C–H Bond Functionalization under Electrochemical Flow Conditions


Abstract: Electrochemical C–H functionalization is a rapidly growing area of interest in organic synthesis. To achieve maximum atom economy, the flow electrolysis process is more sustainable. This allows shorter reaction times, safer working environments, and better selectivities. Using this technology, the problem of overoxidation can be reduced and less emergence of side products or no side products are possible. Flow electro-reactors provide high surface-to-volume ratios and contain electrodes that are closely spaced where the diffusion layers overlap to give the desired product, electrochemical processes can now be managed without the need for a deliberately added supporting electrolyte. Considering the importance of flow electrochemical C–H functionalization, a comprehensive review is presented. Herein, we summarize flow electrolysis for the construction of C–C and C–X (X = O, N, S, and I) bonds formation. Also, benzylic oxidation and access to biologically active molecules are discussed.

Keywords: C–H bonds activation, Flow electrochemistry, Microreactors, Green and sustainable chemistry, Reaction engineering

1. Introduction

Organic compounds have vast structural diversity that consists of chains or rings of carbon atoms decorated with a large number of hydrogen atoms.[1] Organic synthesis is the process of constructing new organic molecules either by introducing new desirable functional groups or transforming the functional group. Functionalization of the particular C–H bond is omnipresent in the organic synthesis. Selective functionalization of C–H initiates the organic synthesis reaction, although the functionalization of the C–H bond has been recognized as a challenging task in organic synthesis. C–H bond functionalization has gained attention as a new and promising area for the construction of C–C and C–X (X = O, N, S, I, etc.) bonds. C–H bond functionalization strategy would allow the versatile transformation in the organic synthesis.[2] Due to the presence of strong C(sp³)–H and C(sp³)–C(sp³) bonds, alkanes are the least reactive organic molecules.[3] Many methods are derived to activate the C–H bond of alkane. The classical method carries out functionalization of the non-reactive C–H bond by the formation of free radicals.[4] There has been explosive growth in the development of methods for C–H bond functionalization. There are many verified and simple techniques available to operate the stereoselective and site-selective functionalization in organic synthesis.[5] Enzyme catalysis, organometallic catalysis, and electrochemical approaches for the functional group introduce methods to invigorate the application of organic synthesis.[6–8]

Mostly, five methods of C–H bond functionalization are well known: (i) stepwise radical pathways,[9] (ii) carbene/nitrene insertion mechanism,[10] (iii) metal-mediated C–H bond activation,[11,12] (iv) enzymatic functionalization,[6] and (v) photochemical method.[13] Alkane transformation by using radical pathways of carbene/nitrene insertion is somewhat

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applicable to small-scale production. Using highly reactive radicals in the reaction is relatively expensive and less applicable for the functionalization of the linear alkane.\[^3\] Transition metal-catalyzed C–H bond functionalization is a relatively cost-effective and environment-friendly technique, besides many advantages, this method also suffers from very low efficiency and less selectivity.\[^3,14\] Electro-organic synthesis is the best alternative to traditional synthetic procedures for organic synthesis because it uses clean electrons from electrodes placed at their nearest proximity instead of particular reductants or oxidants.\[^15–17\] The relatively small-scale production of important chemicals can be performed in a stirred tank.

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batch reactor. However, applications of such reactors in large-scale production are limited by inefficient control over reaction parameters such as temperature, stirring efficiency, and pressure. For the first time, Kolbe studied the electrolysis of organic compounds in 1840s.\[18\] After this achievement, more researchers were concerned about electro-organic synthesis. C–H functionalization strategies have developed enormously in the last decade. Electrochemical C–H activation has been considered as a powerful strategy that uses electricity in place of non-eco-friendly chemical transformation. The continuous-flow method is a more reliable and easily optimizable procedure in preference to the traditionally used batch procedure. The continuous-flow procedure also brings numerous advantages in the pharmaceutical industry, but the implementation is not so easy.\[19\]

For electrochemical synthetic transformation, there are different strategies such as batch electrochemistry,\[20\] photo-electrocatalysis,\[21\] metallo-electrocatalysis,\[22\] organo-electrocatalysis,\[23\] etc. To reduce the use of expensive reagents, to increase the effectiveness and productivity, all the electrochemical methods are based on simple electron transfer from the electrode to the substrate or vice versa. There are three different scenarios for the electron transfer from the electrode to the substrate (Figure 1).\[24\] Electrochemistry substituted the conventional chemical oxidizing and reducing agents by inexpensive, renewable, and inherently benign electrolysis techniques.\[25\] The electrochemical reaction involves the electron transfer at the electrode-electrolyte interface.\[26\] Kolbe\[27\] pioneered the field of electro-organic synthesis in the 19th century for the decarboxylation of carboxylic acid. The application of electrochemistry in organic synthesis helps to scale up the manufacturing of organic products.\[28,29\] Due to the rapid, cost-effective, environmentally benign, and extensive synthetic application electrochemical method of C–H bond functionalization is considered a very effective technique among other traditional methods.\[27\]

Excellent heat and mass transfer, environmentally benign, and high productivity are some reasons why continuous flow electrochemical methods overcome the disadvantages of batch techniques and have been increasingly used as effective tools to boost the rate of chemical reactions.\[30\] Because of the several advantages of flow electro-organic synthesis such as due to small inter-electrodes distance small or no amount of electrolyte is consumed, continuous and safer reactions set-up, and the high surface-to-volume ratio of flow electrochemical reactor to catalyze the reaction, researchers are keen on developing the flow technique for C–H bond functionalization in organic synthesis. The implementation of the flow technique increases the rate and yield of chemical reactions.\[2,7,30,31\] The combination of flow technology and

![Figure 1. Different operation modes of electrodes in electro synthetic applications.\[25\]](image-url)
Electrochemistry provides very effective applications of electrochemistry. The development of microreactors enhanced the performance of the electrochemical flow reactions. A thin layer flow cell microreactor can be constructed by separating thin electrodes by an adhesive non-conductive tape, with a very thin channel on it for movement of electrolyte solution. Microreactor is a reactor device with a microchannel on it about micrometer scale. Yoshida et al. showed a microreactor with a PTFE membrane about 75 µm thick and 3 µm pore size. Electrochemical flow cells are becoming increasingly popular over conventional batch electrochemistry. Flow electrochemistry helps to synthesize the complex organic compound by automated flow configuration. This method of the flow technique offers safety and economic benefits by reducing the need for the purification process. There is no question on more advantages of the flow electrochemistry over conventional techniques, commercialization of the flow electrochemistry is hindered by some challenges. It is well known that photoelectrochemical cells effectively transform sunlight into chemical fuel energy. Photocatalytic cells (PEC) were first reported in the early 1980’s. Researchers are nowadays more attracted to the study and development of photoelectrochemical cells, due to their endless, inexpensive, environmentally friendly, and endless renewable sunlight source. The strong oxidizing power of photoanode and reducing the power of metal cathode of the PEC, make these cells applicable in different organic reactions. Comparatively inert C–H bonds of alkane can be functionalized using PEC, this cell is also commonly used for oxidation and coupling reactions. Besides many advantages, there are some difficulties in using photoelectrochemical cells such as complex setup, no uniform standard for equipment, difficulty in reaction scale-up etc.

1.1. Advantages of Flow Electrochemical Reactions

Flow electrosynthesis via microreactor is an environmentally friendly and green synthetic route for organic synthesis. Due to the microchannel and parallel large electrodes in the microreactor chamber, it increases activation process and reaction productivity. The main characteristics of the microreactor chambers are listed below.

