

# Cathodic Electrolysis: Electroreductive Organic Synthesis

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Cathodic reductive electrolysis in organic transformations is used to generate radical anions. These electrochemical reduction reactions are very useful in various carbonyl groups transformation (such as aldehydes, ketones, esters, and amides), new bond formations as well as reduction of saturated and unsaturated molecules. Reductive electrocarboxylation reactions to access various valuable chemicals are one of the important applications of cathodic reductive electrolysis. Herein,

we review particularly the electrochemical organic transformation reactions taking place at the cathode. We also discuss how alternative strategies such as paired electrolysis, photo-electrolysis, and alternating current electrolysis can be used to overcome the limitations associated with cathodic electrolysis and how they will improve sustainable electrochemical transformations.

## 1. Introduction

Traditional organic synthesis involves the synthesis of a target compound by incorporating a functional group into an organic molecule. An alternative to this method is electro-organic synthesis in which instead of chemical oxidants or reductants (that are required in traditional synthesis), electrons are used to perform redox reactions<sup>[1]</sup> making organic synthesis even more selective and effective.<sup>[2]</sup> It was in the 1840s that Kolbe first investigated electro-organic transformation reactions.<sup>[3]</sup> Currently, electro-organic synthesis has attracted considerable interest from contemporary synthetic scientists.<sup>[2]</sup> Three main approaches are employed in electro-organic synthesis: net reductive cathodic electrolysis, net oxidative anodic electrolysis, and neutral electrolysis where two half-reactions occur in both electrodes.<sup>[4]</sup>

The electrochemical reduction can be performed in two types of cells: paired or unpaired cells, and the approach may be either direct electrolysis or indirect electrolysis. The transformation may be conducted either under constant current conditions or under constant potential conditions which prolongs the reaction time.<sup>[5]</sup> In direct electrolysis, transfer of an electron to the molecules occurs on the electrode surface, whereas in indirect electrolysis, the redox mediator is oxidized or reduced first and then it transfers the electron to the organic molecule.<sup>[6]</sup> For example, the electrochemical reduction of CO<sub>2</sub> into CO can be performed in two different electrochemical cells. In indirect electrolysis, TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) was used as a redox mediator (Scheme 1a) whereas in direct electrolysis organic compound was reduced without a mediator (Scheme 1b).<sup>[7]</sup> The overall redox reaction happening during electrochemical cathodic reduction includes an oxidation reaction with the release of electrons at the anode. The electrons released at the anode are then continuously pumped to the cathode assisting in the reduction of the organic compound at the cathode.<sup>[8]</sup>

Although anodic oxidative electrosynthesis has widely been explored, cathodic reductive electrosynthesis is still less popular among scientists.<sup>[9,10]</sup> The primary drawback associated with the reductive technique include its reliance on a sacrificial electrode<sup>[6]</sup> and the need for a suitable counter-oxidation reaction at the anode.<sup>[8]</sup> Cathodic reductive electrosynthesis is undoubtedly safer than conventional reduction strategy because we can avoid use of hazardous chemical reductants like metal hydrides, boranes and silanes. In recent years, cathodic reduction has assumed a pivotal role in coupling reactions and carbon-hetero bond formation. Nevertheless, enhancing the efficiency and selectivity of these reactions for optimal product generation continues to pose challenges. Additionally, utilization of toxic heavy metals in the cathode material could give rise to significant health risks. Therefore, the judicious selection of an appropriate cathodic material stands as a crucial factor for achieving success in electro-cathodic reactions.<sup>[8]</sup> Despite these obstacles, cathodic electrosynthesis has made significant progress. In this review, we highlighted the application of cathodic

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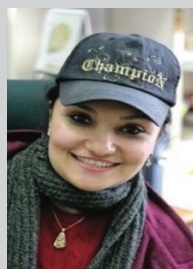
Manisha Paudel is currently doing her Master's degree with a major in Organic Chemistry at Central Department of Chemistry, Tribhuvan University, Nepal. She is currently doing her thesis on Essential Oil under the supervision of Assoc. Prof. Dr. Achyut Adhikari. Her major research area includes Natural product chemistry, Organic Synthesis, Nanotechnology and Analytical chemistry.



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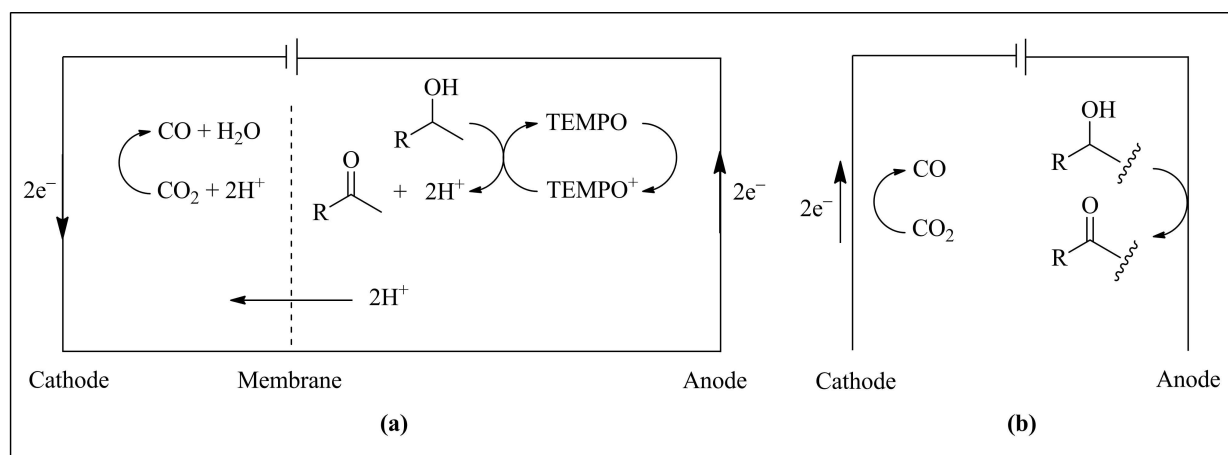
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**Scheme 1.** Reduction of carbon-dioxide gas at the cathode. **a)** indirect electrolysis **b)** direct electrolysis.<sup>[7]</sup>

reductive electrolysis in the generation of radical anions, various carbonyl groups transformation (such as aldehydes, ketones, esters, and amides), new bond formations, and reduction of saturated and unsaturated molecules. We also discussed how alternative strategies such as paired electrolysis, photo-electrolysis, and alternating current, can be used to overcome the limitations associated with cathodic electro-synthesis and will improve sustainable electrochemical transformations.

## 2. Cathodic reductive electrolysis to generate radical anions

Organic radicals are highly reactive reaction intermediates that play a crucial role in drug synthesis, material science, and agrochemicals.<sup>[11]</sup> Different organic compounds like alkyl or aryl halides, carbonyl compounds, and alkenes can be used as a precursor to synthesize organic radicals via cathodic electrolysis. The synthesized radicals can be used in different organic transformations: addition to a carbon-carbon double bond, a second cathodic reduction to carbanion, and radical-radical cross-coupling.<sup>[12]</sup> For example, Lin and co-workers<sup>[13]</sup> synthesized alkyl radicals by electroreduction of alkyl/aryl halides. They performed electroreductive carbonylation of alkenes by using haloalkanes as a radical precursor. The proposed mechanism of the transformation involves the initial reduction of bromoalkane **5** at the cathode to form an alkyl radical. The alkyl radical then undergoes addition to the C=C bond of alkene to form a new C-centered radical **6**. Further reduction of the newly formed radical **6** at the cathode yields carbanion **7** which finally reacts with electrophiles like DMF (CHO donor), MeCN (H<sup>+</sup> donor), and CO<sub>2</sub> to give an alkylated product **8** (Scheme 2). They reported this method to be highly chemoselective and regioselective.<sup>[13]</sup>

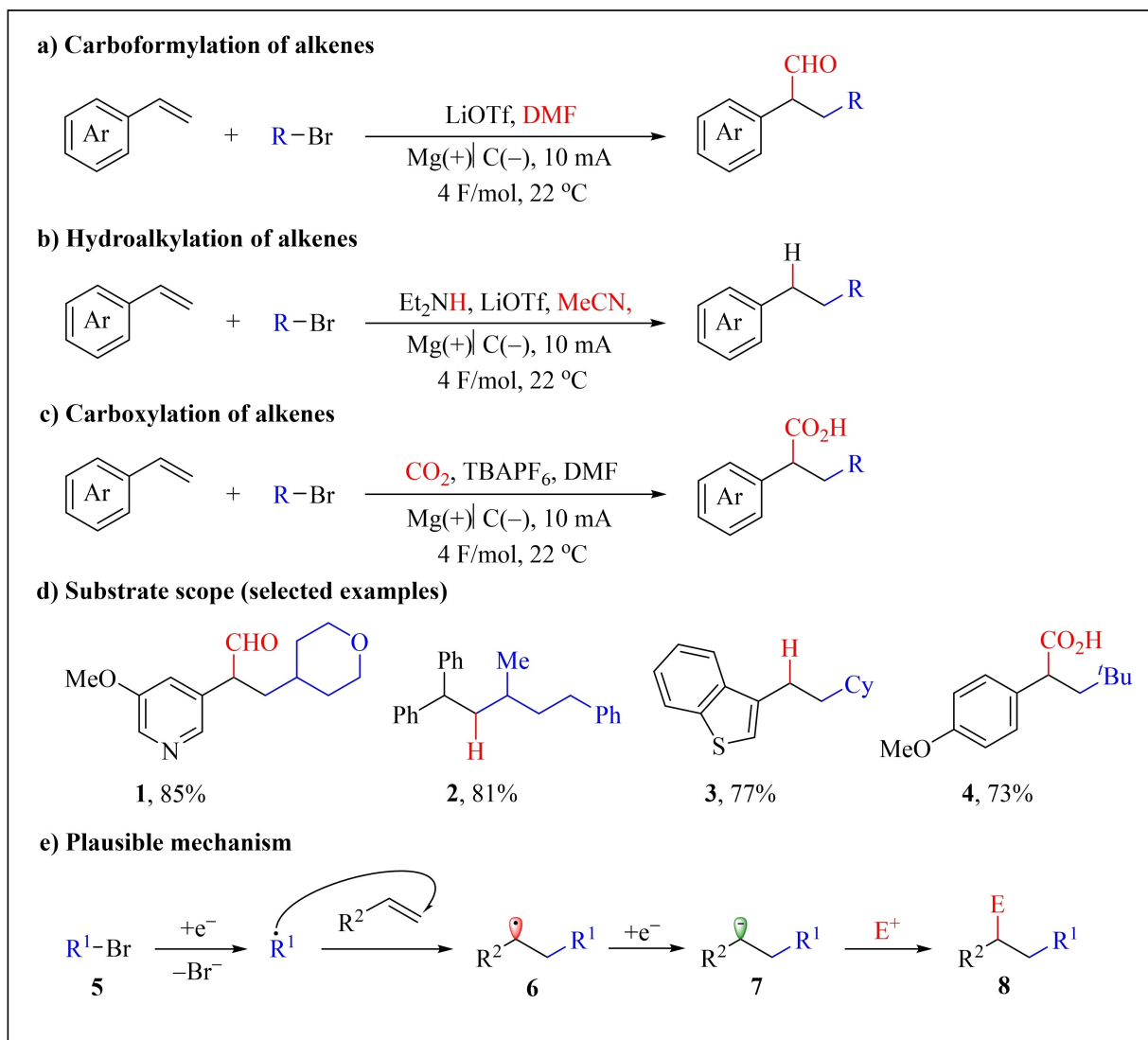
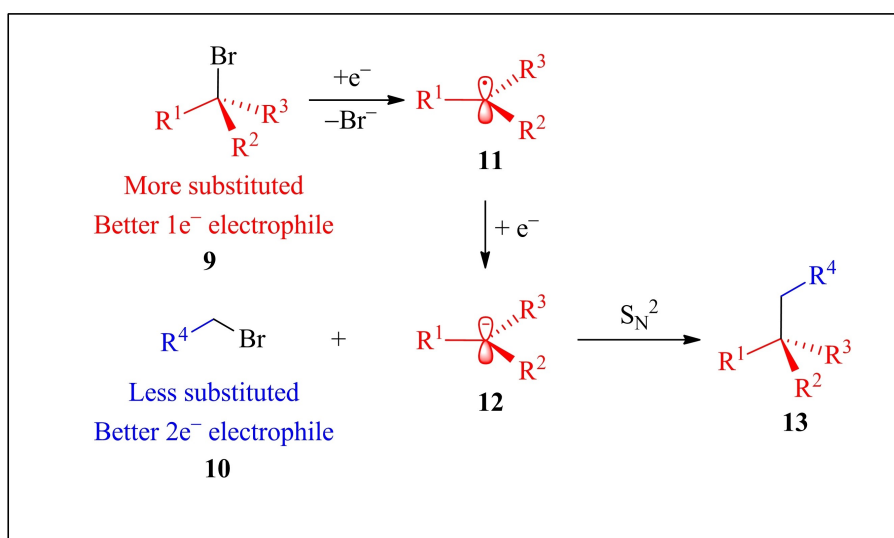
In 2022, Zhang et al.<sup>[14]</sup> performed electroreductive cross-coupling of two differently substituted haloalkanes and reported high selectivity and differential activation of haloalkanes. Here, since the alkyl substituents in the more substituted

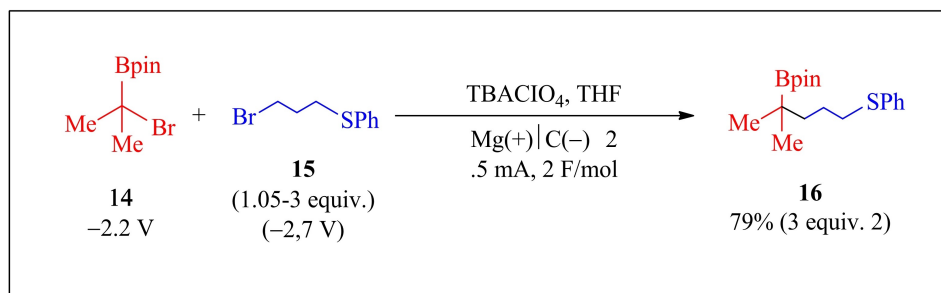
haloalkanes provide extra stability to the alkyl radicals, they undergo single electron reduction whereas the substituted haloalkane acts as an electrophile because of lesser steric hindrance in the molecule. Therefore, the reaction involves selective reduction of a more substituted haloalkanes **9** at the cathode to form C-centered radical **11** which after the second reduction forms a carbanion **12**. Subsequently, the carbanion **12** is preferentially coupled with less substituted haloalkane **10** through the S<sub>N</sub><sup>2</sup> mechanism forming a new C(sp<sup>3</sup>)-C(sp<sup>3</sup>) bond in the final product **13** (Scheme 3). Interestingly, electrolysis of a mixture of tertiary  $\alpha$ -bromo Bpin **14** and primary alkyl bromide **15** by using graphite cathode and magnesium anode formed the product **16** in 79% yield (Scheme 4). Here, in tertiary  $\alpha$ -bromo Bpin **14**, anion stabilizing boryl substituent is introduced which forms p-p or p- $\pi$  conjugation with resultant carbanion facilitating the desired 2e<sup>-</sup> reduction process. This stabilization effect also contributes to the high chemoselectivity of the reaction thereby increasing its synthetic value.<sup>[14]</sup>

Recently, Hu et al.<sup>[15]</sup> synthesized tertiary alcohols by electroreduction of a mixture of ketone and unactivated alkene. They used Sn as a cathode, Zn as a sacrificial anode, and nBu<sub>4</sub>NBr as an electrolyte. The reaction proceeds via the initial reduction of ketone substrate **22** at the cathode to form ketyl radical anion **23** which further reacts with the alkene to give a C-centered radical **24**. The radical **24** is then further reduced to nucleophilic C-centered species **25**. Finally, a proton is abstracted by the species **25** from  $\alpha$ -position of another ketone molecule to give a tertiary alcohol **27** (Scheme 5).<sup>[15]</sup>

## 3. Carbonyl group transformation

The C=O bond of carbonyl groups is present in different organic compounds like aldehydes, ketones, carboxylic acids, and their derivatives (esters and amides). This carbonyl group can form a versatile ketyl radical intermediate via a single-electron cathodic reduction.<sup>[16]</sup> Further transformation of the ketyl intermediate can be obtained by hydrogenation, deoxygenation, or functionalization.

Scheme 2. Electroreductive synthesis of alkyl radicals by using haloalkanes as a precursor.<sup>[13]</sup>Scheme 3. Proposed mechanism for electroreductive cross-coupling of two differently substituted haloalkanes.<sup>[14]</sup>



Scheme 4. Electroreductive cross-electrophile coupling of tert- $\alpha$ -bromo Bpin and alkyl bromides.<sup>[14]</sup>

### 3.1. Reductive hydrogenation of C=O bond

Aldehyde and ketones, on reductive hydrogenation, gives their respective alcohols and deoxygenated alkanes. In 2021, Siewert and co-workers successfully carried out constant-potential electrolysis for the electroreduction of aliphatic aldehydes/ketones to alcohols. It involves the use of Mn catalyst in 7.5 equivalent phenol in a divided cell of a three electrode system.<sup>[17]</sup> 2,2,2-trifluoroacetophenone was promoted electrochemically in presence of Ru catalyst to perform enantioselective transfer hydrogenation as reported by the groups of Wang and Lu. It involves a Pt cathode and sacrificial Mg anode and the product  $\alpha$ -trifluoromethyl benzyl alcohol was formed with 96% yield and 94% enantiomeric excess.<sup>[18]</sup> Recently, they showed that in the presence of Sodium azide (NaN<sub>3</sub>) with graphite felt electrodes in acidic medium, the specific electroreduction of ketones to methylene compounds, pinacols or alcohols can be achieved. During the process, few reductive transformation of phthalimides are also observed.<sup>[19]</sup> Due to the toxic and explosive nature of NaN<sub>3</sub>, it should be handled cautiously.

Recently, Kawamata and co-workers devised a practical electroreductive protocol for carbonyl compounds with the application of square waveform to deliver alternating current to attain chemoselectivity which is impossible through DC electrolysis<sup>[20]</sup> or reagents like LiBH<sub>4</sub>, diisobutyl aluminum hydride (DIBAL), and Ph<sub>2</sub>SiH<sub>2</sub> (Scheme 6).<sup>[21]</sup> Clearly, this technique exhibits dominance of imide reduction over other carbonyl groups, such as ketones, aldehydes, and ester, and it applies to some groups or positions of the substrate that are sensitive to reduction and oxidation.<sup>[22]</sup>

In 2021, Chiba's group devised an electrochemical deoxygenative hydrogenation of secondary amides with the application of a Zn, Al sacrificial anode or boron-doped diamond (BDD), to yield a wide range of tertiary amides of various structures.<sup>[23]</sup> It shows that phenylsilane (PhSiH<sub>3</sub>) in stoichiometric proportion acts as a hydrogen source, that reacts with the main ketyl intermediate produced through cathodic reduction, however, either Zn, Al metal, or Br<sup>-</sup> electrolyte acts as a sacrificial anode.<sup>[22]</sup>

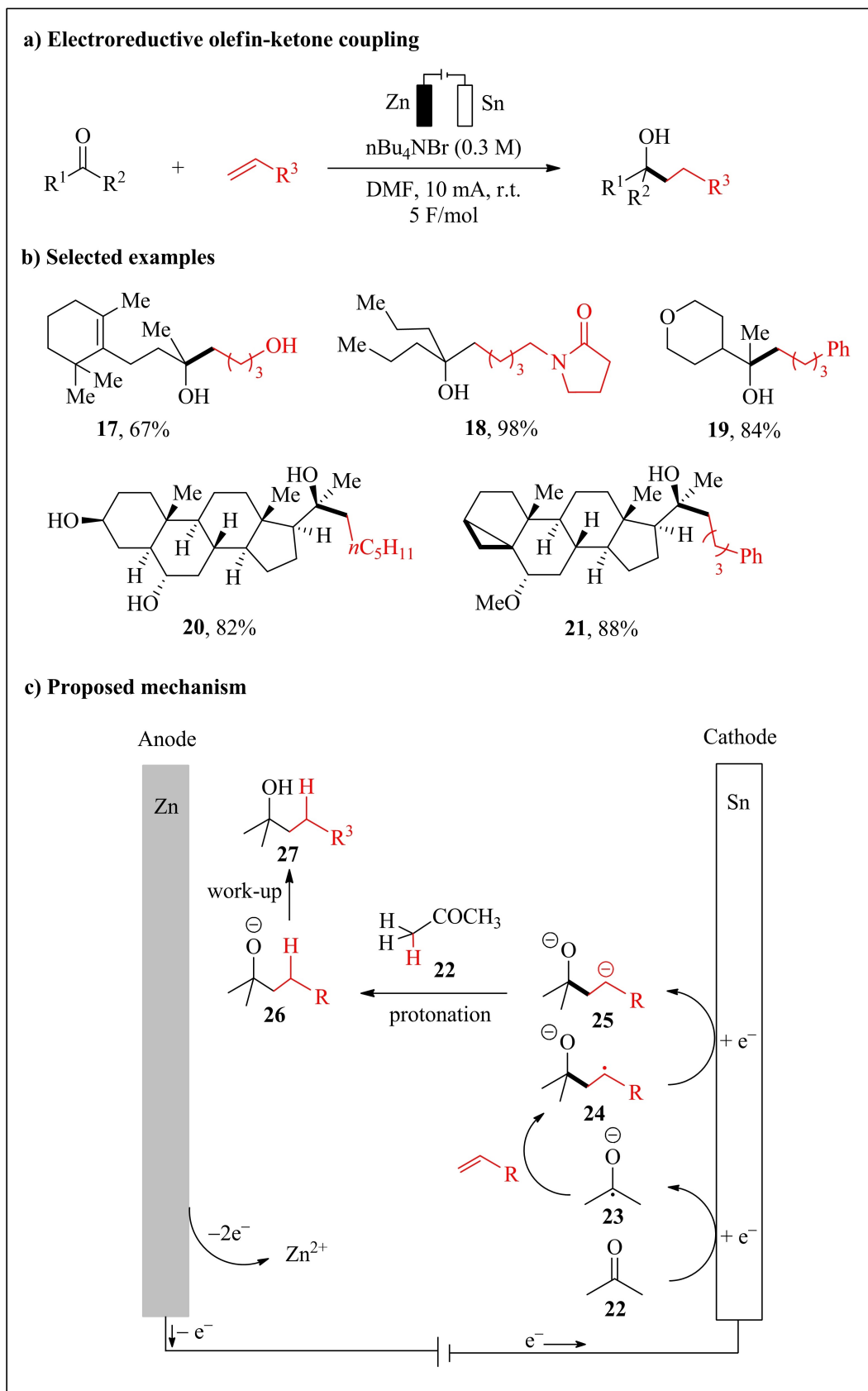
Although the traditional constant-potential electrolysis provides simple method for the electroreduction of aliphatic aldehydes/ketones to alcohols ensuring an efficient enantioselectivity, a more practical electroreductive protocol for the

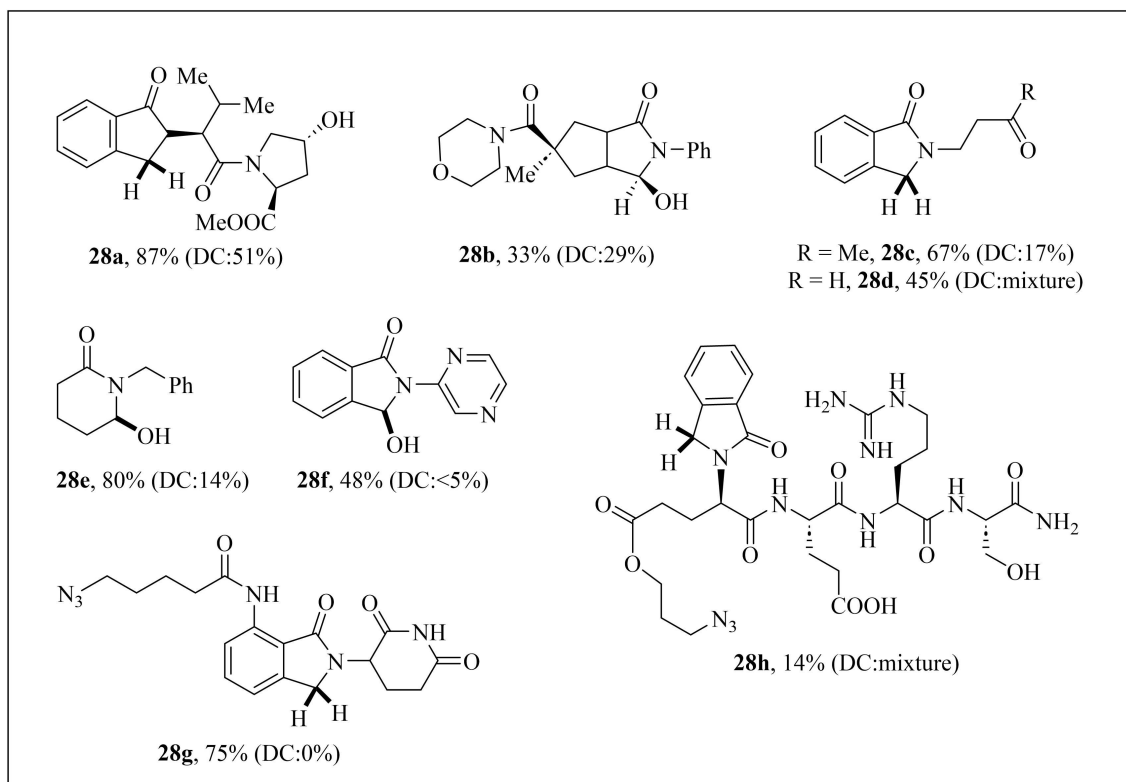
carbonyl compounds can be achieved with the application of square waveform to deliver alternating current to attain chemoselectivity that applies to groups or positions of the substrate which are sensitive to oxidation and reduction. Similarly, an electrochemical deoxygenative hydrogenation of secondary amides provides a promising technique to obtain tertiary amides exhibiting various structures with the use of a Zn, Al sacrificial anode or boron-doped diamond (BDD).

