Evolution of Earth-Abundant 3d-Metallaelectro-Catalyzed C–H Activation: From Chelation-Assistance to C–H Functionalization without Directing Groups

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Abstract: Catalyzed C–H functionalizations have emerged as a transformative platform for molecular syntheses. Despite of indisputable advances, oxidative C–H activations have been largely restricted to precious transition metals and stoichiometric amounts of chemical oxidants. In contrast, we herein discuss the potential of earth-abundant, environmentally-benign 3d transition metals for C–H activation, which has recently gained major momentum. Thus, a strategy for full resource economy has been established in our group, with green electricity as a renewable redox agent, giving valuable hydrogen as the sole byproduct under redox mediator-free conditions. In this account, we detail our accomplishments in 3d metallaelectrocatalysis towards green syntheses until March 2021.

Keywords: oxidation-induced transformations, 3d metals, selectivity control, resource economy, C–H activation, mechanism

1. Introduction
The state of contemporary organic syntheses is the result of continuous efforts over the decades which set the stage to access novel molecules in an efficient manner. In this regard, metal-catalyzed transformations have significantly contributed.[1,2] Particularly, metal-catalyzed cross-coupling reactions[3] have considerably advanced organic syntheses by unique methods for C–C and C–Het stitching.[4] However, these methods largely fail to fully address the principles of green chemistry,[5] since they require prefunctionalization of the starting materials and produce stoichiometric waste products that significantly reduce the resource economy[6] of these transformations.

In sharp contrast, C–H activation[7] has emerged as an increasingly viable tool for improved sustainability with wide applications in natural product synthesis,[8] pharmaceuticals[9] and material sciences.[10] In oxidative C–H activation strategies, a C–H bond transforms into a stable C–metal bond that subsequently reacts with another C–H or Het–H functionality to result in a cross-dehydrogenative transformation and the formation of the reduced metal species (Scheme 1). The reduced catalyst must be reoxidized to ensure catalytic turnover.[7c] Generally, excess amounts of metal salts or
hypervalent iodine reagents are required, that produce stoichiometric amounts of undesired byproducts. While, early advances were realized by precious metal catalysts, a sustainable approach should ideally involve earth-abundant 3d metal-catalyzed \(^{11,12}\) C–H activation devoid of chemical oxidants. In this regard, the oxidation by molecular oxygen \(^{13}\) is rather limited due to its fixed redox potential and major safety hazards, \(^{14}\) particularly when using flammable organic solvents.

As a potential alternative, the recently growing photoredox catalysis has been suggested for the reoxidation of reduced catalyst. \(^{15}\) Laborious syntheses of the required photocatalysts to guarantee individual redox potentials limit its application. Moreover, photoredox catalysts absorb a narrow range of the visible light spectrum and often require external light sources which are indeed powered by electricity.

In this context, the direct use of electricity is superior since the whole range of viable redox potentials could be accessed by simply using a potentiostat. Thus electricity would serve as a formal oxidant, while molecular hydrogen by cathodic proton reduction would be the sole byproduct.

In recent years, organic electrosynthesis \(^{16}\) has experienced a major renaissance, exploiting the innate reactivity encoded in the substrates. Among others, the pioneering work by Shono \(^{17}\) indicated the potential of electrochemical approaches for functionalization of the weakest bond in the molecules (Scheme 2).

However, the merger of electrochemical oxidation with transition metal catalysis was realized recently. \(^{18}\) Thus, anodic oxidation was elegantly applied for the reoxidation of hydroquinone that was used as a redox-mediator in a palladium-catalyzed, N-chelation-assisted C–H activation by Jutand. \(^{19}\) In a chelation-assisted, palladium-catalyzed electrochemical chlorination reaction, Kakiuchi has successfully exploited electricity to oxidize halide ions in situ. \(^{20}\) While representing major advances, these transformations did not involve the

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challenging direct anodic oxidation of soluble metal complexes at the heterogeneous electrode surface through the electrical bilayer, thus jeopardizing the resource-economy. In addition, precious palladium catalysts and strongly-coordinating auxiliaries reduced the sustainability of these transformations.

Within our program on resource-economical catalysis we devised concepts to merge 3d metal-catalyzed C–H activation with direct electrochemical oxidation to achieve the highest efficacy with reduced environmental impact. Green electricity serves as a redox reagent to directly reoxidize the reduced metal species on the anode surface producing molecular hydrogen as the sole byproduct. Furthermore, an oxidation-induced, facile reductive elimination has been identified as the key elementary step for metallaelectrocatalysis under exceedingly mild conditions. In this account, we summarize our endeavours on 3d metallaelectro-catalyzed C–H functionalizations.

