Recent Advances in Paired Electrosynthesis

Frank Marken,* Alexander J. Cresswell, and Steven D. Bull[a]

Abstract: Progress in electroorganic synthesis is linked to innovation of new synthetic reactions with impact on medicinal chemistry and drug discovery and to the desire to minimise waste and to provide energy-efficient chemical transformations for future industrial processes. Paired electrosynthetic processes that combine the use of both anode and cathode (convergent or divergent) with minimal (or without) intentionally added electrolyte or need for additional reagents are of growing interest. In this overview, recent progress in developing paired electrolytic reactions is surveyed. The discussion focuses on electrosynthesis technology with proven synthetic value for the preparation of small molecules. Reactor types are contrasted and the concept of translating light-energy driven photoredox reactions into paired electrolytic reactions is highlighted as a newly emerging trend.

Keywords: electroorganic synthesis, energy conversion, diffusion and reaction layer, atom economy, electrification

1. Introduction to Paired Electrosynthesis with Innocent/Sacrificial Reactions

Electrosynthesis offers tools to the synthetic chemist not only of relevance to the synthesis of drugs and other fine chemicals,[1] or natural products,[2] but also in processes for upgrading and transforming natural raw materials[3] such as biogenic renewable compounds.[4] Microbial bioelectrosynthesis has been developed to harness the electrocatalytic capabilities of microorganisms in electrosynthesis.[5] Electrosynthesis based on renewable energy has been recognised as providing a potentially “green” chemical processing tool,[6] provided some key conditions are met such as: (i) minimal waste production and need for energy-intensive recycling processes, (ii) high yields and time-saving, radical-based, multi-step reaction sequences, (iii) a simple experimental design without the need for specialist tools and expensive equipment,[7][8] (iv) use of low cost electrode materials (e.g. avoiding platinum), and (v) good energy efficiency.[5]

Although organic electrosynthesis has been developed and employed for a century or more,[8] there are still several deficiencies that limit the practical transformation of processes from the laboratory bench to industry scale. Now is an important point in the development of new electroorganic processes due to the need to switch from fossil to renewable resources and the associated need to restructure the chemical industry to operate with renewable electricity. Flow syntheses based on high yielding and energy-efficient transformations are especially desirable.[9]

There is considerable excitement about new electroorganic methodologies and opportunities. Siu, Fu, and Lin have suggested catalytic electrosynthesis as a new tool in “reaction discovery”.[10] Meyer et al. have highlighted four examples of cases where electrosynthesis can be seen to impact on the development of sustainable chemical technologies.[11] Organic electrosynthesis can be seen to increasingly make the jump from laboratory to industrial application, particularly when based on microreactors, flow, and based on paired processes.[12] The general principle of
adding value and achieving energy efficiency has been highlighted by Llorente et al.\textsuperscript{[13]} In recent reviews Ibanez et al.\textsuperscript{[14]} introduced a systematic approach to paired electro-synthesis process design and Wu et al.\textsuperscript{[15]} highlighted the application of paired electrochemical reactions for on-site on-demand generation of chemical reagents. The field of paired organic electrosynthesis is now in rapid development.

It is desirable to “pair” the anodic and cathodic electrode reactions in electrosynthesis.\textsuperscript{[16]} That is, anode and cathode are not separated and more complex reaction pathways including both oxidation and reduction in a multi-step reaction pathway are allowed to happen. The paired electrosynthesis approach allows a simpler reactor design and better energy efficiency. Electrode processes that are paired can be (case A) independent (e.g. when forming innocent or sacrificial side products, or when forming divergent products from one or two substrates) or (case B) coupled so that both anode and cathode contribute to the formation of the product (see Figure 1).\textsuperscript{[17]}

When employing independent electrode reactions, paired electrosynthesis can be considered “convergent” or “divergent” depending on the way products are generated. In a convergent process, one product is obtained typically from two starting materials. However, in a divergent process two useful products are obtained from a single (or multiple) starting material, such as the conversion of 5-(hydroxymethyl)furfural (HMF) to biobased monomers for polymer synthesis.\textsuperscript{[18]} When coupling anode and cathode processes, the gap between electrodes can be large (with independent diffusion layers for both electrodes) or close (with overlapping diffusion layers). Each of these cases has potential benefits or potential drawbacks in terms of reactor design and chemical complexity. Very commonly employed is case A, as the complexity of the chemical processes is limited, but some of the benefits of pairing processes can still be realised. In a recent review, Zhang and Sun have summarised work on membrane-separated reactor systems for paired organic oxidation and reduction reactions involving water.\textsuperscript{[19]} The approach can lead to reaction discovery, as seen for example for the recently reported three-component coupling reaction of benzylic halides, carbon dioxide, and N,N-dimethylformamide to yield N-methyl-N-(phenylacetoxy)-methylformamides.\textsuperscript{[20]} More desirable is case B, especially for very small gaps between anode and cathode, and for “self-supported” reactions that do not need added electrolyte (\textit{vide infra}). As a result, there is no electrolyte separation step, there is less waste, and products are potentially obtained pure.

