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Review Article

The “Ex-cell” approach to organic electrochemistry

Sarah B. Coppock and Alastair J. J. Lennox



Abstract

The “ex-cell” approach to organic electrochemistry has enabled important progression to be made in numerous systems. Separating out the electrochemical step from the subsequent chemical step means that substrate scopes can be expanded and a broader scope of reagents are more easily prepared. Moieties can be included that otherwise readily undergo single-electron transfer redox events at the electrode surface. We detail several examples of this, including those based on the ex-cell synthesis and use of bases, cations and hyper-valent iodine reagents, among others.

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Keywords

Electrosynthesis, Ex-cell, Electrochemistry, Synthesis.

Introduction

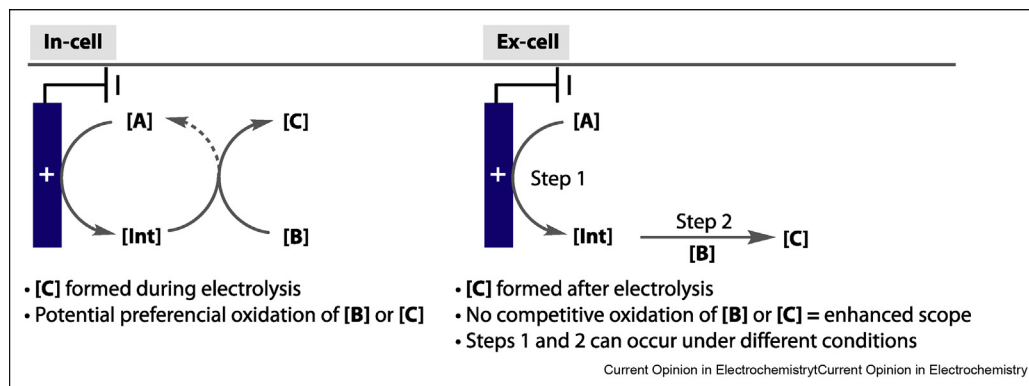
Synthetic organic electrochemistry has regained popularity in recent years, as it provides several advantages, which are pertinent to contemporary organic synthesis, over classical redox strategies. Alternative reaction mechanisms, involving surface-bound species, and the precise control of reaction rate and applied potential can lead to different or new selectivity. The physical and spatial separation of the two redox half reactions, provides a lever of control that translates inherent sustainability; the stoichiometric oxidant or reductant can be designed such that little or no waste is produced on the counter electrode. The separation of redox events also provides the opportunity to control the interaction of the 2 electrode processes, and reduce it if necessary. These controls have led to explorations and developments in novel reactivity, as well as in scale up and sustainability [1–3].

A synthetic electrochemical transformation is initiated by an electrode process of substrate or reagent [A] that produces a reactive intermediate [Int], which is either used or functionalised directly, or is used as a mediator to functionalise another substrate or reagent [B] to form product [C]. The conventional approach is to run the reaction in-situ, and have the electrochemical and chemical steps run in parallel. This has been termed an “in-cell” approach, [Figure 1](#) [4]. This approach works well for catalytic systems where the redox potentials of all reaction components are aligned. However, as it is facile for a precise amount of charge to be passed, it is possible to temporally separate the electrochemical redox reaction and the follow-up functionalisation reaction (steps 1 and 2, [Figure 1](#)). Hence, the electrochemical process is performed first, and when then desired quantity of redox equivalents have passed, it is switched off and reagents can then be added to initiate the chemical reaction. This approach is commonly named “ex-cell,” as the synthetic reaction of interest occurs “out of the cell,” not always literally, but at least not during the electrolysis. It can be more challenging to replicate ex-cell conditions using standard redox reagents due to the frequent need to use excess redox reagents and over multiple steps [5,6]. In addition, the imprecise knowledge of reaction progression, and the presence of by-products can interfere with the follow-up chemical reaction [7]. The obvious limitation to an ex-cell process is that the electrochemically generated intermediate must be sufficiently stable to survive transfer to the follow-up reaction. Nevertheless, this review will highlight key examples where an “ex-cell” method has led to specific advantages or benefits to a reaction.

