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# From Bench to Plant: An Opportunity for Transition Metal Paired Electrocatalysis

Julien C. Vantourout<sup>\*1</sup>

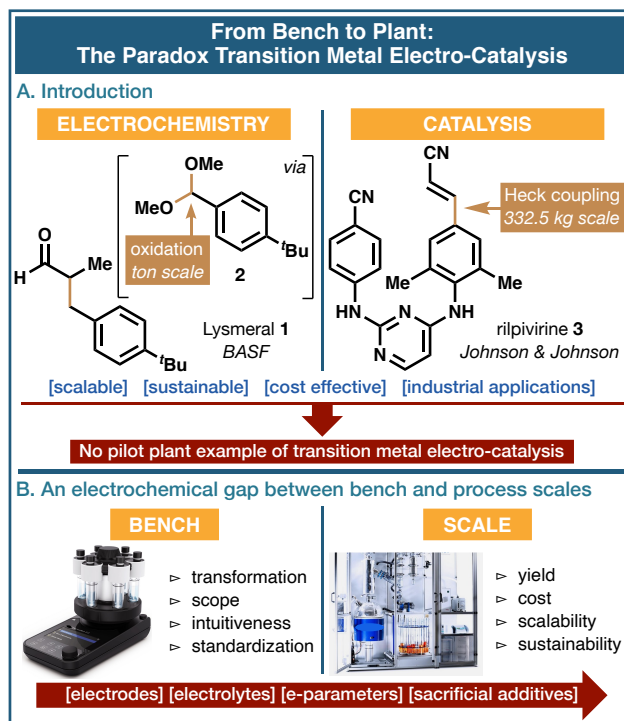
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**ABSTRACT:** Electrochemistry and transition metal catalysis are gigantic fields from where several methodologies have found applications in both medicinal and process chemistry. Surprisingly, the transfer from bench to plant is much more difficult for transition metal electrocatalysis. While a plethora of those transformations have emerged in the landscape of medicinal chemistry since more than 50 years, they were not further developed on larger scale. Of course, extra parameters have to be considered when running an electrocatalytic reaction, but they cannot justify the absence of transition metal electrocatalysis examples in process chemistry. This perspective aims to demonstrate that intrinsic characteristics related to the different electrocatalytic modes are responsible for the absence of such processes on large scale. It will also highlight why paired electro-catalyzed reactions have the potential to fill the gap between medicinal and process chemistry. Finally, a strategy to develop unprecedented and process oriented paired electro-catalyzed methods will be disclosed, and hopefully will motivate electro-practitioners to study challenging and applicable transformations.

**Keywords:** *Electrochemistry – Catalysis – Paired Electrolysis – Transition Metal*

## INTRODUCTION

For years, synthetic organic electrochemistry has been valued for the redox advantages it offers compared to purely chemical methods.<sup>1</sup> When it comes to manipulation of electrons, electrochemistry is certainly the easiest and most economical method to use.<sup>2</sup> However, due to misconceptions and categorization of electrochemistry as a “black box”, it took years – and the development of intuitive and standardized equipment – for the scientific community to appreciate the potential electrochemical processes can offer, especially in the context of sustainability and scalability.<sup>3</sup> Similarly, over the past 40 years, transition metal-catalyzed cross-couplings have become a mainstream, reliable and indispensable tool for carbon-carbon and carbon-heteroatom bond formation.<sup>4</sup> These reactions allow for the synthesis of complex pharmaceutical ingredients including several marketed drugs or drug candidates under development in laboratories around the world.<sup>5</sup>