### 3.2. Reductive functionalization of C=O bond

The alkylation/arylation of aldehydes/ketones to secondary/tertiary alcohols is a widely researched area for the functionalization of carbonyl compounds.<sup>[22]</sup> The traditional nucleophilic reactions can be replaced by a promising alternative using highly reactive organometallic reagents such as Grignard reagents is by employing a mild electrochemical approach to generate ketyl radicals/anions for subsequent addition or cross-coupling.<sup>[22]</sup> In 2019, for instance, Kise and co-workers carried out a two-electron cathodic reduction of diaryl ketones using trimethylsilyl chloride (TMSCl) to hydrofunctionalize chromones<sup>[24]</sup> and 4-quinolones;<sup>[25]</sup> the TMS-protected alcohols or similar compounds thus formed are found to be capable of undergoing further different transformations to attain various functionalized structures.

The groups of Minter and Baran showed that the cathodic reduction of unactivated aliphatic ketones can be carried out using an undivided cell with an Sn cathode; which yields tertiary alcohols on subsequent cross-coupling (Scheme 7).<sup>[26]</sup> Cheaper Zinc as sacrificial anode and a lower current is employed in this protocol in comparison to the prior electrochemical approach leading to better-functionalized group tolerance; however, this minor procedure also requires no exclusion of air or moisture.<sup>[22]</sup> A wide range of alkenes and aliphatic ketones with a variety of structures are coupled successfully with high efficiency and chemoselectivity under the established conditions, which can be scaled up readily in either batch or flow systems (Scheme 7a). It gives continuous access to the reductive coupling of alkene **30g** consisting of an amine protected by 2-(trimethylsilyl) ethoxycarbonyl (Teoc) and ketone **29g** containing a steroid core has been employed in a hedgehog signalling modulator **31g** that involves two-step synthesis, which required seven steps in the previous approach (Scheme 7b).<sup>[26]</sup>

Scheme 5. Synthesis of tertiary alcohols by electroreductive olefin-ketone coupling.<sup>[15]</sup>



Scheme 6. Chemoselective electroreduction of cyclic imides using rapid alternating polarity.<sup>[21]</sup>

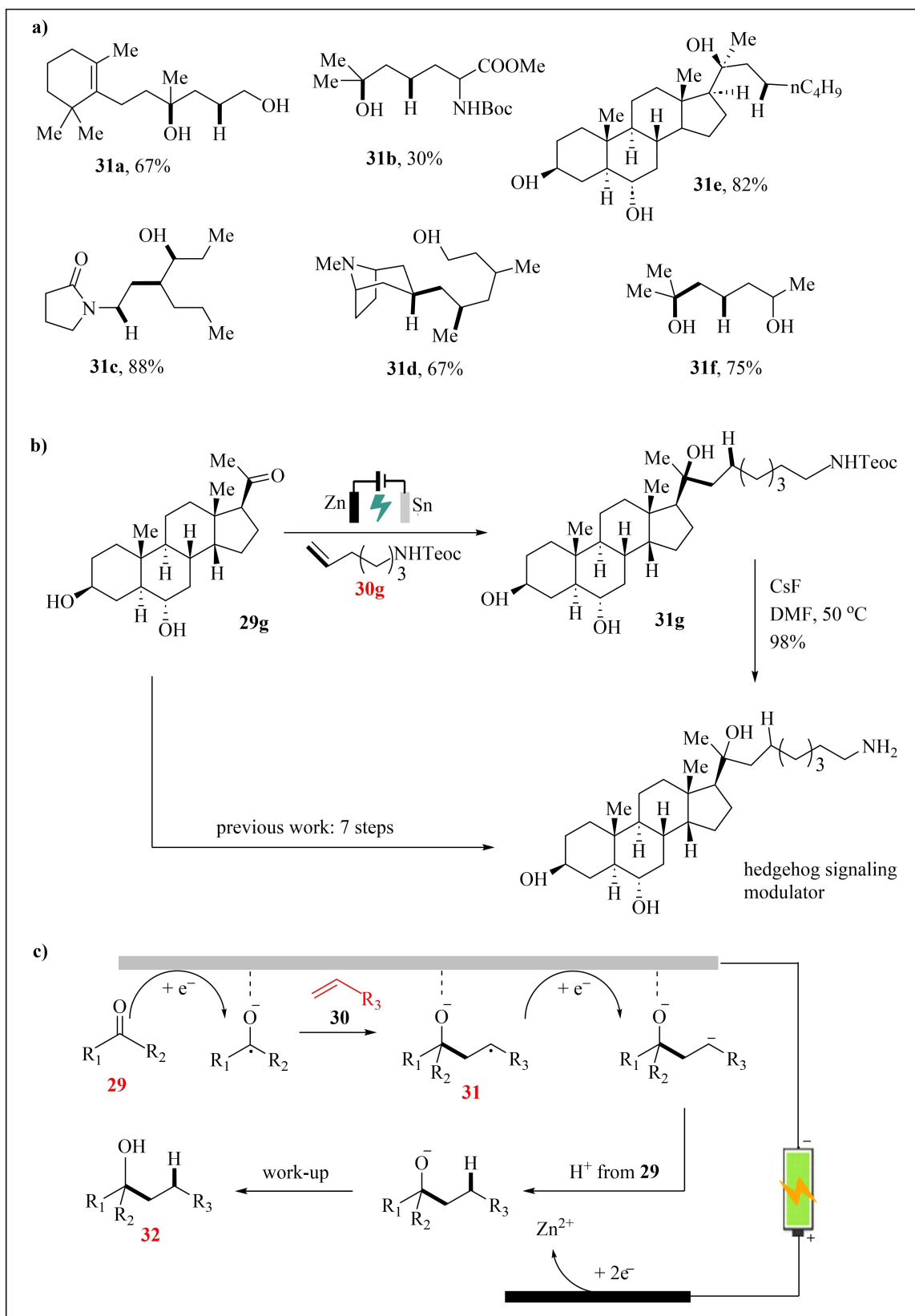
After a series of mechanistic investigations, an electrochemical–chemical–electrochemical–chemical (ECEC) mechanism was proposed for this electrochemical transformation. As demonstrated by comparative study of the CV experiments using glassy carbon (GC) or Sn as a working electrode, at the Sn cathode, Ketyl radical is produced having strong adsorption upon one-electron reduction of ketone **29**.<sup>[22]</sup> The radical anion **31** is obtained by the radical addition of previously formed ketyl radical on the acceptor alkene **30**. The dianion species which is obtained by one-electron reduction of **31**, is further protonated by another molecule of **29** despite the reaction solvent to afford the desired product **32** as demonstrated by the deuteration experiments (Scheme 7c). In the second electron reduction, to facilitate  $Zn^{2+}$  as a thermodynamic sink is one of the vital role of sacrificial Zn anode according to the results of SWV analysis with  $ZnBr_2$  as a catalyst.<sup>[22]</sup>

In 2021, the groups of Zhang, Xu, and Findlater jointly devised a technique in which aromatic ketones and aldehydes are arylated electroreductively in presence of cyanoarenes having electron deficiency. With minor alteration,  $\alpha$ -arylation of benzylic alcohols can be carried out in the identical reaction conditions (Scheme 8).<sup>[27]</sup> Valeraldehyde which acts as a scavenger for the harmful cyanide ions that are produced during the electrolysis, is added to the system, that also exhibits positivity on reaction performance. This protocol applies to a wide range of aromatic ketones, aldehydes, and alcohols, as well as cyanoarenes consisting of additional EWG at 4-position (Scheme 8, **36 a–h**); the yields are generally lower for alcohols

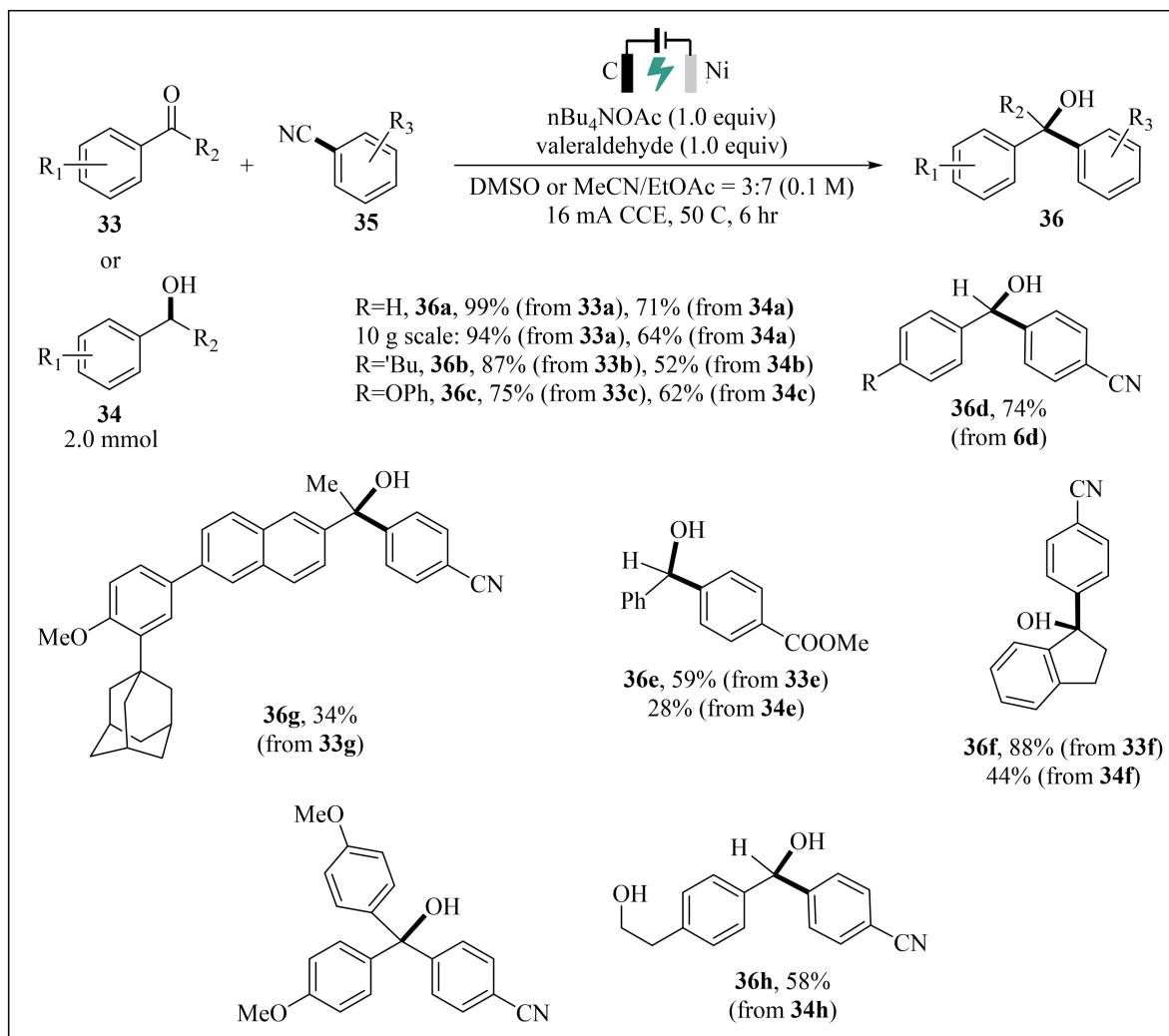
products **36** from alcohols **34** than those obtained from corresponding aldehydes and ketones **33**. It can be noted that both of the representative reactions of **36a** were carried out successfully on a 10 g-scale by using an easy homemade setup with larger electrode surface areas.<sup>[22]</sup>

The dimerization of ketyl radicals into vicinal diols is another famous transformation of ketyl radicals. For the generation of pinacols using different aromatic ketones and aldehydes, carbon fiber paper was observed to be the best cathode, with 99% selectivity and 96% Faraday efficiency according to a recent paper published by Zhang and co-workers.<sup>[28]</sup> De Vos, Kim, and co-workers developed a linear pair electrolysis method to achieve sequential anodic oxidation of three benzylic alcohols assisted by the 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and the synthesis of  $\alpha$ -hydroxyl acids through the cathodic carboxylation of thus formed aldehydes/ketones in the presence of pressurized  $CO_2$  (5 bar).<sup>[29]</sup>

Recently, phthalimides was alkoxyated electroreductively taking  $SmCl_3$  as a cathodic mediator in an Sm cathode using TMSCl in stoichiometric proportion as reported by Mellah's group (Scheme 9).<sup>[30]</sup> 2-substituted isoindolinones were obtained by the reaction of N-substituted phthalimide with a wide range of alcohols involving terminal alkenes/alkynes. Observing the mechanism, firstly  $SmCl_3$  undergoes reduction at the cathode followed by a single-electron transfer (SET) mechanism with phthalimide **37**. The radical **40** is resulted by the capture of thus obtained ketyl radical by  $TMS^+$ , which in turn receives an electron and a proton from the electrogenerated  $Sm^{2+}$  and

Scheme 7. Electroreductive coupling between unactivated ketones and alkenes.<sup>[26]</sup>





**Scheme 8.** Electrochemical arylation of aldehydes, ketones, and alcohols with cyanoarenes.<sup>[22]</sup>

alcohol **38** respectively. The ultimate product **39** is obtained by the elimination of TMSO<sup>-</sup> followed by the addition of an alkoxide anion.<sup>[30]</sup>

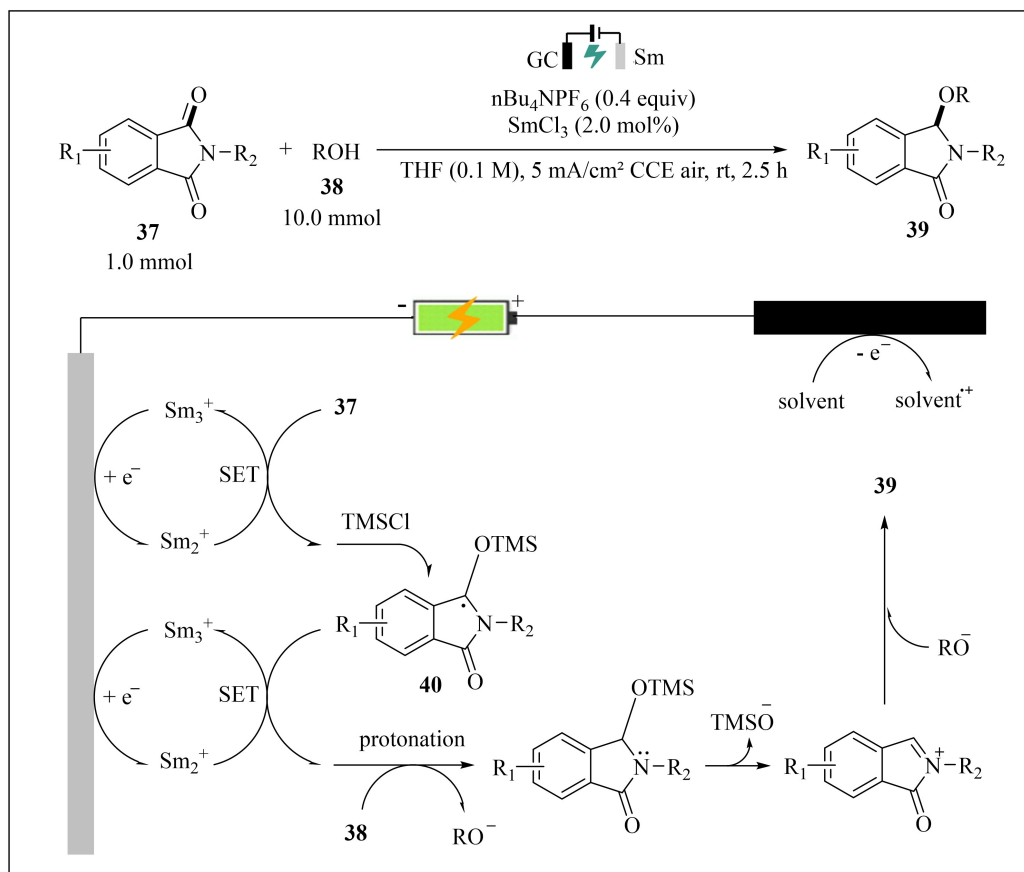
## 4. Carbon–Nitrogen bond formation reaction at the cathode

Nitrogen-containing compounds are very crucial as a biological component such as amino acid, Deoxyribonucleic acid (DNA) contains C–N bonds.<sup>[31]</sup> Due to the wide existence of nitrogen-containing compounds in natural products, medicines, therapeutic molecules, and multifunctional materials, the formation of C–N bonds has immense value in organic chemistry.<sup>[32]</sup> The conventional method for the coupling of C–N bonds requires different harsh conditions and makes use of expensive catalysts, therefore these conventional methods need to be revolutionized. Recently, an electrochemical method for C–N bond-forming reactions has gained more attention due to its

potential to be more environmentally friendly as this method doesn't require high temperatures, high pressures, and toxic solvents and chemical reagents. Thus, this method has several benefits, including low cost, wide substrate application, and scalability.<sup>[33]</sup>

### 4.1. Carbon–Nitrogen bond formation from CO<sub>2</sub>

Organic synthesis involving the utilization of CO<sub>2</sub> is limited to carboxylation and hydrocarbon. Electrochemical carbon-nitrogen bond formation from CO<sub>2</sub> has been considered an efficient strategy. CO<sub>2</sub>, being a stable molecule remains unreactive with other chemicals. So, prior activation of CO<sub>2</sub> is necessary. For instance, using CO<sub>2</sub> in electrochemical reactions to produce C–N bonds requires breaking or hydrogenating one of its oxygen atoms. To build C–N bond formation systems utilizing CO<sub>2</sub>, an electrochemical system designed to produce the precursor for C–N coupling is the initial step. Through the utilization of a nitrogen supply, the electrochemical intermedi-



Scheme 9. Sm-catalyzed electroreductive alkoxylation of phthalimides.<sup>[30]</sup>

ates adsorbed on the electrocatalyst during CO<sub>2</sub> reduction can be used to form C–N bonds.<sup>[33]</sup>

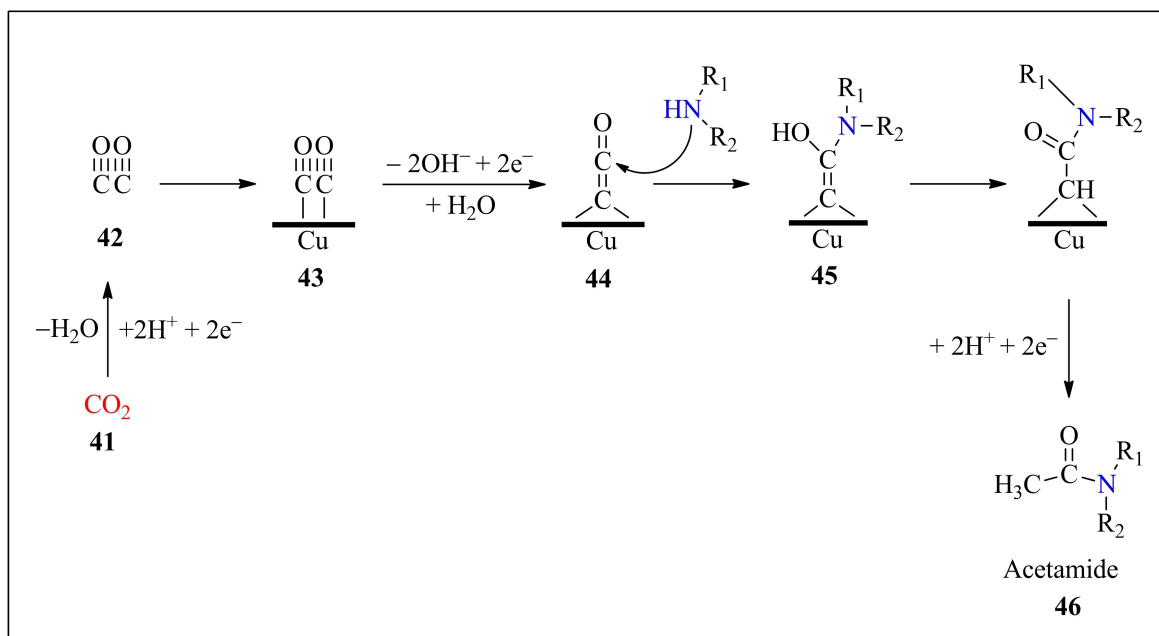
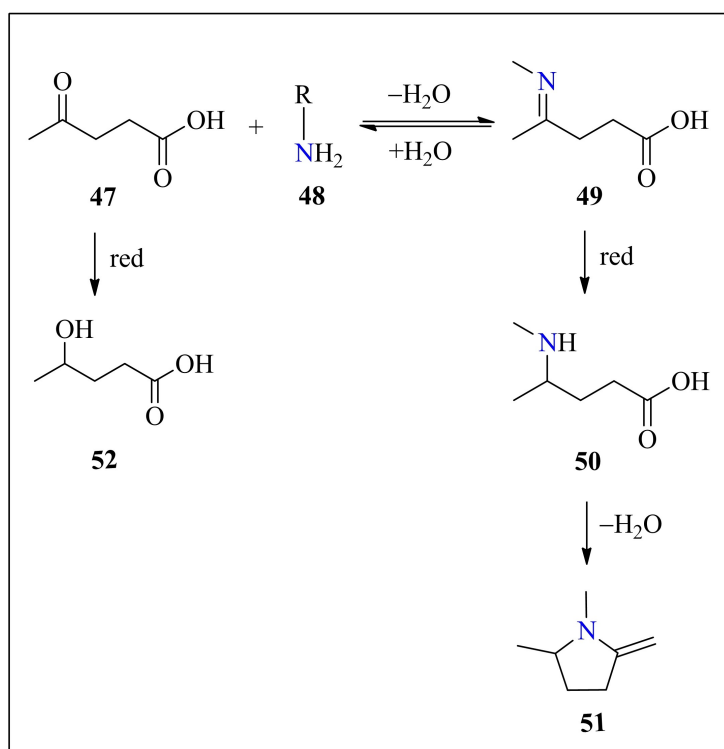
In 2019, Jiao and Goddard's groups reported the electrochemical synthesis of acetamide containing C–N bond from the electroreduction of CO with amines.<sup>[34]</sup> CO<sub>2</sub> undergoes reduction to produce CO which remains adsorbed in Cathode. Both the chemical and electrochemical synthesis of CO have already been developed into productive synthetic techniques. Therefore, utilizing CO directly for electrochemical C–N bonding is an alternate starting point to using CO<sub>2</sub>, which needs reduction. In this instance, a catalyst made of copper is employed to convert CO to acetate in a relatively high overpotential manner. As illustrated in Scheme 10, mechanistic investigations show acetamide (46) which is the final product formed by a continuous protonation of ketene intermediate, which is produced from the dimerization of two CO molecules that are obtained from the reduction of the CO<sub>2</sub> molecule. The CO<sub>2</sub> (41) molecule undergoes reduction to form CO (42). They remain adsorbed on the cathode (43) which further undergoes dimerization to give ketene intermediate (44). Amines then undergo nucleophilic attack on the electron-deficient carbon atom of the ketene intermediate where the coupling of carbon and nitrogen occurs (45) that finally proceeds to form acetamide (46).<sup>[34]</sup>

