Organic synthesis via Kolbe and related non-Kolbe electrolysis: Enabling electro-strategy

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Abstract

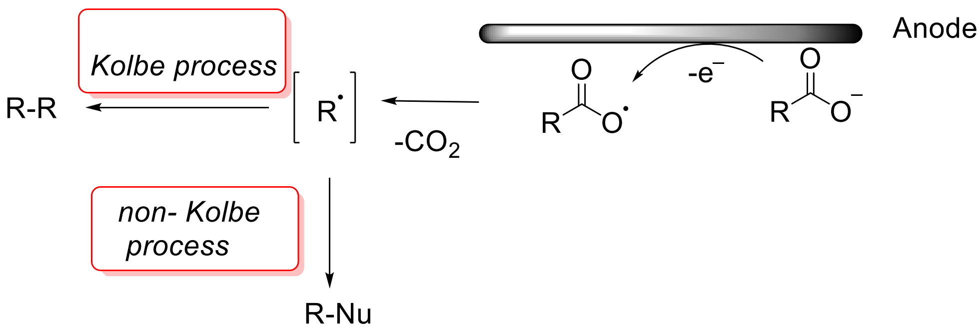
Enabling and environmentally friendly synthetic methodology is preferred over conventional methods that require expensive chemicals & oxidants to achieve value-added organic transformations. Electrochemical conversions encounter the conventional shortcomings and introduce easy scale-up methods to synthesize complex and hindered molecules employing electricity as a clean reagent and catalyzing entity. Electrochemical conditions minimize waste formation and increase the chances to get maximum target product under ambient conditions. The Kolbe and related non-Kolbe electrolysis process where the anodic oxidation of carboxylic acids leads to a decarboxylation can be used intelligently to build new bonds and end up with value-added molecules and stereoselective products. The memory of chirality where we have contributed too is a more fascinating strategy to achieve highly desired asymmetric products via electrochemical decarboxylation (ED). Besides this, coupling (homo, hetero), dimerizations, additions, cyclizations, CH activations via ED are also significant aspects of this strategy. Flow electrochemistry and photochemistry using ED strategy could enhance the selectivity and product yield, avoiding overoxidations. Herein, we discussed several examples of ED and its applications to drive value-added transformations under mild, clean and sustainable conditions

and also addressed mechanistic aspects. This ED approach will enable and provide inspiration for future applications in electro-organic synthesis.

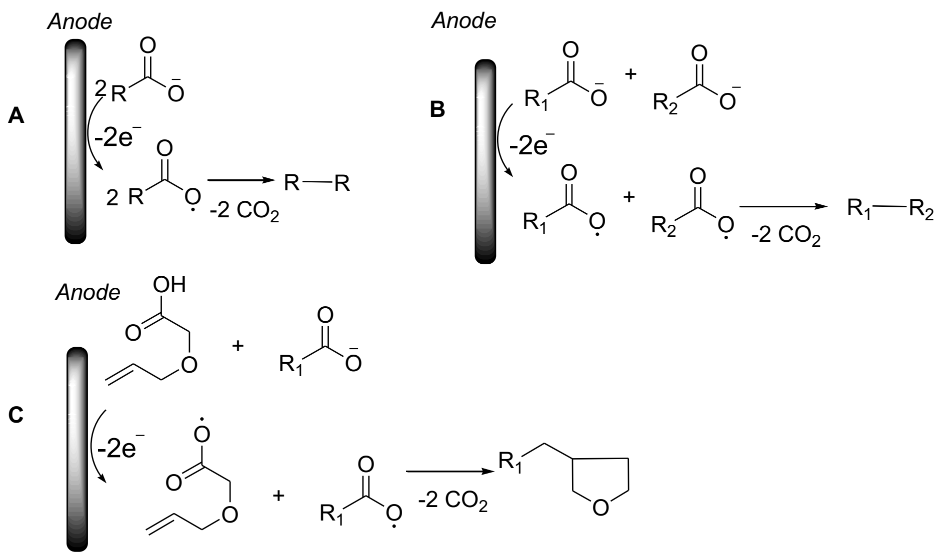
1. Introduction

Organic synthesis via electrolysis by the addition or removal of electrons happens at the surface of electrodes and therefore is regarded as a heterogeneous and clean catalysis. This single electron transfer (SET) process converts the starting material into a reactive intermediate that finally gives rise to the direct anticipated product[1-6]. Past developments in the field such as the Kolbe electrolysis and recent advancements by others have encouraged the adoption of electrosynthesis as a clean tool in organic transformations. Different strategies are being used in electrosynthesis to accelerate the electrocatalysis and achieve high atom economies. These methods are named as direct and indirect electrolysis. Indirect electrolysis is performed using metal catalysts and organic mediators also known as catalyst-control, and chemical-control electrolysis respectively. Thus, indirect electrolysis makes the potential range more pleasant, and less side reactions can occur. In direct electrolysis, the reaction occurs directly on the surface of the electrode without any mediators. In electrochemical functionalization, the pre-functionalized molecules, especially those that are prone to generate radical or cation intermediates, have attraction for selective transformations. In this context, the substrates with carboxylic acids group are famous. In recent developments, such substrates gained more importance in asymmetric transformations via the process of "memory of chirality".[7]

Electrochemical conditions are successfully used to minimize waste formation and increase the chances of getting maximum target products under ambient conditions. In the past, wide range of electrolysis applications were achieved, such as the synthesis of N-hetrocycles[8], O-hetrocycles[9], S-hetrocycles[10], deoxygenation reaction[11], phosphorylation reactions[12], annulations reactions[13] and one of the most important application is the decarboxylation reaction namely Kolbe and related non-Kolbe electrolysis process[14]. During the Kolbe process, carboxylic acid derivatives's anodic oxidation leads to a decarboxylation process to provide key radical intermediates. The famous results in the Kolbe process are the dimerization of radical intermediate (scheme 1) to form homo-dimers[15](scheme 2 A), or to obtain unsymmetrical radical[16](scheme 2 B) and also to perform a cyclization process[17-20] (scheme 2 C). Alternatively, the non-Kolbe process, which is effective for anodic oxidation of α-heteroatoms such as lactams, amides, N-acylated amino acids, and carbamates, is defined as the two-electron oxidation of carboxylate ions with decarboxylation that provides to carbenium ions which are trapped by nucleophiles[21] (scheme 1). The advantage for constructing these new bonds via a C-C bond cleavage is the process performed under free catalyst and oxidant or reduction reagents free.



Scheme1. General scheme for the Kolbe and non-Kolbe reaction



Scheme 2. Examples of the Kolbe reaction

The Kolbe electrolysis and related process has been successfully used to synthesize some ligands such as biophosphine oxide[22], synthesize fatty acids[23], benzathine derivatives[24], and it was used for the dimerization of silylacetic acids[25]. The Kolbe electrolysis process to generate the desired molecules is controlled by the reaction conditions, such as current, temperature, the solvent, concentration, pH value, and types of electrodes. The influence of these parameters in Kolbe reaction has been reviewed in 1990 by Weiper and co-workers[26].The reviews reported on the electrochemical organic transformations using carboxylic acids derivatives[17-20] were mainly focused on derivatization from aromatic esters and selective bond cleavage. However, there has not been addressed the electrochemical transformations resulting via "memory of chirality"[27-31] or recent developments. Herein, we discussed recent several examples of electrochemical decarboxylation (ED) and its applications to drive value-added transformations under mild, clean and sustainable conditions and also addressed related mechanistic aspects.

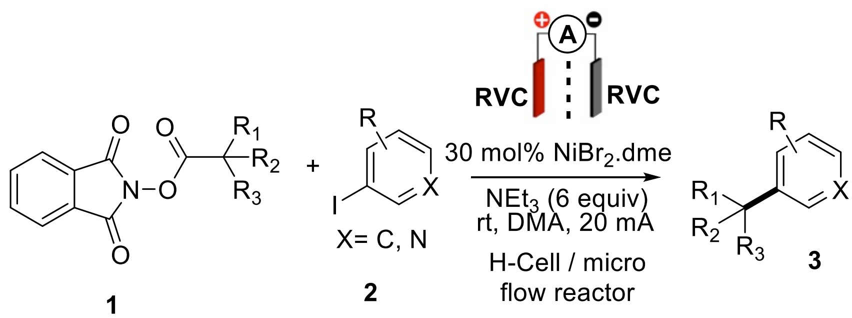
2. Kolbe and related non-Kolbe electrolysis for chemical transformations

2.1. Coupling reactions (homo and hetero)

2.1.A. Carbon-Carbon Coupling

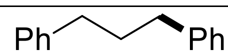
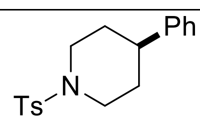
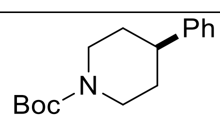
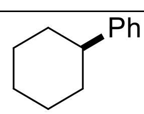
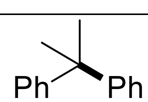
The development of catalytic methods for C-C bond formation represents a prominent challenge in organic synthesis. However, the use of toxic oxidants, reducing reagents or expensive catalysts makes it a less than ideal methodology[32]. The chemical decarboxylative C-C coupling from the reaction of esters or acids derivatives in the presence of a catalyst and zinc powder as a reducing agent is well established[33]. Nonetheless, reactive metal powders are generally challenging to work with, particularly on large scales due to purity, surface oxidation, and safety issues. An electrochemical free- reducing agent work was reported by Bio and co-workers[34, 35], where aryls derivatives **3** were prepared using Ni as a catalyst. N-hydroxyphthalimide esters **1** and aryl halides derivatives **2** were used as reagents in the presence of the catalytic amount of tertiary amine as reductant (scheme 3). The electrolysis was carried out in a divided cell at a constant current of 20 mA, representing a good approach for small scale less than 5 mmol but it was found to be a limited approach for larger scope production. The microflow reactor[36] could be an alternative for this approach. This technology's key advantage is to decrease the inter electrode distance and increase the interfacial ratio of two electrodes resulting in larger-scale production. RVC anode and graphite cathode were found to be useful with a current density of 38 mA. This decarboxylation was found to tolerate a large variety of functional groups, as summarized in Table 1. Independently to Bio and co-workers, Wang and co workers[36] reported an excellent method for the alkylation of quinoxalinone derivatives **6** by carbazate derivatives **5** via an electrochemical process (scheme 4). Using platinum/carbon as anode/cathode electrodes and $^{n}BuNClO_4$ as electrolyte, the desired deoxygenative alkylation take place at a constant current of

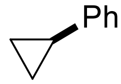
6 mA in an undivided cell, in acetonitrile/DMSO and gave the desired product in 87% yield after 8 h.The authors find that primary, secondary and tertiary alkyl radicals can be readily accessed via the sequential anodic oxidative fragmentation for the direct functionalization of N-heteroarenes. A plausible mechanism of this methodology is shown in scheme 5. At the start, a consecutive anodic oxidation of carbazate **5** and deprotonation to generate hydrazinecarboxylate radical **B** and diazenecarboxylate **C**. Further anodic oxidation cleaves diazene to form acyl radical **E** with releases molecular nitrogen. The second step is decarboxylation of acyl radical **E** to furnish alkyl radical **F**.

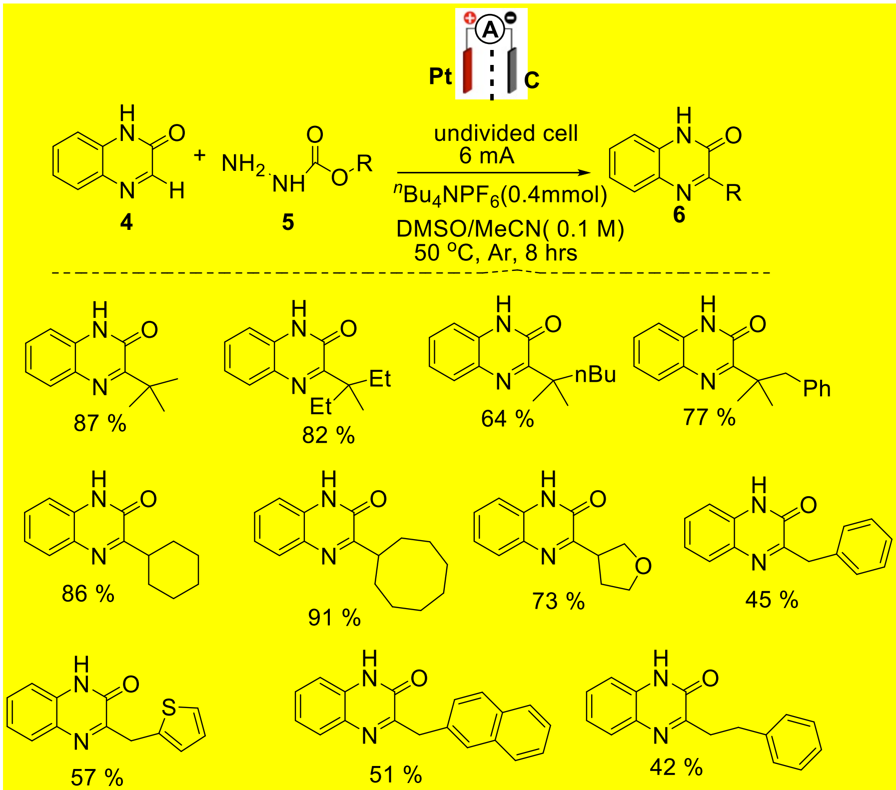


Scheme 3: Electrosynthesis of aryls derivativesvia non-Kolbe electrolysis.