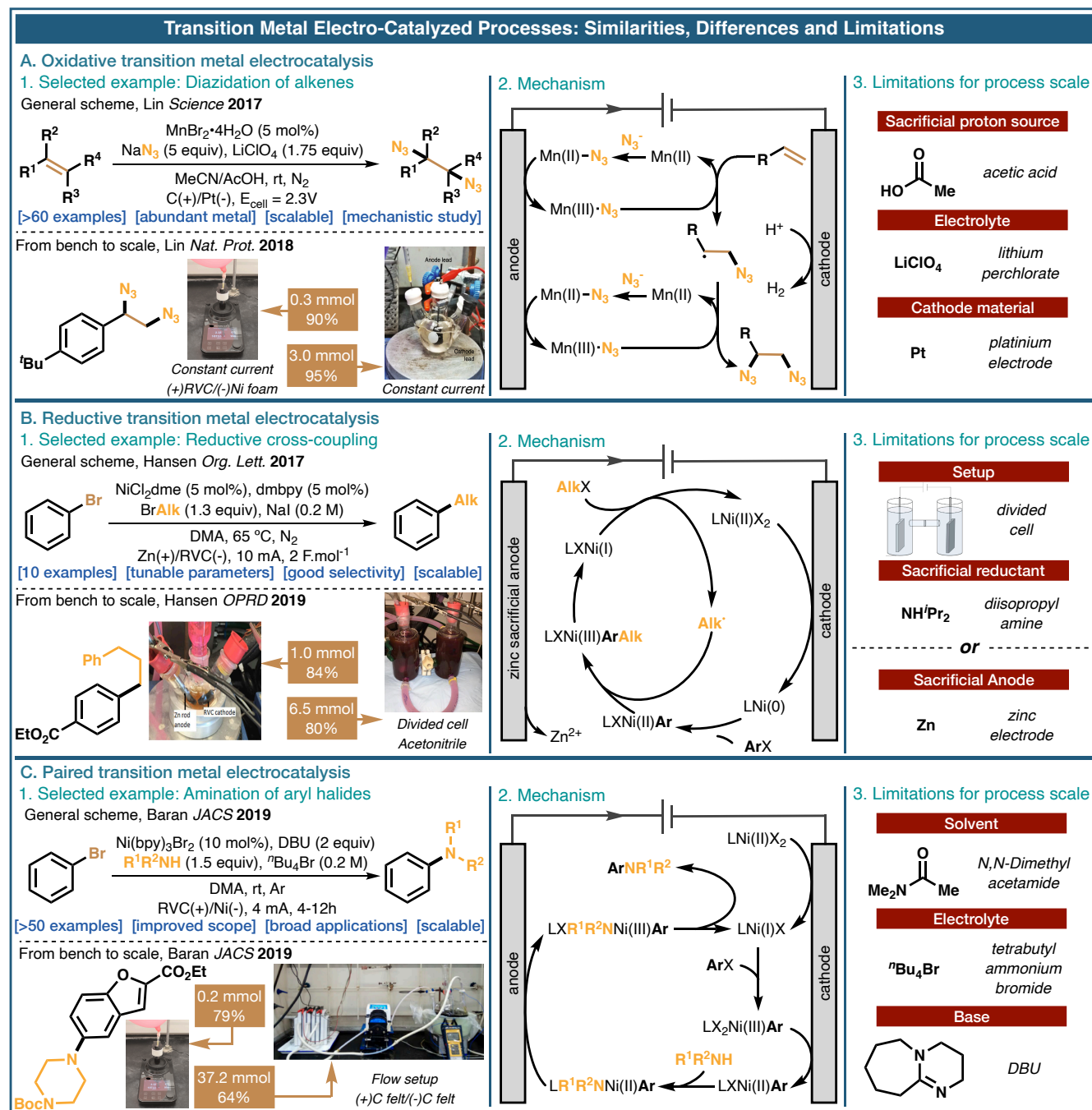


**FIGURE 1.** From bench to plant: The paradox of transition metal electrocatalysis. (A) Introduction (B) An electrochemical gap between bench and process scales.

