Trends in Chemistry

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Review

Steroids under voltage: unlocking reactivity with electrochemistry

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Steroids are ubiquitous natural compounds that play essential physiological roles in both plants and animals. Owing to their diverse biological activities, including anti-inflammatory, antitumor, antiviral, and antimicrobial effects, steroidal compounds have found widespread therapeutic uses in the treatment of numerous clinical conditions. Unsurprisingly, the global steroid market is valued at approximately US$4 billion. Despite their broad impact in chemical research and the pharmaceutical industry, the synthesis of steroids remains challenging due to the structural complexity and limited availability of efficient synthetic methodologies. This review highlights recent advances in electrochemically enabled approaches for steroid activation and functionalization, aiming to inspire innovative and sustainable strategies for steroid manipulation and production.

Highlights

The selective functionalization of steroids remains a significant challenge due to their complex structure and site-specific reactivity.

Electrochemistry enables unprecedented transformations of both the steroidal core and side chains, expanding chemical space and enabling rapid analog generation.

The diversity of electrochemical strategies, including redox-mediated couplings, hydrogenations, and electrophotocatalysis, offers versatile tools for late-stage steroid elaboration.

Several methods discussed are scalable and compatible with flow systems, positioning electrochemistry as a practical and sustainable solution for industrial synthesis.

Benefiting from their sustainability, selectivity, and operational simplicity, electrochemical methods will become increasingly valuable for the synthesis of steroidal active pharmaceutical ingredients and bioactive derivatives.

Steroids: structure, biological relevance, and impact on drug discovery

Steroids (from the Greek *stereos* = solid) are a unique class of organic compounds characterized by a 17-carbon skeleton arranged in four fused rings, known as cyclopentanoperhydrophenanthrene (Figure 1A) [1]. This rigid core typically presents methyl substituents at C10β and C13β and a β-oriented side chain at C17, while degrees of unsaturation and the stereochemistry at C5 confer substantial conformational diversity, influencing molecular shape and property. While rings at the steroid nucleus generally adopt a chair-like conformation to minimize strain, the presence of double bonds or bulky groups can induce distortions or alternative conformations, which in turn impact chemical reactivity and interactions with biological targets and steroid-transforming enzymes [2]. Steroids encompass a broad range of natural and synthetic molecules, including sterols (e.g., cholestanes, stigmastanes), sex hormones (estranes, androstanes, pregnanes), bile acids (cholanes), cardiac glycosides (cardanolides, bufanolides), and phytosterols (Figure 1B,C). Structural diversity is further expanded by the introduction of heteroatoms, yielding aza-, oxo-, and thio-steroids, or by ring opening (secosteroids; e.g., vitamin D), expansion, or contraction.

Since their structural elucidation in the early 20th century, steroids have played a pivotal role in advancing chemistry, biology, and medicine. The discovery of cortisone's (**1**) therapeutic efficacy against rheumatoid arthritis in 1948 marked the dawn of the 'golden age of steroids' (Figure 1C) [3]. This milestone was built on synthetic efforts by leading chemists like Robinson, Woodward, Barton, and Djerassi, culminating in the partial synthesis of cortisone (**1**) from deoxycholic acid (37 steps) on a scale that made the initial clinical trial possible. The combination of promising clinical outcomes and the synthetic challenge prompted intense research activities aimed at the development of a more efficient, robust, and innovative route to cortisone (**1**). A more practical synthesis was achieved with the identification of *Rhizopus* fungus ATCC 11145, which could selectively hydroxylate progesterone at the C11 position, dramatically reducing the cost (30-fold lower) and the timing of cortisone production [4]. Another milestone came in 1960, with the FDA approval of the first oral contraceptive pill, Enovid [noretynodrel (**2**) and

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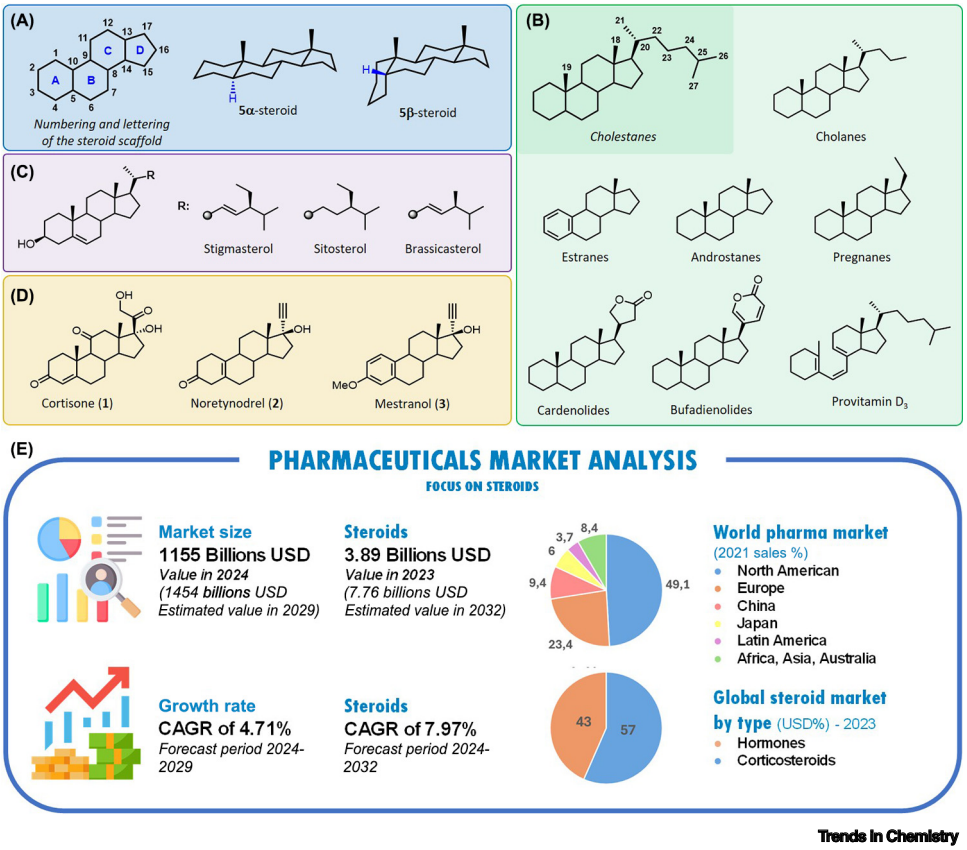

Figure 1. (A) General structure, numbering, and lettering of steroids. (B) Major classes of steroidal compounds. (C) Representative examples of phytosterols. (D) The steroids of the golden age: cortisone (**1**), noretynodrel (**2**), and mestranol (**3**). (E) Pharmaceutical market data analysis of steroids. Abbreviation: CAGR, compound annual growth rate.

mestranol (**3**)] (Figure 1C). Beyond its medical impact, the pill had profound societal consequences, contributing to the emancipation and self-determination of women [5,6]. Notably, seven Nobel Prizes have been awarded in recognition of ground-breaking research in the steroid field, including those for the discovery of cortisone (Kendall, 1950), sex hormones (Butenandt, 1939), and the elucidation of cholesterol and fatty acid metabolism (Bloch and Lynen, 1964).

