

Arenes and Heteroarenes C–H Functionalization Under Enabling Conditions: Electrochemistry, Photoelectrochemistry & Flow Technology

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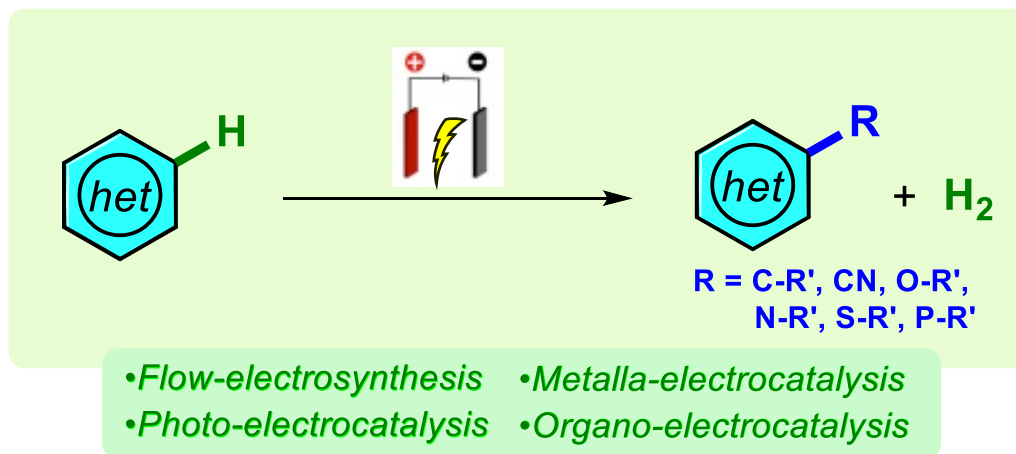
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Keywords: C–H functionalization; Flow electrosynthesis; Photoelectrocatalysis; Metalla-electrocatalysis; Organo-electrocatalysis

Abstract:

C-H bond functionalization generates molecular complexity in single-step transformation. However, the activation of C-H bonds requires expensive metals or stoichiometric amounts of oxidizing/reducing species. In many cases, they often require pre-functionalization of starting molecules. Such pre-activating measures cause waste generation and their separation from the final product is also troublesome. In such a scenario, reactions activating elements generating from renewable energy resources such as electricity and light would be more efficient, green, and cost-effective. Further, incorporation of growing flow technology in chemical transformation processes will accelerate the safer accesses of valuable products. Arenes & (hetero) arenes are ubiquitous in pharmaceuticals, natural products, medicinal compounds, and other biologically important molecules. Herein, we discussed enabling tools and technologies used for the recent C–H bonds functionalization of Arenes / (Hetero)Arenes.



Introduction

In recent years, there has been a correlation between the implementation of new technologies and quality compliance in scientific research ^[1–2]. With the growing concern about the environment and the impacts on nature during chemical processes, the industry is constantly highlighting the need for synthetic methods with less residue formation. Considering this, chemists are seeking to develop synthetic methods to reduce or, even more desirable, avoid the generation of waste^[3]. Thus, the development and integration of new technologies in organic synthesis, as well as the use of more efficient and environmentally friendly routes are desirable. The electrochemical coupling via anodic oxidation of R–H stands out for generating only hydrogen gas as waste via cathodic reduction, in which compared to other methods that generate large amounts of by-products, the electrochemical oxidative method delivers the same product in environmentally friendly conditions ^[4–5]. Although it may appear to be a disadvantage, there are situations where using a large amount of electrolyte is necessary in electrosynthesis reactions. This is often required to maintain efficient process performance or to control reaction conditions, and to ensure proper electrical conductivity. In systems with high electrical resistivity or low ionic mobility, a large amount of electrolyte may be necessary. Furthermore, using a large amount of electrolyte can increase the mass transfer of reactive species to the electrodes, improving the efficiency of the reaction. However, to overcome these limitations, new strategies are being developed, for example Little and co-workers have developed a polymeric ionic liquid–Super P carbon black composite ^[6]. The system allows electrolysis to be performed without adding an additional supporting electrolyte, with efficient recovery and reuse.

Commonly, to favor a chemical transformation it is necessary for an atom susceptible to cleavage, substitution, addition or migration. The C–H functionalization may represent a change in this logic, since it is possible to obtain a functionalization of C–H bonds even in the presence of apparently more reactive functional groups^[7–8], however regio- and chemoselectivity represent the greatest challenges for chemists. This process can be induced by an external energy source, a neighbor functional group with the electronic or steric features, and/or an external agent, making a specific atom more reactive for synthetic transformation ^[9]. Several reports describe progress using electrosynthesis for the functionalization of C–H bonds, increasing the selectivity, making cleaner, more efficient, safer, and often avoiding the use of external oxidizers^[9–12], being an emerging strategy for the discovery of new molecules, also of great interest to the medicinal

chemistry^[13–14]. Many organic synthesis techniques can be elegantly coupled with the electrolytic cell, such as batch^[15–16], continuous flow^[17–19], microwave^[20–21] or photochemical reactions^[22–26]. Likewise, electrosynthetic processing of organic chemicals on an industrial scale has been carried out, with the production of compounds such as sorbitol, mannitol, benzidine, hydroquinone, 1,4-dihydronaphthalene, salicylic aldehyde, chloroform, iodoform, vanillin, pinacol, chloral, indigo, etc^[27].

