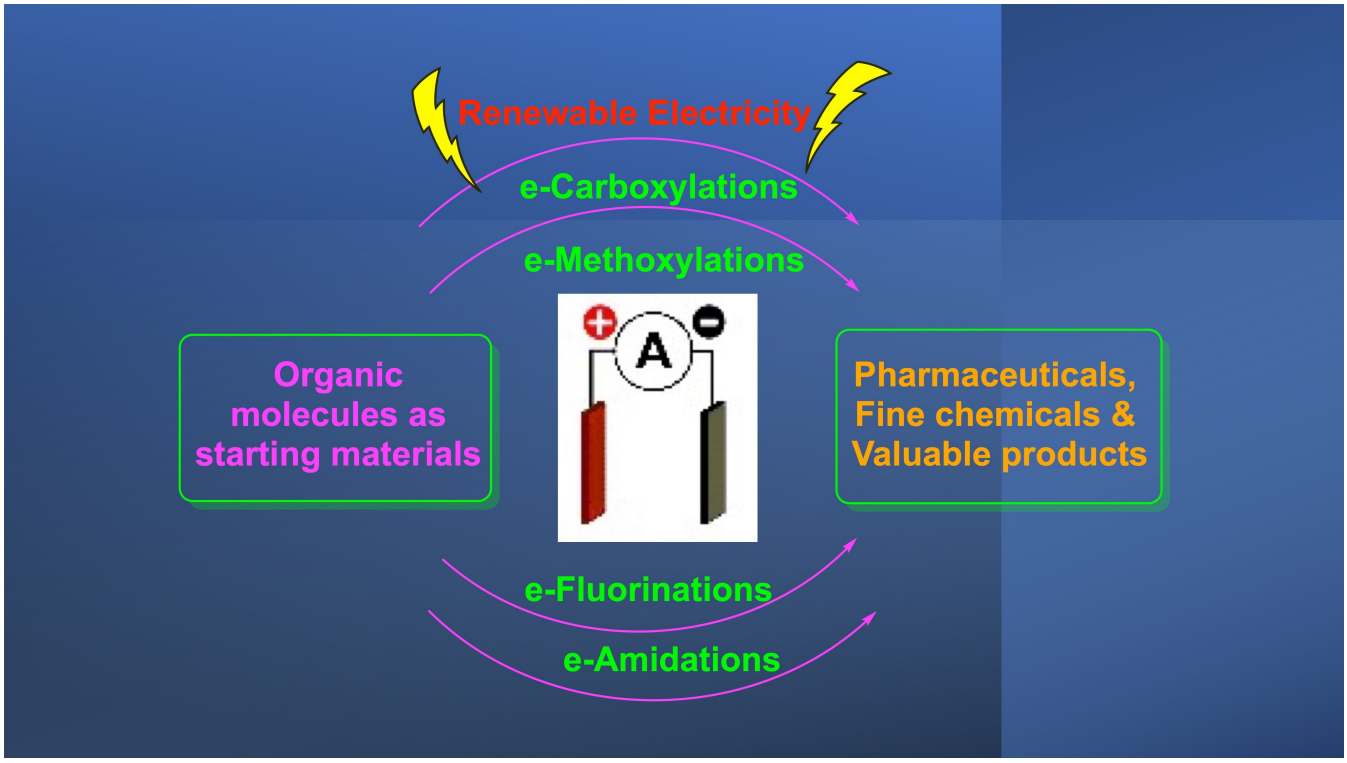
Review

THE CHEMICAL RECORD

doi.org/10.1002/tcr.202100296
tcr.wiley-vch.de

Renewable Electricity Enables Green Routes to Fine Chemicals and Pharmaceuticals

Ayesha Murtaza,[a] Muhammad Awais Qamar,[b] Kaynat Saleem,[a] Tomas Hardwick,[c, d, e] Zia ul haq,[f] Bahareh Shirinfar,[g] and Nisar Ahmed*[c]



Abstract: Syntheses of chemicals using renewable electricity and when generating high atom economies are considered green and sustainable processes. In the present state of affairs, electrochemical manufacturing of fine chemicals and pharmaceuticals is not as common place as it could be and therefore, merits more attention. There is also a need to turn attention toward the electrochemical synthesis of valuable chemicals from recyclable greenhouse gases that can accelerate the process of circular economy. CO_2 emissions are the major contributor to human-induced global warming. CO_2 conversion into chemicals is a valuable application of its utilisation and will contribute to circular economy while maintaining environmental sustainability. Herein, we present an overview of electro-carboxylation, including mechanistic aspects, which forms carboxylic acids using molecular carbon dioxide. We also discuss atom economies of electrochemical fluorination, methoxylation and amide formation reactions.

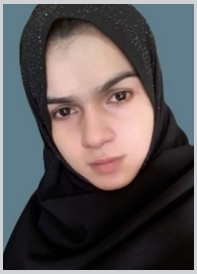
Keywords: Electro-carboxylation, Circular economy, Electro-fluorinations, Electro-methoxylations, Electro-amides

1. Introduction

Electrosynthesis of chemicals using renewable electricity could lead to sustainability benefits over conventional methods. The whole electrolysis process (oxidation and reduction) occurs at two electrodes (an anode as working electrode and a cathode as counter electrode) in the electrochemical cell (divided or undivided cell) with an external electric power supply. The transportation of ions in the reaction mixture is maintained by a conductive solution such as water or some supporting electrolyte. Electrifying organic synthesis is a fast growing green approach in which to perform chemical reactions in an environmentally friendly manner at mild conditions. The electrochemical reactions can be conducted in a better (in terms of yield, selectivity, purity, time – particularly if flow chemistry is employed – to name a few) and controlled way by the choice of electrode material, applied potential, electrolyte(s) and system configuration.[1–4] Moreover, the synthesis of fine chemicals and manufacturing of pharmaceuticals via environmentally friendly, cost effective, and energy efficient methods is no longer seldom to researchers. The challenge is to overcome the use of hazardous reagents when designing chemical pathways to such commodities. Electrical current could play a role in forming reaction intermediates in such chemical transformations with minimal, or in the absence of, waste production by direct or indirect electrolysis processes using batch and flow technologies. Furthermore, the merging of technologies can accelerate production yields.[5–9] At present, considering ongoing climate challenges, stakeholders related to the production of fine chemicals and pharmaceuticals are enamoured to introduce green and sustainable techniques that conserve energy, generate fewer by-products, and derive maximum atom economies with low cost. Carboxyl-, fluorine-, methoxy-, amide-, sulfur-, and nitrogen-containing heterocycles are important in the pharmaceutical industry due to their role in drug discovery. Examples include Remdesivir, Favipiravir, Baricitinib, Levaquin Antibiotic, Lipitor Hypercholesterolemia, Atorvastatin, Ciprofloxacin, Fluoxetine, Panomifene and Cyhalothrin etc.[10–16] (Figure 1). In this regard, electrochemical transformations are acknowledged as a prospective, sustainable, cost-effective and easily scalable methodology with potentially improved selectivity.[17]

Owing to its high abundance, low toxicity and cost, CO_2 has been used in many syntheses as a one-carbon (C1) source, including under mild conditions and at atmospheric pressure, with high efficiency and yields, typically when a sacrificial anode (i.e. Al or Mg) is applied. Carboxylation (carbon dioxide fixation), discussed herein, occurs when CO_2 is reacted with an organic species to afford carboxylic acids via the formation of a carbon-carbon bond. Carboxylation has proven

[a] *A. Murtaza, K. Saleem*
Department of Chemistry, Khwaja Fareed University of Engineering and Information Technology, Rahim Yar Khan 64200, Pakistan
[b] *M. A. Qamar*
College of Chemistry and Chemical Engineering, Northwest Normal University, Lanzhou-730070, Gansu, China
[c] *T. Hardwick, N. Ahmed*
School of Chemistry, Cardiff University, Main Building, Park Place, Cardiff, CF10 3AT, UK
E-mail: AhmedN14@cardiff.ac.uk
[d] *T. Hardwick*
National Graphene Institute, University of Manchester, Oxford Road, Manchester, M13 9PL, UK
[e] *T. Hardwick*
Department of Materials, University of Manchester, Oxford Road, Manchester, M13 9PL, UK
[f] *Zia ul haq*
Chemical Engineering department, Khwaja Fareed University of Engineering and Information Technology, Rahim Yar Khan 64200, Pakistan
[g] *B. Shirinfar*
Department of Chemistry, University of Bath, BA2 7AY, Bath, UK



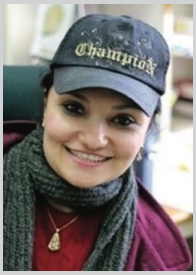
Ayesha Murtaza completed her Master's degree in organic chemistry in 2020 at Khawaja Fareed University of Engineering and Information Technology Rahim Yar Khan, (Pakistan) under the supervision of Dr. Farrukh Mansoor Janjua in the Department of Chemistry. Her research interest focused on Electrosynthesis of organic compounds. Currently, she is taking research's guidance from Dr. Nisar Ahmed (Cardiff University, UK).

Zia Ul Haq completed his B.Sc in Chemical Engineering from Punjab University Lahore (Pakistan). Now he is doing Master in chemical engineering from Khawaja Fareed University of Engineering and Information Technology Rahim Yar Khan, (Pakistan) under the supervision of Prof. Dr. Suleman Tahir in the Department of Chemical Engineering with the research interest of adsorption and photocatalysis of waste water.

Muhammad Awais Qamar obtained his B.S. in Organic Chemistry in 2016 from Government College University Faisalabad (Pakistan). Then he moved to Northwest Normal University Lanzhou, Gansu(China) for his master studies under the guidance of Prof. Du Zheng Yin.

Kaynat Saleem obtained her master's degree in chemistry in 2020 at Khwaja Fareed University of Engineering and Information Technology Rahim Yar Khan, (Pakistan) under the supervision of Dr. Muhammad Khalid in the Department of Physical Chemistry. Her research interests are development of novel electrolytic material by using hydrothermal method and structure designing and modelling by using computational approaches.

Tomas Hardwick obtained his master's degree in chemistry at Cardiff University, performing organic chemistry research focused on electrochemical organic synthesis in batch and flow. During such time, he spent a year working on heterogeneous catalysis at the University of Florida. He is currently a Ph.D. student at the University of Manchester working with the Advanced Nanomaterials Group, with research interests involving two-dimensional materials for electrochemical, photovoltaics and photoelectrochemistry and flow technology.



Bahareh Shirinfar obtained her Ph.D in 2014 in organic supramolecular chemistry, working in the group of Prof. Kwang S. Kim (POSTECH, Korea). Then, she moved to Switzerland to continue her career as a post-doctoral fellow at the University of Zurich. She arrived in Bristol in January 2015 to take up a Royal Society Newton Fellowship. After two years at this position, she has continued her research as a research scientist at the University of Bristol. Further, she has been awarded Daphne Jackson Fellowship at University of Bath, UK (2020). She is also associated with Dr. Nisar Ahmed (Cardiff University) for electrochemical applications. Her research focuses on molecular recognition.

Nisar Ahmed obtained his PhD in organic chemistry (2012) under Brain Korea BK21 fellowship working in the group of Prof. Kwang S. Kim (POSTECH, Korea). Then, he moved to the University of Zurich, Switzerland (2013) for a postdoctoral stay with a Novartis Fellowship. Subsequently (2015), he joined the University of Bristol as a research associate. He started his independent research career in 2017 at School of Chemistry, Cardiff University, United Kingdom with Marie Curie COFUND fellowship as Sêr Cymru Fellow. Further, he has continued his research career as faculty in molecular synthesis (organic chemistry) and Research Fellow - EPSRC Investigator at Cardiff University. He is also an Adjunct faculty at HEJ Research Institute of Chemistry, ICCBS since 2018. His fields of research include synthesis of value-added chemicals, fine chemicals and pharmaceuticals using modern synthetic tools (electrochemistry, photochemistry, sonochemistry, flow technology, digital chemistry, automation chemistry)

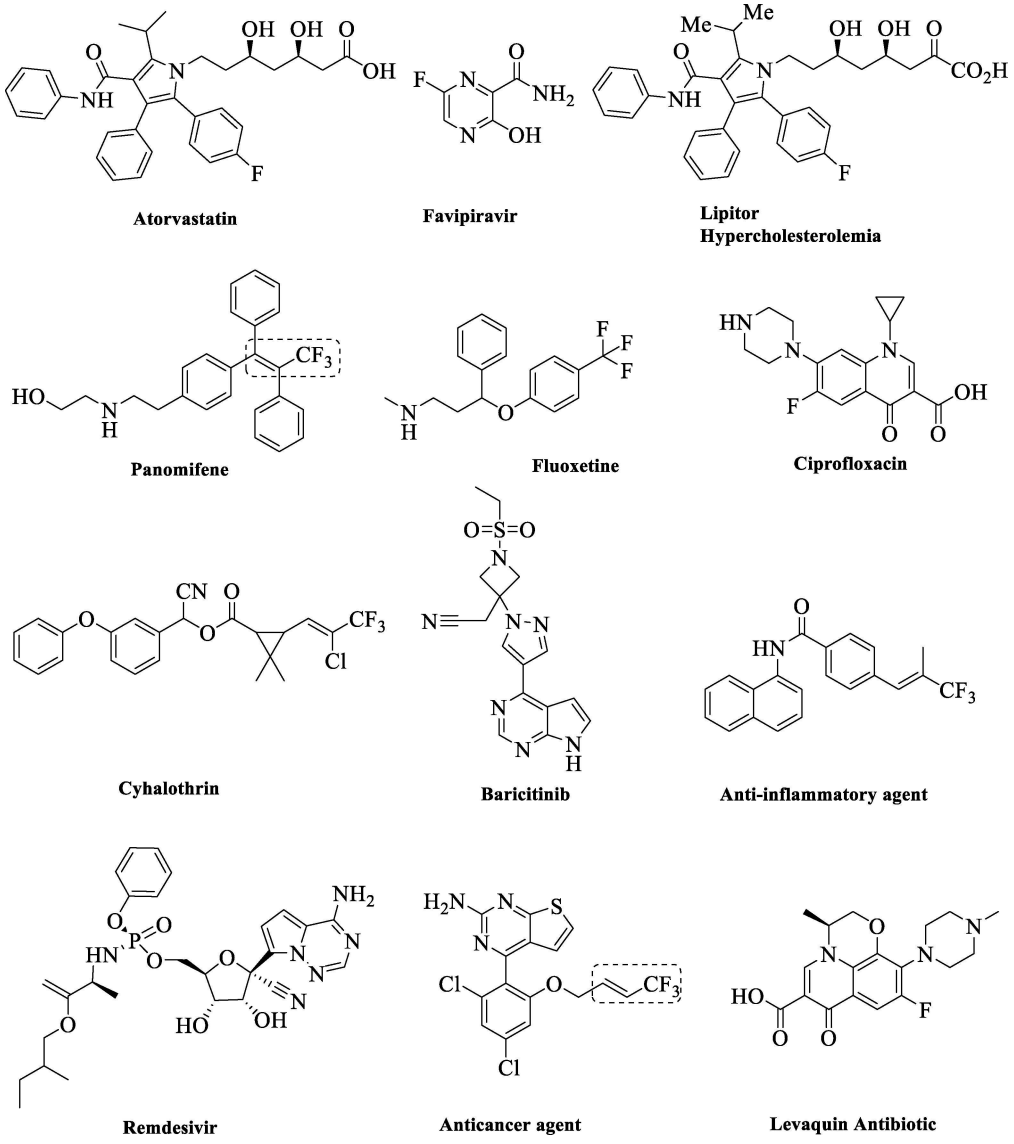


Figure 1. Structures of Atorvastatin, Favipiravir, Lipitor Hypercholesterolemia, Panomifene, Fluoxetine, Ciprofloxacin, Cyhlothrin, Baricitinib, Anti-inflammatory agent, Remdesivir, Anticancer agent and Levaquin Antibiotic

itself one of the best ways to produce carboxylic acids in recent times. Moreover, carbonates or carbamates can be produced by a similar process involving the formation a carbon-heteroatom bond. Unfortunately, it is difficult, owing to the stable and unreactive nature of CO_2, to producer carboxylic acids in this way, often requiring high temperatures, pressures, very reactive organolithium and Grignard nucleophiles and dangerously basic conditions. An attractive alternative and one that is more environmentally friendly, inexpensive and has the ability to safely handle dangerous and sensitive is electrochemical CO_2 fixation. This is because electrochemistry is an established methodology in the area of sustainable organic synthesis that can allow the immediate reaction of carbon dioxide with highly reactive nucleophiles.

Another class of reactions covered in this work concerns electrochemical fluorinations. Numerous applications for fluorine-containing organic compounds have been developed, some of which are in drugs, polymers, surfactants, fire extinguishers, lubricants and refrigerants. Commonplace in bioactive molecules, improvements to pharmacokinetics, metabolic stability, membrane permeability intrinsic potency and pKa can be achieved by incorporating fluorine. Organic fluorinations are therefore highly sort after, particularly considering the scarcity of naturally occurring organoflorione

compounds. However, doing so usually employs extremely reactive and dangerous chemicals, such as fluorine gas which is reactive, tremendously toxic and difficult to control (making selective fluorinations a problem). Electrochemistry offers a safe lab-level synthesis technique, in accordance with green chemistry, that does not require hazardous reagents, and has the ability of easy scale-up.

Another important motif is the amide bond, prevalent in a huge number of organic compounds, including natural products, functional materials, agrochemicals, peptides and proteins Most notably of which is in medicinal chemistry where the linage is found in many biological systems and may be the most frequently used transformation in the pharmaceutical industry, currently believed to be ubiquitous in *ca.* 50 % of drug compounds. Normally, however, amides are synthesised from amines, aldehydes and carboxylic acids, requiring expensive oxidants and catalysts, inert atmospheres, high temperatures, hazardous reagents, reagents with limited stability, and large waste production. As with the above, coupling amidation with electrochemistry could address these problems. Other than being safer and more environmentally benign, atom economy may be improved since external oxidants, mediators or transition metals are not essential, and thus waste can be minimised for this extensively used reaction.

2. Circular Economy and Electro-Carboxylation

To benefit society and the environment, the circular economy (CE) is a general approach towards future development; the aims of which are to progressively decouple the growth after the utilisation of limited resources, in comparison to the linear 'take-make-waste' model. To define the circular process twelve principals have been formulated, analogous to green chemistry.[18–20]

The objectives of circular economy are to attain an economic system which is renewable and restorable by preserving products, materials, components and designs at their maximum use and utility, so as to represents an 'umbrella' framework.[21,22] Moreover, on reusability, reutilising policies of life cycles of materials, products and waste,[23] the EU European commissions broadcasted the 'EU circular Economy Action Plan (EU CEAP)[24] as a package of governmental proposals in December 2015. As the consumption of primary carbon resources progressively reduces, secondary waste materials are utilised gradually and specify the incentive for a transitioning from a linear to circular carbon economy. This is due to the demand to sustainably produce the products (i. e., ethanol and H_2 by secondary carbon resources such as waste, biomass and from renewable resources, PVC etc.).[25]

The average temperature of the Earth has increased by *ca.* 0.6 °C over the past 100 years and is anticipated to rise continuously at a rapid rate.[26] The continuous emission of CO_2 for a long time period is predicted to occur due to human reliance on fossil fuels. Therefore, it is necessary to identify useful methods that will enable CO_2 as primary raw material in a practical, economical and sustainable point of view. The reaction of organic molecules with CO_2 fixation can be characterised into two groups: reaction of CO_2 for carbon-heteroatom bond formation e. g., reaction with nitrogen or oxygen to yield carbamates or carbonates, and reaction for carbon-carbon bond formation to yield carboxylic acids.[27–29] Electrochemistry is one of the best methods to do this, and to produce useful fine chemicals, pharmaceuticals and value-added products. Electrochemical methodology has already been used for CO_2 fixation to many organic compounds such as olefins,[30–32] imines,[33–35] benzylic halides[36,37] and ketones.[38–41]

To normalise the CO_2 cycle, electrochemical synthesis points to potentially sustainable and green solutions.[42–45] Since CO_2 is inexpensive, electrocarboxylation takes this advantage and uses it as C1 source for the building block of many synthetically important carboxylic acids, which in contrast to the process of photosynthesis.[46–50] On the other hand, these carboxylic acids undergo electrochemical decarboxylative functionalities with the liberation of CO_2 molecules, but at the same time transform these chemical compounds into further value-added functionalised organic species.[51,52] Currently, carboxylic aids have attracted more interest due to their extensive manipulation in the manufacturing of polymers, food extracts[53] and pharmaceuticals.[54] The carboxylic acids are mainly produced via carboxylation of carbon nucleophiles with CO_2,[55] and are included amongst the most expanded motifs in a variety of compounds that exhibit considerable biological properties.[14,15]

3. Electrochemical Carboxylation with Different Functional Groups

3.1. Electro-Carboxylation of Alkenes Using CO_2

The formation of C–C bonds by the reaction of olefines with CO_2 is generally known as carboxylation. In synthetic organic and medicinal chemistry, the carboxylation of olefins to produce carboxylic acids is a vital transformation as these compounds have extensive applications in many fields.[56–58] Carbon dioxide is abundant in nature, nontoxic and inexpensive, and so acts as green and ideal one-carbon (C1) building block for chemical synthesis.

Electrochemical fixation of CO_2 **1** with a 1,3-butadiene **2** has been broadly examined in the polymer industry due to the great importance of adipic acid(s), such as the production of nylon-6,6. By the dehydrogenation of linear butenes and steam cracking, 1,3-butadiene is an extensively available reactant. A

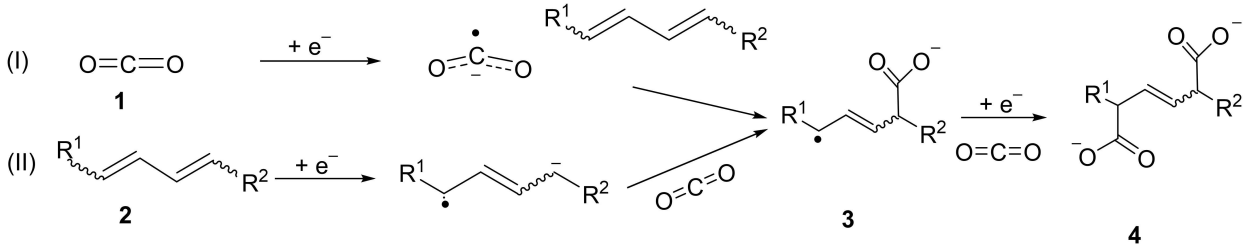
mixture of 3-hexene-1,6-dioic acid isomers **4** have been obtained from decarboxylation reactions of 1,3-butadiene, which are only one hydrogenation step away from the nylon monomer, adipic acid,.[59–63]

In conjugated dienes the general mechanism of CO_2 fixation is explained in (Scheme 1). It is noted that per CO_2 molecule **1**, merely one electron is utilised, making this an energy efficient reaction step. To attain the monocarboxylate radical anion intermediate **3** there are two feasible pathways: the first involves the reduction of CO_2 to a reactive radical anion, namely $CO_2^{\bullet-}$, and the second involves the formation of a radical anion. Both of these pathways may work concurrently, as has been illustrated in the literature.[64] Which mechanism is the preferred depends on other parameters such as CO_2 pressure, cathode material[65] and diene type.[66]

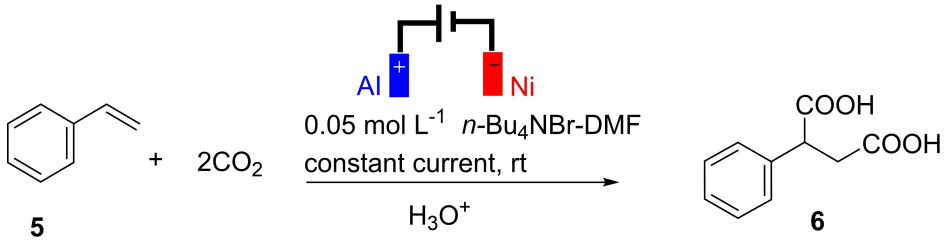
Jiang *et al.* reported an efficient and simple electrochemical method for the synthesis of 2-arylsuccinic acids **6** via aryl-substituted alkenes **5** and CO_2 using aluminium or magnesium as the anode and nickel as the cathode.[64] In an undivided cell the electrochemical dicarboxylation of aryl-substituted alkenes can be carried out smoothly using tetrabutylammonium bromide-dimethylformamide (*n*-Bu_4NBr-DMF) as the electrolyte and 4 MPa pressure of CO_2 under constant current. In the absence of additional catalysts, at room temperature, **6** was afforded with high selectivity (98%) in good yields of 50–87%[67,68] (Scheme 2).

A precursor of adipic acid i.e., 3-hexene-1,6-dioic acid **8**, was achieved in the absence of additional catalysts, using CO_2 and 1,3-butadiene **7** as a starting material with an Al sacrificial anode and Ni cathode, using *n*-Bu_4NBr-DMF as electrolyte and 3 MPa pressure of CO_2 at constant current. Under moderate reaction conditions **8** was produced in 84% yield; this carboxylic acid is envisioned to possess many industrial applications[69] (Scheme 3).

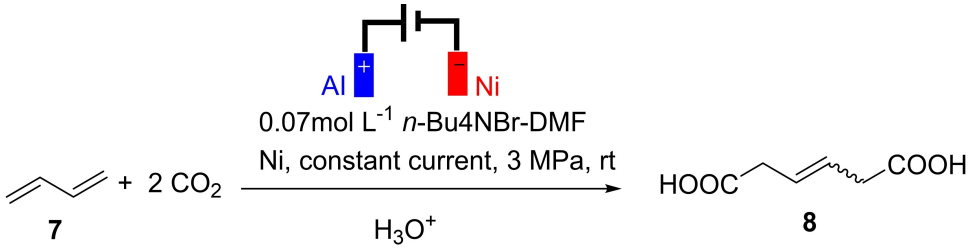
Comparing nickel to other cathode materials such as Zn, Cu, Pt and Ag, nickel has the largest current efficiency and transition state because of the formation of strong carbonates promoted by strong adsorption of CO_2. As such, nickel is the



Scheme 1. General mechanism of the electrochemical dicarboxylation of conjugated dienes



Scheme 2. Electrochemical dicarboxylation of styrene to produce 2-arylsuccinic.



Scheme 3. Aryl-substituted alkenes in solvents, i.e. DMF and tetrabutyl ammonium bromide (n-Bu_4 NBr), via an Al sacrificial anode and Ni cathode.

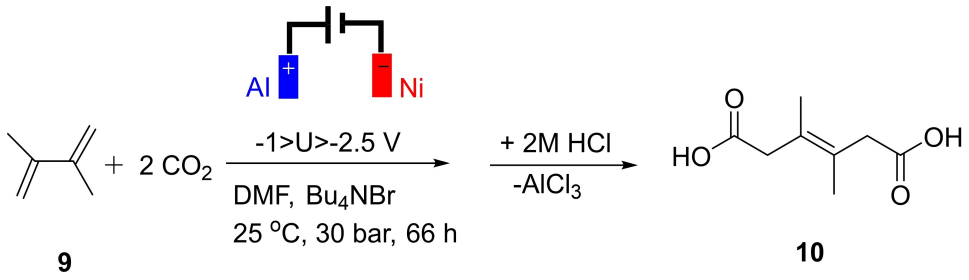
favoured catalyst for carboxylation reactions of di-alkenes[70] and alkynes. In particular, the electro-carboxylation of dienes is an attractive goal.

