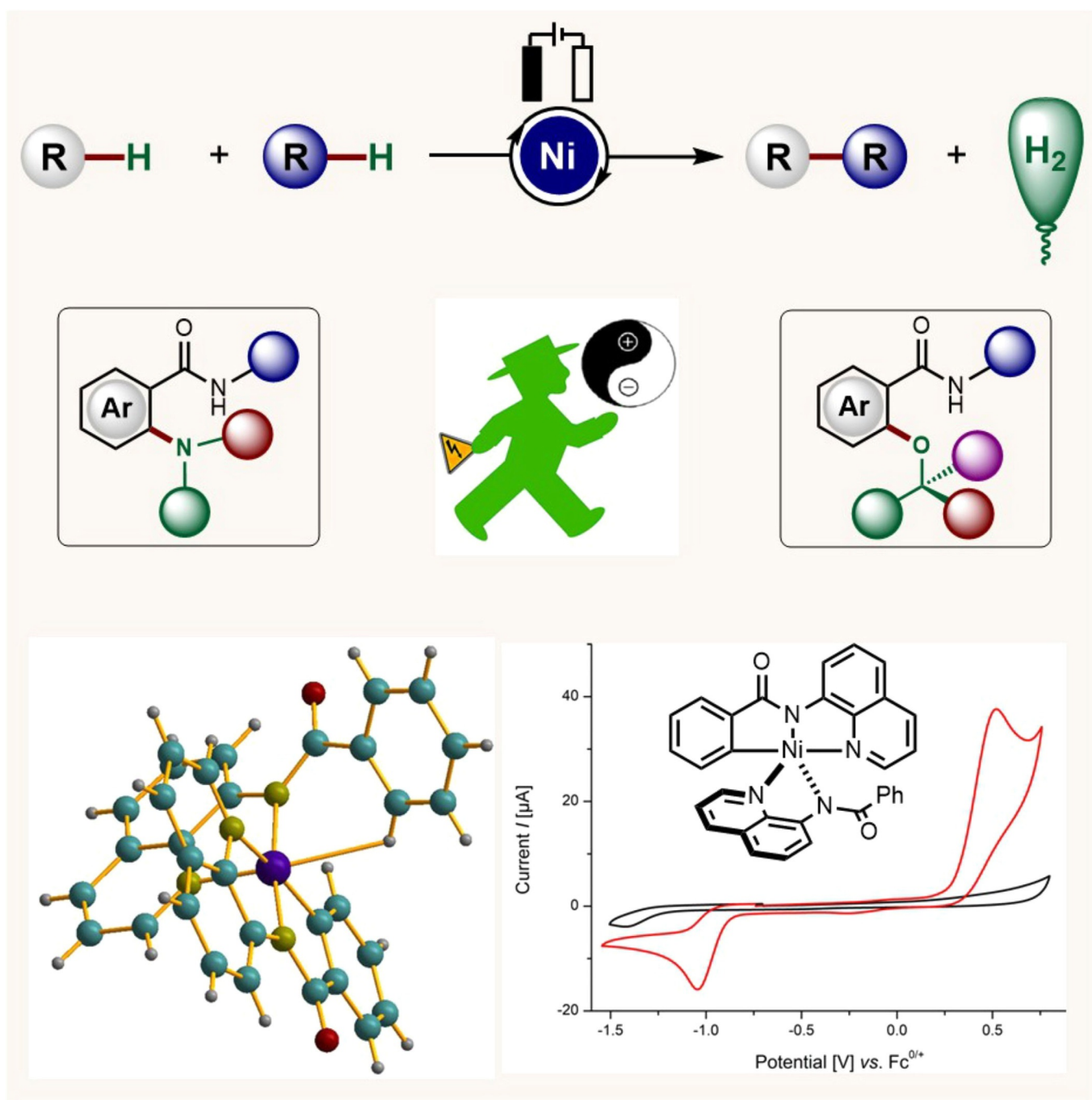


■ Electrochemistry | *Reviews Showcase*

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

Shou-Kun Zhang,<sup>[a]</sup> Ramesh C. Samanta,<sup>[a]</sup> Antonio Del Vecchio,<sup>[a]</sup> and Lutz Ackermann\*<sup>[a, b]</sup>

**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 redox reagents, such as silver(I) or copper(II) salts, are largely required for oxidative C–H activations. Recently, electro-synthesis 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 nickela-electrocatalysis has until recently proven elusive for oxidative C–H activations. Herein, the early developments of nickela-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.<sup>[1]</sup> Particularly, palladium-catalyzed cross-couplings have thus revolutionized molecular syntheses, with transformative applications, to medicinal chemistry, crop protection, material sciences and pharmaceutical industries.<sup>[2]</sup> While inter alia Mizoroki–Heck,<sup>[3]</sup> Suzuki–Miyaura,<sup>[4]</sup> Migita–Stille,<sup>[5]</sup> and Negishi<sup>[6]</sup> cross-couplings have largely benefited from the power of versatile palladium catalysts,<sup>[7]</sup> early findings by inter alia Corriu, Kumada<sup>[8]</sup> and Kochi<sup>[9]</sup> have indicated the until recently largely untapped potential of Earth-abundant and less toxic nickel catalysis.<sup>[10]</sup> 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.<sup>[2]</sup> The synthesis of the organic nucleophile is predominantly accomplished by the oxidative addition or halogen/metal-exchange of an organic electrophile.<sup>[11]</sup> As a consequence, cross-electrophile couplings directly between two different organic (pseudo)halides have been recognized as a more step-economical

approach.<sup>[12]</sup> 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.<sup>[13]</sup> Oxidative C–H activations require terminal oxidants,<sup>[14]</sup> typically stoichiometric amounts of often expensive and/or toxic transition metal salts. Early contributions by Volta,<sup>[15]</sup> Kolbe,<sup>[16]</sup> and Faraday<sup>[17]</sup> have indicated the potential of electrochemistry. Within a remarkable renaissance of organic electro-synthesis,<sup>[18]</sup> inexpensive electricity has very recently been identified as a viable redox equivalent in electrooxidative C–H activations.<sup>[19]</sup> 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.


## Reductive cross-electrophile coupling


In 1976, Jennings and co-workers<sup>[20]</sup> described the first electrochemical synthesis enabled by nickel catalysis to generate the homo-coupling product **2a** of phenyl or benzyl bromides **1a** with copper as the sacrificial anode material (Scheme 1a). Later, for electroreductive homo-coupling reactions of alkenyl 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 1c).<sup>[21]</sup> 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).<sup>[22]</sup> Subsequently, alternative dihalo(hetero)arenes and even 1,2-diiodoethyne were successfully employed for nickela-electroreductive coupling reactions to synthesize different films and polymers.<sup>[23]</sup>


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<sup>[24]</sup> 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  $\alpha$ -hal-


[a] S.-K. Zhang, Dr. R. C. Samanta, Dr. A. Del Vecchio, 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/>

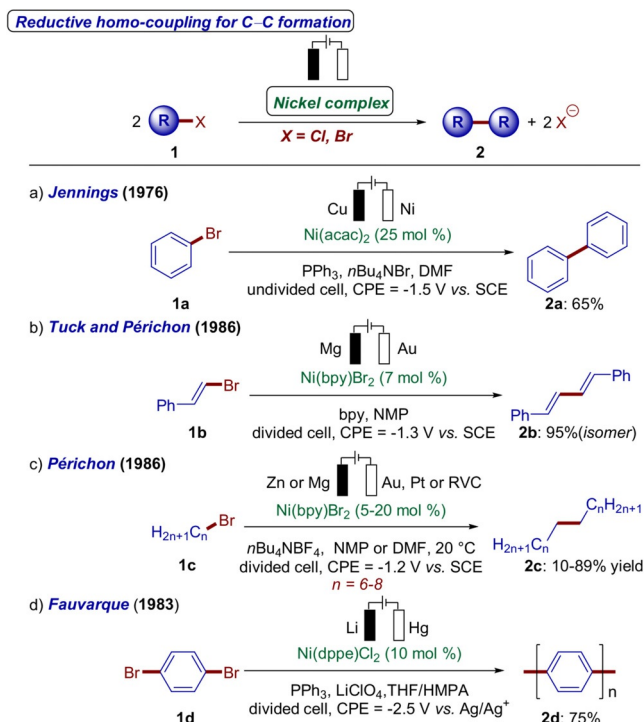
[b] Prof. Dr. L. Ackermann  
Woehler Research Institute for Sustainable Chemistry (WISCH)  
Georg-August-Universität Göttingen  
Tammannstraße 2, 37077 Göttingen (Germany)

 The ORCID identification number(s) for the author(s) of this article can be found under:  
<https://doi.org/10.1002/chem.202001318>.