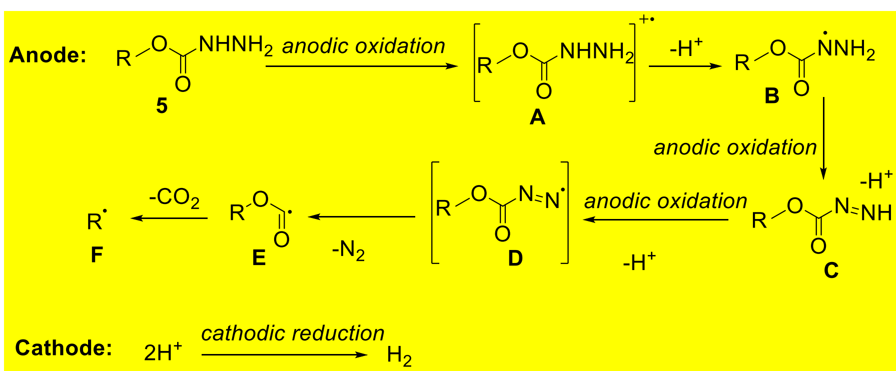
Table 1: Substrate scope of the electrosynthesis of aryls derivatives.

Final products **3**	Yield of products **3**
	67 %
	63 %
	65 %,
	62 %,
	2 %

	41 %

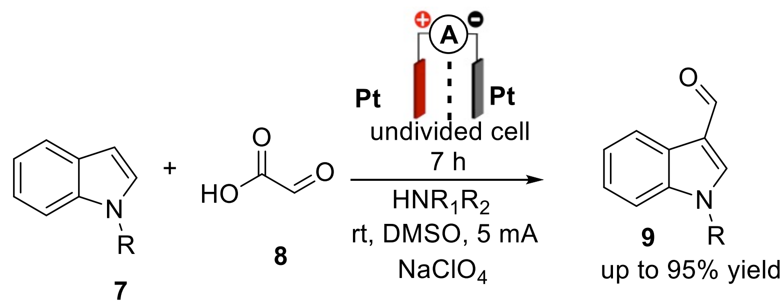


Scheme 4: Electrochemical alkylation of quinoxalinone derivatives.

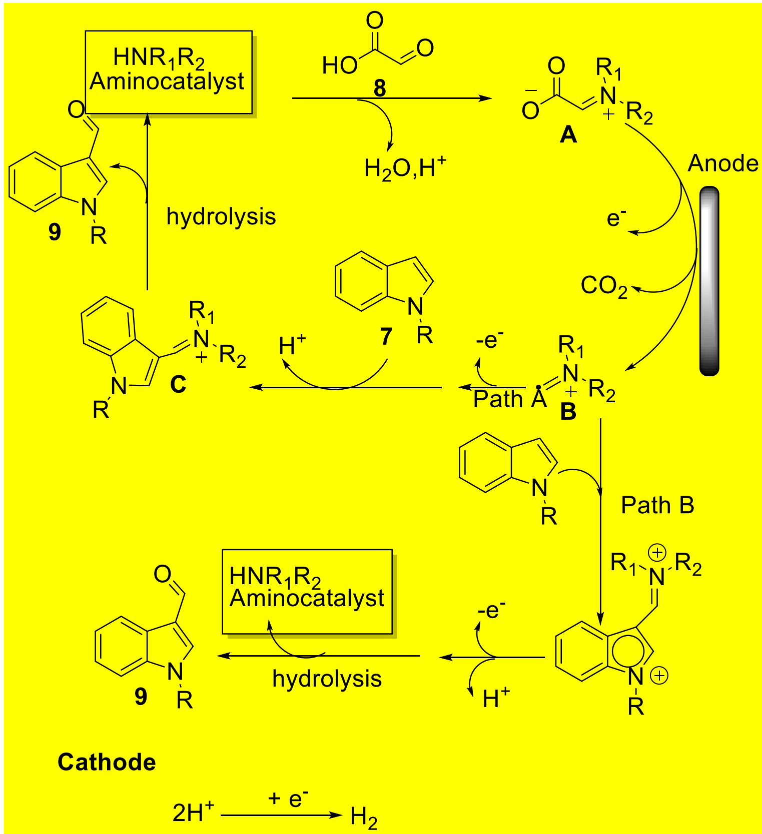


Scheme 5: A plausible mechanism for the electrochemical alkylation of quinoxalinone derivatives.

In an attempt to improve glyoxylic acid's decarboxylation, it was envisaged that, in the presence of an excess of amino catalyst and glyoxylic acid, the formamide was formed easily[37], which is a classic mode for carbonyl activation to facilitate nucleophilic attack[38]. The cyclic amine substrates **7** was electrolyzed in an undivided cell with glyoxylic acid **8** at platinum anode (scheme 6), which would lead to 3-formylindoles **9** via the mechanism illustrated in scheme 7. First, glyoxylic acid condenses with amino catalyst to give imino carboxylate **A** followed by an oxidative decarboxylation to form intermediate **B**. An electron from **B** was rapidly removed, followed by a nucleophilic attack of methyl indole to produce **C**. Then **C** underwent hydrolysis to form the desired products **10** and release the amino catalyst to furnish the catalytic cycles. The authors proved that dimethylamine amino catalyst gives an optimal yield instead of aniline, and when piperidine was used as a catalyst no reaction was detected. The experimental results demonstrated that no reaction was detected when DMSO was replaced by CH_3CN or DMF.

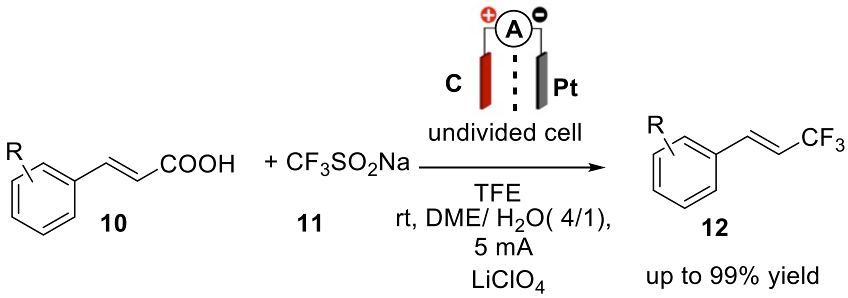


Scheme 6: The electrosynthesis of 3-formylindoles via non-Kolbe electrolysis

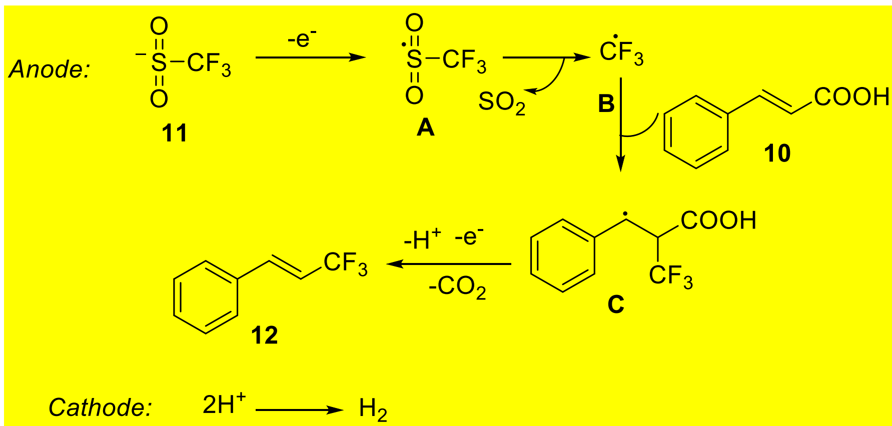


Scheme 7: A plausible mechanism for the electrosynthesis of 3-formylindoles

Trifluoromethyl moiety has shown a remarkable versatility in synthetic electrochemistry[39], and this is further demonstrated by their use in pharmaceutical, agrochemicals production[40, 41]. Normally, C-CF_3 bond formation, especially for the C_{vinyl}-CF_3[42] by the way, unsaturated carboxylic acid electrolysis proved a useful cleavage of C-C bond[35]. It was investigated that, in the presence of CF_3SO_2Na, the electrolysis of unsaturated carboxylic acid **10** in an undivided cell (scheme 8), leads to vinyl trifluoromethyl products **12** via a simple mechanism illustrated in scheme 9. At the start, the oxidation of CF_3SO_2Na **11** at the anode leads to the intermediate **A**followed by a fast cleavage to form the fluoroalkyl radical **B**. Subsequently, **B** reacts with acid derivatives **11** to form the radical **C**. This latter, after further decarboxylation via anodic oxidation, leads to the final product **13**. Carbone anode and platinum cathode were found to be useful with a current density of 5 mA. This decarboxylation was found to tolerate a large variety of functional groups, as summarized in Table 2

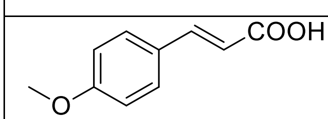
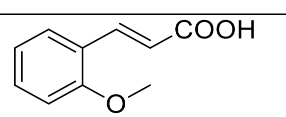
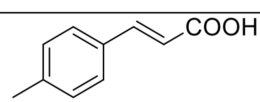
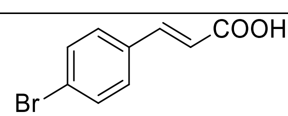


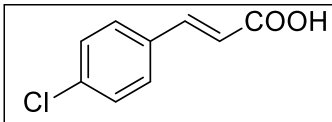
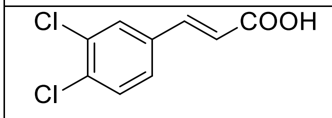
Scheme 8: The electrosynthesis of vinyl trifluoromethyl products



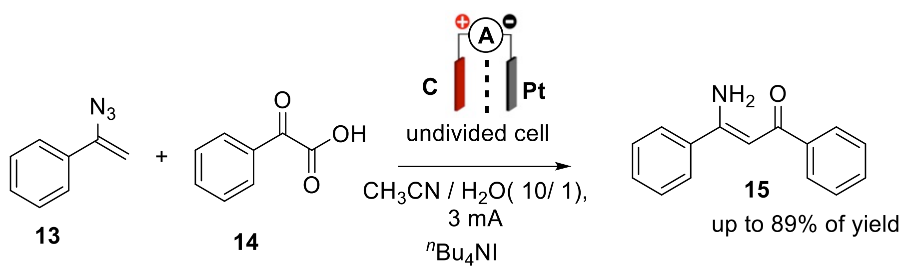
Scheme 9: A plausible mechanism for the electrosynthesis of vinyl trifluoromethyl products via non-Kolbe electrolysis

Table 2: Substrate scope of the electrosynthesis of vinyl trifluoromethyl

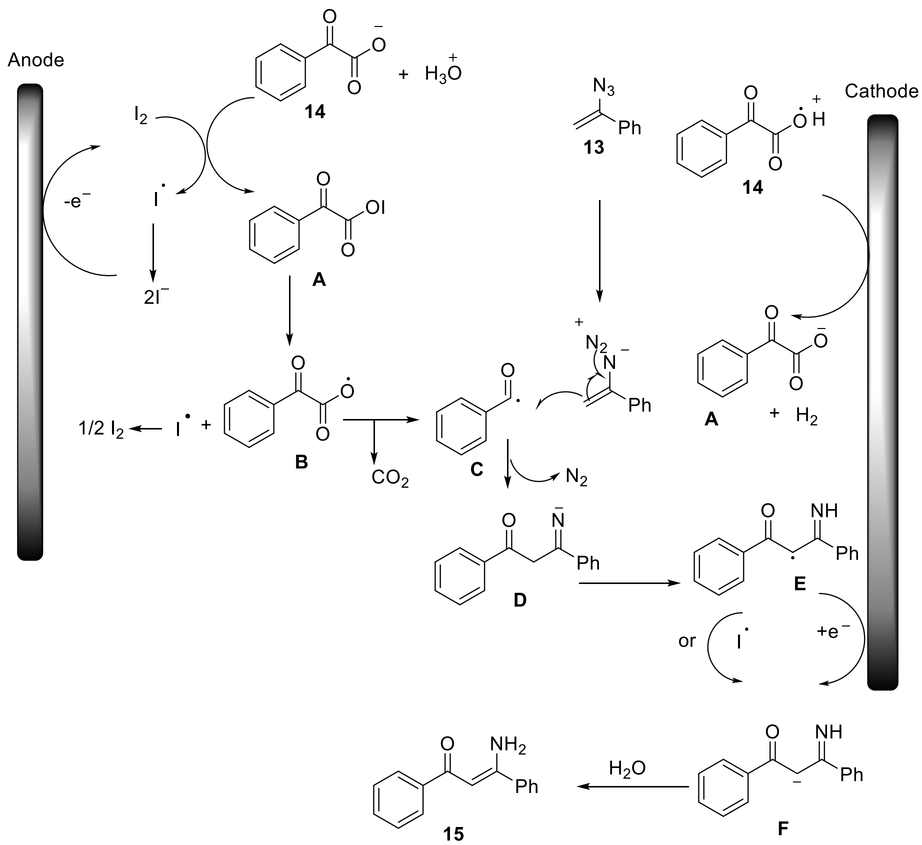
Unsaturated carboxylic acids	Yield of the final products **12**
	80 %
	68 %
	72 %
	69 %

	51 %
	45 %

Due to the homocoupling methodology's success, α-keto acids **14** were tested in such type of decarboxylative reaction with vinyl azide substrates **13** (scheme 10)[43]. The reaction proceeds in an undivided cell equipped with carbon as anode and a platinum plate as a cathode at a constant current of 3 mA. By using $^{n}Bu_4NI$ as a catalyst, this transformation leads to forming a large scope of enaminones derivatives **15** via the mechanism illustrated in scheme 11. At the start, the reduction of **14** at the cathode leads to the formation of the anion **A**. Meantime, the anodic oxidation of iodide ion gives I_2, which could react with an α-keto carboxylate anion **A** to form acyl hypoiodite **B**along with an iodide ion. Then, the acyl hypoiodite **B** undergoes hemolytic dissociation to give iodine and aroyloxy radicals. Decarboxylation of the aroyloxy radical gives acyl radical **C**, which adds to the vinyl azide **13** to form the intermediate **D** by releasing N_2. Finally, the protonation of intermediate **F** results in the final product **15**.