Both electrochemical and transition metal-catalyzed processes have been employed in the synthesis of important materials and are usually run on process scales ranging from kilograms to thousands of metric tons. The BASF process to synthesize Lysmeral 1, a prevalent fragrance molecule, is one of the most famous examples that perfectly demonstrates the scalability of electrochemical processes (Figure 1A).<sup>6</sup> In the synthetic route, key intermediate 2 is obtained using an over 10,000 ton per year scale double anodic oxidation of 4-tert-butyl toluene. From a transition metal catalysis perspective, many processes can provide kilogram quantities of pharmaceuticals (Figure 1A). As an example, Johnson and Johnson developed a 332.5 kg scale Heck reaction in the preparation of rilpivirine 3, a potent non-nucleoside reversed transcriptase inhibitor developed as part of their HIV program.<sup>7</sup>

Despite those striking examples, the development and the use of transition metal electrocatalysis in the pharmaceutical and agrochemical industries is rare and even no reported examples could be identified. This is certainly not due to a lack of motivation to develop such methods but mainly due to the difficulty to transfer them from bench to process scale. Indeed, out of the many useful transition metal electro-catalyzed methods that flourishes in the literature, none have been applied so far in a process chemistry context. This can be explained by the number of parameters one has to consider when transposing an electrochemical reaction from bench to

process scale (Figure 1B). In addition to usual parameters such as yield, cost, scalability and sustainability, electrochemistry adds on several variables (electrode materials, electrolyte, sacrificial additives, current density...) which can be seen as a serious impediment compared to classic redox processes (Figure 1B). However, the recent enthusiasm and interest for synthetic organic electrochemistry provides the scientific community with the unique opportunity to develop transition metal electro-catalyzed methodologies that could be more easily transferred from bench to plant.



**FIGURE 2.** Transition metal electro-catalyzed processes: Similarities, differences and limitations. (A) Oxidative transition metal electrocatalysis. (B) Reductive transition metal electrocatalysis. (C) Transition metal paired electrocatalysis.

This perspective aims to describe the similarities and distinctions between the different transition metal electro-catalyzed processes. It will also highlight their limitations when transitioning to process chemistry applications. Finally, it will attempt to demonstrate that paired electrolysis in addition to offering a smoother transition from bench to scale compared to purely oxidative or reductive methods, is also the perfect platform for reaction discovery.

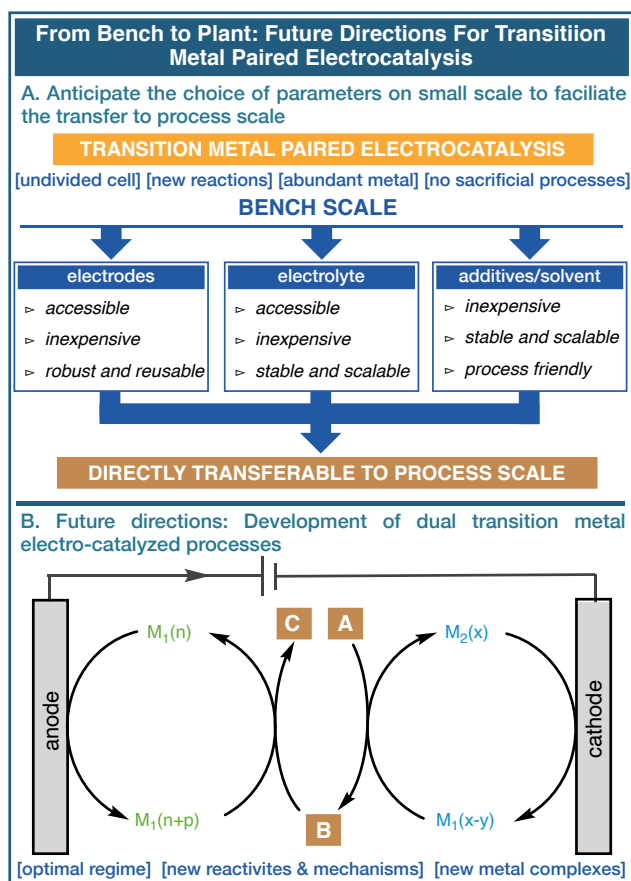
## TRANSITION METAL ELECTRO-CATALYZED PROCESSES: SIMILARITIES, DISTINCTIONS AND LIMITATIONS