1.1.1. Temperature Control

The high surface-to-volume ratio of the microchannel allows rapid heat transfer, due to which the microreactor cools rapidly. The temperature controlling mechanism of the microreactor helps to conduct the reaction that requires high temperature.

1.1.2. Safe reacting Mechanism for Hazardous Reagent

The invention of the electro-flow-based microreactor promotes environment-friendly organic synthesis. Unlike batch electrolysis, a small quantity of the reactant is required due to the micro-sized reacting channel. Hazardous and explosive chemical reactions can also be carried out in the electrochemical microreactor.

1.1.3. High Temperature and Pressure Tolerance

Due to the fast heat transfer properties of the microreactor and small micro space in the channel, an electrochemical microreactor is advantageous for those reactions that require high temperature and pressure.

1.1.4. Short Reaction Time

Minimum reaction mixing time between the reactants increases the rate of reaction. In a microreactor time required to diffuse the reactant is proportional to the square of the path length, therefore shortening of the path length speeds up the rate of reaction.

1.1.5. Mass Transfer Between Phases

Due to the high surface-to-volume ratio of the microchannel, phase boundary reactions between gas/liquid, liquid/liquid, liquid/solid are more efficient.

1.1.6. Sufficient Residence Time

Reactant molecules get sufficient time inside the microreactor channel to combine to give products. Due to the long microchannel reactant molecules can be converted into the product so the productivity of the reaction increases.

1.2. C–C Bond Formation

Over the past decades, visible light photocatalysis has made possible the so-called inaccessible redox-neutral reactions that proceed via single electron transfer (SET) mechanism. But this approach requires photocatalysts which have limitations like the significant tuning of redox potentials, high cost of the photocatalyst, and difficulty in its removal during purification step. Recently, Mo et al. proposed microfluidic redox-neutral electrochemistry (µRN-eChem) which applies to single-electron transfer (SET) redox-neutral chemistries. In conventional electrochemical systems, the larger electrode separation permits radical decomposition during their migration. But, in a microfluidic redox-neutral system, the inter-electrode gap is very thin and rapid radical transport occurs via...
diffusion. Therefore, radical decomposition could be prevented so that cross-coupling product is formed selectively. Mo et al. designed a µRN-eChem flow cell with variable interelectrode separation (25 to 500 µm). Two different glassy carbon (GC) plates were used to prepare electrodes. Thin fluorinated ethylene propylene (FEP) film was sandwiched in between the GC electrodes creating a thin-gap channel. The interelectrode distance was controlled by the thickness of the FEP spacer. The GC plates and FEP spacer were compressed in between two aluminum plates to ensure the sealing of the flow cell. An exploded view of the cell is shown in Figure 2.

![Figure 2. Exploded-view CAD drawing of the µRN-eChem flow cell.](image)

The basic conceptual framework of µRN-eChem designed by Mo et al. for the cross-coupling reaction of persistent and transient radicals is illustrated in Figure 3.

To test the performance of the µRN-eChem system, Mo et al. selected carboxylic acid as a precursor (decarboxylative Kolbe electrolysis) for an anodic transient alkyl radical whereas electron deficient aryl nitriles was selected as a precursor for cathodic persistent radical. On cathode, an electron deficient aryl nitrile undergoes a SET event to form a persistent radical anion (Scheme 1). At the same time, on the anode, alkyl carboxylic acid is deprotonated in the presence of a Bronsted base to give carboxylate anion. The carboxylate anion then undergoes SET oxidation with subsequent loss of CO₂ to form a transient alkyl radical (Scheme 1). From this experiment, Mo et al. reported that the yields of cross-coupling products were reduced with increasing interelectrode distance. Moreover, they reported improved selectivity and scale-up of the µRN-eChem system over conventional electrochemical setup. The excellent conductivity in the microfluidic channel also omits the need for additional supporting electrolyte.

Note: R-COOH, carboxylic acid (where R is the alkyl group); R*, alkyl radical; EWG, electron-withdrawing group

Radical cross-coupling is an almost diffusion-controlled phenomenon. Therefore, selective cross-coupling of radicals is a challenging task. However, if the rate of formation of persistent radical and transient radical is the same and their
lifetime is different, selective cross-coupling becomes dominant. This kinetic phenomenon of selective cross-coupling is called persistent radical effect (PRE).

Momeni and Nematollahi designed a parallel plate flow reactor for the electrochemical synthesis of inherently active compound, quinone sulfonimide (QSI) by oxidation of 4-aminophenyl ether (APE) in the presence of arylsulfinic acids (ASAs). In this way, QSIs were synthesized in a short time with excellent yields and purity without using supporting electrolyte. The cell design includes a flow cell with eight rectangular parallel plates. A carbon plate (with a thickness of 6.0 mm) was used as an anode whereas stainless steel plate (with a thickness of 2.0 mm) was used as a cathode. At the back of the carbon electrode, a copper plate (1.0 mm thickness) was placed to improve the potential distribution. The thickness of the spacer controls the interelectrode distance (Figure 4).


Most recently, Momeni and Nematollahi synthesized different biologically important pyrimidine derivatives by using electrochemical batch reactor and electrochemical flow reactor. Different catechols were converted into their pyrimidine derivatives in the presence of barbituric acid derivatives with excellent yield (Scheme 3). Some of the products were spiro compounds. The setup for a flow cell includes a working electrode of rectangular graphite plate (200×100×6 mm) and a counter electrode of stainless-steel plate (200×100×1 mm), channel length was 190.0 mm with 6.0 mm width and interelectrode gap of 1.0 mm. Likewise, in batch synthesis, carbon rod anode and stainless-steel cathode were used in 0.15 M sodium acetate solution.

1.2.1. Flow-Metallaelectro-Catalyzed C–H Activation

C–H bonds in organic compounds can be functionalized oxidatively by using oxidants such as copper(II) and silver(I) salts. As compared to the oxidation potentials of common functional groups and organic solvents, the oxidation potentials of the C–H bond are higher. This renders a serious challenge in the site-selective anodic oxidation of C–H bonds. Therefore, to avoid the unwanted oxidation of other functional groups and solvents, a mediator (redox catalyst) assisted indirect electrolysis is used in which initially electron transfer occurs between electrode and mediator and then between mediator to reactants. Transition metal catalysts are considered as one of the best candidates for mediators because simply a ligand modification can access the tuning of redox potentials of these complexes so that over potentials can be prevented. Therefore, as an alternative strategy, a combination of electrochemistry and transition metal catalysis can afford a synergistic effect for site-selective C–H functionalization.

The major challenges of the flow-metallaelectrocatalytic C–H activation are harsh reaction conditions, effective mass and electron transfer, and undesired cathodic reduction of the catalyst. For the first time, devised a flow-
rhodaelectro-catalyzed system for the annulation of aryl imidate 16 and unsymmetrical alkyne 17 (Scheme 4). The cell design includes porous graphite felt (GF) anode and a nickel plate (Ni) cathode with a thin meshed PTFE plate as a turbulence promoter between the anode and cathode. A peristaltic pump was used to pump the solution from the external reservoir to the flow reactor (Figure 5). Further optimization of the cell leads to 83% yield of the product 21 by annulation of alkyne 20 with imidate 19 (Scheme 5). For this synthesis, methanol was used as a solvent, 2.5 mol% [RhCp*Cl₂]₂ as a catalyst, and sodium pivalate (NaOPiv) and pivalic acid (HOPiv) as additives. The versatility of the approach was further tested with different imidates substrates which were successfully converted into annulated products. For instance, the annulated products 24a, 24b, 24c, 24d–e, and 24f were obtained from the corresponding imidates: sterically hindered isopropyl benzimidate, imidates with electron-releasing groups, imidates with electron withdrawing groups, heterocyclic imidates, and cyclohexene imidate, respectively (Scheme 6). The approach was also applicable to intramolecular annulation of the species 25 to give azo-tetracyle 26 (Scheme 7). A high level of functional group tolerance, regioselectivity, and easy scale-up was reported as salient features of the approach.