#### 4.2. Carbon–Nitrogen bond formation from levulinic acid and amine

Murtz and coworkers<sup>[35]</sup> have reported the formation of C–N bond in 1,5-dimethyl-2-pyrrolidone via electrocatalytic reduction of levulinic acid. As depicted in Scheme 11, the amine (48) undergoes nucleophilic addition with levulinic acid (47) which leads to the formation of an imine intermediate (49). This further goes reduction to produce 4-(methylamino)-pentanoic acid (50) which on dehydration yields 1,5-dimethyl-2-pyrrolidone (51). 4-hydroxypentanoic acid (52) is obtained from the side reaction of levulinic acid (47).<sup>[35]</sup>

#### 4.3. Carbon–Nitrogen bond formation from oxalic acid and nitrate

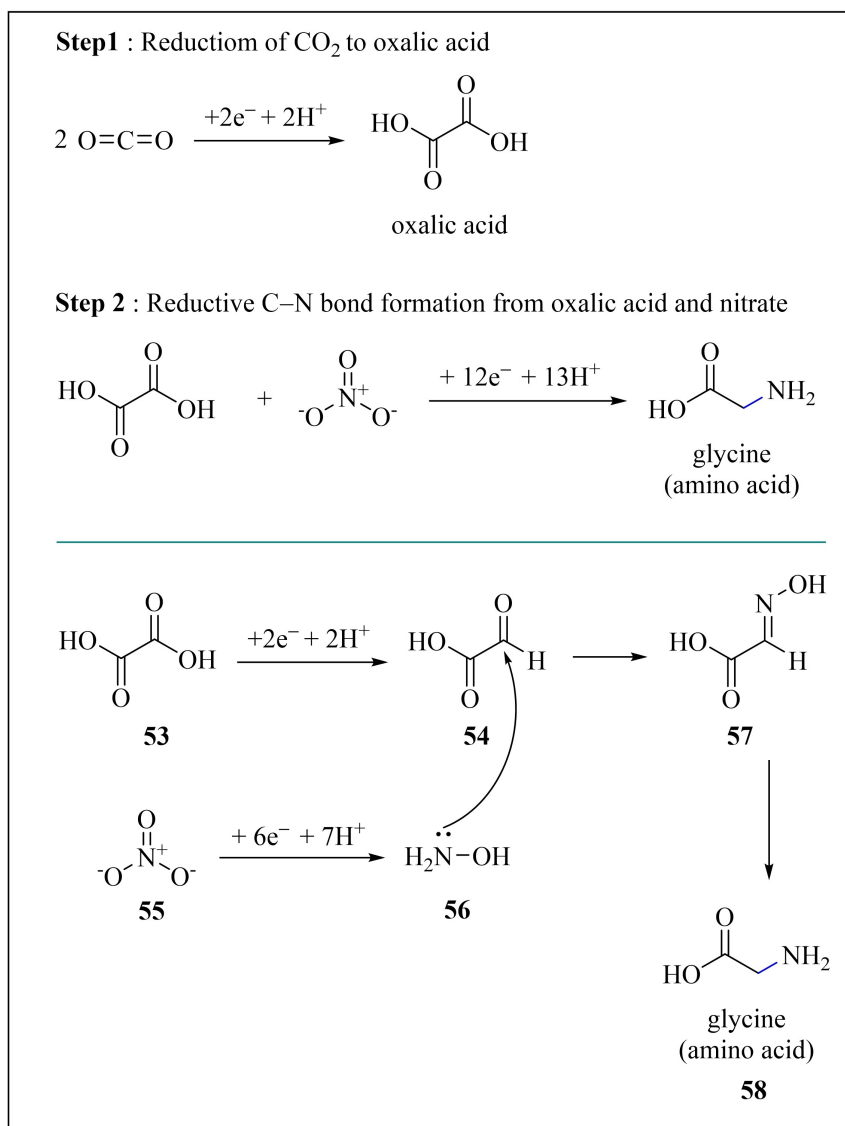
Kim and his coworkers<sup>[36]</sup> reported the formation of the C–N bond by using oxalic acid and nitrate as a substrate. Scheme 12 illustrates the formation of glycine via 2 steps. The prior step involves the reduction of CO<sub>2</sub> to oxalic acid and the second involves the C–N bond formation from oxalic acid and nitrate. After the formation of oxalic acid (53), it further undergoes a 2-electron reduction process to form glyoxylic acid (54). At the same time, nitrate (55) also undergoes reduction to hydroxylamine (56). The electron-rich nitrogen center of hydroxylamine

Scheme 10. Electrochemical C–N bond formation using  $\text{CO}_2$ .<sup>[34]</sup>Scheme 11. Formation of C–N bond from levulinic acid and amines.<sup>[35]</sup>

(56) attacks the electrophilic center of glyoxylic acid (54) and undergoes dehydration to form glyoxylic oxime (57). Glyoxylic oxime (57) contains C–N double bond so, one additional electron reduction step is required. Thus glycine (58) containing C–N single bond is synthesized from 4 electron reduction of the glyoxylic oxime. Thus, overall 12 electrons are utilized in order

to synthesize glycine molecule from a single oxalic acid and nitrate molecule.<sup>[36]</sup>

In summary, the Scheme 10, 11, and 12 clearly represents detailed mechanism for the formation of C–N bond using different substrate as a starting material. In Scheme 10,  $\text{CO}_2$  being the starting material undergoes reduction to CO followed



**Scheme 12.** Formation of glycine from oxalic acid and nitrate.<sup>[36]</sup>

by dimerization to give ketene intermediate. Carbon of ketene intermediate being electron deficient further undergoes nucleophilic attack by amine which clearly illustrates the formation of C–N bond in acetamide, the final product. Similarly, in Scheme 11 the imine intermediate formed from the nucleophilic addition of amine with levulinic acid on further reduction and dehydration results in the formation of 1,5-dimethyl-2-pyrrolidone which also has the C–N bond in it. Scheme 12 also shows the presence of C–N bond in product glycine which is formed from oxalic acid and nitrate as starting material. The mechanism involved in this process is also nucleophilic addition. The electron rich hydroxylamine formed from reduction of nitrate undergoes nucleophilic addition with glyoxylic acid (formed from reduction of oxalic acid) resulting in the formation of glycine which contains C–N bond.

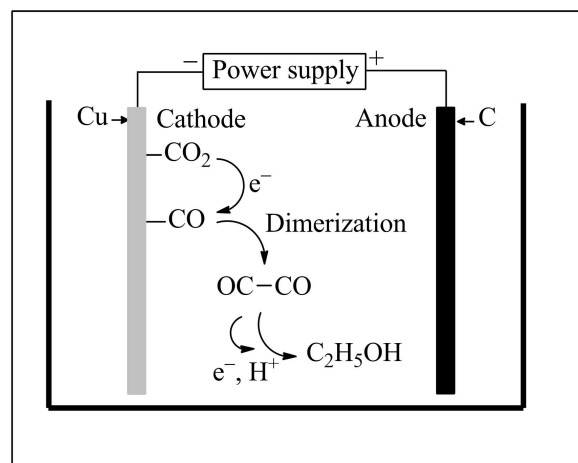
## 5. Carbon–Oxygen bond formation reaction

Organic synthesis involving the formation of C–O bonds is very important because of the prevalence of C–O bonds in many pharmaceuticals as well as bioactive compounds. Formation of C–O bond formation via a metal-catalyzed reaction involving an oxidation reaction has previously been reported. Synthesis of diaryl ether involving the formation of a C–O bond, by reaction of iodobenzene with para cresol which uses a catalyst (copper salt along with base KF/Fe<sub>3</sub>O<sub>4</sub>) has also been reported in the literature.<sup>[37]</sup> But since we are focusing on C–O bond formation via an electrochemical process, we consider mainly toward electroreduction method for C–O bond formation.

### 5.1. Electrochemical C–O bond formation from CO<sub>2</sub>

Similar to C–N bond formation using CO<sub>2</sub> as a starting material, C–O bond formation from the electroreduction of CO<sub>2</sub> has also gained major attention. CO<sub>2</sub> gas being the abundant gas in the atmosphere also contributes toward global warming, so its utilization in electrochemical reduction not only forms a carbon-oxygen bond but also shifts the reaction toward green chemistry. C–O bond formation via the electrochemical reduction method by utilizing CO<sub>2</sub> is beneficial regarding product selectivity and materials simplicity being economical avoiding the use of high temperature and vacuum conditions.<sup>[38]</sup>

In 2018, the synthesis of ethanol from CO<sub>2</sub> via an electrochemical method has been reported<sup>[39]</sup> which employs the use of a Carbon-Polyvinyl (C-PVC) electrode. In the scheme shown below, Carbon being anode behaves as an oxidizing agent along with copper cathode as a reducing agent. The effect of the concentration of electrolytic solution NaHCO<sub>3</sub> has also been observed to affect the concentration of ethanol produced. Here, the electrochemical transfer of an electron to CO<sub>2</sub> occurs. The intermediate thus formed binds to the copper cathode via a carbon atom, thereby producing CO. The formed CO intermediate further undergoes dimerization followed by protonation and the final product ethanol is obtained.<sup>[39]</sup>



Scheme 13. Electrochemical reduction of CO<sub>2</sub> to ethanol.<sup>[39]</sup>

### 5.2. Electroreductive alkoxylation of phthalimides

In Scheme 14, the formation of 2-substituted isoindolines was reported by reacting different alcohols with N-substituted phthalimides.<sup>[8]</sup> The formation of the C–O bond was also observed in the product formed. Mellah's and coworkers,<sup>[40]</sup> in presence of TMSCl, performed electroreductive alkoxylation of phthalimides where Samarium chloride (SmCl<sub>3</sub>) was used as a cathodic mediator over Samarium (Sm) cathode. In this scheme, the reaction is initiated by the reduction of SmCl<sub>3</sub> at cathode followed by single electron transfer (SET) with Phthalimide **59**. Ketyl radical generated further reacts with TMSCl to give radical **62**. An electron generated from the reduction of Sm<sup>+3</sup> to Sm<sup>+2</sup> and proton from alcohol **60** is utilized by **62** to give **63**, which further undergo elimination of TMSO<sup>-</sup> gives **64** which on further addition of alkoxide anion yields final product **61**.

Therefore, the Scheme 13 and 14 clearly indicates the formation of C–O via electrochemical process. In Scheme 13, CO<sub>2</sub> first undergo reduction to CO which on further dimerization followed by protonation yields ethanol having new C–O. Similarly, in Scheme 14, 2-substituted isoindoline is formed from reaction between alcohol and N-substituted phthalimides which clearly indicates the formation of C–O bond. The reaction type indicated in this scheme is electroreductive alkoxylation of phthalimide.

## 6. Reduction of C–N bond

The C–N unsaturated systems are prominent in organic compounds namely nitrile derivatives, imines, and heteroarenes

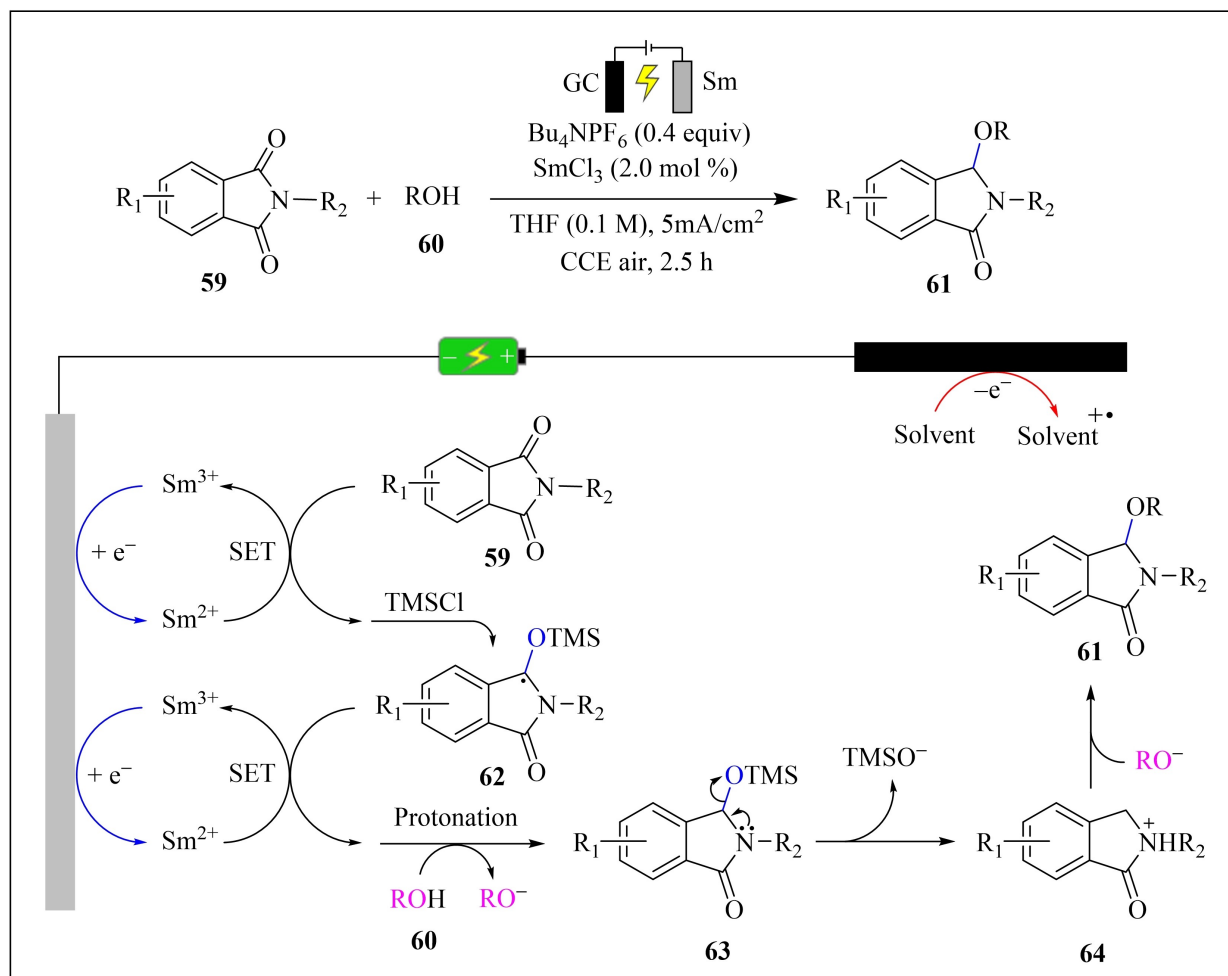
containing N-atoms. Primarily, under electrolysis followed by protonation results in convenient reduction of C=N bonds of imines as well as further functionalization yields secondary amines due to the fragile functionality of such bonds. However, it is very difficult to reduce C≡N in simple nitriles. Partially or fully hydrogenated products are realized from the compounds such as pyridines, quinolines, and their derivatives through dearomative hydrogenation of electron-deficient heteroarenes containing N-atoms using electrochemical methods. The process involved is easier in comparison to the reduction of corresponding electron-rich arenes via direct electro-Birch reduction method.<sup>[22]</sup>

### 6.1. Reductive hydrogenation of C–N bond

Li, Huang, and co-workers<sup>[41]</sup> devised a reductive amination of aldehydes, as in situ protocol for the electrochemical hydrogenation of C=N bonds which proceeds through sequential condensation and cathodic reduction (Scheme 15). Both aromatic and aliphatic coupling partners are used as a substrate, and the added hydrogen or deuterium comes from the reaction solvent (Scheme 15a, **67 a–g**). The imine cation **68**, which after abstraction of hydrogen from DMSO (Scheme 15b) undergoes reduction at the cathode for the generation of compound **67** is proposed as a key reaction intermediate.<sup>[41]</sup>

In 2021, Herbert and co-workers, in acidic media, realized electrochemical hydrogenation of C=N bonds in benzoxazinones in presence of a RVC working electrode.  $\alpha$ -ketoesters also undergo reduction in the above mentioned conditions.<sup>[42]</sup> During the same year, Waldvogel's group accessed the formamide acetate having synthetic versatility by exploring the electroreduction of cyanamide in acidic aqueous media in which scale-up synthesis was achieved using electrolyte-free continuous flow strategy by employing a narrow gap cell to achieve high yields.<sup>[43]</sup>

In 2020, the groups of Yen, Yang, and Wang reported a new dearomative transfer hydrogenation of heteroaromatic systems



Scheme 14. Sm-catalyzed electroreductive alkoxylation of phthalimides.

containing N-atoms, viz. imidazopyridines, that are induced electrochemically employing secondary amines as hydrogen donors (Scheme 16).<sup>[44]</sup> In the mixed solvent of MeCN and THF under electrochemical conditions, the alkyl, halogen, and alkoxy which acts as tolerating groups (Scheme 16, 70a–f), a series of 2-(hetero)aryl substituted imidazopyridines undergoes immediate reduction. However, this technique is not compatible with heterocycles containing N-atoms as well as imidazopyridines with other strong EWGs, viz. trifluoromethyl group. For this electroreduction, the proposed mechanism is ECEC, and the secondary amine additive acts as both the proton donor as well as the sacrificial reductant.<sup>[44]</sup>

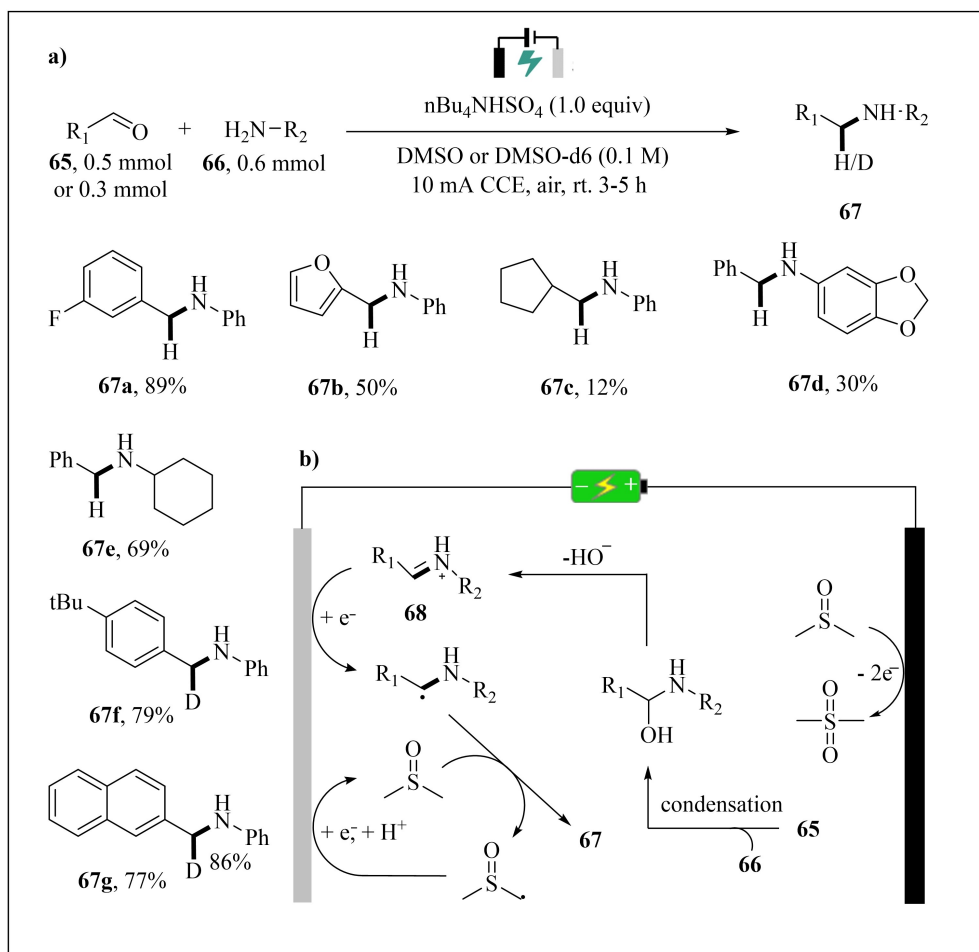
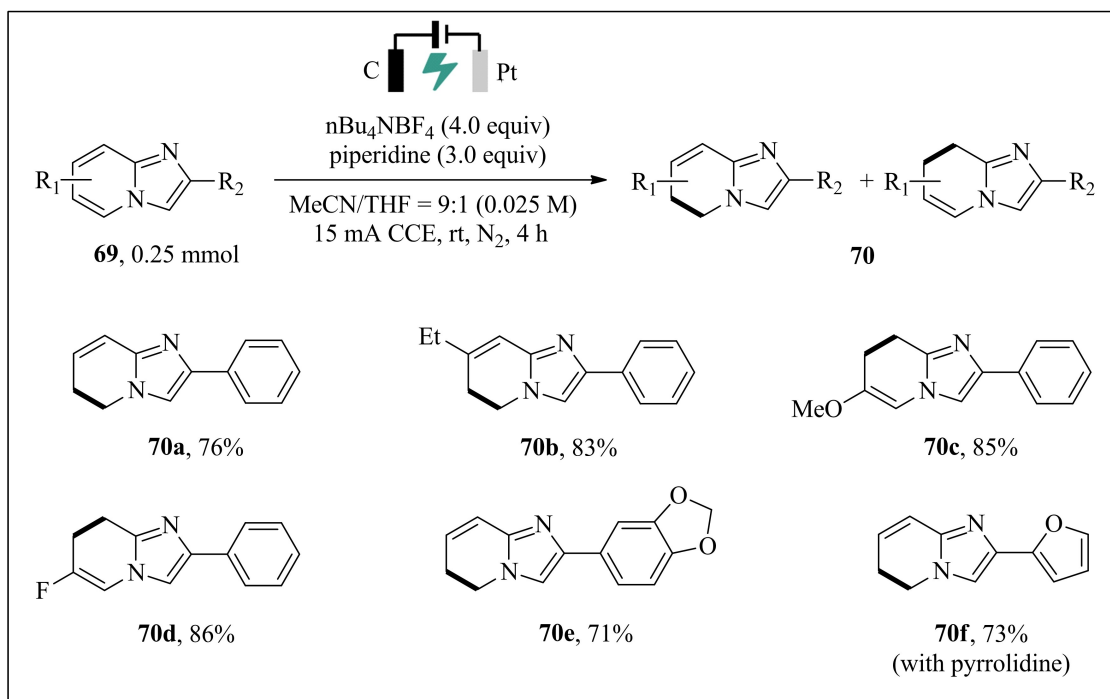
In 2021, Zhang and co-workers used the active hydrogen atom ( $\text{H}^*_{\text{ads}}$ ) liberated from the reduction of water on the surface of  $\text{MoNi}_4$  nanosheets ( $\text{MoNi}_4\text{NSs}$ ) cathode (Scheme 17) to devise an electrocatalytic transfer hydrogenation/ deuteration of heteroaromatic systems containing N-atoms in aqueous media.<sup>[45]</sup> Under the standard conditions, a wide range of 1,2,3,4-tetrahydroquinoxalines (Scheme 18a, 76a–f), provides products with excellent conversion yields, along with high selectivity, except for Cl- or Br-substituted substrates which undergo competitive dehydrohalogenation (Scheme 18a, 76c,