Electroorganic reactions are based either on single electron transfer at the electrode surface to give radical intermediates (followed by homogeneous reaction steps in solution) or on heterogeneous multi-electron transfer on catalytic electrode surfaces, where interactions with the substrate material provide conditions for multi-step reaction pathways. Radical intermediates generated homogeneously in single electron transfer processes can lead to interesting reaction products.\textsuperscript{[21]} Mediated electrosyntheses, for example based on halogen reaction intermediates,\textsuperscript{[22]} allows highly reactive (and potentially dangerous) species to be generated \textit{in situ} and in low concentration. However, the complexity of reaction sequences with radical intermediates and with mediators can be considerable, and therefore simple coupling of anode and cathode processes in paired electrode reactions in these cases is often impossible. Shunt processes based on electrons transferring between cathode and anode without producing products are likely. A commonly employed approach for anodic reactions to avoid

![Figure 1. Overview of paired electrosynthesis in terms of approaches, mechanisms or types of products, electrode designs, and the emerging link to photoredox catalysis.](image-url)
interference from the cathodic process, is the sacrificial evolution of hydrogen as an “innocent” cathodic side reaction. Gaseous hydrogen is not easily oxidised for example on carbon anodes (preventing shunt processes) and therefore acceptable as an easily separable and potentially valuable side product. In work for example by Onomura and coworkers, a wide range of heterocycle synthesis protocols have been developed based on this strategy including “chiral memory effects” and for multi-functional target molecules.

Paired electrosynthesis is based on two simultaneously occurring reactions at anode and cathode combined into one overall reaction. By considering both anode and cathode process as a contribution to the synthetic transformation, problems with waste and energy recovery can be addressed. For example, Ollivier and coworkers reported a process for the C–H phosphorylation of tetrahydroisoquinolines based on a stirred reactor with a carbon anode and carbon cathode generating an iminium cation and a phosphite anion as intermediates (illustrated in Figure 2). The reaction occurs with sub-stoichiometric amounts of added electrolyte in a single compartment with yields up to 70 %. The mechanism has been proposed to involve a cation-anion cross-coupling. This type of process has many advantages linked to low concentration of intentionally added electrolyte, a simple reactor design, and good product yields, even with only modest levels of extra electricity being supplied. The hydrogen evolution reaction is employed as a convenient cathode reaction and the hydrogen side product can potentially be re-employed as an energy source (Case A).

A paired photoelectrosynthetic Minisci reaction based on hydrogen co-production was reported by Xu and coworkers, in which HCl serves a dual role as proton source (for cathodic H₂ generation) and chloride source (as hydrogen atom transfer catalyst). The power of this Minisci transformation is in the generation of a wide range of different functionalised heterocycles for drug discovery applications. A platinum cathode and carbon anode were combined in a single compartment with λ = 392 nm LED illumination (Figure 3) to give a wide range of alkylated heteroaromatics in good yields. In this process the cathode produces hydrogen as an innocent side product. At the anode, molecular chlorine is generated and subsequently homolysed by irradiation, giving highly electrophilic chlorine radicals to activate the C–H bonds of the alkane coupling partners. The simultaneous formation of two products (at anode and at cathode) is appropriate in order to simplify the overall reactor design. There could be further improvements ideal in terms of efficiently pairing the electrode processes.

Another innovative C–C coupling reaction (a catalytic asymmetric electrochemical α-arylation of cyclic β-ketocarboxyls using anodically-generated benzene intermediates) in a single compartment electrolytic cell has been developed by Li and co-workers. Anodic oxidation of the 1-aminobenzotriazole to allow benzene intermediates to be added to carboxyls with excellent levels of enantiocontrol (Case A) through use of a chiral amine catalyst. The process occurs with a platinum anode and a platinum cathode (again producing a sacrificial hydrogen side product). Cobalt acetate is suggested to stabilise the benzene reaction intermediate (Figure 4). This reaction occurs at the platinum anode but can be carried out under these conditions in a single stirred reactor compartment.

