nickel(IV) species (Scheme 17). Thereby, coordination of high-valent...
intermediate NiIII with alcohols, followed by oxidation-induced reductive elimination deliver the desired alkoxylation products.

Notably, the 6-methylquinuoline was easily removed in a traceless fashion to provide efficient access to benzamide 25 benzoic acid 26 and aromatic aldehyde 27 (Scheme 18).

**Summary and Outlook**

In recent years, Earth-abundant nickel complexes have emerged as powerful catalysts for the construction of C–C and C-Het bonds. Significant momentum has been gained by the merger of homogeneous nickel catalysis with electrochemistry towards molecular syntheses under mild reaction conditions. While great progress has thereby been achieved in cross-couplings and reductive cross-electrophile couplings, a major drawback is constituted by the prefunctionalizations of both substrates, and the sacrificial anode approach. In contrast, nickela-electrooxidative chemo- and position-selective C–H nitrogeneations have very recently been proven viable with various cyclic and acyclic amines. Likewise, challenging C–H alkoxylation were realized with secondary alcohols. These electrochemical C–H activations exploit electricity as green oxidant, with molecular hydrogen as the only byproduct to avoid expensive metal oxidants. While these approaches have largely exploited chelation-assistance,[11] recent progress was made towards electrocatalyzed C–H activations without directing groups.[12] In consideration of the environment-friendly nature of nickel-electrocatalytic oxidations, further exciting developments are expected in this rapidly evolving research arena, such as the direct use of renewable forms of energy.[13] C(sp3)–H activations, C–H alkylations,[14] or particularly enantioselective electrochemical transformations.[15]

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**Conflict of interest**

The authors declare no conflict of interest.

**Keywords:** C–H activation • electrochemistry • electrosynthesis • heterocycles • nickel

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