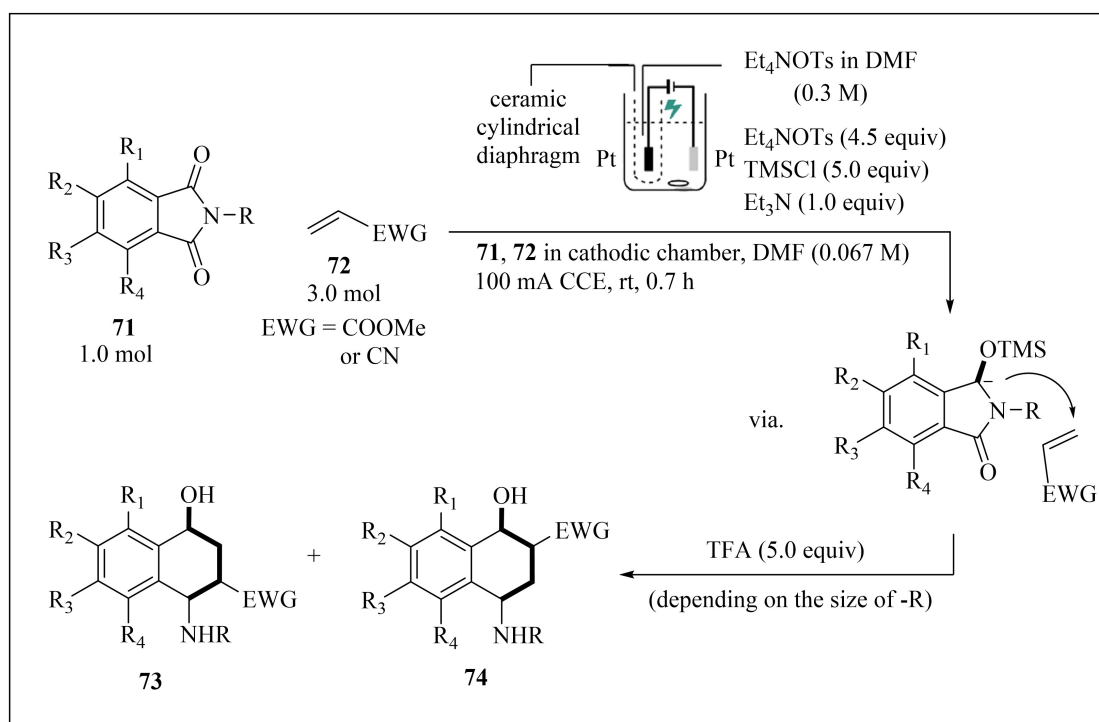
76d). However, low conversion yields are obtained with compounds such as quinolines and isoquinolines (Scheme 18a, 76g, 76h). t-Using t-BuOH as a hydrogen atom scavenger, the *in-situ* generation of  $\text{H}^*_{\text{ads}}$  through the Volmer process is supported by both the control experiments and EPR measurements. The radical anion species that are generated cathodically and  $\text{H}^*_{\text{ads}}$  radicals undergoes two sequential radical-radical cross-coupling (Scheme 18b).<sup>[45]</sup>

The sequential condensation and cathodic reduction for the electrochemical hydrogenation of C=N bonds has provided an efficient technique for the reductive amination of aldehydes; however, scale-up synthesis was achieved by the electroreduction of cyanamide in acidic aqueous media using electrolyte-free continuous flow strategy.

## 6.2. Reductive functionalization of C=N bond

In 2019, Lehnerr, Rovis, and co-workers<sup>[46]</sup> formulated the challenging synthesis of hindered primary/ secondary amines using an electrochemical method with benchtop-stable iminium salts and cyanoheteroarenes (Scheme 19). Based on the

Scheme 15. Electrochemically mediated coupling of phthalimides with Michael acceptors, followed by acid-catalyzed rearrangement.<sup>[41]</sup>Scheme 16. Electrochemically induced transfer hydrogenation of imidazopyridines.<sup>[44]</sup>



**Scheme 17.** The electroreductive coupling of phthalimides with Michael acceptors followed by an acid-catalyzed rearrangement.<sup>[45]</sup>

outcome of electrode screening, zinc with high overpotential for  $H^+$  evolution, in combination with a graphite anode, was chosen as the cathode. A wide range of 2- or 4-cyano pyridines and other cyano-substituted heterocycles have proven to be practicable substrates, such as pyrimidine, for this decyanative coupling transformation with various iminium hydrogen chloride salts (Scheme 19a, **79 a–i**). Initially, the authors proposed several tentative reaction pathways for such an electroreductive coupling via either convergent radical-radical coupling processes or sequential reduction events. The outcome of control experiments and DFT studies shows that the direct cathodic reduction of iminium salts,<sup>[30]</sup> followed by a concerted PCET process of cyanoarenes<sup>[47]</sup> having higher reduction potentials and accompanied by cross-coupling of the persistent and transient radicals was finally concluded to be the most believable mechanistic scenario (Scheme 19b).

Atobe and coworkers devised an electrochemical flow micro-reactor for the green synthesis of  $\alpha$ -amino acids through reductive carboxylation of imines with  $CO_2$ .<sup>[48]</sup> As imine substrates are normally hygroscopic and unstable for isolation, the combined synthesis of  $\alpha$ -amino acids from aldehydes and anilines using  $CO_2$  via sequential condensation was realized by using a new flow system with two inlets and a desiccant-bed column.<sup>[49]</sup>

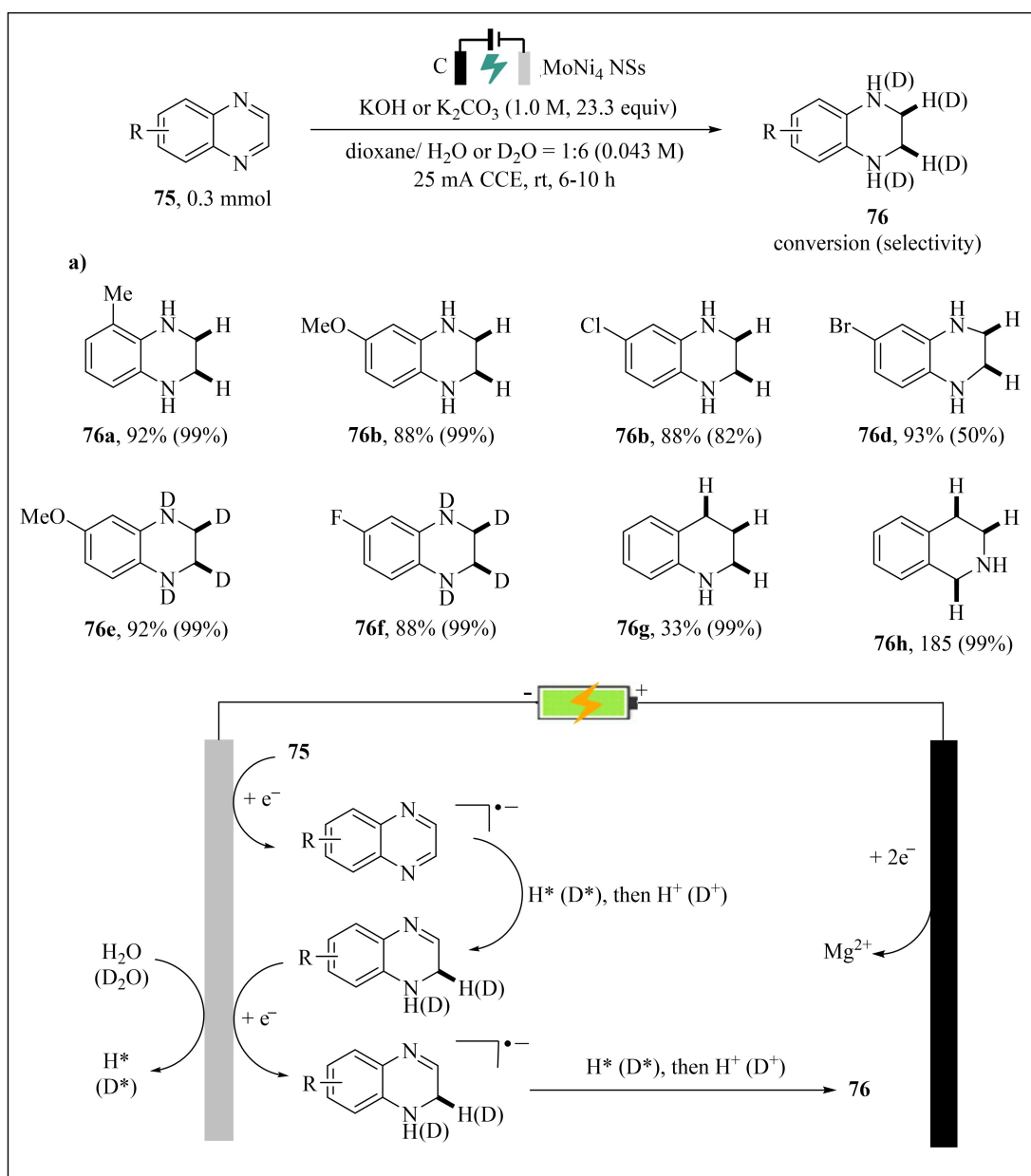
Cheng and coworkers, in 2021, devised a reaction in which Hantzsch ester-based pyridine undergoes reductive ring contraction using a new Lewis Acid which follows an unusual 4-electron continuous cathodic reduction pathway with the aid of  $H_2O-BF_3$  as both the source of proton and the activator, preferably at the stage of ring contraction (Scheme 20).<sup>[22]</sup>

## 7. Reduction of C–S bond

The adjacent C–S bonds are susceptible to specific breakage through cathodic reduction apart from the reducible  $-SO_2-$  moieties.<sup>[22]</sup> Ye and coworkers, using  $CO_2$  as a feedstock, designed an electrochemical technique for the desulfonylative carboxylation of benzylic sulfones, manufactured easily from their respective halides (Scheme 21).<sup>[50]</sup> A wide range of multifunctionalized benzylic carboxylic acids containing electron-donating groups (EDG<sub>s</sub>), EWG<sub>s</sub> on the aromatic rings, or C=C or C≡C are obtained in high yields, together with allylic compounds whose purification is extremely difficult (Scheme 21a, **83 a–g**). The mechanistic pathway is supposed to involve a two-electron mechanism for the generation of leaving phenylsulfinate ion and the key benzyl anion intermediate and results in protonation products **84** (Scheme 21b) when  $CO_2$  is replaced with TEOA. Furthermore, in *N*-Boc- $\alpha$ -aminosulfones, Senkoku and coworkers discovered the electrochemical cleavage of C–S bonds for the easy preparation of *N*-Boc- $\alpha$ -amino acids, accompanied by carboxylation with bubbling  $CO_2$ .<sup>[51]</sup>

In 2021, Hu and coworkers developed the electrochemical hydro-fluoroalkylation of activated alkenes with sulfones **85** as a source of fluoroalkyl radicals using triethylamine as a sacrificial reductant (Scheme 22).<sup>[52]</sup> This technique is applicable to alkene acceptors with different structures and compatible to bioactive complex molecules resulted from late-stage modification (Scheme 22, **87 a–f**). Under electroreductive conditions, fluoroalkyl heteroarylsulfones have been used as fluoroalkyl radical precursors with  $ArSO_2^-$  as the leaving anion after reductive cleavage of C–S bond.<sup>[22]</sup>





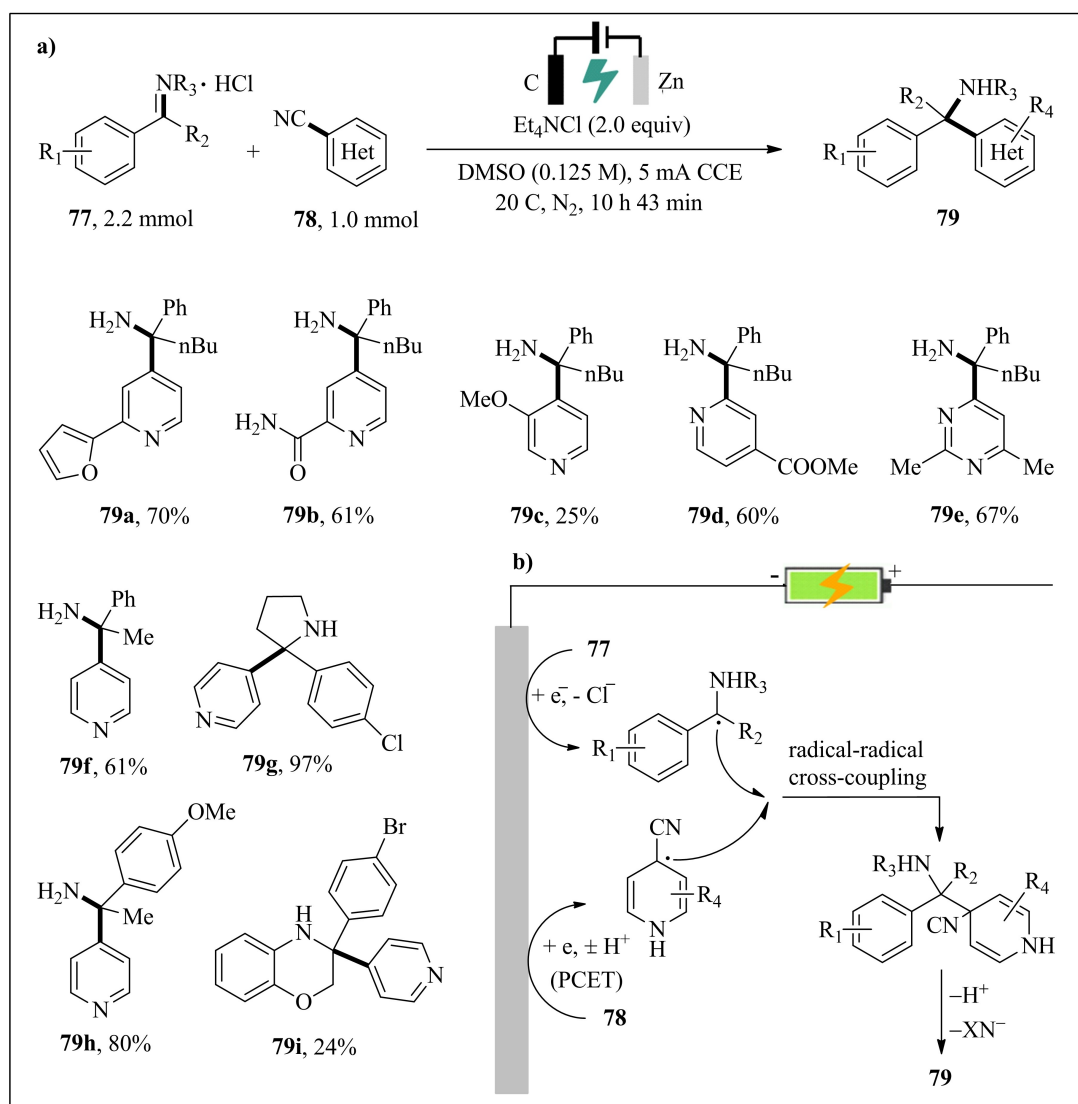
**Scheme 18.** Electrochemical transfer hydrogenation/deuteration of N-containing heteroarenes.<sup>[45]</sup>

Quing and coworkers employed reductive C–S bond cleavage of trifluoromethylsulfones in an oxygen atmosphere to form trifluoromethoxylated (hetero)aromatics (Scheme 23).<sup>[53]</sup> Under moderate condition, the complications in the formation of  $\text{OCF}_3$ -reagents, and other (hetero)aromatics, involving bio-relevant molecules, are smoothly functionalized (Scheme 23a, **90a–h**) by the application of **88** as the  $\text{CF}_3$ -source, along with the incorporation of O from  $\text{O}_2$ . In part reactions, especially those with non-heteroarenes, regioisomeric compounds are obtained, exhibiting the properties of radical addition mechanism (Scheme 23a, **90f–h**). The believable mechanistic pathway involves the cathodic production of  $\text{CF}_3$  radical from the hydrogen-bonded **88**, followed by interaction with O to form the  $\text{OCF}_3$  radical which on further addition of  $\text{OCF}_3$  radical onto

(hetero)arene **89** gives the ultimate product **90** followed anodic rearomatization (Scheme 23b).<sup>[53]</sup>

## 8. Reduction of carbon–halogen bond

One of the widest studies of reductive transformation in organic chemistry is the reduction of organic halides, because of its dynamic synthetic utility and major role in minimizing the detrimental effects of halogen containing environmental pollutants.<sup>[54,55]</sup> In electrochemistry, via cathodic reduction, the C–halogen bonds are also easily reduced to give the major C-centered radical ( $1e^-$ ) or anion ( $2e^-$ ) intermediates after the removal of halide ions. Using these active intermediates,



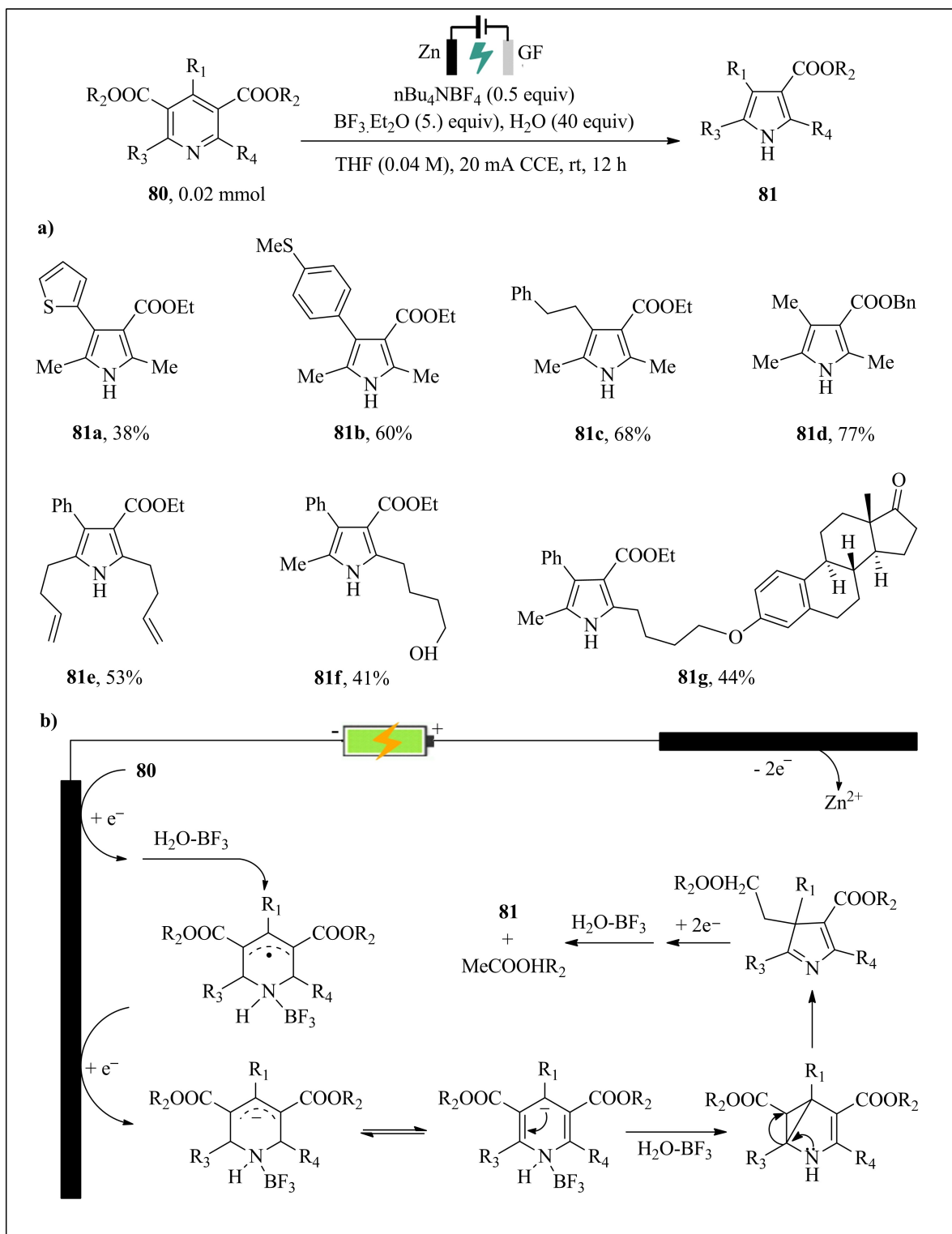
**Scheme 19.** Electrochemical synthesis of hindered primary and secondary amines.

functionalization or dehalogenative hydrogenation products can be achieved upon interaction with the other components in the reaction system.