In this context, a high pressure, single compartment, stainless-steel reactor was

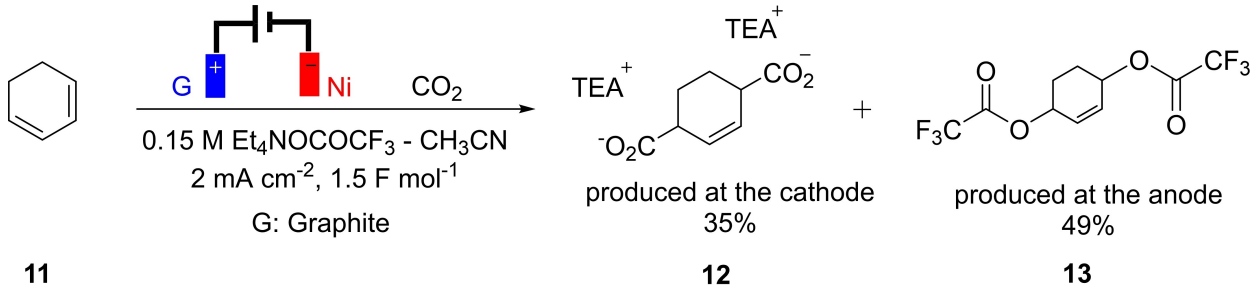
employed, equipped with aluminium as the anode, nickel foam as the cathode and Platinum wire as the reference electrode.[71] Before use, the reactor was dried and sealed at 50 °C for 12 h in vacuum. Then 13 ml of tetrabutylammonium bromide (Bu_4NBr) and 67 ml DMF solution were added followed by degassing in Ar. After that, substrate 2,3-dimethyl-1,3-butadiene **9** was added, the reactor was then closed, and its pressure subsequently increased by the insertion of CO_2. The electrodes were connected to a potentiostate; the reactor was cooled down to room temperature by stabilising the pressure. Before and after the electrosynthesis, cyclic voltammetry experimentations were carried out at a scan rate of 50 $mV\,s^{-1}$. For the synthesis of diacids, chronopotentiometric experiments were carried out (Scheme 4) in order to achieve the desired potential range while the current density was managed between 5 and 10 $mA\,cm^{-2}$. Under vacuum DMF was eliminated after the synthesis, then using 2 M HCl the residue was acidified for 6 h. Before the product was isolated by dimethyl ether the side products, formic acid and oxalic acid, were measured by lC measurements and then dried with Na_2SO_4. To validate the end product hexadienoic acid **10**, ^1H and ^{13}C NMR spectroscopy were performed in dimethyl sulphide (DMSO). However, this process was not satisfactory, producing low values for selectivity (21 %) and yield (33 %) for the diacid with a 32 % faradaic efficiency and 51 % conversion efficiency of the diene.

De Vos and co-workers conjugated dienes through simultaneous cathodic carboxylation and anodic acetoxylation for the synthesis of a diol and diacid via electrochemistry using divergent paired electrolysis.[72] To construct the divergent paired electrolysis set-up, conjugated diene **11** underwent oxidative acetoxylation, which is also a substrate for cathodic carboxylation and used as an anodic reaction, instead of the use of a sacrificial anode. The complex tetraethylammonium trifluoroacetate ($Et_4NOCOCF_3$) was employed both as acetoxylating reagent and as a supporting electrolyte. On the other hand, at the cathode, conjugated dienes such as 1,3-butadiene, isoprene, 2,4-hexadiene and 1,3-cyclohexadiene in acetonitrile were also tolerated, with **11** affording 1,4-dicarboxylic acids **12**, in good yields[73] (Scheme 5).

By using a quasi-divided cell set-up, the allylic bromides **14** were used for sacrificial anode-free convergent paired electrochemical carboxylation, using tetrabutylammonium tetrafluoroborate (Bu_4NBF_4-DMF) as the electrolyte at 10 $mA\,cm^{-2}$ of current. What is of significance is that the carboxylate products are obtained in isomeric mixture, the ester of β, γ-unsaturated carboxylic acids **15** and **16**, and so can readily be differentiated through column chromatography using silica gel. Conversely, when a sacrificial anode was employed in the conventional electrochemical carboxylation,



Scheme 4. Electro carboxylation reaction of 2,3-dimethyl-1,3-butadiene on a Ni catalyst.



Scheme 5. Sacrificial anode-free electrocarboxylation using divergent paired electrolysis.

an intimate mixture of β, γ-unsaturated carboxylic acids was offered (Scheme 6).[74]

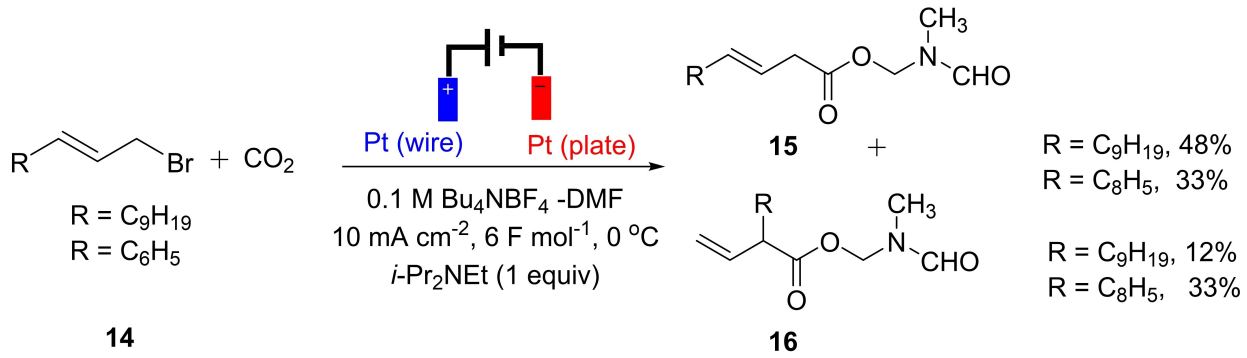
Moreover, in the tandem cyclisation/carboxylation reaction, the advancement of electrochemistry can also have recognised when unsaturated compounds react with CO_2. Over nickel complexes, Olivero and Dunach revealed that the 2,3-dihydrobenzonfuran-3-ylacetic acid **18** is formed when the electrochemical reduction of 2-allyloxybromobenzene **17** and CO_2 occurs.[75] Two other products are simultaneously produced, namely 2-allyloxy benzoic acid **19** and 3-methyl-2,3-dihydrobenzofuran **20** (Scheme 7). The reactivity and chemoselectivity of the carboxylation may be controlled by the appropriate choice of electrodes and ligands for the nickel complexes. This electrochemical reaction was accomplished in a single compartment electrolytic cell (Mg-Nię stainless) using a catalyst $[Ni(cyclam)^{2+}\cdot 2BF^{-}_{4}]$ or $[Ni(cyslam)Br_2]$ to afford the cyclised carboxylic acids in 8–70% yields. From **17** the three different products **18, 19** and **20** are obtained, as illustrated in the mechanism below showing the different pathways to isolate these products over the $Ni[cyclam]^{2+}$ catalyst. From the electrochemical reduction of the Ni^{II} complex, CO_2 coordinates to Ni, producing the Ni^{III} intermediates **I** followed by oxidative addition to the C–Br bond of **17**. The cyclised intermediate **II** could be generated by the annulation of the terminal double bond which would be induced by this Ni^{III} group. Next, the Ni^{II} carboxylated species **III** is produced by the continued electrochemical reduction of intermediate **II**. From the anodic oxidation of Mg, the liberated magnesium cations facilitated the revival of the Ni^{11} group, and might then be used in the upcoming cyclisation process to generate the magnesium carboxylate **IV** that ultimately undergoes hydrolysation to produce the product **18**. Alongside this, the protonation of **III** by the solvent yielded the unsought product **20**. From the carboxylationę reduction of intermediate **I**, another viable product **19** is produced; in addition to this, by employing different anodes or iodide substrates, the dimer was also observed[75] (Scheme 7).

Another cyclisation/carboxylation, reported by Katayama and Senboku in 2016, examined the electrochemical reaction of vinyl bromide **21** via CO_2 to afford the γ, δ-unsaturated carboxylic acid **22**.[76] Furthermore, the bicyclic γ-lactones **23** may be produced via lactonisationę iodo reaction by this acid which is successively used as a starting material (Scheme 8). The mechanism involves the oxidation of Mg to Mg^{2+} ions occurring at the Mg anode. At the cathode, methyl-4-tert-butylbenzoate undergoes a one electron reduction to be used as mediator for the transfer of an electron to stimulate the corresponding radical anion. Through the radical anion of methyl 4-tert-butylbenzoate, the vinyl bromide **21** undergoes one electron reduction, generating its corresponding radical anion, resulting in the formation of vinyl radical **I** by the cleavage of a carbon-bromine bond. Cyclised radical intermediate **II** is then produced via cyclisation of the resultant vinyl radical **I**. Anion **III**, generated by a further one electron reduction of **II**, then reacts with CO_2 to afford the carboxylate intermediate **IV**. Finally, carboxylic acid **22** is produced by acidic treatment. The product selectivity of the cyclised carboxylic acid could be reduced in the absence of the mediator, due to the competition among radical cyclisation and the one electron reduction of the resultant vinyl radical at the cathode.

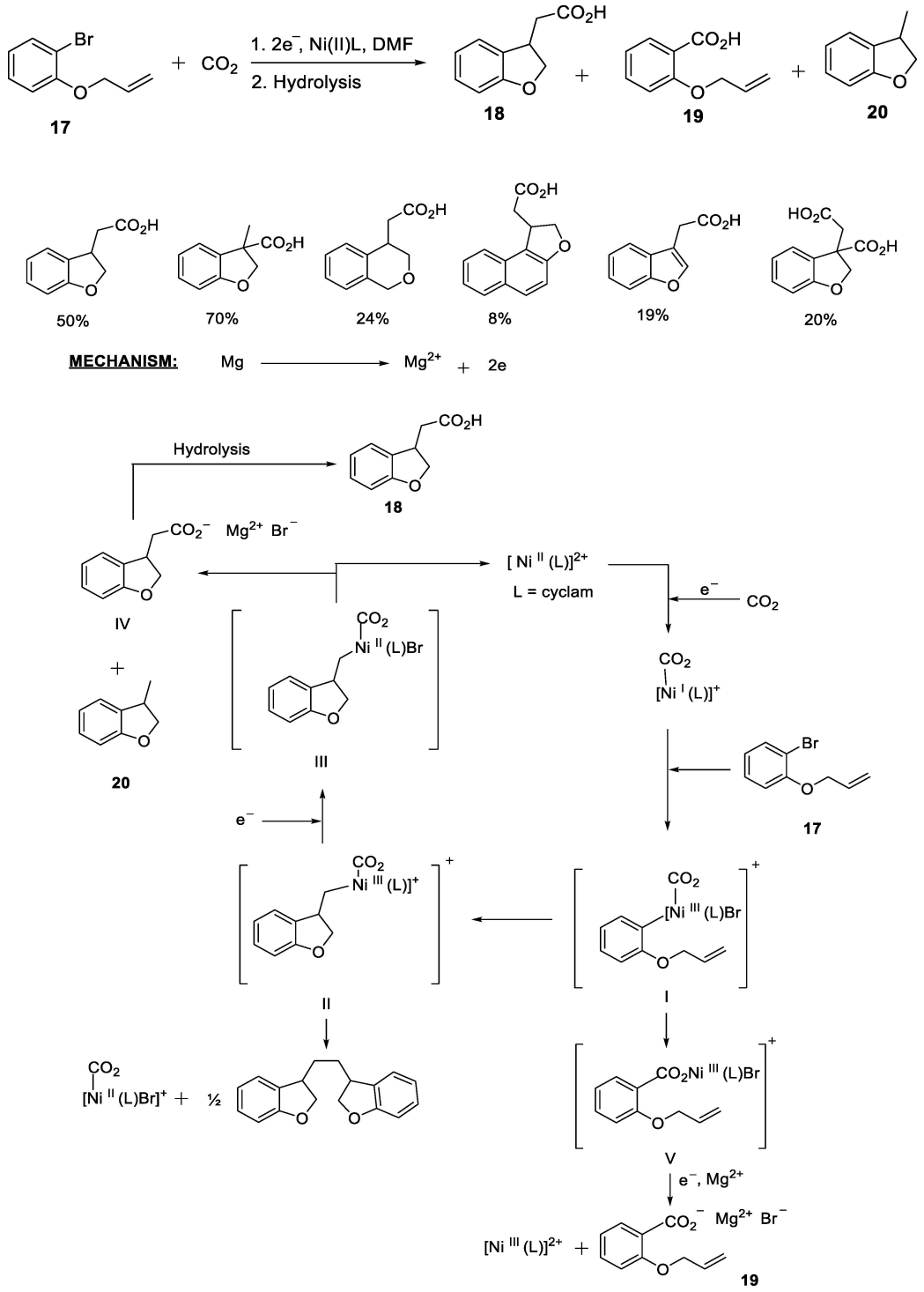
The synthesis of indoline **25**, from the reductive carboxylationę cyclisation of N-alkenyl-bromide **24** via CO_2, is another characteristic feature of electrochemistry in the tandem reactions. By using a two compartment cell, the reaction was carried out with a catalyst of 5 mol% $PdCl_2(PPh_3)_2$, using a solvent mixture containing tetraethylammonium p-toluenesulfonate (Et_4NOTs) and DMF, providing the indoline derivative **25** in a yield of 67%[77] (Scheme 9).

3.2. Electro-Carboxylation of Alkynes Using CO_2

Jacques and co-workers described the unusual regioselectivity of terminal alkynes with CO_2 with Ni based catalysts to obtain

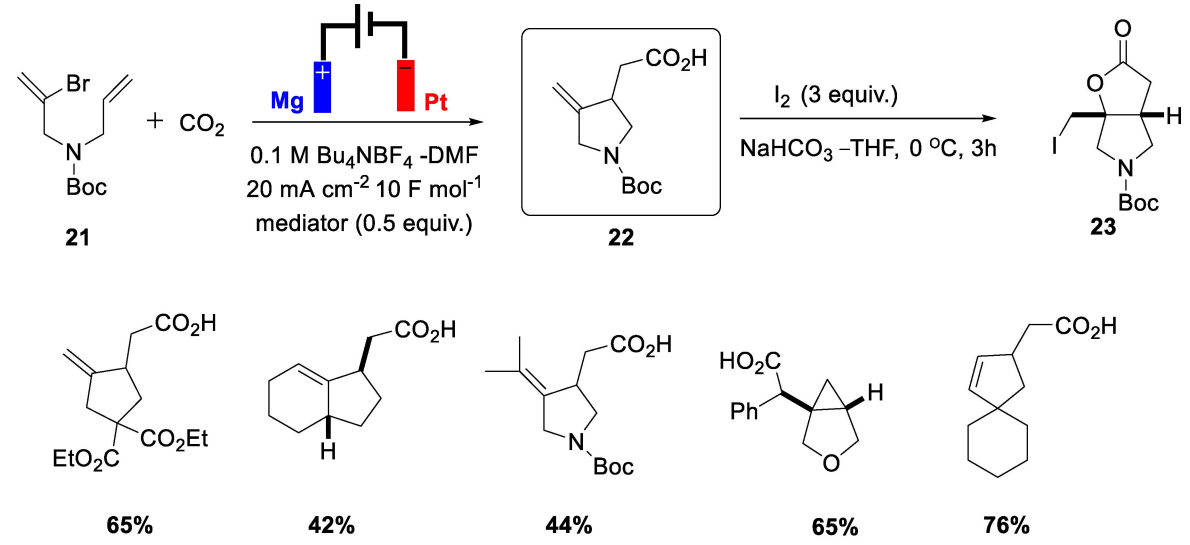


Scheme 6. Sacrificial anode-free electrocarboxylation of allylic bromides using a quasi-divided cell (convergent paired electrolysis).

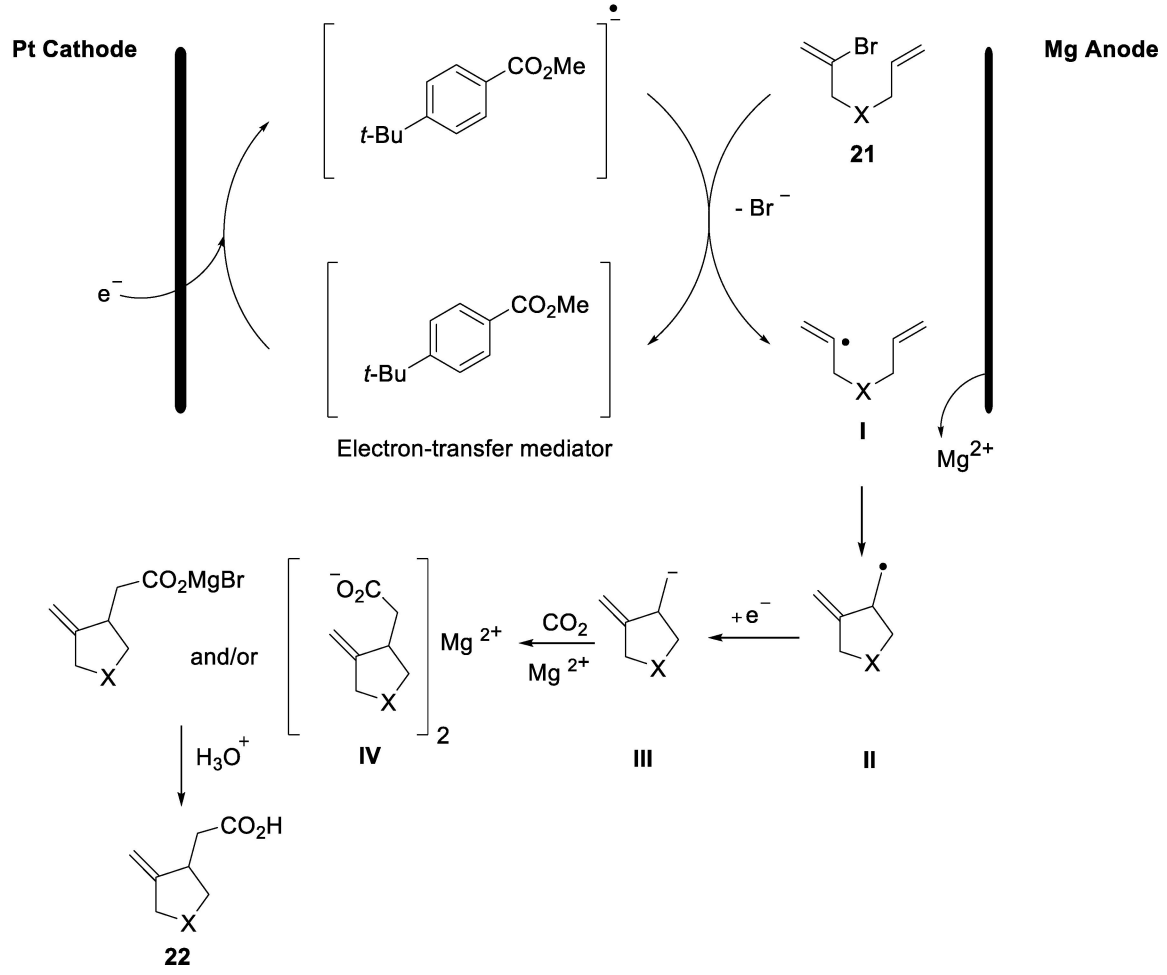


Scheme 7. Ni-mediated electrochemical tandem cyclisation/carboxylation of 2-allyloxybromobenzene to afford 2,3-dihydrobenzofuran-3-ylacetic acid.

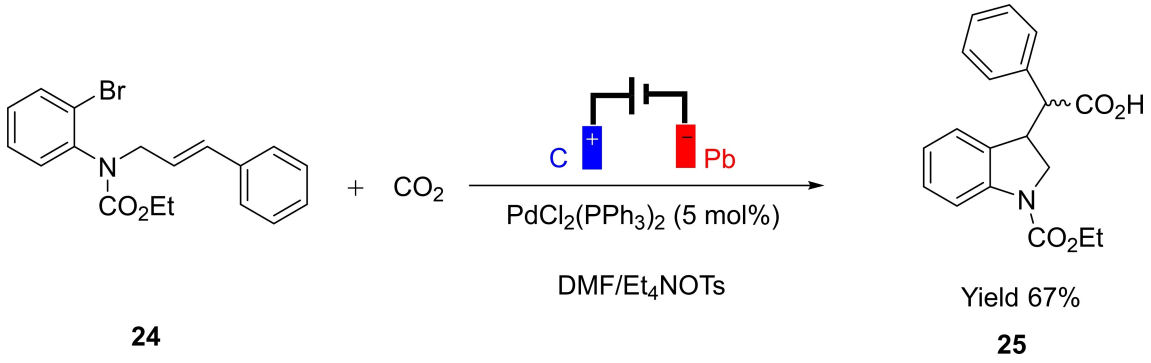
α-substituted acrylic acids **27** via terminal alkynes **26**, with a high selectivity's of 65–90% and in good yields[78] (Scheme 10). By the electrochemical reduction of the stable precursor nickel(II) catalyst i.e., $Ni(bipy)_3(BF_4)_2$ (bipy = bipyridine), the corresponding nickel(0) complex was produced "in situ", which catalysed the reaction. This nickel



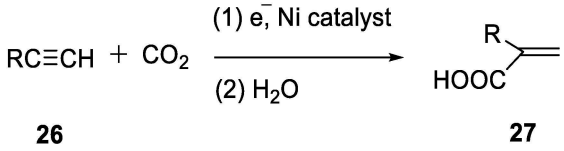
MECHANISM:



Scheme 8. Electrochemical cyclization/carboxylation of CO_2 for the construction of cyclic γ, δ-unsaturated carboxylic acids using a mediator.



Scheme 9. Electrochemical synthesis of indoline from CO_2 and *N*-alkenyl-bromide.



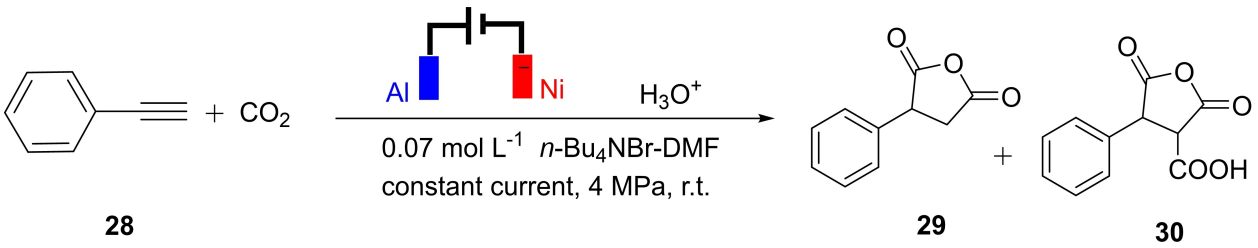
Scheme 10. Electrochemical carboxylation of terminal alkynes catalysed by nickel.

mediated CO_2 fixation proceeds with the generation of a carbon-carbon bond between the alkyne and CO_2, hence no alkyne-oxygen bond is observed in any of the products.[79] In many synthetic applications, electrochemically produced nickel(0) have been already been employed, for example in coupling[80,81] and dimerization reactions.[82] However, for the alkyne reactions, the nickel catalyst has been seldom employed.

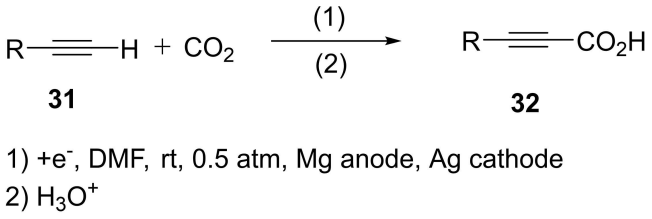
Li *et al.* performed the electro-carboxylation of alkyne **28** with carbon dioxide in the presence of some common metal salt (CuI, $FeCl_3$) as the catalyst. Alkynes were effectively carboxylated with CO_2 in an undivided cell with a Ni cathode and Al sacrificial anode, *n*-Bu_4NBr-DMF as supporting electrolyte, constant current, and at room temperature.[83] The main product, saturated tricarboxylic acids **30**, was formed along with the dicarboxylic acid **29** in good yields (Scheme 11).

Furthermore, electrochemical incorporation of CO_2 into terminal alkynes **31** and diynes on silver cathodes has been found to occur selectively to afford derivatives of monocarboxylic acid **32** in good yield (Scheme 12). The electrolysis was carried out in one-compartment cell fitted with a magnesium anode under mild conditions. At the anode, the oxidation of the magnesium rod into Mg^{2+} ions take place, while at the cathode, the reduction of the organic substrate takes place (Scheme 13). In addition, a side reaction takes place whereby the radical anion oxalate is formed by the direct electroreduction of CO_2 in DMF solvent.[84]

At present, most of the approaches for the production of γ-alkylidene lactones require the use of complex catalysts and a multistep reaction system.[85–89] Under electrochemical conditions, the coupling of 1,4-diarylbuta-1,3-diynes **33** with CO_2 led to the production of γ-alkylidene, as reported by Li *et al.* in 2013.[90] From the tuneable electrochemical reaction of **33**, the major products are γ-alkylidene lactones **34** and γ-keto carboxylic acids **35** (Scheme 14). With the use of 0.1 equivalent of catalyst CuI, the predominant product would be **34**, whereas in the absence of CuI catalyst the formation of **35** was preferable. In this context, at the cathode, compound **33** accepted a single electron and generated the anionic radical (**I**), followed by the formation of monocarboxylated radical **II** with the insertion of CO_2. At the same time CO_2 was reduced into $[CO_2]^{\bullet-}$ and then reacted with **I** to affords **II**. The dicarboxylated anion **III** was produced as radical **II** underwent further carboxylation, and thus provoked the formation of annulated



Scheme 11. Electro-carboxylation of an alkyne in the presence of *n*-Bu_4NBr-DMF as the electrolyte.



Scheme 12. Electrochemical carboxylation of terminal alkynes.

intermediate **IV**, driven by the CuI catalyst. Finally, by the subsequent protonolysis, reduction and acidification of **IV**, the target products (lactones) **34** were produced in excellent yields.

Then in 2010, upon starting from terminal aryl alkynes **36**, Li *et al.* reported the production of 2,5-dioxo-4-aryl-tetrahydro-furan-3-carboxylic acids **38** as the major product and 3-aryl-dihydro-furan-2,5-diones **37** as the minor product, with minimal adaptation in the electrochemical setup.[91] For the purposes of optimisation, the exploitation of CuI in 0.07 M solution of Bu_4NBr-DMF was considered best for the success of this reaction, producing excellent yields of the product (70–98%), the mechanism of which is shown in (Scheme 15).

3.3. Electro-Carboxylation Reactions of Ketones and Aldehydes with CO_2

Conventionally, the carboxylation of aldehydes requires a powerful base, and experiences low selectivity and productivity. However, it would be attained instantly when electrochemical reduced CO_2 attacks the carbon atom of the carbonyl group.

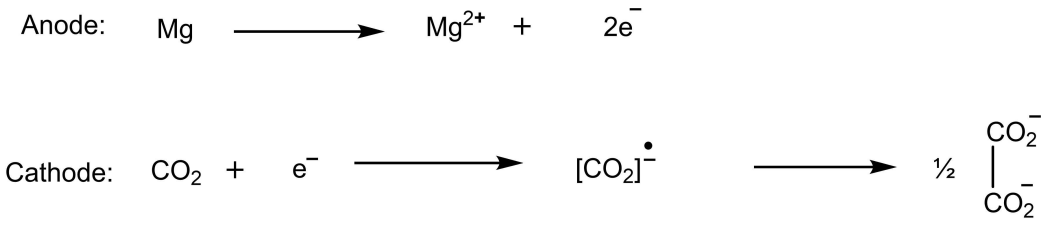
A novel electrochemical method for the electro-catalytic carboxylation of aromatic ketones to α-hydroxy-carboxylic acid methyl esters **39** using CO_2 with an ionic liquid i. e., 1-butyl-3-methylimidazolium tetrafluoborate ($BMIMBF_4$) was reported for the first time by Feng and co-workers in 2011.[92] Under mild reaction conditions in an undivided cell with Pt and Mg plates as working and counter electrodes, respectively, the electrolysis process proceeded without any supporting electrolytes, toxic catalysts and solvents, with the addition of an alkylating agent to deliver out the product α-hydroxycarboxylic acid methyl ester (62% yield). Other cathode materials were also tested including Fe, Cu and stainless steel; the highest reductive ability of acetophenone was, however, exhibited by Pt (Scheme 16). Furthermore, the ionic liquids that were used during this reaction were recycled successfully, hence contributing to a circular economy.