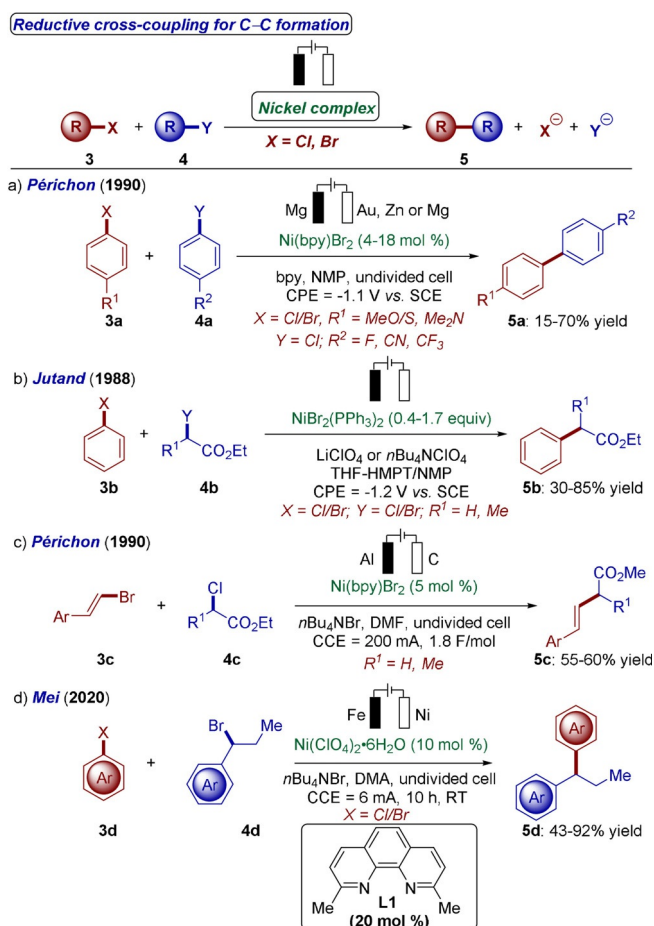
 © 2020 The Authors. Published by Wiley-VCH Verlag GmbH & Co. KGaA. This is an open access article under the terms of Creative Commons Attribution NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

 Part of a Special Issue for the 8th EuChemS Chemistry Congress consisting of contributions from selected speakers and conveners. To view the complete issue, visit Issue 48.

 Selected by the Editorial Office for our Showcase of outstanding Review-type articles <http://www.chemeurj.org/showcase>.



Scheme 1. Nickel-catalyzed electroreduction for C–C homo-couplings.



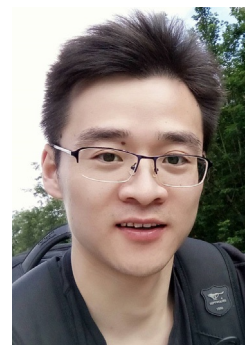
Scheme 2. Nickela-electroreductive cross-coupling for C–C formation.

oesters **4b–4c** with aryl and alkenyl halides **3b–3c**, 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).<sup>[25]</sup> 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 nickela-electroreductive relay cross-couplings between aryl (**3d**) and alkyl (**4d**) halides (Scheme 2d).<sup>[26]</sup>

Achieving full selectivity control in terms of asymmetric electro-synthesis continues to be challenging.<sup>[27]</sup> 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).<sup>[28]</sup> As a result, chiral arylpropionic acid derivatives **8a** were obtained from aryl halides **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)Cl<sub>2</sub> as the precatalyst along with the indanyl-substituted bis(oxazoline) ligand **L2** (Scheme 3b).<sup>[29]</sup>

A general catalytic cycle of nickela-electroreductive cross-electrophile couplings is depicted in Scheme 4. The active species  $\text{L}_n\text{Ni}^0$  (**9b**) is reductively formed at the cathode from the precursor  $\text{L}_n\text{Ni}^{\text{II}}\text{X}$  (**9a**), which is stabilized by ligands, such as PPh<sub>3</sub> or bipyridine.<sup>[18g]</sup> Then, the intermediate  $\text{L}_n\text{R}^1\text{Ni}^{\text{II}}\text{X}$  (**9c**) is formed through an inherently faster oxidative addition of R<sup>1</sup>X onto the nickel(0) species **9b** with the reactivity order being ArBr > ArCl; ArBr > PyCl; ArI >  $\alpha$ -chloroester.<sup>[30]</sup> Subsequently, a

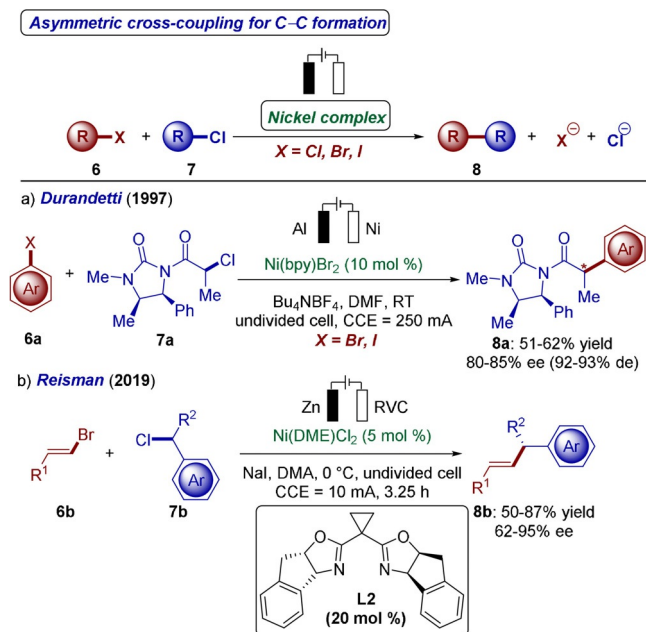
Shou-Kun Zhang was born in 1990 in Henan Province, P. R. China. He obtained his bachelor's degree of Materials Chemistry in 2013 at South-Central University for Nationalities (China) and master's degree of Organic Chemistry under the supervision of Pro. Dr. Mao-Ping Song in 2016 at Zhengzhou University (China). Since 2016, he is pursuing Ph.D. at Georg-August-Universität Göttingen (Germany) under the supervision of Prof. Dr. Lutz Ackermann. His current research involves the development of sustainable, electrochemical methods for organic syntheses.



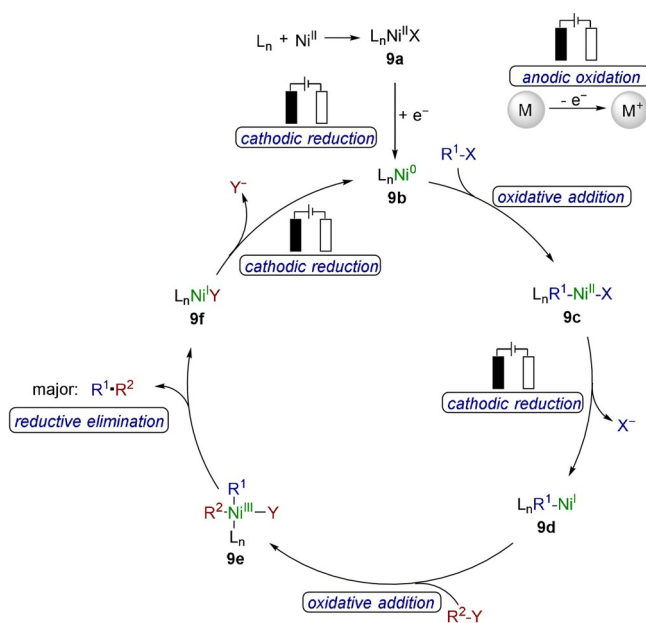
Ramesh C. Samanta has received his B. Sc. in chemistry from Vidyasagar University in 2008. After completion his M. Sc. from the Indian Institute of Technology (IIT), Kanpur in 2010, he moved to Germany for his doctoral study and has received his Ph.D. from the University of Münster under the supervision of Prof. Armido Studer in 2013, working on oxidative N-heterocyclic carbene catalysis. Then, he was working as a Japan Society for the Promotion of Science (JSPS) postdoctoral fellow with Prof. Hisashi Yamamoto in Japan on chiral Bronsted acid catalysis before he moved to the Georg-August-Universität Göttingen (Germany) for his second postdoctoral study. Since 2018, he is working there as an Alexander von Humboldt postdoctoral fellow with Prof. Lutz Ackermann, focusing on electrochemical C–H activation.







Scheme 3. Stereoselective cross-electrophile-couplings.



Scheme 4. General mechanism for nickela-electroreductive cross-electrophile coupling.

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  $R^2Y$  to obtain the nickel(III) species **9e**, followed by reductive elimination to deliver the desired cross-electrophile coupling product, while yielding the reduced nickel(I) complex **9f**.<sup>[30]</sup> Homo-coupling products could be observed from the reductive elimination at a nickel(III) species, when the differences in terms of oxidative addition reactivity between  $R^1X$  and  $R^2Y$  are minor. Finally, the catalytically

competent complex  $L_nNi^0$  **9b** is regenerated from the nickel(I) species **9f** through cathodic reduction.

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

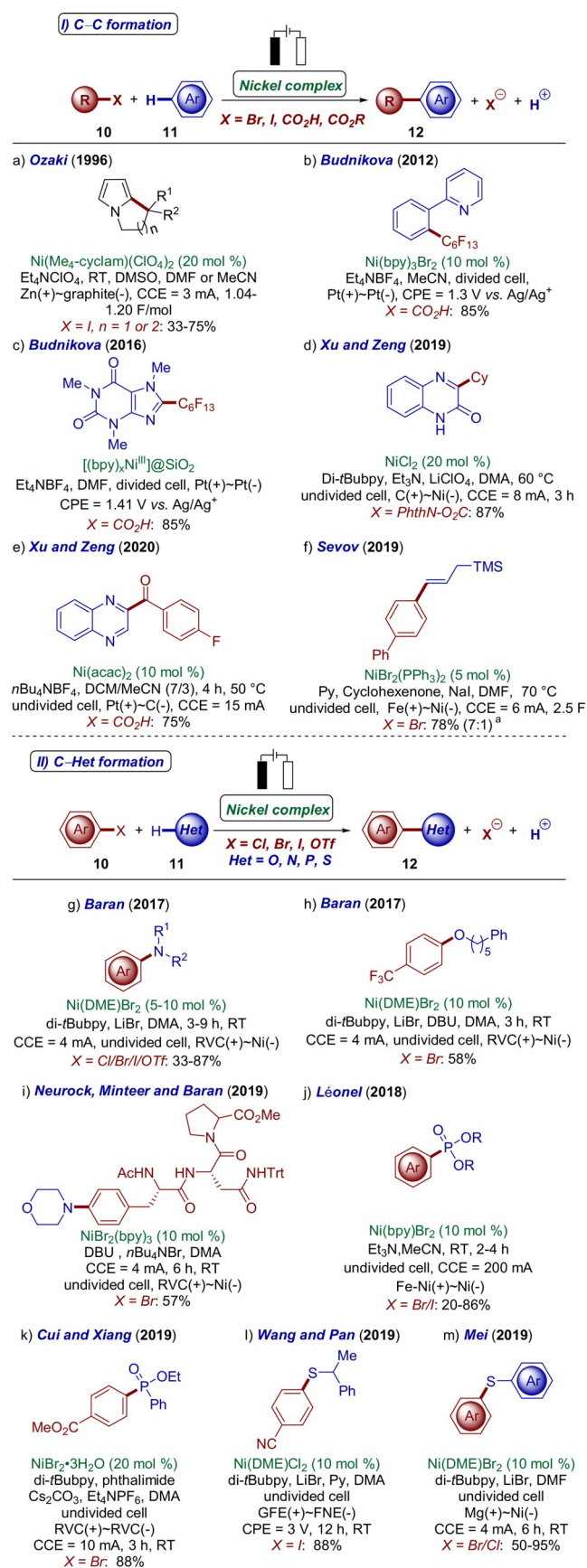
In contrast to reductive cross-electrophile couplings, net redox-neutral transformations can require only one prefunctionalized substrate **10**. Even though there is overall no need for an oxidant or a reductant for net redox-neutral transformation electrochemistry can facilitate the formation of the corresponding coupling products **12** with a non-prefunctionalized substrate **11**. Hence, in 1996, Ozaki reported a radical cycloaddition for the preparation of pyrrolopyridine and pyrrolopyrrole under nickel-catalyzed electroreductive conditions (Scheme 5a).<sup>[31]</sup> 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).<sup>[32]</sup> For instance, typical radical reactions, such as Minisci-type alkylations and acylations, were facilitated by electro-mediated nickel-cat-