2. Metallaelectro-Catalyzed C–H Activation

2.1. Cobaltaelectro-Catalyzed Guided C–H Activation

As a proof of concept, the merger of electrochemistry with cobalt-catalyzed C–H activation was reported by our group in 2017. Thus, the study featured direct C–H oxygenation of aryl 1 and alkylaryl amides 2 bearing pyridine N-oxide (PyO) with various primary alcohols 3 using catalytic amounts of earth-abundant and inexpensive Co(OAc)₂·4H₂O at ambient temperature, under constant current electrolysis (CCE) (Scheme 3). Molecular hydrogen was produced as the sole byproduct, thereby further enhancing the sustainability of the C–H activation. Notably, the electrooxidative C–H oxygenation did not require any redox mediator. Indeed, this study turned out to be the first example for 3d transition metal-electro-catalyzed C–H activation. In a subsequent report, we used carboxylic acids as the oxygen source in a cobalt-catalyzed C–H oxygenation reaction, guided by 8-aminoquinoline (Q). In order to understand the cooperative action of electricity and cobalt catalysis for C–H activations, cyclometalated cobalt (III) intermediates were independently synthesized by applying constant potential electrolysis (CPE) and detailed mechanistic studies were performed (Scheme 4). Cyclic voltammetry experiments at low temperatures showed a reversible redox event that could account for the generation of a transient high-valent cobalt(IV) intermediate. Importantly, these cobalt(III) complexes failed to deliver the desired oxygenation products 4 when they were treated with the corresponding alcohols, unless electricity was applied (Scheme 5). This observation directly refers to the intermediates.

Scheme 3. Cobaltaelectro-catalyzed C–H oxygenation of aryl 1 and alkylaryl amides 2.

Scheme 4. a) Synthesis of cobalta(III) intermediate [Co(III)-6]; b) Cyclic voltammograms of cobaltacycles [Co(III)]-6 in MeOH (3.5 mM) at different scan rates. The voltammograms were recorded in 0.1 M [n-Bu₄N⁺][PF₆⁻] at 273 K.

Scheme 5. Stoichiometric experiments with [Co(III)-6] for C–O formation.
acy of the cobalt(IV) complex in the C–H oxygenation reaction. Based on detailed mechanistic studies we hence proposed a plausible catalytic cycle involving a cobalt(II/III/IV) manifold (Scheme 6). Initially, the cobalt(II) precatalyst is converted to the catalytically relevant cobalt(III) by anodic oxidation and a subsequent chelation-assisted C–H activation forms the cyclo- metalated cobalt(III) complex 6. Then ligand exchange with the alcohol and a subsequent anodic oxidation generates the cobalt(IV) intermediate 7. A facile C–O bond forming reductive elimination gives cobalt(II) intermediate 8 which releases the product 4 upon substrate coordination and finally the catalytically competent cobalt(III) is regenerated by anodic oxidation. This proposed oxidation-induced reductive elimination was further validated by detailed cyclic voltammetry experiments. In addition to these mechanistic experiments, the thermodynamically viable oxidation of cobalt(III) to cobalt(IV) was further supported by DFT calculations at the PBE0-D3(BJ)/def2-TZVP+SMD(MeOH)//PBE0-D3(BJ)/def2-SVP level of theory.

The versatility of cobaltaelectro-catalyzed C–H activations was substantiated in various enabling, yet challenging transformations. Thus, an intermolecular C–N bond formation strategy was developed in our laboratories (Scheme 7).\textsuperscript{25} Differently decorated benzamides 1, were selectively transformed into the ortho-aminated products 11 using various cyclic secondary amines 10. The biomass-derived γ-valeralactone (GVL) was employed as a sustainable reaction medium and the direct electrocatalysis was again devoid of any redox mediators. The sole byproduct formed in this reaction was molecular hydrogen, which was confirmed by headspace gas chromatography analysis. A related C–H amination was realized using 8-aminoquinoline (Q) as a bidentate directing group by Lei group.\textsuperscript{26}

A cobalt-catalyzed C–H allylation was realized in an electrochemical setup, using a biomass-derived solvent as a sustainable reaction medium avoiding stoichiometric chemical oxidants (Scheme 8).\textsuperscript{27} The approach provided access to the allylation products 14 with nonactivated olefins 13 in a cross-dehydrogenative coupling, while redox mediators were again not mandatory.\textsuperscript{28}

The potential of cobaltaelectrocatalysis was further demonstrated in the synthesis of biologically relevant isoquinolones 16 and pyridones 17 from the corresponding aryl and alkenyl amides derived from pyridine N-oxide in a C–H/N–H activation reaction (Scheme 9).\textsuperscript{29} The transformation proved viable under exceedingly mild reaction conditions at ambient temperature in a water-based solvent mixture that displayed ample scope with high yields.