The first electro-carboxylation of ketones was reported by Wawzonek and Gundersen, wherein acetophenone was converted into benzophenone 2-hydroxy-2-phenylpropionic acid and benzylic acid.[93] This methodology, therefore, offers an electrochemical pathway to many commercially important α-aryl propionic acids, typically used in nonsteroidal anti-inflammatory drugs (NSAIDs).[94] Hence, electro-carboxylation of aromatic ketones via sacrificial anodes has been investigated extensively.

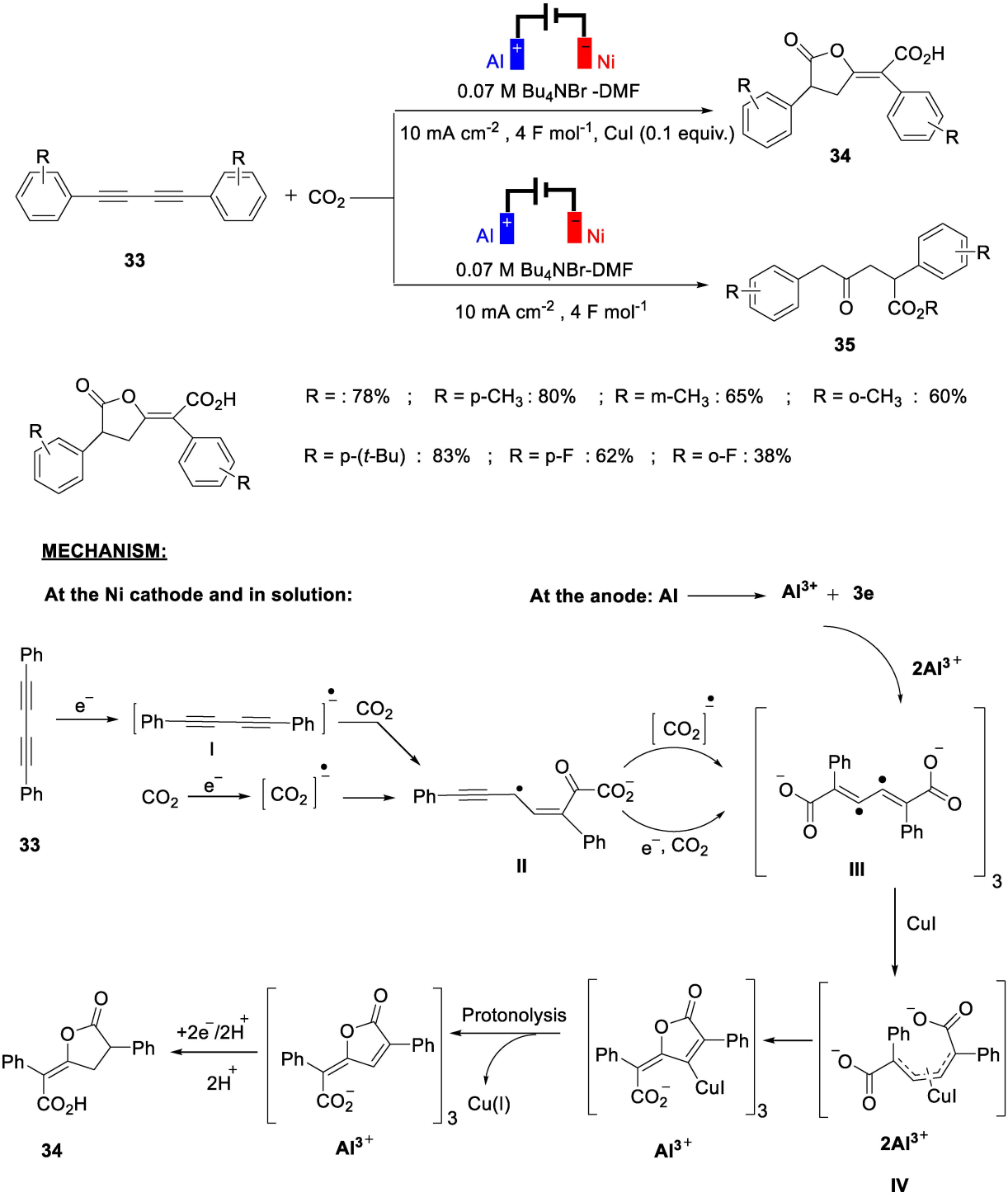
By electrosynthesis, aromatic ketones **42** have been effectively electro-carboxylated with CO_2 (4 MPa) in an undivided cell with Al as anode, Ni as cathode, *n*-Bu_4NBr-DMF as electrolyte under constant current at room temperature. The corresponding α-hydrocarboxylic acids **43** were afforded with excellent yields of 56–90% (Scheme 17).[95]

Moreover, electro-carboxylation of aromatic ketones by stable electrodes has also been performed (Scheme 18).[96] Here, *p*-isobutyl acetophenone underwent carboxylation to produce hydroxyl ibuprofen, which is immediately hydrogenolised to yield ibuprofen. Nafion is used as a membrane which permits a selective pathway for tetraalkylammonium (TAA) cations (and protons) to pass from anolyte to catholyte. To scavenge the anodically formed bromine, cyclohexene is added to the anolyte. With a graphite anode and copper cathode a current efficiency up to 90% was reached. For the synthesis of other NSAIDs, such as cicloprofen, carprofen, fenoprofen, isoprofen, naproxen and flurbiprofen, this method was deemed suitable.

There is also evidence for the electrochemical carboxylation of aliphatic aldehydes such as 3-methylmercapto-propionaldehyde (MMP) producing 2-hydroxy-4-methylmercaptobutyric acid (MHA) via both stable anode[97,98] as well as sacrificial anode[99] (Scheme 19). This set-up uses stable electrodes and can be extended to amines, ketones and aldehydes. MHA is prepared through a conventional method by using cyanides; the proposed preparatory system for which consists of a Pt coated permeable anode and boron-doped

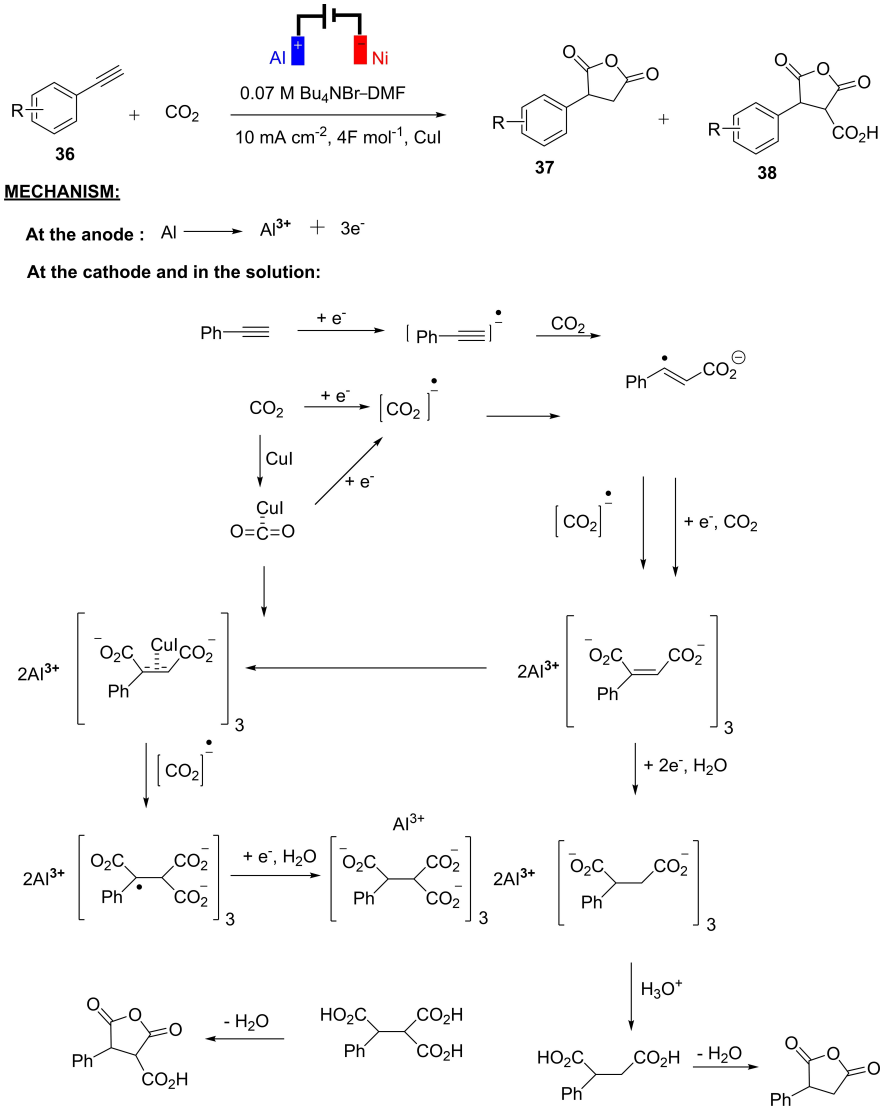


Scheme 13. Oxalate formation as a cathodic side reaction.



Scheme 14. Electrochemical synthesis of γ-alkylidene lactones from 1,4-diarylbuta-1,3-diynes and CO_2.

diamond coated permeable cathode resting directly on a cation exchange membrane (CEM), in order to decrease the ohmic resistance via the CEM, and hence minimise the necessary voltage. The end carboxylic acid products are produced by protons formed from molecular hydrogen in the anolyte, which then progressively enter the catholyte; both anolyte and

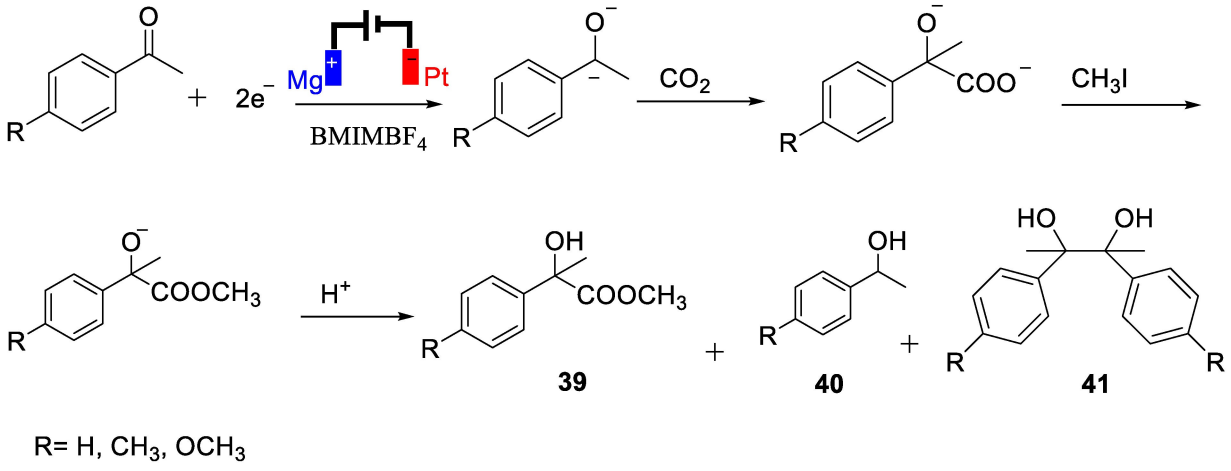


Scheme 15. Concurrent synthesis of 3-aryl-dihydro-furon-2,5-diones and 2,5-dioxo-4-aryl-tetrahydro-furan-3-carboxylic acids from the electrochemical carboxylation of CO_2 and terminal aryl alkynes.

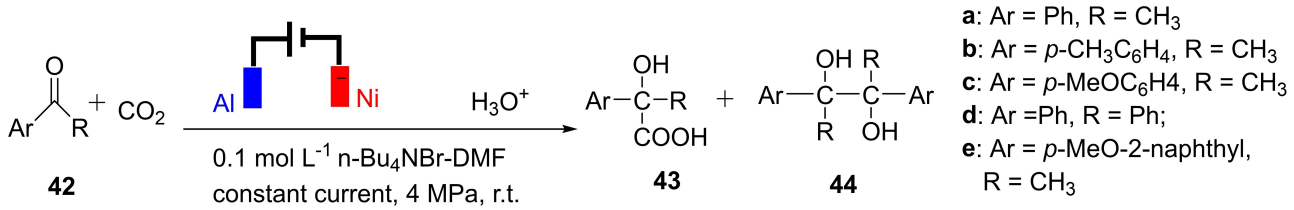
catholyte are based upon DMF.[99] Importance of MHA stems from its use as an industrial scale feed additive, unfortunately however, current efficiencies and yields do not exceed more than 30%.

3.4. Electro-Carboxylation of Organic Halides

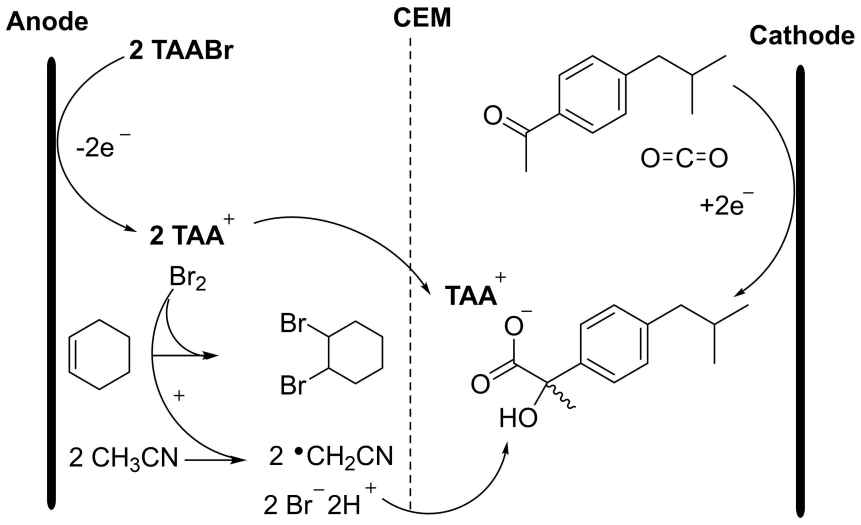
Turning to the electro-carboxylation of organic halides, several reports have already been published.[100–111] With the exception of cyclic products, there are many examples of precursors to NSAIDS via the electrochemical conversion of CO_2 into carboxylic acids.[112] A variety of α, β-unsaturated carboxylic acids have been delivered by the electrochemical reaction of different vinyl bromides with CO_2, with corresponding NSAIDs obtained in high enantioselectivity after hydrogenation.[112] Current developments on the electrochemical fixation of CO_2 regarding NSAIDs mainly emphasis on trials of novel electrode materials, reaction conditions, starting reactants, and use of ionic liquids which may act as substitutes for the supporting electrolytes or reaction media, for applications in pharmaceutical chemistry. As an illustration, Tokuda *et al.* reported the electrochemical carboxylation of 2-(1-chloro-ethyl)-6-methoxynaphthalene **45** via supercritical CO_2 ($scCO_2$), using Bu_4NBF_4-CH_3CN as an electrolyte at 40 °C, to afford the racemic mixture of naproxen **46** in a good yield of 74%[112] (Scheme 20).



Scheme 16. Electro-carboxylation of aromatic ketones in the CO_2-saturated ionic liquid, $BMIMBF_4$.

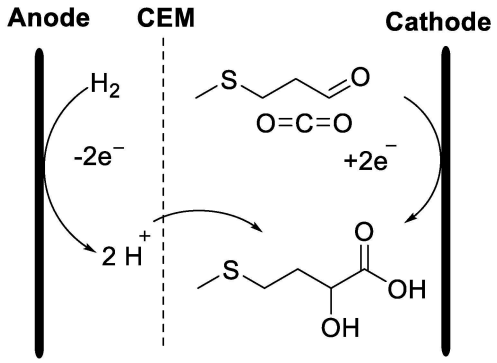


Scheme 17. Synthesis of α-hydroxycarboxylic acids from aromatic ketones and CO_2.



Scheme 18. Electro-carboxylation of *p*-isobutylacetophenone with tetraalkylammonium (TAA) cations.

In organic synthesis, alongside traditional batch electrolysis, electrochemical flow microreactors have emerged as an effective synthetic tool.[5,113] In contrast to batch electrolysis reactions, reactions in electrochemical flow microreactors generally occur in a more sustainable and efficient manner, exhibiting several advantages such as high-speed mixing and precise control of temperature. Moreover, in gas-liquid two-phase reactions, the electrochemical flow microreactor is remarkably advantageous, for, say the electro-carboxylation of CO_2. More attractively, due to the distinctive operation of



Scheme 19. Electrochemical carboxylation of 3-methylmercapto-propionaldehyde (MMP) to 2-hydroxy-4-methylmercaptobutyric acid (MHA).

continuous laminar flow in microreactors, unstable species can more easily be controlled than when produced in the traditional batch reactor. Hence, unstable and demanding species may be readily achieved in highly selective reactions.[114]

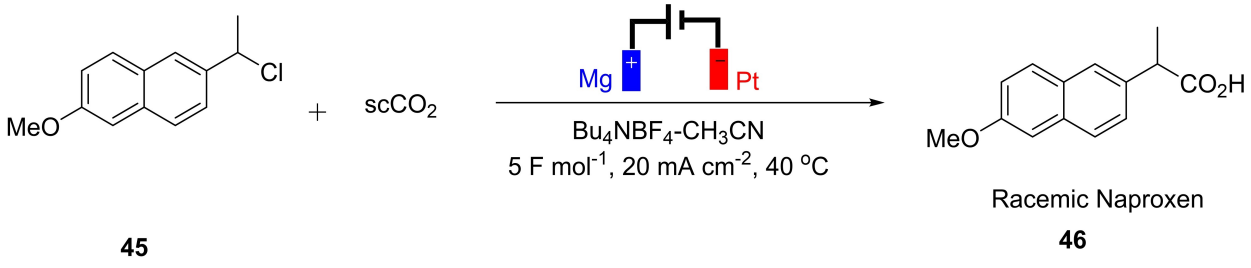
For the investigation of the electrochemical carboxylation of benzylic halides, new microreactors have been prepared and comprise of different cathode metals and distances between electrodes. Then at constant current, screening of the electrolysis of benzylic halides was carried out in a flow microreactor with Pt plates as both electrodes and appropriate distances between them. Using a syringe pump, under optimised reaction conditions, solutions of benzylic halides **47** and saturated carbon dioxide in 0.1 M Bu_4NBF_4-DMF solvent underwent electrolysis in a microreactor to give the carboxylic acids **48** in good to excellent yields[115] (Scheme 21).

Another thought-provoking research topic is asymmetric electro-carboxylation via CO_2.[116–188] The notable point is that, in the production of new chiral centres, both the carbon and oxygen atoms of CO_2 might be involved. Most reported reactions are symmetric in nature and provide racemic mixtures, specifically in the case of C–CO_2 bond formations.[119–121] If the synthesis based upon CO_2 is substituted to well-known industrial methods, such as for the production of fine chemicals and pharmaceuticals, the significant point would be that catalytic CO_2 absorption can impart enantioselectivity. Pioneer studies have been carried out by the Feroci and co-workers on the diastereoselective electro-carboxylation of chiral α-bromocarboxylic acid derivatives (Scheme 22).[122,123]

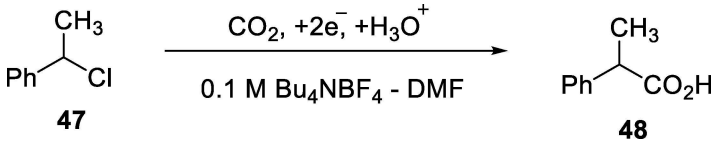
Excellent diastereoselective (98 : 2) and good yield (80 %) was achieved for the carboxylated product **50** using Oppolzer's camphorsultam, and an undivided cell with Et_4NBF_4 as an electrolyte at −20 °C.[123]

In contrast, when conducting the reaction in a divided cell, only moderate yields were produced.[124,125] By employing Mg anodes and sacrificial anodes, the reaction efficiency increased dramatically. Pt and Ag cathode materials are more desirable because they give the maximum carboxylation selectivity. A more selective CO_2 fixation and better current efficiency might be achieved using redox mediators which permits the reaction at a less negative cathodic potential.[126] Most commonly used redox mediators are palladium,[127] cobalt complexes,[128–132] and nickel.[133–135]

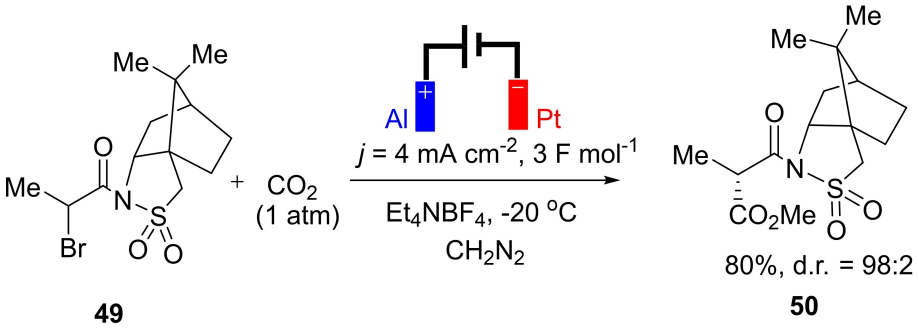
Benzylic chlorides **51** underwent CO_2 fixation which in turn produced 2-arylpropionic acids **52** for usage in the pharmaceutical industry, generally as NSAIDs (Scheme 23). For electro-carboxylation reactions, ionic liquids are used as solvents, thereby enhancing the efficiency of the reaction as well as safety, and have described in some other articles.[136,137]



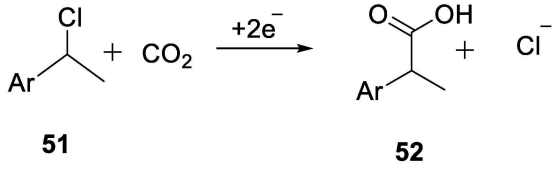
Scheme 20. Electrochemical production of racemic naproxen from CO_2.



Scheme 21. Electrochemical carboxylation of 1-phenyl ethyl chloride.



Scheme 22. Diastereoselective electro-carboxylation with an Oppolzer's camphorsultam auxiliary.



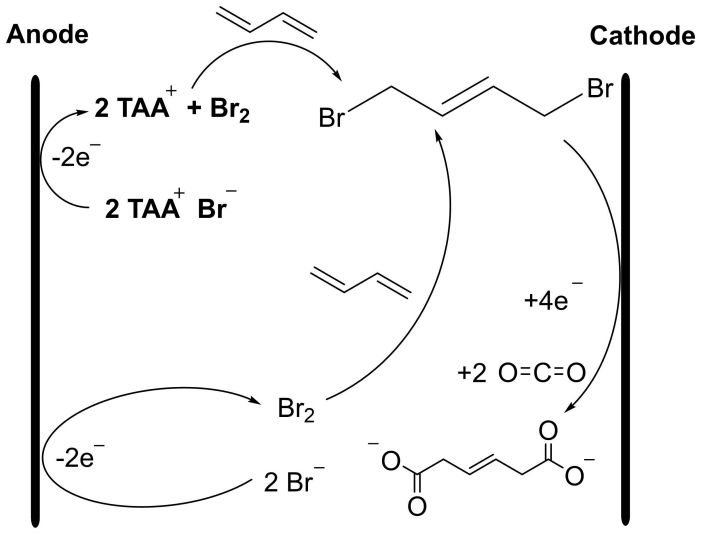
Scheme 23. Electro-carboxylation of benzylic chlorides as a synthetic route for NSAIDs.

In many trial applications, the industrial potential for this reaction has been evaluated, such as the use of a sacrificial anode setup. A constant and narrow interelectrode gap was able to be adjusted in the vessel space and over time in a 400 L reactor, so during the consumption of anodic material the ohmic drop is avoided. Between the electrodes, a polyethylene grid is placed, which permits the anode to press down at the cathode due to its own weight. Unfortunately, because of the presence of impurities produced by solvent degradation, industrial production was not acquired because of complications in purifying the product.[138] For the production of NSAIDs, another experiment was conducted in an undivided cell using graphite as the anode. The oxidation of lithium oxalate occurs at the anode, giving rise to 2-pheylproionic acid in up to 85% yield. When the same group examined a system with, a metal powder at the anode, i.e., zinc is oxidised, corresponding to similar results.[139]

The electro-carboxylation of organic halides is an appealing method to recycle waste products like carbon tetrachloride (CCl_4), a noxious liquid, which is one of the chemicals responsible for ozone depletion, and so synthesis of halogenated reagents is harmful. Besides, when using an undivided cell with acetonitrile as solvent, tri and dichloroacetic acid were produced, with current efficiencies between 50 and 60%. However, accurate anodic reactions were not really identified. Chloride, which originates from the CCl_4 reactant, underwent oxidation resulting in partial chlorination of the acetonitrile solvent, in addition to attacking the cathodically formed carbanions, resulting in the formation of chloroform.[140] Furthermore, for the CO_2 fixation into aliphatic halides, an undivided electrosynthesis system with a stable anode can be used. In the electro-carboxylation of 1-bromo-2-methylpentane, the anodic oxidation of tetraethylammonium oxalate is used, leading to the formation of 3-methylhexanoic acid.[141] Grinberg and co-worker performed another reaction involving a stable anode - the electro-carboxylation of 1,4-dibromo-2-butene, using an undivided cell.[142] The objective here was to form a precursor of adipic acid, which is 3-hexenedioic acid, though very poor current efficiencies and yields were attained. Moreover, in a one-compartment cell, 1,3-butadiene and 1,4-dibromo-2-butene were added and captured anodically generated bromine, producing the product in (Scheme 24). The oligomerisation and debromodimerisation are the main cause for low yields.

Nevertheless, a noteworthy effort has been offered to effectively produce cyanoacetic acid in chloroacetonitrile via CO_2 fixation as an alternative to hazardous synthesis by alkali metal cyanides.[143–145] In agrochemical and pharmaceutical synthesis, derivatives of cyanoacetic acid are used as a reactant.[146] When oxidation of halides occurs at the anode, lower current efficiencies can be assigned to consecutive oxidation and reduction of halides and halonium species, respectively. This effect can be minimised by employing a glass frit or a membrane. In a divided cell using a sacrificial anode, the decarboxylation of chloroacetonitrile produced cyanoacetic acid. This appeared to give higher current efficiencies,[147] however, the release of halides in carboxylating the organic halides are the major drawback in the procedure, inducing a significant number of unwanted side reactions in a non-sacrificial system, leading to an unfavourable atom economy.

Akihiro Nomoto and co-workers reported novel photo-induced reductions using samarium diiodide (SmI_2) that occur upon visible light irradiation since the light is absorbed by samarium diiodide with a wavelength range between 560 and 800 nm.[148] Reductive carboxylation of alkyl halides **53** took place upon visible light irradiation using a mixed system, i.e., SmI_2/Sm with tetrahydrofuran (THF) as the solvent, under

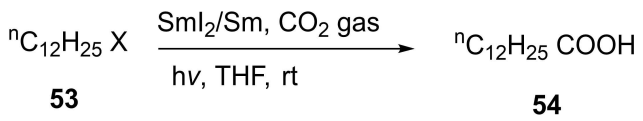


Scheme 24. Electro-carboxylation of 1,4-dibromo-2-butene.

atmospheric CO_2, which in turn produced good to excellent yields of carboxylic acids **54** (Scheme 25). Under various reaction conditions, *n*-dodecyl halide **53** underwent reductive carboxylation with SmI_2 /Sm, and then the reaction mixture, upon irradiation by tungsten or xenon lamp, successfully produced the tridecanoic acid **54** in a good yield of 68%. Visible light is necessary for this carboxylation reaction because the carboxylation reaction did not occur in the dark.