Antonio Del Vecchio obtained the MSc degree in Chemistry and Pharmaceutical Technologies at University of Ferrara (Italy) in 2015. After a research stay at the same university, he moved to Aptuit Research Center in Verona as an early stage researcher in the Medicinal Chemistry Group. In October 2016, he joined the Service de Chimie Bio-orthogonale et de Marquage (SCBM) at CEA-Saclay (French Atomic Energy Commission) under the supervision of Dr. Davide Audisio and Dr. Frédéric Taran. Here, he received his Ph.D. working on new synthetic methodologies involving  $CO_2$  and carbon radio-labeling. In 2019, he joined the Prof. Dr. Ackermann group at the Georg-August-Universität Göttingen (Germany) as postdoctoral researcher, working on metalla-electrocatalyzed C–H activations.



Lutz Ackermann studied chemistry at Christian-Albrechts-University Kiel (Germany) and received his Ph.D. in 2001 with Prof. Dr. A. Fürstner at the Max-Planck-Institut für Kohlenforschung in Mülheim/Ruhr. He was a postdoctoral co-worker in the laboratories of Prof. Dr. R. G. Bergman at the University of California at Berkeley before initiating his independent research career in 2003 at the Ludwig-Maximilians-University München supported by the Emmy Noether program of the DFG. In 2007, he was appointed as Full Professor at Georg-August-Universität Göttingen. His recent awards and distinctions include an ERC Grant (2012) and a Gottfried-Wilhelm-Leibniz-Preis (2017) as well as visiting professorships at the Università degli Studi di Milano, the University of Wisconsin at Madison, the Università di Pavia, Osaka University, the Ecole supérieure de Physique et de Chimie Industrielles de la ville de Paris, the Università degli Studi di Perugia, Kyoto University, École Polytechnique, the Indian Institute of Technology Bombay and the Université de Strasbourg. The development and application of novel concepts for sustainable catalysis constitute his major current research interests, with a topical focus on C–H activation and organic electrocatalysis.





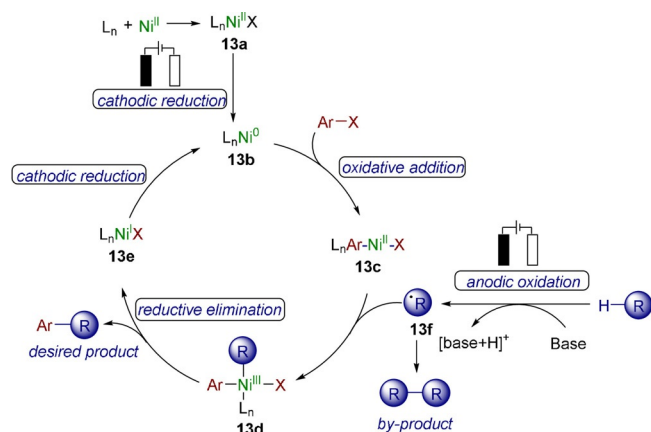
**Scheme 5.** Redox-neutral C–C and C–Het cross-couplings. [a] Ratio of linear to branched products.

alysis likewise (Scheme 5d and 5e).<sup>[33]</sup> 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  $\alpha$ -keto acids by anodic oxidation. Very recently, Sevov 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).<sup>[34]</sup> 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 alkoxylation of prefunctionalized aryl electrophiles with aliphatic amines and alcohols were realized at room temperature by Baran (Scheme 5g and 5h).<sup>[35]</sup> Later, amino acid esters, nucleosides and oligopeptides were addressed employing Ni(bpy)<sub>3</sub>Br<sub>2</sub> as the catalyst along with DBU as an external base (Scheme 5i).<sup>[36]</sup> In 2018, Léonel developed the phosphorylation of aryl halides with dialkyl phosphites by nickela-electrocatalysis using a sacrificial iron-nickel alloy anode (Scheme 5j).<sup>[37]</sup> 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 diphenylphosphine oxide (Scheme 5k).<sup>[38]</sup> In 2019, a nickela-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).<sup>[39]</sup> In the meantime, Mei independently developed the nickela-electrocatalyzed C–S coupling of more challenging aryl bromides and chlorides with aryl thiols in the absence of an external base (Scheme 5m).<sup>[40]</sup>

A proposed mechanism for nickela-electrocatalyzed cross-coupling reactions was suggested based on related nickela-photoredox-catalyzed cross-couplings (Scheme 6).<sup>[41]</sup> The L<sub>n</sub>Ni<sup>0</sup> complex **13b** is generated from the precursor L<sub>n</sub>Ni<sup>II</sup>X **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(I) 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.



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

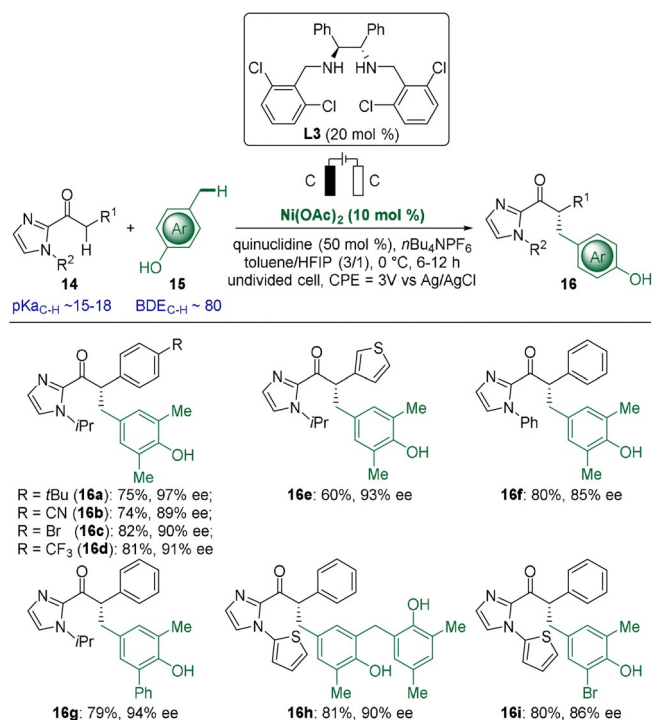
## Nickela-Electrocatalyzed Oxidative Transformations

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.<sup>[13,42]</sup> 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 reagent for C–H activations.<sup>[43]</sup> While electrocatalyzed C–H activation witnessed considerable advances with the aid of 4d and 5d metals, such as palladium,<sup>[44]</sup> ruthenium,<sup>[45]</sup> rhodium<sup>[46]</sup> and iridium complexes,<sup>[47]</sup> the development of cost-effective and less toxic 3d metals<sup>[19a,48]</sup> cobalt,<sup>[49]</sup> iron,<sup>[50]</sup> manganese,<sup>[50]</sup> copper<sup>[51]</sup> and nickel continue to be scarce, but bear unique potential towards ideal resource-economy.