To help the reader understand the technique of electrosynthesis, we recommend the review article recently published by Gerhard Hilt^[28] which highlights the basic strategies and types of applications in organic electrochemistry, as well as the article published by Charlotte Willans and co-workers^[29] that aims to facilitate the exploration of electrosynthesis to newcomers. Likewise, we highlight an interesting discussion on the advantages of electrosynthesis compared to traditional methods, presented by Lei and Yuan^[5].

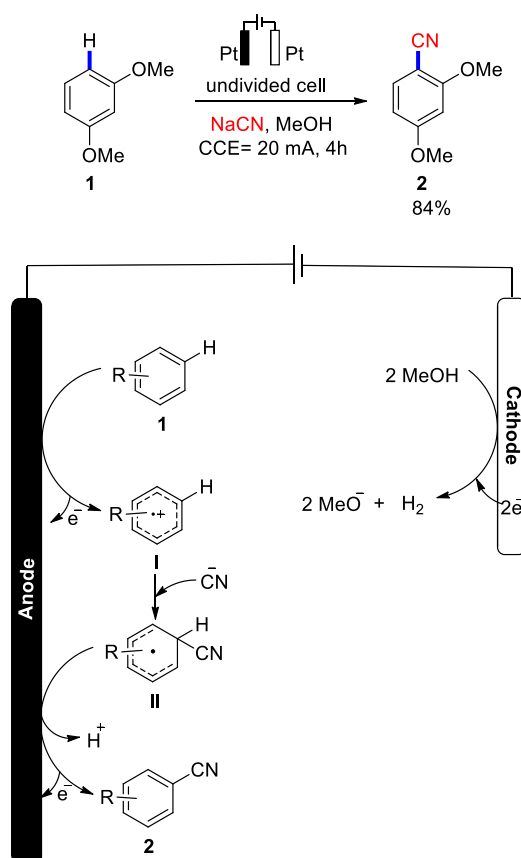
In addition to the advantages of electrosynthesis, combining it with other techniques such as organic photochemistry can lead to even more benefits. Organic photoelectrochemistry is a rapidly growing field that has gained significant attention in recent years due to its potential for renewable energy conversion and storage applications. However, with so many different sub-types and combination strategies, it can be challenging for readers to navigate the concepts and nomenclature of this field. Therefore, to aid readers in understanding the fundamental principles and current advancements in organic photoelectrochemistry, introductory reviews have been recommended. These reviews can provide a comprehensive overview of the different sub-types and combination strategies, as well as the basic principles of photoelectrochemical reactions and their applications^[30–31].

Herein, this review article aims to provide an overview of recent advances in electrochemical arenes/(hetero) arenes C–H functionalization through batch reactions, continuous flow, metalla-, photo- and organo-electrocatalysis. The development of methodology and mechanistic studies was emphasized, seeking to provide inspiration for future synthetic applications in the field of electrosynthesis in organic chemistry.

1. Arenes / Heteroarenes C–H Functionalization via batch electrochemistry

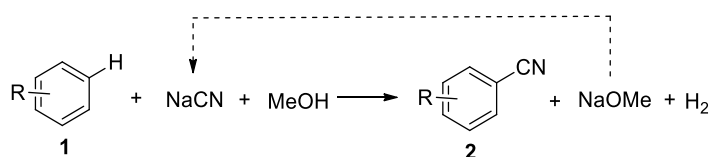
In the past ten years, C–H functionalization technologies have advanced significantly, as evidenced by the large number of publications that have been made in the literature and are attracting significant interest from researchers in various fields^[32–34], with the protocols being mostly in batch conditions^[33]. So, neither flow nor batch are novel concepts. The real purpose of batch technology must be acknowledged, even when flow chemists urge getting rid of "outdated" batch technology. Batch synthesis allows you to perform a wide range of tasks without requiring you to learn numerous new skills. However, it can be highly inefficient in a world with narrow profitability margins and environmental concerns.

Batch technology is well-known, straightforward and versatile. The same batch reactor design is used for process development from the lab to the production scale, which speeds up research and lowers costs. The most cost-effective approach to carry out many chemical operations is still batch technology. In order to explain the C–H functionalization via batch electrochemistry, in 2018, Gooßen and co-workers reported that an open, simple and undivided electrochemical cell using sodium cyanide (NaCN) as the reagent allows for the electrochemical C–H cyanation of arenes and heteroarenes to occur at room temperature in methanol (MeOH). Adsorbed cyanide maintains the quality of the platinum electrodes, enabling the conversion of a remarkable variety of electron-rich substrates all the way down to dialkylarenes. Due to the abundance of nucleophilic cyanide sources and the difficulty of handling and storing electrophilic cyanide reagents, electrochemical oxidation would be a highly advantageous technique for aromatic C–H cyanations. The benzonitrile**2**, along with hydrogen and one equivalent of base, would result from the electrochemical coupling of NaCN with 1,3-Dimethoxybenzene**1** in 84% yield as a single isomer using methyl alcohol with low water content. NaCN was selected as cyanide source because it is non-volatile from a safety standpoint and because its ionic nature allows us to avoid using more expensive supporting electrolytes. At a current of 20 mA for four hours, galvanostatic electrolysis was performed^[35]. The arene underwent sequential anodic oxidation to produce radical cation**I**, which was then attacked by the cyanide nucleophile to produce cyclohexadienylradical**III**, which experienced additional oxidation to produce benzonitrile**2** (Scheme 1).