Today, steroid-based active pharmaceutical ingredients (APIs) constitute a cornerstone of drug discovery with applications spanning anabolic therapies, contraception, anti-inflammatory treatments, cardiotonics, and cancer therapies. Beyond classical uses, steroids show promise in antifungal, antiviral, and metabolic disorder interventions, with over 200 steroidal drugs marketed globally [7]. The commercial significance is underscored by a market valued at nearly US$4 billion in 2023, forecasted to double within a decade (Figure 1D) [8]. This landscape requires continuous innovation in synthetic methodologies to gain efficiency, cost, and sustainability. Achieving this necessitates not only advanced chemical strategies but also inventive rethinking of steroid synthesis and modification.

In this review, as a complement to prior reviews highlighting the importance of electrochemistry in organic synthesis and medicinal chemistry [9–14], we discuss recent contributions that showcase the transformative impact of electrochemical approaches on steroid chemistry. Providing

Glossary

Anode: where oxidation occurs and where electrons are removed from molecules. It functions as the positive electrode in an electrolytic system and, in most instances, forms reactive intermediates such as radicals or cations that trigger the desired chemistry.
Cathode: the electrode where reduction occurs; that is, species that accept electrons. In an electrolytic cell, it is the negative electrode, and it has a tendency to catalyze bond forming or the neutralization of oxidized intermediates.
Current: amperage; the value at which electricity flows through a system, in amperes (A). It is a measure of how many electrons are transferred per unit of time. The current can influence the rate of an electrochemical reaction directly and, in some cases, the selectivity thereof.
Electrocatalyst: any material, often used as an electrode, that enhances the rate or selectivity of an electrochemical reaction. These materials facilitate electron transfer and lower energy barriers, playing a pivotal role in clean energy technologies and synthetic chemistry.
Electrochemical cell: a cell that uses electricity to drive chemical reactions or, conversely, generates electricity from chemical reactions. It typically comprises two electrodes, a cathode and an anode, immersed in an electrolyte that allows the ions to move and form a circuit. Electrochemical cells exist in two main configurations. (i) In an undivided cell, both electrodes are employed in the same reaction vessel but without physical separation. This is a cheap and straightforward arrangement, but allows free mixing of species generated at the cathode and anode, which can lead to undesirable side reactions or product degradation. (ii) A separated cell contains a membrane or permeable barrier separating the anodic and cathodic compartments. This prevents cross-reactions between reductive and oxidative species and offers better control over selectivity and product stability, especially in sensitive or complex transformations.
Electrolyte: the charge-transmitting phase that facilitates charge transport between electrodes. Typically a polar-solvent-solubilized salt, it is electrically neutral and may even control reaction outcomes by stabilizing intermediates or modifying electrode surfaces.

a comprehensive overview remains challenging, as relevant examples are often buried within broader synthetic studies, or steroids are used merely as complex test substrates with little emphasis on their specific chemistry. Here, we evaluate the recent rise (past 5 years) of electrochemically enabled transformations in steroid synthesis, organizing the discussion by reaction type with an emphasis on late-stage functionalization (LSF), selectivity, and synthetic relevance. Where appropriate, we compare electrochemical methods with conventional approaches, highlighting their advantages in terms of selectivity, efficiency, and sustainability.

Voltage: electric potential difference; energy that drives electrons from one electrode to another. Voltage in electrochemistry determines whether a specific redox process will be thermodynamically feasible and governs the rate and selectivity of the conversion.

Why electrochemistry, why now?

In the pharmaceutical industry, where innovative molecular design is key to medicinal chemistry, the development of new synthetic methodologies is essential to access complex leads and drug candidates [15–17]. Innovation in method development has become a central strategy in expanding the chemical space and providing medicinal chemists with tools to rapidly generate compound libraries for structure–activity relationship (SAR) studies [18]. It also enables the optimization of molecular properties through direct modifications of natural products and lead compounds without resorting to *de novo* synthesis [19,20].

With this in mind, the site-selective functionalization of inactivated positions in the steroid scaffold is an area of growing interest. It offers a way to overcome challenges associated with complex molecule synthesis and to streamline access to derivatives that would otherwise require substantial time and effort. Despite notable progress, the synthesis and selective modification of steroids still face persistent challenges, including long reaction times, moderate yields, narrow substrate scope, and the reliance on toxic, unstable, or hazardous reagents. To address these issues, chemists have turned to enabling technologies and methodologies such as flow chemistry, photochemistry, catalysis, electrochemistry, and mechanochemistry to unlock new transformations and steroidal molecules previously inaccessible or difficult to make [2,21–24].

Electrochemical methods, in particular, have emerged as a sustainable and selective platform for complex molecule functionalization [9–11] (Box 1). By enabling precise control of redox events and *in situ* generation of reactive intermediates, electrochemistry circumvents the need for stoichiometric oxidants or reductants. These features are especially attractive for steroid chemistry, where positional selectivity is critical and functional group tolerance is essential. Recent advances highlight electrochemical C–H activation, oxidation, and reduction strategies that streamline steroid derivatization. These advances not only contribute to more efficient and environmentally compatible methods for steroid modification but also open new avenues for API intermediates and the design of bioactive steroid derivatives with improved or tailored properties.

Electrophotocatalysis: merging light and electrons for steroid functionalization

The integration of photoredox catalysis and electrosynthesis, a strategy known as electrophotocatalysis [25–28], has been shown to leverage the strengths of both disciplines: the ability of light to generate high-energy photoexcited species and the precise redox control afforded by electrochemistry. The result is a powerful method for LSF of complex molecules, such as steroids, under mild, scalable, and sustainable conditions. The strategy often avoids the need for stoichiometric reagents, minimizes side reactions, and tolerates sensitive functional groups, making it particularly suitable to address challenges in steroid chemistry.

A compelling example was reported by Ackermann and coworkers in 2020, who applied electrophotocatalysis to the non-directed C–H trifluoromethylation of (hetero)arenes, including estrone 3-methyl ether (**4**) (Figure 2A) [29]. Trifluoromethylated derivatives are particularly attractive in medicinal chemistry for their unique binding affinity and pharmacokinetic/pharmacodynamic (PK/