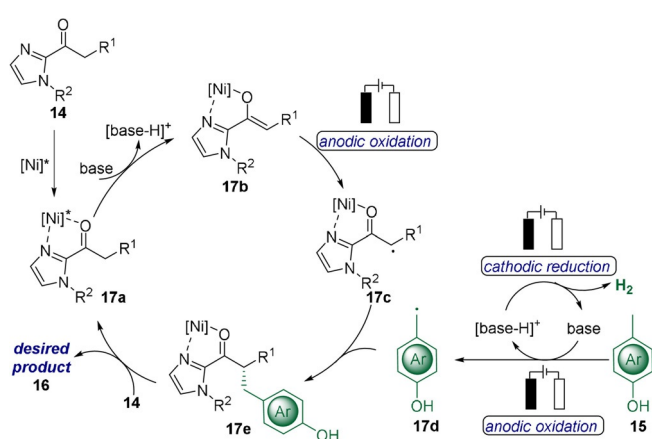
### Asymmetric functionalization of enolates

In 2019, nickel-catalyzed electrochemical asymmetric C(sp<sup>3</sup>)–H functionalization was reported by Guo (Scheme 7).<sup>[52]</sup> Thus, an enantioselective  $\alpha$ -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)<sub>2</sub> 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  $\alpha$ -aryl substituents at the ketones to enhance its acidity ( $pK_{aC-H} \approx 15–18$  in DMSO) and activated toluene derivatives **15** with a bond dissociation energy (BDE<sub>C-H</sub>) of  $\approx 80$  kcal mol<sup>-1</sup> to guarantee high efficacy.<sup>[53]</sup>

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



**Scheme 7.** Asymmetric electrochemical benzylation of activated ketones **12**.



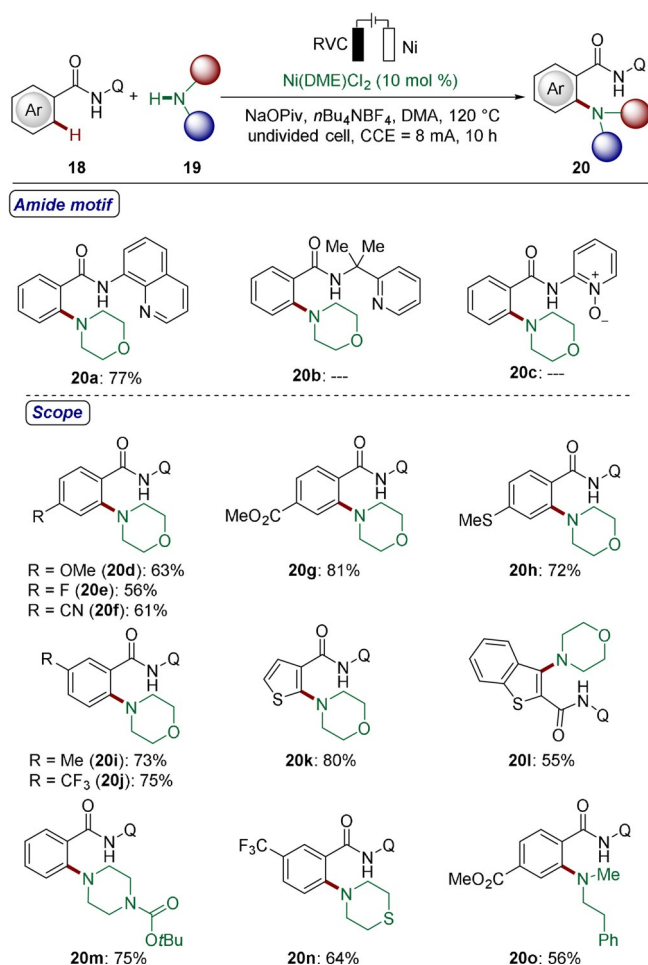
**Scheme 8.** Proposed catalytic cycle for asymmetric benzylation.

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(sp<sup>2</sup>)–H activations by nickel catalysis remain elusive until recently. In 2018, Ackermann reported on the first nickela-electrooxidative C–H activation of benzamides **18** and secondary amines **19** (Scheme 9).<sup>[54]</sup> The reaction was realized with Ni(DME)Cl<sub>2</sub> as the catalyst and NaOPiv as the base in an operationally simple undivided cell. The *N,N*-bidentate motif 8-aminoqui-



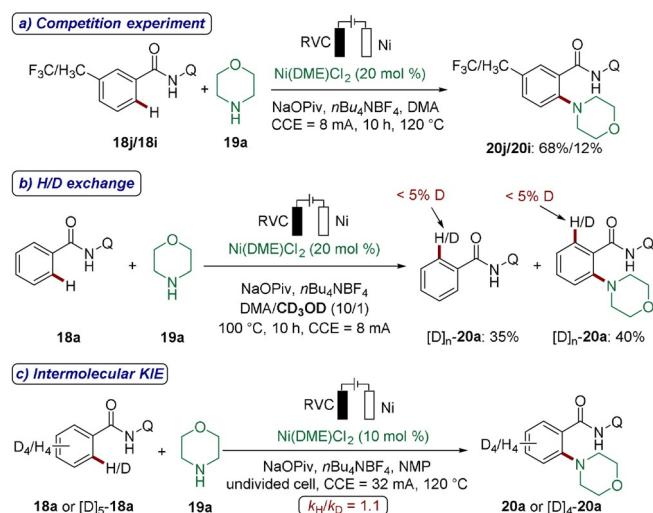


**Scheme 9.** Nickela-electrocatalyzed C–H nitrogenation.

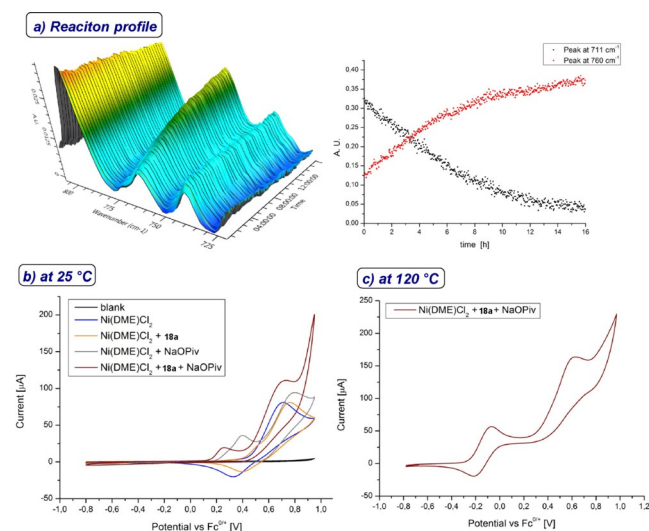
noline (AQ)<sup>[55]</sup> displayed best results over *N,O*-chelation, thus far mostly used for complementary cobalta-electrocatalyzed C–H activations.<sup>[19a]</sup> Within the redox-mediator-free reaction conditions, the robustness of the nickela-electrochemical C–H aminations of decorated arenes **18** with cyclic and acyclic secondary amines **19** were established.<sup>[54]</sup> A broad range of valuable functional groups, including ester, halo, cyano, thio, and thioester, were well tolerated as were heteroarenes (**20a–20m**). Noteworthy, thiazine and challenging acyclic amines gave the corresponding products (**20n–20o**) with satisfactory yields, as compared to the cobalta-electrocatalysis.<sup>[49g, i]</sup>

To gain insights into the mechanism, the *modus operandi* was also interrogated. Compared with the ruthenium-,<sup>[45]</sup> rhodium-,<sup>[46]</sup> iridium-,<sup>[47b]</sup> cobalt-,<sup>[43f, 49]</sup> or iron-catalyzed<sup>[50]</sup> 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)<sup>[56]</sup> mechanism (Scheme 10a).<sup>[54]</sup> In addition, a kinetic isotope effect (KIE) of  $k_H/k_D = 1.1$  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



**Scheme 10.** Mechanistic studies on nickel-electrocatalytic C–H amination.

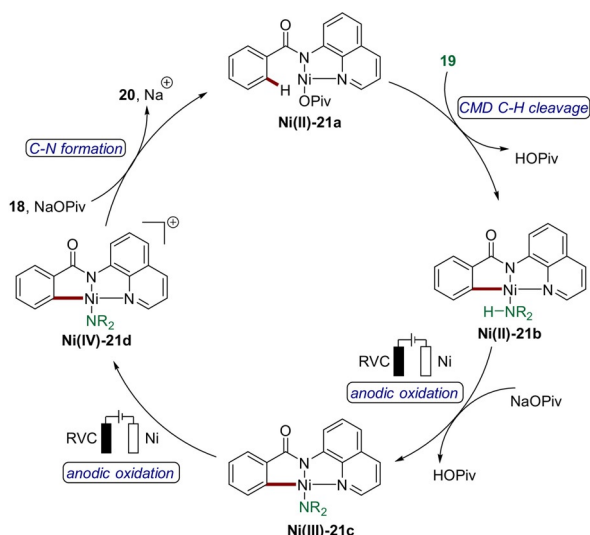


**Figure 1.** a) Reaction profile. CV spectra (DMA, 0.05 M  $[n\text{Bu}_4\text{N}][\text{BF}_4]$ , 100  $\text{mV s}^{-1}$ ) for b)  $\text{Ni(DME)Cl}_2$  with the individual components of the catalysis; c)  $\text{Ni(DME)Cl}_2$ , NaOPiv and **18a** after preheating at 120 °C for 30 min.

initiation period (Figure 1a).<sup>[54]</sup> 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  $E_p = +0.26 \text{ V vs. Fc}^{+/0}$

(Figure 1b). Moreover, at a higher temperature, the reversible oxidation wave of nickel(II/III) event was significantly shifted to  $E_p = -0.18 \text{ V vs. Fc}^{+/0}$ , which could be rationalized the generation of a cyclometalated nickel(III) intermediate (Figure 1b). Furthermore, an additional reversible oxidation wave was observed at  $E_p = +0.49 \text{ V vs. Fc}^{+/0}$  (Figure 1c).<sup>[57]</sup>

According to these mechanistic findings, a plausible catalytic cycle was proposed to start with a carboxylate-assisted C–H nickelation to generate the nickel(II) species **Ni<sup>II</sup>-21b**

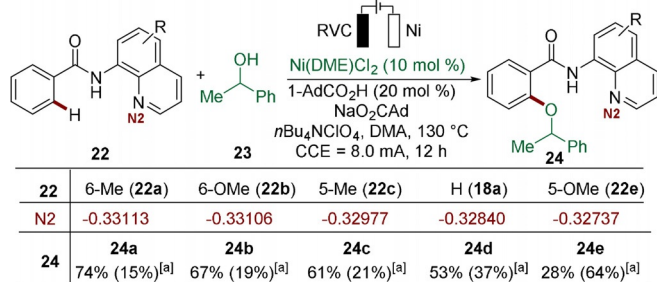


Scheme 11. Plausible catalytic cycle.