![Figure 2](image-url)
Figure 3. Schematic for the paired photoelectrosynthetic Minisci reaction based on hydrogen co-production. Reprinted with permission from [25]. Copyright (2020) Wiley.

Figure 4. Catalytic asymmetric electrochemical α-arylation of cyclic β-ketocarboxyls with anodic benzyne intermediates. Reprinted with permission from [26]. Copyright (2020) Wiley.
Methods to recover and re-use the hydrogen would further improve the energy efficiency of this process, for example by introducing tandem hydrogenation processes to employ H₂ to catalytically reduce ketone/alkene groups.

A similar hydrogen evolution strategy was reported by Lei and coworkers for decoupling anode and cathode reactions for a paired reaction in a single compartment based on heteroarene annulation reactions (see Figure 5).

The formation of a carbocation intermediate leads to clean annulation for a wider range of substrates with a platinum cathode again providing hydrogen as an innocent side product. The reaction occurs at a carbon cloth anode in organic solvent and with a small amount (typically one equivalent) of added supporting electrolyte.

The oxytrifluoromethylation of alkenes via paired electrolysis in organic-aqueous media was reported by Jud et al. The trifluoromethylation is particularly useful in medicinal and drug chemistries and the process was shown to be economic, safe, and environmentally benign. In the conversion of biomass, Chadderdon et al. have demonstrated the paired electrocatalytic oxidation and hydrogenation of 5-(hydroxymethyl)furfural to give monomers for the production of sustainable polymer products. The use of a silver catalyst in the hydrogenation process proved essential to ensure high yields. A further example for the use of sacrificial hydrogen evolution in a single compartment process was reported by Sauer and Lin. Vicinal difunctionalisation reactions of alkenes were achieved with scope for a broad range of diazido, dichloro, or trifluoro-chloro products.

These processes are proposed to be associated with an anodic reaction sequence with a Mn(III/II) redox catalyst at a graphite electrode coupled to hydrogen co-evolution at a platinum electrode (Figure 6).

The vicinal diazidised products were shown to be formed in a step-by-step reaction sequence (by investigating radical clock experiments) and good yields were observed for complex substrates with ester, amine, epoxy, or ferrocenyl substituents. Further reduction in a tandem diazidation-reduction led to further conversion to vicinal diamines.

Hydrogen is often encountered (or intentionally chosen) as a side product formed at the cathode in a single compartment reaction system. This approach of pairing reactions by choice of an “innocent” process is clearly highly successful, although the hydrogen is produced only as a convenient side product and not produced in the stricter sense of a paired electrosynthesis process. Hydrogen is an energy carrier and simply venting hydrogen gas during electrolysis can lead to hazards as well as problems with multi-phase conditions (e.g. bubble formation in reactor channels).

An elegant and energy-efficient solution to this problem in terms of paired electrosynthesis with hydrogen side products has been reported recently by Sherbo, Delima, Berlinguette et al. This work has been extended to the use of palladium films also in flow through microfluidic reactors and to the use of lower cost polymer-palladium hybrid membranes. In this approach, an anodic electrolytic process (see the TEMPO-catalysed alcohol oxidation in Figure 7) is coupled to hydrogen formation at a palladium film cathode. The special ability of the palladium film to absorb the hydrogen, transfer hydrogen to the opposite side, and to release hydrogen via catalytic hydrogenation of alkynes and alkenes was demonstrated. The surface of the palladium film was modified to optimise the catalytic

Figure 5. Scheme for electrochemical oxidative [4 + 2] benzenannulation of heteroarenes with alkenes/alkynes. Also shown is the substrate scope of heterobiaryl compounds (carbon cloth anode, platinum plate cathode, constant current 3 mA. Reprinted with permission from [27]. Copyright (2020) Wiley.
reaction and to provide a truly galvanically paired process in which anode reaction and cathode reaction are separated by the palladium film. The two compartments for catalysis and for electrolysis are completely separated and therefore avoid any cross-over. The energy efficiency and atom economy of this type of process are proposed to be very high. The hydrogenation reaction does not require any electrolyte as it is separated from the electrolytic cell.

A further alternative to beneficial hydrogen harvesting (instead of venting during paired electrolysis) is the use of a divided cell with Nafion membrane and hydrogen transfer as suggested by Moeller and coworkers.[33] In this closely related methodology, hydrogen is re-used for example in palladium-catalysed hydrogenation processes in a separate reaction vessel (Figure 8).