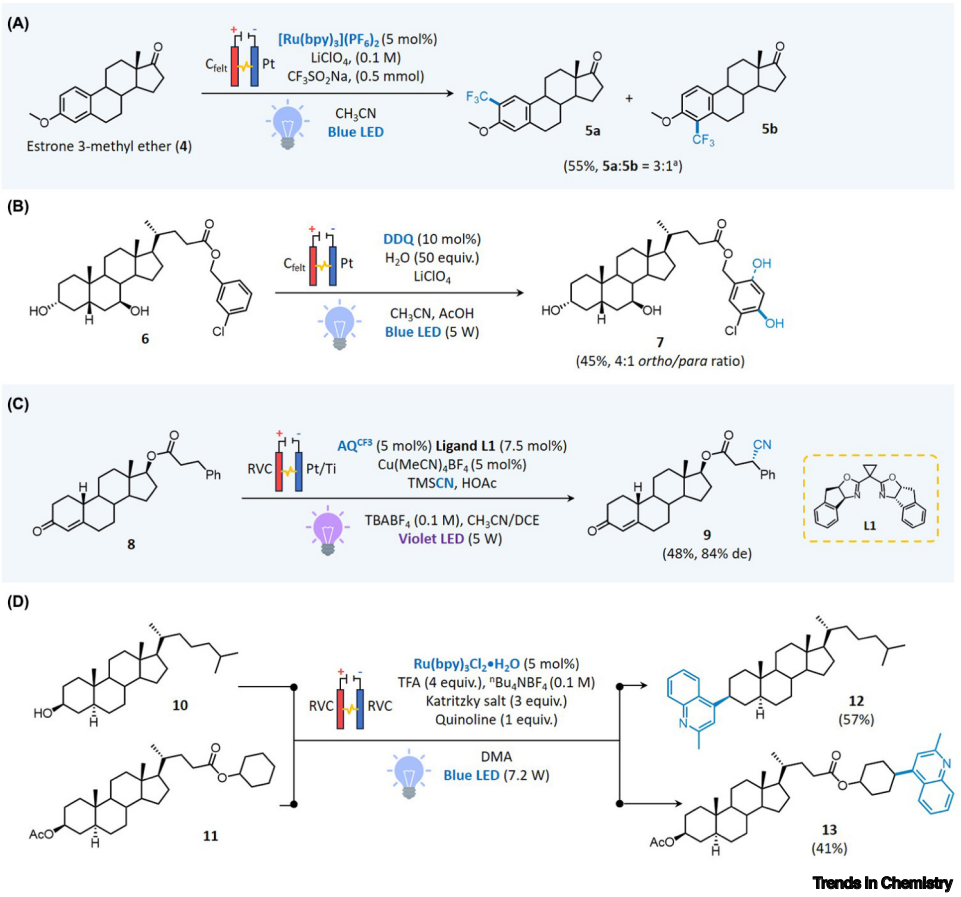

Figure 2. Examples of electrophotochemical functionalization of steroids. Abbreviations: C_{felt}, carbon felt; RVC, reticulated vitreous carbon.

PD) profiles [30]. However, the selective introduction of CF_3 groups onto complex scaffolds remains a synthetic challenge. In this study, estrone 3-methyl ether (**4**) was reacted with mesitylene and the Langlois reagent (CF_3SO_2Na) in a simple undivided **electrochemical cell** (see Glossary) to afford monosubstituted C2- (**5a**) and C4- (**5b**) trifluoromethylated products in a 3:1 ratio and 55% yield (Figure 2A). While the reaction mechanism remains to be fully clarified, it is likely that the transformation proceeds via the generation of a CF_3 radical and single-electron transfer (SET). Interestingly, the method was tested under flow conditions telescoping the electrochemical and the photoinduced step.

Another relevant application was described by Lambert *et al.* in 2021, who reported the oxidative C–H functionalization of arenes, enabling hydroxylation, alkoxylation, and amination reactions without external oxidants [31]. Under visible light irradiation and mild electrochemical potential, and using 10 mol% 2,3-dichloro-5,6-dicyanoquinone (DDQ) as electrophotocatalyst, they achieved selective hydroxylation at the aromatic portion of the ursodeoxycholate ester derivative (**6**) in 45% yield (Figure 2B). Other examples include the enantioselective benzylic cyanation of the nandrolone derivative (**8**) via independent hydrogen atom transfer (HAT) (Figure 2C) [32] and the deaminative alkylation of cholesterol (**10**) and lithocholic acid derivatives (**11**) using Katritzky salts under oxidant-free conditions (Figure 2D) [33].

Electrochemical cross-coupling reactions: building bonds on a steroidal scaffold

Cross-coupling reactions are central to modern organic synthesis, enabling C–C bond formation under mild, functional group-tolerant conditions [34–36]. Their reliance on transition-metal catalysis makes them particularly suited for complex molecule derivatization, including steroids [22,37]. In this context, Stille and Suzuki couplings have been widely applied to functionalize key positions such as the C17, allowing the introduction of heterocyclic motifs relevant to the synthesis of bioactive bufenolide and cardenolide derivatives (Figure 1B) [38]. These strategies expand the structural diversity of steroidal scaffolds for medicinal chemistry applications.

One of the earliest methods for C–C bond-forming reaction is via Kolbe electrolysis, which has regained momentum because of its simplicity and effectiveness. This classical approach relies on the oxidative decarboxylation of aliphatic carboxylic acids to generate transient alkyl radicals that dimerize to form $C(sp^3)$–$C(sp^3)$ bonds. Despite its straightforwardness, traditional Kolbe conditions often show poor functional group tolerance, limiting its use in complex molecule synthesis. To overcome this, Baran and coworkers developed a Ni-electroreductive decarboxylative coupling using redox-active esters (RAEs) and a simple ElectraSyn 2.0 setup (Zn **anode**, Ni foam **cathode**) (Figure 3A) [39]. The protocol involves the *in situ* formation of RAEs from carboxylic acids using NHPI, *N*,*N*′-diisopropylcarbodiimide (DIC), and 4-dimethylaminopyridine (DMAP), followed by electrolysis in dimethylformamide with a Ni catalyst and ligand. This operationally simple method enables access to complex molecular fragments, including steroid derivatives, in just two steps. For instance, chenodeoxycholic acid (**14**) and C3-keto lithocholic acid (**17**) were homologated in 60% and 54% yield, respectively, compared with the much lower overall yields (47% and 23%) from traditional seven- or eight-step sequences [40,41].

A similar strategy was applied for the enantioselective electrochemical Nozaki–Hiyama–Kishi (NHK) coupling between a steroidal RAE and a 1,3-benzodioxole-5-carboxyaldehyde (**20**) (Figure 3B) [42]. In contrast to the conventional NHK reaction, this electroreductive protocol made use of silyl chloride as an oxophilic additive, $CrCl_3$ rather than $CrCl_2$, a lower **current**, and a Ni foam cathode. When the reaction was tested on dehydrocholic acid (**19**) and triacetyl cholic acid (**22**), it resulted in the formation of corresponding 1,3-benzodioxole derivatives in 49% and 62% yield, respectively (Figure 3B). Optimizing ligands, Cr and Ni sources, and electrochemical parameters eliminates the need for superstoichiometric metal reductants while significantly broadening the reaction scope.

Another valuable approach comprises electroreductive olefin–ketone coupling, which offers a more user-friendly alternative to traditional Grignard additions. This method provides access to tertiary alcohols by reversing conventional reactivity: ketones act as nucleophiles toward simple, unactivated olefins. Baran and coworkers demonstrated that this procedure is scalable, chemoselective, and air and moisture tolerant [43], enabling the synthesis of various derivatives from different steroid scaffolds, including the efficient two-step synthesis of the hedgehog signaling modulator (**15**) (Figure 3C). Recently, Liu and collaborators extended this concept by applying similar electrochemical conditions to achieve e-allylation of the C17 ketone (Figure 3D) [44].