4. Electrochemical Fluorinations

In the agrochemical and pharmaceutical industries fluorinated species are of great interest due to their distinctive effect on the bioactivity of a compound.[149–154] Understanding of the distinctive impacts of fluorine on the reactivity, structure and function of fluorine-containing molecules has been advanced due to past progress in organic synthesis.[155–157] The implantation of fluorine atoms into organic substrates, due to their small atomic radius and high electronegativity, results in significant fluctuations in chemical and physical properties such as lipophilicity, potency, pharmacokinetics, metabolic stability and biological penetrability. Hence, in 1970 there were merely 2% of fluorine-containing medicines on the marketplace, whereas the present figure has increased to



Scheme 25. Reductive carboxylation of alkyl halides in the presence of visible light and SmI_2/Sm under atmospheric CO_2.

approximately 25%. It should be pointed out that pharmaceuticals is not the only area in which fluorine is making an impact, it is also helping to advance the best health care products. The noteworthy point is that three out of five high selling pharmaceutical products now contain fluorine.[158]

Below are a series of the fluorinated derivatives of NSAIDs that were produced in excellent yields from fluorinated reactants via electrochemical carboxylation, under mild reaction conditions, with an electrolytic cell of Mg/Pt (Figure 2).[159]

In many organic reactions, the combination between electrochemistry and the reagents based on hydrogen fluoride (HF) is generally an efficient methodology to oxidatively mount the fluorine moiety into different organic compounds.[160–166] The electrochemical anodic oxidation affords a selective, as well as a tuneable, approach for oxidation and can be easily varied to attain the potential of the mediator or substrate. Natural fluorspar, upon heating in sulfuric acid, corresponds to the formation of HF which is inexpensive and commonly available.[167] Due to the prohibitive and significant safety concerns associated with the anhydrous and aqueous forms of HF,[168] organic sources of HF, such as triethylamine.3HF and pyridinium poly(HF) (Olah's reagents, mixture of 70% HF in pyridine), which are commercially available and highly adaptable fluoride reagents, can be more favourably used in many electrochemical fluorination reactions. These organic HF sources are readily soluble in organic solvents, and so the need for supporting electrolytes is eliminated since these solutions are appropriately conductive due to their ionic nature. As for the fluorination of aromatic rings,[169–172] alkenes,[173–179] alkynes,[180] esters,[181–183] thioketals[184–188] and ketones,[189] the combination of HF and anodic oxidation has

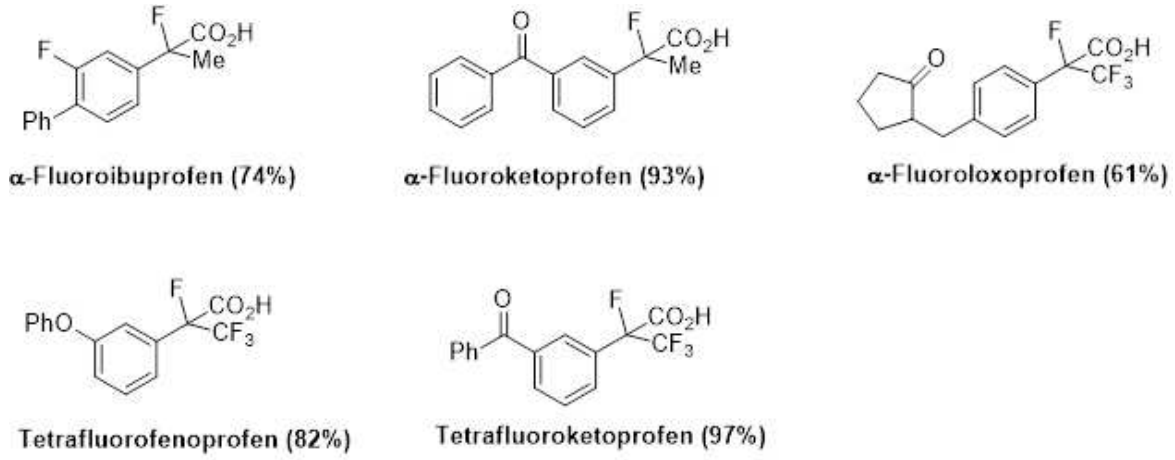


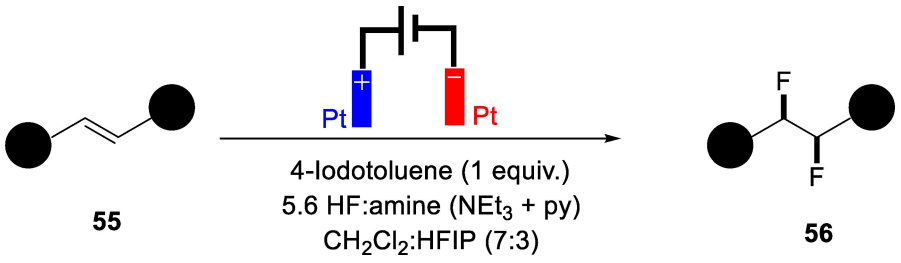
Figure 2. Fluorinated derivatives of NSAIDs from the electrochemical conversion of CO_2.

been successfully employed. However, Lennox et al. reported the electrochemical cells that has been 3D printed and it is a cost effective, facile technique, efficient to handle the harsh reaction conditions integral in the use of HF in organic reactions.[190] Similar work has been reported from Lennox et al. in which alkene **55** undergoes difluorination to form alkane **56** by electrochemical oxidation using a mixture of pyridinium ploy(HF) in CH_2Cl_2 ęhexafluoroisopropanol (HFIP) and $Et_3N.3HF$ with 4-iodotoluene as a mediator[191] (Scheme 26). During this conversion, a divided cell is used for oxidatively sensitive substrates while undivided cell is required for more oxidatively stable substrates. The reaction was established by the commercially available ElectraSyn 2.0 set-up. So, with this variety of corrosive conditions and demonstrated reactor types, the researchers articulate that good conversion of the HF reagents was conducted within the 3D printed electrochemical reactors.

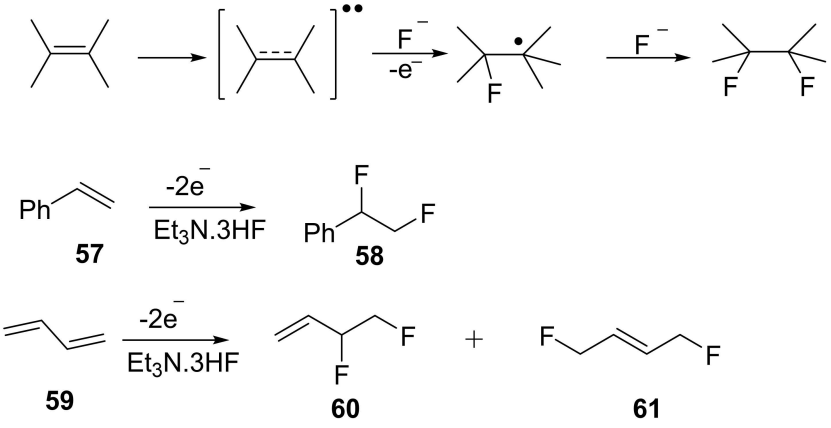
Again, employing $Et_3N.3HF$ as a fluorine source, the styrene **57** underwent electrochemical fluorination in acetonitrile to form *vic*-difluorocompound **58** in good yield. If the fluorination of conjugated diene, butadiene, **59** is used as the substrate, then the formation of 1,2- and 1,4-adducts **60** and **61** in a 1 : 2 mixtures are observed (Scheme 27).

The electrochemical partial fluorination (ECPF) of some electrophilic alkenes (alkenes conjugated with electron withdrawing species) may take place via anodic fluorination, using such precursors as cinnamonitrile, α,β-unsaturated ketones (phenyl 3,5-di-*t*-butyl-4-hydroxystyryl ketone, phenyl styryl ketone and *t*-butyl styryl ketones) and α,β-unsaturated esters (ethyl cinnamates), as reported by Andrés, Dinoiu and co-workers.[192,193] The fluorine sources and supporting electrolytes used in these reactions were $Et_4NF \cdot nHF$ (n = 2,4) and $Et_3N \cdot nHF$ (n = 3,5), respectively, and CH_2CI_2 was used as electrolytic solvent. An attractive fluorination took place once phenyl 3,5-di-*t*-butyl-hydroxystyryl ketones (a chalcone) **62** experienced anodic fluorination using $Et_4NF \cdot 2HF$ as both supporting electrolyte and fluorine source, while CH_2CI_2 was employed as an electrolytic solvent, which lead to the formation of two monofluoro adducts **63** and **64**, each in 30 % yield in a 1 : 1 ratio. (Scheme 28).

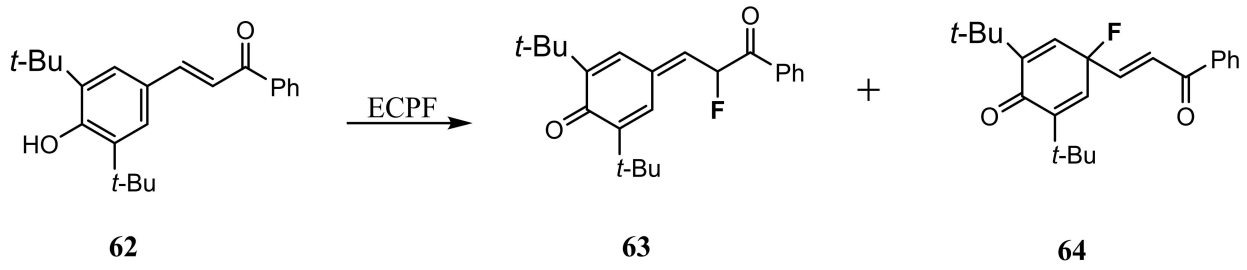
Furthermore, Momota and co-workers, using $Et_4NF \cdot 4HF$ę MeCN formed 1,4-difluorobenzene as the main product of the electrochemical fluorination of benzene.[194,195] Succeeding this,



Scheme 26. Optimised conditions for the electrochemical difluorination of alkenes.



Scheme 27. Electrochemical Fluorination of butadiene.



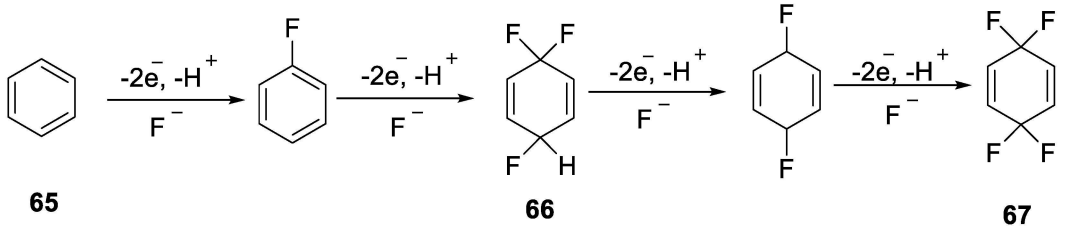
Scheme 28. Synthesis of monofluoro derivatives from the electrochemical fluorination of phenyl 3,5-di-*t*-butyl-4-hydroxystyryl ketone.

fluorobenzene underwent oxidation to produce 3,3,6-trifluorocyclohexadiene compound **66** which afforded the 1,4-difluorobenzene by dehydrofluorination. The end product, 3,3,6,6-tetrafluorocyclohexadiene **67**, is then formed by the consequent anodic fluorination of adduct **66** (Scheme 29).

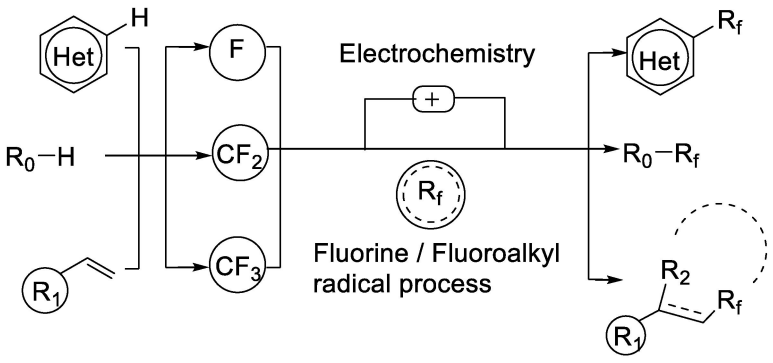
The modulation of metabolic stability via fluorination is another relatively established outcome. On an aromatic ring the substitution of hydrogen by fluorine is a very effective approach and significantly reduces the oxidative metabolic phase by cytochrome P450 monooxygenase of a given drug. By fluorination the hydrolytic metabolism can also be distinctly influenced; the stability of intermediates and reaction rates are significantly influenced by the electron withdrawing property of fluorine. In the design of drugs these common aspects of fluorine offer attractive opportunities.

In addition, one or more fluorine atoms are currently present in about 25% of drug molecules. Hence, to access such fluorinated molecules there is a mounting demand to develop efficient synthetic techniques (Scheme 30).[196]

As of late electrochemistry has been gathering a surplus of attention among researchers in both the industrial and academic worlds, as well as accessing a large diversity and quantity of materials and functionalised molecules.[197–200] Distinguishable from conventional organic reactions, electrochemical conversions employ electrons as reagents in replacement of chemical reductants or oxidants, which considerably



Scheme 29. Electrochemical fluorination of benzene.



Scheme 30. Current advances in electro-fluorination reactions. Reproduced from ref 196.

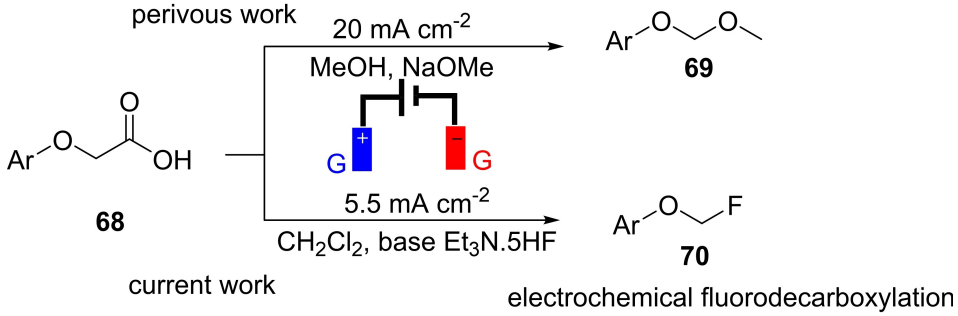
minimise the consumption of fossil fuels and improves atom economies. Such mild conditioned, tuneable and green strategies present a highly selective and efficient methodology to broaden the portfolio of electronically friendly substrates. In previous years many types of reactions promoted by electrons have been developed, such as the Simons fluorination,[201] Shono oxidation,[202] the Monsanto adiponitrile method,[203] and Kolbe reaction.[204] These reactions have been merged with photo redox chemistry,[205,206] flow technology[207,208] and transition metal catalysis,[209,210] and the electrochemical research has been continuously evolving, showing superiority over conventional methods for activation of inert bonds, e.g. C–H bond functionalisations.[6]

The reproducibility of electrochemistry, coupled with significant control all over the reaction conditions, opens a novel platform for organofluorine approaches. The steady conversion of intermediates into the fluorinated products can be ensured by paired electrolysis, and under electrochemical conditions it permits several oxidation and reduction processes to occur simultaneously. In this way the chemoselectivity, as well as the tolerance for functional groups, greatly expands.

In pharmaceutical and agrochemical applications,[211] the fluoromethyl aryl ether has shown interesting properties and an emerging importance.[212] An advanced commonly used method in molecular editing of drugs is the substitution of a hydrogen atom with fluorine as a bioisostere, as for example in the case of methyl groups. The potency rate and metabolic constancy of drugs can be improved by the incorporation of fluorine.[213]

Moreover, in comparison to non-fluorinated analogues, the fluoromethyl aryl ethers display an outstanding shift in scent and volatility, which makes it a possible candidate for fragrances and pheromones.[214] Hence, fluorine selectivity installed into molecules are of great interest in a wide range of applications. For the formation of fluoromethyl aryl ethers, the first synthetic approach involves the electrophilic monofluoromethylation of phenol compounds using FCH_2CI with chloride as the leaving group under basic conditions.[215]

Recently, the aryl methoxymethyl ethers were synthesised by electrochemical decarboxylation of phenoxyacetic acids, as reported by Michael Berger and co-workers (Scheme 31).[216] Aryloxyacetic acid **68** underwent electrochemical decarboxylation followed by fluorination to form fluoromethyl aryl ethers **70**. Using an electric current as the oxidant, this simple electrochemical fluorodecarboxylation provides a green path-



Scheme 31. Conventional vs. electrochemical fluorodecarboxylation of aryloxyacetic acid.

way to several fluoromethoxyarenes derivatives with $Et_3N.5HF$ as a fluoride source and yields of up to 72%.

For the introduction of the CF_3 group into organic substrates, significant synthetic interest has been devoted to develop effective methods. For the production of C_{sp3}–CF_3 bonds a variety of methods are available which is in contrast to the mere few that exist for C_{vinyl}–CF_3 bonds.[217–220]

When it comes to the trifluoromethylation approaches many CF_3 sources are available, for example, the Umemoto reagent,[221,222] trifluoromethyl sulfinates (e.g., Langloisę Baren reagent),[223–226] Ruppert-Prakash reagent[227–229] and Togni reagent.[230,231] Amongst them, trifluoromethyl sulfinates have been confirmed as the best candidates for trifluoromethyl donors for the procedure because of their commercial availabilities and stabilities. By vinyl boronic acids, vinyl borates and vinyl carboxylic acids, the C_{vinyl}-CF_3 substituted compounds are produced while showing specific regioselectivity as well as good reactivity.[232–234]

The mechanistic investigations of sodium trifluoromethanesulfinate revealed that it undergoes anodic oxidation which leads to the formation of an intermediate by rapidly eliminating a SO_2 species, resulting in the formation of a CF_3 radical group. Afterward, cinnamic acid interacted with this highly active CF_3 radical and produced a radical moiety which in turns forms the desired C_{vinyl}-CF_3 product after decarboxylation.[235,236] In organic molecules, the integration of trifluoromethyl (CF_3) species can significantly affect the compounds features, imparting them with distinctive attributes such as lipophilicity, electronic properties, metabolic stability and special size (i.e. despite being nineteen times the mass fluorine atoms are roughly the same size as hydrogen atoms).

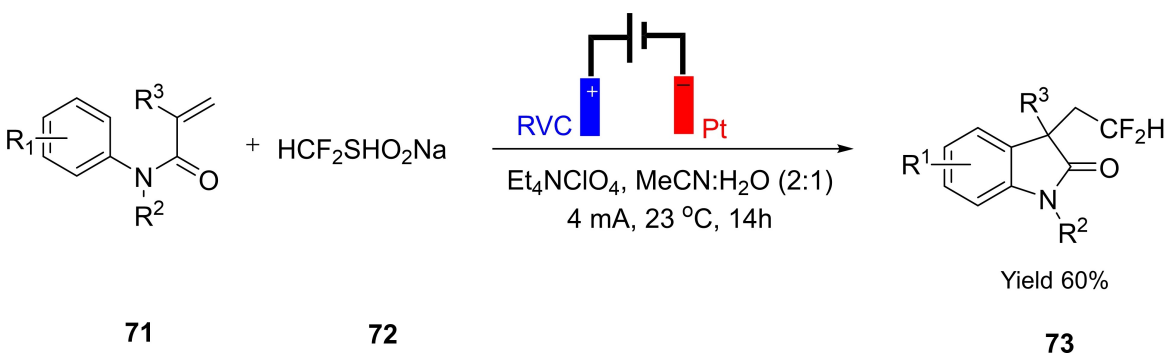
Among several fluorinated groups, the difluoromethyl moiety (–CH_2) is particularly attractive as it is broadly applicable in the design of many drug molecules, such as the ester isomer of alcohols, hydroxamic acid, mercaptan and amides, and because the CF_2 group is used as a bioisostere of carbonyl groups and hydrogen bond donors.[237–240] However, difluoromethylation is underdeveloped because CF_2H sources lack stability, there is no active consumption and difluoromethyl abiogenesis shows potential issues i.e., low reactivity of the difluoromethyl group and difficulty in the generation of radicals. For electrochemical radical difluoromethylation, the use of Langlois type reagent (HCF_2SO_2Na),[241–243] and Baran's difluoromethylsulfonates reagents (DFMS, $ZnSO_2CF_2H$)[244] are considered to be most effective because of their low oxidation potential, high reactivity and electrolytes ionic nature.

In 2019 Ackermann and co-workers performed the electrochemical fluoroalkylationęcyclisation of *N*-substituted acrylamides **71** with $NaSO_2CF_2H$ **72**, affording biologically active dihydroquinolinones or oxindoles **73** in the absence of an oxidant or catalyst, using reticulated vitreous carbon (RVC) and Pt as the electrodes, Et_4NClO_4 as the electrolyte, under 4 mA at 23 °C for 14 h, produced the yield of 60% (Scheme 32).[245]

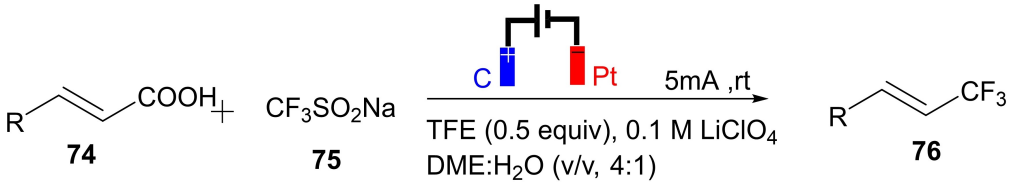
In the life sciences, drug development,[246–252] and novel material synthesis, there is a need to develop sustainable and efficient trifluoromethylation reactions to introduce a CF_3 moiety into organic molecules, since this has a significant research value, i.e., significantly alters the molecular characteristics including bioavailability, stability, lipophilicity etc.[253–256]

Starting from α, β-unsaturated carboxylic acids **74** and sodium trifluoromethanesulfinate (CF_3SO_2Na) **75** Wang *et al.* reported a novel synthesis to produce the vinyl fluoromethyl compounds **76**.[16] Highly stereoselective decarboxylative trifluoromethylation via the electrochemical method was observed with a wide substrate scope under external chemical oxidant-free and metal-free surroundings, to afford the product in good yields using tetrafluoroethylene (TFE) and lithium perchlorate ($LiClO_4$) as fluorinating agent and electrolyte, respectively, in an undivided with 5 mA at rt (Scheme 33).

In industry and academia, the selective introduction of the trifluoromethyl moiety has gained significant attraction. Trifluoromethylation reactions[257–262] might undergo free radical, electrophilic and nucleophilic reactions, and so in recent developments the radical trifluoromthylated reagents,



Scheme 32. Direct electrochemical difluoromethylation of olefines.



Scheme 33. Synthesis of a vinyl fluoromethyl derivative electrochemically by an α,β-unsaturated carboxylic acid.

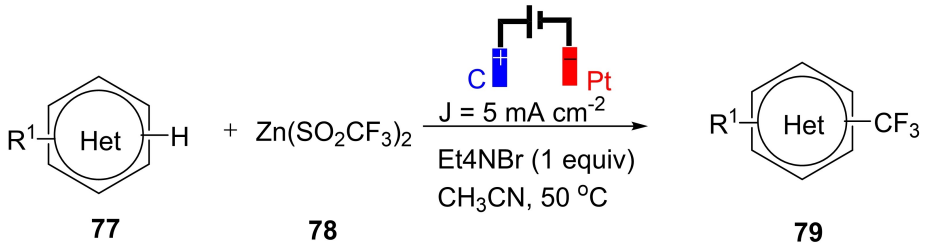
e.g., metallic trifluoromethylsulfonates (CF_3SO_2M), have become a somewhat preferential option due to their stability, practicability, cost and efficiency. The electrochemical trifluoromethylation excludes chemical oxidants ę reductants and precious metal catalysts, and is the extension of redox fluorination. Going into the chemicals, the constant input of electrons enhances the reaction efficiency and reduces energy loss.

In 2019 Dou and co-workers employed an undivided cell system so that corresponding electron deficient heteroarenes **77** would undergo electrochemical trifluoromethylation with zinc trifluoromethanesulfonates, Zn $(SO_2CF_3)_2$, **78**.[263,264] Utilising Et_4NBr as the electrolyte, the corresponding 3-trifluoromethylated derivative **79** based on the Minisci-type reaction was formed (Scheme 34). In this reaction, the bromide in the electrolyte acted as a key medium that initiated the radical addition. Firstly, the anodic oxidation of bromide ion generated the molecular bromine which then, upon reaction with $Zn(SO_2CF_3)_2$, stimulated the production of sulfonyl bromide or sulfonyl hypobromite as a key intermediate. Thus, the CF_3 radical might be released as the active CF_3SO_2Br underwent homolytic cleavage or cathodic reduction, which then participated in the following reaction.

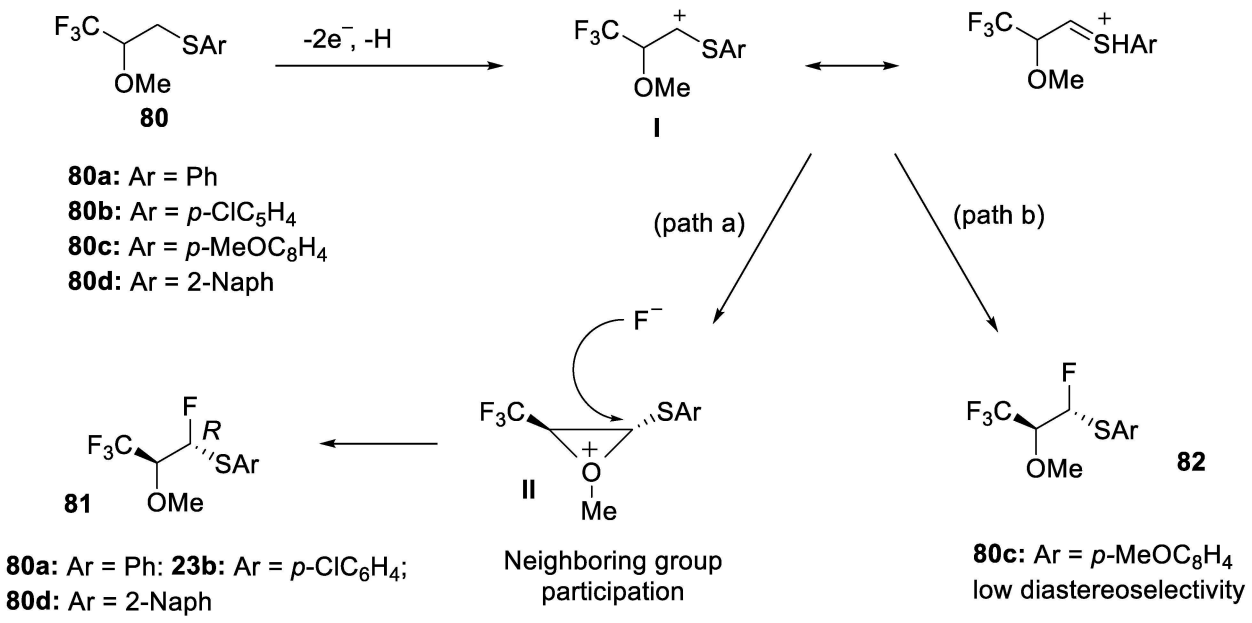
Notwithstanding the aryl species, the diastereoselectivity was always high; even at high temperature it increased 69–74% *de*, except for **80c**.[265] Furthermore, the *de* values were not affected by the HF content in the fluoride salts. The molecular structure of **80** or its intermediates is accountable for the maximum diastereoselectivity, thus by the involvement of an adjacent methoxy group this inherently high distereoselectivity can be explained as shown in (Scheme 35). By a strong electron withdrawing CF_3 species, the α-cationic intermediate **I** is generated at the anode, and is stabilised by the resonance effect of ArS species. To deliver the cyclic cation intermediate **II** with maximum diastereoselectivity, participation of the methoxy group is considered best to stabilise **I** (Path a). The α-cationic intermediate **I** can be destabilised by an electron withdrawing species i.e., *p*-chloro substituent of sulfide **80b**, hence to mediate the maximum diastereoselectivity, the accountability of the neighbouring methoxy group occurs more easily (Path a). On the other hand, if electron donating *p*-methoxy group of sulfides **80c** is attached with α-cation **I**, it is sufficiently stabilised by the *p*-methoxyphenylsulfenyl species and evades the participation of adjacent methoxy group which results in a lower diastereoselectivity (Path b).