### 8.1. Reductive hydrogenation/ deuteration of carbon-halogen bond

Pan and Chi, in a recent example of cathodic hydrodehalogenation for aryl halides, devised an easy electrochemical method employing cheap graphite electrodes and trialkylamines as the sacrificial electron donors; however, it could not encompass any electron-deficient (hetero)aromatic halides that are susceptible to over-reduction.<sup>[54]</sup> After that, the groups of Guo and Xia also discovered a simple electroreductive technique for the hydrodefunctionalization of many organic compounds, in which the selection and reduction control can be realized by simple inclusion or removal of alcohol as co-solvent (Scheme 24).<sup>[56]</sup>

The authors disclosed that activated aliphatic or aromatic bromides and organic iodides can be easily reduced in high yields (**Method A**) in a mixed solvent of DMSO and EtOH; however, for some recalcitrant electron-rich aryl bromides and chlorides, the alternative **Method B** (with DMSO as the solvent) is proved to be excellent method with high efficiency (Scheme 24a, **92a–g**). The transformation of trifluoromethylarenes to methylarenes was obtained under identical conditions (Scheme 24a, **92h, 92i**), although failure to reduce the normal C–F bonds. The substrate was **91jk** with both –Br and –I was introduced via two different methods to compare selectivity. **Method A** provided an 85% yield of deiodination-selective **92j**, however **Method B** via yield 90% via non-selective reduction of **92k** (Scheme 24b). This versatile protocol also applies to other reductive transformations, in addition to hydrodehalogenation, namely the hydrodeazolation of N-benzylic azole drugs, the deprotection of sulfonyl- or acyl-

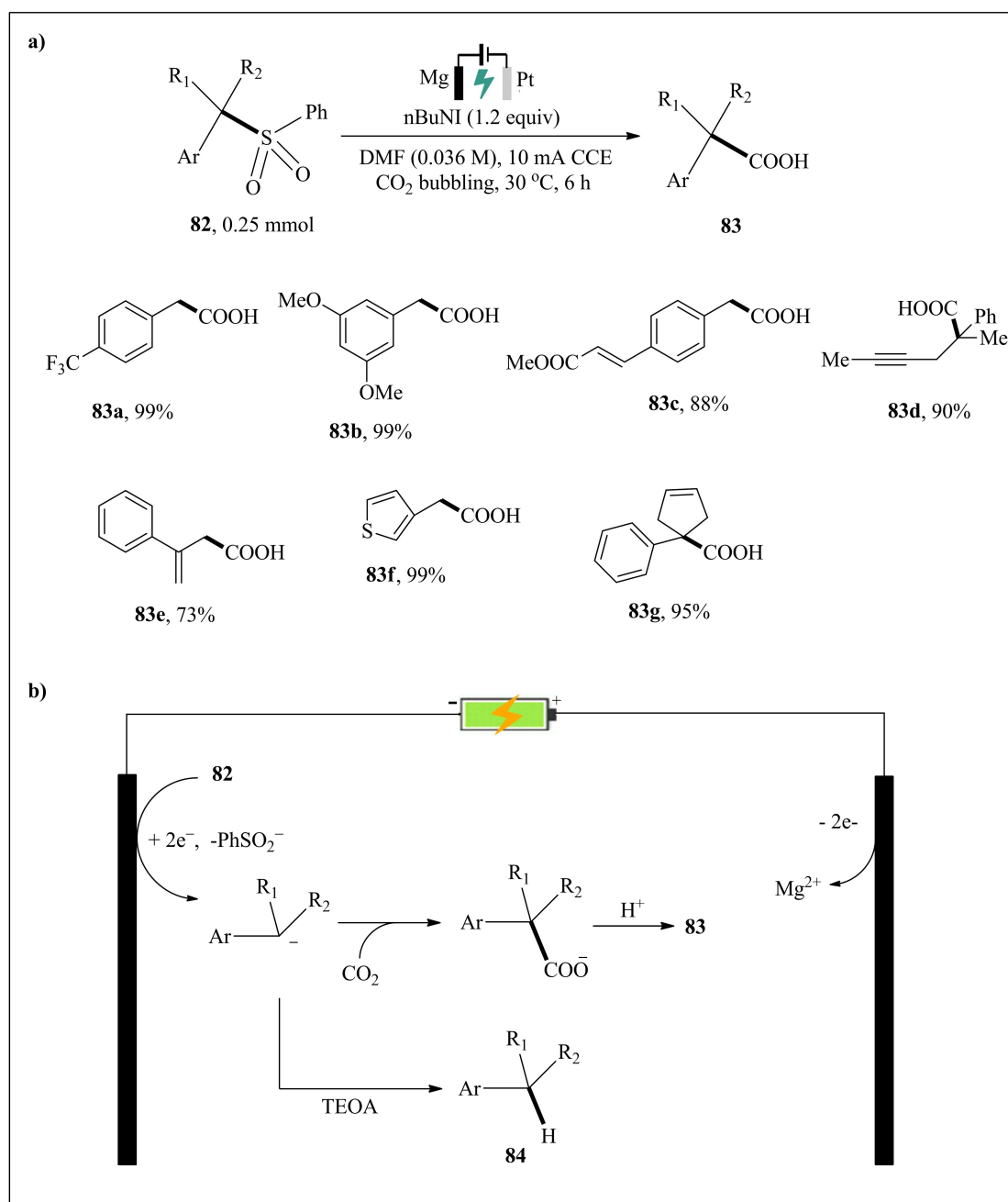


**Scheme 20.** Ring contraction of Hantzsch ester-based pyridines to pyrroles by using electroreductive approach.<sup>[22]</sup>

protected amines and alcohols/phenols, as well as the hydrodecyanation of aromatic nitriles.<sup>[56]</sup>

In 2020, organic iodides and bromides were subjected to dehalogenative deuteration in a three-compartment divided cell by Zhang and coworkers using copper nanowire arrays as

the cathode that are formed *in situ* and  $\text{D}_2\text{O}$  as the deuterium source, the retainment of the C–C and C–X unsaturated structures on the substrates demonstrated an excellent chemoselectivity; and the specific deuteration on many pharmaceuticals compounds was also illustrated.<sup>[57]</sup> During the same year,

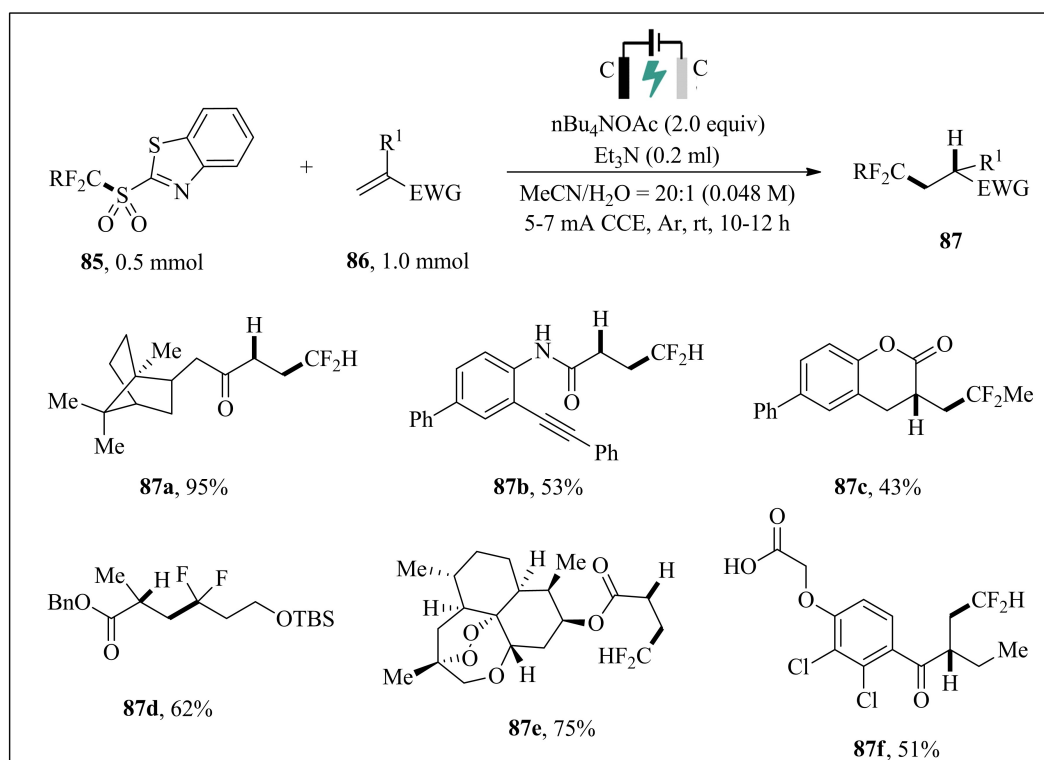


**Scheme 21.** Electrochemical desulfonylative carboxylation of benzylic sulfones with  $\text{CO}_2$ .

using Pb cathode and a Pt anode in an undivided cell, (hetero)aryl halides was subjected to cathodic dehalogenative deuteration as reported by a group of Lei. Alternatively, the reaction can also be carried out without requiring professional equipment by using a common AA-size battery as a source of power and cheap graphite rod (+) | (-) lead plates as electrodes in test tubes.<sup>[58]</sup> The mechanistic studies have shown that both methods proceed through the cross-coupling of cathodically generated carbon and deuterium free radicals.<sup>[57,58]</sup>

The selective hydro-monodefluorination of tri-fluoromethylketones was carried out via electrochemical method using TMSCl, as reported by Lennox and coworkers, in an H-type

divided cell under CCE (Scheme 25), to access medically important difluoromethylketones.<sup>[59]</sup> During condition optimization,  $n\text{Bu}_4\text{NBr}$  was found to be the best sacrificial reductant, that was oxidized in the anodic chamber to give  $\text{Br}_3^-$ ; the non-protic environment created by reductively stable  $\text{Et}_4\text{NPF}_6$  are found to be vital. A wide range of tri-fluoromethylketones and imines undergoes easy reduction to respective monodefluorination compounds with excellent selectivity and group compatibility (Scheme 25a, **94a–g**). The reaction pathway proceeds through silylenol ether intermediate **95**, that is produced by O–Si bond formation, fluoride elimination sequence and cathodic reduction (Scheme 25b).<sup>[59]</sup>



**Scheme 22.** Electrochemical hydro-fluoroalkylation of activated alkenes.

In 2018, Lei and coworkers found out that the halide ions generated by the cathodic hydrodehalogenation of small-molecule organic halides viz,  $\text{CBr}_4$ ,  $\text{CCl}_3\text{Br}$ , and  $\text{CCl}_4$  can also be reoxidized to give C–H bromination and chlorination reactions, at the counter anode.<sup>[60]</sup> Huang and coworkers also accessed  $\alpha,\alpha$ -dihaloketones by employing halides such as  $\text{CHCl}_3$  and  $\text{CH}_2\text{Br}_2$  as the halogen source and water as the source of oxygen for the electrochemical oxydihalogenation of aromatic alkynes.<sup>[61]</sup>

## 8.2. Reductive functionalization of C–halogen bond

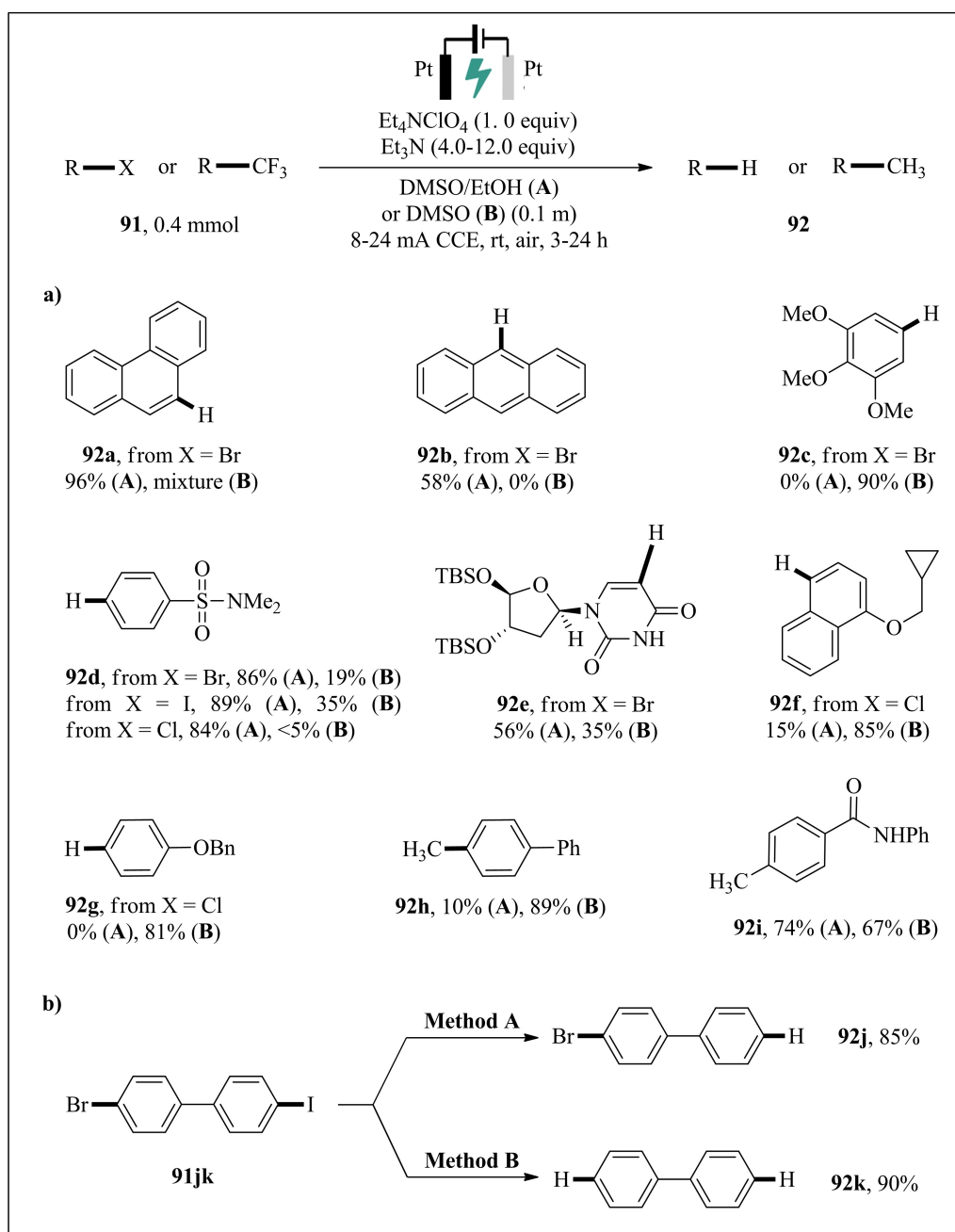
To carry out cathodic reduction under moderate conditions, in 2019, Mo and coworkers, to access the synthetically important arylboronic esters, disclosed that the aryl iodides can be borylated radically with commercially available bis(pinacolato) diboron ( $\text{B}_2\text{Pin}_2$ ) as the boron source.<sup>[62]</sup> In 2021, Qi, Lu, and coworkers reported a much demanding technique for the electroreductive borylation of alkyl halides (–I, –Br, and –Cl) (Scheme 26).<sup>[63]</sup> Many structurally diverse primary, secondary, and tertiary boronic esters are easily obtained using  $\text{B}_2\text{cat}_2$  as the boron source under high constant current through short-term electrolysis and subsequent pinacol treatment, and the practicability of this protocol can be further demonstrated by the various late-stage borylation instances (Scheme 26a, **98a–h**). A radical pathway (Scheme 26b) was suggested by the control experiments and DFT studies. Dimethylacetamide (DMAc) ligated  $\text{b}_2\text{cat}_2$  **99** serves as the redox mediator solvent

to ease the indirect reduction of alkyl halide **96**, and the cathodically reduced **100** serves as coupling partner for the reaction with alkyl radical thereby forming a novel C–B bond.

Manthiram's group carried out a sacrificial anode-free carboxylation of organic halides using  $\text{MgBr}_2$  as an inexpensive  $\text{Mg}^{2+}$  source to suppress unnecessary nucleophilic reactions.<sup>[64]</sup> Employing a specifically constructed reactor facilitated with a Pt anode and an Ag cathode, the carboxylation of a wide range of aliphatic, benzylic, and aromatic halides is successfully carried out, with a non-stop supply of  $\text{CO}_2$ . The role of  $\text{Mg}^{2+}$  to maintain selectivity by stabilizing carboxylate and preventing  $\text{S}_\text{N}2$  reactions can be accessed from the mechanistic studies. Mitigation of cathodic passivation by the precipitation of  $\text{MgCO}_3$  that occurs simultaneously with the reduction of  $\text{CO}_2$  to CO has also been reported by the group.

In 2019, a new reductive carboxylation of benzylic halides via the activation of  $\text{CO}_2$  despite C–X partners was reported by Mellah and coworkers by exploiting a “soluble” Sm electrode (Scheme 27).<sup>[65]</sup> Distinctly, catalytic Sm(II) species are released into the reaction system by pre-electrolysis with an Sm anode, that activates the  $\text{CO}_2$  (successively added as dry ice) followed by radical substitution with substrate of benzylic halide **101** to afford the intermediate samarium carboxylate **103**. The desired product **102** is obtained by subsequent interaction of **103** with  $\text{TMSCl}$  after acidic workup; however, the reduction of Sm(III) to Sm(II) is eased by the Sm cathode capable of switching polarity, thus completing the whole catalytic cycle. During the same year, the authors were able to realize the reductive carboxyla-

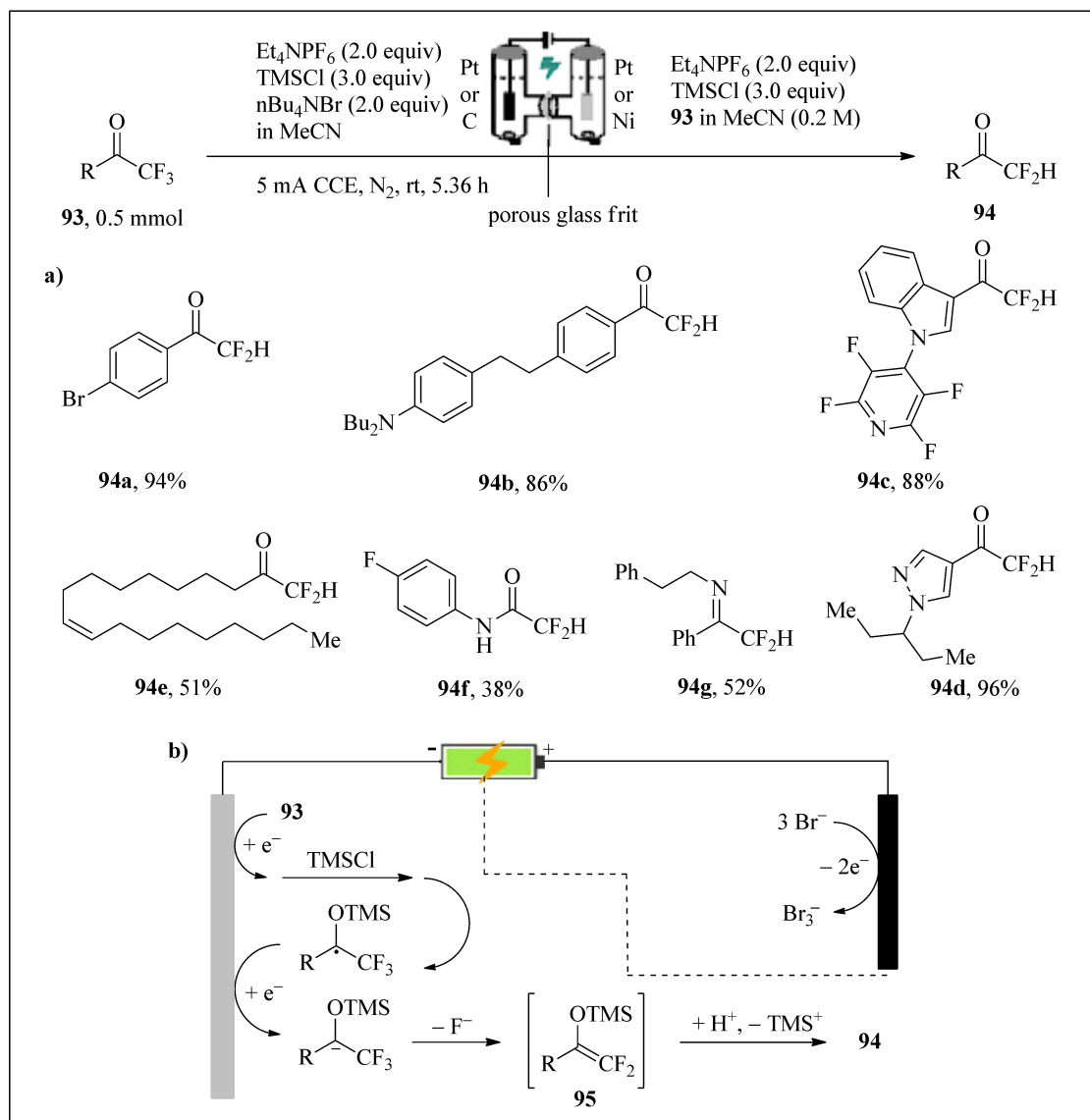


Scheme 24. Electroreductive hydrodehalogenation of organic halides.<sup>[56]</sup>

reduction of C=C or C≡C bonds and protonation by either additives or solvents, involving moisture (2e<sup>-</sup> and 2H<sup>+</sup> in total) is the typical mechanism for this type of transformation. In 2019, 1,4-reduction of α,β-unsaturated ketones in a favourable environment via an electrochemical method (Scheme 28) was discovered by Xia and coworkers.<sup>[68]</sup> Besides the mixed solvent of dimethyl sulfoxide (DMSO) and methanol, this constant current electrolysis uses a low-cost salt, ammonium chloride (NH<sub>4</sub>Cl), as the only additive. Under standard conditions (Scheme 28a, **105a–e**), a variety of substituents on the α,β-unsaturated ketones are well tolerated. Mechanistic studies show that both NH<sub>4</sub>Cl and co-solvent methanol are the source

of hydrogen, that undergoes transfer of proton with the anion intermediates produced by direct cathodic reduction; DMSO is used as a sacrificial reductant in an anodic process (Scheme 28b). The applicability of this method is somewhat limited as it only involves α,β-unsaturated ketones despite its simplicity in operation and its cost-effectiveness.

In the subsequent year, using two graphite rod electrodes under favorable environment, a metal-free electroreduction of activated alkenes was reported by the team of Li and Huang.<sup>[69]</sup> This method facilitates the simple 1,4-reduction of α,β-unsaturated acids, amides, esters, and nitriles, and thus its application is similar to that in Xia's work.<sup>[68]</sup> However, this method fails to



Scheme 25. Electrochemical hydro-monodefluorination of trifluoromethylketones.<sup>[59]</sup>

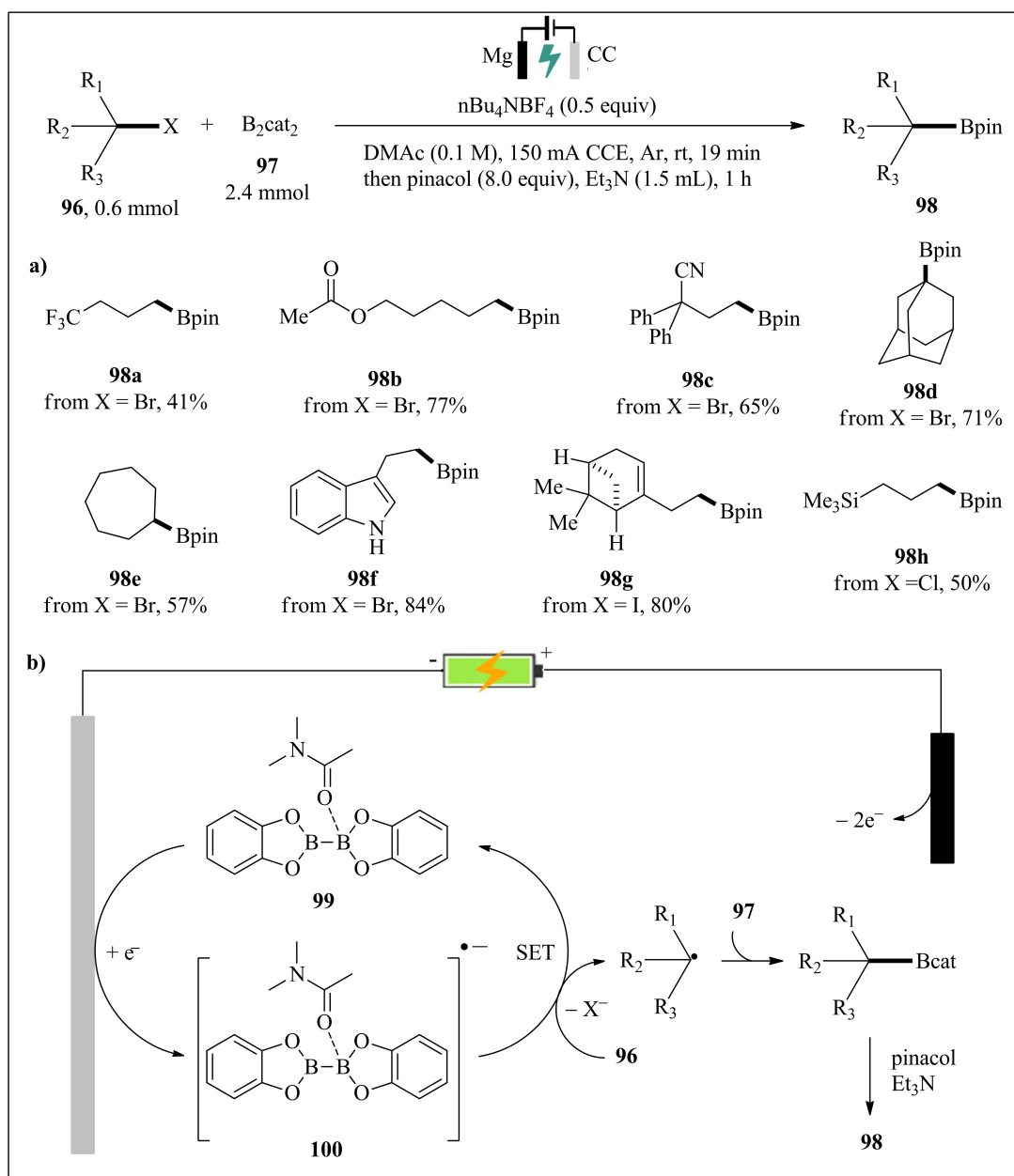
correlate the tolerance of functional group as demonstrated by the studies of substitution pattern of the substrates. Later in 2021, an electrochemical reduction of ketene dithioacetals and ynones was combinedly designed by Yang and Wen, which involves  $\text{KSCN}$  and  $\text{Ph}_2\text{S}$  as the respective anodic sacrificial reagents.<sup>[68]</sup>

Ammonia shares the majority of inorganic industrial chemical production in the world due to its application in various fields.<sup>[22]</sup> Using gaseous ammonia as a source of hydrogen, Cheng and coworkers, in 2019, realized a new technique in which the unsaturated compounds are subjected to electrochemical reduction (Scheme 29).<sup>[70]</sup> Using two graphite felt (GF) electrodes at room temperature, a variety of  $\text{C}=\text{C}$  or  $\text{C}\equiv\text{C}$  bonds adjacent to EWGs, or aryl groups are subjected to electrolysis to facilitate reduction under 5–7 V constant voltage (Scheme 29a, 107a–g). From the mechanistic investigation, the authors put forward a stepwise hydrogenation mechanism (Scheme 29b).