This redox mediator-free C–H/N–H annulation was also achieved in glycerol as a biomass-derived reaction medium using solar or wind power as the renewable energy source, further substantiating the green nature of sustainable C–H activation (Scheme 10).\textsuperscript{30}
To shed light into the mechanism of this C–H/N–H annulation, competition experiments, kinetic-isotope-effect (KIE) measurement and CV studies were performed. Based on our mechanistic findings, a plausible reaction mechanism was proposed that follows a plausible cobalt(II/III/I) manifold (Scheme 9). A chelation-assisted C–H activation on the anodically generated cobalt(III) species delivers the cyclometalated cobalt(III) intermediate 18. Next, the alkyne insertion forms intermediate 19. A subsequent C–N bond forming reductive elimination releases the desired products 16 or 17 and the catalytically active cobalt(III) complex is regenerated by anodic oxidation.

Subsequently, the cobaltaelectro-catalyzed C–H/N–H annulation was shown to be viable for allenes (Scheme 11). Thus, differently substituted allenes 20 or 21 were annulated by various benzamides 1 in an undivided cell setup under exceedingly mild reaction conditions to deliver the corresponding isoquinolones 22. Apart from terminal allenes 20, more challenging internal allenes 21 were also effective substrates to deliver the isoquinolones 23 with exo-methylene functionalities. Later, the redox mediator-free transformation was also achieved in a green reaction medium using biomass-derived glycerol and water as solvent. Cobaltaelectro-catalyzed alkyne annulation was later likewise achieved as well, applying the 8-aminoquinoline amide or sulfonamide as complementary chelating groups by the Lei group.

The cobalt-catalyzed electrochemical C–H activation was predominantly achieved with pyridine N-oxide or 8-aminoquinoline amides. The removal of those exogenous directing groups is not trivial. To circumvent this obstacle, we first applied pyridinebenzhydrazides in a cobalt-catalyzed electrochemical C–H/N–H annulation (Scheme 12). Notably, even internal alkynes 26 underwent the desired C–H/N–H annulation efficiently with diversely decorated pyridinebenzhydrazides 25 to deliver the desired products 27 in high yields. High levels of regioselectivities were observed in the case of unsymmetrically substituted alkynes. On a different note, we could remove the hydrazide group electrochemically with catalytic amounts of samarium diiodide.
Likewise, dialkynes\(^\text{[35]}\) 29 and allenes\(^\text{[36]}\) 21 were shown to be viable in the cobalt-catalyzed electrochemical C–H/N–H annihilation with pyridinehydrazide as the directing group (Scheme 13) and the corresponding annihilation products 30 and 31 were obtained in high yields.

To further demonstrate the robustness of the electro-removable pyridinehydrazides, our team extended the cobaltaelectrocatalysis to a [4 + 1] annihilation with isocyanides 32 (Scheme 14).\(^\text{[37]}\) In addition, phthalimide derivatives 34 were also accessed from benzhydrazides 25 using carbon monoxide (1 atm) at 23°C under a cobalt catalysis regime. A similar approach was concurrently disclosed by Lei, albeit with 8-aminoquinoline amides.\(^\text{[38]}\)

### 2.2. Nickelaelectro-catalyzed Guided C–H Activation

Due to cost effectiveness and trace metal impurity allowance, nickel has frequently been considered as an alternative for precious palladium catalysts in molecular syntheses. As a consequence, during the past decade, the field of C–H activation with nickel catalysts\(^\text{[11]}\) has gained major momentum.

The first example of nickelaelectro-catalyzed C–N formation through organometallic C–H activation was realized by our research group in 2018.\(^\text{[39]}\) Thus, devised an ortho-selective C–H amination of benzamides 12 with secondary amines 10 under electrochemical conditions using commercially available Ni(DME)Cl\(_2\) in an undivided cell setup (Scheme 15). Notably, under these conditions, acyclic amines 10-that were unreactive under cobalt catalysis-were efficiently converted. To gain insights into the modus operandi, cyclic voltammetry was performed for Ni(DME)Cl\(_2\) in the presence of substrate 12 and NaOPiv in DMA. These findings were suggestive of a facile oxidation-induced reductive elimination.