Scheme 10: The electrosynthesis of enaminones derivativesvia non-Kolbe electrolysis

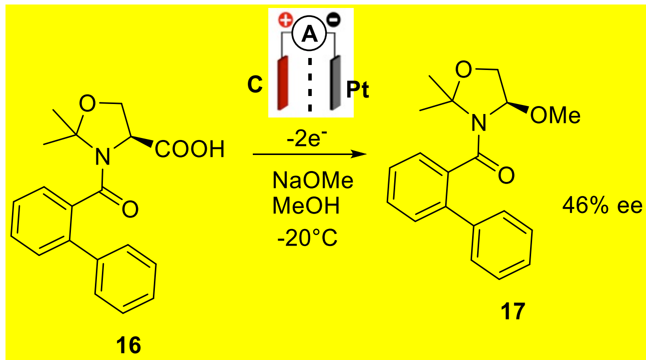


Scheme 11: A plausible mechanism for theelectrosynthesis of enaminones derivatives

2.1.B. Carbon-Heteroatom Coupling

2.1.Ba. C-O Coupling

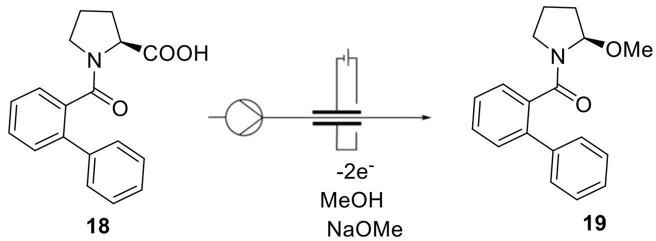
The memory of chirality outlines a phenomenon in which "the chirality of a starting substrate having a chiral sp^3 carbon is conserved in the reaction product even if the reaction proceeds at the chiral carbon[27]. The first example of cationic memory of chirality by non-Kolbe electrolysis reported the electro formation of N, O-acetal **17**, when N-benzoylated serine derivative **16** is oxidized at graphite anode in methanol to give an N, O-acetal derivative **17** [28,30] (scheme 12). These interesting results were obtained when the electrolysis was performed in an undivided cell at a constant current equipped with a graphite plate anode and a platinum plate cathode. The authors found that the optimal yield was obtained by the combination of methanol as a solvent and NaOMe as a base. The experimental results show an interesting effect of the anode material on the yield of **17**. Different anode materials were examined, such as glassy carbon, Pt, and Au, a racemic of **17** was obtained. Only graphite gave some positive result concerning the ee of **17** with 46% (ee).



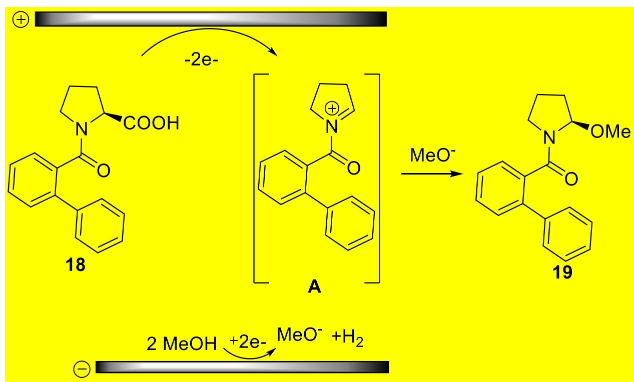
Scheme 12: The electroformation of N, O-acetal derivatives via non-Kolbe electrolysis

On the basis of this concept, recently we developed an efficient example of memory of chirality method via non-Kolbe electrolysis to provide enantiomerically N, O-acetal derivative **19** via the electrochemical transformation of the corresponding substrate **18** (scheme 13)[31]. The direct oxidation of proline-based substrate **18** provides a decarboxylation reaction and affords a radical cation iminium ion **A**, which is then trapped by MeO^-, resulting in the desired product **19** via the mechanism illustrated in scheme 14. The presence of the bulky substituent at the nitrogen atom is responsible for the face selectivity of the nucleophilic addition of methanol. This method's key is to perform the reaction under flow reactor conditions, which offers a lot of opportunities for developing some elegant chemical transformations with high efficiency, selectivity, and yields. In collaboration work[29], the commercial flow electrochemical reactor at low temperature was coupled to the 2D-HPLC system for immediate analysis; within only 15 min the percentage yield and the percentage enantiomeric excess were obtained. With this rapid analytical method, it was demonstrated that the wealth of information about the reaction was obtained in a very short time. This decarboxylation was found to tolerate a large variety of functional groups, as summarized in Table 3. The yields of final products (N, O-acetal derivatives) vary according to the reaction condition. (A) Platinum as the cathode and glassy carbon as an anode at -10 °C. (B) graphite as an anode at 20 °C. In our apprach[31], the substrate **18** was subjected for decarboxylation in a home-made room temperature flow electrochemical reactor using Pt and graphite electrodes. However, with Pt both as an anode and a cathode along with a catalytic amount of an electrolyte

(NaOMe), methoxylated product **19** was obtained in a good yield (71%) and a higher enantiomeric excess (64%ee).

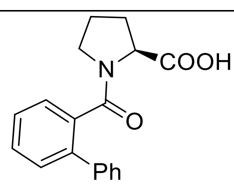
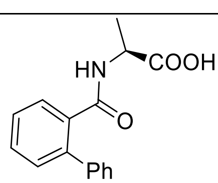


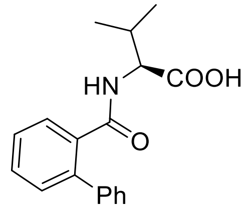
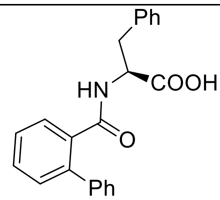
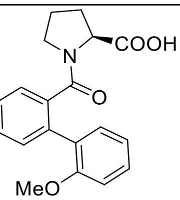
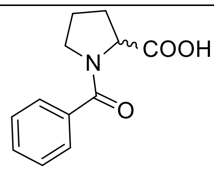
Scheme 13: The electroformation of N, O-acetal derivatives via non-Kolbe electrolysis by flow reactor.



Scheme 14: A plausible mechanism for the electroformation of N, O-acetalderivatives

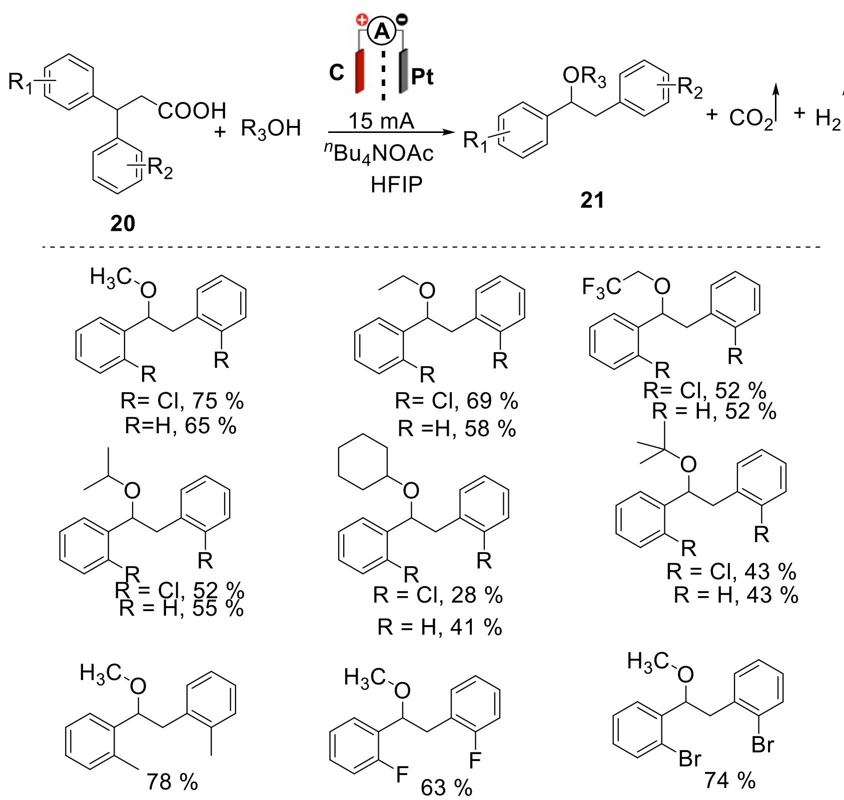
Table 3: The substrate scope of the electrosynthesis of N, O-acetal derivatives. (A) Platinum as the cathode and glassy carbon as an anode at -10 °C. (B) graphite as an anode at 20 °C

Amino acids	Yields of the N, O-acetal derivatives
	A: 52%, 58% ee B: 56%, 20%ee
	A: 22%, 7% ee B: 73%, 8 %ee

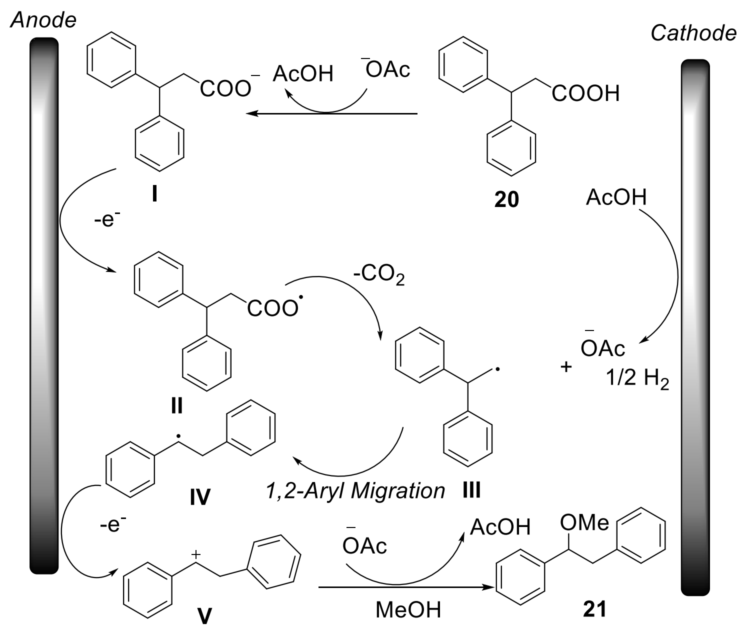
	A: 43 %, 7% ee B: 72%, 0 % ee
	A: 52 %, 13 % ee B: 67 %, 6% ee
	A: 28 %, 50 % ee B: 62 %, 19 % ee
	A: 25 %, 0 % ee B: 49 %, 0 % ee

In the same context, Bu and Co-worker[44] reported the advantage use of alcohols derivatives for the formation of C-O bond via a Kolbe process. The authors reported an efficient electrochemical method to synthesize a series of 1,2-diaryl ethers **21** via an oxidative decarboxylation reaction (scheme 15). Electrolyzing 3,3-diarylpropionic acids derivatives **20** at a constant current of 15mA in the presence of alcohols derivatives provides a large family of the desired compounds with a yield up to 78%. The electrolysis was carried out in an undivided cell using carbon as anode and platinum as cathode using the system $^{n}Bu_4NOAc$/MeOH and HFIP (hexafluoroisopropanol) as the electrolyte/ solvent at room temperature for 3.5 hours. The key advantage of this process is to use $^{n}Bu_4NOAc$ as electrolyte and as a base in the reaction, the results show that changing $^{n}Bu_4NOAc$ by other bases such as KOMe, Li_2CO_3 or $^{n}Bu_4NOH$ provides a lower yield of the final products. The authors suggested the following plausible mechanism (Scheme 16). At the start 3,3-diphenylpropionic acid **20** is deprotonated in the presence of acetate to generate carboxylate **I**, which was oxidized at the anode to give carboxyl radical **II**. The following decarboxylation can afford the primary carbon radical **III**.

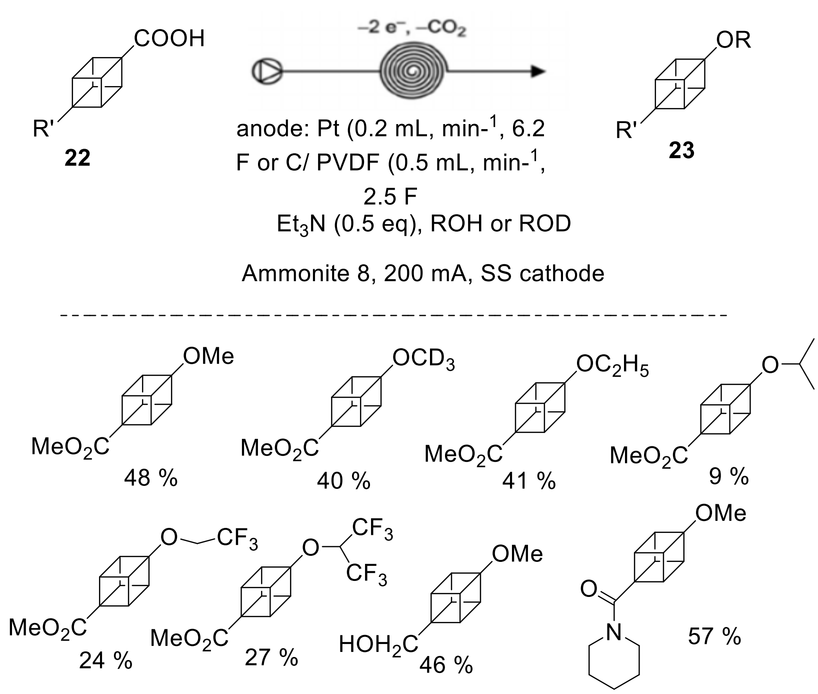
Subsequently, benzyl carbocation **V** was formed through successive 1,2-aryl migration and anodic oxidation. At the reaction between benzyl carbocation **V** and methanol provide the desired product **21** in the presence of acetate. Then, the acetate can be regenerated at the cathode with the liberation of dihydrogen concomitantly. Similarly, the group of Collin and co-workers[45] reported an excellent electrochemical methodology of alcohols derivatives in the decarboxylation of cubane derivatives **22**. The methoxycubane derivatives **23** were formed from the commercially available cubane carboxylate derivatives **22** by only using methanol as solvent and triethylamine (0.5 equiv) as reagent in an undivided flow reactor composed with stainless steel (SS) cathode and platinum as anode (scheme 17). No supporting electrolytes were required. The Plausible mechanism for this transformation is shown in scheme 18. Firstly, the anodic oxidation of the cubane carboxylate **22** generating a radical intermediate **A**, which oxidized at the anode to form the cation intermediate **B**. This latter se combines with MeOH to produce the final compound **23**. At the cathode, the reduction of MeOH gave the anion RO^-.