Although hydrogen offers an elegant option as cathodic side product for one-compartment paired electrosynthetic
reactions, it is not always desirable or convenient. For cathodic reactions, an alternative to the production of gaseous side products is the use of sacrificial anode electrode materials such as Mg, Zn, or Ti (strictly speaking these are not paired processes, but useful here for comparison). For example, Ackermann and coworkers have developed a reductive, nickel-catalysed aromatic C–H alkylation process with 10 mol% homogeneous nickel at a nickel cathode.\textsuperscript{[34]} A nickel foam electrode as cathode and zinc metal as anode provided optimised conditions for a diverse range of coupling reactions (Figure 9).

\textbf{Figure 8.} A paired electrolysis approach to coupling an alcohol oxidation to catalytic reactions that required hydrogen gas. Reprinted with permission from [33]. Copyright (2019) Wiley.

\textbf{Figure 9.} Reductive, nickel-catalysed aromatic C–H alkylation process driven by the cathode with a sacrificial zinc anode. Reprinted with permission from [34]. Copyright (2020) Wiley.
A cobalt-mediated process for aromatic alkylation was developed by Ackermann et al. with graphite anode and platinum cathode (in this case to produce hydrogen). A related nickel-catalysed anodic reaction forming aromatic and vinyl phosphinates was reported by Léonel and co-workers as a single compartment electrolytic process with homogeneous nickel complexes at Fe/Ni anodes with a nickel cathode (possibly also producing some sacrificial hydrogen).

Based on these example reactions, it can be seen that single compartment electrosynthesis is desirable and that, although complete pairing of anode and cathode processes is not always achievable, the use of sacrificial processes (predominantly/ideally the use of cathodic hydrogen evolution) can offer a way for an electrolytic process to become more energy efficient and less waste producing, particularly if H₂ is then used as reductant for another transformation. An instructive case of a paired electrolysis with a single nickel catalyst working in conjunction with anode and cathode (without hydrogen) was reported by Zhang et al. for a direct arylation of benzylic C–H bonds. A diverse set of diarylmethanes was obtained as an important building blocks in medicinal and materials chemistry. Generally, avoiding ion-conducting membranes in reactors (separating anode and cathode compartment) is important to lower complexity of paired electrosynthesis reactions and to improve energy efficiency. The next section summarises progress in the development of reactor types that can be useful in paired electrosynthesis, that are aimed to address some of these limitations.

2. Reactor and Electrode Developments for Paired Electrosynthesis

Paired Processes at a Single Electrode: AC Electrosynthesis.
There is a particular need for innovation in electrochemical reactor design in view of producing improved performance in electrosyntheses. There are many options to develop and improve reactors, but often simplicity is a factor in making a process more feasible/attractive for applications in industry. A simple approach to paired electrosynthesis is that of using a symmetric cell (anode and cathode based on the same materials) and applying AC electricity. This results in pairing of anodic and cathodic reaction at the same electrode. For example, when conducting electrocatalytic reactions such as the conversion of carbon dioxide to formate, it can be beneficial to alternate the working electrode potential to switch from cathodic to anodic in an attempt to maintain high catalyst activity. For symmetric cells, it could be desirable to switch polarity for example to maintain active electrodes, but the “translation” of a DC electrolysis to an AC electrolysis may not always be simple. A recent example is the observation that alternating potential facilitated direct, rather than mediated, electrochemical benzylic C–H oxidation of toluene derivatives. The transition time from one type of steady state (anodic) to the other opposite steady state (cathodic) may take time and can affect product yields and reaction pathway. Rodrigo et al. report a high yield for the trifluormethylation of heteroarenes by employing AC electrosynthesis. This is potentially a very useful transformation for medicinal chemistry. A rational approach to process optimisation was proposed.

Paired Processes in Single Compartments. The overwhelming majority of electrosynthetic reactions are carried out in single compartment reactors with optimised anode/cathode pairs to allow paired electrolysis conditions with diffusionally independent electrodes. Halide radical involvement in thiocyanation of α,β-unsaturated carbonyl systems under paired electrolysis conditions has been observed. In this process (see Figure 10) bromine is produced at the anode and sacrificial hydrogen is proposed to be generated at the cathode. The formation of hydrogen from protons leads locally to more basic conditions which aids the reaction.