The primary benefit of adopting an ex-cell procedure is that enhanced areas of chemical space can be accessed, which are otherwise off-limits using a standard in-cell approach. By terminating the electrolysis, the substrates or reagents added afterwards are not subject to the electrode processes that would otherwise decompose them. Most commonly, an electron-rich substrate or nucleophile, which would readily undergo anodic oxidation, is added after the electrochemical generation of a reactive intermediate or mediator, thereby, enhancing the range of suitable reagents to the transformation.

Early examples of exploiting this approach to gain improvements in scope include the formation of

Figure 1



In-cell vs ex-cell electrolysis reactions.

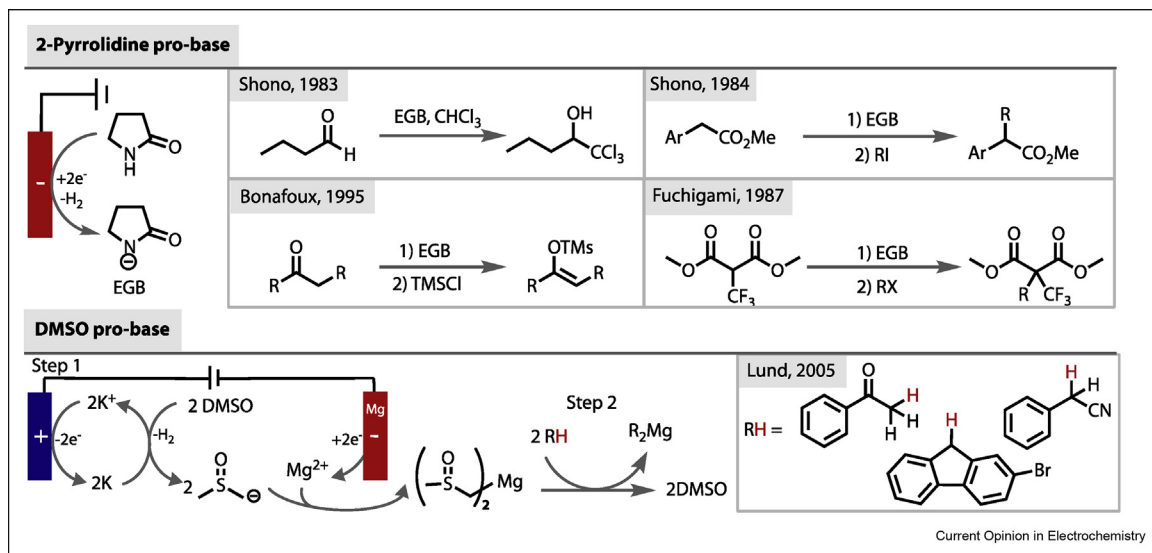
electrochemically generated bases (EGB), where the conjugate acid undergoes cathodic reduction to liberate hydrogen gas and the anionic base. Iversen and Lund initially developed the concept of EGBs for Wittig reactions [8], where, generating the base electrochemically first, meant the concentration of it could be controlled by the current, and, in the absence of substrate, any competitive substrate reduction is avoided. The use of 2-pyrrolidine as a pro-base has been especially successful to deprotonate substrates that then undergo alkylation or silylation reactions, Figure 2 [9–12]. This avoids competitive reduction of the electrophilic alkylating reagents, or of the substrate, such as ketone reduction [11] or reductive defluorination [12]. Atobe has also shown that microfluidic systems are useful flow cell set-ups for the ex-cell formation and use of the 2-pyrrolidine anion [13]. Similar microfluidic devices have also been used to generate *o*-benzoquinones ex-cell for use in Diels–Alder reactions [14] and reactions with benzenethiols [15].

Interesting and more unusual Grignard reagents have also been successfully prepared from EGBs. Lund reported a method that proceeds via reduction of DMSO to form intermediate dimethyl magnesium salt, which was then used to deprotonate weakly acidic substrates to generate the target Grignard type reagent (R_2Mg), Figure 2 [16]. By using an ex-cell deprotonation strategy to generate the reagent, as opposed to a reduction strategy, R_2Mg reagents with electrophilic substituents, such as halogen, carbonyl and cyano groups, could be tolerated, thereby broadening the scope of Grignard reagents that are available to prepare. A final example is the cathodic reduction of acetonitrile, which leads to the formation of the cyanomethyl anion, a strong base that has found uses in the synthesis of a range of heterocycles in the presence readily reducible functionality, such as α -halocarbonyl, aromatic ketones, and thioureas [17].