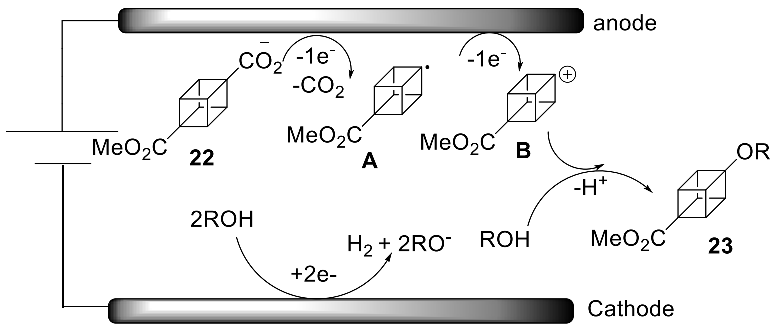
Scheme 15: The electrochemical synthesis of 1,2-diaryl ethers derivatives



Scheme 16: A plausible mechanism for the electrochemical synthesis of 1,2-diaryl ethers derivatives

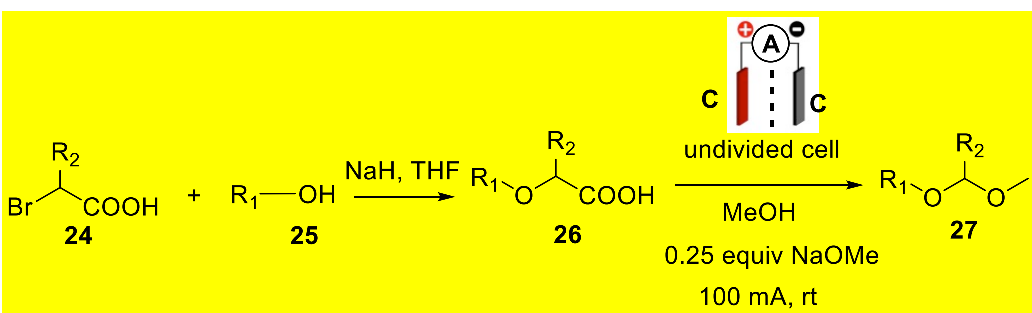


Scheme 17: The electrochemical decarboxylation of cubane derivatives

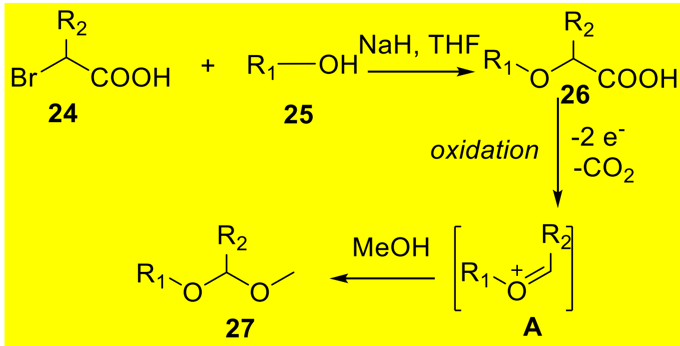


Scheme 18: A plausible mechanism for the electrochemicaldecarboxylation of cubane derivatives

Methoxymethyl (MOM) ethers proved to be a popular choice for protecting alcohols derivatives and phenols due to their high tolerance toward a wide range of reaction conditions[46, 47]. However, their preparation needs the use of toxic reagents such as chloromethyl methyl ether under basic condition[48]. The electrochemical methoxy methylation of alcohols can be an alternative to solve and remove these typical problems; it represents a safe and green approach for the synthesis of MoM ethers and other acetals[21]. Lam and co-workers[49] developed the electrochemical methoxymethylation (scheme 19) of 2-methoxypropanoic acid **26** starting from alcohols derivatives **25** and bromo-acids derivatives **24** via an oxidative reaction via the mechanism illustrated in scheme 20. The reaction contains two steps, firstly alcohols **25** reacts with Bromo-acids derivatives **24** in the presence of NaH as a base to form the substrate **26**. Then **26** is oxidized at the anode providing the intermediate **A**, which is in the presence of methanol to provide the desired product **27**. The reaction proceeds at a constant current in an undivided cell equipped with two graphite electrodes in methanol, using NaOMe as electrolytes.

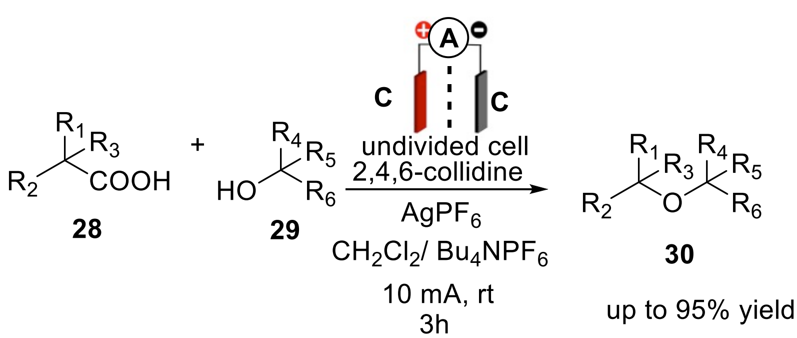


Scheme 19: Electrochemical methoxymethylation via non-Kolbe electrolysis

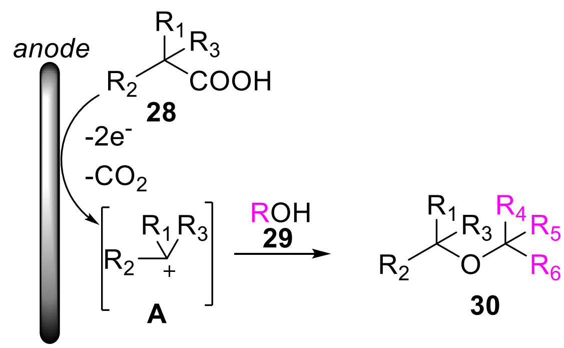


Scheme 20: A plausible mechanism for the electrochemical methoxymethylation

From the same perspective, alcohols derivatives were applied for the electrosynthesis of ethers derivatives to form a new C-O bond. In organic chemistry, these families of compound have an interesting use in many applications, but it is still hard to synthesize these derivatives via conventional reaction[50]. In this case, it was established that carboxylic acid derivatives and alcohols derivatives in the electrochemical conditions without catalyst could afford a large scope of ethers derivatives[51]. In this context, Baran and co-workers[52] reported an efficient and safe method for the electrochemical synthesis of ethers derivatives **30**. From a simple reaction between carboxylic acid derivatives **28** and alcohols derivatives **29**, as shown in scheme 21, a large scope (around 80 examples) of the desired product was obtained in very good yields up to 95%. The reaction proceeds at a constant current of 3 mA, in an undivided cell equipped with carbon electrodes both as anode and cathode, using dichloromethane as a solvent. The simple mechanism of this transformation is illustrated in scheme 22; the reaction starts at the anode by the direct oxidation of carboxylic acid derivatives **28** to form the carbocation intermediate **A**. Finally, alcohols substrates **29** attacks **A** to provide the desired product **30**.

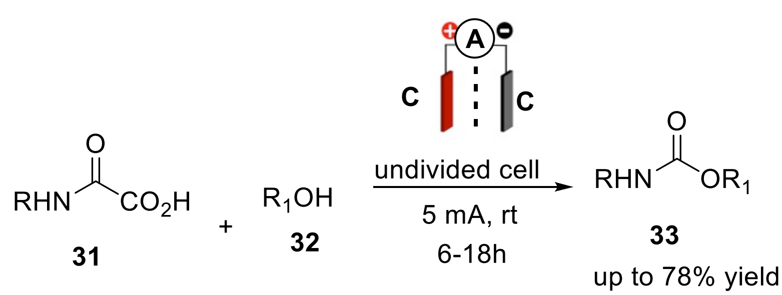


Scheme 21: The electrochemical synthesis of ethers derivatives via non-Kolbe electrolysis

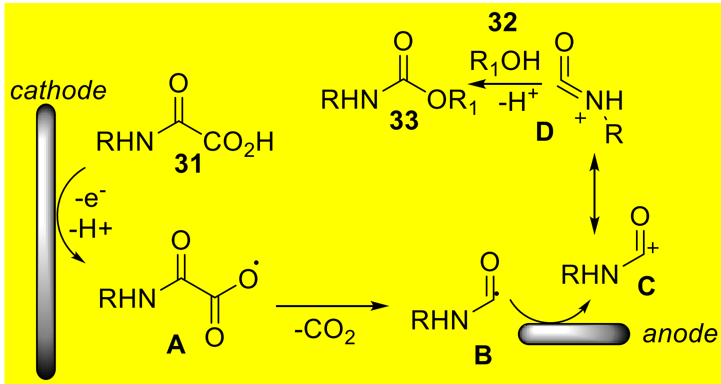


Scheme 22: A plausible mechanism for the electrochemical synthesis of ethers derivatives

Similarly, alcohols derivatives were applied for the electrosynthesis of urethane derivatives to form a new C-O bond. This family of product present a large use in pharmaceutical and agrochemicals [53], while their classical synthesis needs some toxic reagents[54]. Electrolysis could be an alternative for the formation of urethanes derivatives. In this context, the electrolysis of oxamic acid **31**, which was used for the protection of the desired alcohols **32**, under mild conditions using graphite electrodes in methanol afforded high yields of the desired Urethanes **33** in excess of 78% was investigated (scheme 23)[55]. The plausible mechanism of this transformation in scheme 18 shows that the reaction occurs at the anode. The oxidation of substrates **31** gives the intermediate radical **A**, which would then suffer decarboxylation, providing the carbamoyl radical **B**. Further oxidation of **B** gives the carbamoyl cation **C** and its tautomer **D**. Finally, alcohol **32** attacks **D** leads to the desired product **33**.

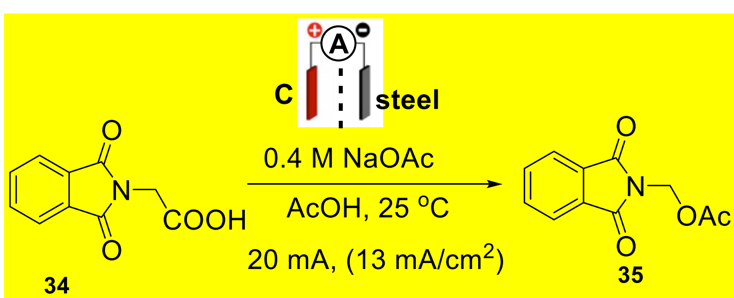


Scheme 23: The electrosynthesis of urethanes derivatives

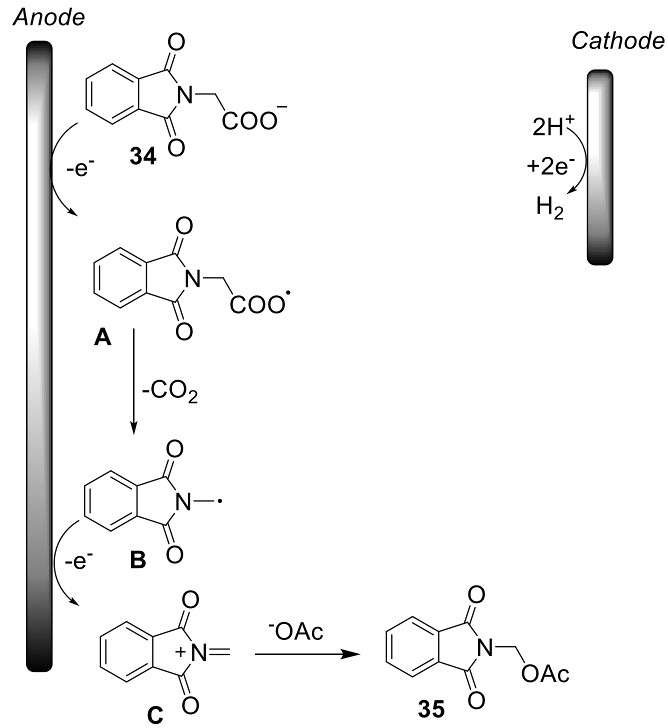


Scheme 24: A plausible mechanism for the electrosynthesis of urethanes derivatives

Differently of alcohols derivatives, AcOH as a solvent containing NaOAc as base was found to be useful for the formation of C-O bond. The process which was reported by David and Co-worker[56], describes a general and scalable electrochemical procedure for the decarboxylative acetoxylation of amino acids **34** (scheme 25). By using carbon graphite as anode and steel cathode, in an undivided cell a large family of the acetoxylated **34** was formed in a very good to excellent yield. Successfully, the electrochemical procedure has been translated to a continuous flow electrochemical cell. The authors find that under flow conditions, in a flow cell of only 190 μL volume, the reaction throughput has been multiplied more than 5-fold with respect to batch, and the space–time yield increased by two orders of magnitude. The Plausible mechanism for this transformation is shown in scheme 26. Firstly, the anodic oxidation of the carboxylate group **33**, generating a carboxyl radical **A** which rapidly decomposes to release CO_2 as gas. The resulting alkyl radical **B** is again oxidized, generating the cation **C**, which is trapped by a nucleophile AcO^- present in solution. Simultaneously, protons are reduced at the cathode, releasing H_2 gas.