Beyond $C(sp^3)$–$C(sp^3)$ bond formation, increasing attention has turned to $C(sp^3)$–$C(sp^2)$ couplings [45,46]. Transition-metal-catalyzed reductive cross-coupling methods are particularly appealing as they bypass the need for preformed organometallic reagents. Alcohols, due to their abundance, stability, and benign nature, are emerging as valuable alkyl radical precursors. Traditional Friedel–Crafts alkylation suffers from rearrangements, harsh conditions, and poor compatibility with electron-deficient arenes [47]. To address these challenges, Wang *et al.*

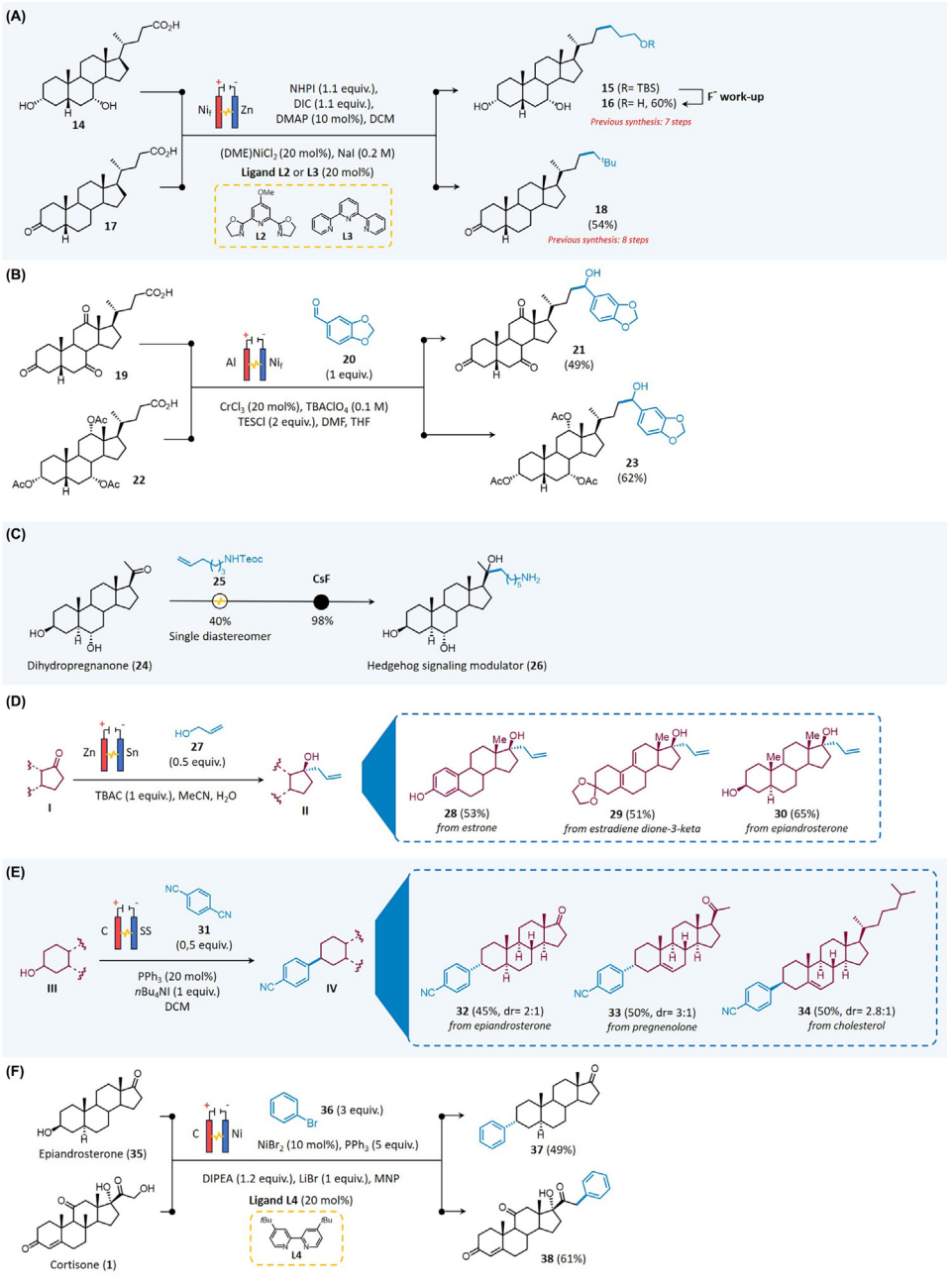

Figure 3. Representative examples of electrochemical cross-coupling reactions on steroids. Abbreviations: Ni_f, nickel foam; SS, stainless steel.

developed a fully electrochemical, metal-free method for dehydroxylative arylation [48]. Their protocol involves anodic oxidation of a $P^{(III)}$ reagent to generate alkoxy radicals from nonactivated alcohols, which undergo β-scission and couple with reduced arenes (Figure 3E). Li and collaborators reported a complementary Ni-catalyzed electrochemical approach, enabling $C(sp^3)$–$C(sp^2)$ coupling between aryl bromides and unactivated alcohols directly on the steroid core [49]. The

method expanded the synthetic repertoire for modification of unactivated positions of the steroidal nucleus rather than the side chain (compounds **37**, **38**) (Figure 3F).

Electrochemical hydrogenation/deuteration of steroids

Hydrogenation is a crucial transformation in organic synthesis due to its broad applicability, the ability to selectively reduce a wide range of functional groups, and its scalability for industrial applications [50–52]. Although there have been significant developments in conventional, long-established hydrogenations, the vast majority of these reactions remain limited by the use of expensive and toxic transition-metal catalysts. Moreover, in some cases, they can be problematic under conventional conditions, especially at a large scale. The presence of hydrogen-rich headspace in flammable organic solvents raises significant safety issues [53–55]. Transition-metal electrocatalysis presents a promising opportunity to replace H_2 with electrons and protons, enabling safer and milder hydrogenation reactions.

In the past decades, significant advances have been made in electrochemical hydrogen-free hydrogenations via sequential SET and protonation [53,56]. In 2023, a metal-free methodology using hydrazine as an inexpensive source of H_2 was applied for the reduction of ethinylestradiol (**39**) (Figure 4A) [57]. The reaction proceeded via a cyclic transition state to enable the transfer of hydrogen from *cis* diimide (HN=NH) to the triple bond of compound **39** (81% yield). In a more recent paper by Fu and colleagues, an electrochemical Ni-catalyzed hydrogenation was applied to the synthesis of steroidal substrate derivatives of progesterone (**41**) and testosterone (**42**) (Figure 4B) [58]. By using alternating polarity to avoid the depletion of Ni^{II} (via cathodic reduction) and a simple and bench-stable nickel salt as the catalyst ($NiCl_2$•$6H_2O$), the chemoselective reduction of the Δ^4 double bond over the ketone was achieved in high yield. Although the reduction provided a mixture of C5α- and C5β-epimers, the method appeared robust as the reaction was scaled up to 10 mmol.

Aldehyde and ketones can be reduced by electrochemical deoxygenative hydrogenation. Merging the classical Clemmensen reduction with electrochemistry, it is possible to reduce carbonyls at steroids under mild reaction conditions with good functional tolerance [59]. The reaction made use of aqueous HCl as the hydrogen source and Bu_4NPF_6 as **electrolyte** in an undivided cell in the presence of triethanolamine (TEOA) (Figure 4C). In this case, a sacrificial anode (Zn) acted as an electron conductor converting ketones/aldehydes into radical anions, which is then protonated and dehydrated to furnish a C-centered radical cation. The following transfer of electrons from the cathode and the capture of protons from acidic aqueous solution led selectively to the desired reduced steroids **43**–**46** (Figure 4C).