1.2.2. C–C Bond Formation Using Flow-Metallaelectro-Catalyzed System

Li et al. designed a method for C–C bond formation which uses N-hydroxyphthalimide esters (NHP esters) as a radical precursor. They reported continuous flow Ni-catalysed electrochemical decarboxylative C–C coupling of NPH esters 27 with aryl halides 28 (Scheme 8). The reaction was performed in a divided electrochemical flow-cell using tertiary amine as a reductant. Electrochemically generated highly reactive radicals were incorporated into Ni-catalyzed Csp³–Csp² coupling manifold to synthesize structurally diverse molecules.

The cell design includes a C-flow cell with reticulated vitreous carbon (RVC) foam attached to the anode and cathode graphite plates. The RVC foam helps to increase the

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**Scheme 2.** Electrochemical Oxidation Pathway of APE in the presence of ASA. [59]
Figure 4. Schematic of designed and constructed flow electrolysis cell. (a) Exploded view of the cell. (b) Assembled and side view of the cell. (c) Photograph of reactor.\textsuperscript{53}

Scheme 3. The structures of Catechol (11a-c), barbituric acid (12) derivatives, and synthesized products (13-15).\textsuperscript{54}

\[ R^1 = \text{H, Me, OMe} \]
\[ R^2 = \text{H, Me, Et} \]
\[ R^3 = \text{O, S} \]
surface area of the electrodes. Anodic and cathodic streams were delivered into the electrochemical cell by using a Harvard syringe pump. The two streams were separated by a Nafion membrane which allows the cross-membrane flow of ions but not neutral molecules (Figure 6, Figure 7). The proposed mechanism of the reaction is that, at the cathode, the redox-active NHP ester is reduced and decarboxylative fragmentation results in the formation of a Csp3 alkyl radical. At anode, oxidative addition of aryl halide on Ni-catalyst forms homogeneous either Ni(0) or Ni(II) species. Then, the alkyl radical is intercepted by the Ni(0) or Ni(II) species to form Ni(III) species. Finally, reductive elimination leads to the formation of Csp3/Csp2 coupling product 33 and Ni(I) species (Scheme 9). At the cathode, the Ni(I) would be reduced to Ni(0) thereby halting the catalytic cycle. Therefore, electron-rich tertiary amines are used as a sacrificial reductant that supplies electrons to the electrochemical system after their anodic oxidation.

1.2.3. Electrochemical Microflow System (Cation Flow Method)

Suga et al. designed a cation flow method that involves the continuous generation of a carbocation in the absence of nucleophiles by low-temperature electrolysis. The carbocation so formed were then reacted with carbon nucleophile in the


Figure 5. Schematic representation of the electrochemical flow reactor with rubber gasket (red) and turbulence promoter (meshed).
Scheme 5. Flow-rhodaelectro-catalysed C–H Annulation of Alkyne with Imidate.\textsuperscript{[55]}

Scheme 6. Flow-Rhodaelectro-Catalyzed C–H Activation with Imidates.\textsuperscript{[55]}
microflow system to achieve direct oxidative C–C bond formation. The reactor was made of a diflone and stainless-steel body. The cell contains two compartments separated by a polytetrafluoroethylene (PTFE) membrane (Figure 8). Dry ice baths were used to lower the temperature of the system which avoided the decomposition of carbocations. Carbocations were generated at the anode (made of carbon felt) whereas nucleophiles were generated at the cathode (made of Pt wire) and they were directly reacted to form C–C bond in the final product (Figure 9).\(^\text{[56,61]}\)

To test the effectiveness of the cation flow method, methyl pyrrolidinecarboxylate 18 (a carbamate) was used as a carbocation precursor and allyltrimethylsilane was used as a nucleophile (Scheme 6). Solution of methyl pyrrolidinecarboxylate in DCM with \(\text{Bu}_4\text{NBF}_4\) as supporting electrolyte was pumped to the anodic chamber and solution of the supporting electrolyte and trifluoromethanesulphonic acid (TfOH) was injected into the cathodic chamber (with a platinum wire cathode) as a proton source. Then, low-temperature electrolysis of 34 (Scheme 10) forms carbocation intermediate which is immediately transferred to a vessel in which it reacts with a
nucleophile (allyltrimethylsilane) to form the final coupling C–C formation product 35 (Scheme 10). Therefore, Suga et al. extended the cation flow method to a more effective electrochemical paired microflow system in which both the anodic oxidation and cathodic reduction play a role in the product formation. The two-compartment reactor divided by a diaphragm of PTFE membrane was designed. Each compartment has a channel (width $W$ 1.5 mm × depth $D$ 4 mm × length $L$ 57 mm), which is filled with carbon felt electrode made of carbon fibers (φ = 10 µm) (Figure 10, Figure 11). A carbocation is generated at the anode whereas a nucleophile is generated at the cathode. In paired electrolysis, at the anode, silyl-substituted carbamate 36 was oxidized to generate an N-acyliminium ion and at the cathode cinnamyl chloride 37 was reduced to cinnamyltrimethylsilane 38 in the presence of chlorotrimethylsilane. Finally, compounds 37 and 38 undergo cross-coupling to yield compound 39 (Scheme 11).

Later on, Suga et al. designed an integrated synthesis to combine multiple components in a single step instead of a conventional step-by-step synthesis. They performed experiments based on time integration and space integration and reported that space integration using flow microreactor systems is more effective than time integration. In the time integration experiment, carbocation intermediate N-acyliminium ion 41 was generated by the cation pool method which was stirred with an electron-rich optically active olefin 2-tert-butyl-3-methoxycarbonyloxazole 40 for 10 s at a −78 °C to generate a new cation pool 42. During this, cation 41 was added regioselectively to the carbon-bearing oxygen in 40. The newly formed cationic species 42 was reacted with allyltrimethylsilane (carbon nucleophile precursor) to give C–C coupling product 43 as a single diastereomer in 54 % yield. Hydrolysis of the compound 43 in the presence of TfOH as catalyst formed 44 with 81 % yield (Scheme 12).

Likewise, space integration was examined by using a microflow system. Suga et al. designed a microflow reactor system with two micro-mixtures (M1 and M2) and two microtube reactors (R1 and R2). Compound 40 was mixed with cation 41 in M1 to form cation 42. Then, the cation 42 was reacted with allyltrimethylsilane in M2 to give the product 43 (Scheme 13). The yield of the product was 79 % which was
significantly higher than that obtained with time integration. The reaction was carried out even at 0°C (much higher than in the time integration approach) and due to higher temperature conditions reaction was faster with better yield.\(^\text{[62]}\)

Horii and co-workers\(^\text{[63]}\) developed an electro synthetic system for anodic substitution reaction using a micro-flow reactor. They used a parallel laminar flow technique in which electrolytic solutions containing substrate and nucleophile were introduced via inlet 1 (anode side inlet) and inlet 2 (cathode side inlet), respectively (Figure 12). The channel of the microflow reactor is so small that the flow of the streams becomes parallel and laminar with a stable liquid-liquid interface. Carbocations generated at the anodic side rapidly diffuse to the bulk of the electrolytic solution and react with nucleophile at the cathodic side to form the product. Parallel laminar flow of the carbocation and nucleophile streams in the reactor prevented the nucleophile from reaching the anode and hence unwanted oxidation of the nucleophile does not occur. The issues related to the stability of the carbocation were overcome by using carbocation stabilization ionic liquid and fast diffusion of the carbocation that is possible in the laminar flow technique.\(^\text{[63]}\)