In an undivided cell, the monofluorinated product **84** was formed in 81% yield by potentiostatic fluorination of *s*-triazolo-[3,4–*b*]-thiazines **83**, using a solution of Et_4NF-4HF in dimethoxyethane (DME). By the direct anodic fluorination of **84** the difluorinated product **85** was obtained in 84% yield (Scheme 36).[266]

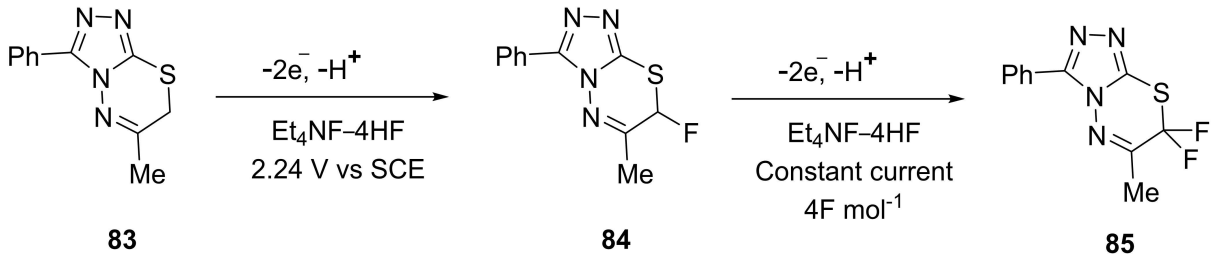
For the electrochemical fluorination of organic compounds, a frequently used electrolytic solvent is acetonitrile (MeCN) due to its wide potential window. However, as a side reaction, anodic passivation or acetamidation often occurs. The effect of DME and MeCN on the electrochemical fluorination of α-(heteroarylthio) acetophenone **86** and alkyl phenyl sulfide have been examined.[267] With the use of DME as the solvent the yield of fluorinated products **87** increased significantly, whereas with the use of MeCN no fluorinated products were delivered out. The cationic part of the fluoride salt can easily be solvated with DME, so the nucleophilicity of the fluoride ions was enhanced. Additionally, as the fluorinated



Scheme 34. Electrochemical Minisci-type trifluoromethylation by anodic oxidation.

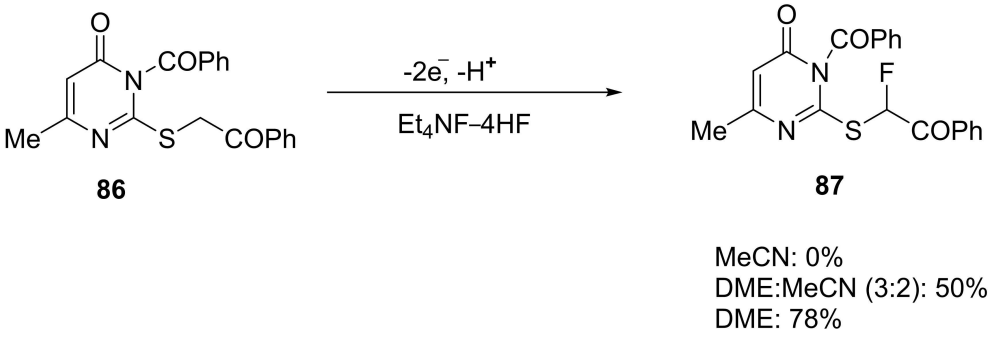


Scheme 35. Reaction mechanism for diastereoselective electrochemical fluorination of sulfides.



Scheme 36. Anodic mono- and difluorination of *s*-triazolo-[3,4-*b*]-thiazines.

product was produced, DME suppressed the overoxidation as well as anodic passivation. Both the current efficiency and the yield of the product may be substantially increased by the addition of DME into the electrolytic solution of MeCN (Scheme 37).[268]



Scheme 37. Solvent effects on anodic fluorination of α-(heteroarylthio) acetophenone.

5. Electrochemical Synthesis of Amides

Amides are commonly present in pharmaceuticals, dyes, agrochemicals and natural products.[269–271] Amide bonds have emerged as an essential component with respect to pharmaceuticals as they act as a backbone in various compounds such as paracetamol, diflufenican and colchicines.[272,273]

2-oxazolidinones, which are a five membered ring of cyclic carbamates, are extensively found in a huge collection of pharmaceuticals.[274,275] Various derivatives of this cyclic framework can be exploited as antibacterial agents, antidepressants, anticoagulants, phospholipase inhibitors and antibiotics (Figure 3). The carboxylative reaction of allyl amines by CO_2 mediated by *tert*-butyl hypoiodite (*t*-BuOI) results in the synthesis of 2-oxazolidinones.[276] By mounting active starting materials or iodinating reagents, successive developments in this reaction have occured.[277]

Conventionally, the reaction of derivatives of carboxylic acids (anhydrides, esters and acyl halides) with amines usually produce the amides.[278,279] The primary reason for the shortage of these methods is the preparation of dangerous reagents, the difficulty in the experimental set-up, release of volatile and corrosive gases, generation of abundant waste and limited stability of various acyl halides. For the synthesis of amides, several novel methods have been developed recently.[280–283]

Dewia and co-workers reported the electrochemical *N*-acylation of methyl ester **88** with amines **89**.[284] The supporting electrolyte and solvent are NH_4I and DMSO repectively, the electrocatalysis proceeded with high regioselectivity as well as chemoselectivity, allowing electrochemical *N*-acylation under ambient reaction conditions to give the corresponding amides **90** (Scheme 38).

In chemical synthesis, formation of amides is an important reaction because of their utility in polymers, pharmaceuticals and natural products, and hence the amide functional group is a basic motif.[285,286] By a new electrochemical method, the direct conversions of methyl ketones to secondary and tertiary amides have been exploited. In situ generated iodine promotes the transformation via electrolysis of sodium iodide under metal-free and mild reaction conditions. The use of stoichiometric iodine could be avoided in the electrochemical method and afford the targeted product in excellent yields.

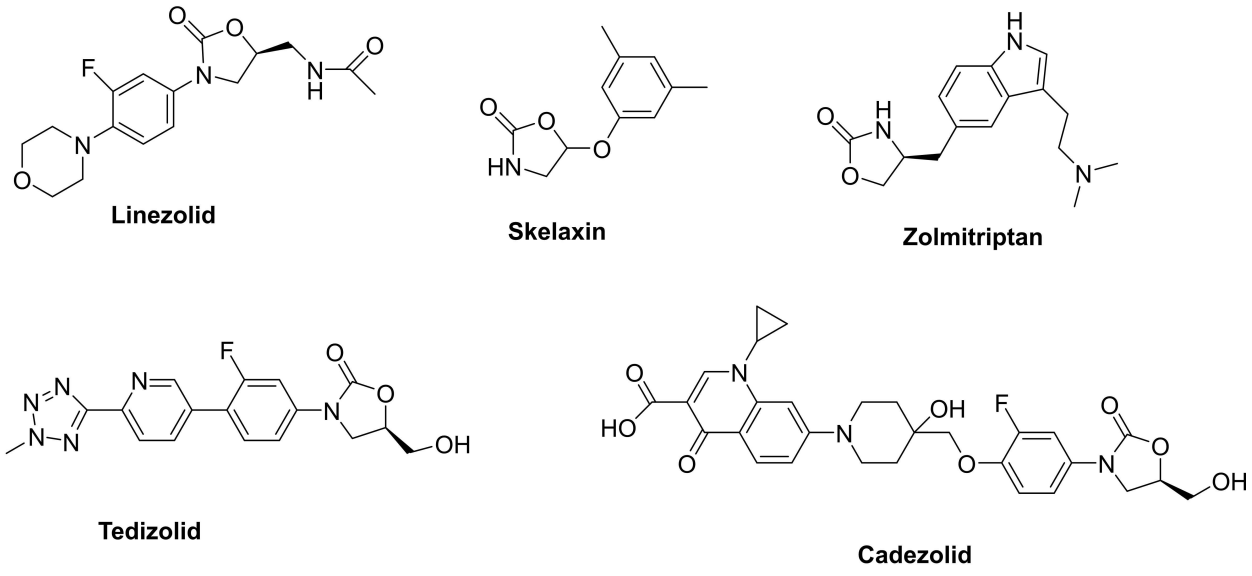
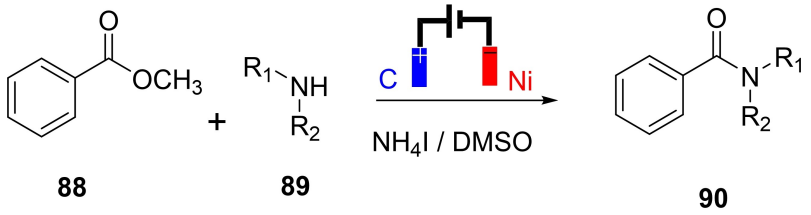


Figure 3. Representative scaffolds of oxazolidinones in pharmaceuticals.



Scheme 38. Strategies for the synthesis of amides from carboxylic esters.

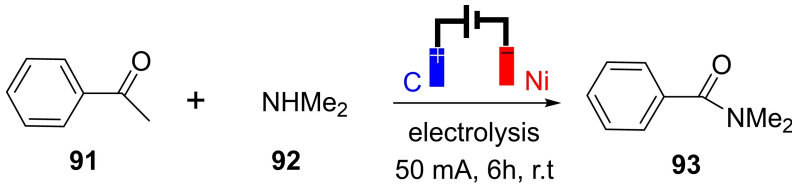
In an undivided cell the condensation of acetophenone **91** occurs by dimethylamine **92** using carbon as an anode, nickel as the cathode, and the supporting electrolyte, NH_4I, results in the formation of amides derivatives **93** (Scheme 39).[287]

At Annamalai University and Emcure Pharmaceutical Limited, the researchers Vaidyanathan and co-workers incorporated *N*,*N*′-Carbonyldiimidazole (CDI) into a developed amidation method that corresponded to the formation of trimethobenzamide **97**, which is used for the treatment of nausea as an antiemetic agent (Scheme 40).[288]

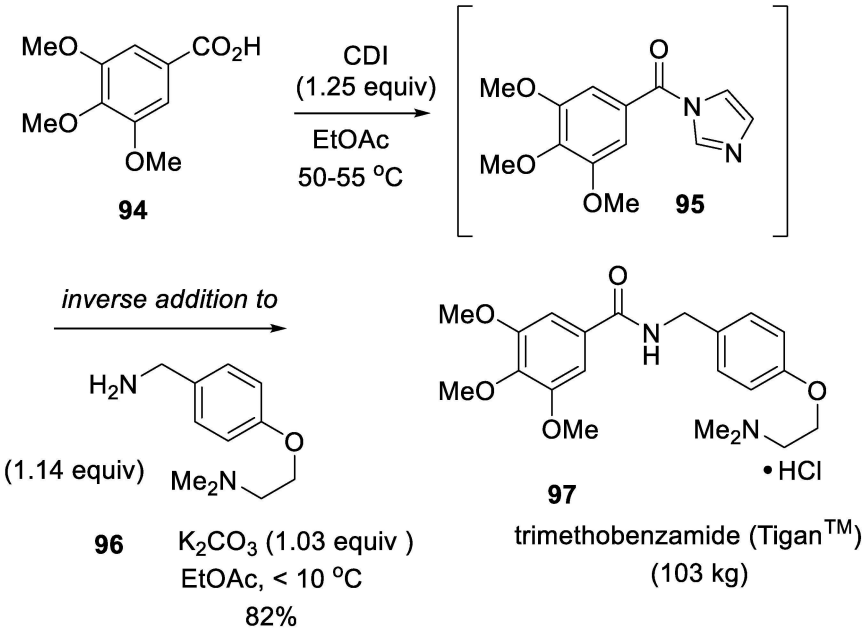
For the functionalisation of oxazolidinones by an alkyl group, triazabicyclodecene (TBD) and $Pd(PPh_3)_4$ were considered with DMSO for photo-induced CO_2 fixation using alkyl bromides and allyl amines **98** to afford oxazolidinone derivatives **99**.[289] Several alkylated oxazolidinones might be delivered out by the photochemical synthesis using a plethora of allyl amines and alkyl bromides. By the photo excitation of LPd(0) the active catalyst LPd(0)* was produced, then a mixture of LPd(l) and the alkyl radical is formed through the single electron transfer (SET) process towards the alkyl bromide. Tertiary radical **II** was produced by the addition of the alkyl radical to the carbamate **I** and the zwitterion **III** was produced with the regeneration of catalyst LPd(0), as the SET reaction among LPd(l) and **II** took place. At the end of reaction, the target product oxazolidinone were produced by the ring closure of **III** (Scheme 41).

A sacrificial anode-free electrocarboxylation facilitated by employing a quasi-divided cell[290] with Pt anodic wire having much smaller surface area than the PT plate and using Bu_4NBF_4 as an electrolyte was conducted (Scheme 42). As a major anodic reaction, the oxidation of DMF solvent occurs due to maximum current density at the anode electrode, thus electrochemical carboxylation of benzylic bromides **100** progressed efficiently. Then, the addition of the carboxylate anion to the oxidatively generated *N*-methyl-*N*-formyliminium ion via nucleophilic reaction delivered out three component CO_2 fixation of product **101**.[291]

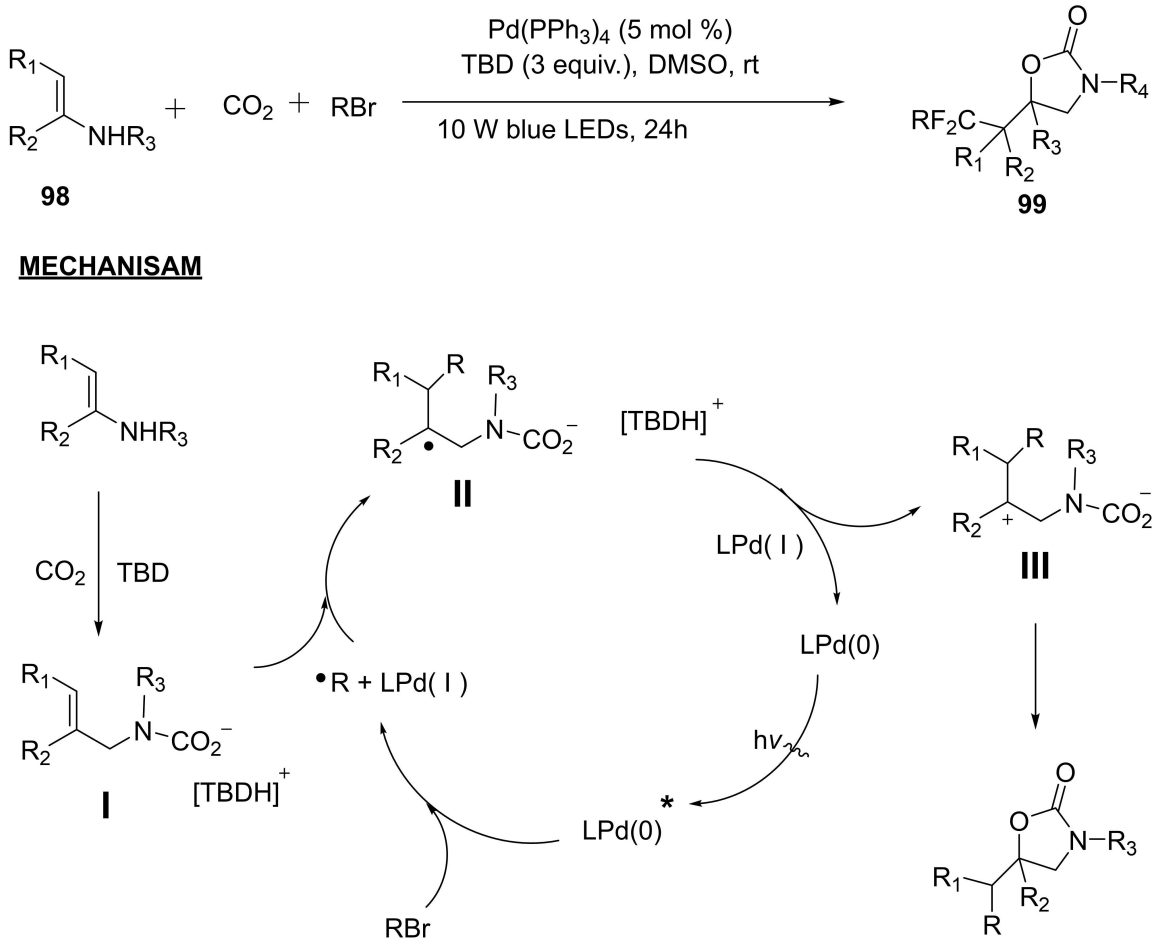
By using convergent paired electrolysis, sacrificial anode-free electrocarboxylation was also carried out independently.[292] A quasi-divided cell was used[290,291] for



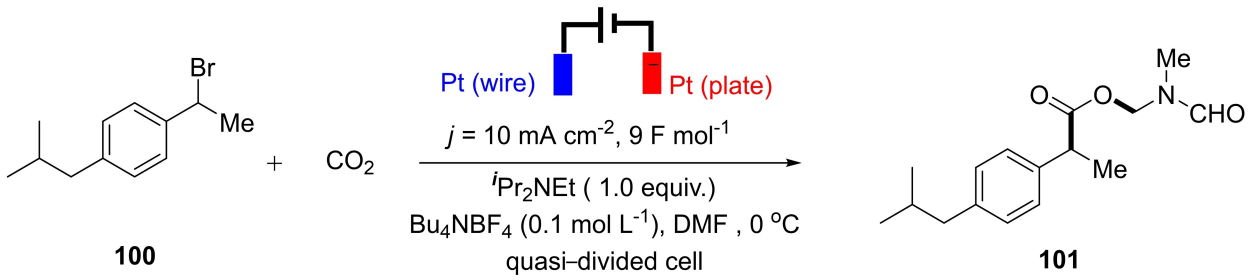
Scheme 39. Transformation of a ketone to an amide with dimethylamine.



Scheme 40. Amide coupling via imidazolide for the synthesis of trimethobenzamide.



Scheme 41. Photo/Pd complex/base mediated oxy-alkylation of allyl amines, alkyl bromides and CO_2 towards alkylated oxazolidinones.



Scheme 42. Sacrificial anode-free carboxylation in quasi divided cell.

electrocarboxylation of benzylic halides, instead of a sacrificial anode in a set-up of undivided cell. In the quasi-divided cell, a high current density was recognised at the anode (counter electrode); the reason being that this cell was equipped with a smaller counter electrode (Pt wire anode) than the working electrode (Pt plate cathode). Hence, substrate, intermediates and any products did not oxidise while the DMF solvent oxidised via anodic reaction. Moreover, benzylic halides **102** underwent electrocarboxylation using a quasi-divided cell, Pt wire as anode and Pt plate as cathode. Carboxylate ions obtained at the cathode would then couple with the N-methyl-N-formyliminium ions produced at the anode by oxidation of the DMF solvent. After screening the reaction conditions, the formation of carboxylated products, i.e.,

phenylacetic acids, was carried out to give *N*-phenylacetoxy-*N*-methylformamides **103** in good yields[293] (Scheme 43).

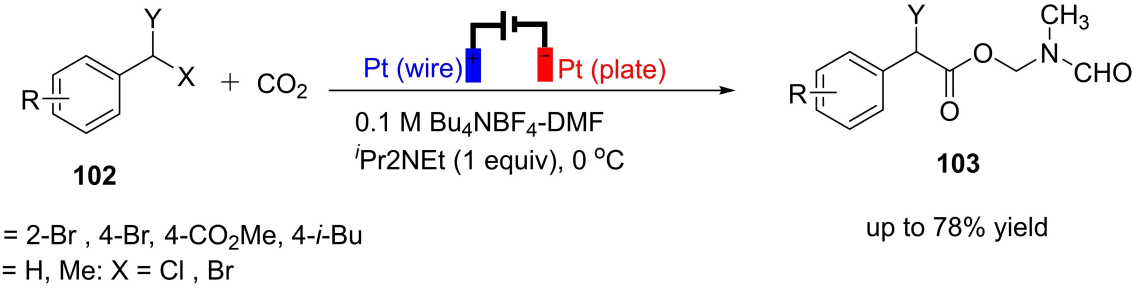
6. Electrochemical Methoxylation Reactions

Methoxy derivatives are key compounds in many organic syntheses; recently significant consideration has been given to electrochemical methoxylation reactions.[294] In the production of different types of chemicals, the ring substituted aromatic aldehydes are central intermediates. There are many methoxy derivative which has found a variety of application as detergents, insect attractants, food flavouring, soaps, perfumes, and in drug synthesis.[295]

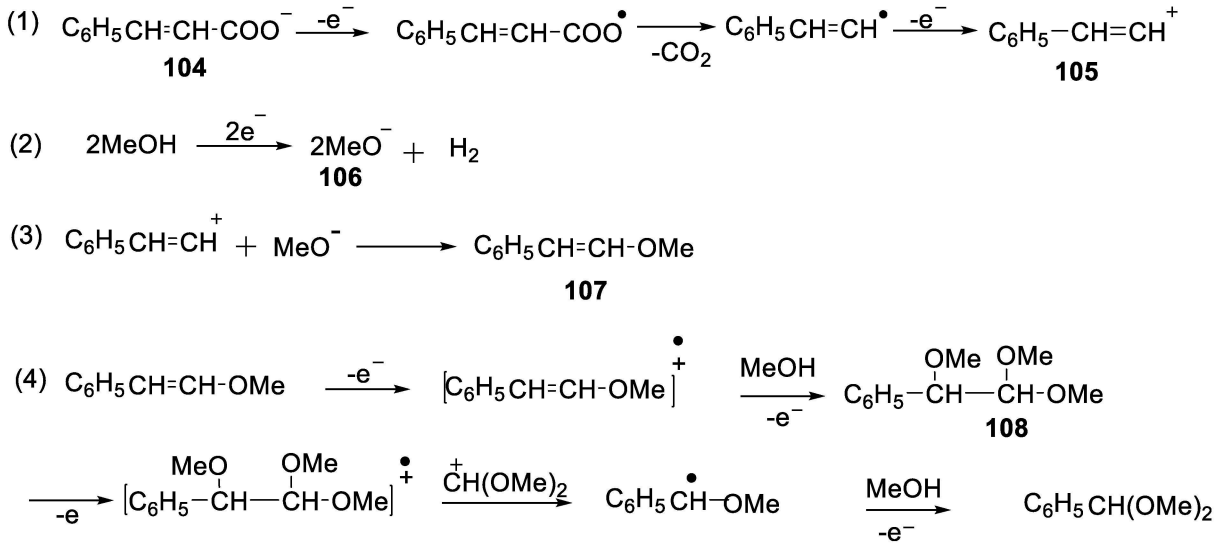
Il′chibaeva and co-workers reported electrochemical methoxylation, attained by decarboxylation of cinnamic acid **104** where two electrons were lost at the anode to give carbocation **105**.[294] After that at the cathode, methoxide ion **106** is produced and combines with **105** in the bulk solution to yield the corresponding methoxy styrene **107**. In the case of unsubstituted styrene, methoxylation take place at the C=C double bond to result in the formation of 1,2,2-trimethoxy-2-phenylethane **108** as the primary product (Scheme 44).

On the other hand the electrochemical methoxylation of 1,4-dimethoxybenzene **109** to produce quinone diketal **110** was performed by L.Weinberg and co-workers.[295] An electrochemically generated methoxy radical reacted with **109** that delivered out quinone diketal. Alternatively, at the anode there is aromatic ring discharge and di-cation and cationic species are produced. At the end of the reaction the main product quinone diketal **110** was produced by reacting with the solvent (Scheme 45).

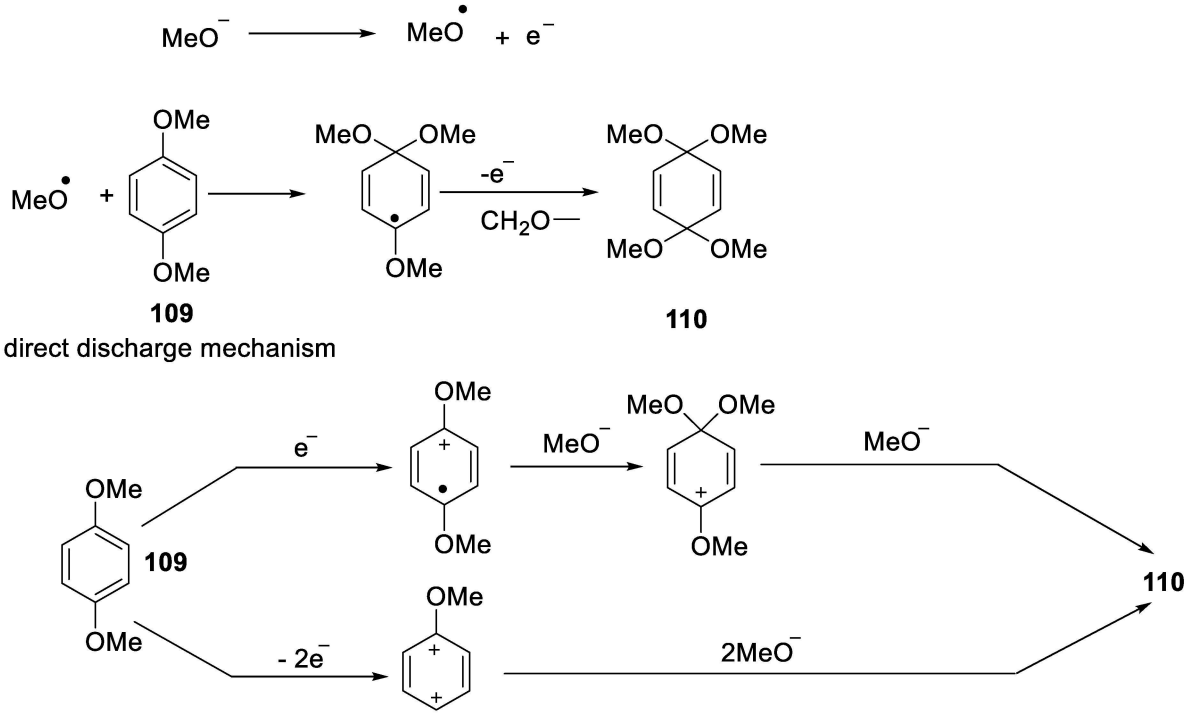
The most synthetically effective electrochemical reactions, such as anodic oxidation of amides, carbamates, lactams and *N*-acylated based amino acids have been shown to be a powerful and unique tool for the synthesis biologically active compounds.[296] Concurrently, the electrolysis of supporting electrolytes in electroorganic synthesis cause waste and separation problems which restrict their synthetic benefits.



Scheme 43. Sacrificial anode-free electrocarboxylation of benzylic halides using a quasi-divided cell.



Scheme 44. Electrochemical methoxylation of cinnamic acid.

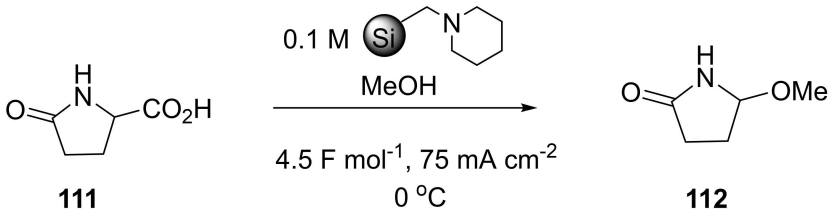


Scheme 45. Mechanism of electrochemical methoxylation of 1,4-dimethoxy benzene.