Scheme 1: Electrochemical Synthesis of aryl nitrile 2 under constant current electrolysis (CCE).

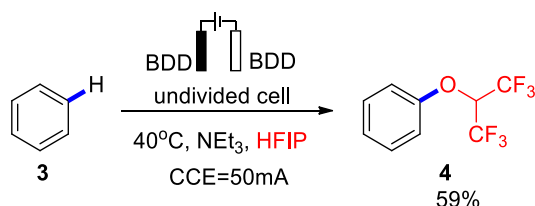
Hydrogen cyanide can be used to refill the cyanide electrolyte, providing the possibility of industrial C–H cyanation without the use of salt (Scheme 2).



Scheme 2: Perspective industry process: combining electrolytic H₂ evolution with anodic cyanation

The 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) aryl ethers 4 were electrochemically obtained by Waldvogel and co-workers employing boron-doped diamond (BDD) electrodes in up to 59% of yield (Scheme 3). Triethylamine (Et₃N) was employed as a base because, when combined with HFIP, it creates a highly conductive medium, eliminating the need for additional supporting

electrolytes. Design of Experiment (DoE) methodologies were used to optimise the synthesis and provide a thorough understanding of the importance of the experimental parameters^[36].

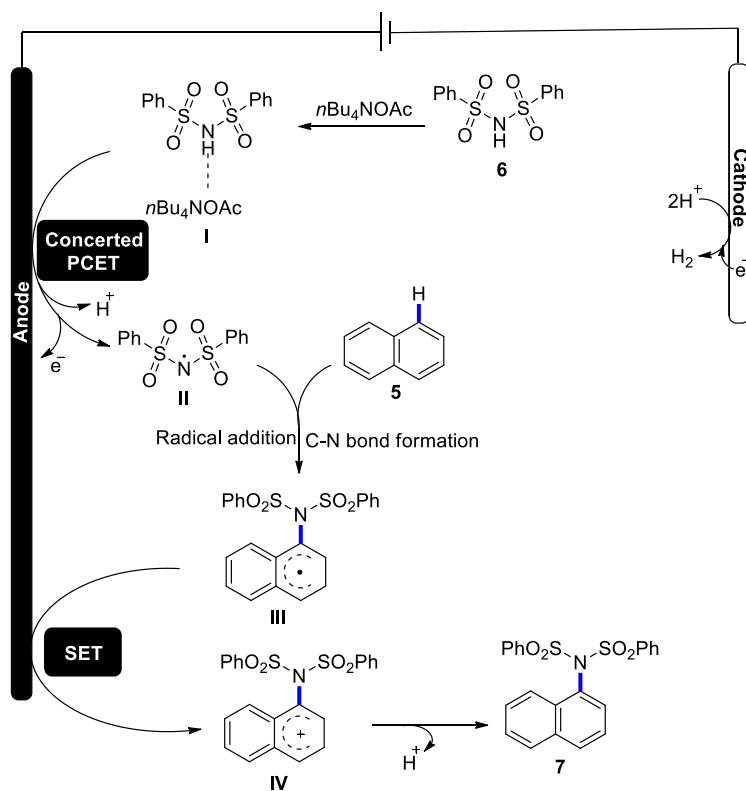
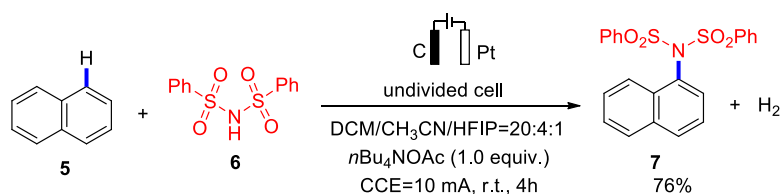


Scheme 3: Electrochemical Synthesis of 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) aryl ethers **4**

A procedure for the dehydrogenative C(sp²)-H/N-H cross-coupling between arenes/alkenes and sulfonimides that is brought on by electrochemical oxidation has been developed. It was possible to complete this reaction without the need of a transition metal catalyst or a stoichiometric extra oxidant. A wide range of aryl sulfonimides and alkenylsulfonimides could be obtained using the electro-synthetic approach. The simplicity with which the reaction can be scaled up shows this technique's potential for synthetic synthesis. The electro-oxidative C-H imidation using naphthalene **5** (0.4mmol) as a template platform and dibenzenesulfonimide **6** (1.5equiv.) as the nitrogen supply were considered. By utilising a carbon rod-anode and a platinum plate-cathode in an undivided cell with a constant current of 10 mA for 4 hours at room temperature, the cross-coupling product **7** can be produced in acetonitrile with a 43% isolated yield. The electrolyte and base utilised were both tetrabutylammonium acetate. A mix-solvent system, DCM/MeCN/HFIP = 20:4:1, provided the greatest result (76% isolated yield)^[37].