A compelling example is the selective electrochemical hydrogenation of epoxides to alcohols reported by Huang and coworkers in 2022 [60]. Remarkably, the regioselectivity of the reaction (Markovnikov vs anti-Markovnikov) could be tuned by substrate structure, enabling access to primary, secondary, and tertiary alcohols under mild conditions. The strategy demonstrated excellent functional group compatibility, including steroidal compounds. In particular, the C3-protected pregnenolone epoxide (**47**) was converted into the corresponding 17-hydroxy alcohol **48** in 55% yield (Figure 4D).

Inspired by the evolution of electrochemical hydrogenation methods, several groups have disclosed new approaches to electrochemically incorporate deuterium (D) into organic molecules, in view of its relevance in mechanistic studies and pharmaceutical sciences [61]. Generally, standard deuteration methods involve the employment of deuterium solvents and paired external reductants such as Mg, SmI_2, Zn, and Mn, which are expensive and unsuitable for scale up.

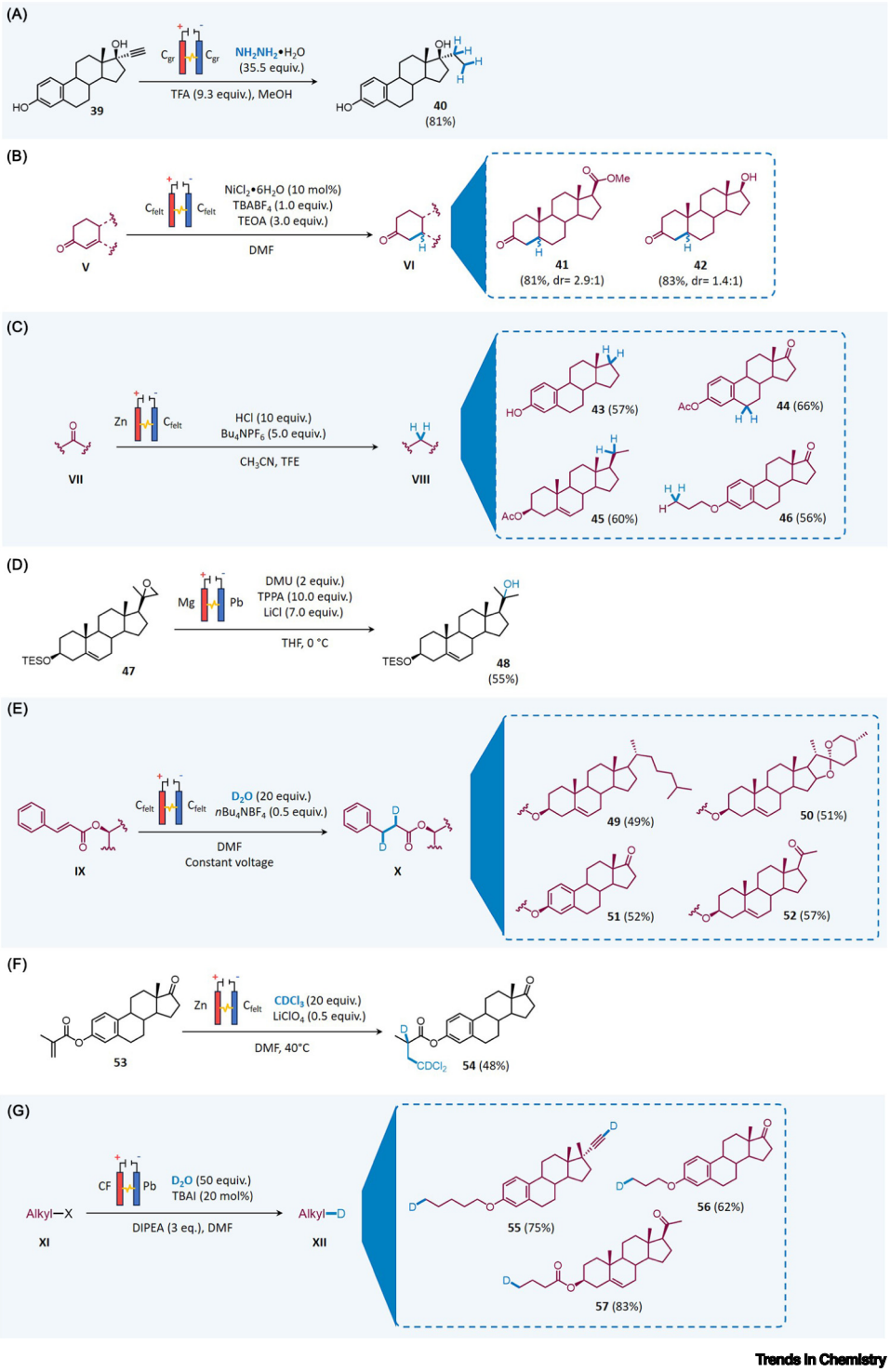

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Figure 4. Electrochemical hydrogenation (A–D) and deuteration (E–G) reactions of steroids. Abbreviations: CF, carbon fiber; C_{felt}, carbon felt; C_{gr}, graphite.

Electrochemistry was found to facilitate deuteration using cheap deuterium sources such as D_2O and in the absence of an external reductant. For example, Cheng and colleagues described the electrochemical deuteration of α,β-unsaturated carbonyl compounds under catalyst- and external reductant-free conditions, with excellent deuteration rates (99%) and yields ranging from 47% to 57% for the C3-functionalized steroidal derivatives (compounds **49**–**52**, Figure 4E) [62]. The same group developed a protocol based on deuterochloroform ($CDCl_3$) as a one-carbon deuteration block to achieve the reductive deuterodichloromethylation of C3-methacryloylestrone (**53**) (48%) (Figure 4F) [63]. Other approaches include the electroreductive deuteration of unactivated alkyl halides in D_2O. The reaction was conducted on both estrone (compounds **55**, **56**) and progesterone derivative (**57**) in the presence of tetrabutylammonium iodide (TBAI) (20 mol %) and *N*, *N*-diisopropylethylamine (DIPEA) (1.5 mmol) under 30 mA constant current in an undivided cell at room temperature with carbon felt as anode and lead plate as cathode (Figure 4G) [64].