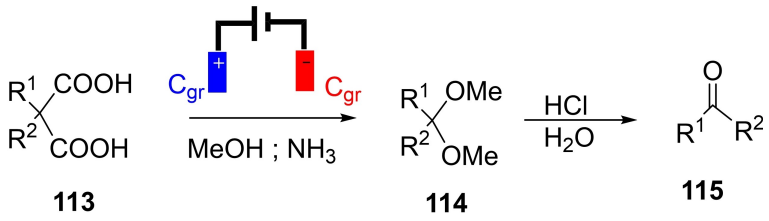
Recently, a new electrolytic system was developed by Tajima *et al.* for anodic acetoxylation[297] and methoxylation[298] using easily reusable and separable solid-supported bases. Therefore, the researchers investigated the non-Kolbe electrolysis of many carboxylic acids, using an electrolytic set-up based on acid-base reactions involving silica gel supported piperidine as the base to obtain the methoxylated species **112**. The non-Kolbe electrolysis *N*-acylated proline **111** was carried out. Here, a new electrolytic set-up was successfully developed by the acid-base reaction using a carboxylic acid substrate and solid supported base, thus in MeOH this reaction reduces the cell voltage. It is expected that, in green chemistry, this method will make a remarkable contribution and in electroorganic synthesis it discloses a novel discussion (Scheme 46).

In organic synthesis, ketones are a most valuable and versatile functional group.[299,300] Ketones and their derivatives are not only found extensively in wide range of man-made compounds, fine chemicals and natural products, but also in many valuable synthetic transformations i.e., aldol reactions. Furthermore, ketones might be further transformed into many other valuable functionalities such as amines, alkenes, amide, esters and alcohols, to quote but a limited number. A new electrochemical method involving oxidative decarboxylation of disubstituted malonic acids **113** transformed them into their corresponding dimethoxy ketals **114**, as reported by Ma and co-workers.[301] Under electrochemical conditions, a wide variety of disubstituted malonic acids **113** leading to the corresponding ketals in the presence of MeOH in NH_3 was achieved in reasonable to excellent yields (Scheme 47).

Correspondingly investigated by the Matsumara group, on the basis of 'memory of chirality' various substituted chiral amino acids **116** underwent anodic oxidative decarboxylation



Scheme 46. Electrochemical decarboxylative C–O bond formation using solid supported bases.



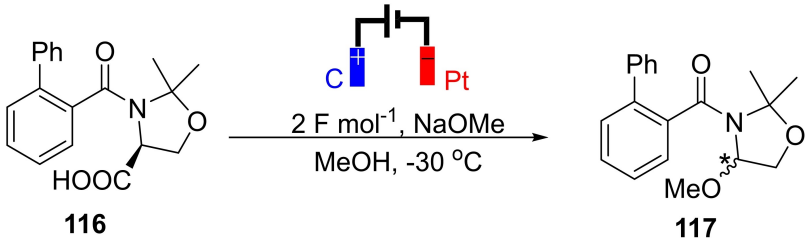
Scheme 47. Decarboxylation of disubstituted malonic acid derivatives.

to yield the methoxylated compounds **117**.[302] The derivatives of these amino acids were analysed to improve the enantiomeric excess, wherein the presence of a graphite anode in methanol the carboxylate anions underwent decarboxylation to provide **117** in 80 % *ee* (Scheme 48).

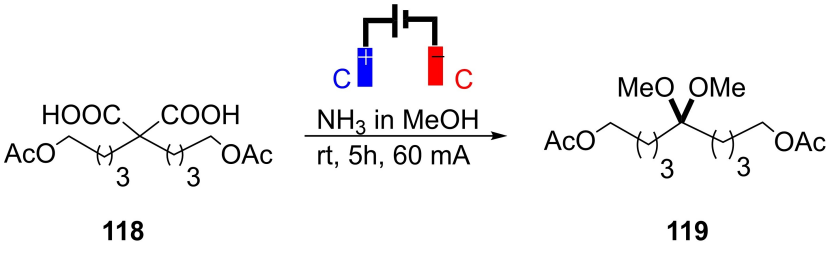
In 2015 Marko *et al.* disclosed a new methodology for the synthesis of symmetrical and unsymmetrical methoxylated compounds **119** via disubstitued malonic acid derivatives **118** through electrochemical decarboxylation. Using NH_3 in MeOH (2.1 equiv) at room temperature with 60 mA of current, the corresponding ketals were formed in a good yield of up to 80 %[303] (Scheme 49).

The electrochamical synthesis of cis-jasmone, a major fragrant element of jasmine flower oil, was proposed by Marko and Lam *et al.* in 2018.[304,305] Synthesis of the target product began with the reaction of cis-hexanol **120** with methanesulfonyl chloride (MsCl), followed by the Finkelstein reaction to afford bromide derivative **121**. The malonic acid **122** was produced over three steps in a good yield of 56 %; firstly, the di-*tert*-butyl malonate alkylation of **121**, followed by the corresponding catalysed addition of sodium tetramethoxyborate, $NaB(OCH_3)_4$,[306] with 3-buten-2-one, and finally classical ester cleavage which led to the formation of **122**. The disubstituted derivative of carboxylic acid **122** was effectively transformed into 1,4-diketone **123** with an excellent yield of 90 %, under the optimised electrochemical conditions. Using 5 % KOH in ethanol the resulting precursor was cyclised to give natural product cis-jasmone **124** in a yield of 83 % (Scheme 50).

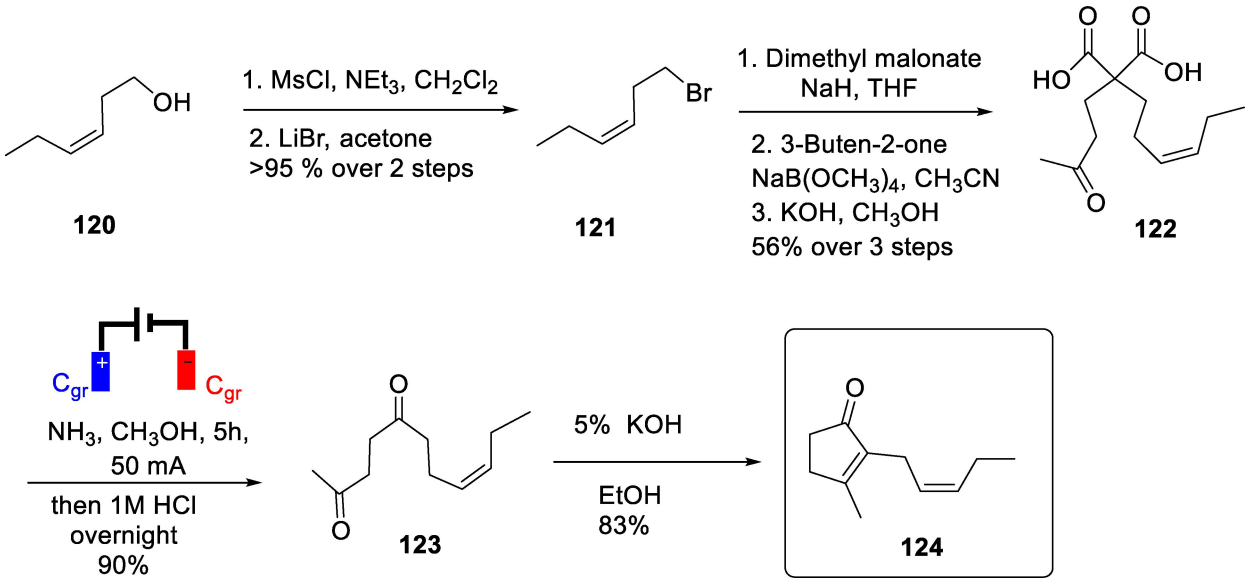
Moreover, as reported by Xiang *et al.*, a reactive carbocation intermediate was generated by an electrochemical oxidative decarboxylation approach which was entrapped using alcohols **126** and derivatives of carboxylic acid **125**, leading to the formation of hindered ethers **127**. In this reaction set-up, at the cathode dichloromethane (CH_2CI_2) was reduced so as to act as an electron sink using tetrabutylammonium hexafluorophosphate ($^nBu_4NPF_6$) as electrolyte with a 3 Å molecular sieve (MS) and 2,4,6 collidine as a base. Concurrently, by adding a better sacrificial oxidant, e. g., silver hexafluorophos-



Scheme 48. Enantiospecific decarboxylative C–O bond formation of amino acids via electrochemistry.



Scheme 49. Electrochemical decarboxylative C–O bond formation of malonic acid derivatives.



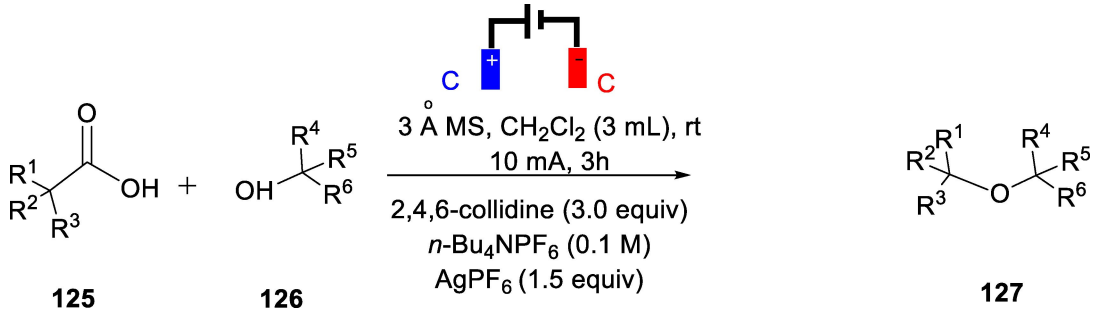
Scheme 50. Synthesis of cis-jasmone by electrochemical decarboxylative C–O bond formation.

phate ($AgPF_6$), significant improvement in the yield of **127** was realised[307] (Scheme 51).

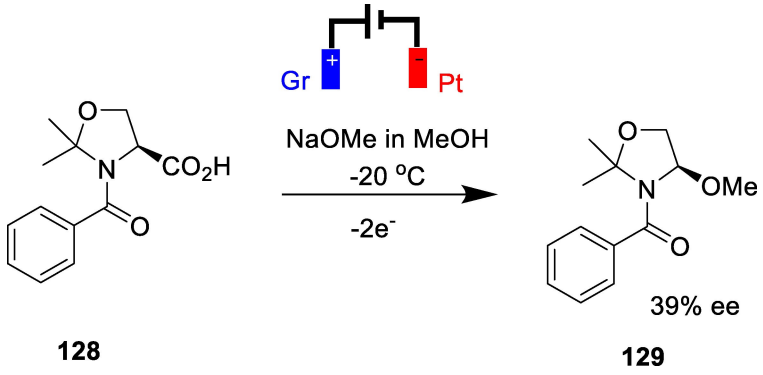
In the pharmaceutical industry, attention towards chiral compounds is increasing significantly as they exhibit numerous biological properties. Alongside, in asymmetric synthesis the perception of "memory of chirality" has been recognised as an effective tool, while flow electrochemistry has initiated its development as a novel enabling technology. In 2000 Matsumura *et al.* reported the first example of cationic memory of chirality with *N*-benzoylated serine derivative **128** using a batch electrochemical oxidation method in methanol to yield the *N*, *O*-acetal **129**[308] (Scheme 52).

A novel yet simple electrochemical microreactor model was employed by Hardwick and co-workers to oxidise the derivatives of L-proline with subsequent decarboxylation taking place in flow a microreactor at room temperature.[309] The reaction is initiated with electrolysis facilitating the decarboxylation reaction to form a radical species. *N*-acyliminium ion is formed by this step, the positive charge of which is localised about the heteroatom. Then, at the neighbouring carbon that underwent decarboxylation, nucleophilic attacks occur at that carbon. The whole scheme is categorised as non-Kolbe reaction due to the assistance of the nitrogen heteroatom. Shono oxidation is defined by the final part of this reaction where the nucleophile attacks the *N*-acyliminium ion. In the flow microreactor the gap among the electrodes is very short (500 μm), and so there is not a requirement for supporting electrolytes since the methanol solvent acts as the charge carrier and nucleophile. At the end of reaction, the electrochemically generated methoxy species acts as a nucleophile that subsequent attacks the *N*-acyliminium ion (Scheme 53)

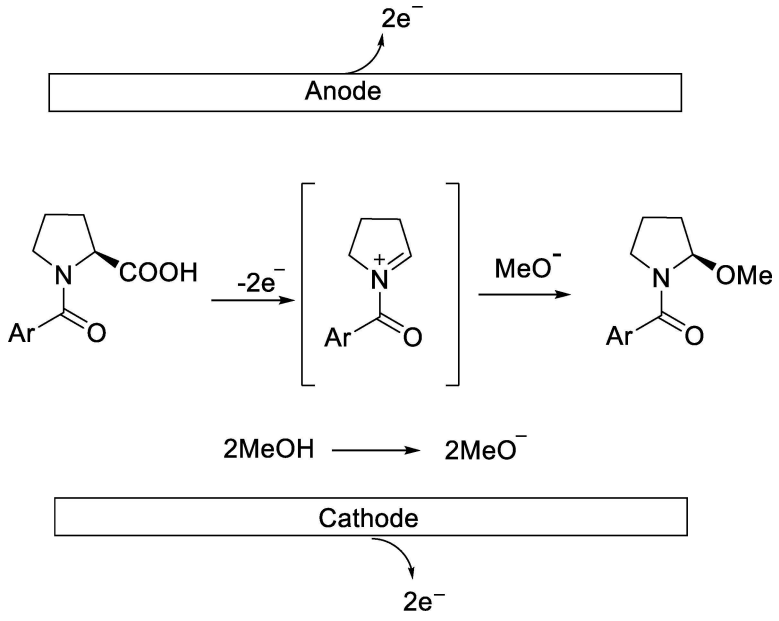
The kinetics and mechanism of 4-methylanisole methoxylation in KF-methanol and $NaClO_4$-methanol solutions



Scheme 51. Electrochemical decarboxylative hindered C–O bond formation.



Scheme 52. Electrochemical oxidation of an *N*-benzoylated serine derivative.



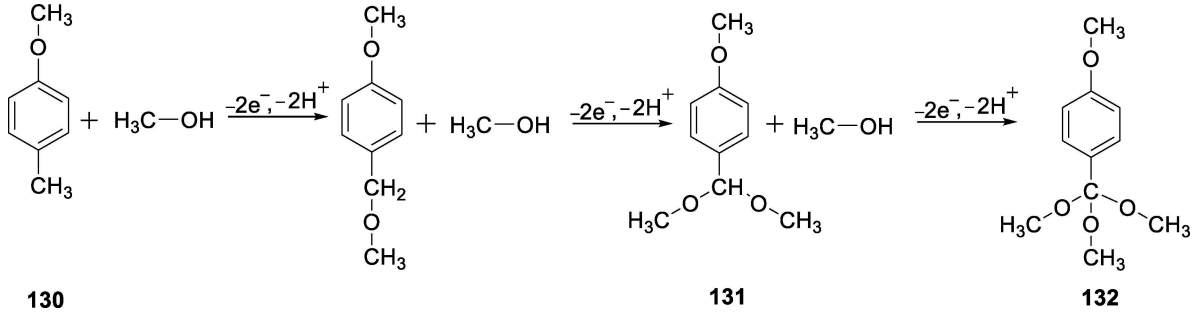
Scheme 53. Schematic illustration of the Shono oxidation proceeding within a short interelectrode distance of the microreactor. Reproduced from ref.[309]

was developed by Bystron and co-workers.[310] Utilising voltammetry on a rotating and stationary disk electrode, the electrochemical performance of 4-methoxybenzaldehdedimethylacetate, 4-methylanisole and 4-methoxy-benzyl-methyl-ether was explored. In the reaction process, $NaClO_4$ acts as a mild electrolyte, and KF is electrochemically active in methanol solutions in the potential area similar to that of the organic compounds examined. In terms of Tafel kinetics, the methoxylation kinetics for the individual compounds was explained but the mechanism of this interaction remains uncertain (Scheme 54).

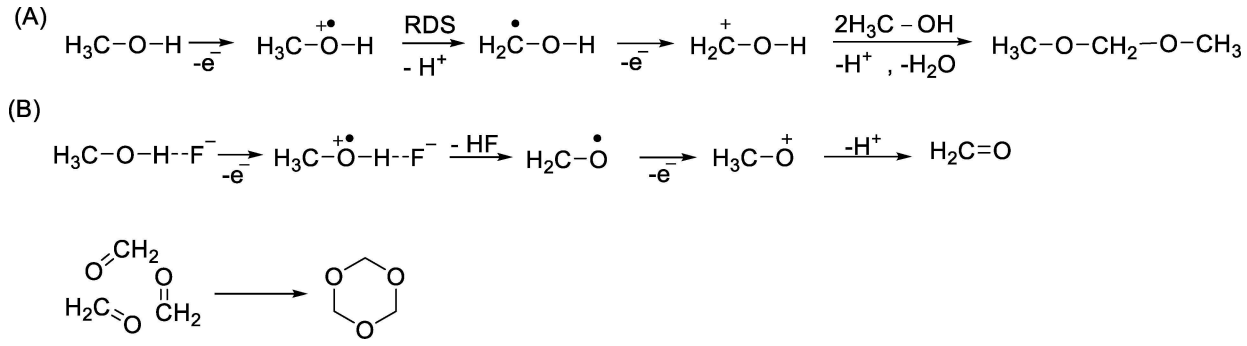
The electrochemical anodic oxidation of 4-methoxyanisole (4-MA) **130** leads to the formation of 4-methoxybenzaldehyde (4-MBA) **131** with the intermediate ether, i.e., 4-methoxybenzyl methyl ether (4-MBME), being formed during the reaction. A third methoxylation step with 4-MBA also takes place due to overoxidation of **131** to afford 4-methoxybenzaldehyde-dimethylacetale (4-MBA DMA) **132**.

In this context, methanol (CH_3OH) has undergone oxidation wherein an electron was removed from the non-bonding pair of electrons from oxygen.[311,312] This radical cation can be stabilised via deprotonation from the carbon on the oxygen atom. By CH_3OH, the ClO_4^- anion is weekly solvated, hence at the carbon atom deprotonation occurs because the bond energy of the C–H bond is less than that of the O–H bond.[313] Consequently, the radical underwent oxidation to form a carbocation which further reacted with CH_3OH (nucleophile) (Scheme 55 A).

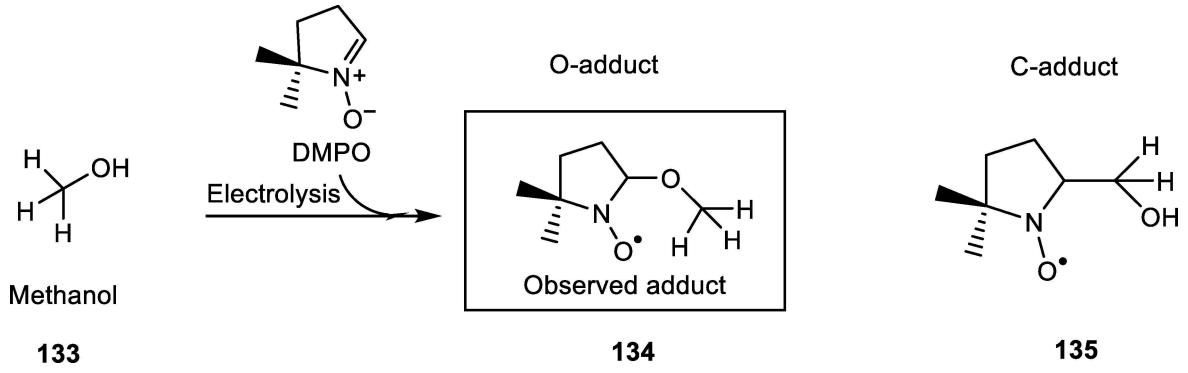
When KF solution was added, a small fluoride anion formed a strong hydrogen bond with the hydrogen of



Scheme 54. The mechanism of 4-methylanisole methoxylation in KF-methanol.



Scheme 55. Mechanism of methanol oxidation. (A) Formation of dimethoxymethane (where $NaClO_4$ is the supporting electrolyte) and (B) formation of formaldehyde and 1,3,5-trioxane (where KF is the supporting electrolyte).



Scheme 56. Trap reaction of the methoxy radical by DMPO.

CH_3OH. Due to the fluoride anion, the stabilisation of the radical cation is more severe, causing a drop in the methanol oxidation potential. This, because of the oxygen atom of the hydroxyl group, makes deprotonation of the hydrogen bond easier Thus, the oxidation reaction followed mechanism B and afforded formaldehyde as the main product. Here, formaldehyde and dimethoxy methane are the electrolysis products if $NaClO_4$ is employed as electrolyte; in this electrolyte, rate of protonation of oxygen and carbon are equivalent. While only formaldehyde is formed as the main product, when KF solution is employed as an electrolyte, formaldehyde was identified in the form of 1,3,5-trioxane. By the trimerisation of formaldehyde under anhydrous conditions, the 1,3,5-trioxane is formed (six membered ring) (Scheme 55 B).

In electrochemical oxidation reactions, evidence of the involvement of radical species can be gathered through electron spin resonance (ESR), such as the study whereby 5,5-dimethyl-1-pyrroline-*N*-oxide (DMPO) was utilised as the radical trapping agent in MeOH[314] (Scheme 56). By employ-

ing constant potential electrolysis (CPE), the oxidation of methanolic solution **133** occurring at anode were carried out using DMPO by boron doped diamond (BDD). In this reaction Pt wire was the cathode and glassy carbon (GC) or Pt electrodes acted as the anode. By the reaction of methoxy with DMPO, nitroxy radical **134** was produced.[315] ESR signal intensities of the obtained radical is different for the anode used: BDD > Pt > GC. Hence, by the electrochemical oxidation of MeOH, the methoxy radical was produced with maximum efficiency when BDD was used as anode, as suggested by ESR spectroscopy. The BDD electrode[316] is widely used in inorganic chemistry and biology, and possesses several applications for the direct generation of hydroxy radical and inorganic peroxides e.g., hypochlorite, persulfate[317] and perphosphate.[318] Nevertheless, merely a few examples exist in which alkoxy or hydroxy radicals are generated by electrochemistry and facilitate highly functionalised organic reactions.

7. Conclusion

This review article focuses upon electrolysis processes that lead to the synthesis of value-added compounds, fine chemicals, and pharmaceuticals. Many instances of the aforementioned electrochemical transformations not only contribute to circular economy, such as electro-carboxylations via introducing green and sustainable methods, but also identify electrochemistry as a modern future tool to address challenging transformations in organic synthesis. Electrochemical asymmetric carboxylations is another positive aspect of this enabling technology to achieve valuable compounds. Electrochemical fluorination reactions are now considered a modern methodology in organofluorine chemistry, although controllability and diversity may sometimes be challenging. Interestingly, the well-known industrially important process of anodic methoxylation reactions is achievable under electrolyte-free conditions in microflow systems. Similarly, electrochemical conversion to amide motifs is another important millstone to access natural small molecules and biopolymers. It is anticipated that further implication of computational studies, digital chemistry, automated chemicals flow systems, artificial intelligence (AI) and machine learning (ML) in electro-organic synthesis could accelerate the process to access the value-added compounds, fine chemicals, and pharmaceuticals in a safer, fast, and an environmentally friendly manner. Moreover, the merging synthetic approaches of electrochemistry and photochemistry is also a preferable choice to achieve high product yields.

Designing new electrochemical routes to commodity, fine chemicals and pharmaceuticals assisted with enabling technologies would be an innovative development and can play a central role in future green and sustainable chemicals synthesis. In contrast, to classical syntheses based on conventional methods, electroorganic synthesis bypasses pre-functionalization of compounds, avoiding the waste generation of by-products facilitating the scalable process of required products. The use of electroorganic synthesis recognizes novel reactivities and defines its application to synthesis of drugs, fine chemicals, value- added products and pharmaceutically significant compounds. Whereas this review is focused on advancing electrochemical methods for synthesis of fine chemicals and pharmaceuticals, one significant broader impact resides in many research activities beyond the laboratory that can evoke in response to new technology with integration of enabling methodologies such as photochemistry, sonochemistry and flow technology.

Acknowledgements

Support from Cardiff University to Dr. Nisar Ahmed is gratefully acknowledged. We would like to thank Dr. G.M. Martins for valuable technical assistance and discussions.

References

[1] G. M. Martins, G. C. Zimmer, S. R. Mendes, N. Ahmed, *Green Chem.* **2020**, *22*, 4849–4870. DOI 10.1039/D0GC01324B.
[2] G. M. Martins, B. Shirinfar, T. Hardwick, A. Murtaza, N. Ahmed, *Catal. Sci. Technol.* **2019**, *9*, 5868–5881. DOI 10.1039/C9CY01312 A.
[3] G. M. Martins, B. Shirinfar, T. Hardwick, N. Ahmed, *ChemElectroChem.* **2019**, *6*, 1300–1315. DOI 10.1002/celc.201801466.
[4] N. Sbei, G. M. Martins, B. Shirinfar, N. Ahmed, *Chem. Rec.* **2020**, *20*, 1530–1552. DOI 10.1002/tcr.202000].
[5] T. Hardwick, N. Ahmed, *RSC Adv.* **2018**, *8*, 22233–22249.
[6] T. Hardwick, N. Ahmed, *ACS Sustainable Chem. Eng.* **2021**, *9* (12), 4324–4340.
[7] N. Sbei, T. Hardwick, N. Ahmed, *ACS Sustainable Chem. Eng.* **2021**, *9*, 18, 6148–6169.
[8] T. Hardwick, N. Ahmed, *Chem. Sci.* **2020**, *11*, 11973–11988.
[9] H. B. Rodrigues, J. O. B. Lira, N. Padoin, C. Soares, A. Qurashi, N. Ahmed, *ACS Sustainable Chem. Eng.* **2021**, *10.*1021/acssuschemeng.1c02989.
[10] T. C. P. D. Azevedo, P. C. Azevedo, R. N. Silveira, A. R. V. Carvalho, M. L. Cezarotti, F. T. Barbosa, F. W. D. S. Ramos, *Rev. Assoc. Med. Bras.* **2020**, *66*, 838–841. https://doi.org/10.1590/1806-9282.66.6.838.
[11] K. Shiraki, T. Daikoku, *Pharmacol. Ther.* **2020**, *209*, 107512. doi:10.1016/j.pharmthera.2020.107512.
[12] M. Napolitano, G. Fabbrocini, E. Cinelli, L. Stingeni, C. Patruno, *J. Asthma and Allergy* **2020**, *13*, 89. do/10.2147/JAA.S206387.
[13] M. M. Baizer, J. L. Chruma, *J. Org. Chem.* **1972**, *37*(12), 1951–1960. https://doi.org/10.1021/jo00977a020.

[14] L. J. Goossen, N. Rodriguez, K. Gooßen, *Angew. Chem. Int. Ed.* **2008**, *47*(17), 3100–3120. https://doi.org/10.1002/anie.200704782.

[15] Z. Zou, W. Zhang, Y. Wang, Y. Pan, *Org. Chem. Front.* **2021**, *8*(11), 2786–2798). DOI: 10.1039/d1qo00054c.

[16] F. Wang, D. Wang, X. Mu, P. Chen, G. Liu, *J. Am. Chem. Soc.* **2014**, *136*(29), 10202–10205. https://doi.org/10.1021/ja504458j.

[17] B. Halford, *Chem. Eng. News.* **2019**, *97*, 43.

[18] J. Korhonen, A. Honkasalo, J. Seppälä, *Ecol. Econ.* **2018**, 143, 37–46. https://doi.org/10.1016/j.ecolecon.2017.06.041

[19] T. Keijer, V. Bakker, J. C. Slootweg, *Nat. Chem.* **2019**, *11*(3), 190–195.

[20] G. Moraga, S. Huysveld, F. Mathieux, G. A. Blengini, L. Alaerts, K. Van Acker, J. Dewulf, *Resour. Conserv. Recycl.* **2019**, *146*, 452–461. https://doi.org/10.1016/j.resconrec.2019.03.045.