(Scheme 11).<sup>[54]</sup> Thus, C–H activation, coordination of the coordinated amine **19** and anodic oxidation deliver nickel(III)-amide complex **Ni<sup>III</sup>-21c**, which undergoes an electrochemical single electron transfer (SET) for an oxidation-induced reductive elimination from the **Ni<sup>IV</sup>** species **Ni<sup>IV</sup>-21d**. Thereby, the catalytically competent complex **Ni<sup>II</sup>-21a** is regenerated upon the coordination by substrate **18**, releasing the desired product **20**.

### Nickela-electrocatalyzed C–H alkoxylation

Transition-metal-catalyzed C–O formations via C–H hydroxylation, acetoxylation, and phenoxylation have experienced significant advances.<sup>[58]</sup> In contrast, C–H alkoxylation<sup>[59]</sup> have remained underdeveloped, which is largely due to alcohols undergoing competitive  $\beta$ -hydride elimination or overoxidation. In 2017, Ackermann reported the first anodic oxidative C–H alkoxylation of arenes with various primary alcohols by cobalt catalysis.<sup>[49k]</sup> Subsequently, palladium-catalyzed electrooxidative C(sp<sup>3</sup>)–H oxygenation with carboxylic acids and menthols was accomplished by Mei.<sup>[44b]</sup> In comparison with the transition-metal-catalyzed electrochemical C–H alkoxylation with primary alcohols, sterically encumbered secondary alcohols were only

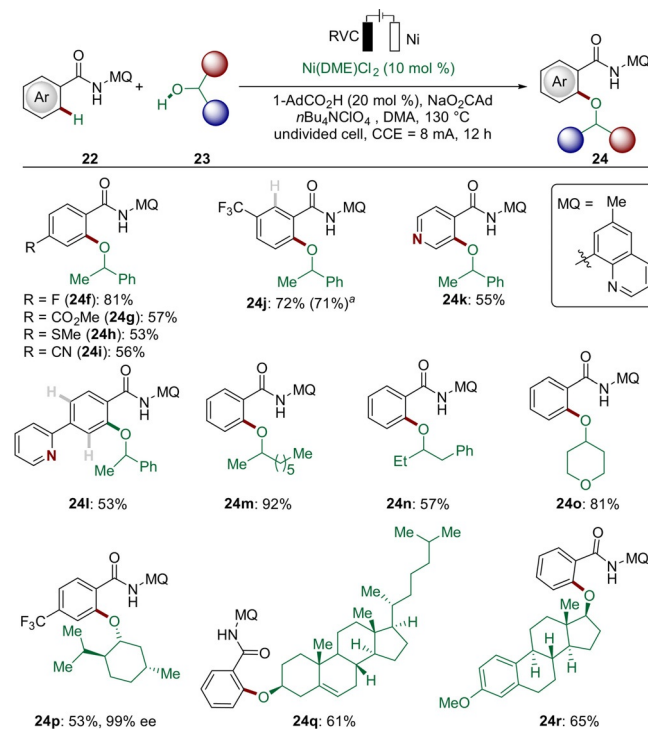


Scheme 12. The impact of substitution pattern on nickela-electrooxidative alkoxylation. Yields of recovered starting materials are in parenthesis. N2 = net atomic charges of the N2 atom.

very recently made viable for electrooxidative C–H alkoxylation.

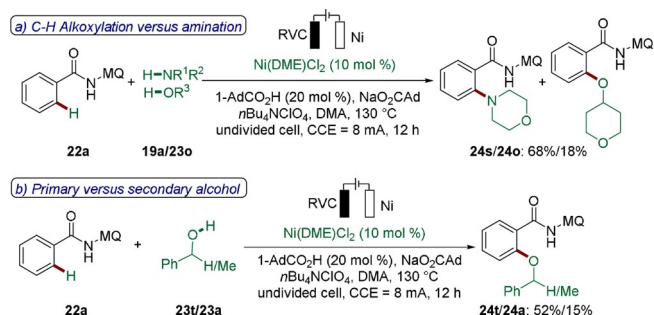
In 2020, the Ackermann group achieved the nickela-electrooxidative C–H alkoxylation of both electron-poor and electron-rich arenes **22** with secondary alcohols **23** using Ni(DME)Cl<sub>2</sub> as the catalyst and bulky NaO<sub>2</sub>CAd as the additive in a user-friendly undivided cell set-up (Scheme 12).<sup>[60]</sup> Under the optimized reaction conditions, the substitution pattern on the quinoline moiety had a strong impact on the efficacy of the nickela-electrochemical oxidation. Computational studies at the PEB0/DefT2TZVP level of theory illustrated that the increased electron-density at the quinolinyl 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 nickela-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 **22f–22i** (Scheme 13).<sup>[60]</sup> In contrast with previous transition-metal-catalyzed chemical or electro-oxidative C–H alkoxylation of arenes utilizing primary alcohols and some simple secondary alcohols as reagent solvent,<sup>[59]</sup> the nickela-electrooxidative C–H oxygenation of arenes provided the desired products in high yields even with sterically encumbered secondary alcohols.<sup>[60]</sup> Notably, naturally occurring alcohols, such as menthol, cholesterol and  $\beta$ -estradiol (**23p–23r**), could be also successfully transformed, maintaining the integrity of the stereogenic centers. Additionally, the gram-scale electrocatalytic oxidation



Scheme 13. Nickela-electrocatalyzed C–H alkoxylation. [a] Gram-scale testing with **22j** (4.0 mmol, 1.32 g).



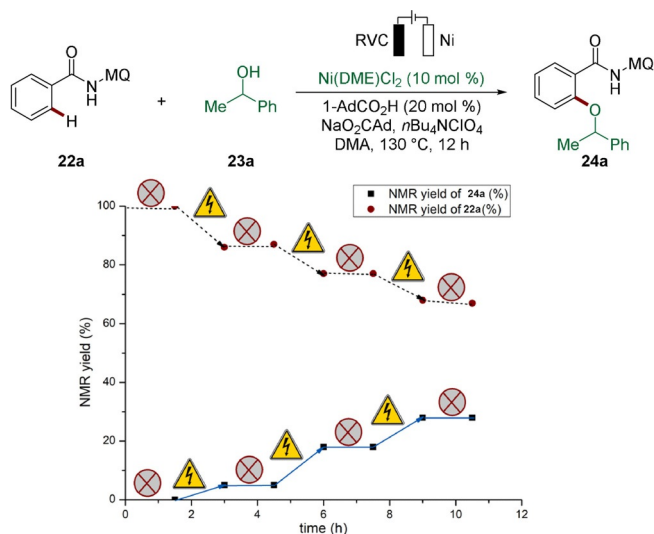


Scheme 14. Competition experiments.

was achieved without compromising the catalysts' efficacy on scale (24j).

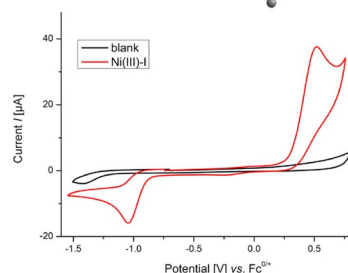
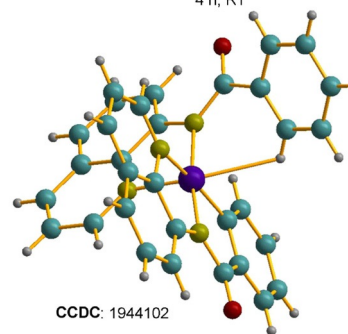
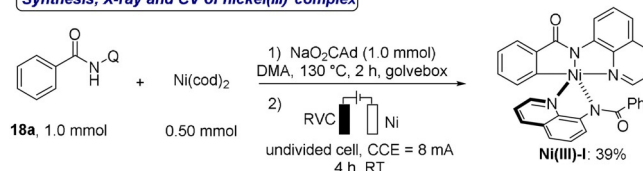
Competition experiments between amines **19a** and alcohols **23o** showed nickel-electrocatalyzed C–H oxygenation to be more challenging than the C–N transformation (Scheme 14a). Moreover, primary and secondary alcohols **23** reflected the particular challenge of secondary C–H alkoxylation (Scheme 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,<sup>[49]</sup> intermolecular competitive reaction showed the more electron-deficient arenes to react inherently faster, being a suggestive of CMD mechanism.<sup>[56]</sup> In good agreement with this observation, no H/D exchange was observed with  $[D_4]$ -MeOH as the cosolvent and a kinetic isotope effect of  $k_H/k_D \approx 1.4$  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-tetramethylpiperidinyloxy (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 con-



Scheme 15. Switch off–on experiment.

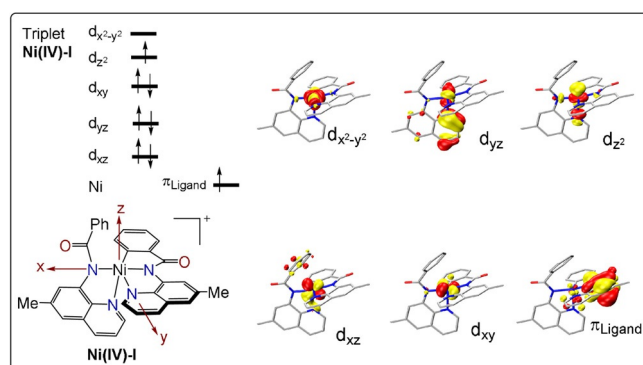
## Synthesis, X-ray and CV of nickel(III) complex

Scheme 16. Synthesis, X-ray and CV data of  $Ni^{III}$ -I; (DMA, 0.1 M  $[nBu_4N][BF_4]$ , 100  $mVs^{-1}$ ).

tinued after switching the electricity back on, rendering a radical-chain process unlikely to be operative.