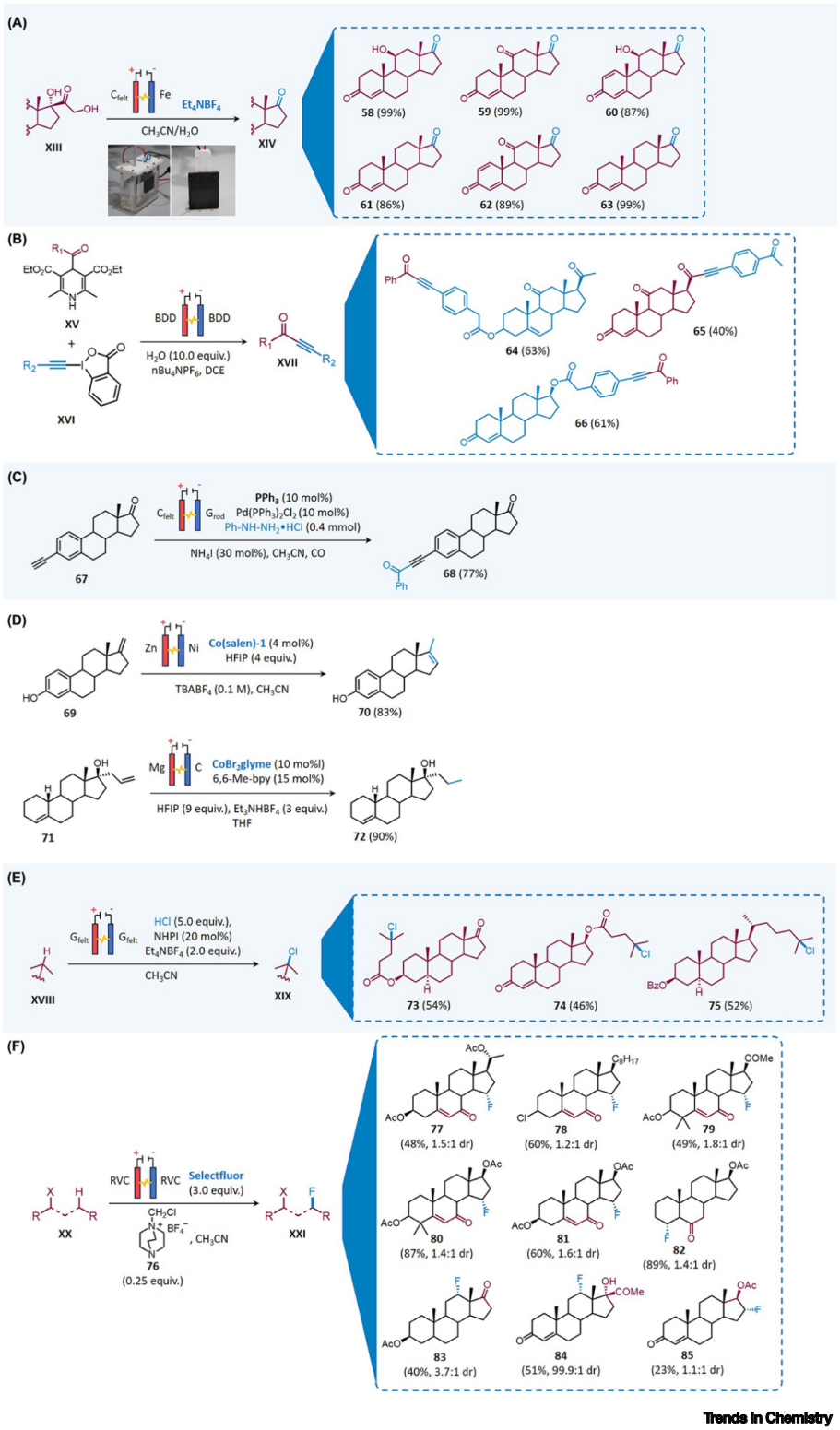
Miscellaneous

This section highlights diverse electrochemical transformations that fall outside the main categories discussed earlier. Although heterogeneous in scope, these reactions further underscore the versatility of electrochemical LSF. This strategy enables rapid diversification of complex molecules without the need for *de novo* synthesis or protecting group strategies. As such, it represents a valuable approach in medicinal chemistry to accelerate SAR campaigns, enhance pharmacokinetic properties, and expand the accessible chemical space of natural products and lead compounds [61–63].

A notable application is the electrochemical C17 side-chain cleavage of corticosteroids to access C19 androgens, reported by Kappe and Cantillo in 2021 (Figure 5A) [65]. This reagent-free method avoids harsh oxidants or biocatalysis, using an undivided cell with graphite and stainless-steel (SS) electrodes (Box 1). The yields for six corticosteroids (compounds **58**–**63**) ranged from 86% to 99%, with the reaction proceeding via anodic oxidation and *in situ* hydrogenation, enabling a one-pot, two-step protocol.

Electrochemistry has also enabled the synthesis of ynones, valuable intermediates for multicomponent reactions, cycloadditions, rearrangements, and stereoselective transformations [66,67]. Wang and coworkers developed a metal- and photocatalyst-free electrochemical approach for the oxidative homolysis of 4-acyl-1,4-dihydropyridines (**XV**), producing acyl and carbamoyl radicals that couple with iodine$^{(III)}$ species (**XVI**, Figure 5B) [68]. Using boron-doped diamond (BDD) electrodes in an undivided cell, the method showed broad scope and late-stage applicability, converting cortisone, pregnenolone, and testosterone derivatives into the corresponding ynones (**64**–**66**) in up to 63% yield (Figure 5B). In the same year, Lei and coworkers reported an electrochemical Pd-catalyzed carbonylation of arylhydrazines with alkynes, avoiding the use of carbon monoxide, molecular oxygen, and chemical oxidants (Figure 5C) [69]. Using anodic Pd$^{(0)}$ reoxidation in a copper-free, undivided cell, the method delivered an estrone-derived ynone (**68**) in 77% yield.

Electrocatalysis has also emerged as a powerful tool for double-bond functionalization. A significant advance in the electrochemical functionalization of unsaturated C–C bonds comprises the generation of cobalt hydrides (Figure 5D) [70]. These species enabled electrocatalytic HAT (e-HAT) for alkene/alkyne isomerization, reduction, and hydrofunctionalization under mild conditions, with compatibility in both batch and flow configurations. When applied to steroids, estratriene isomerization and side-chain reduction proceeded in 83% (**70**) and 90% (**72**) yield, respectively (Figure 5D). Additional strategies include a cobalt-hydride-mediated electrocatalytic hydroetherification via radical-polar crossover [71] and an electrooxidative hydrofluorination



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Box 1. Electrode types and abbreviations

Electrodes can be chemically inert or reactive, and their choice has profound effects on electrochemical outcomes.

Carbon-based electrodes

- Carbon felt (C_{felt}): a porous, sponge-like material made of interconnected carbon fibers. C_{felt} offers high surface area and conductivity and can be applied to flow electrolysis, to low-current-density redox reactions, and as a reusable electrosynthesis support.
- Graphite (C graphite): planar, sheet-like crystalline carbon. C graphite is chemically inert, inexpensive, and widely used in electroorganic synthesis, especially where there is a requirement for stable anodes or cathodes.
- Glassy carbon rod (G_{rod}): a hard, non-porous carbon material with low background currents and great chemical resistance. G_{rod} is commonly employed in electrochemical preparative and analytical uses because of its inert character and well-defined electrochemical properties.
- Carbon fiber (CF): carbon-filament-based CF electrodes are bundled with good conductivity and a moderate surface area. They are much sought after for microfluidic electrochemistry, low-current operations, and compatibility.
- Reticulated vitreous carbon (RVC): an open-cell, 3D, porous carbon foam that is highly conductive and porous. Its large effective surface area makes it a candidate for high-current-density electrosynthesis, particularly in undivided cells.
- Boron-doped diamond (BDD): a highly inert, crystalline boron-doped carbon electrode for the provision of conductivity. BDD electrodes have a very wide electrochemical window and are resistant to fouling, making them suitable for oxidations and reactions under harsh or oxidative conditions.