As a representative reaction, Horii and co-workers\(^\text{[63]}\) performed anodic substitution of \(N\)-(methoxycarbonyl)pyrrolidine 45 with allyltrimethylsilane 46 to form the compound 47 (Scheme 14). They reported that the use of carbocation stabilizing solvent 2,2,2-trifluoroethanol (TFE) dramatically increased the yield of product 47. The yield of 47 was further improved by using ionic liquid.
Figure 8. Electrochemical microflow reactor used for cation flow method. (a) outside (b) inside.\textsuperscript{[61]}

Figure 9. Electrochemical microflow system (cation flow method).\textsuperscript{[61]}

Figure 10. A microreactor composed of diflone and stainless-steel bodies designed for paired electrolysis: a) outside; b) inside.\textsuperscript{[61]}
Scheme 10. Schematic Diagram of “Cation Flow” System for a Typical Reaction.\textsuperscript{[60,61]}

Figure 11. Electrochemical paired microflow system.\textsuperscript{[61]}

Scheme 11. Paired Electrolysis of 36 and 37 Using the Microflow System.\textsuperscript{[61]}
Scheme 12. Cationic Three-component Coupling of Compound 40, Cation pool of 41, and Allyltrimethylsilane Based on Time Integration Followed by Hydrolysis.

Scheme 13. Space Integration of Cationic Three Component Coupling.

1.2.5. C–C Bond Formation Using Electro-Photochemistry

Recently, Qiu et al.,[64] for the first time, developed a sustainable electro-photochemical method for C–H trifluoromethylation of non-activated arenes through single electron transfer (SET) under mild reaction conditions. They performed electrophotochemical non-directed C–H trifluoromethylation of readily accessible mesitylene 48 with Langlois reagent 49 (CF₃SONa) in an undivided batch cell with platinum plate cathode and graphite felt (GF) anode. In the preliminary reaction, [Mes-Acr⁺]ClO₄⁻ was used as a photocatalyst, KOAc as a conductive additive, and CH₃CN as a solvent. The desired product 50 was obtained in 48% yield with mono to di-trifluoromethylated product ratio 93:7 (Scheme 15). However, after further examination, the process was optimized for a metal-free photocatalyst [Mes-Acr⁺]ClO₄⁻ and ruthenium photocatalyst [Ru(bpy)₃](PF₆)₂ because the best yield of the product 50 was reported with these reagents. With [Mes-Acr⁺]ClO₄⁻ as a photocatalyst, the highest yield was obtained when LiClO₄ was used as an additive in CH₃CN solvent (the yield was 85% with mono to di-trifluoromethylated product ratio 93:7), whereas with [Ru(bpy)₃](PF₆)₂ as a photocatalyst, the yield was 88% with 78:22 mono to difluoromethylated product ratio.[64] The electrophotochemical C–H trifluoromethylation of mesitylene was also performed in an electro-flow cell with graphite and nickel as anode and cathode, respectively. With [Mes–Acr⁺]ClO₄⁻, the yield of the desired product 51 was 76%, whereas with [Ru(bpy)₃](PF₆)₂ that was only 15% (Scheme 16).[64]

Scheme 15. Preliminary Electrophotocatalytic C–H Trifluoromethylation.[64]
1.2.6. C–C Bond Formation Using Electrochemical Continuous Flow System

Recently, Xu et al.\textsuperscript{[65]} developed an electrochemical continuous flow method for the synthesis of 4-(sulfonylmethyl)isoquinoline-1,3(2H,4H)-diones \textsuperscript{54} via oxidative coupling of \textit{N}-alkyl-methacryloyl benzamides \textsuperscript{52} and sulfonylhydrazides \textsuperscript{53} (Scheme 17). They synthesized varieties of sulfonylated products in moderate to excellent yields and reported excellent functional group compatibility of method.\textsuperscript{[65]}

The electro-organic technique is a powerful, environment friendly, and effective approach to obtain symmetrical and nonsymmetrical biphenyls.\textsuperscript{[66]} In this experiment, electrochemical synthesis of 3,3',5,5'-tetramethyl-2,2'-biphenol \textsuperscript{56} (Scheme 18) has been studied by changing different parameters like current density, inter-electrodes gap, the concentration of starting materials, etc.\textsuperscript{[66]} Current density were applied at a range between 2.4–45 mA/cm\textsuperscript{2} however higher current density of 45–60 mA/cm\textsuperscript{2} is found to be effective and also reduce the electrolysis time. The inter-electrodes gap was studied on 3 types 0.05 cm, 0.025 cm, 0.012 cm. An inter-electrodes gap of 0.025 cm was found to be more effective among them. Another parameter concentration of the starting material had not shown any significant effect on 0.5 mol/L and 2.0 mol/L concentrations; however, the concentration of 2.0 mol/L is highly advantageous. By analyzing the different parameters, optimized conditions were fixed. Using the same cell geometry different sized electrochemical cells were used to achieve stepwise scale-up of products. For example 2×6 cm flow electrolysis cell (Figure 13), (4×12 cm flow electrolysis cell (Figure 14), and EUT pilot cell 2×6 cm electrolysis cell (Figure 15) were studied comparatively. Table 1 represents the comparative study of achieving scale-up of products in the different electro-flow cells.

1.3. C–O Bond Formation

Oxidation of the very unreactive C–H (sp\textsuperscript{3}) bond is a highly challenging task. There are many organometallic catalytic approaches to oxidize the unreactive C–H bond.\textsuperscript{[67–69]} Pierce et al. describe hydroxylation of aliphatic C–H bond in

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**Scheme 16.** Electrophotocatalytic C–H Trifluoromethylation in Electrochemical Flow Reactor.\textsuperscript{[64]}

**Scheme 17.** Methods for 4-(Sulfonylmethyl)isoquinoline-1,3(2H,4H)-dione synthesis.\textsuperscript{[65]}

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Scheme 18. Electrolysis Conditions of Dehydrogenative Homocoupling of 55

OH

55

Glassy carbon electrodes
HFIP + 15% H2O
0.08 M NEt4Br
6.1 mA/cm²
1.2 F, 50 °C

OH

56

25 mL beaker type cell (25 mmol phenol) 46%
1.5 L beaker-type cell (1 mol phenol) 39%

Figure 13. Technical drawings of 2 cm × 6 cm flow electrolysis cell: a) Cross-section of the Teflon piece with connection for tubing, inlet, outlet, and free space for the electrode. b) Complete half-cell containing Teflon piece, the electrode (yellow), and a stainless-steel plate. c) Half-cell with gasket/ spacer on top. d) Exploded drawing of a complete divided flow electrolysis cell. For the undivided mode.