A potentially green process employing carbon dioxide and based on divergent paired electrolysis was suggested by Matthessen et al. in this process (see Figure 11) CO₂ is employed to generate di-functionalised acids at the cathode (Ni), whereas at the anode (graphite) a diol derivative is produced. The reactor was based on a one-compartment cell without any sacrificial electrode processes. The two products, ionic and neutral, are readily separated out due to their different solubilities.

A convergent paired electrolysis process for the conversion of fatty acids into epoxides has been suggested by Li et al. In a two-compartment reactor (see Figure 12) with cation exchange separator employing natural oils such as castor oil, soybean oil, or corn oil, epoxidation was observed in both compartments due to a chlorine mediated reaction pathway (anode) and a hydrogen peroxide mediated pathway (cathode). Both pathways lead to epoxidation products, although the reduction of oxygen has to be regarded as a low current density process, which may result in a slowing down of this synthesis.

Paired Processes in Microflow Parallel-plate Reactors. Flow electrosynthesis is highly desirable and flow electrolyses have been developed for many applications in synthetic organic chemistry. Microreactors are now accessible in a range of designs to facilitate process development and up-or out-scaling. Parallel plate reactors have been developed and optimised in many laboratories. A comprehensive review of microflow reactors including parallel plate microfluidic and related interdigitated electrode systems has been published for example by Wirth and coworkers. The flow field at the two opposite electrodes is defined by the flow rate, the inter-
Electrode distance, and the total length. A particular benefit from micro-flow reactors (see Figure 13A) when compared to batch reactors is the steady state nature of the electrolysis with better control over reaction conditions under flow (e.g., thermal control). These types of reactors can be scaled up by parallel operation to avoid usual issues with reaction scale up in batch systems. Parallel plate microflow reactors have been employed for a wide variety of electrosynthetic processes. To illustrate the versatility of this approach, recently Atobe and coworkers have demonstrated the anodic formation of an ortho-quinone coupled to a Diels-Alder cycloaddition reaction (Figure 13). The cathode process was a sacrificial innocent hydrogen production. A comparison of batch and flow type reactors demonstrated the superior performance in the micro-flow reactor system. A related catechol oxidation reaction under flow cell conditions has been reported by Nematollahi and coworkers.

Electrosynthesis in the absence of supporting electrolyte is desirable to minimise waste and separation steps during recycling. The possibility of “self-supported” electrolysis reactions in parallel plate flow reactors with very small gap between anode and cathode has been demonstrated before. In a recent theoretical study, this type of process was further investigated, and the importance of low-level ionic species present in the reaction mixture has been highlighted. Very elegant work by Buchwald and Jensen on the translation of photoredox catalysis into paired microflow reactor processes is summarised in more detail below.

**Paired Processes in Interdigitated and Microarray Electrode Reactors.** A very small gap between anode and cathode favours conditions for coupled electrode reactions without additionally added electrolyte salts. Redox processes at anode/cathode generate ionic species and these can be employed to ensure ionic conductivity in the small gap. Although microflow cells are readily designed with flow field separator and two planar plate electrodes, the inherent inefficiencies due to slow flow speed, pressure build up, and occasional blockage effects are detrimental. Closely spaced anode-cathode systems can be obtained as a micro-trench or in a planar 2D arrangement based on interdigitated microband electrodes and similar types of patterned microelectrode assemblies. For electrosynthesis a full 3D arrangement of microanodes and microcathodes would be even better and more effective in microflow reactor systems, but practically this situation is very difficult to realise.

Addressable microelectrode arrays were employed by Moeller and coworkers for multi-step surface chemical transformations (Figure 14). Each element in the array can be addressed individually and complex reactions such as attaching fluorescent pyrene labels were accomplished by first applying a negative potential (borylation) followed by a positive potential (producing an ether linkage).
Figure 11. Paired electrosynthesis of a diacid and a diol employing carbon dioxide. Reprinted with permission from [42]. Copyright (2015) Wiley.

Figure 12. Schematic illustration of the mechanism or epoxidation of fatty acids. Reprinted with permission from [43]. Copyright (2015) Elsevier.

Figure 13. (A) Schematic drawing of a parallel plate microfluidic electrolysis cell. (B) Microflow cell process for ortho-quinone generation coupled to Diels–Alder trapping. (C) Comparison of batch-type and microflow electrolysis results. Reprinted with permission from [47]. Copyright (2019) Thieme Verlag.