Metal electrodes: semi-inert or inert

- Platinum (Pt): a noble metal with widespread applications as a result of its high conductivity, chemical inertness, and corrosion resistance. It is both a working and a counter electrode in electrochemical setups and most appropriate for redox reactions in acidic and basic mediums.
- Titanium (Ti): a resistant metal used frequently as a substrate or support for **electrocatalysts**. While less inert than Pt, its passive oxide layer prevents it from reacting with most electrolytes. It is extensively used in industrial electrolysis and as an anode in anodic oxidations.
- Stainless steel (SS): an inexpensive, durable alloy that largely comprises nickel, chromium, and iron. It is quite conductive as well as resistant to chemicals under various conditions, but when it is subjected to extreme acid or base electrolysis, it corrodes. Often used for scale-up studies.

Metal electrodes: active or sacrificial

- Nickel foam (Ni_f): a porous, high-surface-area electrode that is widely used as a sacrificial anode or in electrocatalysis. Its porous structure allows easy gas evolution and better electrode–solution contact and it is therefore valuable for hydrogen evolution and reductive conversions.
- Aluminum (Al): a reactive metal that finds widespread application as a sacrificial anode in electrochemical synthesis. It can readily dissolve on anodic polarization and give away electrons and Al^{3+} ions. Of use in reductive processes and electrochemical coupling reactions.
- Zinc (Zn): a commonly employed sacrificial anode possessing a standard potential suitable for driving reductive conversions. Zn dissolves during electrolysis and therefore becomes applicable in paired electrolysis or in situations where reducing equivalents are needed.
- Tin (Sn): a quite active metal that can be used as either an anode or a cathode. Tin is valued due to its inertness with respect to reducing conditions and is applied in reductive electrochemical methods or plating reactions.
- Lead (Pb): an active metal of high overpotential; can be utilized for reductive electrolysis, especially proton-coupled electron transfer reactions. Because it is toxic, it is utilized in legacy or special systems only.
- Magnesium (Mg): highly electropositive and likely to be utilized as a sacrificial anode, particularly in highly reducing environments. Mg dissolves readily and can supply electrons as well as serve as a reagent in electrochemical conversions.

employing Pd catalysis with a nucleophilic fluorine source under mild conditions [72]. Both methods demonstrated high functional group tolerance and steric compatibility, enabling the LSF of estrone derivatives.

Electrochemistry has also proved highly effective in late-stage C(sp^3)–H bond functionalization. In 2024, Liu and coworkers developed a practical and scalable electrochemical method for the

Figure 5. Selected examples of electrophotochemical late-stage functionalization of bioactive steroids. Abbreviations: BDD, boron-doped diamond; C_{felt}, carbon felt; G_{felt}, graphite felt; G_{rod}, glassy carbon rod; RVC, reticulated vitreous carbon.

selective halogenation of tertiary and secondary benzylic C–H bonds [73]. Utilizing *N*-hydroxyphthalimide (NHPI) as a redox mediator and operating in an undivided cell with graphite felt as the anode and a platinum plate as the cathode, the protocol enabled efficient and chemoselective chlorination and bromination. The methodology showed broad substrate

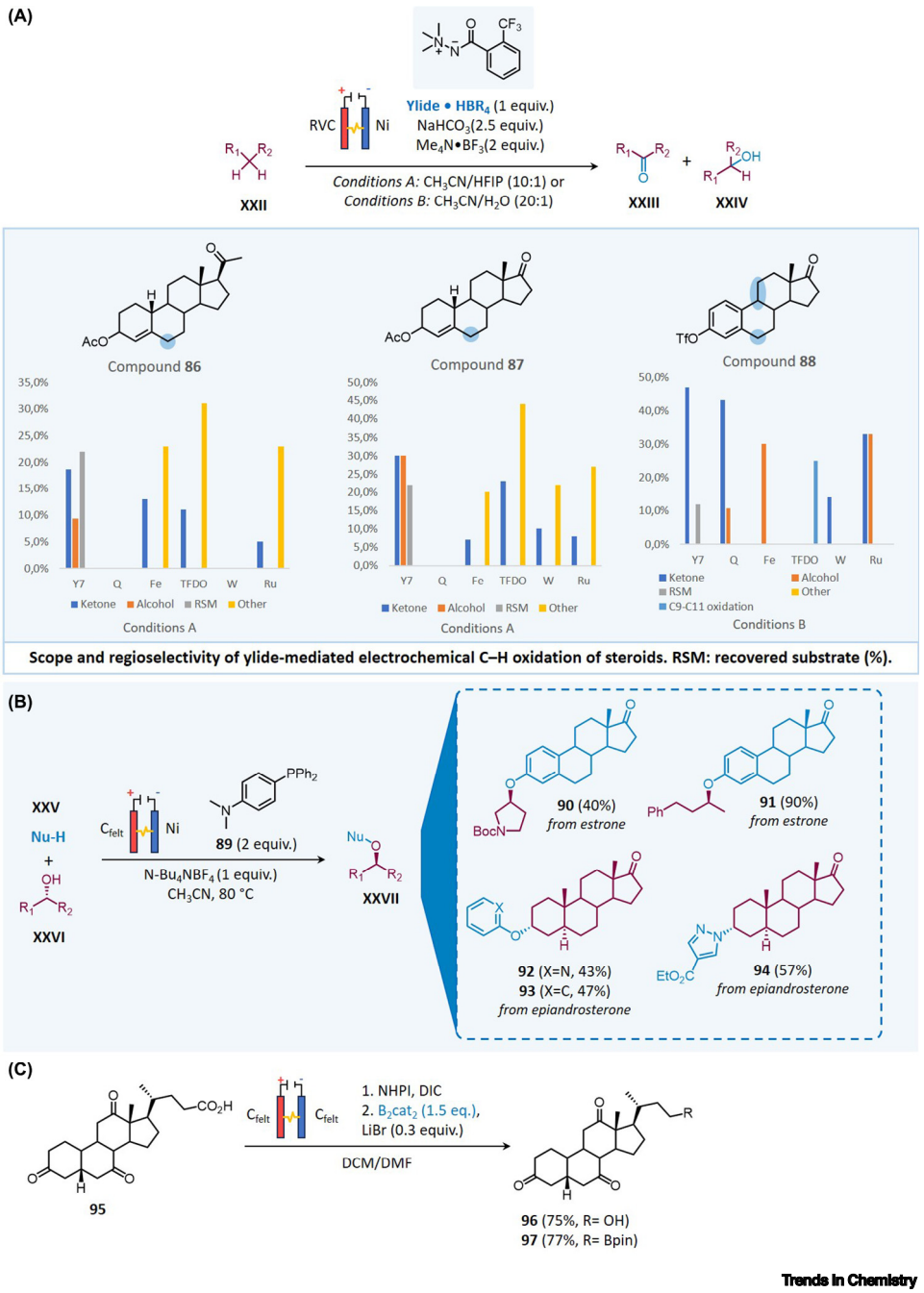

Figure 6. Electrochemical oxidation and Mitsunobu variants applied to steroidal molecules. Abbreviations: C_{felt}, carbon felt; RVC, reticulated vitreous carbon.

scope and functional group tolerance, affording chlorinated derivatives of epiandrosterone (**73**), testosterone isocaproate (**74**), and 5α-cholestan-3β-ol (**75**) in 54%, 46%, and 52% yield, respectively (Figure 5E). Fluorination of unactivated C(sp^3)–H bonds was addressed by Lectka and coworkers using a dabconium mediator (**81**) and Selectfluor (Figure 5F) [74]. This electrochemical method, which used reticulated vitreous carbon (RVC) electrodes and polarity switching, afforded site-selective fluorination of nine diverse steroid scaffolds, with yields of 55–89% (compounds **77**–**85**) (Figure 5F).