Table 1. Comparison of optimized conditions for different electrolysis cells

<table>
<thead>
<tr>
<th>Cell type</th>
<th>Solvent</th>
<th>Applied charge Q [f]</th>
<th>Temp (°C)</th>
<th>Current density J [MA/cm²]</th>
<th>Electrode material</th>
<th>Flow rate (mL/min)</th>
<th>Yield (%)</th>
<th>Production (g/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Batch (25 mL)</td>
<td>HFIP + 15 Vol% H2O</td>
<td>1.2</td>
<td>50</td>
<td>6.1</td>
<td>GC/GC</td>
<td>–</td>
<td>46</td>
<td>0.002</td>
</tr>
<tr>
<td>2×6cm flow</td>
<td>HFIP</td>
<td>1.0</td>
<td>10</td>
<td>60</td>
<td>BDD/SS</td>
<td>2.24</td>
<td>62</td>
<td>0.3</td>
</tr>
<tr>
<td>4×12 cm flow</td>
<td>HFIP</td>
<td>1.0</td>
<td>10</td>
<td>60</td>
<td>BDD/SS</td>
<td>8.95</td>
<td>58</td>
<td>1.3</td>
</tr>
<tr>
<td>EUT pilot cell</td>
<td>HFIP</td>
<td>1.0</td>
<td>0</td>
<td>40</td>
<td>BDD/SS</td>
<td>38.8</td>
<td>59</td>
<td>16.9</td>
</tr>
</tbody>
</table>

Supporting electrolyte for batch is Et4NBr (0.8 mol/L), and for flow and EUT pilot cell is MeBu3NO3SOMe (0.005 mol/L).
presence of organometallic complexes and ketone as catalyst. Jiang et al. described the visible-light induced oxidation of sp³ C–H bonds to ester and ketone. In summary, oxidation of the C–H bond is commonly achieved by highly expensive reagents in multistep reactions but, using electrochemical technology we can achieve the reaction in an exceedingly simple fashion. Continuous flow electrochemical transformation provides an increased electrode surface ratio that helps to achieve a high product ratio.
Green et al. designed a microreactor having an extended spiral electrolyte channel to study the rate of methoxylation of N-formylpyrrolidine 57 (Scheme 19). Carbon filled polyvinylidene fluoride (C/PVDF) disc as anode and circular 316L stainless steel plate act as cathode. The spiral electrolyte channel is created with a spiral spacer that permits the flow of reactants in between electrodes. The length of the electrolyte channel is 1000 mm and 2 mm in width (Figure 16). Different concentrations of the N-formylpyrrolidine were used for methoxylation with different cell current and flow rates of range 0.25 to 3.0 cm$^3$/min$^{-1}$. It is reported that repeated use at a flow rate of 0.25 cm$^3$/min$^{-1}$ at electrolyte concentration 0.05 M and 0.1 M of reactant concentration yield 0.99 fractional conversions. The fractional conversion rate of reactants at different parameters is summarized in (Table 2).

Stalder et al. used 5 drugs to test the continuous flow electrochemical oxidation that are, albendazole, diclofenac, tolbutamide, primidone, and chlorpromazine. DCF (Diclofenac) 59 0.1 M solution was prepared in (acetonitrile and water at 1:1 ratio) solution. The solution mixture was flowing in the presence of a constant current of 113 mA. The flow rate was decreased from 0.235 mL/min to 0.088 mL/min. DCF-5-OH 60 was formed up to 46% with quinone imine derivative DCF-5-QI 61 (Scheme 20).

Bian et al. explain the synthetic approach of selenium-substituted imino-isobenzofuran 63 using 2-vinylbenzamides 62 and diselenides in continuous electrochemical microreactor. (Scheme 21). The electro flow microreactor consists of cannon anode (50×50×0.5) mm and iron plate cathode (50×50×1) mm. The volume of the microflow tube is 1 mL. Mixture of 2-vinyl benzamide (0.2 mM, 1.0 equivalent), diselenide (0.1 mM, 0.5 equivalent) and lithium perchlorate (0.1 mM, 0.5 equivalent) dissolved with ACN and subjected to microreactor chamber by providing 15 mA current flow with flow rate of 225 µL/min. The percentage yield was formed quite attractive in different substituted benzamides.

Compounds containing C–O bond, for instance, esters, are successfully synthesized through carboxylate activation. However, due to less atom economy, use of toxic reagents, waste generation, and drastic reaction conditions, other methods have been studied as an alternative approach. Diederich and co-workers for the first time, applied an anodic oxidation approach for the conversion of Breslow intermediate 66 (formed by the reaction of N-heterocyclic carbene 65 with aldehyde) to intermediate 67 which reacts with an alcohol to give ester 68 (Scheme 22).

Green et al. designed an undivided microfluidic electrolyslic batch cell for oxidative esterification of aldehydes in the presence of catalyst N-heterocyclic carbene (NHC). They performed oxidative esterification of methyl 4-formylbenzoate 70 with methanol. Aldehyde 70, MeOH, thiazolium salt 69, and DMSO in THF were taken in reservoir 1 and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in THF was taken in reservoir 2. The solutions were introduced into a mixing T-
piece with a flow rate of 0.5 mL min$^{-1}$. This leads to the formation of Breslow intermediate 71 which was then oxidized to acylthiazolium 59 while passing through an electrolytic cell. The acylthiazolium 72 finally reacted with MeOH to yield 99% methyl ester 99 (Scheme 23).

Kuleshova and co-workers$^{[76]}$ successfully performed methoxylation of N-formylpyrrolidine 74a and 4-t-butyl toluene 75 by using a microfluidic electrolytic cell. Respectively, methoxylated products 74b and 77 with new C–O bonds were prepared (Scheme 24). Schematics of the experimental setup are illustrated in (Figure 17). An electrolytic round cell with circular electrodes and a star-shaped channel pattern was designed. Anode was prepared from conductive carbon/polyvinylidene fluoride (PVDF) composite whereas cathode was prepared from stainless steel.$^{[76]}$

**Scheme 20.** Electro-flow Conversion of DCF to DCF-5-OH and DCF-5-QI.$^{[72]}$

**Scheme 21.** Methoxylation of 2-Vinyl Benzamides in Presence of Diselenides.$^{[78]}$

1.4. C–I Bond Formation

Iodine is an essential trace element that is required by all living organisms, Iodine plays an important role in the endocrine system.$^{[77]}$ Organic compounds having iodine as functional groups are organic iodide. Several iodine-containing organic compounds have been found in seawater. Organic iodine in seawater is synthesized by macroalgae and phytoplankton.$^{[78]}$ Organic iodide also acts as an important reagent in organic synthesis. Zhdankin et al.$^{[79]}$ reported that organic hypervalent iodine reagent attracts the interest of many researchers as an environmentally benign oxidant in organic synthesis. In this review, we discuss the electro-flow technique to synthesize the carbon-iodide functional group through C–H bond functionalization.

Watt et al.$^{[79]}$ describe the simple and efficient technique for the synthesis of diaryliodonium salt using the electro-
chemical flow microreactor technique. In this mechanism, iodoarenes and alkyl substituted aromatic rings are coupled using a microreactor. For the synthesis of iodine complex simple microreactor was designed, made up of two aluminum
bodies (50 mm diameter and 25 mm height). 0.1 mm thin platinum foil electrode-rod was constructed in the PTFE plates (35 mm diameter and 4 mm height). These electrodes were separated by FEP (fluorinated ethylene propylene) foil of variable thickness. FEP foil consists of a thin reaction channel (3×30 mm) with channel volume of 23 µL. Diaryliodonium salt 81 was synthesized using the electrochemical microreactor by reacting iodoarene and alkyl substituted aromatic compounds. Iodoarene 78 is oxidized at anode and forms a radical cation 80, then this cation undergoes reaction with other arenes and forms an intermediate complex by losing electrons. Acetonitrile, sulfuric acid (2 M), and acetic anhydride were used as a solvent system for this reaction (Scheme 25). The amount of the product formation depends on so many factors

\[74a\] MeOH $\rightarrow$ \[74b\] 

\[CH_3\] \[\begin{array}{c} \text{MeOH} \\ -2e^-, -2H^+ \end{array}\] \[\begin{array}{c} \text{OCH}_3 \\ \end{array}\] 

\[75\] 

\[\begin{array}{c} \text{CH}_3 \\ \text{H}_3\text{C} \end{array}\] 

\[\begin{array}{c} \text{MeOH} \\ -2e^-, -2H^+ \end{array}\] \[\begin{array}{c} \text{OCH}_3 \\ \end{array}\] 

\[76\] 

\[\begin{array}{c} \text{H}_3\text{C} \\ \text{CH}_3 \end{array}\] 

\[\begin{array}{c} \text{MeOH} \\ -2e^-, -2H^+ \end{array}\] \[\begin{array}{c} \text{CO} \\ \text{OCH}_3 \\ \end{array}\] 

\[77\] 