Figure 14. Sequential reduction-oxidation sequences and a synthetic solution to the challenge of surface modification of bromo-styrene on the surface of an electrode. Reprinted with permission from [55]. Copyright (2020) American Chemical Society.
Electrosynthesis with interdigitated microband electrodes was initially demonstrated by Girault and Belmont[54] who described the application of interdigitated electrodes in the methoxylation of furan in the 2-position. Further theoretical insights and the significance of convection over microband electrodes were discussed by Amatore and coworkers.[55]

Recently, Jensen and coworkers developed an interdigitated array electrode device for high throughput experiments under microflow conditions.[56] In this case, microbands of platinum electrodes with 10 μm width and an inter-electrode gap of 10 μm were incorporated into a flow device (Figure 15). The inter-electrode gap $d = 10 \mu m$ defines the inter-electrode diffusion time $t = d^2/D = (10^{-5})^2/10^{-9} = 0.1$ s for a typical diffusion coefficient of $D = 10^{-9} \text{m}^2 \text{s}^{-1}$. That is, intermediates generated at anode and cathode undergo inter-diffusion in the 100 millisecond time domain. The reactor was demonstrated for the $\alpha$-C-H arylation of tertiary amines with dicyanoarenes. The $\alpha$-arylated amine product is obtained as a function of applied potential and reaction time. An HPLC yield of 80% is obtained for 15 minutes reaction time and 2.4 V applied potential.

**Paired Processes at Membranes.** Flow cell devices are important in membrane-based fuel cell systems, usually for energy generation. However, the membrane-based electrolysis fuel cell has many attractive features also for electrosynthesis.[54,57] An ionomer membrane has attached porous electrodes (anode and cathode on opposite sides) that are in contact with external supplies of solutions. A very attractive point in this type of reactor is the possibility to work without added electrolyte and in highly non-polar solvents. The ionomer membrane provides ionic conductivity and the triple phase boundary region ionomer | porous electrode | liquid feed provides the reaction space for electron transfer and follow-up chemical transformations.

Atobe and coworkers[58] employed fuel cell type membrane reactors for the catalytic reduction of alkynes (see Figure 16). The anode was employed to generate protons (immersed in aqueous $\text{H}_2\text{SO}_4$ flow) and the cathode was modified with Pt and Pt–Pd alloy catalysts. Diphénylacetylene in cyclohexane was flown over the cathode to give potential-dependent and catalyst-dependent cis- and trans-stilbene as well as further hydrogenation products. Cis-stilbene was obtained selectively on palladium. Products are obtained pure in cyclohexane without any need for electrolyte addition/separation.

Atobe et al.[59] have developed a similar fuel cell-type reactor system with a membrane also to perform hydrogenation with chiral induction by surface adsorbed reagents. A similar reactor design was employed for the hydrogenation of alkynes.[60] Figure 17 shows the principle of the electrocatalytic asymmetric hydrogenation of $\alpha$,$\beta$-unsaturated acids in a PEM.
reactor with a cinchona-modified palladium catalysts. These types of electrosynthetic reactor designs are particularly amenable to flow synthesis.

3. The Link from Photoredox Catalysis to Paired Electrosynthesis

Photocatalysis plays a major role in organic synthesis to generate reactive intermediates and to energies reactions with
application particularly in drug discovery. The close link from photocatalysis to electrochemistry and to photoelectrochemistry has emerged only recently. [62,63] Parallels between photoredox catalysis (involving paired single electron transfer steps at the dispersed catalyst) and paired electrosynthesis (involving single electron transfer at the two electrodes) have recently been highlighted and exploited. [64,65] In both cases the formation of a paired oxidation and reduction locally within inter-diffusion distance is important. Photoexcitation can lead to charge separation and sequential oxidation/reduction processes within the same diffusion space and similarly coupled oxidation/reduction reaction occur at paired electrodes. For example, an electrochemical Minisci-type arylation has been reported (as an alternative to visible light photoredox processes) based on a diazonium starting material (Figure 18). This C(sp²)–H arylation process using aryldiazonium salts via a paired electrolysis has been reported by Jiang et al. [66] for a range of substrates and for a range of diazonium salts. The mechanism has been suggested to be associated with cathodic aryl radical production and transfer and follow-up reactions either at the anode or in homogeneous phase. This process is reported to happen in a conventional, undivided cell without diffusional coupling of anode and cathode.