Baran's group also developed a site- and chemoselective electrochemical oxidation of aliphatic C–H bonds using novel *N*-ammonium ylides as oxidants (Figure 6A) [75]. These computationally designed reagents showed broad applicability and selectivity. Applied to pregnenolone (**86**), androstane (**87**), and estradiol (**88**) derivatives, the method delivered oxidized products in 28%, 60%, and 47% yield, respectively. Recently, Guo and coworkers described the electrochemical variant of the Mitsunobu reaction (Figure 6B) [76]. Traditionally reliant on hazardous azo reagents and stringent inert conditions [77], the Mitsunobu reaction has now been rendered safer and more practical via a redox-mediated approach. The authors employed an electron-rich triarylphosphine as a redox-active mediator in an undivided cell setup, obviating the need for air- and moisture-free conditions. This operationally mild system allowed the efficient coupling of a diverse range of alcohols and nucleophiles, providing ethers and amines in moderate to excellent yields, often with high enantiomeric excess (Figure 6B). Of particular note is the method's applicability to complex substrates. When applied to steroidal alcohols, such as estrone and androstane derivatives, the transformation delivered single diastereomers in yields ranging from 26% to 90% (compounds **90**–**94**, Figure 6B). Furthermore, gram-scale reactions on estrone and other chiral alcohols afforded the desired products in good yields. In a complementary development [78], the electrochemical conversion of alkyl carboxylic acids to boronic acids via RAEs was reported. This metal-free protocol dispenses with both stoichiometric reducing agents and photochemical activation, relying instead on graphite electrodes. Notably, the borylation of dehydrocholic acid (**95**) furnished the corresponding boronic acid (**97**) in 77% yield (Figure 6C), showcasing the method's compatibility with complex, sterically demanding scaffolds.

Concluding remarks

Steroid synthesis and modification are constrained by conventional methodologies that limit accessible chemical space. Electrochemistry emerges as a sustainable approach for selective functionalization of steroids, utilizing controlled redox processes that enable site-selective modifications even in sterically hindered positions. However, challenges such as optimizing electrochemical conditions, standardizing protocols, and comprehensive product characterization hinder large-scale adoption. Integration with nanotechnology and microfluidic systems presents a promising strategy to address these limitations and expand practical applications. In summary, while electrochemistry offers an innovative and advantageous technique for steroid functionalization, further developments are necessary to overcome technical challenges and realize its full potential (see Outstanding questions). Future efforts should focus on refining reaction conditions, expanding the versatility of the methodology, and integrating it with other advanced technologies.

Steroid synthesis and LSF remain a cornerstone and a persistent challenge of modern medicinal chemistry. Their densely functionalized and conformationally rigid frameworks demand site-selective, sustainable, and operationally versatile methodologies. This review has highlighted how electrochemical strategies, including electrophotocatalysis, metal-free redox processes, and electroreductive cross-couplings, have rapidly expanded the toolbox available for steroid modification.

Outstanding questions

Can electrochemistry achieve truly site-selective C–H functionalization within the steroid nucleus, beyond terminal or activated positions?

When will we see the first industrial-scale electrochemical process applied to steroidal drugs or intermediate synthesis?

Could bioorthogonal electrochemistry or electro-driven library synthesis be used *in vivo* or in early-stage drug discovery?

What role will electrochemistry play in developing sustainable, modular platforms for rapid structure–activity exploration?

Can data-driven approaches (e.g., artificial intelligence/machine learning) help to rationalize or predict optimal conditions for steroid functionalization?

How can electrochemistry be integrated with flow, photochemistry, or biocatalysis to unlock reactivity not accessible by conventional means?

Should electrochemical literacy become a standard part of synthetic chemistry education in both academia and industry?

Across a wide range of transformations, from C–H activation and cross-coupling to hydrogenation, deuteration, and side-chain remodeling, electrochemistry enables access to derivatives that were previously difficult, if not impossible, to obtain. These methods offer unique advantages in terms of redox control, selectivity and functional group tolerance by **voltage** fine-tuning, and reagent economy, with several being compatible with flow electrolysis and bench-stable components. Notably, many of these strategies have been shown to streamline traditional multistep sequences into single-pot or telescoped operations. Despite these advances, widespread adoption in synthetic and industrial settings remains limited. Challenges include the need for reaction condition optimization, standardized reporting of electrochemical parameters, and more thorough mechanistic and scalability studies. Scalability, in particular, remains a critical issue [79]. Although parallel-plate flow electrolysis cells are well established for the scale up of electrochemical processes, they present several drawbacks, including limited mass-transfer efficiency and issues with the solubility of reaction components. Solids should generally be avoided to prevent clogging, often requiring the use of diluted conditions to fully dissolve solid materials thereby undermining the sustainability of the process. This issue is particularly relevant for steroids, which are typically poorly soluble in most organic solvents applicable to electrochemistry.

Additionally, many transformations still focus on appendages rather than directly targeting the steroidal nucleus, leaving open important opportunities for site-selective approaches that can engage more challenging or unactivated positions. The future of the field will likely involve more robust integration with other enabling technologies, such as flow chemistry [80,81], photoreactors [82,83], and biocatalysis [84–86], to access reactivity currently beyond the reach of traditional methods. In parallel, data-driven strategies and machine learning tools may prove essential to streamline the optimization of electrochemical reactions and enhance reproducibility across laboratories.

Moreover, the development of sustainable, modular platforms for rapid optimization and SAR exploration represents a compelling direction [87,88]. The tunability and operational simplicity of electrochemistry offer the opportunity for high-throughput experiments and derivatization of complex scaffolds, enabling fast and systematic access to analogs for SAR studies, particularly valuable in the context of steroids, where minor structural changes can drastically impact biological activity. This emerging workflow, especially when combined with automated or microfluidic systems, could shorten discovery cycles and improve the efficiency of medicinal chemistry pipelines.

Despite growing interest, the translation of electrochemical methods from laboratory scale to industrial settings remains elusive. Demonstrating the feasibility of electrochemical steroid functionalization at scale, especially for the synthesis of APIs or crucial intermediates, represents a key milestone that has yet to be achieved. Additionally, the potential of electrochemistry to operate under biologically relevant conditions remains largely unexplored [89]. Developing bioorthogonal redox systems or electro-driven library synthesis compatible with early-stage drug discovery could open entirely new frontiers for *in situ* molecular editing and functional screening. Overcoming these barriers will require not only technical and methodological advances, but also new models of collaboration between academia and industry, along with stronger educational initiatives and broader infrastructure. Ultimately, electrochemistry is not just a green alternative to classical redox methods, but a distinct paradigm, one that promises to reshape the way we think about complexity, selectivity, and sustainability in steroid chemistry.

Declaration of interests

A.G. is cofounder of Tes Pharma (www.tespharma.com).

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