**Scheme 24.** Methoxylation of N-Formylpyrrolidine and 4-t-Butyltoluene.\(^{[76]}\)

**Figure 17.** Schematic of the experimental setup, where (a) the solvent bottle, (b) pump, (c) ml sample loop, (d) microreactor, and (e) collection vial.\(^{[76]}\)

**Scheme 25.** Formation of Aromatic iodide by Microflow Technique.\(^{[76]}\)
such as current supply, space between electrodes, the flow rate of the substrate, solvent system, etc. (Figure 18).\textsuperscript{79}

Midorikawa et al.\textsuperscript{80} describe the formation of the aromatic iodide by mono-iodination of the aromatic compound with electrochemically generated $I^+$. First of all, iodine radical was generated by oxidation of iodine in acetonitrile given CH$_3$CNI$^+$ and I$^+$ in platinum plate anode and platinum cathode under the constant current condition in H-type divide cells (Scheme 26). Reactive iodine species were characterized by cold spray ionization mass spectroscopy (CSI-MS). Micro mixing technique was used to mix the electrochemically generated $I^+$ and 1,3-dimethoxy benzene using a microsystem consisting of a 1 mm single mixture having channel width 50 µL and a microtube reactor 500 µL×2 m at 0°C results in better mixing performance. This yields about 78% of the monoiodo aromatic compound 84.\textsuperscript{80}

1.5. C–N Bond Formations

Conventional methods used for C–H bond activation and generation of new C–N bond rely exclusively on expensive catalysts as well as the use of stoichiometric toxic oxidants. Generally, reactions are performed at elevated temperatures. Electrochemical flow reactions have now become a very strong and sustainable strategy for the construction of challenging carbon-nitrogen bonds. This review depicts the overview of C–N bond formation strategies. N-containing compounds are famous entities in natural products chemistry. Chemists have developed various conventional C–N bond formation platforms. However, such techniques require elevated temperature. To overcome this problem, the development of electrochemical methodologies has been examined.\textsuperscript{7}

Electrochemical oxidation allows a powerful and important alternative and also shows unique reaction selectivity compared

![Figure 18. Electrochemical microreactor for CI bond formation.\textsuperscript{79}]

![Scheme 26. Formation of Aromatic Iodide Using a Microreactor.\textsuperscript{80}]}
with chemical oxidation. Various electrochemical flow techniques for C–H functionalization are reported. There are various examples of C–H functionalization to yield C–N bonded biomolecules. For instance, many electro-synthetic methods are famous for the synthesis of versatile regioselective/electro-oxidative intermolecular [3 + 2] annulation method to synthesize substituted indolines 87 (Scheme 27). \cite{81}

Researchers used electrochemical flow cell successfully to synthesize indoline derivatives 90 in electrolyte free conditions in the presence of 5 mol% DDQ (Scheme 28). \cite{81}

Green and co-workers\cite{82} developed an electrochemical microfluidic cell in sequence with a heating chip for N-heterocyclic carbene (NHC) mediated anodic oxidative conversion of aldehydes to amides. Thiazolium bistriflimide 92 was used as an NHC precursor. Breslow intermediate 93 which was formed by the reaction of NHC with 3,4,5-Trimethoxybenzaldehyde 91 was oxidized anodically to intermediate 94 which reacts with benzyl amine (BnNH$_2$) to give amide 95 (Scheme 29).

Mikhail and co-worker\cite{83} developed a continuous flow method for the production of benzyl amides by anodic oxidation of aromatic hydrocarbons. An Ammonite reactor equipped with a platinum disk anode, circular stainless steel cathode, and perfluoroelastomer FFKM gasket was used for the synthesis. \cite{83} As a model substrate, p-$t$-butyltoluene 96 in acetonitrile was taken in the presence of LiBF$_4$ or Bu$_4$NPF$_6$ as an electrolyte to form compound 98 (Scheme 30). The presence of a stoichiometric amount of water was found to be crucial for the reaction. \cite{83}

Further, there was the output from continuous flow electrosynthesis. A microreactor was used having a very small inter-electrode gap (100-250 µm). This reactor can be made with an aluminum body or from polymers by using additive manufacturing technology (Figure 19). Large electrode areas separated by FEP (fluorinated ethylene propylene) make it possible to give high productivity and efficiency. \cite{29}

For the synthesis of N-heterocycles 100, a method involving electrochemical oxidation was performed using nitrogen centered radical based on the protocol described earlier. Carbamate was allowed to go for cyclization (Scheme 31). \cite{29}

Ahmed and co-workers have developed a batch electrochemical synthetic approach for cyclic urea derivatives. \cite{84} Nitrogen radicals were reacted with alkenes and then they were trapped with 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) resulting in the addition of nitrogen and oxygen to the double bond.
Scheme 29. Electrosynthesis of Amide 95 from Aldehyde 91 Mediated by Thiazolium Bistriflimide 92.\textsuperscript{[82]}

Scheme 30. Anodic Oxidation of \textit{p}-t-Butyltoluene in Acetonitrile.\textsuperscript{[83]}

Figure 19. Electrochemical flow reactor: schematic diagram.\textsuperscript{[29]}
bond. To achieve high productivity and efficiency, the researchers tried to perform similar reactions by their flow methodology by replacing the inorganic base Na₂CO₃ with the organic base Triton B. The allyl-substituted urea derivatives 101 which act as substrate was easily synthesized from monomethyl aniline and isocyanates. Cyclic ureas 102 was synthesized from substrate 101 using graphite as anode and platinum cathode electrode with the current flow of 3F in flow electrochemical microreactor. The reaction was performed on their specialized reactor in which flow rates could be easily varied (Scheme 32).[85]

Further, Nikolaienko and co-workers[86] have developed an electrochemical intramolecular C–H amination. Several valuable pyrrolidines were obtained in good yields and with enhanced chemo-selectivity. Pyrrolidines rings were the major entities in the five of eight anti-infective drugs approved in 2016 including anti-hepatitis C drug. Organic electrosynthesis can be used to minimize the total energy losses and reduce waste production and ultimately decrease the overall cost of industrial synthesis. In that way, Nikolaienko and co-workers[86] used this technique with subsequent 1,5-HAT (1,5-hydrogen atom transfer) to overcome the problem faced during C(sp³)–H amination and gave the standard protocol. The reaction was applied in either case of batch and continuous flow techniques and there was a better result in the case of the continuous flow method (Scheme 33).[86]
1.6. C–S Bond Formation