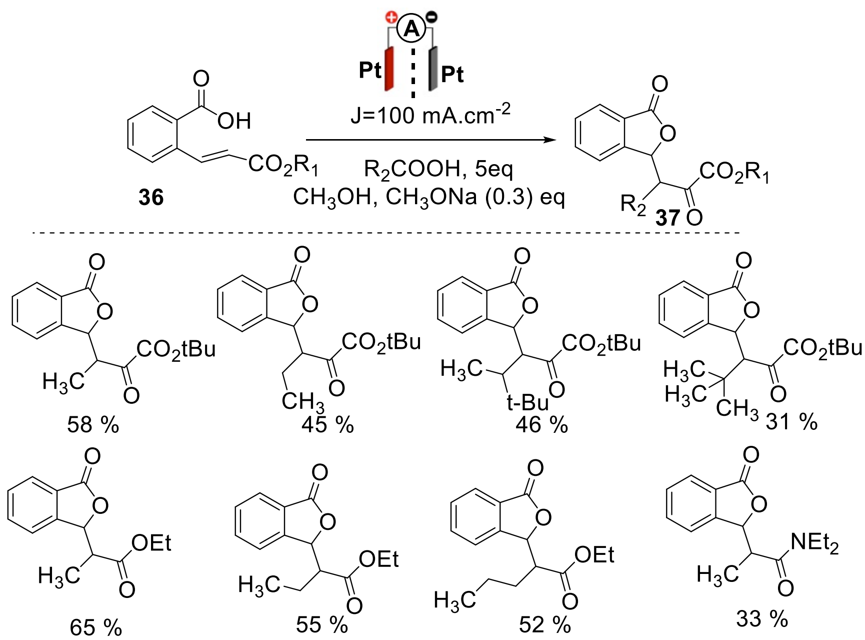


Scheme 25: The electrochemical decarboxylative acetoxylation of amino acids

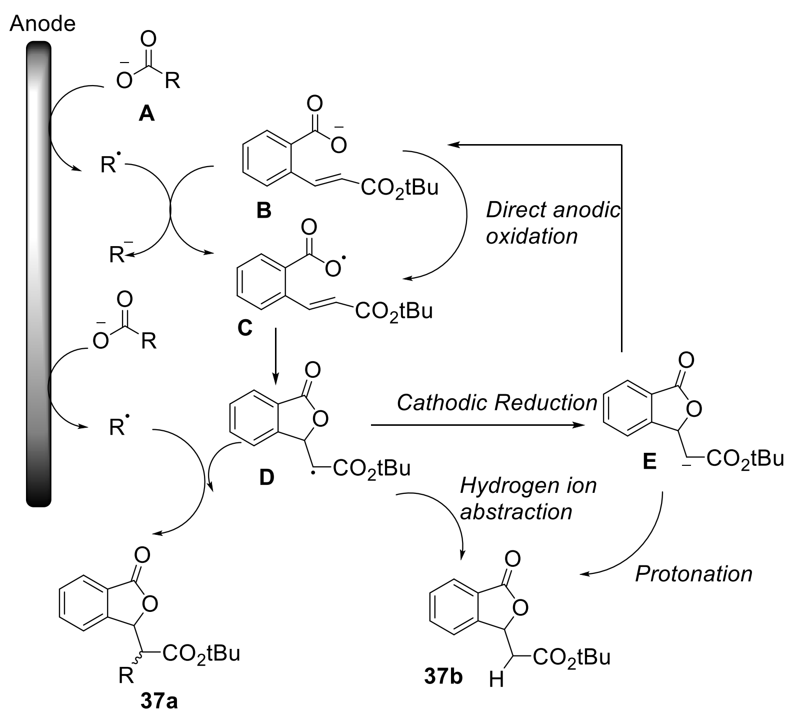


Scheme 26: A plausible mechanism for theelectrochemical decarboxylative acetoxylation of amino acids.

A different family of compound for the C-O bond formation via a cyclisation process has been reported in 2017 by Hayrapetyan and co-workers[57]. The process describes a new electrochemical method for the preparation of phthalides derivatives. Electrolyzing benzoic acid **36** at a constant current in the presence of a catalytic amount of base CH_3ONa in an undivided cell equipped with platinum electrodes in methanol (scheme 27) leads to phthalides derivatives **37.** The authors found that the use of acetic acid as co-acid in this methodology is necessary for the formation of the final compound. This method tolerates a wide range of functional groups such as esters, amides, olefins and halides with a good yield. The plausible mechanism of this transformation was illustrated in scheme 28. At the start an electron transfer between **R·** and **B** allows the formation of the benzoyloxy radical **C** which cyclizing to give the intermediate **D** by a Kolbe produced alkyl radical. This latter could abstract a hydrogen atom from the reaction medium in order to form the non-alkylated lactone **37b**. The second pathway would become predominant when carboxylic co-acids are used. The radical **D** could undergo a cathodic reduction to form the stabilised anion **E**. That anion could then get protonated to form the lactone **37b** or reopen to reform the starting material.



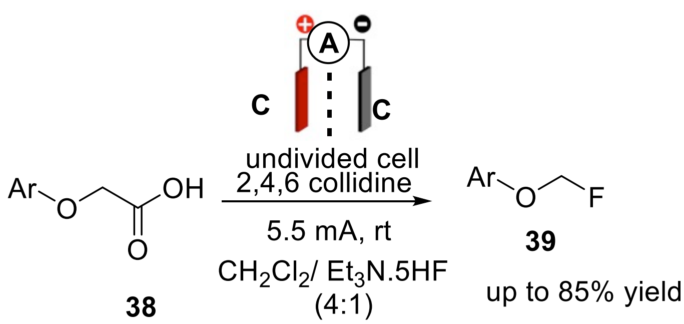
Scheme 27: The electrochemical method for the preparation of phthalides derivatives



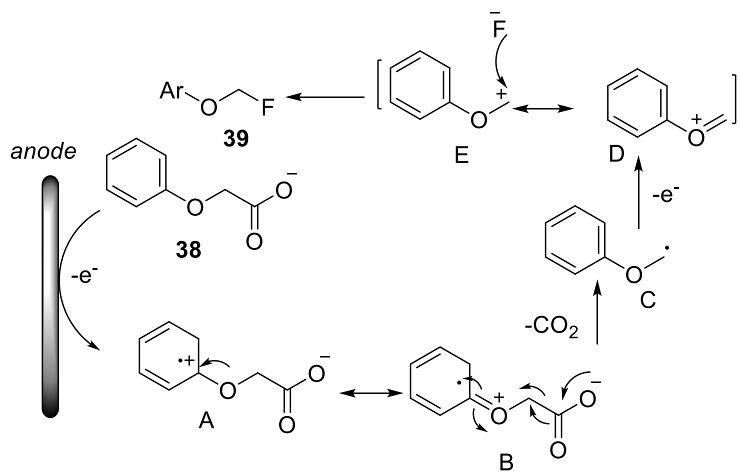
Scheme 28: A plausible mechanism for thepreparation of phthalides derivatives

2.1.Bb. C-F Coupling

The fluoromethyl aryl ethers have an interesting property and important applications in agrochemical and pharmaceutical applications[58]. The first synthesis of fluoromethyl aryl ethers involves an electrophilic mono fluoromethylation of phenol by FCH_2Cl under basic conditions have been reported[59]. Therefore, organic electrochemistry for fluorination reactions attracted a lot of attention in recent years and proved to be a powerful tool for organo fluorine synthesis[60]. In this context, it was reported an efficient approach for electrochemical fluorodecarboxylation via $Et_3N.5HF$ as both fluoride source and as a supporting electrolyte[61]. The decarboxylation of aryloxyacetic acids **38** followed by fluorination provides easy access to fluoromethyl aryl ethers **39** (scheme 29). Electrolyzing aryloxyacetic acids **38** in an undivided cell at carbon anode afford a large scope of fluoromethoxyarenes **39** in very good yields up to 85%. The mechanism of C-F bond formation is shown in scheme 30. The reaction commences at the anode by the oxidation of aryloxyacetate **38** to radical cation **A**. Radical cation **A** can be better mesomerically displayed as oxonium ion **B**, which decarboxylates to form aryloxy methyl radical **C**. Further oxidation of the aryloxy methyl radical **C** gives oxonium ion **D**, which might also be displayed as carbenium ion **E**. Finally, the nucleophilic attack of E by fluoride as nucleophile provides the fluoromethyl aryl ether **39**.



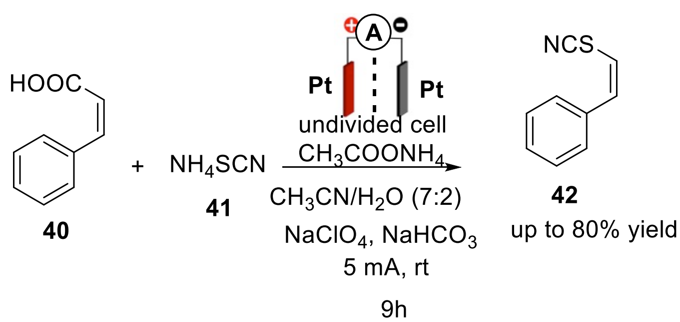
Scheme 29: The electrochemical fluorodecarboxylation of aryloxyacetic acids



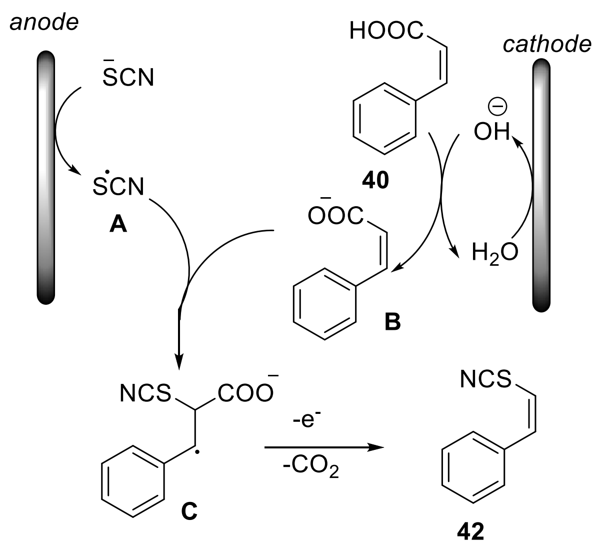
Scheme 30: Proposed mechanism for the electrochemical fluorodecarboxylation of aryloxyacetic acids

2.1.Bc. C-S Coupling

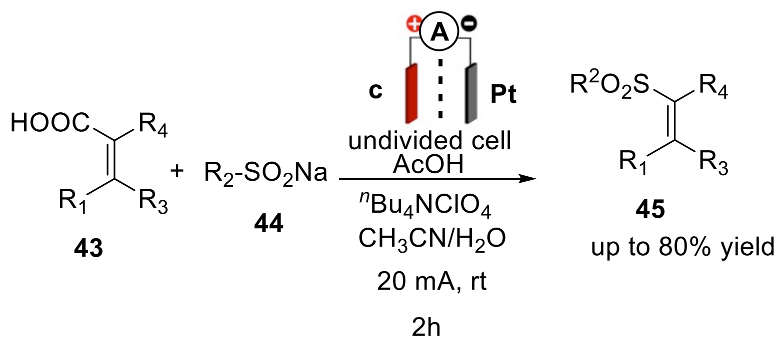
It is well known that organic thiocyanates are useful precursors for many compounds containing the sulfur atom and heterocycles [62]. They also present an important use of drug and biological activities, such as antibacterial, antiparasitic, and antifungal[63]. In the past decades, good progress was made to synthesize aromatic and alkyl thiocyanates[64]. But, a few reports on the construction of C_{vinyl}−SCN bonds were developed. The first method for the electrochemical synthesis of thiocyanation products was reported by Huang and co-workers.[65] The methodology reports the coupling reaction of cinnamic acids **40** with NH_4SCN **41** providing a large scope of vinyl thiocyanates derivatives **42** (scheme 31). The optimal yield was obtained when the electrolysis was carried out in an undivided cell equipped with Platinum electrodes as both anode and cathode in an aqueous solution (CH_3CN: H_2O). Scheme 32 illustrates the plausible mechanism of this methodology. First, at the anode, the oxidation of thiocyanate anion gives a thiocyanate radical intermediate **A**. Meantime, at the cathode, the reduction of water gives hydroxide anion, which deprotonates the cinnamic acid **40** to the anion **B**. Then, the addition of **A** to **B** forms the intermediate **C**. Finally, **C** undergoes decarboxylation to provide the final product **42**. This is not the only application of Cinnamic acids if the formation of C-S bond, recently [66], it was reported that the electro-combination of cinnamic acids **43** and sodium sulfonates **44** could provide a variety of vinyl sulfones **45** in good yield. The process describes a green strategy for the broadly rapid electrosynthesize (E)-vinyl sulfones **45** directly from readily accessible starting materials at room temperature without transition-metal catalysis. The electrolysis was conducted in an undivided cell at a constant current of 20 mA using a carbon rod as an anode and a platinum as a cathode in the combination of $CH_3CN/H_2O/^nBu_4NClO_4$ as solvent/electrolyte (scheme 33). The authors found that the presence of AcOH as an additive result in the increasing of the yield of the final compounds. The plausible mechanism of this transformation was illustrated in scheme 34. The authors suggest that at the start, the oxidation of sodium sulfinates **44** generates a sulfonyl radical intermediate **A**, which thenis attacked by anion **B** to give rise to anion radical **C**, which is easy to be decarboxylated to afford the vinyl sulfone **45**. Similarly, to that, Huang and co-workers[67] developed a similar method to achieve the synthesis of vinyl sulfones derivatives **48** from cinnamic acids **46** and sulfonyl hydrazides **47**. The authors use in their process a platinum electrode both as an anode and as a cathode. The reaction was conducted in an undivided cell at a constant current of 5 mA at room temperature in DMSO as solvent and $^nBu_4NBF_4$ as an electrolyte (scheme 35). The reaction needs the presence of ^{t}BuOLi as a base-catalyst. The authors suggested the following possible mechanism, in Scheme 36. Firstly, aromatic sulfonylhydazide is deprotonated by the base to produce anion **A**, then anion **A** oxidized by the synergistic effect of anodic oxidation and air to produce the radical **B**, followed by a further oxidation to radical **C** with the release of nitrogen in the presence of a base. Subsequently, radical **C** reacted with cinnamate **D** to furnish radical species **E**, which is easily decarboxylated to afford vinyl sulfone **F**.