The anodic oxidation of halide ions to access composite halogen species has taken advantage of an ex-cell approach. Nonaka has reported several examples of the electrochemical generation of halogen composites and their subsequent use in the oxidation or halogenation of organic compounds. The methods are milder than chemical methods that typically involve the use of super acids or molecular halogens. For example, $Br_xCl_y^-$ ions and IF^- , ICl^- , and IBr^- have been generated anodically from the component halide ions and then applied to the oxidation of alcohols, and the halogenation of arenes and alkenes [18–20].

Electrochemical anodic oxidation is a particularly powerful method for the generation of cationic intermediates. Their functionalisation using an in-cell approach is typically either limited to readily oxidised substrates or oxidatively stable nucleophiles, such as alkoxides [21] or cyanide [22]. Yoshida pioneered the versatile cation-pool method that obviates this limitation [23]. The one-pot, two-step, ex-cell procedure sees the generation of cations accumulate at low temperature ($-78^\circ C$), which are then reacted upon addition of a nucleophile, Figure 3. Increased temperatures are also viable with the addition of an anodically stable stabilising reagent, such as a sulfilimine [24] or DMSO [25], or, as reported by Chiba, a nitromethane/ $LiClO_4$ electrolyte system [26] or, by Li, an ionic liquid [27]. The cation pool is typically generated in a divided cell to avoid their cathodic reduction. If performed in an in-cell manner, the nucleophiles would preferentially oxidize, thus the scope of such transformations are expanded. The cation pool can be reacted with a range of nucleophiles that would otherwise readily undergo competitive oxidation, including silyl enol ethers, electron-rich arenes, allylsilanes, malonates [28]. Yoshida also reported using organometallic Grignard reagents as nucleophiles too, which illustrates how broad the nucleophile scope can extend to [29].

Figure 2



The electrochemical generation of bases and their use in synthesis.

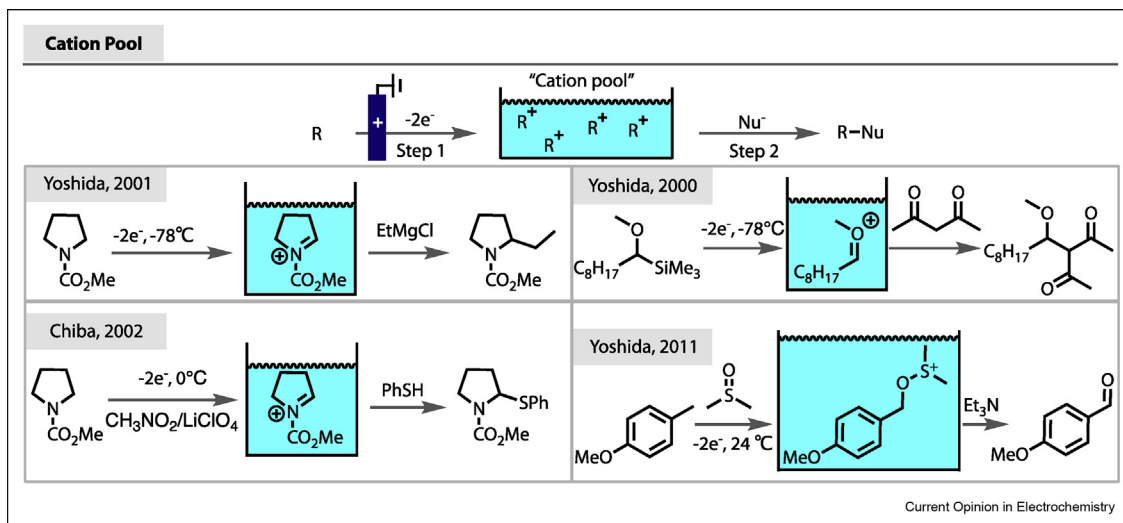
The applicability of the method is dependent on the stability of the reactive intermediate. In their first article, Yoshida report an oxidative carbon–carbon bond forming reaction from the electrochemical generation of iminium cations [28]. This was later expanded to include a number of chemical transformations, involving cationic carbon, oxygen, nitrogen, phosphorous or sulphur intermediates. For example, the anodic generation of alkoxy-carbenium ions from α -silyl ethers [30], which then reacted with a range of organosilicon nucleophiles, and anodically generated sulfur based cations (“ArS⁺”) can be generated ex-cell and reacted [31]. The pooled intermediates have also extended to *radical* cations, which are then applied to C–H/C–H cross-coupling of aromatic compounds [32]. This avoids their unselective homocoupling and any overoxidation of the polyaromatic products. The application of this general methodology was expanded to the “cation flow” method, where cations are continuously generated, removed from the cell, and rapidly quenched [33]. In each case preferential nucleophile oxidation was avoided by prior electrochemical formation of the reactive intermediate.