Electrochemical flow in organic synthesis is a sustainable approach to introduce the functional group. Electrolysis reaction in flow cells also helps to synthesize biologically important sulfur-containing compounds. Islam et al.\textsuperscript{[87]} comparatively studied the effectivity of batch and electron flow techniques to synthesize thiazolidine -2-imine. N-allylic thio-urea 108 was taken as the standard starting material (Scheme 34). Batch electrolysis was tested using graphite electrode as anode and platinum electrode as a cathode, with a constant current of 10 mA. CH\textsubscript{3}CN:H\textsubscript{2}O (19:1) was used as the solvent in the electro-flow system. 35% product was formed due to the incomplete product conversion in batch electrolysis. Then another reaction at the same concentration of reagent at 60°C in three-necked round bottom flasks was equipped with graphite electrode as anode and platinum as a cathode. 62% product conversion was observed; however, the product conversion was not sufficient.\textsuperscript{[87]}

The reaction was transferred in the electro-flow setup (Figure 20). The substrate was used at a concentration of (0.025 M) with a capping agent at a similar solvent ratio at a flow rate of 0.2 mL/min. Electrolysis was carried out at 1.0–3.0 F electricity, however full conversion of the product takes place at the electricity of 3.0 F.\textsuperscript{[87]}

Huang et al.\textsuperscript{[91]} studied the effective dehydrogenative C–S cross-coupling reaction in flow electrolysis. Electrochemical C–S cross-coupling by evolving H\textsubscript{2} is an effective method to

Scheme 33. Regioselective Intramolecular C(sp\textsuperscript{3})–H Bond Amination.\textsuperscript{[86]}

Scheme 34. Electro-Flow Technique to Synthesize Thiazolidine –2-imine.\textsuperscript{[87]}
introduce the C–S bond in organic reaction. An electro flow cell was designed with a platinum cathode and C/PVDF anode (Figure 21). Due to the high electrochemical stability and low over-potential for reduction platinum foil was used as cathode. The reaction condition was set up as a flow rate of 0.3 mL/min and an electrical field of 35 mA for 24 hour. Mix solvent of MeCN:TFA (9:1) in presence of Sc(OTf)$_3$ (0.3 equiv) were used. In this condition, 1,4-benzoxanthines were synthesized by intermolecular dehydrogenation of C–S coupling (Scheme 35).

Folgueiras-Amador et al. studied the electrochemical synthesis of the thiazolo [4,5-C] quinolone B 113 from (N-(quinoline-3-yl) butanethioamide) 112 (Scheme 36). The flow electrolysis consists of platinum as cathode and graphite as anode with a surface area of 8.2 cm$^2$ each. A mixture of acetonitrile and methanol was used as a solvent. Electron flow was supported by a low current density of 0.49 mA cm$^{-2}$. By increasing the substrate concentration and flow rate high product conversion can be obtained, (Table 3 represents the percentage of conversion of the product by changing different variables.)
1.7 Benzylic Oxidation

The benzylic C–H bond is considered the center for the many useful and interesting transformations for preparing varieties of valuable compounds. The oxidation reaction is the most important reaction that can be performed on benzylic position and is heavily performed in synthetic chemistry.\[90,91\]

Due to the massive importance of benzylic C–H oxidation reactions along with so many complications with the traditional method of such reactions, a new and more sophisticated methodology is always desirable. In this report, different successful strategies are discussed for such reactions based upon the electrochemical flow reactions. Mo and co-workers\[92\] have reported electrochemical reactions that were mediated in the air with N-hydroxyphthalimide (NHPI) 117 for the benzylic oxidation and then compared with the batch process simultaneously using varied reaction parameters. They developed new sustainable procedures that involve no metal and are compatible with heterocycles. Two decomposition mechanisms were observed i.e., reductive decomposition of NHPI and (Phthalimide-N-oxyl) PINO self-decomposition. To prevent reductive decomposition of NHPI at the cathode, a Nafion membrane was introduced to check the crossover of NHPI using the RVC electrode on either side. The mechanism of the reaction started with the abstraction of proton from the NHPI by pyridine followed by anodic electron transfer, which leads to PINO radical 118. PINO facilitated the easy hydrogen abstraction from the benzylic compounds to give benzyl radical. The benzyl radical underwent decomposition in presence of molecular oxygen to yield a carbonyl compound. To check the self-decomposition of PINO radicals, the benzyl hydrogen abstraction rate was matched with the PINO radical generation by controlling the overpotential across the electrodes. The whole experiment was monitored using a cyclic voltammetry curve. Hence this study focused on the cost-effective RVC cathode in place of the platinum electrode and improved the slow kinetics of electrochemical flow reaction by the use of NHPI and gaseous molecular oxygen as co-oxidant for the benzylic oxidation reactions (Scheme 37).

Another study conducted by Roth and co-workers\[93\] has developed a new tool in electro-organic synthesis for 4 or 6

<table>
<thead>
<tr>
<th>Entry</th>
<th>Concentration [molL(^{-1})]</th>
<th>Flow rate [mLmin(^{-1})]</th>
<th>Current density [mAcm(^{-2})]</th>
<th>Current [Fmol(^{-1})]</th>
<th>(^1)H NMR conversion [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1[^{[a]}]</td>
<td>0.025</td>
<td>0.05</td>
<td>0.49</td>
<td>2.0</td>
<td>33</td>
</tr>
<tr>
<td>2[^{[a]}]</td>
<td>0.98</td>
<td>4.0</td>
<td>60</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>3[^{[a]}]</td>
<td>1.46</td>
<td>6.0</td>
<td>98</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0.025</td>
<td>0.05</td>
<td>1.46</td>
<td>60</td>
<td>&gt;99</td>
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<tr>
<td>5</td>
<td>0.1</td>
<td>2.93</td>
<td>&gt;99</td>
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</tr>
<tr>
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<td>5.85</td>
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<td>11.71</td>
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<td>[^{[b]}]</td>
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<td>&gt;99</td>
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</tr>
<tr>
<td>9</td>
<td>3.90</td>
<td>2.0</td>
<td>90</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\[^{[a]}\] 5 mol % of TEMPO. \[^{[b]}\] 97 % isolated yield.

1.7 Benzylic Oxidation

The benzylic C–H bond is considered the center for the many useful and interesting transformations for preparing varieties of valuable compounds. The oxidation reaction is the most important reaction that can be performed on benzylic position and is heavily performed in synthetic chemistry.\(^{[90,91]}\) Due to the massive importance of benzylic C–H oxidation reactions along with so many complications with the traditional method of such reactions, a new and more sophisticated methodology is always desirable. In this report, different successful strategies are discussed for such reactions based upon the electrochemical flow reactions. Mo and co-workers\(^{[92]}\) have reported electrochemical reactions that were mediated in the air with N-hydroxyphthalimide (NHPI) 117 for the benzylic oxidation and then compared with the batch process simultaneously using varied reaction parameters. They developed new sustainable procedures that involve no metal and are compatible with heterocycles. Two decomposition mechanisms were observed i.e., reductive decomposition of NHPI and (Phthalimide-N-oxyl) PINO self-decomposition. To prevent reductive decomposition of NHPI at the cathode, a Nafion membrane was introduced to check the crossover of NHPI using the RVC electrode on either side. The mechanism of the reaction started with the abstraction of proton from the NHPI by pyridine followed by anodic electron transfer, which leads to PINO radical 118. PINO facilitated the easy hydrogen abstraction from the benzylic compounds to give benzyl radical. The benzyl radical underwent decomposition in presence of molecular oxygen to yield a carbonyl compound. To check the self-decomposition of PINO radicals, the benzyl hydrogen abstraction rate was matched with the PINO radical generation by controlling the overpotential across the electrodes. The whole experiment was monitored using a cyclic voltammetry curve. Hence this study focused on the cost-effective RVC cathode in place of the platinum electrode and improved the slow kinetics of electrochemical flow reaction by the use of NHPI and gaseous molecular oxygen as co-oxidant for the benzylic oxidation reactions (Scheme 37).\(^{[92]}\)

Another study conducted by Roth and co-workers\(^{[93]}\) has developed a new tool in electro-organic synthesis for 4 or 6
electrons benzylic oxidation called a continuous-flow microfluidic-electrochemical device (flux module) (Scheme 38). They have used electron-rich substrate PMT (p-methoxy toluene) 119 and examined the microfluidic electrochemical reaction conditions. A systematic electrochemical cell used in the study was designed as a plate-based microfluidic cell (Figure 22). PMT was allowed to pass into the flux module at varied flow rates, and the products were monitored with the help of proton nuclear magnetic resonance (1H-NMR), liquid chromatography/mass chromatography (LC/MS). The effect of substituents in the substrate was also demonstrated using varied para substituents as shown in Table 4. The issue of reproducibility was also addressed by monitoring the product ratio.