[21] G. Moraga, S. Huysveld, F. Mathieux, G. A. Blengini, L. Alaerts, K. Van Acker, J. Dewulf, *Resour. Conserv. Recycl.* **2019**, *146*, 452–461. https://doi.org/10.1016/j.resconrec.2019.03.045

[22] F. Blomsma, G. Brennan, *J. Ind. Ecol.* **2017**, *21*(3), 603–614. https://doi.org/10.1111/jiec.12603

[23] M. H. A. Nasir, A. Genovese, A. A. Acquaye, S. C. L. Koh, F. Yamoah, *Int. J. Prod. Econ.* **2017**, 183, 443–457. https://doi.org/10.1016/j.ijpe.2016.06.008.

[24] J. Kirchherr, D. Reike, M. Hekkert, *Resour. Conserv. Recycl.* **2017**, *127*, 221–232. https://doi.org/10.1016/j.resconrec.2017.09.005.

[25] L. A. Lett, *Argent. Microbiol.* **2014**, *46* (1), 1–2. DOI: 10.1016/S0325-7541(14)70039–2.

[26] a) N. L. Poff, M. M. Brinson, J. W. Day, *Pew Center on Global Climate Change, Arlington.* **2002**, *44*, 1–36https://doi.org/10.1038/nature01333; b) T. L. Root, J. T. Price, K. R. Hall, S. H. Schneider, C. Rosenzweig, J. A. Pounds, *Nature* **2003**, *421*, 57–60. https://doi.org/10.1038/nature01333.

[27] H. Senboku, A. Katayama, *Curr. Opin. Green Sustain. Chem.* **2017**, *3*, 50–54.

[28] X. Chai, B. Xie, *Synthesis.* **2013**, *45*, 3305–3324.

[29] Y. Tsuji, T. Fujihara, *Chem. Commun.* **2012**, *48*, 9956–9964.

[30] H. Senboku, H. Kanaya, M. Tokuda, *Synlett.* **2002**, *1*, 0140–0142. DOI: 10.1055/s-2002–19350.

[31] D. A. Tyssee, M. M. Baizer, *J. Org. Chem.* **1974**, *39*(19), 2823–2828. https://doi.org/10.1021/jo00933a001.

[32] I. Brierley, A. J. Jenner, S. C. Inglis, *J. Mol. Biol.* **1992**, *227*(2), 463–479. https://doi.org/10.1016/0022-0728(84)-80232–6.

[33] N. J. Vickers, *Curr. Biol.* **2017**, *27*(14). https://doi.org/10.1016/j.jfluchem.2008.06.010.

[34] V. E. Titov, V. N. Bondarenko, V. G. Koshechko, V. D. Pokhodenko, *Theor. Exp. Chem.* **2008**, *44*(5), 271–277. https://doi.org/10.1007/s11237-008-9038–5.

[35] U. Stojadinovic, L. Matenco, P. Andriessen, M. Toljić, L. Rundić, M. N. Ducea, *Tectonophysics.* **2017**, *710*, 184–204. https://doi.org/10.1016/j.tet.2014.01.054.

[36] O. Sock, M. Troupel, J. Perichon, *Tetrahedron Lett.* **1985**, *26*(12), 1509–1512. https://doi.org/10.1016/S0040-4039(00)-98538–1.

[37] A. Gennaro, A. A. Isse, M. G. Severin, E. Vianello, I. Bhugun, J. M. Savéant, *J. Chem. Soc. Faraday Trans.* **1996**, *92*(20), 3963–3968. https://doi.org/10.1039/B206746C.

[38] Y. Ikeda, E. Manda, *Chem. Lett.* **1984**, *13*(3), 453–454. https://doi.org/10.1246/cl.1984.453.

[39] Y. Ikeda, E. Manda, *Bull. Chem. Soc. Jpn.* **1985**, *58*(6), 1723–1726. https://doi.org/10.1246/bcsj.58.1723.

[40] A. S. C. Chan, T. T. Huang, J. H. Wagenknecht, R. E. Miller, *J. Org. Chem.* **1995**, *60*(3), 742–744. https://doi.org/10.1021/jo00108a047.

[41] O. Scialdone, C. Amatore, A. Galia, G. Filardo, *J. Electroanal. Chem.* **2006**, *592*(2), 163–174. https://doi.org/10.1016/j.jelechem.2006.04.009.

[42] H. C. Erythropel, J. B. Zimmerman, T. M. de Winter, L. Petitjean, F. Melnikov, C. H. Lam, A. W. Lounsbury, K. E. Mellor, N. Z. Jankovic, Q. Tu, L. N. Pincus, M. M. Falinski, W. Shi, P. Coish, D. L. Plata, P. T. Anastas, *Green Chem.* **2018**, *20*, 1929–1961.

[43] B. A. Frontana-Uribe, R. D. Little, J. G. Ibanez, A. Palma, R. Vasquez-Medrano, *Green Chem.* **2010**, *12*, 2099–2119.

[44] H. Senboku, *Chem. Rec.* **2021**, *21*, 2354–2374.

[45] Y. Yuan, A. Lei, *Nat. Commun.* **2020**, *11*, 802. DOI: 10.1038/s41467-020-14322-z.

[46] M. Börjesson, T. Moragas, D. Gallego, R. Martin, *ACS Catal.* **2016**, *6*(10), 6739–6749.

[47] Y. Li, X. Cui, K. Dong, K. Junge, M. Beller, *ACS Catal.* **2017**, *7*, 1077–1086.

[48] A. Tortajada, F. Juliá-Hernández, M. Börjesson, T. Moragas, R. Martin, *Angew. Chem. Int. Ed.* **2018**, *57*(49), 15948–15982.

[49] Y. X. Luan, M. Ye, *Tetrahedron Lett.* **2018**, *59*(10), 853–861.

[50] S. S. Yan, Q. Fu, L. L. Liao, G. Q. Sun, J. H. Ye, L. Gong, D. J. Yu, *Coord. Chem. Rev.* **2018**, *374*, 439–463.

[51] Z. Yang, Y. Yu, L. Lai, L. Zhou, K. Ye, F. E. Chen, *Green Synth. Catal.* **2021**.

[52] Z. Yang, Y. Yu, L. Lai, K. Ye, F. E. Chen, *Green Synth. Catal.* **2020**.

[53] C. Lamberth, J. Dinges, *Different Roles of Carboxylic Functions in Pharmaceuticals and Agrochemicals in Bioactive Carboxylic Compound Classes: Pharmaceuticals and Agrochemicals*; Wiley-VCH Verlag GmbH & Co. KGaA.: Weinheim, **2016**; pp 1–11. https://doi.org/10.1002/9783527693931.ch1

[54] A. M. Appel, J. E. Bercaw, A. B. Bocarsly, H. Dobbek, D. L. DuBois, M. Dupuis, G. L. Waldrop, *Chem. Rev.* **2013**, *113*(8), 6621–6658. https://doi.org/10.1021/cr300463y.

[55] J. Louie, *Curr. Org. Chem.* **2005**, *9*(7), 605–623. https://doi.org/10.2174/1385272053765033.

[56] T. Sakakura, K. Kohno, *Chem. Commun.* **2009**, *11*, 1312–1330. https://doi.org/10.1039/B819997C.

[57] X. Yin, J. R. Moss, *Coord. Chem. Rev.* **1999**, *181*(1), 27–59. https://doi.org/10.1016/S0010-8545(98)00171–4.

[58] A. Correa, R. Martin, *Angew. Chem. Int. Ed.* **2009**, *48*(34), 6201–6204.

[59] Y. Tsuji, T. Fujihara, *Chem. Commun.* **2012**, *48*(80), 9956–9964. https://doi.org/10.1039/C2CC33848C.
[60] X. Cai, B. Xie, *Synthesis* **2013**, *45*(24), 3305–3324. DOI: 10.1055/s-0033–1340061.
[61] W. J. M. Van Tilborg, C. J. Smit, *Recl. Trav. Chim. Pays-Bas* **1981**, *100*(11), 437–438. doi.org/10.1002/recl.19811001113.
[62] D. Pletcher, J. T. Girault, *J. Appl. Electrochem.* **1986**, *16*(6), 791–802. doi.org/10.1007/BF01006524.
[63] J. Bringmann, E. Dinjus, *Appl. Organomet. Chem.* **2001**, *15*(2), 135–140.
[64] C. H. Li, G. Q. Yuan, X. C. Ji, X. J. Wang, J. S. Ye, H. F. Jiang, *Electrochim. Acta.* **2011**, *56*(3), 1529–1534. https://doi.org/10.1016/j.electacta.2010.06.057.
[65] K. Zhang, Y. Xiao, Y. Lan, M. Zhu, H. Wang, J. Lu, *Electrochem. Commun.* **2010**, *12*(12), 1698–1702.https://doi.org/10.1016/j.elecom.2010.09.028.
[66] R. Matthessen, J. Fransaer, K. Binnemans, D. E. De Vos, *RSC Adv.* **2013**, *3*(14), 4634–4642.https://doi.org/10.1039/C3RA00129F.
[67] S. Gambino, A. Gennaro, G. Filardo, G. Silvestri, E. Vianello, *J. Electrochem. Soc.* **1987**, *134*(9), 2172. https://iopscience.iop.org/article/10.1149/1.2100846.
[68] S. Dérien, J. C. Clinet, E. Duñach, J. Périchon, *Tetrahedron.* **1992**, *48*(25), 5235–5248.https://doi.org/10.1016/S0040-4020(01)89021–9.
[69] C. H. Li, G. Q. Yuan, X. C. Ji, X. J. Wang, J. S. Ye, H. F. Jiang, *Electrochim. Acta* **2011**, *56*(3), 1529–1534. https://doi.org/10.1016/j.electacta.2010.06.057.
[70] R. Matthessen, J. Fransaer, K. Binnemans, D. E. De Vos, *RSC Adv.* **2014**, *3*(14), 4634–4642.https://doi.org/10.1039/C3RA00129F.
[71] S. N. Steinmann, C. Michel, R. Schwiedernoch, M. Wu, P. Sautet, *J. Catal.* **2016**, *343*, 240–247.https://doi.org/10.1016/j.jcat.2016.01.008.
[72] H. Maag, *Prodrugs.* **2007**, 703–729.
[73] R. Matthessen, J. Fransaer, K. Binnemans, D. E. De Vos, *ChemElectroChem.* **2015**, *2*(1), 73–76.https://doi.org/10.1002/celc.201402299.
[74] H. Senboku, A. Katayama, *Curr. Opin. Green Sustain. Chem.* **2017**, *3*, 50–54. https://doi.org/10.1016/j.cogsc.2016.10.003.
[75] S. Olivero, E. Duñach, *Eur. J. Org. Chem.* **1999**, 1885–1891.
[76] A. Katayama, H. Senboku, *ChemElectroChem.* **2016**, *3*, 2052–2057.
[77] M. Feroci, A. Inesi, L. Rossi, *Synth. Org.* **1998**, 193–196.
[78] E. Duñach, J. Périchon, *J. Organomet. Chem.* **1988**, *352*(1-2), 239–246. https://doi.org/10.1016/0022-328X(88)83038–9.
[79] D. J. Darensbourg, R. A. Kudaroski, *Adv. Organomet. Chem.* **1983**, *22*, 129–168.
[80] M. Troupel, Y. Rollin, O. Sock, G. Meyer, J. P. Crichon, *Nouv. J. Chim.* **1986**, *11*, 593 and refs. therein. 7.
[81] S. Sibille, *Tetrahedron Lett.* **1987**, *28*, 55.
[82] Y. Rollin, G. Meyer, M. Troupel, J. F. Fauvarque, J. Perichon, *J. Chem. Soc. Chem. Commun.* **1983**, *15*, 793–794.
[83] C. Li, G. Yuan, H. Jiang, *Chin. J. Chem.* **2010**, *28*(9), 1685–1689. https://doi.org/10.1002/cjoc.201090285.
[84] F. Köster, E. Dinjus, E. Duñach, *Eur. J. Org. Chem.* **2001**, *13*, 2507–2511. https://doi.org/10.1002/1099-0690(200107)2001.
[85] G. Haaima, M. J. Lynch, A. Routledge, R. T. Weavers, *Tetrahedron.* **1991**, *47*(28), 5203–5214.
[86] H. Harkat, A. Y. Dembele, J. M. Weibel, A. Blanc, P. Pale, *Tetrahedron.* **2009**, *65*(9), 1871–1879.
[87] C. Haase, P. Langer, *Synlett* **2005**, *3*, 453–456.
[88] M. Lautens, M. L. Maddess, *Org. Lett.* **2004**, *6*(12), 1883–1886.
[89] J. Sun, X. Li, J. Feng, X. Tian, *Water Res.* **2009**, *43*(17), 4363–4369.
[90] C. H. Li, G. Q. Yuan, C. R. Qi, H. F. Jiang, *Tetrahedron.* **2013**, *69*, 3135–3140.
[91] C. Li, G. Yuan, H. Jiang, *Chin. J. Chem.* **2010**, *28*, 1685–1689.
[92] Q. Feng, K. Huang, S. Liu, J. Yu, F. Liu, *Electrochim. Acta* **2011**, *56*(14), 5137–5141.https://doi.org/10.1016/j.electacta.2011.03.061.
[93] S. Wawzonek, A. Gundersen, *J. Electrochem. Soc.* **1960**, *107*(6), 537. /article/10.1149/1.2427738/.
[94] H. Brunner, P. Schmidt, *Eur. J. Org. Chem.* **2000**, *11*, 2119–2133.
[95] G. Yuan, Z. Li, H. Jiang, *Chin. J. Chem.* **2009**, *27*(8), 1464–1470. https://doi.org/10.1002/cjoc.200990246.
[96] J. H. Wagenknecht, *U. S. Patent No. 4,601,797.* Washington, DC: U. S. Patent and Trademark Office. **1986**.
[97] C. Reufer, M. Hateley, T. Lehmann, C. Weckbecker, R. Sanzenbacher, J. Bilz, Process for the preparation of α-substituted carboxylic acids from the series comprising α-hydroxycarboxylic acids and n-substituted-α-aminocarboxylic acids. U.S. Patent 7,332,067, Feb 19, **2008**.
[98] C. F. Hoppe, A. Nordschild, H. Jakob, C. Weckbecker, P. Roth, M. Imad, Preparing alpha-substituted carboxylic acids, comprises cathodic carboxylation of a compound in a conducting salt and an organic solvent containing catholyte with carbon dioxide at a diamond cathode layer. Ger. Patent 102,011,078,468, Jan 3, **2013**.
[99] R. Matthessen, J. Fransaer, K. Binnemans, D. E. De Vos, *Beilstein J. Org. Chem.* **2014**, *10*(1), 2484–2500.
[100] M. M. Baizer, J. L. Chruma, *J. Org. Chem.* **1972**, *37*(12), 1951–1960.doi:10.1021/jo00977a020.
[101] S. Wawzonek, J. M. Shradel, *J. Electrochem. Soc.* **1979**, *126*(3), 401.doi:10.1149/1.2129051.
[102] G. Silvestri, S. Gambino, G. Filardo, A. Gulotta, *Angew. Chem. Int. Ed.* **1984**, *23*(12), 979–980.doi:10.1002/anie.198409791.
[103] M. Heintz, O. Sock, C. Saboureau, J. Perichon, M. Troupel, *Tetrahedron.* **1988**, *44*(6), 1631–1636. Doi: 10.1016/S0040-4020(01)86724–7.
[104] A. A. Isse, A. Gennaro, *Chem. Commun.* **2002**, *23*, 2798–2799.doi:10.1039/b206746c.
[105] A. Gennaro, C. M. Sánchez-Sánchez, A. A. Isse, V. Montiel, *Electrochem. Commun.* **2004**, *6*(7), 627–631. doi:10.1016/j.elecom.2004.04.019.
[106] O. Scialdone, A. Galia, G. Silvestri, C. Amatore, L. Thouin, J. N. Verpeaux, *Chem. Eur. J.* **2006**, *12*(28), 7433–7447. doi:10.1002/chem.200501499.

[107] A. J. Aishah, M. A. Hartini, S. Normala, A. M. Norhuda, H. H. N. Hanis, H. M. Razif, T. Sugeng, *J. Nat. Gas Chem.* **2007**, *16*(3), 273–277. doi:10.1016/S1003-9953(07)60059–0.
[108] D. F. Niu, L. P. Xiao, A. J. Zhang, G. R. Zhang, Q. Y. Tan, J. X. Lu, *Tetrahedron.* **2008**, *64*(46), 10517–10520. doi:10.1016/j.tet.2008.08.093.
[109] D. Niu, J. Zhang, K. Zhang, T. Xue, J. Lu, *Chin. J. Chem.* **2009**, *27*(6), 1041–1044. doi:10.1002/cjoc.200990174.
[110] Y. C. Lan, H. Wang, L. X. Wu, S. F. Zhao, Y. Q. Gu, J. X. Lu, *J. Electroanal. Chem.* **2012**, *664*, 33–38. doi:10.1016/j.jelechem.2011.10.011.
[111] Y. Hiejima, M. Hayashi, A. Uda, S. Oya, H. Kondo, H. Senboku, K. Takahashi, *Phys. Chem. Chem. Phys.* **2010**, *12*(8), 1953–1957.doi:10.1039/b920413j.
[112] M. Tokuda, *J. Nat. Gas Chem.* **2006**, *15*, 275–281.
[113] M. Islam, B. M. Kariuki, Z. Shafiq, T. Wirth, N. Ahmed, *Eur. J. Org. Chem.* **2019**, 1371–1376.
[114] A. Georgiádes, S. B. Ötvös, F. Fülo, *ACS Sustainable Chem. Eng.* **2015**, *3*(12), 3388–3397. https://doi.org/10.1021/acssuschemeng.5b01096.
[115] H. Tateno, Y. Matsumura, K. Nakabayashi, H. Senboku, M. Atobe, *RSC Adv.* **2015**, *5*, 98721–98723.
[116] S. C. Zheng, M. Zhang, X. M. Zhao, *Chem. Eur. J.* **2014**, *20*(24), 7216–7221. https://doi.org/10.1002/chem.201402388.
[117] C. K. Ran, X. W. Chen, Y. Y. Gui, J. Liu, L. Song, K. Ren, D. G. Yu, *Sci. China Chem.* **2020**, 1–16. https://doi.org/10.1007/s11426-020-9788–2.
[118] R. A. Soomro, S. Jawaid, Q. Zhu, Z. Abbas, B. Xu, *Chin. Chem. Lett.* **2020**, *31*(4), 922–930. https://doi.org/10.1002/celc.201402299.
[119] Y. Kim, C. J. Li, *Green Synth. Catal.* **2020**, *1*(1), 1–11. https://doi.org/10.1016/j.cogsc.2016.10.003
[120] B. A. Frontana-Uribe, R. D. Little, J. G. Ibanez, A. Palma, R. Vasquez-Medrano, *Green Chem.* **2010**, *12*(12), 2099–2119. https://doi.org/10.1016/j.cogsc.2016.10.003.
[121] H. C. Erythropel, J. B. Zimmerman, T. M. de Winter, L. Petitjean, F. Melnikov, C. H. Lam, P. T. Anastas, *Green Chem.* **2018**, *20*(9), 1929–1961. https://doi.org/10.1039/C8GC00482J.
[122] Z. Yang, Y. Yu, L. Lai, L. Zhou, K. Ye, F. E. Chen, *Green Synth. Catal.* **2021**, https://doi.org/10.1016/j.gresc.2021.01.009.
[123] M. Feroci, A. Inesi, M. Orsini, L. Palombi, *Org. Lett.* **2002**, *4*(16), 2617–2620. doi.org/10.1021/ol025939z.
[124] D. F. Niu, L. P. Xiao, A. J. Zhang, G. R. Zhang, Q. Y. Tan, J. X. Lu, *Tetrahedron.* **2008**, *64*(46), 10517–10520. https://doi.org/10.1016/j.tet.2008.08.093.
[125] D. Niu, J. Zhang, K. Zhang, T. Xue, J. Lu, *Chin. J. Chem.* **2009**, *27*(6), 1041–1044. https://doi.org/10.1002/cjoc.200990174.
[126] O. Scialdone, A. Galia, G. Silvestri, C. Amatore, L. Thouin, J. N. Verpeaux, *Chem. Eur. J.* **2006**, *12*(28), 7433–7447. https://doi.org/10.1002/chem.200501499.
[127] C. Amatore, A. Jutand, F. Khalil, M. F. Nielsen, *J. Am. Chem. Soc.* **1992**, *114*(18), 7076–7085. https://doi.org/10.1021/ja00044a018.
[128] J. C. Folest, J. M. Duprilot, J. Perichon, Y. Robin, J. Devynck, *Tetrahedron Lett.* **1985**, 26(22), 2633–2636. https://doi.org/10.1016/S0040-4039(00)98122-X.
[129] A. A. Isse, A. Gennaro, E. Vianello, *J. Chem. Soc. Dalton Trans.* **1996**, *8*, 1613–1618. https://doi.org/10.1039/DT9960001613.
[130] G. Zheng, M. Stradiotto, L. Li, *J. Electroanal. Chem.* **1998**, *453*(1-2), 79–88. https://doi.org/10.1016/S0022-0728(98)-00173–9.
[131] W. H. Chung, P. Guo, K. Y. Wong, C. P. Lau, *J. Electroanal. Chem.* **2000**, *486*(1), 32–39. https://doi.org/10.1016/S0022-0728(00)00125-X.
[132] P. L. Fabre, O. Reynes, *Electrochem. Commun.* **2010**, *12*(10), 1360–1362. https://doi.org/10.1016/j.elecom.2010.07.020.
[133] M. Troupel, Y. Rollin, *J. Chim.* **1981**, *5*, 621–625.
[134] C. Amatore, A. Jutand, *J. Am. Chem. Soc.* **1991**, *113*(8), 2819–2825. https://doi.org/10.1021/ja00008a003.
[135] A. Gennaro, A. A. Isse, F. Maran, *J. Electroanal. Chem.* **2001**, *507*(1-2), 124–134. https://doi.org/10.1016/S0022-0728(01)-00373–4.
[136] A. Gennaro, C. M. Sánchez-Sánchez, A. A. Isse, V. Montiel, *Electrochem. Commun.* **2004**, *6*(7), 627–631.. https://doi.org/10.1016/j.elecom.2004.04.019
[137] A. J. Aishah, M. A. Hartini, S. Normala, A. M. Norhuda, H. H. N. Hanis, H. M. Razif, T. Sugeng, *J. Nat. Gas Chem.* **2007**, *16*(3), 273–277. https://doi.org/10.1016/S1003-9953(07)60059–0.
[138] S. Chanfreau, P. Cognet, S. Camy, J. S. Condoret, *J. Supercrit. Fluids.* **2008**, *46*(2), 156–162. https://doi.org/10.1016/j.supflu.2008.04.003.
[139] J. F. Fauvarque, Y. De Zelicourt, C. Amatore, A. J. Jutand, *Appl. Electrochem.* **1990**, *20*, 338–340. doi:10.1007/BF01033614.
[140] J. L. Olloqui-Sariego, V. M. Molina, D. González-Arjona, E. Roldán, M. Domínguez, *J. Electrochem. Soc.* **2008**, *155*(11), E157. op.org/article/10.1149/1.2971028.
[141] R. Matthessen, J. Fransaer, K. Binnemans, D. E. De Vos, *Beilstein J. Org. Chem.* **2014**, *10*(1), 2484–2500. https://doi.org/10.3762/bjoc.10.260.
[142] V. A. Grinberg, T. A. Koch, V. M. Mazin, E. I. Mysov, S. R. Sterlin, *Russ. Chem. Bull.* **1997**, *46*(9), 1560–1564. https://doi.org/10.1007/BF02502939.
[143] P. L. Fabre, O. Reynes, *Electrochem. Commun.* **2010**, *12*(10), 1360–1362. https://doi.org/10.1016/j.elecom.2010.07.020.
[144] O. Scialdone, A. Galia, C. Belfiore, G. Filardo, G. Silvestri, *Ind. Eng. Chem. Res.* **2004**, *43*(17), 5006–5014. doi/full/10.1021/ie034275+.
[145] A. A. Isse, A. Gennaro, *J. Electrochem. Soc.* **2002**, *149*(8). Doi: org/article/10.1149/1.1490358/.
[146] P. L. Fabre, O. Reynes, *Electrochem. Commun.* **2010**, *12*(10), 1360–1362. https://doi.org/10.1016/j.elecom.2010.07.020.
[147] A. A. Isse, A. Gennaro, *J. Electrochem. Soc.* **2003**, *149*(8), 113. Doi.org/article/10.1149/1.1490358/.
[148] A. Nomoto, Y. Kojo, G. Shiino, Y. Tomisaka, I. Mitani, M. Tatsumi, A. Ogawa, *Tetrahedron Lett.* **2010**, *51*(50), 6580–6583. https://doi.org/10.1016/j.tetlet.2010.10.028.