Hypervalent iodine reagents are frequently prepared using electrochemical anodic oxidation from the corresponding aryl-iodides [34,35]. This process avoids the use of expensive and hazardous chemical oxidants, and is a safer, more scalable, alternative. Fuchigami first demonstrated this preparation method would be well suited to an ex-cell procedure, by reporting the gem-difluorination of thioketals using electrochemically generated ArIF₂ [36]. Several other examples have been

reported [37,38], but we will now briefly detail 3 contemporary different hypervalent iodine systems, and highlight how the ex-cell approach to their generation and use has aided access to products that would otherwise be inaccessible, Figure 4.

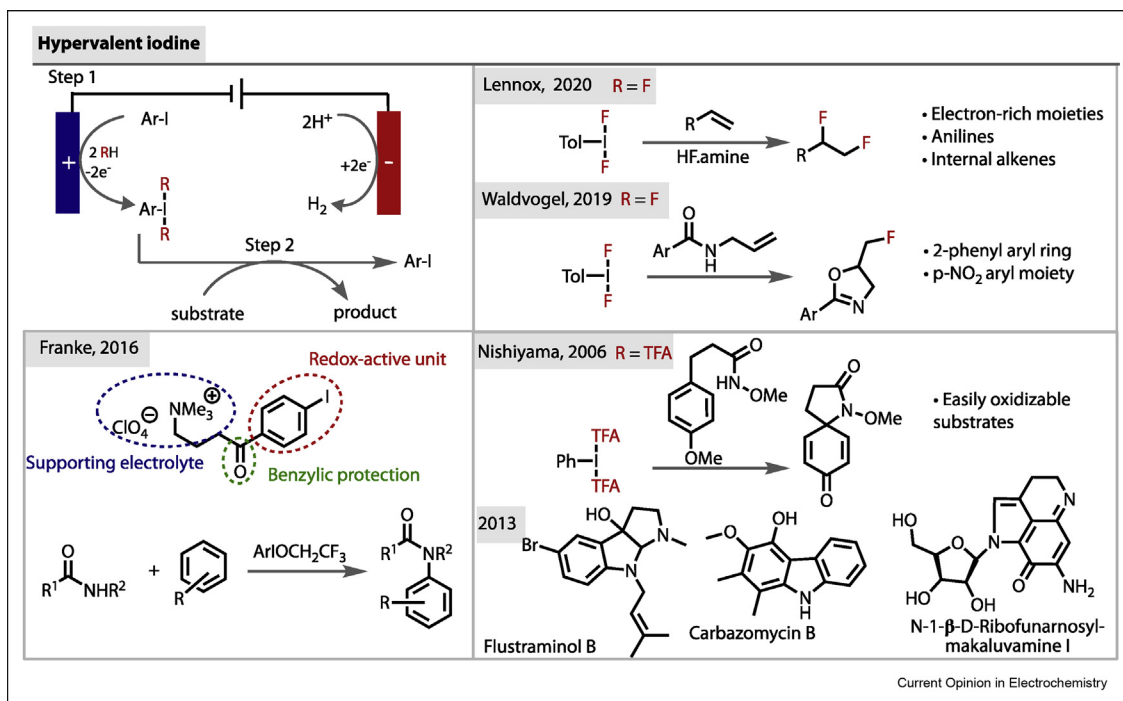
Following on from Fuchigami, Lennox recently electrochemically formed a difluoro λ^3 -iodane (ToIIF₂) mediator for the vicinal difluorination of alkenes [7]. The in-cell methodology developed was tolerant of many substrates, including terminal alkenes or those with electron poor moieties. However, it was intolerant of alkene substrates containing electron-rich moieties or internal alkenes, due to their preferential anodic oxidation. To overcome this problem, an ex-cell method was optimized to access more easily oxidizable substrates, including unactivated, substituted alkenes, as well as electron-rich rings and anilines, which all returned difluorinated products in moderate to excellent yield. Wirth later demonstrated that this reaction could be successfully translated into ex-cell flow [39], which serves as a good example of how flow chemistry is well suited to the generation and reaction of unstable reactive intermediates. Lennox then found the ex-cell approach to be vital for translating the readily oxidisable phenolic ethers into their fluorocyclised products, as the in-cell reaction gave low yields due to SET oxidation pathways [40]. Waldvogel also recently described an ex-cell difluoro λ^3 -iodane mediated approach for the fluorocyclization of both N-allylcarboxamides to 2-oxazolines [41], and N-propargylamides to oxazoles [42]. Several reactions were improved using the ex-cell approach, including the 2-phenyl derivative,