A possible mechanism was predicted (Scheme 4). Tetrabutylammonium acetate and the dibenzenesulfonimide N-H bond would first create a hydrogen-bonded complex **I**. The resultant adduct **I** would go through a coordinated proton-coupled electron transfer event along with a single electron oxidation on the anode, which would cause the N-H bond to homolyze and result in the generation of the crucial sulfonimidyl radical intermediate **II**. A new C-N bond and a vicinal radical **III** with a carbon core were produced by the following radical addition to naphthalene. The radical species was subsequently subjected to further oxidation in order to produce a carbon cation intermediate **IV**, which was subsequently aromatized in order to produce the aryl C(sp²)-H imidation product **7** via proton deletion. During the course of the reaction, concurrent cathodic

reduction of the obtained protons would produce hydrogen gas, avoiding the need for an external oxidant to complete the transformation.

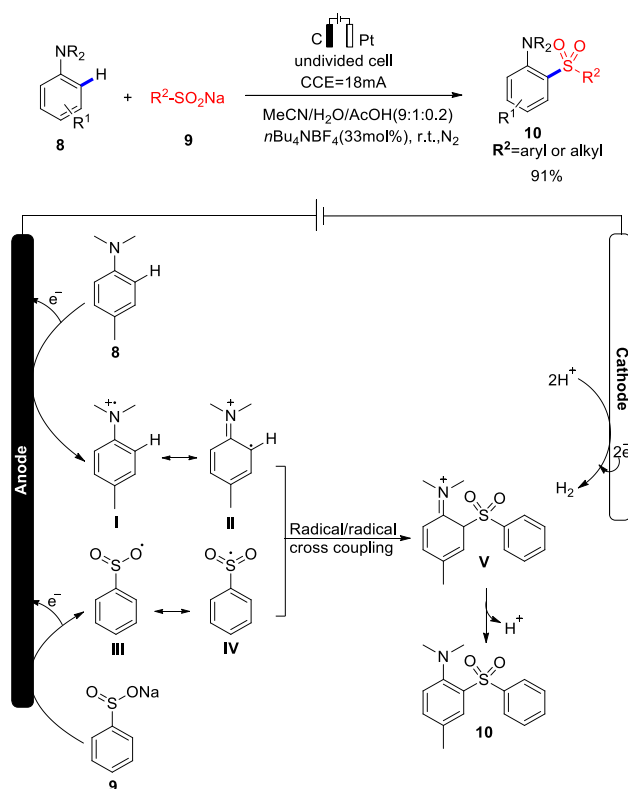


Scheme 4: Electrochemical Synthesis of N-(naphthalen-1-yl)-N-(phenylsulfonyl)benzenesulfonamide **7**

Sulfones are extremely adaptable basic components that have several uses in the pharmaceutical, agrochemical, and functional industries^[38]. Lei and co-workers proposed an oxidatively C–H sulfonylate anilines electrochemically without the use of a metal catalyst or external oxidant. When acetonitrile, water, and acetic acid (10.2 mL, 9/1/0.2, v/v/v) are used as the solvent and various

sodium sulfonates as the electrolyte, the necessary products can be produced in an undivided cell at 18mA constant current for two hours with up to 96% yield^[39]. Using *n*-Bu₄NBF₄ as the electrolyte and CH₃CN/H₂O as co-solvents for 3 hours in an undivided cell (a three-necked round-bottomed flask) furnished with a carbon rod anode and a platinum plate cathode. In 2019, Wu and co-workers reported the preparation of an anodic C–H sulfonylation product with a 91% yield^[40].