Transition metals can lend or withdraw electrons from a reagent depending on the nature of the reaction which makes them excellent catalysts. They have the ability to access and interchange variety of oxidation states, to form complexes with the reagents and to be a good source of electrons making them highly useful in the context of electrochemical transformations. Once those inherent properties and subtleties associated to them are controlled, transition metal electro-catalyzed reactions can mediate oxidative or reductive pathways with better selectivity and functional group tolerance than pure electrochemical processes.<sup>8</sup> In addition, transition metal can activate challenging substrates or bonds (e.g., C-H activation, oxidative addition...) increasing the landscape of electrochemical reactions one could envision.<sup>9</sup>

Transition metal electro-catalyzed processes can be divided into three categories: oxidative, reductive and paired (Figure 2).<sup>1</sup> Those processes share common features but own separate characteristics allowing the practitioner to access the desired reactivity. They also suffer from specific limitations with regards to their application in process chemistry. The following examples were selected to describe the key features of the different transition metal electro-catalyzed regimens and how these characteristics can impact the transfer from bench to plant. Other examples could have been chosen and are cited in the reference section.<sup>10</sup>

**Oxidative transition metal electrocatalysis (Figure 2A).** Recently, Lin and co-workers reported a mild oxidative manganese electro-catalyzed diazidation of alkenes using an undivided cell, equipped with a RVC anode and a platinum cathode, at a constant potential of 2.3 volts (Figure 2A.1).<sup>11</sup> A variety of useful vicinal diazide compounds that can be converted to the corresponding diamines after simple palladium-catalyzed reduction were obtained in moderate to high yields. The authors reported more than 60 examples including terminal, 1,1- and 1,2-disubstituted, trisubstituted, and tetrasubstituted alkenes. Substrates bearing alcohol, aldehyde, enolizable ketone, carboxylic acid, amine, sulfide, and alkyne moieties were tolerated under the reaction conditions. It was also noted that functional groups predisposed to nucleophilic displacement by  $N_3^-$ , such as, ester, alkyl chloride, epoxide and alkyl bromide, were also compatible, likely due to the use of acetic acid as a co-solvent, which attenuates the nucleophilicity of the azide anion. The unanticipated broad substrate scope of the

method motivated the authors to start investigating its mechanism (Figure 2A.2). The combination of radical clock experiments with cyclic voltammetric and spectrophotometric studies confirmed the Mn-assisted dual radical group transfer to the alkene. In this purely oxidative process the Mn(II)- $N_3$  is anodically oxidized to afford a Mn(III)- $N_3$  species able to first induce a C-C  $\pi$ -bond homolysis. The resulting radical then reacts with another Mn(III)- $N_3$  to afford the desired vicinal diazide. To close the electrochemical circuit the proton reduction of acetic acid occurs at the cathode. Following this first report, the Lin group decided to adapt their electro-catalytic process to a standardized electrochemistry kit – ElectraSyn (Figure 2A.1).<sup>12</sup> In this new protocol, constant potential was switched to constant current and the platinum cathode was replaced by nickel foam providing a more accessible protocol. The reactions were conducted on a 0.3 mmol scale and afforded compounds such as **4** in excellent yields. For larger scale experiments (3 mmol), a 3-neck round bottom



**FIGURE 3.** From bench to plant: Future directions for transition metal paired electrocatalysis. (A) Anticipate the choice of parameters to facilitate the transfer to process scale. (B) Development of dual transition metal electro-catalyzed processes.