Figure 3



The cation-pool method takes advantage of an ex-cell process to generate products that would otherwise be inaccessible.

Figure 4



Electrochemical hypervalent iodine reagent generation and use.

which experienced intramolecular coupling when performed in-cell but could be entirely suppressed in ex-cell, and the 4-nitro substrate increased the product yield from trace to 34%.

Nishiyama applied the electrochemical generation of hypervalent iodine species to the synthesis of azacylic derivatives, Figure 4. The ex-cell approach facilitated a wider substrate scope due to the oxidation potential of

iodobenzene being higher than that of many of the substrates, leading to complex mixtures [43]. This “ex-cell” hypervalent iodine mediated method has since been reported in the syntheses of a number of natural products [44–46].

Franke has developed an interesting iodoarene reagent with a tethered alkylammonium group, which acts as both a mediator and supporting electrolyte. This reagent avoids the use of expensive or hazardous electrolyte salts that can be difficult to remove. The mediator-salt was successfully applied to several different C–N and C–C coupling reactions [47], and to the synthesis of benzoxazoles [48] using an ex-cell approach, which led to enhanced yields of substrates containing redox sensitive groups. A range of alternative redox-active supporting electrolyte/mediators have since been developed from iodophenyl sulfonates and iodo-benzoates [49].

Aside from improving the scope of reactions, adopting an ex-cell approach means the electrochemical and chemical steps can be optimized independently, at least with regards to temperature/pressure and additives. In a Cr(II) mediated synthesis of p-hydroxyphenyl acid, Montiel reported that in-cell conditions were not appropriate due to a mismatch in the kinetics of the electrochemical and chemical steps [50]. Thus, it was crucial to optimise the two steps independently, and have them operate under different temperatures in an ex-cell manner. Therefore, the electrochemical reduction of Cr(III) was performed at room temperature, and the resulting Cr(II) was used to reduce the substrate at 95 °C.

Finally, ex-cell procedures have been used to improve current and energy efficiency of processes. By separating the steps, charge is not wasted on the oxidation or decomposition of reagents or substrates, as demonstrated in a Mn(II)/Mn(III) mediated indirect oxidation of o-chlorotoluene to o-chlorobenzaldehyde [51]. For synthetic applications, however, this is rarely a significant concern, considering the difference in cost between electricity and products. Industrial scale processes, such as water treatment, provide a more legitimate need to improve the charge efficiency. In-cell and ex-cell conditions were compared for electrochemical generation of hydrogen peroxide and its use in the Fenton process for wastewater treatment. While destruction of aromatic organic pollutants was achieved in both systems, the ex-cell approach led to greater rates and better charge efficiency [52].

Conclusion

In conclusion, we have described several examples that have demonstrated advantages of running electro-synthetic reactions in an ex-cell manner. If the

electrochemically generated species is sufficiently stable, adding the nucleophile, reagent or substrate after electrolysis can aid the expansion of substrate scopes, by avoiding any competitive electrochemical redox reaction, as well as being able to optimise the steps independently and improving the charge efficiency and in some cases the kinetics of the reaction. Hence, this approach should be considered during reaction optimisation to broaden the applicability of electro-synthetic transformations and enable new or different reactivity.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

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6 Hot topic: Emerging Opinions

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