Radical intermediate **108** is obtained by direct one-electron cathodic reduction of substrate **106**, after which accepts the second electron from the cathode and proton from ammonia to give the final product **107**. Then, the by-product  $\text{NH}_2^-$  is oxidized at the anode to form hydrazine, which can reduce two more equivalents of **106**. During this transformation, the direct formation of hydrazine from ammonia may also occur.

In the subsequent year, the same group became successful to realize the cathodic reduction of  $\alpha$ -tri-fluoromethyl cinnamate derivative to afford *gem*-difluorostyrenes after the extrusion of a fluoride ion using the above mentioned ammonia based electrochemical strategy.<sup>[70]</sup> Lately, they also designed Horner-Wadsworth-Emmons (HWE) olefination/hydrogenation tandem reaction as a metal-free electrochemical technique promoted by  $\text{NH}_3$ , giving a wide range of elongated esters and nitriles having two-carbon, from aldehydes and ketones (Scheme 30).<sup>[71]</sup> This technique dominates over the traditional



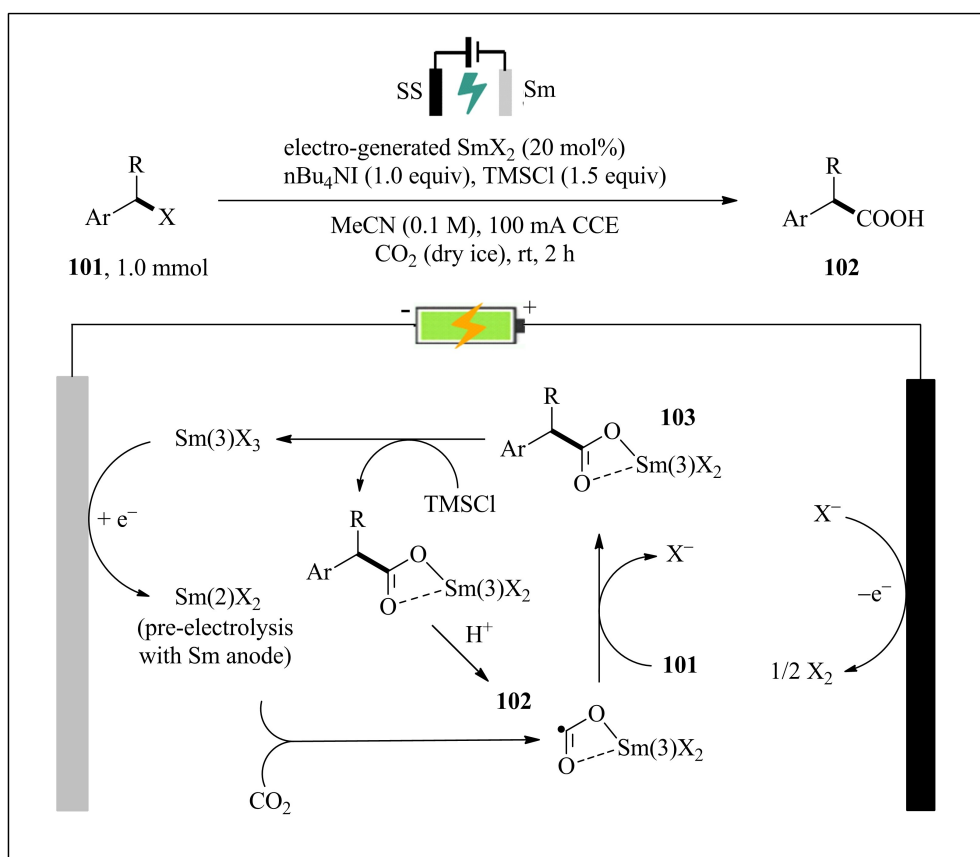
Scheme 26. Electrochemical borylation of alkyl halides.<sup>[63]</sup>

HWE reaction utilizing the fact that this reaction requires only a catalytic amount of base or even not at all, and this transformation becomes even more compelling due to the fact that the resulting  $\alpha,\beta$ -unsaturated compound undergoes electrochemical reduction. During this electrochemical process (Scheme 30a, 111 a–i), different functional groups are well tolerated on the carbonyl partners, consisting of C=C double bonds, hydroxyl, and heterocycles. MeO<sup>-</sup> (a catalytic base) deprotonates phosphate substrate **110**, and thus formed anion immediately undergoes HWE olefination with **109** to afford  $\alpha, \beta$ -unsaturated intermediate **112**, which undergoes reduction followed by protonation to give desired final compound **111** (Scheme 30b).

## 9.2. Catalytic hydrogenation with cathodically generated H<sub>2</sub> or adsorbed hydrogen

In reductive organic electrocatalysis, utilization of the hydrogen gas or adsorbed hydrogen generated by the cathodic reduction of protons via electrocatalytic technique is very compelling. Normally, the transition metals viz. Pd, Ni, Cu promotes these reactions, either in the form of additional catalysts or modified electrodes in protic solvents.<sup>[22]</sup>

Moeller and co-workers, in 2019, revealed that the cathodically generated H<sub>2</sub> during the electrochemical oxidation of substrates can be exploited to facilitate the palladium-catalyzed hydrogenation process (Scheme 31).<sup>[72]</sup> These reactions can be carried out without specially designed cathodic and anodic



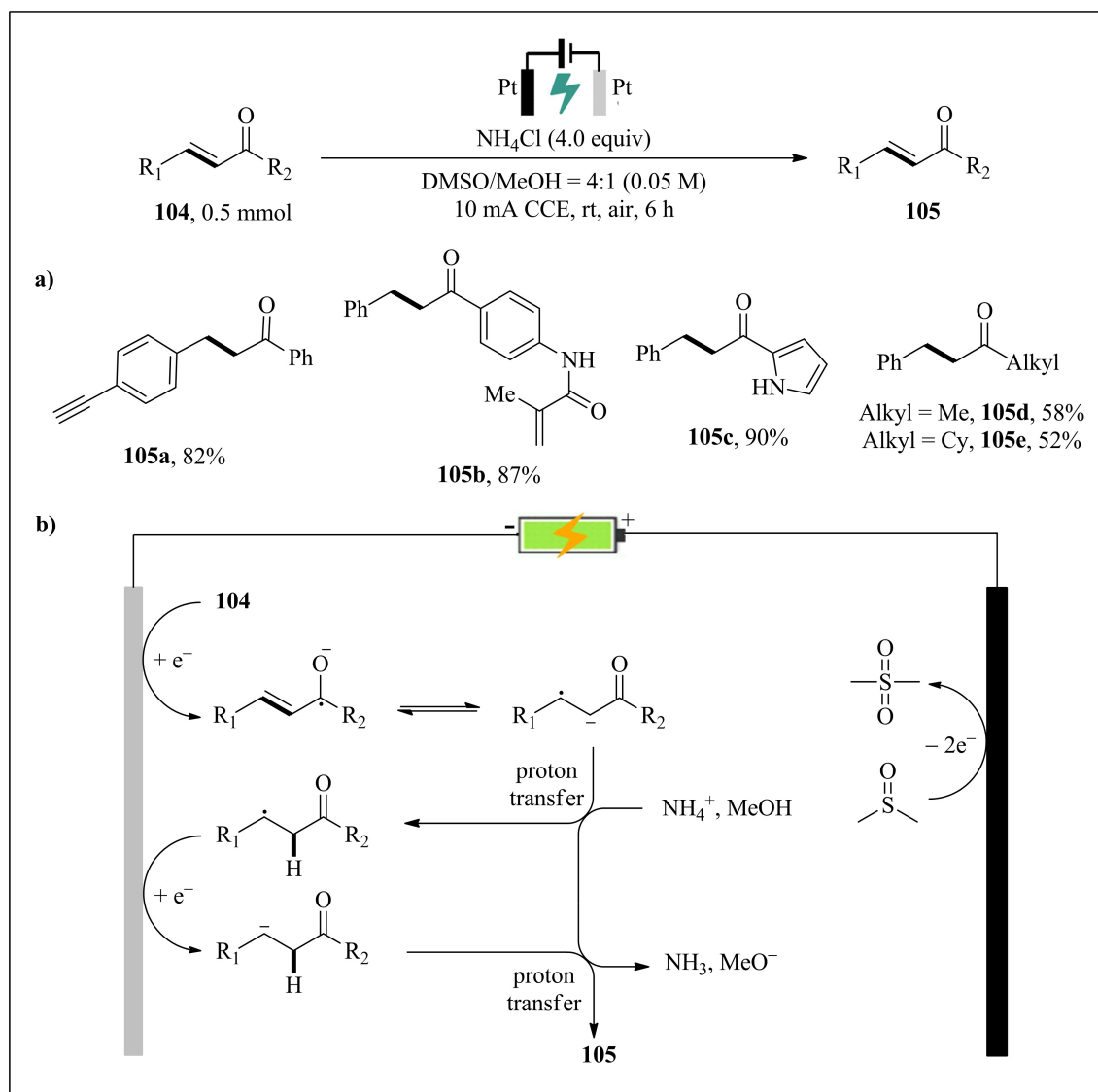
Scheme 27. Electrochemical carboxylation of benzylic halides using a “soluble” Sm electrode.

processes in either divided or undivided cell. For instance, during the electrochemical oxidation of lignin-derived alcohol **113a** to aldehyde **114a** carried out with a reticulated vitreous carbon (RVC) anode in an undivided cell, the hydrogen gas liberated at Pt electrode is shifted to another flask to ease various smaller-scale hydrogenation reactions, like 1,4-reduction of  $\alpha,\beta$ -unsaturated carboxylic acids **115a** and deprotection of benzyloxycarbonyl (Cbz) protected amino acid **115b**. The sustainability and the energy efficiency of the organic electro-synthesis can be greatly enhanced by the technique that involves the combination of anodic oxidation with non-electrochemical reduction exploiting the electrochemically formed side product  $\text{H}_2$ . Moeller and colleagues carried out a similar paired electrolysis system, apart from utilizing the cathodically generated  $\text{H}_2$  in catalytic hydrogenation, that includes the regeneration of a Zn sacrificial anode, the dimerization of activated alkenes via reduction and nitro-arenes, and the deoxygenation of  $\text{Ph}_3\text{P}=\text{O}$  and  $\text{Ph}_3\text{As}=\text{O}$ .<sup>[73]</sup>

Using homogeneous Pd catalysis, Ge and coworkers were able to carry out cathodic hydrogenation making the use of cathodically generated  $\text{H}_2$  in the highly stereoselective semi-reduction of alkynes to Z-alkenes (Scheme 32).<sup>[74]</sup> A variety of aliphatic and aromatic internal alkynes sustain convenient semihydrogenation to the respective alkenes with a Z/E ratio reaching  $>99:1$  (Scheme 32a, **118a–f**), under CCE in MeOH at 60 °C with a carbon anode and a Pt cathode. Clearly, under

slightly varied conditions using MeCN as the solvent (Scheme 32a, **119a**, **119b**), the complete reduction of alkynes or alkenes to alkanes can also be realized. The outcome of the mechanistic investigation, which uses X-ray diffraction (XRD) characterization, scanning electron microscopy (SEM), and deuterium labelling experiments, reveals that a secondary amine additive and the solvent MeOH (a supporting electrolyte) acts as the source of hydrogen, and the generated palladium nanoparticles play the role of chemisorbed hydrogen carriers. Combining these results with the previous reports bolsters the mechanism for electrochemical Z-selective semihydrogenation of alkynes (Scheme 32b). The chemisorbed hydrogen, generated by the cathodic reduction of methanol, is concurrently adsorbed to the cathodically generated Pd(0) nanoparticles. Z-alkene product, generated by the sequential hydrogen transfer process of alkyne **119** with Pd hydrogen carrier, regenerates the adsorption sites following subsequent desorption from Pd. Additionally, the cathode reduces the tetrabutylammonium ions ( $n\text{Bu}_4\text{N}^+$ ) of the electrolyte to give tributylamine, which in turn gives the amine radical cation with the loss of an electron at the anode, that serves as another proton donor for hydrogenation.

Lately, Martín-Matute and colleagues put forward that using heterogeneous Ni catalysis, similar electrochemical transformation can be achieved alternatively.<sup>[75]</sup> In the presence of an Ag/AgCl reference electrode, under potential-controlled environ-

Scheme 28. Electrochemical 1,4-reduction of  $\alpha,\beta$ -unsaturated ketones.

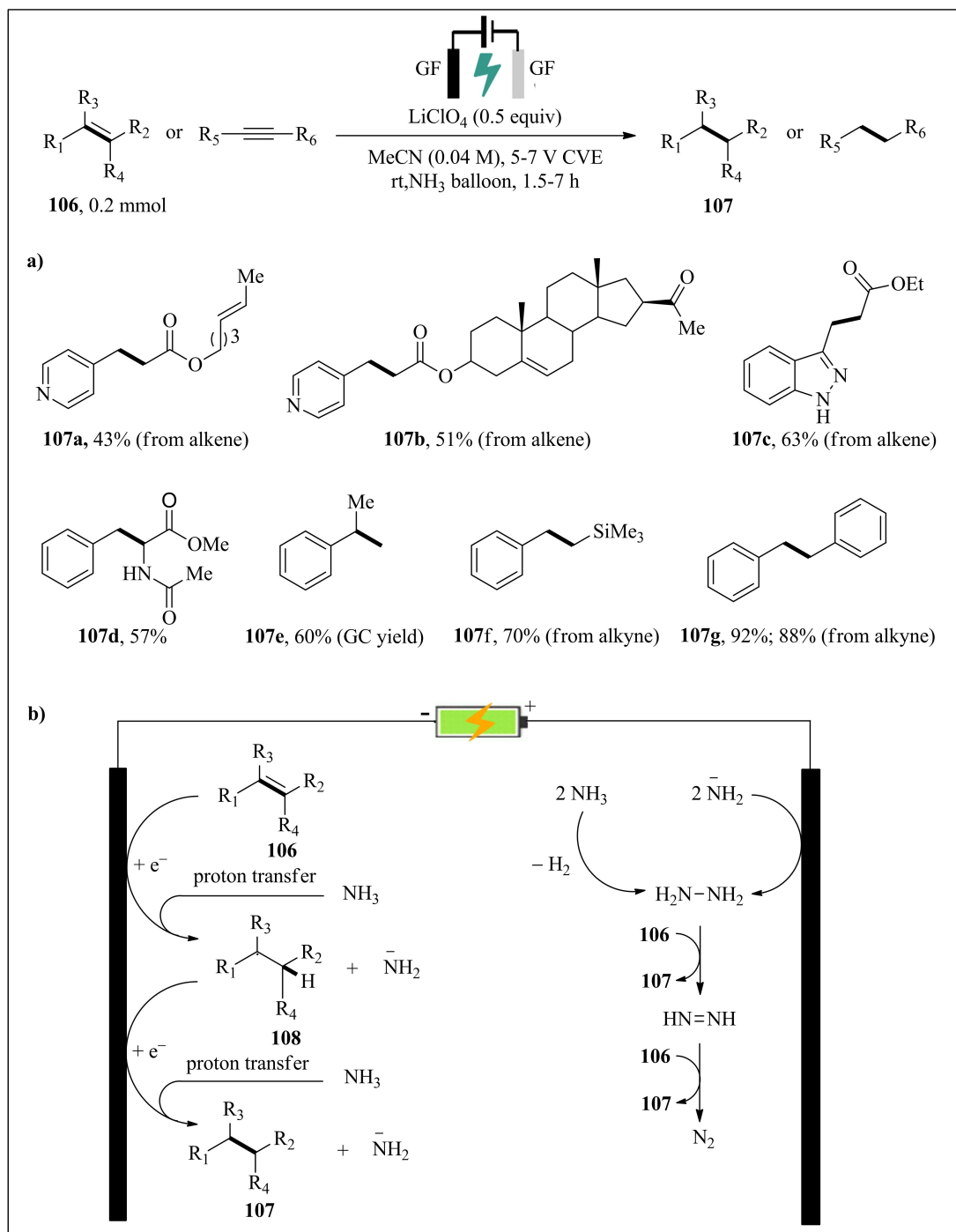
ment, functional alkynes can be semi-reduced *Z*-stereoselectively using carbon cloth (CC) anode and a Ni foam as a cathode that is available commercially.<sup>[75]</sup>

### 9.3. Reductive functionalization of C=C and C≡C bond

The reductive functionalization can also be realized by the seizure of the anionic radical intermediates generated from cathodically reduced C=C and C≡C halves, not only from protonation, by other electrophilic species or radical acceptors. The trending challenge of research in the field of reductive electrocatalysis is the inclusion of CO<sub>2</sub>, that is not only a harmful greenhouse gas but also an easily available, abundant, and renewable C1 building block to produce various carboxylation compounds.<sup>[76–78]</sup> Specifically, the reductive functional-

ization of C=C and C≡C bonds with CO<sub>2</sub> is a compelling research interest in the field of reductive electrocatalysis.

In 2020, a photo-electrochemical technique to produce  $\beta$ -carboxyl ketones from  $\alpha,\beta$ -unsaturated ketones employing CO<sub>2</sub> as a feedstock and silica nanowires (SiNWs) as the cathode was designed by Wang, Zhang, and coworkers.<sup>[79]</sup> Upon irradiation by light, the SiNWs cathode undergoes excitation and produces photoelectrons, that immediately shift to the electrode surface to involve in the reduction of the substrates. During the same year, the groups of Malkov and Buckley employed triethanolamine (TEOA) – an inexpensive sacrificial reductant – instead of a metal sacrificial anode (Scheme 33a) to realize electrochemical hydrocarboxylation of normal aromatic olefins.<sup>[80]</sup> Under 10 V constant-voltage electrolysis, a wide range derivatives of styrene as well as the  $\alpha,\alpha$ -disubstituted and  $\alpha,\alpha,\beta$ -trisubstituted aromatic alkenes react conveniently affording highly  $\beta$ -regioselective hydrocarboxylation products (Scheme 33a, **121 a–h**).

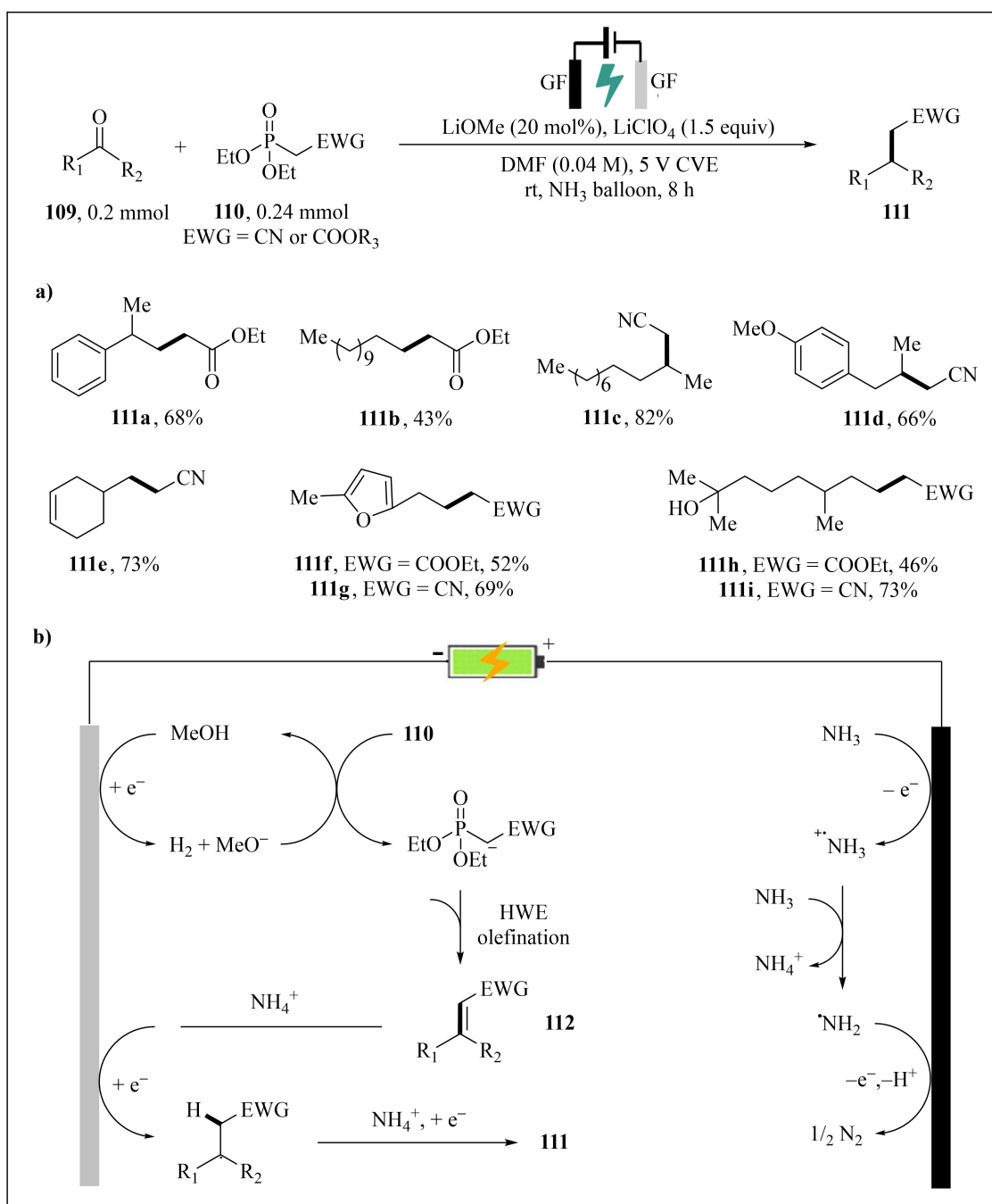


Scheme 29. Electrochemical hydrogenation of C=C or C≡C bonds with gaseous ammonia.