flask was equipped with RVC (anode) and platinum (cathode) electrodes and a constant potential of 2.3V was applied. These changes point out the complications one can encounter when trying to scale an electrochemical reaction. In addition, from a process chemistry

perspective, the use of lithium perchlorate, platinum electrode, and sacrificial acetic acid is an extra barrier that would limit the uptake of this reaction on a larger scale (even if these parameters could be optimized). Reductive transition metal electrocatalysis (Figure 2B). In 2017, Hansen and co-workers disclosed the electrochemical nickel-catalyzed reductive coupling between aryl bromides and alkyl bromides (Figure 2B.1).<sup>13</sup> They observed that the control of the reduction rate via the current passed is a critical feature of the reaction to achieve decent conversion. After optimization of the reaction parameters, the best yields were obtained when a RVC cathode was paired with a sacrificial zinc anode in an undivided cell at a constant current of 10 mA. The scope contains 10 examples bearing important functional groups including amide, ketone, trifluoromethyl, and protecting amines as well as heterocyclic compounds such as pyridine, pyrimidine and aza-indoles. It is worth mentioning the yields are comparable to or sometimes higher than those attained using Zn powder as the reductant demonstrating electrochemistry can broaden the applicability of nickel-catalyzed reductive cross-couplings. The proposed mechanism operates similarly to the one reported by Weix and co-workers for metal powder reductive coupling (Figure 2B.2). First, Ni(0) enters the catalytic cycle via reduction of Ni(II) at the cathode. Then, oxidative addition of the aryl bromide affords a Ni(II) species that reacts with the radical issued from the alkyl bromide after single electron transfer from Ni(I). Finally, the resulting Ni(III) species delivers the desired cross-coupled product after reductive elimination. In parallel to this reductive electro-catalytic cycle, the sacrificial zinc anode is oxidized to close the circuit. Two years after this report, the same group reported a new set of conditions that addresses the challenges associated with cross-electrochemical coupling: the use of amide solvent and the need for sacrificial anode (Figure 2B.3).<sup>14</sup> The reaction occurs in a divided cell using acetonitrile as the solvent, *N,N*-diisopropylamine as sacrificial reductant and tri-*tert*-butyl-terpyridine and di-*tert*-butyl-bipyridine as a combination of ligands affording the desired cross-coupled products in moderate to high yields. As an example, the reaction between ethyl 4-bromobenzoate and (3-bromopropyl)benzene was conducted on a 6.5 mmol scale delivering compound **5** in 80% yield. This new set of conditions is therefore more amenable to scale-up but still suffers from serious limitations such as the use of a divided cell setup<sup>15</sup> and the need for a sacrificial reductant. Transition metal paired electrocatalysis (Figure 2C). In 2019, Baran *et al.* reported an optimized set of conditions of their electrochemically driven nickel-catalyzed aryl amination, initially reported in 2017 (Figure 2C.1).<sup>16,17</sup> The reaction uses RVC (anode) and Ni-foam (cathode) electrodes in an undivided cell at room temperature under constant current conditions. An in-depth mechanistic study including several electrochemical, analytical and spectroscopic techniques highlighted the importance of the nickel/ligand ratio as well as the need for the amine coupling partner to be used in excess. Then, an increase of the amount of ligand and the addition of 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU)

as an external base afforded a much broader scope including amino acids, heteroaryl halides, nucleoside analogs, DNA, natural products, and oligopeptides. The mechanism of the reactions involves several nickel species with disparate oxidation state (Figure 2C.2). The electrocatalytic cycle starts with the reduction of Ni(II) to a Ni(I) species at the cathode. Then, the rapid oxidative addition of Ni(I) to an aryl halide affords a transient Ni(III) species that is readily reduced at the cathode resulting in a stable Ni(II) aryl intermediate. After amine coordination and deprotonation, this Ni(II) complex is oxidized at the anode generating a Ni(III) species which undergoes rapid reductive elimination to produce the desired arylamine product while regenerating the active catalyst. It is worth noting that when a reaction requires both oxidation and reduction of the catalyst, electrochemistry positions itself as the method of choice. Indeed, under paired electrolysis regime, redox events can take place separately at the anode and the cathode. From a large-scale perspective, relevant intermediate **6** for the synthesis of vilazodone – a drug recently approved by FDA for the treatment of major depressive disorder – was obtained in 64% on a 37.2 mmol scale using a flow system equipped with carbon felt electrodes.<sup>16</sup> Importantly, various reaction scales could be envisioned simply by increasing the number of frames. However, reactions components such as the amide solvent (DMA), the electrolyte (*N*-tetra-butylammonium bromide), and the base (DBU) would have to be evaluated and/or changed before being used on a pilot plant scale.