### 1.8. Biologically Active Molecules

Over the last two decades, there has been surplus advancement in the C–H functionalization strategies and the application of those technologies for the synthesis of complex targets like natural and pharmaceutical agents. The modification of the C–H bonds with transition metal-catalyzed form has made it possible to synthesize numerous biologically active molecules and natural products. Such tools have the power to streamline multistep chemical processes by rendering functional group interconversion unnecessary. The synthetic approaches toward transition metal-catalyzed transformations at C–H bonds are divided into two categories: Outer sphere and inner sphere mechanisms. The outer sphere mechanism occurs when there is the direct interaction of the C–H bond with the ligand coordinated with the central metal whereas the formation of a carbon-metal bond as a result of C–H bond

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**Scheme 37.** Electrochemical Reaction for Benzylic Oxidation.  

**Scheme 38.** Electro Benzylic Oxidation in Continuous Flow.
cleavage leads to the formation of the inner-sphere mechanism. Here are some best examples of transition metal-metal catalyzed biologically active molecules. Schipper et al.\cite{99} were the leading researchers in C–H functionalization. They devised a new protocol for aryl C–H bond functionalization and demonstrated the power of this process for rapidly crafting modified arene and heteroarene derivatives.

Flow electro-chemistry is a very beneficial tool to synthesize biologically active molecules. Kabeshov et al.\cite{100} describe continuous flow electrochemistry as an enabling tool, that permits the direct preparation of a library of the indole alkaloids. Continuous flow conditions were applied to methoxylation at α-position of cyclic amine (varying ring size) with N-protected pyrrolidine, piperidine, azepane, and morpholine. α-methoxylation of cyclic amine followed by Pictet-Spengler reaction with tryptamine (two-step synthesis) (Figure 23), Nazlinine synthesized as product, and the yield percentage is 59% (Scheme 39).\cite{100}

<table>
<thead>
<tr>
<th>Exp.</th>
<th>R-group</th>
<th>Oxidation peak potential (V)</th>
<th>Electrons (F/mol)</th>
<th>Temp. (°C)</th>
<th>Aldehyde:ester isolated yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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<td>3</td>
<td>0</td>
<td>21:0</td>
</tr>
<tr>
<td>2</td>
<td>p-OMe</td>
<td>1.66</td>
<td>7</td>
<td>65</td>
<td>0:62</td>
</tr>
<tr>
<td>3</td>
<td>p-tBu</td>
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<td>8</td>
<td>65</td>
<td>38:0</td>
</tr>
<tr>
<td>4</td>
<td>p-OAc</td>
<td>2.14</td>
<td>8</td>
<td>65</td>
<td>n/a¹</td>
</tr>
<tr>
<td>5</td>
<td>p-iPr</td>
<td>2.16</td>
<td>10</td>
<td>65</td>
<td>24:0:9³</td>
</tr>
<tr>
<td>6</td>
<td>p-Cl</td>
<td>2.22</td>
<td>8</td>
<td>65</td>
<td>32:0</td>
</tr>
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<td>7</td>
<td>p-CN</td>
<td>2.52</td>
<td>8</td>
<td>65</td>
<td>n/a²</td>
</tr>
<tr>
<td>8</td>
<td>p-NO₂</td>
<td>2.72</td>
<td>8</td>
<td>65</td>
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<tr>
<td>9</td>
<td>o-OMe</td>
<td>n/a</td>
<td>7</td>
<td>65</td>
<td>3:0:10²</td>
</tr>
</tbody>
</table>

¹ Obtained by cyclic voltammetry, vs. SCE. ² Deacetylation occurs. ³ Isolated yields for aldehyde:ester: methoxy-aldehyde. ⁴ No oxidation.

2. Conclusion and Perspective

Different examples and approaches represented in this review genuinely show the great usefulness of the electrochemical flow technique in the field of organic synthesis to functionalize C–H bonds. Electrochemical flow reactors overcome the
limitation of different traditional techniques, by improving the C–H bond activation time and cost. Due to the environmentally benign, high surface-to-volume ratio, and attractive mass transports between phases, flow electrochemical technology is useful in organic synthesis. Besides many advantages, this method is used only in limited chemical and pharmaceutical industries due to the complex and expensive setup. One of the several challenges that limit the application of flow electrochemistry in the industrial field includes the formation of insoluble solids as the main product or side product which can cause a problem in uniform flow. Moreover, during electrochemical synthesis, different gases like N₂ or H₂ are produced that create a gas-liquid segment and affect the quality of the product. Further research and development of microreactors with easy setup and economic electrochemical flow microreactors will certainly contribute to the field commercialization of electro-flow techniques.

**Scheme 39.** Continuous Flow Electrochemistry Approach to Synthesize Nazlinine Via Two Steps.¹⁰⁰

---

**Step 1: Flow electrochemistry**

\[
\begin{align*}
H \quad & \quad \text{flow rate} = 120 \text{ mL/min} \\
\text{BOC} \quad & \quad \text{electrolyte} = \text{Et}_3\text{N}^+\text{BF}_4^- \text{ (20 mol%) } \\
122 \quad & \quad \text{current} = 43 \text{ mA} \\
\end{align*}
\]

**Step 2: Microwave irradiation**

\[
\begin{align*}
\text{solvent} & = \text{H}_2\text{O} \text{ (0.1M)} \\
\text{temperature} & = 130 \text{ °C} \\
\text{acid} & = \text{CSA (6 equiv)} \\
\text{time} & = 0.5 \text{ hr} \\
124 \quad & \quad \text{125a, R=H} \\
125b, R=6-F \quad & \quad 125c, R=7-Me \\
125d, R=5-Br
\end{align*}
\]

<table>
<thead>
<tr>
<th>123b (equiv)</th>
<th>CSA (equiv)</th>
<th>isol. yield</th>
<th>Nazlinine (126b) 59% over 2 step</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>6</td>
<td>25%</td>
<td>(from 123b+125a)</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td>55%</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>30</td>
<td>90%</td>
<td></td>
</tr>
</tbody>
</table>

¹⁰⁰ Review THE CHEMICAL RECORD Chem. Rec. 2022, e202100338 (34 of 37) © 2022 The Authors. Published by The Chemical Society of Japan & Wiley-VCH GmbH
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References


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Technology-driven electrocatalysis using microreactors for typically inert C–H bonds functionalization to generate molecular complexity, will allow access various chemicals (such as medicinally relevant compounds, fine chemicals, and other valuable derivatives) in continuous, scalable, and sustainable fashion. Flow electrochemistry would be a future enabling technology to handling challenging and difficult synthesis for medicinal and pharmaceutical process chemistry in an environmentally benevolent way.