After prolonged electrolysis under optimized conditions, a novel hydrocarboxylation have also been successfully carried out for more sterically demanding  $\alpha,\beta,\beta$ -trisubstituted and even  $\alpha,\alpha,\beta,\beta$ -tetrasubstituted alkenes producing only the  $\alpha$ -hydro- $\beta$ -carboxylation products (Scheme 33a, **121 i-k**).

Acknowledging the fact that both the  $CO_2$  as well as the aromatic alkenes exhibit identical reduction potentials, for this electrochemical hydrocarboxylation (Scheme 33b), two viable mechanistic pathways are proposed. The reduction of alkene to

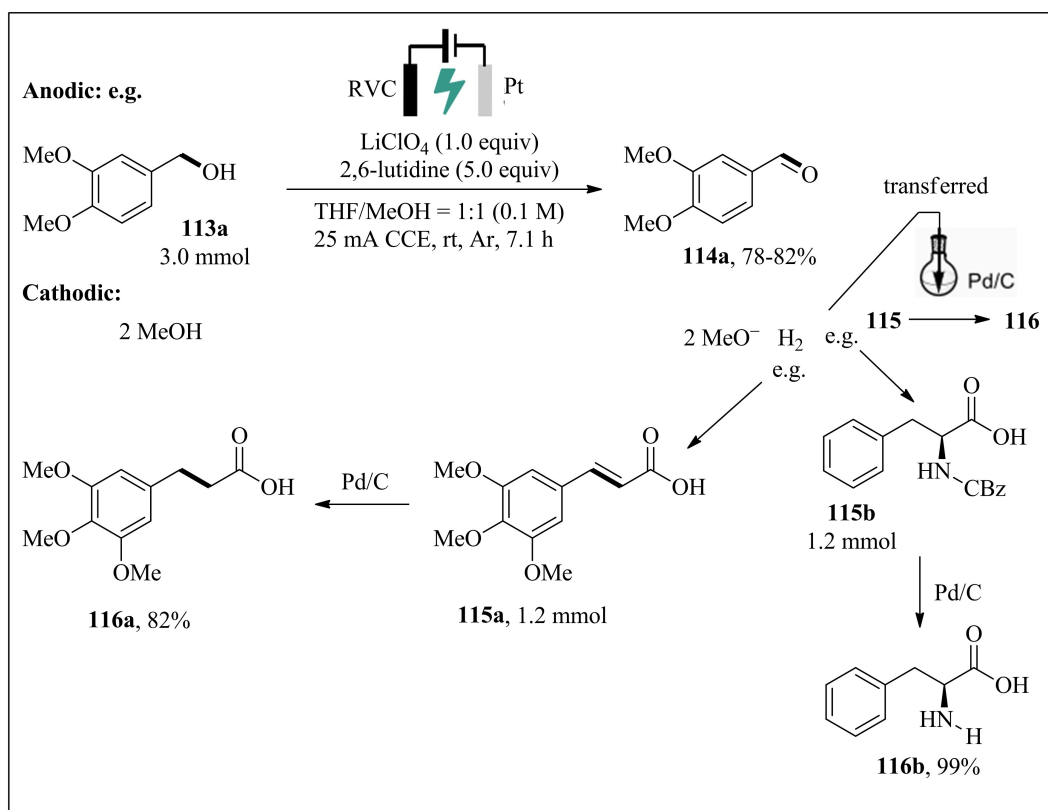
a surface adsorbed-radical anion is illustrated by the CV experiments on a reaction mixture with or without  $CO_2$  saturation. It subsequently reacts with the dissolved  $CO_2$  to give the desired carboxylic acid or causes polymerization and electrode passivation. Subsequent studies have also supported the mechanism: the adsorbed alkenes receive an electron from the cathode to form a surface adsorbed radical anion **95**, that then undergoes a sequence of carboxylation and protonation to afford an adsorbed radical **95**; further electron transfer,



**Scheme 30.** NH<sub>3</sub>-promoted electrochemical HWE olefination/hydrogenation tandem reaction.

dissociation from the electrode, and protonation give the ultimate compound **94** (Scheme 33b, path a). However, it is impossible to discard an alternative mechanistic pathway through the direct reduction of CO<sub>2</sub> (Scheme 33b, path b). Nam and coworkers have also proposed similar cases in their detailed investigation into the dicarboxylation and hydrocarboxylation of styrenes.<sup>[81]</sup> Buckley and coworkers, after the publication of this work, continued their research on the electroreductive functionalization of unsaturated compounds with CO<sub>2</sub> and ultimately designed the regioselective hydrocarboxylation of

conjugated dienes<sup>[82]</sup> and  $\alpha,\beta$ -unsaturated compounds<sup>[83]</sup> under identical environment.

Scheme 31. Pd-catalyzed reduction with cathodically generated H<sub>2</sub>.

## 10. Alternative strategies to overcome limitations of cathodic electroreductive synthesis

### 10.1. Paired electrolysis

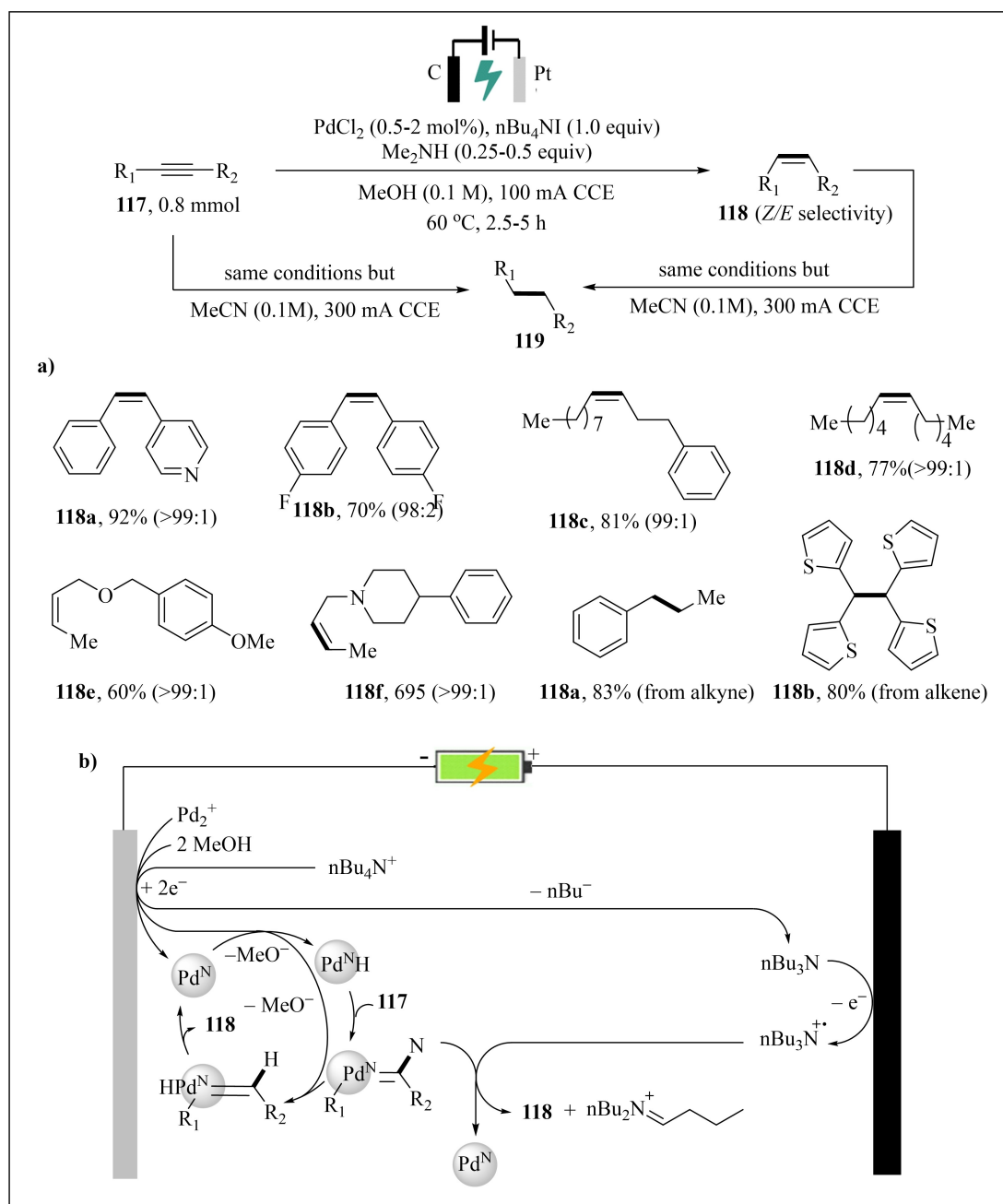
Although cathodic reductive cross-coupling is an efficient approach for C–C bond formation, it faces challenges caused due to need for a sacrificial electrode.<sup>[84]</sup> Here, the desired reaction occurs only at one electrode whereas the sacrificial reaction occurs at the counter electrode. Therefore, in this approach, the sustainability and energy efficiency of the conversion is compromised. This challenge can be addressed by using paired electrolysis in which simultaneous occurrence of two desirable half-reactions is possible at both electrodes.<sup>[85]</sup>

Waldvogel and Morandi<sup>[86]</sup> applied paired electrolysis for reversible halide-shuttle reactions. By using simple dihalogenated solvents as the halide source, vicinal dihalogenations of various alkenes can easily be achieved.<sup>[6]</sup> In 2020, Zhang et al.,<sup>[87]</sup> used parallel paired electrocatalysis (simultaneous anodic and cathodic reactions give two non-reacting products) to synthesize azoxyaromatics derivative **126** upto 99% yield. At the anode, oxidation of amine derivative **123** formed nitrile product **124** whereas at cathode nitrobenzene **125** was reduced to the final product **126** (Scheme 34).<sup>[87]</sup>

### 10.2. Electrophotocatalysis

Electrophotocatalysis is an emerging alternative to cathodic electrocatalysis which exploits the synergistic benefits of both electricity and light.<sup>[88–90]</sup> In this approach, a suitable photocatalyst is used which is sequentially activated via electrolysis and photoexcitation making it possible to achieve extremely oxidizing or reducing potentials.<sup>[90,91]</sup> Therefore, this approach is specifically useful for highly redox-neutral reactions and can normally go beyond the reach of common methods.<sup>[1,92,93]</sup> For example, by using a dual electrophotocatalytic system, Zhang and co-workers successfully oxidized extremely unactivated aliphatic alcohols **127** even under mild reaction conditions (Scheme 35a).<sup>[94]</sup> In 2020, Lai and co-workers effectively alkylated heteroarenes **130** with organotrifluoroborate salts in an oxidant free environment (Scheme 35b).<sup>[95]</sup>

Likewise, under the mild photo- and electrochemical conditions (Scheme 36), the group of Lambert and Lin used a photo-excitable mediator, dicyanoanthracene (DCA) to realize extreme reduction potentials.<sup>[96]</sup> Aromatic C–C, C–B, and C–Sn bonds can be easily formed via reductive cross-coupling of aromatic chlorides and bromides with trapping reagents viz. B<sub>2</sub>pin<sub>2</sub>, Sn<sub>2</sub>Me<sub>6</sub>, and (hetero)arenes (Scheme 36a, **132 a–g**). Mechanistic pathway shows that the catalyst DCA undergoes cathodic reduction to form radical anion DCA, which upon blue light irradiation, is excited to highly reducing species **133**. The regeneration of DCA from **133** and aryl halide **131** via the SET process simultaneously gives anionic radical intermediate **134**,

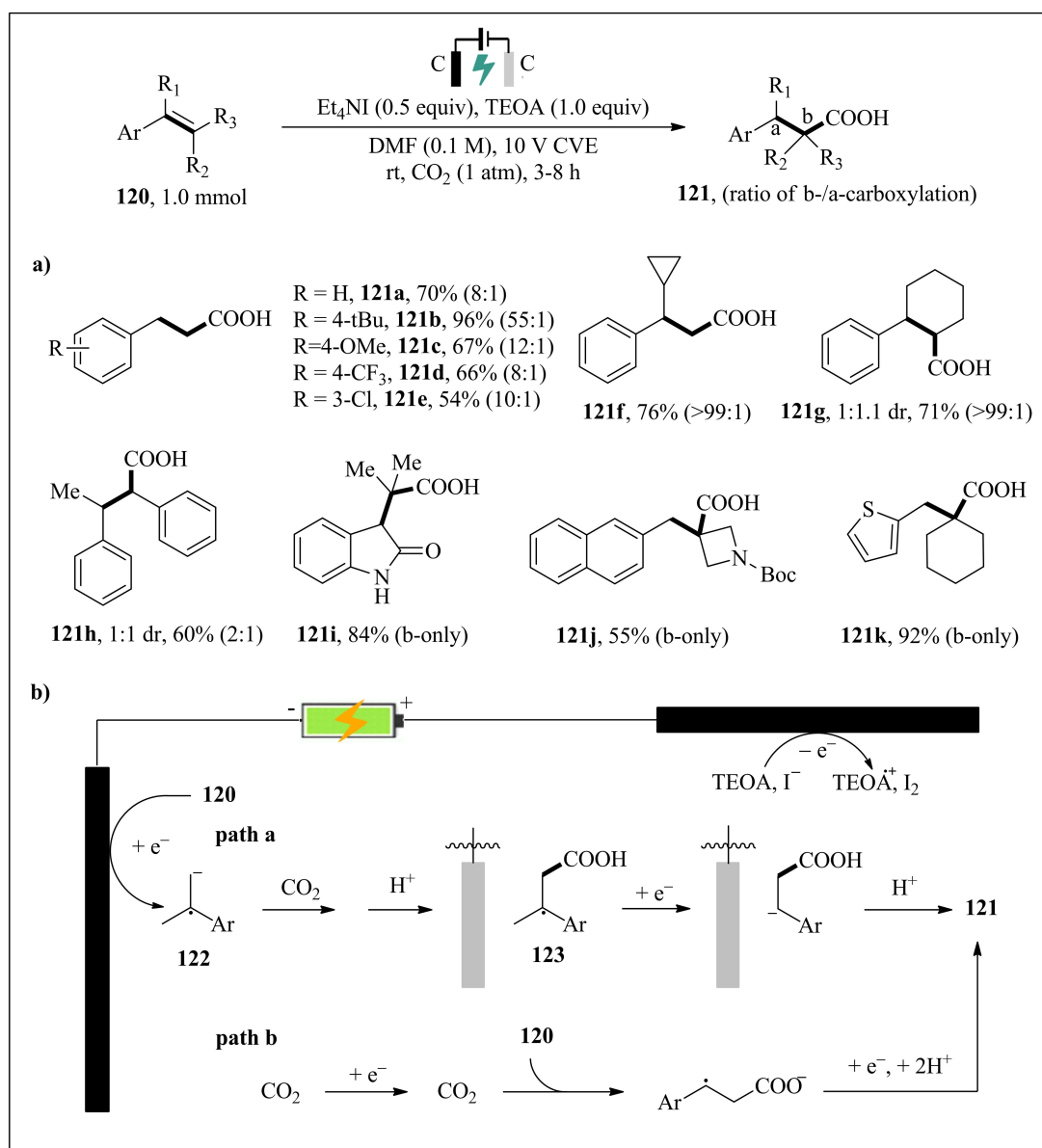


**Scheme 32.** Pd-catalyzed semireduction of alkynes to Z-alkenes, and further reduction.

that immediately take part in mesolytic cleavage to give an aryl radical for the subsequent functionalization (Scheme 36b). Meanwhile, Wickens and coworkers, with the help of electricity and an imide catalyst, reported an electrophotocatalytic technique to surpass the energetic limitations of visible light.<sup>[97]</sup> Highly reducible aryl chlorides were effectively reduced to aryl radicals, enabling the formation of C–P or C–C bonds. This approach exhibited superior selectivity and tolerance towards functional groups compared to direct electrolysis.

### 10.3. Alternating current

On one hand, direct current (DC) electrolysis, which is the most commonly applied approach involving a flow of the electric current only in one direction, is conducted at either constant current or constant potential conditions. On the other hand, alternating current (AC) electrolysis – a less explored approach but a promising alternative to DC electrolysis<sup>[98]</sup> – involves a periodic change of direction of charge flow.<sup>[99]</sup> It is suggested that a sequence of redox-opposite reactions could be performed because of periodic polarity reversal in AC. Specifically, AC electrolysis is suitable if the reaction is highly irreversible or



Scheme 33. Electrochemical hydrocarboxylation of general aromatic olefins.

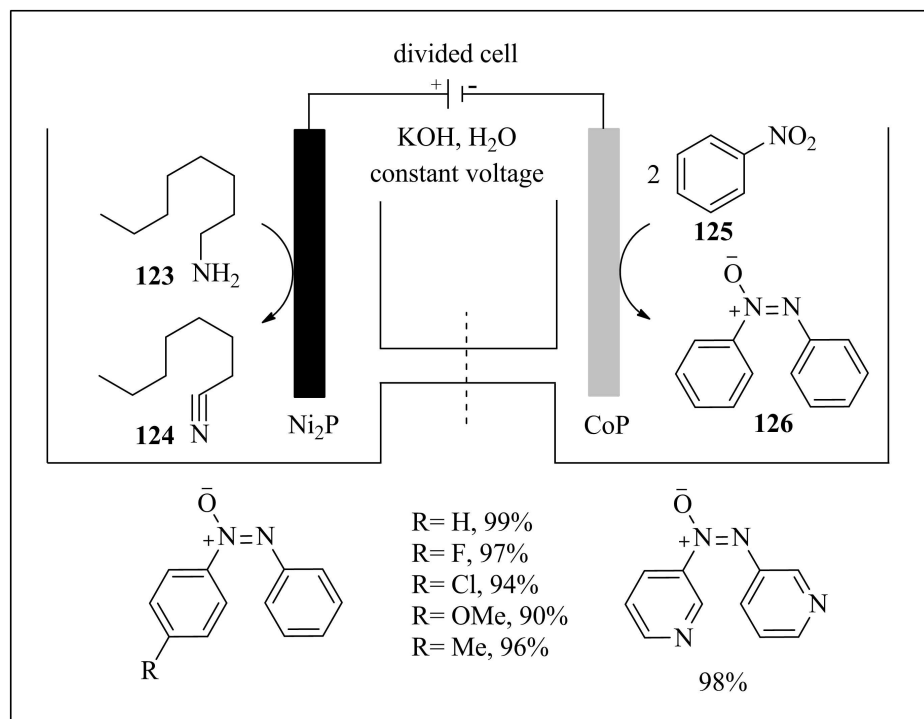
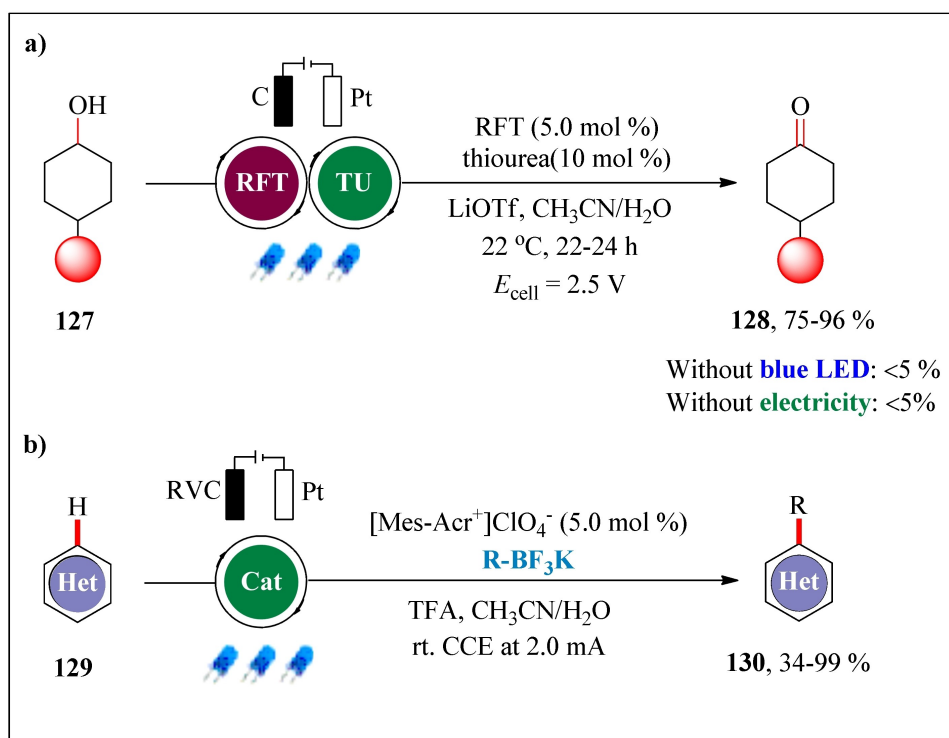
it involves a sequence of reactions stabilizing the reaction products upon polarity reversal. For example, in 1982, Alkire et al.<sup>[100]</sup> synthesized propylene oxide by electrolysis of propylene solution saturated with NaBr. This reaction involves a sequence of irreversible reactions at both the cathode and anode. Firstly, oxidation of NaBr takes place to form  $\text{Br}_2$ . Once the reversal of polarity occurs, electrolysis of water occurs to the form  $\text{OH}^-$  and  $\text{H}_2$ . Then,  $\text{Br}_2$  reacts with propylene in the presence of  $\text{OH}^-$  to form propylene bromohydrin. Finally,  $\text{OH}^-$  ion catalyses the dehydrogenation of dibromide to form propylene oxide.<sup>[101]</sup>

### 10.3.1. Minimizing over-oxidation/reduction

The main advantage of AC electrolysis over DC electrolysis is that it helps to minimize over-oxidation/reduction of reagents, catalysts, and solvents. In DC electrolysis, although over-oxidation/reduction may occur under constant potential (occurs when the reaction species have close redox potential values), it is more common under constant current conditions compromising the yield and selectivity of the reaction. Here, to maintain a constant current in the reaction system, the applied potential is varied which is responsible for unwanted side reactions.<sup>[99]</sup>