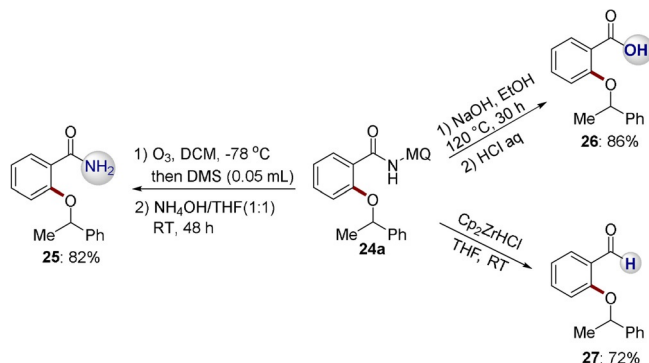
Importantly, the well-defined nickel(III) complex  $Ni^{III}$ -I could be independently synthesized by electrooxidation (Scheme 16). CV analysis displayed a facile oxidation wave at the potential of 0.50 V vs.  $Fc^{0/+}$ , indicating the formation of a formal nickel(IV) complex (Scheme 16). Moreover, stoichiometric reactions of  $Ni^{III}$ -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

Scheme 17. Calculated electronic configuration of the  $Ni^{IV}$ -I ground triplet state.

intermediate  $\text{Ni}^{\text{IV}}$ -I with alcohols, followed by oxidation-induced reductive elimination deliver the desired alkoxyated 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).



Scheme 18. Removal of 6-methylquinuoline.

## 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 electrocatalysis 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, nickel-electrooxidative chemo- and position-selective C–H nitrogenations 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,<sup>[61a]</sup> recent progress was made towards electrocatalyzed C–H activations without directing groups.<sup>[61b]</sup> 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,<sup>[62]</sup> C(sp<sup>3</sup>)–H activations, C–H alkylations,<sup>[63]</sup> or particularly enantioselective electrochemical-transformations.<sup>[64]</sup>

## Acknowledgements

Generous support by the CSC (fellowship to S.K.Z.), the DFG (Gottfried-Wilhelm-Leibniz award to L.A.), and the Alexander von Humboldt foundation (fellowship to R.C.S.) is gratefully acknowledged.

## Conflict of interest

The authors declare no conflict of interest.

**Keywords:** C–H activation · electrochemistry · electrocatalysis · heterocycles · nickel

- [1] a) A. de Meijere, F. Diederich, *Metal-Catalyzed Cross-Coupling Reactions 2nd ed.*, Wiley-VCH, Weinheim, **2004**; b) F. Diederich, P. J. Stang, *Metal-Catalyzed Cross-Coupling Reactions*, Wiley-VCH, Weinheim, **1998**.
- [2] C. C. C. Johansson Seechurn, M. O. Kitching, T. J. Colacot, V. Snieckus, *Angew. Chem. Int. Ed.* **2012**, *51*, 5062–5085; *Angew. Chem.* **2012**, *124*, 5150–5174.
- [3] a) R. F. Heck, *Synlett* **2006**, *2006*, 2855–2860; b) T. Mizoroki, K. Mori, A. Ozaki, *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581.
- [4] N. Miyaoura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457–2483.
- [5] J. K. Stille, *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508–524; *Angew. Chem.* **1986**, *98*, 504–519.
- [6] E. Negishi, *Acc. Chem. Res.* **1982**, *15*, 340–348.
- [7] L. Ackermann, *Modern Arylation Methods*, Wiley-VCH, Weinheim, **2009**.
- [8] a) K. Tamao, K. Sumitani, M. Kumada, *J. Am. Chem. Soc.* **1972**, *94*, 4374–4376; b) R. J. P. Corriu, J. P. Masse, *J. Chem. Soc. Chem. Commun.* **1972**, 144a.
- [9] M. Tamura, J. K. Kochi, *Bull. Chem. Soc. Jpn.* **1971**, *44*, 3063–3073.
- [10] a) B. M. Rosen, K. W. Quasdorf, D. A. Wilson, N. Zhang, A.-M. Resmerita, N. K. Garg, V. Percec, *Chem. Rev.* **2011**, *111*, 1346–1416; b) R. Jana, T. P. Pathak, M. S. Sigman, *Chem. Rev.* **2011**, *111*, 1417–1492.
- [11] P. Knochel, *Handbook of Functionalized Organometallics: Applications in Synthesis*, Wiley-VCH, Weinheim, **2005**.
- [12] a) D. J. Weix, *Acc. Chem. Res.* **2015**, *48*, 1767–1775; b) C. E. I. Knappe, S. Grupe, D. Gärtner, M. Corpet, C. Gosmini, A. Jacobi von Wangelin, *Chem. Eur. J.* **2014**, *20*, 6828–6842.
- [13] L. Ackermann, R. Vicente, A. R. Kapdi, *Angew. Chem. Int. Ed.* **2009**, *48*, 9792–9826; *Angew. Chem.* **2009**, *121*, 9976–10011.
- [14] H. Wang, X. Gao, Z. Lv, T. Abdelilah, A. Lei, *Chem. Rev.* **2019**, *119*, 6769–6787.
- [15] A. Volta, *Philos. Trans. R. Soc.* **1800**, *90*, 403–431.
- [16] a) H. Kolbe, *Liebigs Ann. Chem.* **1849**, *69*, 257–294; b) H. Kolbe, *Justus Liebigs Ann. Chem.* **1848**, *64*, 339–341.
- [17] M. Faraday, *Philos. Trans. R. Soc.* **1825**, *115*, 440–466.
- [18] a) S. R. Waldvogel, S. Lips, M. Selt, B. Riehl, C. J. Kampf, *Chem. Rev.* **2018**, *118*, 6706–6765; b) M. Yan, Y. Kawamata, P. S. Baran, *Chem. Rev.* **2017**, *117*, 13230–13319; c) A. Jutand, *Chem. Rev.* **2008**, *108*, 2300–2347; d) S. Condon, J.-Y. Nédélec, *Synthesis* **2004**, 3070–3078; e) E. Duñach, D. Franco, S. Olivero, *Eur. J. Org. Chem.* **2003**, 1605–1622; f) J.-Y. Nédélec, J. Périchon, M. Troupel, *Springer Berlin Heidelberg* **1997**, 141–173; g) J. Chaussard, J.-C. Folest, J.-Y. Nédélec, J. Périchon, S. Sibille, M. Troupel, *Synthesis* **1990**, 369–381; h) R. Francke, R. D. Little, *Chem. Soc. Rev.* **2014**, *43*, 2492–2521; i) J.-i. Yoshida, K. Kataoka, R. Horcajada, A. Nagaki, *Chem. Rev.* **2008**, *108*, 2265–2299.
- [19] a) L. Ackermann, *Acc. Chem. Res.* **2020**, *53*, 84–104; b) K.-J. Jiao, Y.-K. Xing, Q.-L. Yang, H. Qiu, T.-S. Mei, *Acc. Chem. Res.* **2020**, *53*, 300–310; c) Y. Qiu, J. Struwe, L. Ackermann, *Synlett* **2019**, *30*, 1164–1173.
- [20] P. W. Jennings, D. G. Pillsbury, J. L. Hall, V. T. Brice, *J. Org. Chem.* **1976**, *41*, 719–722.
- [21] a) Y. Rollin, M. Troupel, D. G. Tuck, J. Périchon, *J. Organomet. Chem.* **1986**, *303*, 131–137; b) S. Mabrouk, S. Pellegrini, J.-C. Folest, Y. Rollin, J. Périchon, *J. Organomet. Chem.* **1986**, *301*, 391–400.
- [22] J.-F. Fauvarque, M.-A. Petit, F. Pfluger, A. Jutand, C. Chevrot, M. Troupel, *Makromol. Chem. Rapid Commun.* **1983**, *4*, 455–457.
- [23] a) M. Kijima, Y. Sakai, H. Shirakawa, *Chem. Lett.* **1994**, *23*, 2011–2014; b) K. Faid, A. Siove, D. Adès, C. Chevrot, *Polymer* **1993**, *34*, 3911–3916; c) G. Zotti, G. Schiavon, N. Comisso, A. Berlin, G. Pagani, *Synth. Met.* **1990**, *36*, 337–351; d) A. Siove, D. Adès, C. Chevrot, G. Froyer, *Makromol. Chem.* **1989**, *190*, 1361–1368; e) G. Schiavon, G. Zotti, G. Bontempelli, F. Lo Coco, *Synth. Met.* **1988**, *25*, 365–373.
- [24] G. Meyer, M. Troupel, J. Périchon, *J. Organomet. Chem.* **1990**, *393*, 137–142.