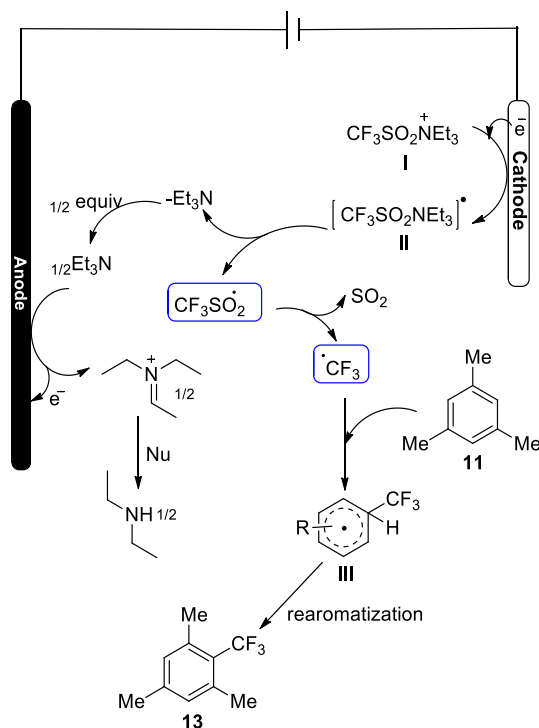
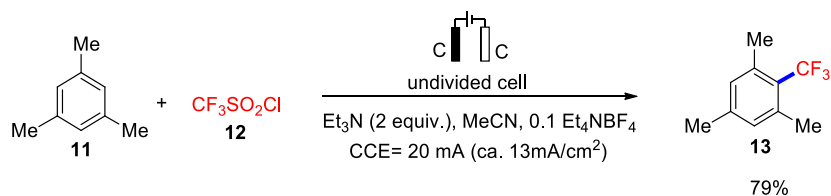
The suggested mechanism in Scheme 5 is as follows. First, the anodic oxidation of sulfonate salts produces the arylsulfonyl radical **IV**. Aniline **8** underwent oxidation at the same moment, resulting in radical cation **I**. Then, through tautomerization, radical cation **I** would yield radical cation **II**. Arylsulfonyl radical **IV** and radical cation **II** undergo radical/radical cross-coupling before being successively deprotonated and aromatized to produce the required sulfonylated aniline **10**. During the reaction, the co-solvent water or acetic acid may be reduced at the cathode to produce hydrogen gas (Scheme 5).



Scheme 5: Electrochemical Synthesis of sulfonylated aniline **10**

Recently, Cantillo and co-workers described for the first time that arenes and heteroarenes undergo cathodic-trifluoromethylation. Mesitylene **11** was used as a template platform (Scheme 6), and graphite was used as the anode and cathode materials in an undivided cell arrangement (IKA ElectraSyn 2.0). In order to elucidate the oxidation product of the amine, in addition to Et₃N, other bases were investigated. Likewise, assays with MeCN-d₃ helped to understand the electrochemical trifluoromethylation reaction^[41].

The suggested reaction mechanism tells about a change that would mostly occur on the cathode surface. A neutral radical is produced when trifluoroammonium complex **I** is reduced by one electron. The process is based on an electrochemical reduction of an unstable triflyltriethylammonium complex produced in-situ from triflyl chloride and triethylamine, which results in the production of CF₃ radicals that are captured by arenes on the cathode surface.



Scheme 6:Electrochemical synthesis of trifluoromethyl arene **13**

Even having a long history, electroorganic synthesis did not for a very long time contribute to the mainstream of chemical study. This is most often caused by a lack of tools and established procedures. However, organic electrochemistry is currently experiencing a revival, and a wide variety of intriguing electrochemical transformations and techniques have been devised, not just for academic reasons but also for massive industrial production. Electrochemical processes can be naturally green, environmentally safe, and simple to manage to reach high degrees of selectivity, depending on the source of electricity. Furthermore, it is possible to produce and consume hazardous reagents and reactive or unstable intermediates in a secure manner. Electrochemical flow cells can be used to overcome some of the drawbacks of conventional batch-type electrochemical processes, such as the constrained electrode surface, the requirement for supporting electrolytes, and the challenges of scaling up. High surface-to-volume ratios in microreactors make it possible to precisely manage the temperature, residence duration, flow rate,

and pressure. Furthermore, handling of small amounts, improved mass and heat transmission, and effective mixing reduce safety issues and simplify scaling-up procedures. In contrast to conventional batch-type electrolysis cells, electrolysis under flow circumstances lowers the likelihood of overoxidation because the reaction mixture is flown continually out of the reactor^[28].

2. Arenes / Heteroarenes C–H Functionalization via flow-electrochemistry

The interest in electrochemical C–H functionalization in organic synthesis is expanding quickly. The flow electrolysis procedure is more environmentally friendly and allows for optimum atom economy. As a result, reaction times can be speedier, workplaces can be safer, and selectivities can be higher. With the use of this innovation, the issue of over-oxidation can be mitigated, and side products may even not form at all. Electrochemical processes can now be controlled without the requirement for a purposefully supplied supporting electrolyte thanks to flow electro-reactors, which have electrodes that are closely placed where the diffusion layers meet to generate the desired result. Despite its many benefits, this approach is only employed in a small number of chemical and pharmaceutical firms because of the elaborate and costly setting. The creation of insoluble substances as the primary or by-product, which might interfere with uniform flow, is one of the many difficulties that restrict the use of flow electrochemistry in the industrial field. Additionally, other gases including H₂ or N₂ are formed during electrochemical synthesis, which results in a gas-liquid phase and affects the product's quality. The implementation of electro-flow methodologies will undoubtedly benefit from additional advancement and research of micro-reactors with simple setup and affordable electrochemical flow microreactors^[42].