The power of nickelaelectrocatalysis was manifested in a C–O forming reaction using challenging secondary alcohols, which was not viable with other chemical or electrochemical methods.\(^\text{[40]}\) Thus, the C–O formation was conveniently accomplished with commercially available Ni(DME)Cl\(_2\) as the catalyst in an undivided electrochemical setup with the
assistance of 6-methyl 8-aminoquinoline (MQ) auxiliary (Scheme 16). The approach was compatible with a wide variety of secondary alcohols, including naturally occurring cholesterol, menthol and β-estradiol, to deliver the alkoxylation products 41 in good to excellent yields. Detailed mechanistic studies in terms of experiments, kinetics and DFT calculations were performed to understand the catalyst’s mode of action. For this purpose, a cyclometalated nickel(III) complex 42 was synthesized. The complex was found to be catalytically active under electrochemical conditions, which was in line with an oxidation-induced reductive elimination. Moreover, CV studies were in good agreement with an oxidation-induced reductive elimination. To further validate the reaction mechanism, DFT calculations revealed the non-innocent nature of the quinoline substrate that facilitates the reductive elimination from a higher oxidation state.

2.3. Copper-Catalyzed Electrochemical Directed ortho-C–H/N–H Activation

After successful demonstration of electrochemical C–H activation employing cobalt and nickel catalysis, environmentally-benign copper catalysis was realized in an annulation of benzamides with alkynes (Scheme 17). In sharp contrast to the cobalt electrocatalysis (vide supra),[29] [4+1] annulation products 44 were obtained.[41] Importantly, alkyne carboxylic acids 43 were also viable to undergo this reaction by C–C cleavage. The mechanistic studies revealed that the ortho-alkynylation product 47 is initially formed under the electrocatalytic conditions. The subsequent cyclization takes place under thermal conditions to deliver the [4+1] annulation product. Copper-catalyzed electrochemical C–N formation for activated anilides was realized by Mei by the assistance of a pyridine amide directing group.[42]

2.4. Iron-Catalyzed Electrochemical C–H Arylation

Being the most earth-abundant transition metal, along with the lowest toxicity and lowest price, iron catalysts have rather limited applications in C–H activation as they had heavily relied on costly chemical oxidants, such as dichloroisobutane (DCIB).[11] Our research group reported a first strategy for iron-catalyzed C–H arylation using electricity in lieu of chemical oxidants, with molecular hydrogen as the sole stoichiometric byproduct (Scheme 18).[13] Thus, a variety of triazolylidimethylmethyl (TAM) amides 48 were efficiently converted to the ortho-arylation products 50 using various nucleophiles 49 under redox mediator-free conditions. Detailed mechanistic studies by experiments and DFT calculations were performed. These studies revealed that initially a ligand-to-ligand hydrogen transfer (LLHT) C–H activation occurs. Then, ligand exchange takes place and finally an SET event is crucial for a fast reductive elimination.
2.5. Manganese-electro-Catalyzed C–H Activation

The electrochemical C–H arylation was likewise realized by inexpensive, non-toxic manganese catalysis (Scheme 19).[43]

Thus, the manganese-electrocatalysis strategy enabled the arylation of picolinamide[54] using 4-methoxyphenyl magnesium bromide[49] in an undivided electrochemical cell setup, with commercially available MnCl₂ as the catalyst. Notably, a weakly coordinating amide hence served as the orienting group to deliver the product[55] in good yield.

3. Electrochemical C–H Functionalization devoid of Directing Group

In recent years merger of electrochemistry with 3d transition metal-catalyzed C(sp³)–H activations have been well established for chelation-assisted C(sp³)–H functionalizations. Tailored-substrate manipulation by installation and removal of the orienting entity jeopardizes the step-economy in direct C–H activations. In a recent report, we have achieved an electrochemical palladium-catalyzed atroposelective trans-formation,[44] with the aid of a transient directing group strategy.[45] Moreover, electrocatalysis with weakly coordinating groups have been largely devised using precious ruthenium,[46] rhodium,[47] iridium catalysis.[48] In contrast, undirected C–H activations provide versatile opportunities in catalyst-controlled selectivity with improved resource economy.