- [25] a) J. C. Folest, J. Périchon, J. F. Fauvarque, A. Jutand, *J. Organomet. Chem.* **1988**, *342*, 259–261; b) A. Conan, S. Sibille, E. d'Incan, J. Périchon, *J. Chem. Soc. Chem. Commun.* **1990**, 48–49.
- [26] a) K.-J. Jiao, D. Liu, H.-X. Ma, H. Qiu, P. Fang, T.-S. Mei, *Angew. Chem. Int. Ed.* **2020**, *59*, 2565–2576; *Angew. Chem.* **2020**, *132*, 2585–2596; b) S. K. Gaddale, A. Peshkov, A. Brzozowska, P. Nikolaienko, C. Zhu, M. Rueping, *Angew. Chem. Int. Ed.* **2020**, *59*, 6513–6519.
- [27] a) X. Chang, Q. Zhang, C. Guo, *Angew. Chem. Int. Ed.* **2020**, <https://doi.org/10.1002/anie.202000016>; *Angew. Chem.* **2020**, <https://doi.org/10.1002/ange.202000016>; b) Q. Lin, L. Li, S. Luo, *Chem. Eur. J.* **2019**, *25*, 10033–10044.
- [28] M. Durandetti, J. Périchon, J.-Y. Nédélec, *J. Org. Chem.* **1997**, *62*, 7914–7915.
- [29] T. J. DeLano, S. E. Reisman, *ACS Catal.* **2019**, *9*, 6751–6754.
- [30] C. Gosmini, S. Lasry, J.-Y. Nédélec, J. Périchon, *Tetrahedron* **1998**, *54*, 1289–1298.
- [31] S. Ozaki, S. Mitoh, H. Ohmori, *Chem. Pharm. Bull.* **1996**, *44*, 2020–2024.
- [32] a) M. N. Khrizanforov, S. V. Fedorenko, S. O. Strelakova, K. V. Kholin, A. R. Mustafina, M. Y. Zhilkin, V. V. Khrizanforova, Y. N. Osin, V. V. Salnikov, T. V. Gryaznova, Y. H. Budnikova, *Dalton Trans.* **2016**, *45*, 11976–11982; b) Y. B. Dudkina, D. Y. Mikhaylov, T. V. Gryaznova, O. G. Sinyashin, D. A. Vivic, Y. H. Budnikova, *Eur. J. Org. Chem.* **2012**, 2114–2117.
- [33] a) H. Ding, K. Xu, C.-C. Zeng, *J. Catal.* **2020**, *381*, 38–43; b) F. Lian, K. Xu, W. Meng, H. Zhang, Z. Tan, C. Zeng, *Chem. Commun.* **2019**, *55*, 14685–14688.
- [34] B. R. Walker, C. S. Sevov, *ACS Catal.* **2019**, *9*, 7197–7203.
- [35] C. Li, Y. Kawamata, H. Nakamura, J. C. Vantourout, Z. Liu, Q. Hou, D. Bao, J. T. Starr, J. Chen, M. Yan, P. S. Baran, *Angew. Chem. Int. Ed.* **2017**, *56*, 13088–13093; *Angew. Chem.* **2017**, *129*, 13268–13273.
- [36] Y. Kawamata, J. C. Vantourout, D. P. Hickey, P. Bai, L. Chen, Q. Hou, W. Qiao, K. Barman, M. A. Edwards, A. F. Garrido-Castro, J. N. deGruyter, H. Nakamura, K. Knouse, C. Qin, K. J. Clay, D. Bao, C. Li, J. T. Starr, C. Garcia-Irizarry, N. Sach, H. S. White, M. Neurock, S. D. Minter, P. S. Baran, *J. Am. Chem. Soc.* **2019**, *141*, 6392–6402.
- [37] S. Sengmany, A. Ollivier, E. Le Gall, E. Léonel, *Org. Biomol. Chem.* **2018**, *16*, 4495–4500.
- [38] Y. Bai, N. Liu, S. Wang, S. Wang, S. Ning, L. Shi, L. Cui, Z. Zhang, J. Xiang, *Org. Lett.* **2019**, *21*, 6835–6838.
- [39] Y. Wang, L. Deng, X. Wang, Z. Wu, Y. Wang, Y. Pan, *ACS Catal.* **2019**, *9*, 1630–1634.
- [40] D. Liu, H.-X. Ma, P. Fang, T.-S. Mei, *Angew. Chem. Int. Ed.* **2019**, *58*, 5033–5037; *Angew. Chem.* **2019**, *131*, 5087–5091.
- [41] R. Sun, Y. Qin, D. G. Nocera, *Angew. Chem. Int. Ed.* **2020**, *59*, 1098; *Angew. Chem.* **2020**, *132*, 1114.
- [42] a) Q. Zhao, G. Meng, S. P. Nolan, M. Szostak, *Chem. Rev.* **2020**, *120*, 1981–2048; b) S. Rej, Y. An, N. Chatani, *Chem. Rev.* **2020**, *120*, 1788–1887; c) J. Wang, G. Dong, *Chem. Rev.* **2019**, *119*, 7478–7528; d) S. Santoro, F. Ferlin, L. Ackermann, L. Vaccaro, *Chem. Soc. Rev.* **2019**, *48*, 2767–2782; e) S. Rej, N. Chatani, *Angew. Chem. Int. Ed.* **2019**, *58*, 8304–8329; *Angew. Chem.* **2019**, *131*, 8390–8416; f) A. Dey, S. K. Sinha, T. K. Achar, D. Maiti, *Angew. Chem. Int. Ed.* **2019**, *58*, 10820–10843; *Angew. Chem.* **2019**, *131*, 10934–10958; g) K. Hirano, M. Miura, *Chem. Sci.* **2018**, *9*, 22–32; h) P. Gandeepan, L. Ackermann, *Chem* **2018**, *4*, 199–222; i) H. Yi, G. Zhang, H. Wang, Z. Huang, J. Wang, A. K. Singh, A. Lei, *Chem. Rev.* **2017**, *117*, 9016–9085; j) Y. Yang, J. Lan, J. You, *Chem. Rev.* **2017**, *117*, 8787–8863; k) Y. Park, Y. Kim, S. Chang, *Chem. Rev.* **2017**, *117*, 9247–9301; l) C. G. Newton, S.-G. Wang, C. C. Oliveira, N. Cramer, *Chem. Rev.* **2017**, *117*, 8908–8976; m) K. Murakami, S. Yamada, T. Kaneda, K. Itami, *Chem. Rev.* **2017**, *117*, 9302–9332; n) J. He, M. Wasa, K. S. L. Chan, Q. Shao, J.-Q. Yu, *Chem. Rev.* **2017**, *117*, 8754–8786; o) D. L. Davies, S. A. Macgregor, C. L. McMullin, *Chem. Rev.* **2017**, *117*, 8649–8709; p) Q. Wang, Y. Su, L. Li, H. Huang, *Chem. Soc. Rev.* **2016**, *45*, 1257–1272; q) S. A. Girard, T. Knauber, C.-J. Li, *Angew. Chem. Int. Ed.* **2014**, *53*, 74–100; *Angew. Chem.* **2014**, *126*, 76–103; r) F. Chen, T. Wang, N. Jiao, *Chem. Rev.* **2014**, *114*, 8613–8661; s) A. J. Hickman, M. S. Sanford, *Nature* **2012**, *484*, 177–185; t) C. Sambri, D. Schönbauer, R. Blicke, T. Dao-Huy, G. Pototschnig, P. Schaaf, T. Wiesinger, M. F. Zia, J. Wencel-Delord, T. Besset, B. U. W. Maes, M. Schnürch, *Chem. Soc. Rev.* **2018**, *47*, 6603–6743.
- [43] a) P. Xiong, H.-C. Xu, *Acc. Chem. Res.* **2019**, *52*, 3339–3350; b) T. H. Meyer, L. H. Finger, P. Gandeepan, L. Ackermann, *New Trends Chem. Teach.* **2019**, *1*, 63–76; c) Q.-L. Yang, P. Fang, T.-S. Mei, *Chin. J. Chem.* **2018**, *36*, 338–352; d) S. Tang, Y. Liu, A. Lei, *Chem* **2018**, *4*, 27–45; e) N. Saueremann, T. H. Meyer, Y. Qiu, L. Ackermann, *ACS Catal.* **2018**, *8*, 7086–7103; f) N. Saueremann, T. H. Meyer, L. Ackermann, *Chem. Eur. J.* **2018**, *24*, 16209–16217; g) S. Möhle, M. Zirbes, E. Rodrigo, T. Gieshoff, A. Wiebe, S. R. Waldvogel, *Angew. Chem. Int. Ed.* **2018**, *57*, 6018–6041; *Angew. Chem.* **2018**, *130*, 6124–6149; h) C. Ma, P. Fang, T.-S. Mei, *ACS Catal.* **2018**, *8*, 7179–7189; i) M. D. Kärkäs, *Chem. Soc. Rev.* **2018**, *47*, 5786–5865; j) R. Feng, J. A. Smith, K. D. Moeller, *Acc. Chem. Res.* **2017**, *50*, 2346–2352.
- [44] a) A. Shrestha, M. Lee, A. L. Dunn, M. S. Sanford, *Org. Lett.* **2018**, *20*, 204–207; b) Q.-L. Yang, Y.-Q. Li, C. Ma, P. Fang, X.-J. Zhang, T.-S. Mei, *J. Am. Chem. Soc.* **2017**, *139*, 3293–3298; c) C. Ma, C.-Q. Zhao, Y.-Q. Li, L.-P. Zhang, X.-T. Xu, K. Zhang, T.-S. Mei, *Chem. Commun.* **2017**, *53*, 12189–12192; d) Y.-Q. Li, Q.-L. Yang, P. Fang, T.-S. Mei, D. Zhang, *Org. Lett.* **2017**, *19*, 2905–2908; e) F. Saito, H. Aiso, T. Kochi, F. Kakiuchi, *Organometallics* **2014**, *33*, 6704–6707; f) H. Aiso, T. Kochi, H. Mutsutani, T. Tanabe, S. Nishiyama, F. Kakiuchi, *J. Org. Chem.* **2012**, *77*, 7718–7724; g) C. Amatore, C. Cammoun, A. Jutand, *Adv. Synth. Catal.* **2007**, *349*, 292–296.
- [45] a) Z.-Q. Wang, C. Hou, Y.-F. Zhong, Y.-X. Lu, Z.-Y. Mo, Y.-M. Pan, H.-T. Tang, *Org. Lett.* **2019**, *21*, 9841–9845; b) M.-J. Luo, M. Hu, R.-J. Song, D.-L. He, J.-H. Li, *Chem. Commun.* **2019**, *55*, 1124–1127; c) F. Xu, Y.-J. Li, C. Huang, H.-C. Xu, *ACS Catal.* **2018**, *8*, 3820–3824; d) Y. Qiu, C. Tian, L. Massignan, T. Rogge, L. Ackermann, *Angew. Chem. Int. Ed.* **2018**, *57*, 5818–5822; *Angew. Chem.* **2018**, *130*, 5920–5924; e) R. Mei, J. Koeller, L. Ackermann, *Chem. Commun.* **2018**, *54*, 12879–12882.
- [46] a) Z.-J. Wu, F. Su, W. Lin, J. Song, T.-B. Wen, H.-J. Zhang, H.-C. Xu, *Angew. Chem. Int. Ed.* **2019**, *58*, 16770–16774; *Angew. Chem.* **2019**, *131*, 16926–16930; b) Y. Qiu, A. Scheremetjew, L. Ackermann, *J. Am. Chem. Soc.* **2019**, *141*, 2731–2738; c) W.-J. Kong, L. H. Finger, A. M. Messinis, R. Kuniyil, J. C. A. Oliveira, L. Ackermann, *J. Am. Chem. Soc.* **2019**, *141*, 17198–17206; d) Y. Qiu, W.-J. Kong, J. Struwe, N. Saueremann, T. Rogge, A. Scheremetjew, L. Ackermann, *Angew. Chem. Int. Ed.* **2018**, *57*, 5828–5832; *Angew. Chem.* **2018**, *130*, 5930–5934.
- [47] a) Q.-L. Yang, Y.-K. Xing, X.-Y. Wang, H.-X. Ma, X.-J. Weng, X. Yang, H.-M. Guo, T.-S. Mei, *J. Am. Chem. Soc.* **2019**, *141*, 18970–18976; b) Y. Qiu, M. Stangier, T. H. Meyer, J. C. A. Oliveira, L. Ackermann, *Angew. Chem. Int. Ed.* **2018**, *57*, 14179–14183; *Angew. Chem.* **2018**, *130*, 14375–14379.
- [48] a) P. Gandeepan, T. Müller, D. Zell, G. Cera, S. Warratz, L. Ackermann, *Chem. Rev.* **2019**, *119*, 2192–2452; b) J. Loup, U. Dhawa, F. Pescioli, J. Wencel-Delord, L. Ackermann, *Angew. Chem. Int. Ed.* **2019**, *58*, 12803–12818; *Angew. Chem.* **2019**, *131*, 12934–12949.
- [49] a) R. Mei, X. Fang, L. He, J. Sun, L. Zou, W. Ma, L. Ackermann, *Chem. Commun.* **2020**, *56*, 1393–1396; b) C. Tian, U. Dhawa, J. Struwe, L. Ackermann, *Chin. J. Chem.* **2019**, *37*, 552–556; c) R. Mei, W. Ma, Y. Zhang, X. Guo, L. Ackermann, *Org. Lett.* **2019**, *21*, 6534–6538; d) L. Zeng, H. Li, S. Tang, X. Gao, Y. Deng, G. Zhang, C.-W. Pao, J.-L. Chen, J.-F. Lee, A. Lei, *ACS Catal.* **2018**, *8*, 5448–5453; e) C. Tian, L. Massignan, T. H. Meyer, L. Ackermann, *Angew. Chem. Int. Ed.* **2018**, *57*, 2383–2387; *Angew. Chem.* **2018**, *130*, 2407–2411; f) S. Tang, D. Wang, Y. Liu, L. Zeng, A. Lei, *Nat. Commun.* **2018**, *9*, 798; g) N. Saueremann, R. Mei, L. Ackermann, *Angew. Chem. Int. Ed.* **2018**, *57*, 5090–5094; *Angew. Chem.* **2018**, *130*, 5184–5188; h) T. H. Meyer, J. C. A. Oliveira, S. C. Sau, N. W. J. Ang, L. Ackermann, *ACS Catal.* **2018**, *8*, 9140–9147; i) R. Mei, N. Saueremann, J. C. A. Oliveira, L. Ackermann, *J. Am. Chem. Soc.* **2018**, *140*, 7913–7921; j) X. Gao, P. Wang, L. Zeng, S. Tang, A. Lei, *J. Am. Chem. Soc.* **2018**, *140*, 4195–4199; k) N. Saueremann, T. H. Meyer, C. Tian, L. Ackermann, *J. Am. Chem. Soc.* **2017**, *139*, 18452–18455.
- [50] C. Zhu, M. Stangier, J. C. A. Oliveira, L. Massignan, L. Ackermann, *Chem. Eur. J.* **2019**, *25*, 16382–16389.
- [51] a) C. Tian, U. Dhawa, A. Scheremetjew, L. Ackermann, *ACS Catal.* **2019**, *9*, 7690–7696; b) S. Kathiravan, S. Suriyanarayanan, I. A. Nicholls, *Org. Lett.* **2019**, *21*, 1968–1972; c) Q.-L. Yang, X.-Y. Wang, J.-Y. Lu, L.-P. Zhang, P. Fang, T.-S. Mei, *J. Am. Chem. Soc.* **2018**, *140*, 11487–11494.
- [52] Q. Zhang, X. Chang, L. Peng, C. Guo, *Angew. Chem. Int. Ed.* **2019**, *58*, 6999–7003; *Angew. Chem.* **2019**, *131*, 7073–7077.
- [53] a) Y.-D. Wu, C.-L. Wong, K. W. K. Chan, G.-Z. Ji, X.-K. Jiang, *J. Org. Chem.* **1996**, *61*, 746–750; b) F. G. Bordwell, J. A. Harrelson Jr, *Can. J. Chem.* **1990**, *68*, 1714–1718; c) J. I. Genco, F. R. Duke, M. Griffel, L. D. Jennings, Vol. 136, *Ames Laboratory ISC Technical Reports*, **1956**.
- [54] S.-K. Zhang, R. C. Samanta, N. Saueremann, L. Ackermann, *Chem. Eur. J.* **2018**, *24*, 19166–19170.