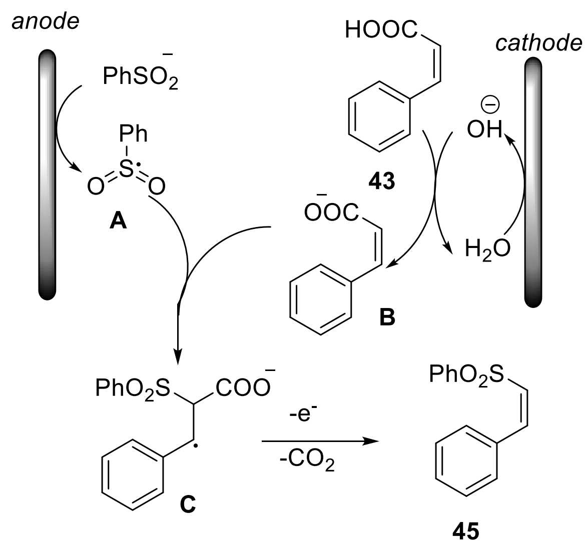
Scheme 31: The electrosynthesis of vinyl thiocyanates derivatives



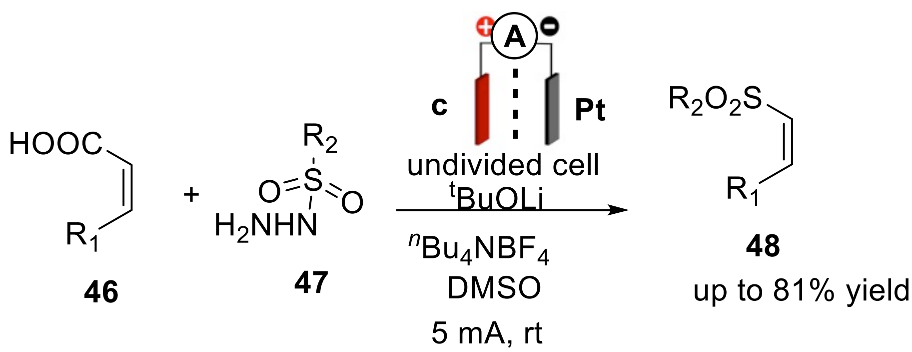
Scheme 32: Proposed mechanism for the electrosynthesis of vinyl thiocyanates derivatives



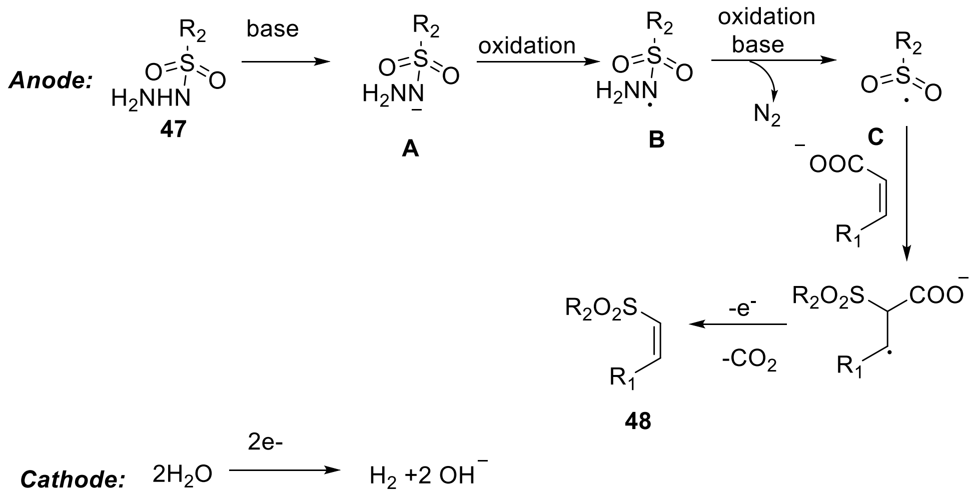
Scheme 33: The electrosynthesis of vinyl sulfones derivatives



Scheme 34: Proposed mechanism for the electrosynthesis of vinyl sulfones derivatives



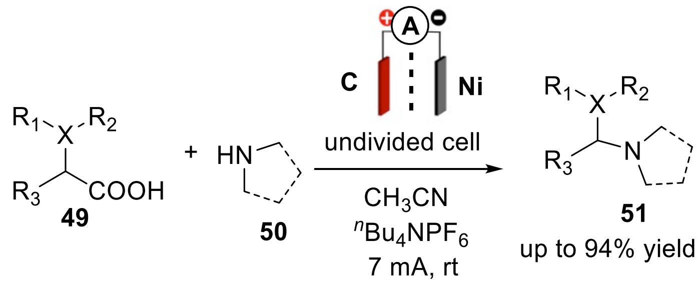
Scheme 35: The electrosynthesis of vinyl sulfones derivatives



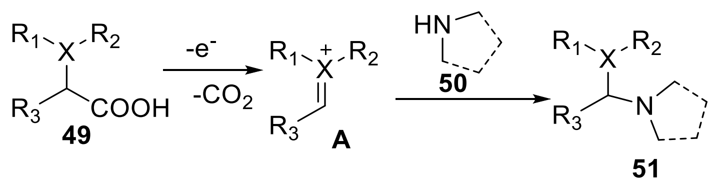
Scheme 36: Proposed mechanism for the electrosynthesis of vinyl sulfones derivatives

2.1.Bd. C-N Coupling

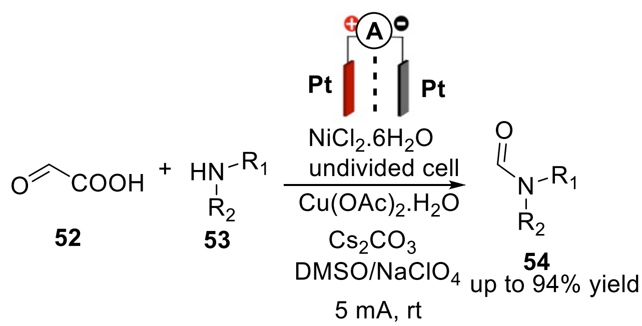
It is well known that carbon-nitrogen bond formation is one of the most important organic chemistry reactions. It has a successful use of pharmaceuticals, agrochemicals, and natural products[68]. This is why their synthesis has attracted more attention since the last decades[69-71]. In this concept, Wang and co-workers[72] reported electrochemical decarboxylative C_{sp3}−N coupling reactions by electrochemical oxidation of carboxylic acids derivatives **49** with cyclic amine **50**, giving the final product **51** with an excellent yield up to 94% (Scheme37). The reaction proceeds in an undivided cell equipped with carbon anode and nickel cathode at a constant current of 7mA. At the anode, the oxidation of carboxylic acids **49** leads to the formation of stabilized carbocation **A**, which is trapped by cyclic amine **50** to build C−N bond (scheme 38).In an attempt to improve the decarboxylation of glyoxylic acid, it was envisaged that, in the presence of secondary amine **53** and glyoxylic acid **52**, the formamide derivatives **54** was formed easily with a broad range of functional group tolerance[37].The optimal yields were obtained by the combination of $Cu(OAc)_2.H_2O$ as a mediated catalyst and Cs_2CO_3 as a base. The experimental results proved that in absence of Cs_2CO_3 the final product was formed in traces. If DBU (1,8-Diazabicyclo[5.4.0]undec-7-ene) was used instead of Cs_2CO_3 the desired product was formed with less yield of 64%. We can conclude that the presence of base is required for this transformation. The amine substrates **53**, was electrolyzed in an undivided cell with glyoxylic acid **52** at platinum anode, at a constant current of 5 mA (Scheme 39), would lead to formamide derivatives **54** via the mechanism illustrated in scheme 40. First, cesium carbonate deprotonates glyoxylic acid **52** to form carboxylate anion **A**. **A** condensed with the amine **53** to form intermediate **B** and its tautomer **C**. Intermediate **C** was oxidized by Cu, followed by the decarboxylation to provide **D**. Finally, after further oxidation of **D**, the desired product was formed **45**.



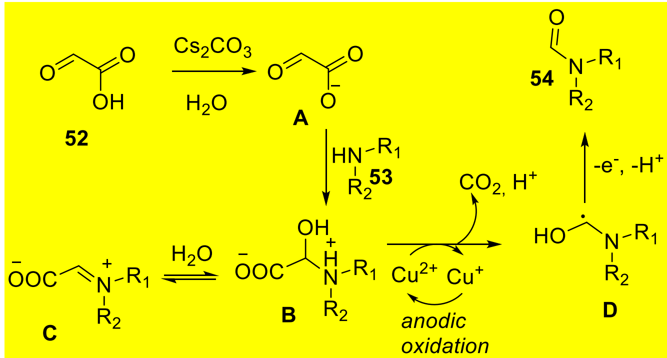
Scheme 37: The electrochemical decarboxylative C_{sp3}–N coupling reactions



Scheme 38: A plausible mechanism for the electrochemical decarboxylative C_{sp3}–N coupling reactions



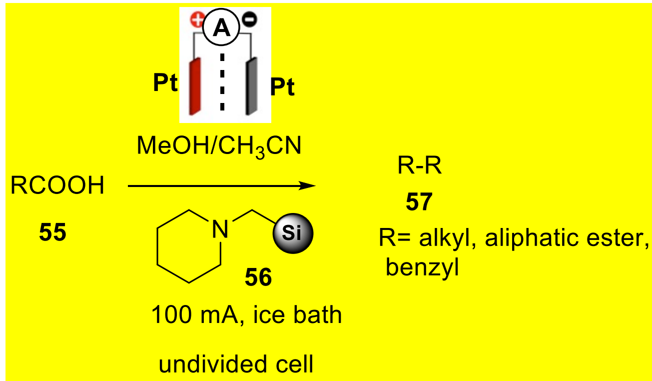
Scheme 39: The electrochemical formation of formamide derivatives



Scheme 40: A plausible mechanism for the electrochemical formation of formamide derivatives

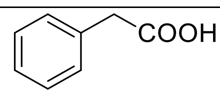
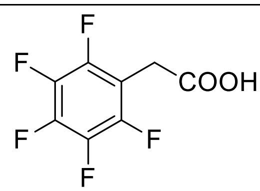
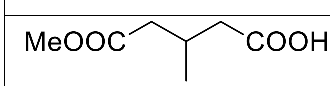
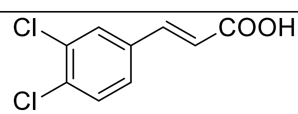
2.2. Dimerizations

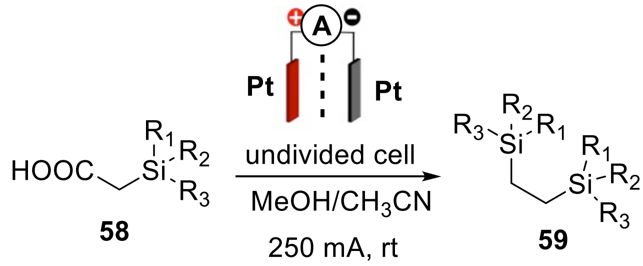
As we mentioned previously, Kolbe electrolysis is the oldest electrochemical reactions[14]; it was basically used to synthesize alkanes derivatives[73]. Recently Tajima group[74] reported a novel electro catalytic system for Kolbe C-C coupling. The methodology reports the coupling reaction of carboxylic acid **55** in the presence of Si-supported piperidine **56** as bases to provide the desired compound **57** with a good yield (scheme 41). It is known that platinum anode has high 0p conditions, which are favored for Kolbe electrolysis because they lead to a high concentration of radicals at the surface of platinum anode to provide homocoupling preferentially products[75] This decarboxylation was found to tolerate a large variety of functional groups, as summarized in Table 4. The optimal yield was obtained when the electrolysis was carried out in an undivided cell at a constant current of 100 mA, equipped with Platinum electrodes as both anode and cathode. In an attempt to improve the Kolbe anodic oxidation, a new approach for the electrosynthesis of disilylalkanes **59** has been developed by Becker and co-workers[76] (scheme 42). Electrolyzing α-silylcarboxylicacids **58** in an undivided cell, equipped with two platinum plate electrodes at a constant current, leads to the desired **59** in good yield up to 77% (Table 5).