Despite examples on metallaelectro-catalyzed C(sp²)–H activations, the merger of electrochemistry with transition metal-catalyzed C(sp³)–H activation remains underdeveloped, with an acetoxylation of C(sp³)–H bonds being realized with precious palladium catalysts and strong N-directing groups.[49]

Undirected 3d transition metallaelectro-catalyzed C(sp³)–H functionalization remained until very recently unfortunately elusive.

In contrast to C(sp³)–H bonds, C(sp³)–H bonds represents low reactivity towards organometallic C–H activations.[50] This is largely due to their low acidity and lack of proximal available orbitals to readily interact with metal orbitals, unlike C(sp³)–H bonds that possess vacant low-energy orbitals and filled high energy orbitals for favorable interactions. Electrochemical C–O formations via C(sp³)–H functionalizations have precedents by applying biomimetic iron-oxo complexes.[51] Whereas, similar transformations for direct C–N formation are rare. Recently, our team has devised a metallaelectro-catalyzed C(sp³)–H functionalization under a manganese catalysis regime. Thus, C(sp³)–H azidations were realized using a readily available manganese(III) complex[58] and NaN₃ as the azide source (Scheme 20).[52] This concept does neither require a redox mediator, nor a directing group for step-and atom-economical syntheses. Non-activated C(sp³)–H bonds were likewise converted to the corresponding azidation products[57] in good to excellent yields.

The corresponding manganese(III) azide[60] and manganese(IV) diazide[61] complexes were independently synthesized and the reaction mechanism was investigated by means of cyclic voltammetry, UV-vis absorption studies and control experiments.[53] Cyclic voltammogram of the isolated diazido manganese(IV) complex[61] and the manganese(III)chloro complex[58] in the presence of tetrabutylammonium azide.
revealed identical redox events, being suggestive of the intermediacy of a manganese(IV) species in this manganese-electro-catalyzed C–H azidation reaction (Scheme 21). In addition, the UV-Vis spectrum of a solution of the manganese(III) chloride complex 58 and NaN₃ that was electrolyzed by constant current electrolysis at 8.0 mA for 30 min showed absorption at 440 nm, which is in line with the absorption of the independently prepared manganese(IV) diazido complex 61.

Based on our studies, a manganese(III/IV) manifold was proposed for this C(sp³)–H azidation (Scheme 22). A facile ligand exchange by the azide ion forms the manganese(III)-azide complex 62, which then undergoes anodic oxidation to form manganese(IV) diazido complex 63. This high-valent manganese(IV) complex is responsible for the hydrogen atom transfer (HAT) process from 56 to generate the corresponding alkyl radical. Next, subsequent manganese-catalyzed azide radical transfer delivers the azidation product 57. A complementary photo-induced electro-azidation was concurrently realized, albeit under photo irradiation with blue light.[53]

4. Conclusion

Our group initially realized the merger of electrochemistry with earth-abundant 3d transition metal-catalyzed C–H activation. As a proof of concept, C–H oxygenations were hence realized by environmentally-benign cobaltaelectrocatalysis, employing electricity as the green redox reagent with molecular hydrogen as the sole byproduct. Key to success was a novel mechanistic scenario – namely oxidation-induced reductive elimination-to lower the activation barrier by electrochemistry. Subsequently, the cobaltaelectrocatalysis was successfully implemented to C–N formation, C–H/N–H annulations with alkynes, allenes, CO and isonitriles. The versatility of the metallaelectrocatalysis strategy was proven viable for nickel catalysis in C–N formation and C–O formation with more challenging secondary alcohols, copper catalysis in [4 + 1]-alkyne annulation and iron and manganese catalysis for C–H arylation reactions. These transformations proceeded via a chelation-assisted C–H activations that require a functionality to orient the C–H activation and were mostly limited to C(sp³)–H activation. In contrast, a catalyst-controlled undirected C–H functionalization was devised to improve the efficacy of the C–H activation strategy. In this regard, we have demonstrated 3d metallaelectrocatalysis for C(sp³)–H azidations of aliphatic groups devoid of directing group. Further future suitable catalyst design will provide a new dimension to regio- and stereoselective bond functionalizations. In addition to oxidative transformations, metallaelectrocatalysis has also benefitted net redox-neutral, paired cross-couplings,[54] as well as redox-neutral C–H activation.[55]

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Electrochemical C–H activation by 3d transition metals, under redox mediator-free condition has enabled ideal resource-economy. Exceedingly mild reaction conditions have largely been achieved by oxidation-induced reductive elimination.