Figure 1 shows an undivided (a) and a divided cell (b) under flow conditions. In undivided flow cell (Fig.1a), pumping the reagent solution into a system of two electrodes (anode and cathode) separated by a spacer, with only a gap between electrodes, is usually all that is needed to perform electrolysis under flowing conditions. Because of the reduced ohmic resistance caused by the close proximity of the two electrodes, electrolysis can be performed with low concentration or no supporting electrolyte. The use of fluorinated ethylene propylene (FEP) spacer with flow channel in electrochemical cells can help to improve both the productivity and efficiency of the cell, by allowing for more controlled and efficient reactions to occur. Although the anode and cathode are

physically separated, the cell still allows sharing of the electrolyte solution and/or gas flow path between the two electrode regions. This separation helps prevent unwanted side reactions or degradation of cell components, which can increase the efficiency and longevity of the electrochemical cell. In divided flow cell (Fig.1b), the addition of an ion-exchange membrane (e.g., Nafion membrane) and a second flow channel allow a separation of the anodic and the cathodic processes. The separation of the electrode processes is advantageous as both the cathodic and the anodic reaction (paired electrolysis) can be utilised and do not interfere with each other. Usually, the reaction products at the counter electrode in undivided cell reactions are wasted. However, in divided flow cell products are obtained at both electrodes, and paired electrosynthesis can either prevent unwanted side reactions at the other electrode or protect the other electrode from corrosion by reactive species^[42].

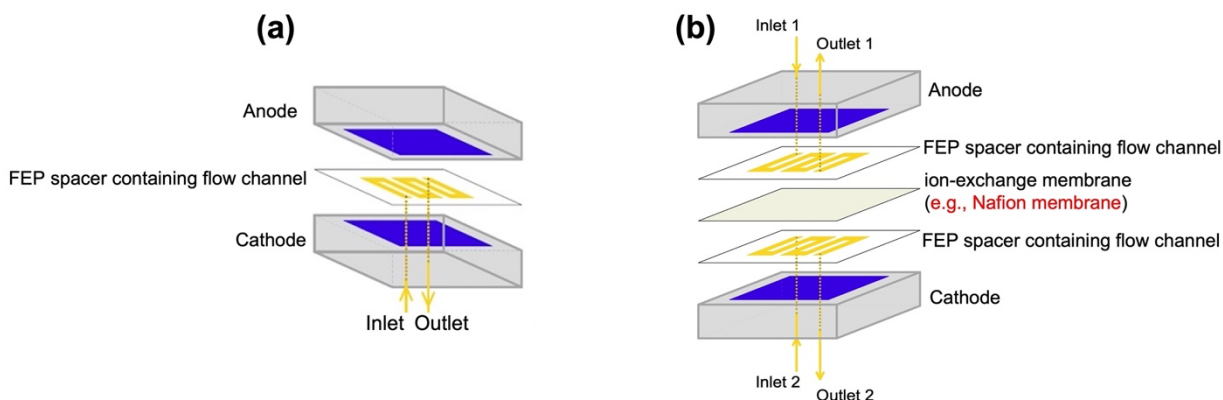
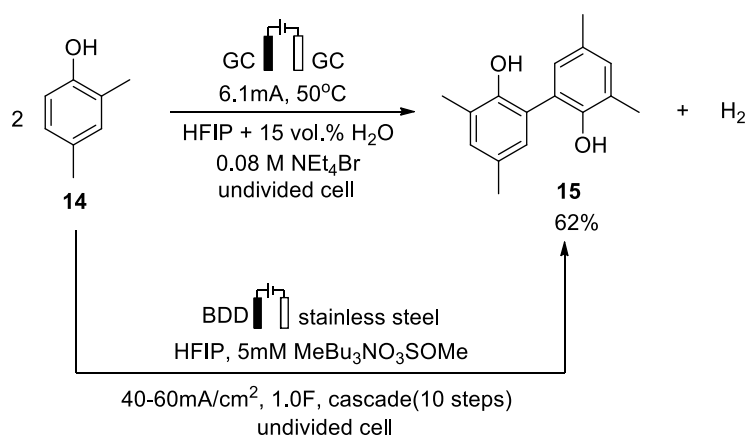


Figure 1: Schematic representation of electrolysis under undivided (a) and divided (b) flow conditions.

It is of special industrial significance since 3,3',5,5'-Tetramethyl-2,2'-biphenol is well known for being an exceptional fundamental basis for ligands in transition-metal catalysis. In highly modular narrow gap flow electrolysis cells, the dehydrogenative anodic homocoupling of 2,4-dimethylphenol **14** is shown to scale up successively from the laboratory scale to the technically applicable scale. Up to 62% of the necessary biphenol might be produced. The electrolysis of **14** was completed using HFIP as solvent at a temperature of 50°C in order to transfer the electrosynthesis of **15** into the 2cm x 6cm flow electrolysis cell (Scheme 7). Bromination can be efficiently controlled as a side reaction by supplying H₂O to the electrolyte. For both electrodes,