- [55] a) O. Daugulis, J. Roane, L. D. Tran, *Acc. Chem. Res.* **2015**, *48*, 1053–1064; b) M. Corbet, F. De Campo, *Angew. Chem. Int. Ed.* **2013**, *52*, 9896–9898; *Angew. Chem.* **2013**, *125*, 10080–10082.
- [56] a) L. Ackermann, *Chem. Rev.* **2011**, *111*, 1315–1345; b) D. Lapointe, K. Fagnou, *Chem. Lett.* **2010**, *39*, 1118–1126.
- [57] E. Chong, J. W. Kampf, A. Ariafard, A. J. Canty, M. S. Sanford, *J. Am. Chem. Soc.* **2017**, *139*, 6058–6061.
- [58] a) F. Yang, K. Rauch, K. Kettelhoit, L. Ackermann, *Angew. Chem. Int. Ed.* **2014**, *53*, 11285–11288; *Angew. Chem.* **2014**, *126*, 11467–11470; b) Y. Yan, P. Feng, Q.-Z. Zheng, Y.-F. Liang, J.-F. Lu, Y. Cui, N. Jiao, *Angew. Chem. Int. Ed.* **2013**, *52*, 5827–5831; *Angew. Chem.* **2013**, *125*, 5939–5943; c) J. Roane, O. Daugulis, *Org. Lett.* **2013**, *15*, 5842–5845; d) F. Mo, L. J. Trzepakowski, G. Dong, *Angew. Chem. Int. Ed.* **2012**, *51*, 13075–13079; *Angew. Chem.* **2012**, *124*, 13252–13256; e) X. Chen, X.-S. Hao, C. E. Goodhue, J.-Q. Yu, *J. Am. Chem. Soc.* **2006**, *128*, 6790–6791; f) T. Yoneyama, R. H. Crabtree, *J. Mol. Catal. A* **1996**, *108*, 35–40.
- [59] a) Z.-I. Li, K.-k. Sun, C. Cai, *Org. Chem. Front.* **2019**, *6*, 637–642; b) L.-B. Zhang, X.-Q. Hao, S.-K. Zhang, Z.-J. Liu, X.-X. Zheng, J.-F. Gong, J.-L. Niu, M.-P. Song, *Angew. Chem. Int. Ed.* **2015**, *54*, 272–275; *Angew. Chem.* **2015**, *127*, 274–277; c) Z. Yin, X. Jiang, P. Sun, *J. Org. Chem.* **2013**, *78*, 10002–10007; d) S. Bhadra, C. Matheis, D. Katayev, L. J. Gooßen, *Angew. Chem. Int. Ed.* **2013**, *52*, 9279–9283; *Angew. Chem.* **2013**, *125*, 9449–9453.
- [60] S.-K. Zhang, J. Struwe, L. Hu, L. Ackermann, *Angew. Chem. Int. Ed.* **2020**, *59*, 3178–3183; *Angew. Chem.* **2020**, *132*, 3204–3209.
- [61] a) M. N. Khrizanforov, S. O. Strelakova, K. V. Kholin, V. V. Khrizanforova, M. K. Kadirov, T. V. Gryaznova, Y. H. Budnikova, *Catal. Today* **2017**, *279*, 133–141; b) L. Massignan, X. Tan, T. H. Meyer, R. Kuniyil, A. M. Messinis, L. Ackermann, *Angew. Chem. Int. Ed.* **2020**, *59*, 3184–3189; *Angew. Chem.* **2020**, *132*, 3210–3215.
- [62] T. H. Meyer, G. A. Chesnokov, L. Ackermann, *ChemSusChem* **2020**, *13*, 668–671.
- [63] R. C. Samanta, J. Struwe, L. Ackermann, *Angew. Chem. Int. Ed.* **2020**, <https://doi.org/10.1002/anie.202004958>; *Angew. Chem.* **2020**, <https://doi.org/10.1002/ange.202004958>.
- [64] U. Dhawa, C. Tian, T. Wdowik, J. C. A. Oliveira, J. Hao, L. Ackermann, *Angew. Chem. Int. Ed.* **2020**, <https://doi.org/10.1002/anie.202003826>; *Angew. Chem.* **2020**, <https://doi.org/10.1002/ange.202003826>.

---

Manuscript received: March 16, 2020

Revised manuscript received: April 22, 2020

Accepted manuscript online: April 24, 2020

Version of record online: June 25, 2020