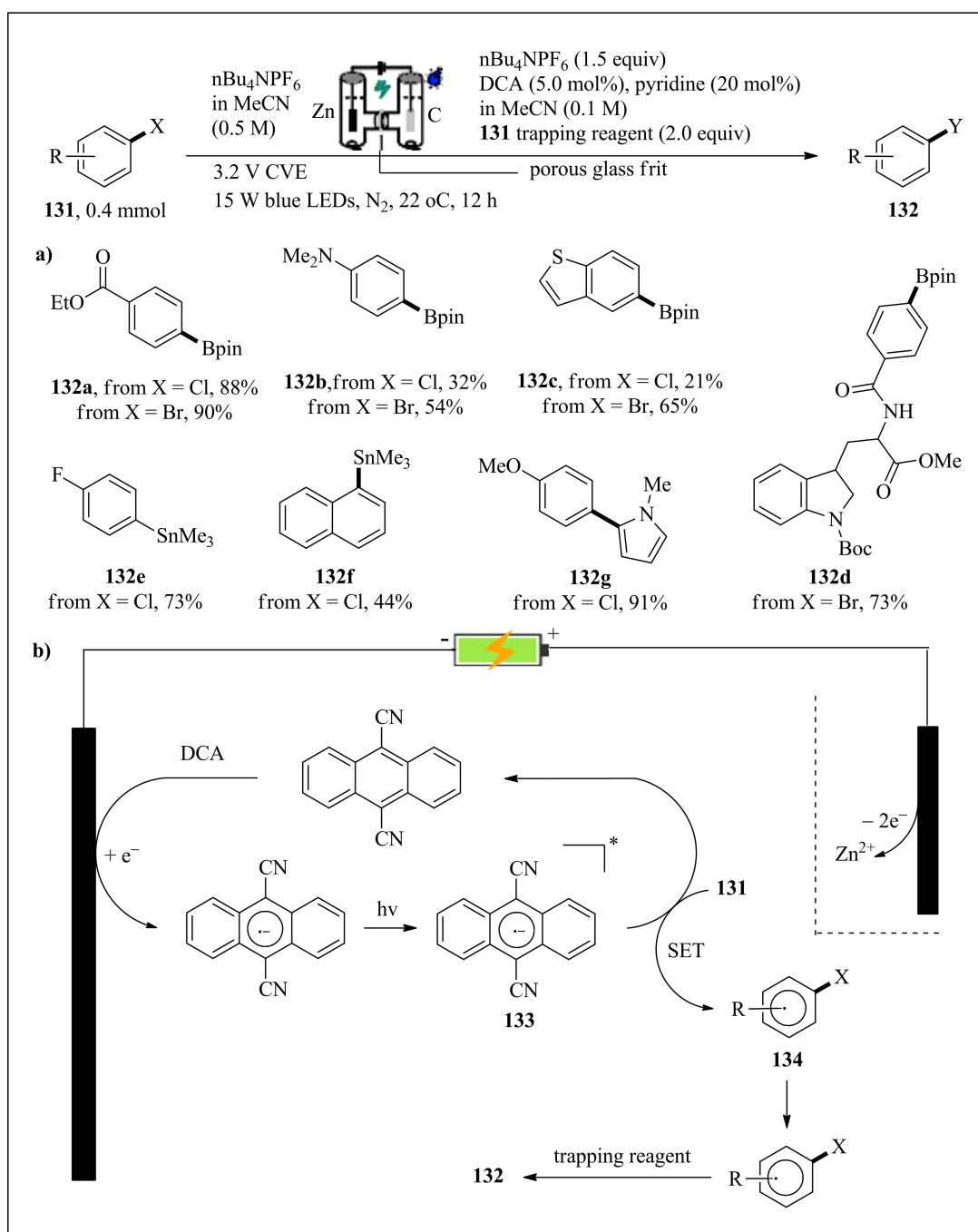
Sattler et al.<sup>[102]</sup> utilized the AC approach in the sulfur-sulfur bond metathesis of symmetrical disulfides and reported that it can prevent the formation of by-products and the unproductive consumption of reagents (Scheme 37). During DC electrolysis



Scheme 34. Electroformation of azoxy-aromatics and nitriles derivatives.<sup>[87]</sup>Scheme 35. Application of electrophotochemistry in highly redox-neutral reactions. a) oxidation of highly unactivated aliphatic alcohols;<sup>[94]</sup> b) electrophotochemical C–H alkylation.<sup>[95]</sup>

under constant current, upon electrolysis for long period, the yield of product **137** was drastically decreased probably due to over-oxidation/reduction of disulfides. At the anode, disulfide

was over-oxidized to form an oxo by-product whereas, at the cathode, it was over-reduced to undefined black precipitate. However, under AC electrolytic conditions, the formation of

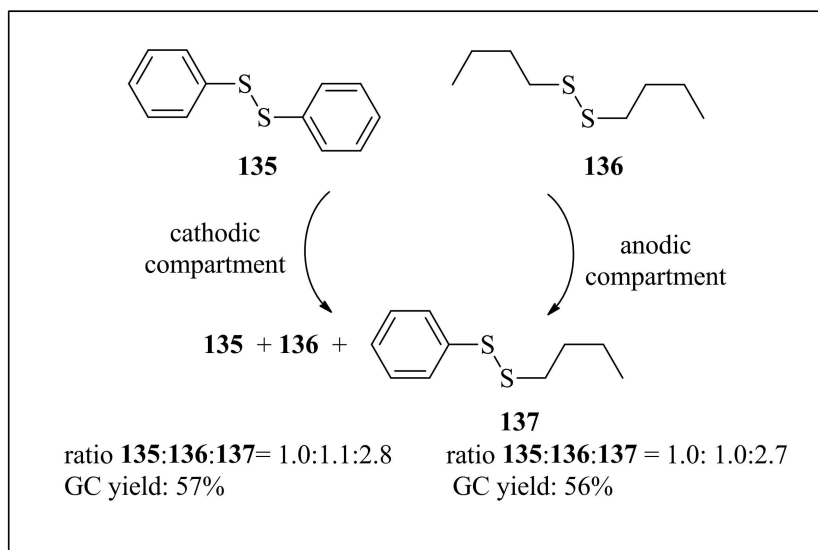


Scheme 36. Reductive functionalization of aromatic halides via electrocatalysis.

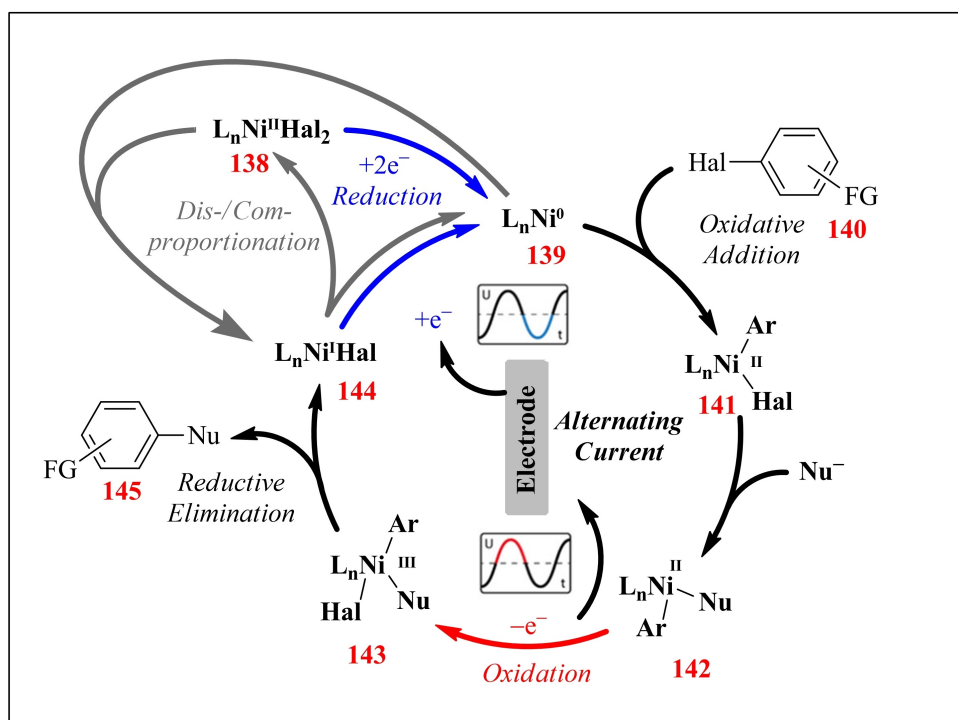
black precipitate and oxo-product was completely prevented. Here, they performed electrolysis of symmetrical disulfides **135** and **136** in a divided cell using tetrabutylammonium tetrafluoroborate ( $TBABF_4$ ) as a supporting electrolyte, and unsymmetrical disulfide product **137** was formed almost in equal percentages both in anodic and cathodic compartments (as identified by gas chromatography, GC).<sup>[102]</sup>

Bortnikov et al.<sup>[103]</sup> suggested that AC-assisted electrocatalysis is particularly applicable if the transformation involves catalytic cycles and the rate-determining step involves reductive

elimination or oxidative addition. They successfully performed several Ni-catalysed aminations, esterification, and etherification reactions using the AC method. The proposed mechanism of the transformation involves initial electrical reduction of Ni(II) catalyst **138** to Ni(0) species **139**. Then,  $[NiL(Ar)Nu]$  species **142** is formed after the oxidative addition of aryl halide **140** to the Ni(0) species followed by ligand exchange with a nucleophile. Further oxidation of **142** followed by reductive elimination gives desired cross-coupling product **145** and Ni(I) species **144** (Scheme 38). In this experiment, AC electrolysis gave higher



**Scheme 37.** Results of AC approach in the sulfur-sulfur bond metathesis of symmetrical disulfides. Conditions: divided cell; Pt / Pt (1.0 cm<sup>2</sup> each); 10 mA; 1/2 (0.5 mmol each), CH<sub>3</sub>CN (10 mL), TBABF<sub>4</sub> (0.3 M), rt.<sup>[102]</sup>



**Scheme 38.** The proposed mechanism of Ni-catalysed catalytic cycle for cross-coupling reactions using the AC method.<sup>[103]</sup>

yields and selectivity than DC electrolysis. The researchers provided two possible explanations for this outcome. The first explanation is that, during DC electrolysis, unwanted over-reduction of species 142 to Ni(I) takes place which is followed by second oxidative addition to form [NiNu(Ar)<sub>2</sub>] intermediate. The second explanation is that since periodic voltage reversal occurs in AC electrolysis, species 142 has a short life which prevents its further disproportionation to form [NiL<sub>n</sub>(Ar)<sub>2</sub>].<sup>[103]</sup>

### 10.3.2. Successful N–H/S–H cross-coupling that cannot occur through DC electrolysis

Yuan et al.<sup>[98]</sup> demonstrated that AC electrolysis can be used to radical-radical cross-coupling reactions forming N–S bonds that are impossible to deliver via DC electrolysis. They successfully applied AC electrolysis for oxidant and catalyst-free oxidative radical cross-coupling of sulfonyl- or acyl-substituted aniline derivatives with thiophenols/thiols and synthesized forty differ-

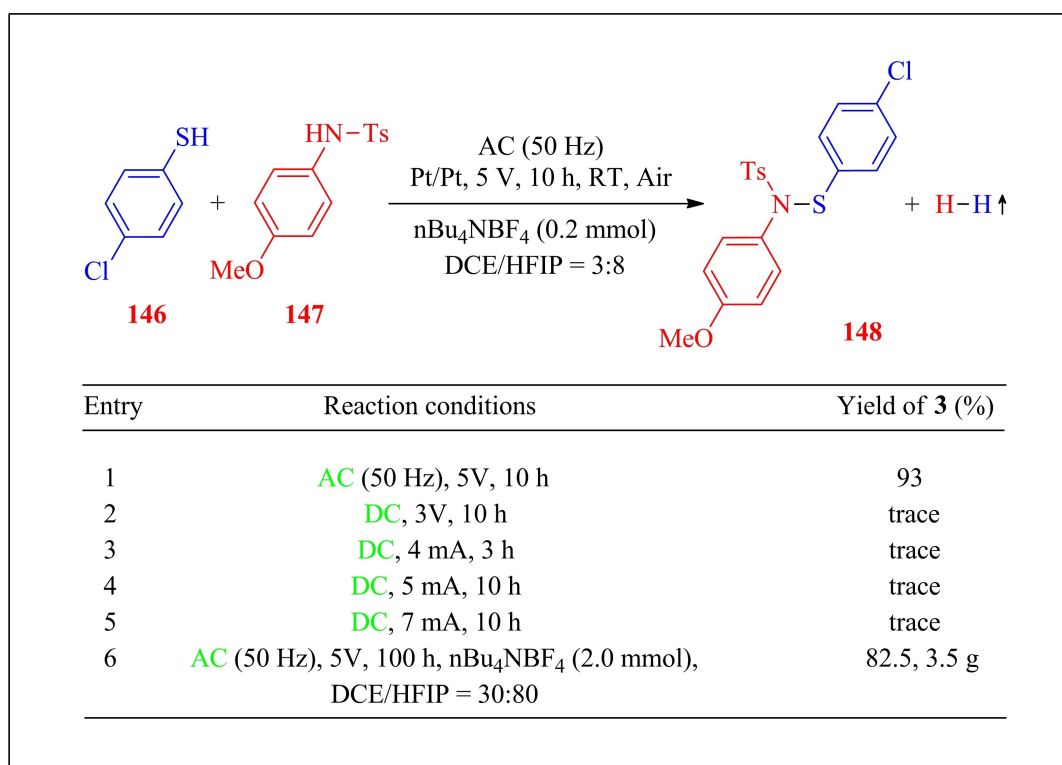
ent N–S bond containing compounds with excellent yield and selectivity. As a model reaction, they performed cross-coupling of 4-chlorothiophenol **146** and *N*-Ts-4-methoxyaniline **147**. After AC electrolysis by using  $n\text{Bu}_4\text{NBF}_4$  (0.2 mmol) as an electrolyte and a 3:8 mixture of 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP, 8 mL) and 1,2-dichloroethane (DCE) as co-solvent, they isolated the desired product **148** in 93% yield (Scheme 39, entry 1). However, under DC electrolysis, the only trace of product **148** with poor selectivity was reported (Scheme 39, entry 2–5). In addition, they successfully performed this synthesis on a gram scale by taking 10 mmol of **146** and **147** each in the presence of 2.0 mmol of  $n\text{Bu}_4\text{NBF}_4$  and a 30:80 mixture of DCE and HFIP. The reported yield of product **148** was 82% (Scheme 39, entry 6).<sup>[98]</sup>

The proposed mechanism of the transformation involves electrochemical oxidation of thiol **149** followed by deprotonation to form thiyl radical **150**. The unstable thiyl radical then immediately dimerizes to give disulfide intermediate **151** which is accumulated on the electrode. Once the polarity reversal occurs,  $\text{H}_2$  is released to the same electrode by the reduction of  $\text{H}^+$ . Thereafter, disulfide intermediate **151** is again reduced to release thiyl radical **150** and thiolate anion **153**. The next polarity reversal results in the deprotonation of amine reagent **152** to form a nitrogen-centered radical **154**. Finally, radical-radical cross-coupling of thiyl radical **150** and nitrogen radical **154** leads to the final product which contains an N–S bond. Here, all these reactions are taking place at the same reaction and the same happens at another electrode. The thiolate anion

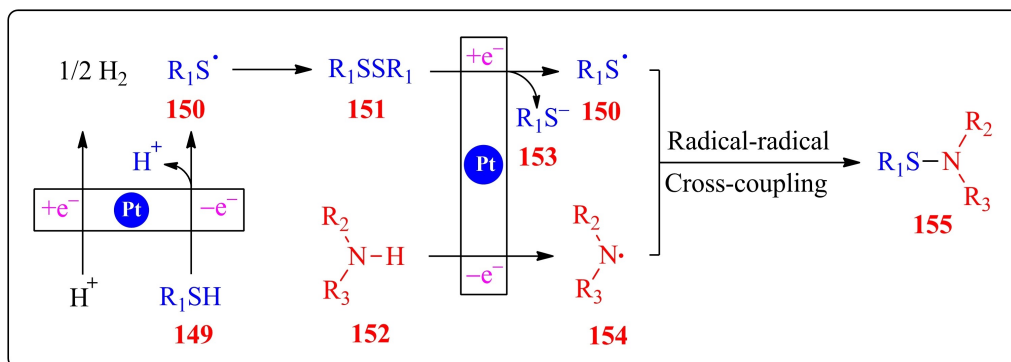
**153** is also converted to thiyl radical **150** by losing an electron, so it is not a side product (Scheme 40).<sup>[98]</sup>

### 10.3.3. Enhancing the efficiency of the reaction of electrochemically generated intermediates within the diffusion layer

Although paired electrolysis using direct current is considered an energy efficient and sustainable alternative to cathodic reductive electrolysis, its practical scope is limited due to slow mass transfer between electrodes and the short lifetime of intermediates. If the reaction intermediate has a short lifetime, it is lost during mass transfer and hence low product yield is obtained. This limitation of paired electrolysis can be overcome by using AC electrolysis. In this approach, since the alternating voltage is applied, the redox reaction occurs sequentially at the same electrode and intermediates do not need to migrate from one electrode to another. Therefore, even the less stable intermediate reacts immediately upon the polarity reversal.<sup>[104]</sup> Rodrigo et al.<sup>[105]</sup> comparatively studied trifluoromethylation of (hetero)arenes using paired electrosynthesis and AC electrosynthesis. As a model substrate, they used 2-acetylpyrrole (**157**) and reported only 13% yield from paired electrosynthesis whereas AC electrolysis gave 84% yield.<sup>[105]</sup> Initially, triflyl chloride (**156**) is reduced to  $\text{CF}_3$  radical which then combines with 2-acetylpyrrole (**157**) to form the radical intermediate **158**. In the next step, once the polarity is reversed, the radical intermediate **158** undergoes oxidation to form an allylic cation



**Scheme 39.** Comparative study of AC electrolysis and DC electrolysis for cross-coupling of 4-chlorothiophenol and *N*-Ts-4-methoxyaniline.<sup>[98]</sup>



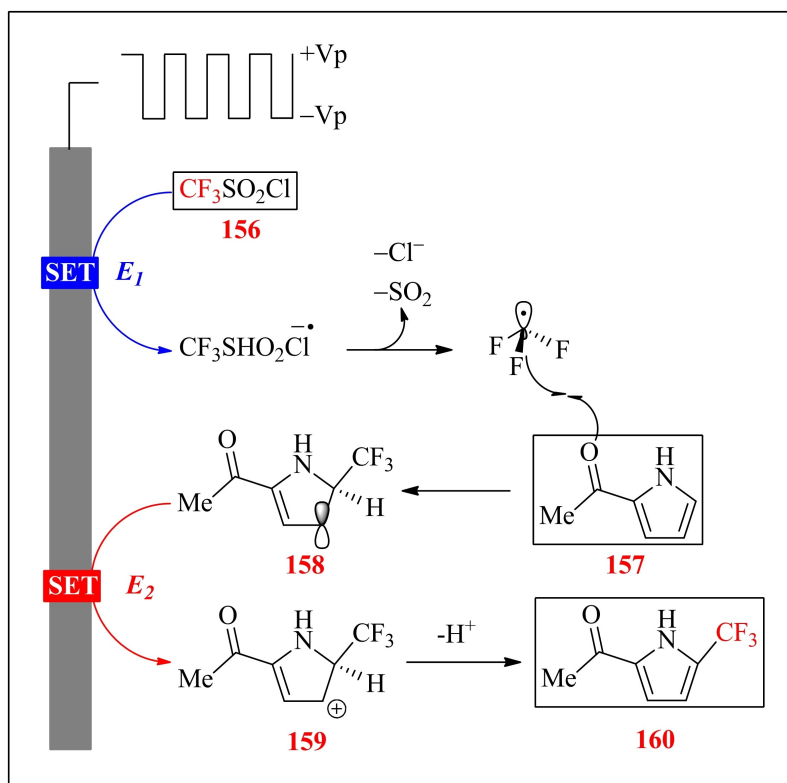
Scheme 40. Proposed mechanism for radical cross-coupling of aromatic amines with thiols to form N-S bond containing compounds.<sup>[98]</sup>

(159) which after rapid deprotonation, yield the final product 160 (Scheme 41). Here, the radical intermediate 158 is highly unstable and short lived because it has lost aromaticity. The main culprit behind low yield in DC electrolysis using paired electrolysis is the inherent instability of the radical intermediate 158.<sup>[105]</sup>

## 11. Conclusion and Perspective

In recent years, electro-organic synthesis has experienced a resurgence as a green and sustainable alternative to traditional organic synthesis, using electrons as a controllable and traceless

redox reagent. While anodic oxidative electrosynthesis has been extensively studied, cathodic reductive electrosynthesis is still a developing field that has recently gained significant attention from the scientific community and indeed, many of new electroreductive hydrogenation and functionalization reactions have been developed. Taking inspiration from this significant progress, this review not only explores various electroreductive bond formation and reduction reactions but also discusses the role of cathodic reductive electrolysis in generating radical anions and their subsequent transformations through addition to carbon-carbon double bonds, reduction to carbanions, and radical-radical cross-coupling. Electro-organic synthesis using cathodic electrode can convert small organic



Scheme 41. Proposed mechanism for AC electrosynthesis-based trifluoromethylation of 2-acetylpyrrole.<sup>[105]</sup>

compound to high value biologically and industrially important compound. This review further discusses alternative strategies such as paired electrolysis, photo-electrolysis, and alternating current to overcome challenges faced by the cathodic reductive technique. Despite the challenges, there has been significant progress in recent years, and ongoing research is expected to continue to improve the efficiency and versatility of this approach. The review aims to inspire further developments in the field of electro-organic synthesis. At low potentials, inert organic molecules can be activated by direct reductive electrolysis. However, indirect electrolysis allows for precise selectivity control (for example important in asymmetric electro-synthesis) and mild reaction conditions. By using photoexcitable redox mediators, electrophotocatalysis has just lately become a novel method for reductive electrosynthesis. Numerous organic transformations have been accomplished under these various mechanistic frameworks. We anticipate that further advancements in electroreductive techniques will keep the field of electroorganic synthesis, which is expanding, more progressive, and offer useful solutions to synthetic problems. Moreover, the corrosion of certain heavy metal electrodes during cathodic reduction poses another challenge. Skillful deployment of alloy metals as cathodes may offer a solution, potentially mitigating toxicity concerns.

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## Conflict of Interests

The authors declare no conflict of interest.

**Keywords:** Reductive electrolysis · cathodic transformations · electrosynthesis · reductive photoelectrocatalysis · reductive functionalizations

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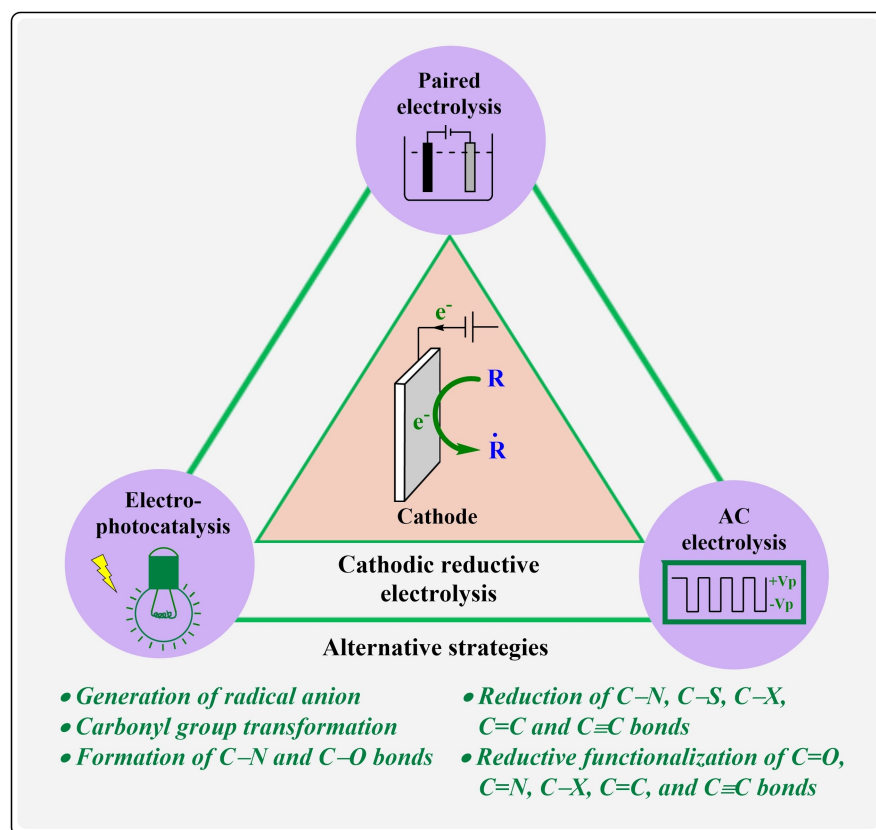
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## REVIEW



**Cathodic electrolysis** holds great promise in generation of radical anions that enables the formation of new chemical bonds & functionalizations. However, its main concern lies in the use of a sacrificial electrode and

the necessity for a suitable counter-oxidation reaction at the anode. To address these issues, alternative strategies such as paired electrolysis, photo-electrolysis, and alternating current, provide solutions.

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1 – 40

**Cathodic Electrolysis: Electroreductive Organic Synthesis**