In a recent landmark study, Jensen and Buchwald have pioneered work on the “translation” of photoredox processes into electrochemical reactions, based on the realisation that both are fundamentally paired processes. [67] The concept is illustrated in Figure 19 comparing photocatalytic and electrochemical single electron transfer processes in overall “redox-neutral” processes. Here, a parallel-plate microfluidic cell was developed to allow anode and cathode to be placed opposite each other with a small gap of typically 25 to 500 microns. A range of different materials was tested for anode and cathode to optimise the reactor performance. The reactor gap was varied by a spacer layer and processes were shown to yield better product selectivity for smaller gaps (that is for faster inter-diffusion). Therefore, the diffusion layer of anode and cathode are coupled and reactive intermediates from both electrodes can collide and react to replicate conditions in typical photocatalytic processes in homogeneous solution, in which oxidised and reduced species are formed in close vicinity. The benefit here is that no expensive photoredox catalysts are required and the electrode type and reaction conditions are easier to optimise. Instead of individually optimising HOMO and LUMO energy levels for each type of process with the photocatalyst, in paired electrosynthesis the applied potential at anode and cathode are varied to match the energy requirements of the anode/cathode process.

Several reaction types are considered. Kolbe-type decarboxylation is paired with cathodic aryl radical formation to give effective cross-coupling products. But, also α-amino radicals, radicals from anodic deboronation, and allylic radical intermediates (generated via a thiol-mediated HAT process) are shown to undergo arylation. The approach was further developed into a high-throughput testing system for electro-organic radical reactions. [49] Although currently only very specific types of coupling reactions can be performed under paired electrolysis conditions, the link of photoredox catalysis to paired electrosynthesis is important to open the doors for a more systematic approach to the invention of new electro-organic reactions and to novel reactor designs.

![Figure 18](image-url) Proposed reaction mechanism for arylation with aryldiazonium salts. Reprinted with permission from [66]. Copyright (2019) Wiley.
4. Conclusion and Outlook

Paired electroorganic synthesis has long been seen as an important approach to electrolytic production of synthetic chemicals, but tools for the development of this field were very limited. However, in the recent 1–2 years much more progress has been made and both conceptual development of paired processes as well as practical tools for paired electrolysis are now much more accessible and abundant. Several types of new reactors based on (i) undivided cells, (ii) membrane or PEM fuel-cell style cells, (iii) microfluidic parallel plate flow cells, or (iv) interdigitated array electrosynthesis cells have been demonstrated for a wider range of reaction types. The intriguing link from photocatalysed redox transformations to paired electrosynthetic processes has emerged. The need for high-throughput screening of reaction conditions has been highlighted\[49\] as a way to overcome the challenges of multi-parameter process optimisation. These types of approaches will be very important also for the better fundamental understanding of paired and coupled electrode processes as systematic data sets from high-throughput experimentation can be fed into computational analysis tools to verify or propose reaction mechanisms.

Acknowledgement

A. J. C. thanks the Royal Society for a University Research Fellowship (UF150533) and the University of Bath for generous financial support. F. M. thanks EPSRC for support (EP/N013778/1).