Scheme 41: The electrocatalytic system for Kolbe C-C coupling

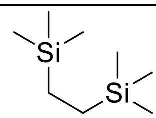
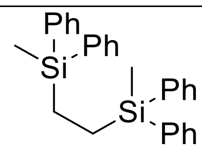
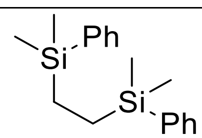
Table 4: Substrate scope of the Kolbe C-C coupling

Unsaturated carboxylic acids	Yields in decarboxylation
	90 %
	52 %
$C_5H_{15}CO_2H$	90 %
$C_9H_{19}CO_2H$	99 %
	91 %
	45 %



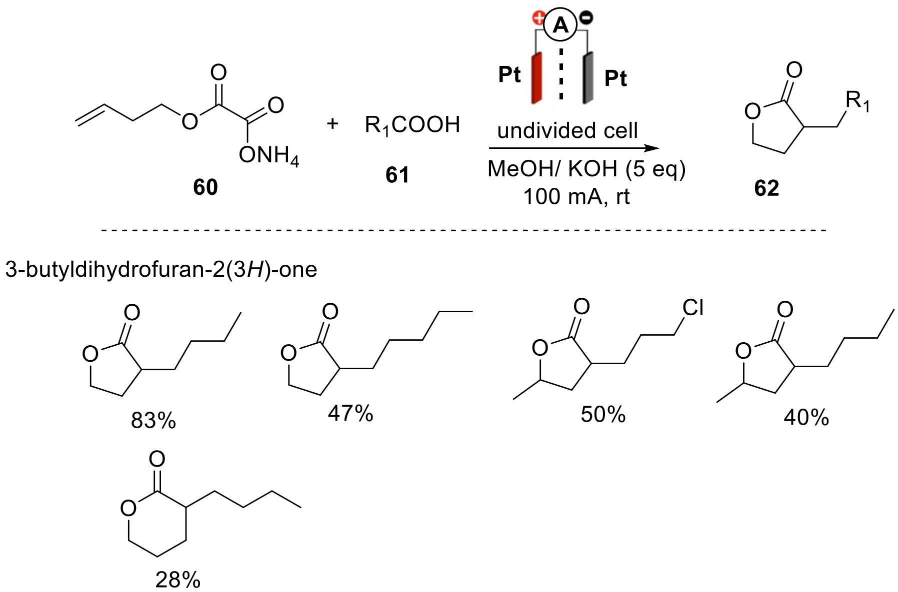
Scheme 42: The electrosynthesis of disilylalkanes derivatives

Table 5: Substrate scope of the Kolbe C-C coupling

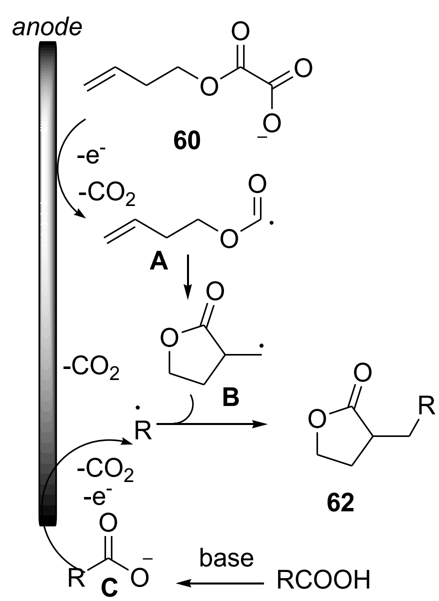
disilylalkanes	Yields in decarboxylation
	77%
	71 %
	76 %

2.3. Additions, Cyclizations

It is known that compounds with γ-butyrolactone fragments have various uses in pharmaceuticals applications such as antibiotic[77], and anticancer agents[78]. This is why their synthesis has attracted more attention. Many synthetic strategies[79] have been reported to achieve a family of these derivatives. The classical synthesis of γ-butyrolactone derivatives based on the use of an expensive catalyst and toxic reagents[80, 81]. Woefully, these methods are not ideal due to their reliance on toxic and expensive catalysts. In this context, electrosynthesis methods could be an alternative to achieve butyrolactone derivatives in a green way and under free catalyst. Lam and co-workers[82] reported a new electrochemical approach to generate γ-butyrolactones derivatives **62**. Under mild conditions hemioxalate salts **60** and carboxylic acid **61** derivatives provide a large scope of the desired product **62** in a good yield of up to 83% (scheme 43). Furthermore, the authors investigated the methodology's applicability to the synthesis of δ-valerolactonesin moderate yield of 28%, by a simple modification of hemioxalate salts (scheme 43). The reaction proceeds in an undivided cell equipped with platinum electrodes, in methanol, at a constant current of 100 mA. The mechanism in scheme 44 shows that the reaction takes place on the anode. The oxidation of the hemioxalate salt **60** on the anode results in decarboxylation to give an intermediate radical **A**, which rapidly undergoes a 5-*exo*-trig cyclization to give a five-membered ring radical **B**. Concurrently, deprotonation of the co-acid **61** provides intermediate **C**. This later, after anodic decarboxylation, results in alkyl radicals, which recombine with the cyclized radical **B** to form the desired lactone **62**.

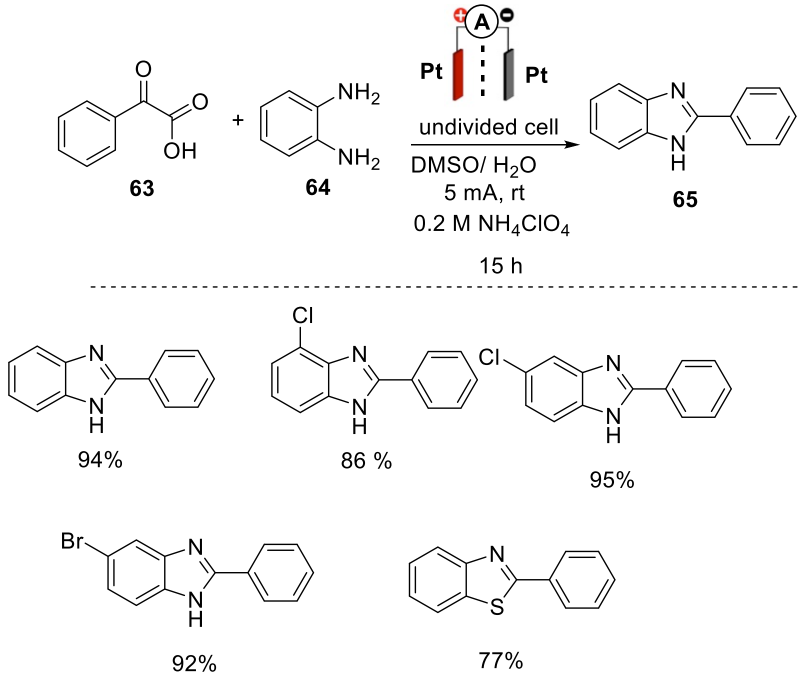


Scheme 43: The electrochemical formation of γ-butyrolactones derivatives andδ-valerolactones via Kolbe electrolysis

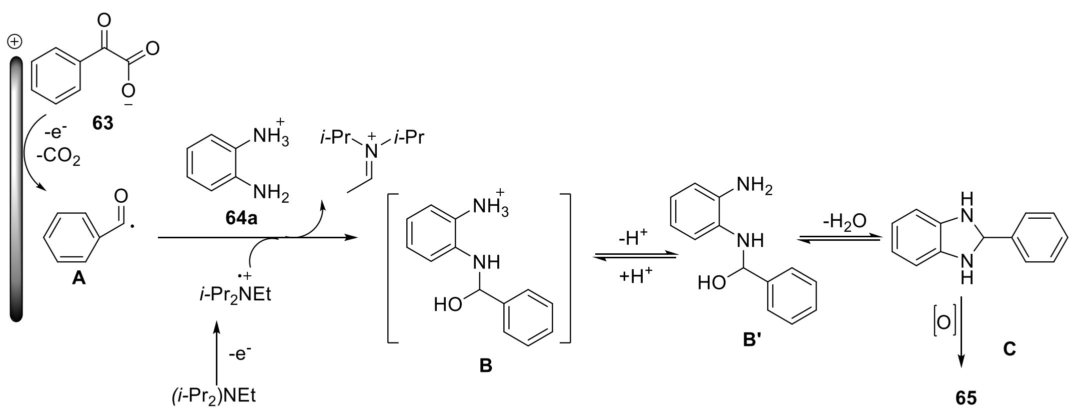


Scheme 44: A plausible mechanism for the electrochemical formation of γ-butyrolactones derivatives andδ-valerolactones

Benzimidazole derivatives could also be obtained by the electrochemical method. In 2016, Huang and co-workers[83] reported an efficient approach for the electrochemical synthesis of benzimidazole derivatives **65** in aqueous media. Under mild conditions, α-keto acid **63** and ortho-phenylenediamines **64** could afford a large family of the desired product **65** in good yield up to 95% (scheme 45). The authors demonstrated that benzothiazoles could also be synthesized with a yield of up to 77% under these conditions. The reaction proceeds in an undivided cell equipped with platinum electrodes, in DMSO/ water, at a constant current of 5 mA. The plausible mechanism of this transformation is shown in scheme 46. Firstly, α-keto acid anion **63** loses an electron to generate after decarboxylation the radical acyl **A**. **A** couples with partially protonated diamine **64a** and a hydrogen atom transfers from the electrogenerated amine radical cation [$(i\text{-Pr})_2NEt^{\cdot+}$)] to afford the product **B**. **B** is then transformed to the intermediate benzimidazoline **C**. Subsequent dehydrogenation of **C** by O_2 and oxidation provides the final product **65**.

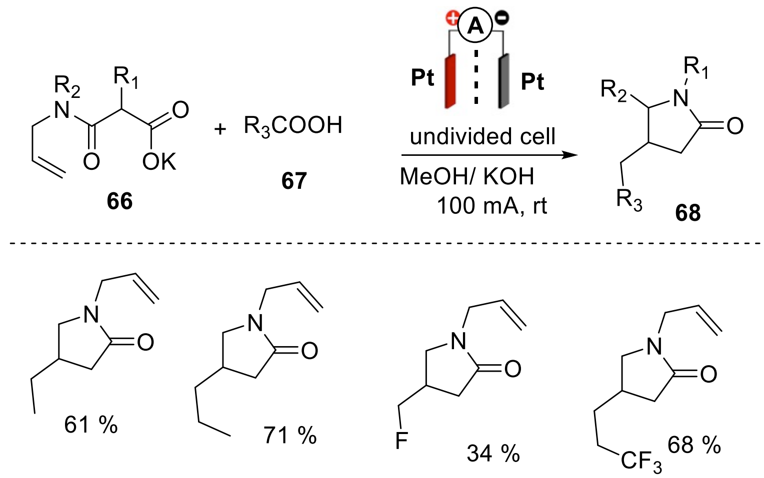


Scheme 45: The electrochemical synthesis of benzimidazole derivatives

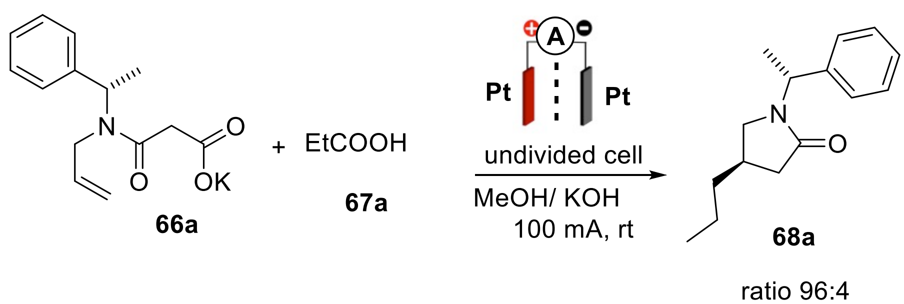


Scheme 46: A plausible mechanism for the electrochemical synthesis of benzimidazole derivatives

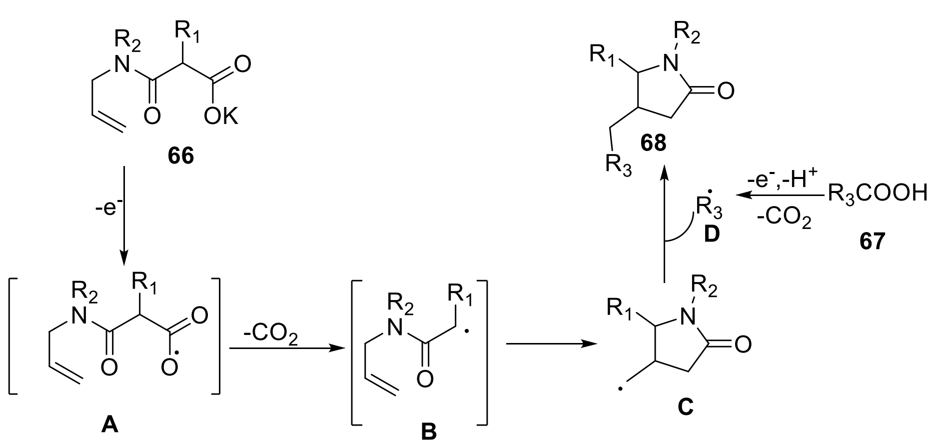
The development of new green methods to synthesize pyrrolidone derivatives is one of the important organic synthesis objectives. In this context, Riant and co-workers[84] reported an efficient approach to generate the electrosynthesis of pyrrolidones derivatives **68** (scheme 47) via a Kolbe decarboxylation, followed by an intramolecular radical cyclization and a radical–radical cross-coupling as shown in scheme 49. The reaction proceeds in an undivided cell equipped with platinum electrodes in methanol, using KOH as an electrolyte, at a constant current of 100 mA. Different potassium 3-ethoxy-3-oxopropanoate derivatives **66** with carboxylic acid derivatives **67** were tolerated in this transformation. The authors tested the diastereoselective electrocyclization of pyrrolidinones. In the same conditions, a good diastereoselective ratio for this electrochemical transformation was obtained, the compound **68a** was formed with a diastereoselective ratio of 96:4 (scheme 48).