## TRANSITION METAL PAIRED ELECTRO-CATALYSIS: THE IDEAL PLATFORM FOR REACTION DISCOVERY AND PROCESS CHEMISTRY

All the aforementioned electrochemical modes have proven useful on bench scale but still suffer from foreign considerations preventing their use in process chemistry (Figure 2). Some of those drawbacks, related to chemical parameters, can be optimized to render the reaction conditions process friendly. On the other hand, the nature of the electrochemical transformation cannot be modified. A purely oxidative electrochemical process always requires the use of a sacrificial oxidant to be reduced at the cathode (most of the time a proton source), while a purely reductive electrochemical reaction necessitates a metal-based sacrificial anode or the use of a sacrificial reductant to be oxidized at the anode. Even if these parameters seem insignificant and can undoubtedly be addressed, still they represent extra constraints one has to consider when envisioning a process scale experiment. In a paired electrolysis transformation, both the anodic oxidation and the cathodic reduction are indispensable features of the reaction pathway. Therefore, no sacrificial counterpart is needed facilitating adoption and transfer to process scale.

The notion of anticipation is also important when designing, developing and optimizing a transition metal-catalyzed reaction. Recently, a lot of effort has been dedicated to the development of process friendly set of conditions where all the components are studied toward

scalability and sustainability.<sup>20</sup> In addition, several technologies such as flow chemistry have been developed to facilitate the transition from bench to plant.<sup>21</sup> The same vision could and should be applied to transition metal electro-catalyzed methods to give the practitioner more options than its current toolbox contains. Based on its aforementioned characteristics, paired electrolysis places itself as the ideal mode to investigate as the optimization will be similar to the one usually performed for a standard chemical process – judicious choice of solvent, chemical variables, and simple electrochemical parameters (electrode material and electrolyte).

Recently, several research groups started to combine electrochemistry with photoredox catalysis to achieve new transformations including transition metal paired electro-catalysis.<sup>20,21</sup> However, similarly to purely reductive or oxidative electrochemical reactions, cathodic or anodic sacrificial processes cannot be avoided. In addition, merging photoredox and electrochemistry clearly complexifies the setup and increases the finesses one will have to control. Overall, these limitations will certainly limit the uptake in process chemistry. Therefore, transition metal paired electro-catalyzed methodologies provide the scientific community with the unique opportunity to develop new transformations based on unprecedented electrochemical reaction pathways (Figure 3B). Such reactions will be aligned with future process chemistry developments. As an example, dual transition metal electrocatalysis is a field that has not been deeply investigated due to the challenges associated with such a complex system. Indeed, from a mechanistic standpoint, a metal will have to be oxidized when the other will have to be reduced. Therefore, a perfect control of both oxidation and reduction events is required to ensure successful outcome. In depth optimization, ligand screening, and mechanistic investigations including techniques such as kinetic studies, cyclic voltammetry, and UV-Vis analyses will have to be conducted to ensure the success of such an approach. Keeping in mind the notion of scalability and sustainability the use of earth abundant metal should be prioritized but will undoubtedly increase the level of difficulty.

## CONCLUSION

The fields of electrochemistry and transition metal catalysis are in constant expansion allowing for the development of diverse and useful methodologies. While the combination of these two valuable areas, transition metal electrocatalysis, has the potential to benefit both medicinal and process chemistry projects, it will have to target meaningful reactions such as key skeleton bond forming transformations. Following this idea, paired electrocatalysis seems to be the perfect match as it provides the practitioner with a unique opportunity to develop unprecedented, applicable and sustainable methods.

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## NOTES

The author declares no competing financial interest.

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