References

[1] a) C. Kingston, M. D. Palkowitz, Y. Takahira, J. C. Vantour-out, B. K. Peters, Y. Kawamata, P. S. Baran, Acc. Chem. Res. 2020, 53, 72–83; b) M. C. Leech, A. D. Garcia, A. Petti, A. P. Dobbs, K. Lam, React. Chem. Eng. 2020, 5, 977–990; c) C. Schotten, T. P. Nicholls, R. A. Bourne, N. Kapur, B. N. Nguyen, C. E. Williams, Green Chem. 2020, 22, 3358–3375; d) A. Wibec, T. Gieshoff, S. Möhnle, E. Rodrigo, M. Zirbes, S. R. Waldvogel, Angew. Chem. Int. Ed. 2018, 57, 5594–5619; Angew. Chem. 2018, 130, 5694–5721; e) M. D. Kärkäs, Chem. Soc. Rev. 2018, 47, 5786–5865; f) S. Möhle, M. Zirbes, E. Rodrigo, T. Gieshoff, A. Wibec, S. R. Waldvogel, Angew. Chem. Int. Ed. 2018, 57, 6018–6041; Angew. Chem. 2018, 130, 6124–6149; g) M. Yan, Y. Kawamata, P. S. Baran, Angew.
[51] C. A. Paddon, G. J. Prior, T. Thiemann, F. Marken, Angew. Chem. Int. Ed. 2018, 57, 4067–4092.
[52] A. M. F. Phillips, A. J. L. Pombeiro, Angew. Chem. Int. Ed. 2017, 56, 3929–3932.
[53] J. L. Meyer, J. Fransaer, S. Kuhn, Chem. Rev. 2017, 117, 4111–4115.
[54] R. S. Delima, R. S. Sherbo, D. J. Dvorak, V. A. Chiykowski, B. P. MacLeod, Angew. Chem. Int. Ed. 2016, 55, 16782–16817.
[55] S. Fransen, J. Fransaer, S. Kuhn, Chem. Rev. 2016, 116, 2111–2116.
[56] T. Shanks, W. Z. Li, Org. Lett. 2015, 17, 2429–2432.
[57] F. Amemiya, D. Horii, T. Fuchigami, M. Atobe, Tetrahedron Lett. 2015, 56, 2226–2229.
[58] G. J. Pritchard, T. Pfennig, B. H. Nguyen, L. Luo, Chem. Sci. 2015, 6, 4722–4726.
[59] C. A. Paddon, M. Atobe, T. Fuchigami, P. He, P. Watts, S. J. Haswell, G. J. Prior, T. Chadderdon, D. Bull, F. Marken, J. Am. Chem. Soc. 2015, 137, 12723–12726.
[60] K. Yamamoto, M. Kuriyama, O. Onomura, Acc. Chem. Res. 2015, 48, 105–110.
[61] A. Ollivier, S. Sengmany, M. Rey, T. Martens, E. Leonel, Synlett 2020, 31, 1191–1196.
[62] P. Xu, P. Y. Chen, H. C. Xu, Angew. Chem. Int. Ed. 2020, 59, 14275–14280.
[63] L. J. Li, Y. Li, N. K. Fu, L. Zhang, S. Z. Luo, Angew. Chem. Int. Ed. 2020, 59, 14347–14351.
[64] K. Yamamoto, M. Kuriyama, O. Onomura, Acc. Chem. Res. 2020, 53, 105–120.
[52] F. Marken, K. Mathwig, *Curr. Opinion Electrochem.*, 2018, 7, 15–21.

[53] Q. W. Jing, K. D. Moeller, *Acc. Chem. Res.*, 2020, 53, 135–143.

[54] C. Belmont, H. H. Girault, *J. Appl. Electrochem.*, 1994, 24, 719–724.

[55] C. Amatore, C. Pebay, C. Sella, L. Thouin, *ChemPhysChem*, 2012, 13, 1562–1568.

[56] Y. M. Mo, G. Rughoobur, A. M. K. Nambiar, K. Zhang, K. F. Jensen, *Angew. Chem. Int. Ed.*, 2020, 59, 20890–20894.

[57] T. Fuchigami, M. Atobe, S. Inagi, *Fundamentals and applications of organic electrochemistry: Synthesis, materials, devices*, Wiley, New York 2015, 129–185.

[58] S. Nogami, K. Nagasawa, A. Fukazawa, K. Tanaka, S. Mitsushima, M. Atobe, *J. Electrochem. Soc.*, 2020, 167, 155506.

[59] A. Fukazawa, K. Tanaka, Y. Hashimoto, Y. Sato, M. Atobe, *Electrochem. Commun.*, 2020, 115, 106734.

[60] A. Fukazawa, J. Minoshima, K. Tanaka, Y. Hashimoto, Y. Kobori, Y. Sato, M. Atobe, *ACS Sustain. Chem. Engineer.*, 2019, 7, 11050–11055.

[61] P. J. Li, J. A. Terrett, J. R. Zbieg, *ACS Med. Chem. Lett.*, 2020, 11, 2120–2130.

[62] J. P. Barham, B. Koenig, *Angew. Chem. Int. Ed.*, 2020, 59, 11732–11747.

[63] J. J. Liu, L. X. Lu, D. Wood, S. Lin, *ACS Cent. Sci.*, 2020, 6, 1317–1340.

[64] R. H. Verschueren, W. M. De Borggraeve, *Molecules*, 2019, 24, 2122.

[65] O. R. Luca, J. L. Gustafson, S. M. Maddox, A. Q. Fenwick, D. C. Smith, *Org. Chem. Front.*, 2015, 2, 823–848.

[66] Y. Y. Jiang, G. Y. Dou, L. S. Zhang, K. Xu, R. D. Little, C. C. Zeng, *Adv. Synth. Catal.*, 2019, 361, 5170–5175.

[67] Y. M. Mo, Z. H. Lu, G. Rughoobur, P. Patil, N. Gershfeld, A. I. Akinwande, S. L. Buchwald, K. F. Jensen, *Science*, 2020, 368, 1352–1356.

*Manuscript received: February 15, 2021
Revised manuscript received: March 31, 2021
Version of record online: April 8, 2021*