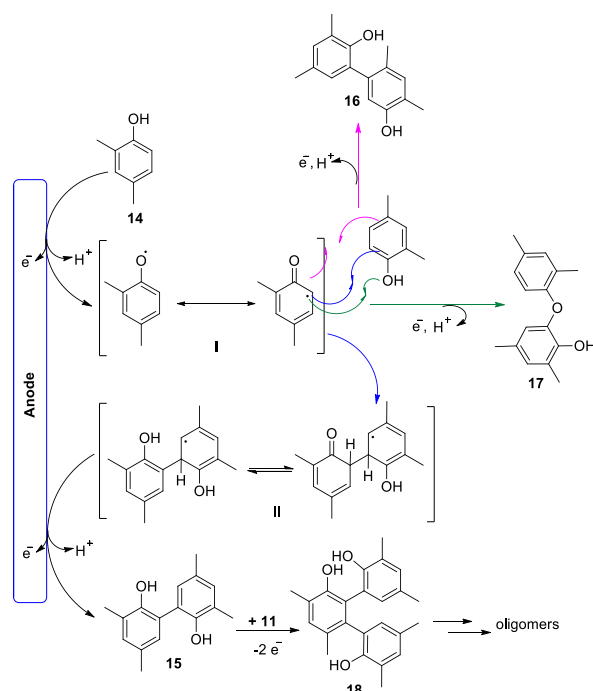
glassy carbon was utilized as the electrode material. To get the most thorough conversion to the intended **15**, a small excess of charge of 1.2F was introduced. 6.1 mA/cm² of applied current was a moderate amount. Additionally, a higher flow rate in the cascade mode can effectively convey the resultant gaseous hydrogen(H₂) out of the flow cell^[43].

The anode material was changed from glassy carbon to BDD with the goal of creating an all-encompassing procedure that is also appropriate for other phenols. Because stainless steel is affordable and has a minimal impact on electrolysis, it was recommended as the cathode material. Me-Bu₃NO₃SOMe was used as a supportive electrolyte throughout the electrolysis process and was used in pure HFIP without any other additives. Additionally, electrolysis in cascade mode might greatly boost the output of 62%^[44].



Scheme 7:Electrochemical synthesis of 3,3',5,5'-Tetramethyl-2,2'-biphenol**15**

Instead linear and oligomeric byproducts, like ortho, meta-coupling product **16**, and diaryl ether **17**, can be obtained under neutral to acidic conditions in addition to the required bi-phenol **15**. This substantially relies on the regioselectivity of the phenoxy radical **I** action. A dehydrotrimer of 2,4-dimethylphenol **18** as well as oligomeric compounds can develop because **15** is susceptible to overoxidation^[44] (Scheme 8).

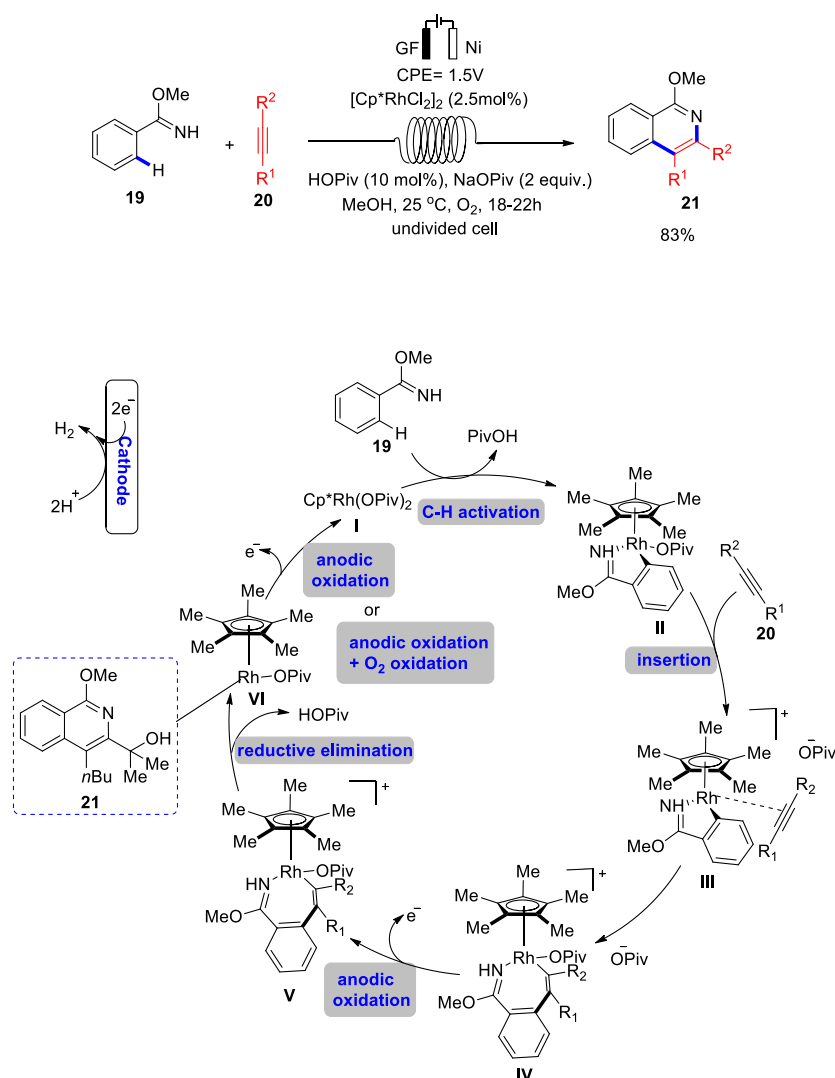


Scheme 8: Proposed mechanism for the electrochemical Synthesis of 3,3',5,5'-Tetramethyl-2,2'-biphenol **15**