Scheme 47: The electrosynthesis of pyrrolidones derivatives

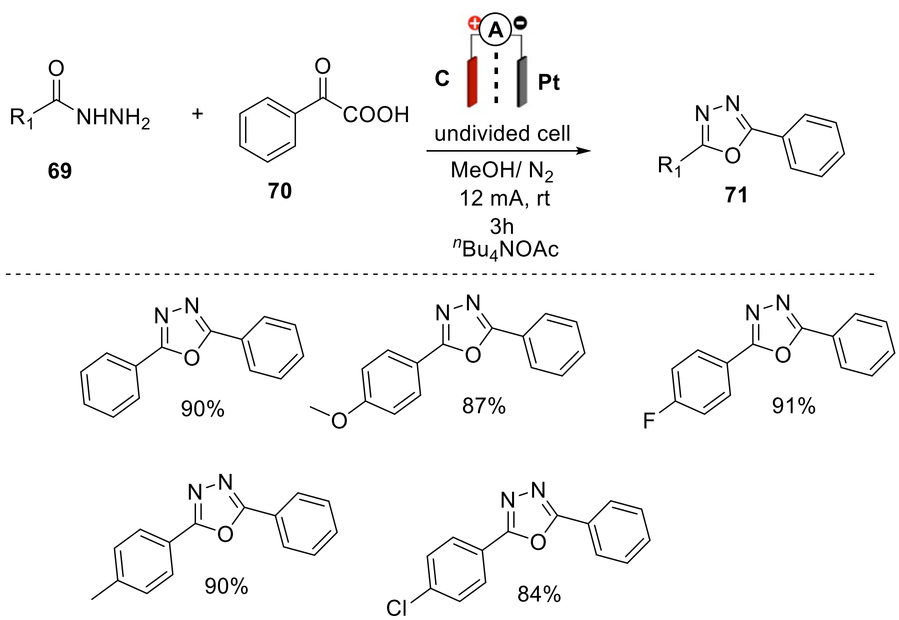


Scheme 48: Diastereoselective pyrrolidinone electrosynthesis

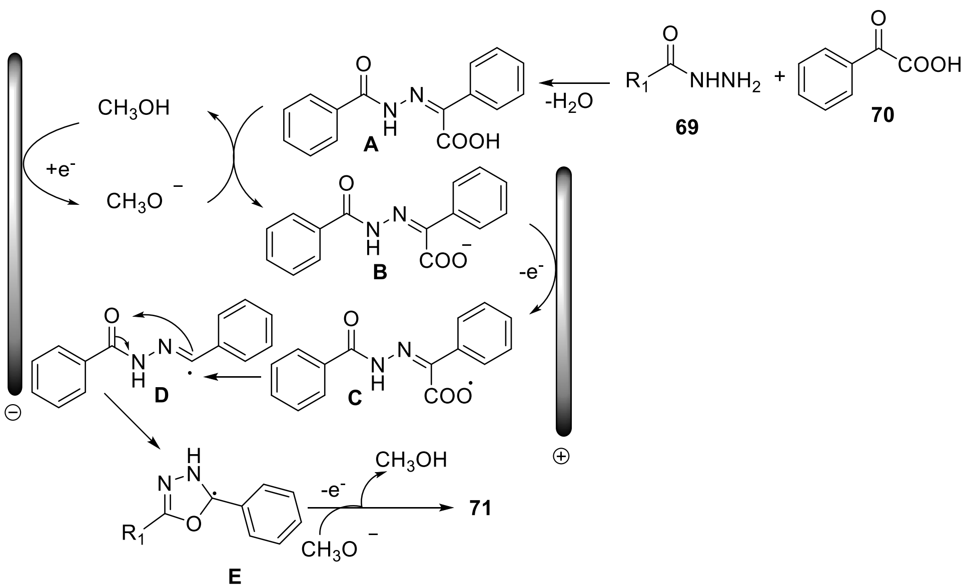


Scheme 49: A plausible mechanism for the electrosynthesis of pyrrolidones derivatives

Kolbe electrolysis was successfully used for the electro formation of 1,3,4-Oxadiazoles derivatives[85]. This methodology has been reported by Lei and co-workers in 2020. A different family of α-keto acids **70** and acylhydrazines derivatives **69** could be well tolerated in this transformation, yielding the desired product **71** with a good yield of 91% (scheme 50). Different aromatic groups with electron-donating or electron-withdrawing substituents were well tolerated in this transformation. The electrolysis was carried out in an undivided cell equipped with a carbon anode and platinum as a cathode at a constant current, using methanol as solvent and $^{n}Bu_4NOAc$ as an electrolyte. The authors proposed the following mechanism for this transformation (scheme 51). At the start, intermediate **B**, which is formed by condensation of **69** and **70** with the following deprotonation, undergoes anodic oxidation to provide radical intermediate **C**, which proceeds with decarboxylation to give **D**. The following intramolecular radical addition can yield **E**. Finally, the consecutive single electron anodic oxidation and deprotonation of **E** providing the desired product **71**.



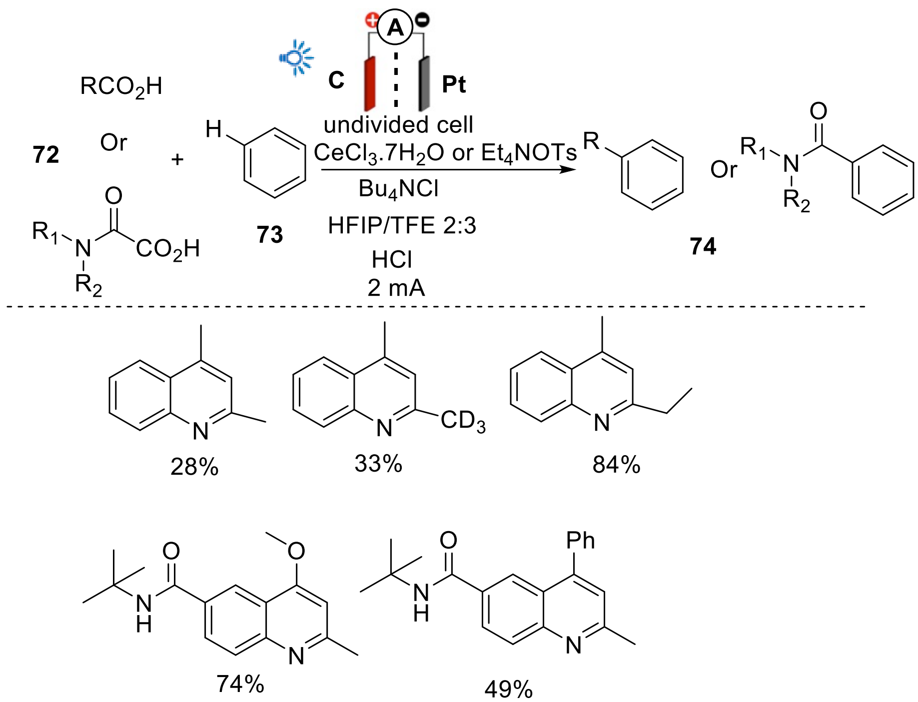
Scheme 50: The electroformation of 1,3,4-Oxadiazoles derivatives



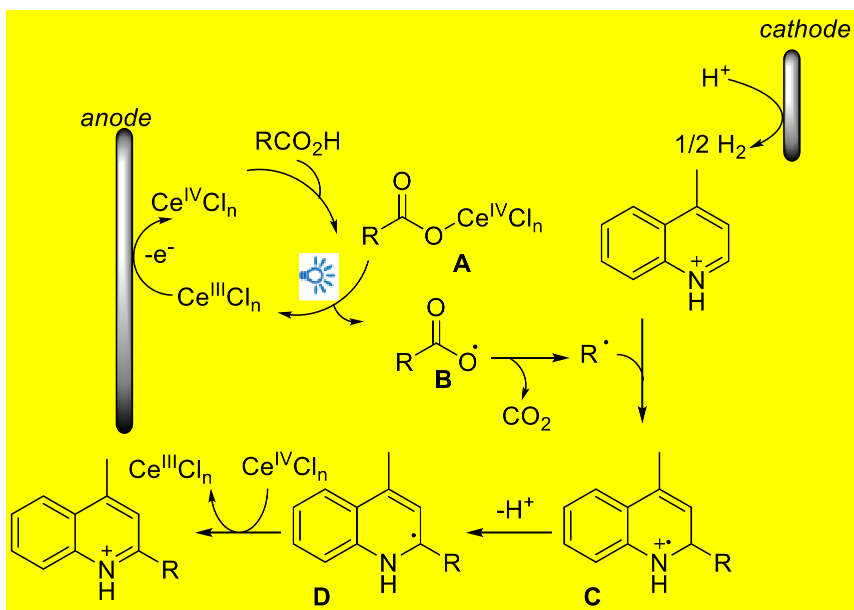
Scheme 51: A plausible mechanism for the electroformation of 1,3,4-Oxadiazoles derivatives

2.4. CH activations (electrophotocatalysis)

As we mentioned previously, carboxylic acids present the most attractive precursors of C-C bond formation due to their availability, structural diversity, and affordability. The direct decarboxylative C–H functionalization reactions without chemical oxidants occur with a release of dihydrogen[86]. In this context, Ackermann groups[87] reported an oxidant-free decarboxylative C–H alkylation of heteroarenes. However, the electrophotocatalytic decarboxylation was investigated[88], The reaction describes an oxidant-free method for the decarboxylative C–H alkylation and carbamoylation of heteroarenes **74**. Under mild conditions, carboxylic acids or oxamic acids **72** with arene derivatives **73** could provide a large scope of the desired product **74**. The reaction occurs in the presence of photocatalysis. The electrosynthesis method is carried out in an undivided cell equipped with a carbon anode and a platinum plate as a cathode (scheme 52). This decarboxylation was found to tolerate a large variety of functional groups. Scheme 53 describes the proposed mechanism of this transformation. The reaction commences at the anode by the oxidation of Ce^{III} to Ce^{IV}, which coordinates with a carboxylic acid to give complex **A**. Then, **A** undergoes photo-induced ligand-to-metal charge transfer (LMCT) to regenerate Ce^{III} and afford a carboxyl radical **B**. The decarboxylation of **B**, followed by the addition of the resultant alkyl radical, affords a radical cation **C**. Then **C** loses a proton to give radical **D**. Finally, **D** undergoes highly exothermic oxidation, mediated by Ce^{IV}, to generate the desired product.



Scheme 52: The electrocatalytic alkylation



Scheme 53: A proposed mechanism for electrocatalytic alkylation

3. Conclusion and Perspective

Easy access to value-added chemicals using modern synthetic tools[89-92] (such as electrochemistry, photochemistry, flow chemistry, biochemistry, digital chemistry) have been progressing fast due to their environmentally friendly approach with less or no waste / side products, giving a safe and steady route to get desirable products. Asymmetric electrochemical transformations remain highly desired. However, toward this, the concept of "memory of chirality" via retention mechanism and electrochemical decarboxylation has been applied successfully by various researchers to achieve significant chiral products without using axillaries and chemical catalysts under mild conditions. The Kolbe and related non-Kolbe electrolysis process via ED is an inexpensive valuable strategy to introduce new bonds via coupling, dimerizations, additions, cyclizations, and CH activations without applying expensive chemicals & oxidants. However, for best electrochemical transformations via ED, screening of electrodes, solvents, temperature, flow rate (in case of flow electrosynthesis), would play a significant role and should be selected carefully. Herein, we discussed several such electrochemical transformations of this ED strategy to drive value-added chemicals and also addressed their mechanistic aspects. This ED approach will enable for easy access of chemicals and in the future could be improved and mingled with other modern synthetic tools.

List of acronyms and abbreviations

ED: Electrochemical Decarboxylation
SET: Single Electron Transfer
DMA: Dimethylacetamide
LMCT: ligand-to-metal charge transfer
DBU: 1,8-Diazabicyclo[5.4.0]undec-7-ene
DMSO: Dimethyl sulfoxide

Author contributions

‡These authors equally contributed to this work.

Conflicts of interest

There are no conflicts to declare.

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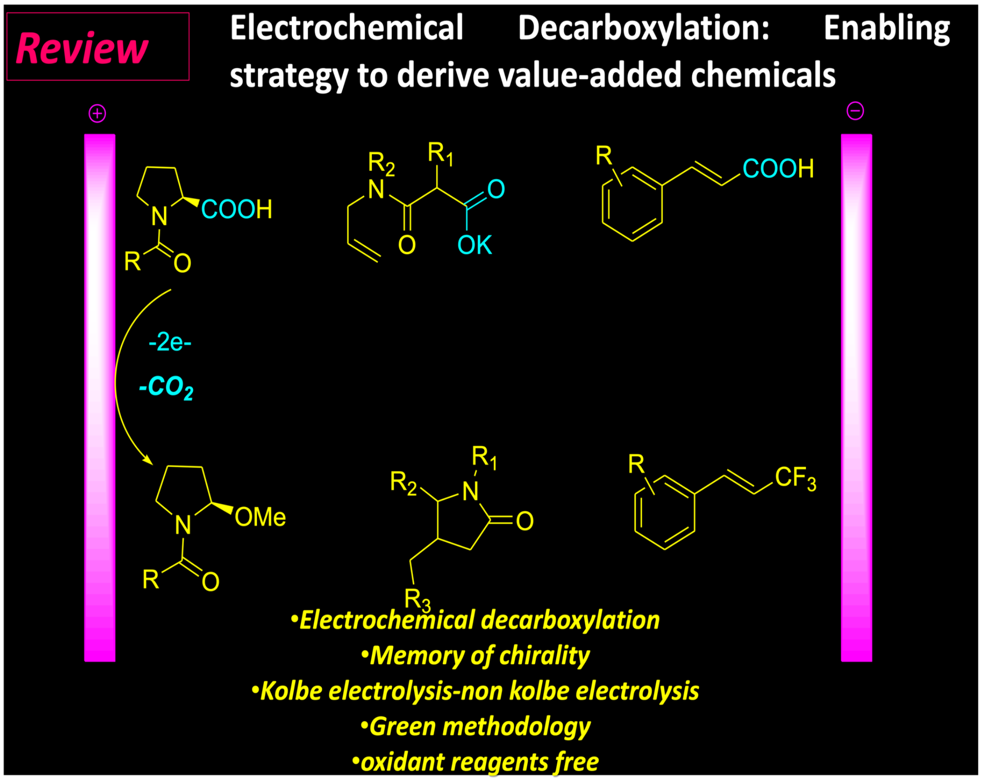

Text for Table of Contents:

Herein, the electrolysis process where the anodic oxidation of carboxylic acids leads to a decarboxylation, has been discussed to synthesize organic molecules.

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