[149] J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.* **2014**, *114*, 2432–2506.
[150] B. M. Johnson, Y. Z. Shu, X. Zhuo, N. A. Meanwell, *J. Med. Chem.* **2020**, *63*(12), 6315–6386.
[151] J. Han, A. M. Remete, L. S. Dobson, L. Kiss, K. Izawa, H. Moriwaki, D. O'Hagan, *J. Fluorine Chem.* **2020**, 109639.
[152] E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly, N. A. Meanwell, *J. Med. Chem.* **2015**, *58*(21), 8315–8359.
[153] M. Inoue, Y. Sumii, N. Shibata, *ACS Omega* **2020**, *5*(19), 10633–10640.
[154] T. Fujiwara, D. O'Hagan, *J. Fluor Chem.* **2014**, *167*, 16–29.
[155] S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*(2), 320–330. https://doi.org/10.1039/B610213 C.
[156] J. P. Bégué, D. Bonnet Delpon, *Bioorganic and Medicinal Chemistry of Fluorine*, John Wiley & Sons, Inc., New York, **2008**. DOI:10.1002/9780470281895.
[157] T. Umemoto, *J. Fluorine Chem.* **2000**, 105(2), 211–213.
[158] Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Aceñ, V. A. Soloshonok, K. Izawa, H. Liu, *Chem. Rev.* **2016**, 116(422), 10–1021. DOI: 10.1021/acs.chemrev.5b00392.
[159] S. Yamashita, N. Kurono, H. Senboku, M. Tokuda, K. Orito, *Eur. J. Org. Chem.* **2009**, (*8*), 1173–1180.
[160] T. Fuchigami, S. Inagi, *Acc. Chem. Res.* **2020**, *53*(2), 322–334.
[161] T. Fuchigami, S. Inagi, *Springer. Sci. Rev.* **2018**, 1–22.
[162] S. Kuribayashi, T. Kurioka, S. Inagi, H. J. Lu, B. J. Uang, T. Fuchigami, *Beilstein J. Org. Chem.* **2018**, *14*(1), 389–396.
[163] T. Fuchigami, S. Inagi, *Chem. Commun.* **2011**, *47*(37), 10211–10223.
[164] M. Noel, V. Suryanarayanan, S. Chellammal, *J. Fluorine Chem.* **1997**, *83*(1), 31–40.
[165] T. Fuchigami, T. Tajima, *J. Fluorine Chem.* **2005**, *126*(2), 181–187.
[166] S. Doobary, A. J. Lennox, *Synlett.* **2020**, *31*(14), 1333–1342.
[167] A. Harsanyi, G. Sandford, *Green Chem.* **2015**, *17*(4), 2081–2086.
[168] M. Özcan, A. Allahbeickaraghi, M. Dündar, *Clin. Oral Investig.* **2012**, *16*(1), 15–23.
[169] K. Momota, T. Yonezawa, Y. Hayakawa, K. Kato, M. Morita, Y. Matsuda, *J. Appl. Electrochem.* **1995**, *25*(7), 651–658.
[170] K. Momota, H. Horio, K. Kato, M. Morita, Y. Matsuda, *Electrochim. Acta.* **1995**, *40*(2), 233–240.
[171] K. Momota, T. Yonezawa, K. Mukai, M. Morita, *J. Fluorine Chem.* **1998**, *87*(2), 173–178.
[172] K. Momota, M. Morita, Y. Matsuda, *Electrochim. Acta.* **1993**, *38*(8), 1123–1130.
[173] J. D. Haupt, M. Berger, S. R. Waldvogel, *Org. Lett.* **2019**, *21*(1), 242–245.
[174] H. Nagura, S. Kuribayashi, Y. Ishiguro, S. Inagi, T. Fuchigami, *Tetrahedron.* **2010**, *66*(1), 183–186.
[175] H. Nagura, S. Inagi, T. Fuchigami, *Tetrahedron.* **2009**, *65*(8), 1559–1566.
[176] P. Xiong, H. Long, H. C. Xu, *Asian J. Org. Chem.* **2019**, *8*(5), 658–660.
[177] V. Dinoiu, K. Kanno, T. Fukuhara, N. Yoneda, *J. Fluorine Chem.* **2005**, *126*(5), 753–758.
[178] V. Dinoiu, T. Fukuhara, S. Hara, N. Yoneda, *J. Fluorine Chem.* **2000**, *103*(1), 75–80.
[179] J. D. Haupt, M. Berger, S. R. Waldvogel, *Org. Lett.* **2019**, *21*(1), 242–245.
[180] J. D. Herszman, M. Berger, S. R. Waldvogel, *Org. Lett.* **2019**, *21*(19), 7893–7896.
[181] M. Hasegawa, T. Fuchigami, *Electrochim. Acta.* **2004**, *49*(20), 3367–3372.
[182] M. Hasegawa, H. Ishii, T. Fuchigami, *Tetrahedron Lett.* **2002**, *43*(8), 1503–1505.
[183] M. Hasegawa, H. Ishii, T. Fuchigami, *Green Chem.* **2003**, *5*(5), 512–515.
[184] T. Fuchigami, M. Shimojo, A. Konno, K. Nakagawa, *J. Org. Chem.* **1990**, *55*(25), 6074–6075.
[185] S. Narizuka, T. Fuchigami, *J. Org. Chem.* **1993**, *58*(16), 4200–4201.
[186] T. Fuchigami, M. Sano, *J. Electroanal. Chem.* **1996**, *414*(1), 81–84.
[187] T. Fuchigami, K. Mitomo, H. Ishii, A. Konno, *J. Electroanal. Chem.* **2001**, *507*(1-2), 30–33.
[188] T. Fuchigami, T. Fujita, *J. Org. Chem.* **1994**, *59*(24), 7190–7192.
[189] S. Hara, T. Hatakeyama, S. Q. Chen, K. Ishi-i, M. Yoshida, M. Sawaguchi, N. Yoneda, *J. Fluorine Chem.* **1998**, *87*(2), 189–192.
[190] D. M. Heard, S. Doobary, A. J. Lennox, *ChemElectroChem.* **2021**.
[191] S. Doobary, A. T. Sedikides, H. P. Caldora, D. L. Poole, A. J. J. Lennox, *Angew. Chem. Int. Ed.* **2020**, 59, 1155–1160.
[192] D. F. Andrés, U. Dietrich, E. G. Laurent, B. S. Marquet, *Tetrahedron.* **1997**, 53(2), 647–658. https://doi.org/10.1016/S0040-4020(96)00997–0.
[193] V. Dinoiu, K. Kanno, T. Fukuhara, N. Yoneda, *J. Fluorine Chem.* **2005**, *126*(5), 753–758. https://doi.org/10.1016/j.jfluchem.2005.02.021.
[194] K. Momota, K. Kato, M. Morita, Y. Matsuda, *Electrochim. Acta.* **1994**, *39*(1), 41–49. https://doi.org/10.1016/0013-4686(94)85009–7.
[195] K. Momota, M. Morita, Y. Matsuda, *Electrochim. Acta.* **1993**, *38*(8), 1123–1130. https://doi.org/10.1016/0013-4686(93)80222-L.
[196] Z. Zou, W. Zhang, Y. Wang, Y. Pan, *Org. Chem. Front.* **2021**, *8*(11), 2786–2798. DOI: 10.1039/D1QO00054C.
[197] E. J. Horn, B. R. Rosen, P. S. Baran, *ACS Cent. Sci.* **2016**, *2*, 302–308.
[198] M. Yan, Y. Kawamata, P. S. Baran, *Chem. Rev.* **2017**, *117*, 13230–13319.
[199] Y. Jiang, K. Xu, C. Zeng, *Chem. Rev.* **2018**, *118*, 4485–4540.
[200] A. Wiebe, T. Gieshoff, S. Möhle, E. Rodrigo, M. Zirbes, S. R. Waldvogel, *Angew. Chem. Int. Ed.* **2018**, *57*, 5594–5619.
[201] J. H. Simons, *J. Electrochem. Soc.* **1949**, *95*, 47–52.
[202] D. E. Danly, *J. Electrochem. Soc.* **1984**, *131*, 435C–442.
[203] D. Nematollahi, S. Dehdashtian, A. Niazi, *J. Electroanal. Chem.* **2008**, *616*, 79–86.
[204] H. Kolbe, *J. Prakt. Chem.* **1847**, *41*(1), 137–139. https://doi.org/10.1002/prac.18470410118.

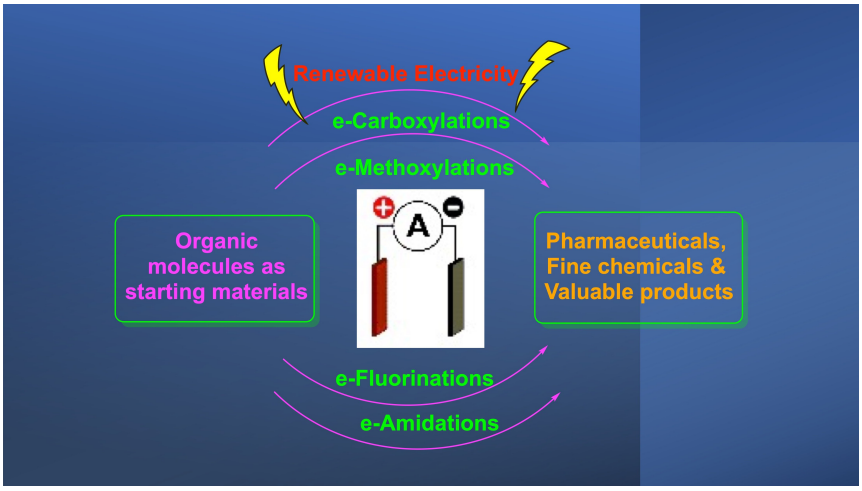
[205] P. Xu, P. Chen and H. Xu, *Angew. Chem. Int. Ed.* **2020**, *59*, 14275–14280; https://doi.org/10.1002/ange.202005724.
[206] H. Yan, Z.-W. Hou, H.-C. Xu, *Angew. Chem. Int. Ed.* **2019**, *58*, 4592–4595. https://doi.org/10.1002/anie.201814488.
[207] M. Elsherbini, T. Wirth, *Acc. Chem. Res.* **2019**, *52*, 3287–3296. https://doi.org/10.1021/acs.accounts.9b00497,.
[208] C. Huang, X. Qian, H. Xu, *Angew. Chem. Int. Ed.* **2019**, *58*, 6650–6653. https://doi.org/10.1002/anie.201901610.
[209] K. J. Jiao, D. Liu, H.-X. Ma, H. Qiu, P. Fang, T. S. Mei, *Angew. Chem. Int. Ed.* **2020**, *59*, 6520–6524.
[210] Y. Wang, L. Deng, X. Wang, Z. Wu, Y. Wang, Y. Pan, *ACS Catal.* **2019**, *9*, 1630–1634.
[211] L. Xing, D. C. Blakemore, A. Narayanan, R. Unwalla, F. Lovering, R. A. Denny, M. E. Bunnage, *ChemMedChem.* **2015**, *10*(4), 715–726. https://doi.org/10.1002/cmdc.201402555.
[212] T. Besset, P. Jubault, X. Pannecoucke, T. Poisson, *Org. Chem. Front.* **2016**, *3*(8), 1004–1010. DOI: 10.1039/C6QO00164E.
[213] N. Levi, D. Amir, E. Gershonov, Y. Zafrani, *Synthesis.* **2019**, *51*(24), 4549–4567. DOI: 10.1055/s-0039–1690027.
[214] P. T. Lowe, D. O'Hagan, *J. Fluorine Chem.* **2020**, *230*, 109420. https://doi.org/10.1016/j.jfluchem.2019.109420.
[215] T. G. Miller, J. W. Thanassi, *J. Org. Chem.* **1960**, *25*(11), 2009–2012. https://doi.org/10.1021/jo01081a048.
[216] M. Berger, J. D. Herszman, Y. Kurimoto, G. H. de Kruijff, A. Schüll, S. Ruf, S. R. Waldvogel, *Chem. Sci.* **2020**, *11*(23), 6053–6057. Doi: /10.1039/d0sc02417a.
[217] J. J. Ma, W. B. Yi, G. P. Lu, C. Cai, *Adv. Synth. Catal.* **2015**, *357*(16-17), 3447–3452. https://doi.org/10.1002/adsc.201500631.
[218] P. Xu, A. Abdukader, K. Hu, Y. Cheng, C. Zhu, *Chem. Commun.* **2014**, *50*(18), 2308–2310. https://doi.org/10.1039/C3CC48598F.
[219] S. L. Zhang, C. Xiao, *J. Org. Chem.* **2018**, *83*(18), 10908–10915. https://doi.org/10.1021/acs.joc.8b01586.
[220] T. Umemoto, *Chem. Rev.* **1996**, *96*(5), 1757–1778. https://doi.org/10.1021/cr941149u.
[221] C. Zhang, *Org. Biomol. Chem.* **2014**, *12*(34), 6580–658. https://doi.org/10.1039/C4OB00671B.
[222] M. Tordeux, B. Langlois, C. Wakselman, *J. Org. Chem.* **1989**, *54*(10), 2452–2453. Https://doi.org/10.1021/jo00271a041.
[223] B. R. Langlois, E. Laurent, N. Roidot, *Tetrahedron Lett.* **1991**, *32*(51), 7525–7528. https://doi.org/10.1002/adsc.201400370.
[224] Y. Ji, T. Brueckl, R. D. Baxter, Y. Fujiwara, I. B. Seiple, S. Su, P. S. Baran, *Proc. Nat. Acad. Sci.* **2011**, 108(35), 14411–14415. https://doi.org/10.1073/pnas.1109059108.
[225] H. Guyon, H. Chachignon, D. Cahard, *Beilstein J. Org. Chem.* **2017**, *13*(1), 2764–2799. https://doi.org/10.3762/bjoc.13.272.
[226] I. Fleming, A. Barbero, D. Walter, *Chem. Rev.* **1997**, *97*(6), 2063–2192. https://doi.org/10.1021/cr9408991.
[227] L. Chu, F. L. Qing, *Acc. Chem. Res.* **2014**, *47*(5), 1513–1522. https://doi.org/10.1021/ar4003202.
[228] X. Liu, C. Xu, M. Wang, Q. Liu, *Chem. Rev.* **2015**, *115*(2), 683–730. https://doi.org/10.1021/cr400473a.
[229] M. Shimizu, T. Hiyama, *Angew. Chem.* **2005**, *117*(2), 218–234. https://doi.org/10.1002/chem.201404005.
[230] M. Lübbesmeyer, D. Leifert, H. Schäfer, A. Studer, *Chem. Commun.* **2018**, *54*(18), 2240–2243.
[231] H. Egami, M. Sodeoka, *Angew. Chem. Int. Ed.* **2014**, *126* (32), 8434–8449. https://doi.org/10.1021/cr500223 h.
[232] Y. Gao, H. Mei, J. Han, Y. Pan, *Chem. Eur. J.* **2018**, *24*(65), 17205–17209. DOI: 10.1039/C7CC09302K.
[233] Y. Gao, H. Mei, J. Han, Y. Pan, *Chem. Eur. J.* **2019**, *24*, 17205–17215. https://doi.org/10.1002/chem.201804157.
[234] P. Xiong, H. H. Xu, J. Song, H. C. Xu, *J. Am. Chem. Soc.* **2018**, *140*(7), 2460–2464. https://doi.org/10.1021/jacs.8b00391.
[235] F. Y. Li, D. Z. Lin, T. J. He, W. Q. Zhong, J. M. Huang, *ChemCatChem.* **2019**, *11*(9), 2350–2354. https://doi.org/10.1002/cctc.201900438.
[236] V. Ramadoss, Y. Zheng, X. Shao, L. Tian, Y. Wang, *Chem. Eur. J.* **2021**, *27*(10), 3213–3228. https://doi.org/10.1002/chem.202001764.
[237] A. K. Ghosh, L. M. Swanson, H. Cho, S. Leshchenko, K. A. Hussain, S. Kay, H. Mitsuya, *J. Med. Chem.* **2005**, *48*(10), 3576–3585. /doi.org/10.1021/jm1013693.
[238] J. A. Erickson, J. L. McLoughlin, *J. Org. Chem.* **1995**, *60*(6), 1626–1631. https://doi.org/10.1021/jo00111a021.
[239] J. Rong, C. Ni, J. Hu, *Asian J. Org. Chem.* **2017**, *6*(2), 139–152. https://doi.org/10.1002/ajoc.201600509.
[240] N. Levi, D. Amir, E. Gershonov, Y. Zafrani, *Synthesis.* **2019**, *51*(24), 4549–4567. DOI: 10.1055/s-0039–1690027.
[241] B. R. Langlois, E. Laurent, N. Roidot, *Tetrahedron Lett.* **1991**, *32*(51), 7525–7528. https://doi.org/10.1016/0040-4039(91)80524-A.
[242] B. Xing, C. Ni, J. Hu, *Chin. J. Chem.* **2018**, *36*(3), 206–212.
[243] Z. He, P. Tan, C. Ni, J. Hu, *Org. Lett.* **2015**, *17*(8), 1838–1841. doi.org/10.1021/acs.orglett.5b00308.
[244] Y. Ji, T. Brueckl, R. D. Baxter, Y. Fujiwara, I. B. Seiple, S. Su, P. S. Baran, *Proc. Nat. Acad. Sci.* **2011**, *108*(35), 14411–14415. https://doi.org/10.1021/ja211422g.
[245] Z. Ruan, Z. Huang, Z. Xu, G. Mo, X. Tian, X. Y. Yu, L. Ackermann, *Org. Lett.* **2019**, *21*(4), 1237–1240. Https://doi.org/10.1021/acs.orglett.9b00361.
[246] K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*(5486), 1881–1886.
[247] A. K. Ghosh, L. M. Swanson, H. Cho, S. Leshchenko, K. A. Hussain, S. Kay, H. Mitsuya, *J. Med. Chem.* **2005**, *48*(10), 3576–3585. https://doi.org/10.1021/jm050019i.
[248] X. Tang, L. Huang, Y. Xu, J. Yang, W. Wu, H. Jiang, *Angew. Chem.* **2014**, *126*(16), 4289–4292. https://doi.org/10.1002/ange.201311217.
[249] T. Koike, M. Akita, *Top. Catal.* **2014**, *57*(10), 967–974. DOI 10.1007/s11244-014-0259–7.
[250] E. H. Oh, H. J. Kim, S. B. Han, *Synthesis* **2018**, *50*(17), 3346–3358. DOI: 10.1055/s-0037–1610085.
[251] H. Y. Zhang, C. Ge, J. Zhao, Y. Zhang, *Org. Lett.* **2017**, *19*(19), 5260–5263. https://doi.org/10.1021/acs.orglett.7b02353.
[252] X. Yang, G. C. Tsui, *Org. Lett.* **2018**, *20*(4), 1179–1182.https://doi.org/10.1021/acs.orglett.8b00101.
[253] C. Feng, T. P. Loh, *Chem. Sci.* **2012**, *3*(12), 3458–3462. https://doi.org/10.1039/C2SC21164E.

[254] A. Carboni, G. Dagousset, E. Magnier, G. Masson, *Chem. Commun.* **2014**, *50*(91), 14197–14200. https://doi.org/10.1039/C4CC07066F.
[255] J. Liao, W. Guo, Z. Zhang, X. Tang, W. Wu, H. Jiang, *J. Org. Chem.* **2016**, *81*(3), 1304–1309. https://doi.org/10.1021/acs.joc.5b02674.
[256] Y. F. Cheng, X. Y. Dong, Q. S. Gu, Z. L. Yu, X. Y. Liu, *Angew. Chem.* **2017**, *129*(30), 9009–9012. Https://doi.org/10.1002/ange.201702925.
[257] F. Wang, D. Wang, X. Wan, L. Wu, P. Chen, G. Liu, *J. Am. Chem. Soc.* **2016**, *138*(48), 15547–15550. https://doi.org/10.1021/jacs.6b10468.
[258] N. J. Straathof, S. E. Cramer, V. Hessel, T. Noël, *Angew. Chem.* **2016**, *128*(50), 15778–15782. https://doi.org/10.1002/ange.201608297.
[259] T. Liang, C. N. Neumann, T. Ritter, *Angew. Chem. Int. Ed.* **2013**, *125* (32), 8372–8423.
[260] H. Xiao, H. Shen, L. Zhu, C. Li, *J. Am. Chem. Soc.* **2019**, *141*(29), 11440–11445. https://doi.org/10.1021/jacs.9b06141.
[261] C. Alonso, *Chem. Rev.* **2015**, *115*, 1847–1935. https://doi.org/10.1021/cr500368h.
[262] S. Arita, T. Koike, Y. Kayaki, T. Ikariya, *Angew. Chem.* **2008**, *120*(13), 2481–2483. https://doi.org/10.1002/ange.200705875.
[263] *A. G.* O'Brien, A. Maruyama, Y. Inokuma, M. Fujita, P. S. Baran, D. G. Blackmond, *Angew. Chem. Int. Ed.* **2014**, 53(44), 11868–11871. doi:10.1002/anie.201407948.
[264] G. Y. Dou, Y. Y. Jiang, K. Xu, C. C. Zeng, *Org. Chem. Front.* **2019**, *6*(14), 2392–2397. https://doi.org/10.1039/C9QO00552H.
[265] T. Fuchigami, S. Inagi, *Acc. Chem. Res.* **2020**, *53*(2), 322–334. https://dx.doi.org/10.1021/acs.accounts.9b00520.
[266] M. R. Shaaban, T. Fuchigami, *Tetrahedron Lett.* **2002**, *43*, 273–276.
[267] M. R. Shaaban, H. Ishii, T. Fuchigami, *J. Org. Chem.* **2000**, *65*, 8685–8689.
[268] Y. Hou, T. Fuchigami, *J. Electrochem. Soc.* **2000**, *147*, 4567–4572.
[269] M. Hosseini, M. Sarvari, H. Sharghi, *J. Org. Chem.* **2006**, *71*, 6652. doi.org/10.1021/jo060847z.
[270] C. J. Gerack, L. McElwee-White, *Molecules.* **2014**, *19*(6), 7689–7713. https://doi.org/10.3390/molecules19067689.
[271] S. Vishnoi, V. Agrawal, V. K. Kasana, *J. Agric. Food Chem.* **2009**, *57*(8), 3261–3265. doi.org/10.1021/jf8034385.
[272] J. Chen, Z. Wang, C. M. Li, Y. Lu, P. K. Vaddady, B. Meibohm, W. Li, *J. Med. Chem.* **2010**, *53*(20), 7414–7427. .https://doi.org/10.1021/jm100884b.
[273] A. R. Kennedy, N. L. King, I. D. Oswald, D. G. Rollo, R. Spiteri, A. Walls, *J. Mol. Struct.* **2018**, *1154*, 196–203. https://doi.org/10.1016/j.molstruc.2017.10.047.
[274] D. J. Diekema, R. N. Jones, *Lancet.* **2001**, *358*(9297), 1975–1982.
[275] D. Shinabarger, *Expert Opin. Invest. Drugs* **1999**, *8*(8), 1195–1202.
[276] Y. Takeda, S. Okumura, S. Tone, I. Sasaki, S. Minakata, *Org. Lett.* **2012**, *14*, 4874–4877.
[277] Z. Zhang, J. H. Ye, D. S. Wu, Y. Q. Zhou, D. J. Yu, *Chem. Asian J.* **2018**, *13*, 2292–2306.
[278] M. T. Sabatini, L. T. Boulton, H. F. Sneddon, T. D. Sheppard, *Nat. Catal.* **2019**, *2*(1), 10–17. https://doi.org/10.1038/nature10702.
[279] J. R. Dunetz, J. Magano, G. A. Weisenburger, *Org. Process Res. Dev.* **2016**, *20*(2), 140–177. https://doi.org/10.1021/op500305 s.
[280] H. Lundberg, F. Tinnis, N. Selander, H. Adolfsson, *Chem. Soc. Rev.* **2014**, *43*(8), 2714–2742. https://doi.org/10.1039/C3CS60345H,.
[281] A. Ojeda-Porras, A. Hernández-Santana, D. Gamba-Sánchez, *Green Chem.* **2015**, *17*(5), 3157–3163. https://doi.org/10.1039/C5GC00189G,.
[282] M. T. Sabatini, L. T. Boulton, H. F. Sneddon, T. D. Sheppard, *Nat. Catal.* **2019**, *2*(1), 10–17. https://doi.org/10.1038/nature10702.
[283] M. C. Bryan, P. J. Dunn, D. Entwistle, F. Gallou, S. G. Koenig, J. D. Hayler, F. J. Weiberth, *Green Chem.* **2018**, *20*(22), 5082–5103. DOI: 10.1039/C8GC01276H.
[284] H. A. Dewia, B. S. Fangben Mengb, C. Guoa, B. Norlingc, X. Chenb, S. Lima, *RSC Adv.* DOI: 10.1039/x0xx00000x.
[285] V. V. Ryakhovskii, S. V. E. Agafonov, Y. M. Kosyrev, *Russ. Chem. Rev.* **1991**, *60*(8), 924. doi.org/10.1021/cr950005 s.
[286] J. S. Carey, D. Laffan, C. Thomson, M. T. Williams, *Org. Biomol. Chem.* **2006**, *4*(12), 2337–2347. doi.org/10.1039/B602413K.
[287] H. Huang, G. Yuan, X. Li, H. Jiang, *Tetrahedron Lett.* **2013**, *54*(52), 7156–7159. doi.org/10.1016/j.tetlet.2013.10.101.
[288] R. Vaidyanathan, V. G. Kalthod, D. P. Ngo, J. M. Manley, S. P. Lapekas, *J. Org. Chem.* **2004**, *69*(7), 2565–2568. https://doi.org/10.1021/jo049949k.
[289] L. Sun, J. H. Ye, W. J. Zhou, X. Zeng, D. J. Yu, *Org. Lett.* **2018**, *20*, 3049–3052.
[290] K. Danielmeier, E. Schierle, E. Steckhan, *Tetrahedron.* **1996**, *52*, 9743–9754.
[291] H. Senboku, K. Nagakura, T. Fukuhara, S. Hara, *Tetrahedron.* **2015**, *71*, 3850–3856.
[292] B. Wermeckes, F. Beck, *Electrochim. Acta.* **1985**, *30* (1985) 1491–1500.
[293] H. Senboku, A. Katayama, *Curr. Opin. Green Sustain. Chem.* **2017**, *3*, 50–54.
[294] I. B. Il'chibaeva, E. S. Kagan, A. P. Tomilov, *Russ. J. Org. Chem.* **2001**, *37*(11), 1592–1595. doi:10.1023/a:1013812321096.
[295] N. L. Weinberg, B. Belleau, *Tetrahedron.* **1973**, *29*(2), 279–285. doi:10.1016/s0040-4020(01)93291–0.
[296] T. Tajima, H. Kurihara, T. Fuchigami, *J. Am. Chem. Soc.* **2007**, *129*(21), 6680–6681. doi:10.1021/ja070283w.
[297] T. Tajima, T. Fuchigami, *Angew. Chem. Int. Ed.* **2005**, *44*(30), 4760–4763. doi:10.1002/anie.200500977 doi:10.1002/anie.200500977.
[298] T. Tajima, T. Fuchigami, *Chem. Eur. J.* **2005**, *11*(21), 6192–6196. doi.org/10.1002/chem.200500340.
[299] X. Ma, X. Luo, S. Dochain, C. Mathot, I. E. Marko, *Org. Lett.* **2015**, *17*(19), 4690–4693. doi:10.1021/acs.orglett.5b02084.

[300] S. H. Yang, K. L. Wu, Y. Chi, Y. M. Cheng, P. T. Chou, *Angew. Chem.* **2011**, *123*(36), 8420–8424. doi:10.1002/anie.201303587.
[301] X. Ma, X. Luo, S. Dochain, C. Mathot, I. E. Markò, *Org. Lett.* **2015**, *17*(19), 4690–4693. doi:10.1021/acs.orglett.5b02084.
[302] G. Ng'ang'a Wanyoik, O. Onomura, T. Maki, Y. Matsumur, *Org. Lett.* **2002**, *4*(11), 1875–1877. doi:10.1021/ol025865r.
[303] X. Ma, X. Luo, S. Dochain, C. Mathot, I. E. Markò, *Org. Lett.* **2015**, *17*(19), 4690–4693. doi:10.1021/acs.orglett.5b02084.
[304] X. Ma, D. F. Dewez, L. Du, L. Luo, I. E. Markó, K. Lam, *J. Org. Chem.* **2018**, X doi:10.1021/acs.joc.8b01994.
[305] P. Dabrowska, W. Boland, *ChemBioChem.* **2007**, *8*, 2281–2285.
[306] A. G. Campana, N. Fuentes, E. Gomez-Bengoa, C. Mateo, J. E. Oltra, A. M. Echavarren, J. M. Cuerva, *J. Org. Chem.* **2007**, *72*, 8127–8130.
[307] J. Xiang, M. Shang, Y. Kawamata, H. Lundberg, S. H. Reisberg, M. Chen, P. S. Baran, *Nature.* **2019**, *573*(7774), 398–402.https://doi.org/10.1038/s41586-019-1539-y.
[308] Y. Matsumura, *Org. Lett.* **2000**, *2*, 1689–1691.
[309] T. Hardwick, R. Cicala, N. Ahmed, *Sci. Rep.* **2020**, *10*(1). doi:10.1038/s41598-020-73957–6.
[310] T. Bystroň, Z. Hasnik, K. Bouzek, *J. Electrochem. Soc.* **2009**, *156*(12), E179. DOI: 10.1149/1.3231485.
[311] J. Volke, F. Liška, *Electrochem. Org. Syn.* **1994**, 45–139.
[312] H. Lund, O. Hammerich, *Org. Electrochem.* **2001**, 612.
[313] M. B. Smith. J. March, March′s Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, 5th ed.; Wiley-Interscience: New York, **2001**; p 1231.
[314] T. Sumi, T. Saitoh, K. Natsui, T. Yamamoto, M. Atobe, Y. Einaga, S. Nishiyama, *Angew. Chem. Int. Ed.* **2012**, *51*(22), 5443–5446. doi:10.1002/anie.201200878.
[315] E. G. J. Janzen, E. G. Julia, P. Liu, *J. Magn. Reson.* **1973**, *9*, 510.
[316] N. Vatistas, C. Comninellis , *Electrochemistry for the Environment* (eds C. Comninellis, G. Chen), Springer. **2010**, 229–244.
[317] J. Iniesta, P. A. Michaud, M. Panizza, C. Comninellis, *Electrochem. Commun.* **2001**, *3*(7), 346–351. doi:10.1016/s1388-2481(01)00174–6.
[318] P. Cañizares, F. Larrondo, J. Lobato, M. A. Rodrigo, C. Sáez, *J. Electrochem. Soc.* **2005**, *152*(11), 191.

Manuscript received: November 13, 2021
Revised manuscript received: January 5, 2022
Version of record online: ■■ ■■, ■■■■

REVIEW



*A. Murtaza, M. A. Qamar, K. Saleem, T. Hardwick, Zia ul haq, B. Shirinfar, N. Ahmed**

In the present state of affairs, electrochemical manufacturing of fine chemicals, pharmaceuticals and valuable compounds is not as common place as it could be and therefore, merits more attention. Herein, we describe an overview of atom economies to access fine chemicals, pharmaceuticals and value-added compounds *via* electrochemical carboxylation, fluorination, methoxylation and amide formation reactions, including their mechanistic aspects.