The intended isoquinoline **21** was synthesized by focusing experiments on the envisioned rhodaelectro-catalyzed C–H annulation with imide **19** and unsymmetrical alkyne **20** in batch, adopting methanol as the solvent, 2.5 mol% $[\text{RhCp}^*\text{Cl}_2]_2$ as the catalyst, sodium pivalate and pivalic acid as additives under air in an undivided cell, employing graphite felt (GF) anode and Nickel plate cathode. With this improved flow cell in hand, additional tuning allowed for the production of product **21** in 83% yield at a constant potential of 1.5 V and a flow rate of 400 L/min while operating under 1 atm of oxygen at room temperature^[42,45].

A realistic catalytic cycle is suggested based on the mechanistic investigations and is shown in Scheme 9. $\text{Cp}^*\text{Rh}(\text{OPiv})_2$ **I**, which is obtained via ligand exchange between the catalytic precursor and NaOPiv, is then directed by substrate **19** to supply the cyclometallated rhodium complex **II** through simple C–H activation. Rhoda(III)cycle **III** is then produced by alkyne coordination and migratory insertion. Rhodium(II) intermediate **V** is produced fast by anodic oxidation of rhodium(IV)cycle **IV**. The catalyst is then regenerated via anodic oxidation, which can be quickened by oxygen. Aerobic and anodic oxidation appear to be plausible processes for the rhodium(II)-rhodium(III) reoxidation phase. Preventing cathodic reduction of extremely reactive

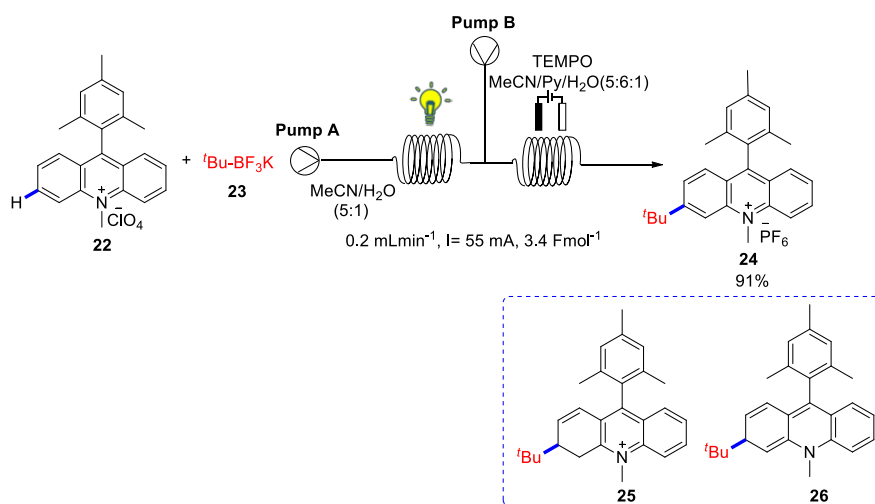
rhodium intermediates, most likely rhodium(II) species, is another benefit of molecular oxygen. In contrast, rhoda(III)cycle **VI** can also produce product **21** directly together with a reduced rhodium species that may reoxidize at the anode. Overall, cathodic proton reduction produces only molecular hydrogen as a stoichiometric by-product, and rigorous head-space GC analysis has proven this to be the case.



Scheme 9: Electrochemical Synthesis of isoquinoline **21**

Due to their advantageous excited-state characteristics, such as their high reduction potential and long lifespan, acridinium dyes are one of the most commonly investigated groups of organic photocatalysts. Modulating their catalytic performance through a structural change is still difficult. Xu and co-workers described a site-selective late-stage C(aryl)-H functionalization of the

acridinium core using a continuous-flow, two-step method for the production of functionalized acridinium photocatalysts. The parent acridinium dye is consecutively pumped through a photoreactor to achieve cross-coupling with an organotrifluoroborate and an electrochemical reactor for electrocatalytic dehydrogenation in order to perform the alkylation. A variety of different alkyl groups can be introduced at the 3-position of the acridinium dye using the two-step automated technique. A second alkylation of 3-alkylated acridinium salts in the flow system results in 3,6-disubstituted acridinium dyes. The reactor system comprises of an electrolytic microreactor and a photoreactor consisting of perfluoroalkoxy (PFA) tubing tied around blue light-emitting diodes (LEDs). It can be difficult to work with salts in microflow reactors because particles can precipitate and clog the microchannels **22**(0.05M) and *t*Bu-BF₃K (0.075M) was dissolved in MeCN/H₂O (5:1) and fed into the reactor system to assure the solubility of salts. The 3,4-dihydroacridine **25** resulting from the photoreactor was difficult to oxidize and needed deprotonation to produce 3,10-dihydroacridine **26**, which is easily oxidized. In order to combine with the photoreactor's eluent before entering the electrochemical reactor, pyridine (Py) was delivered via pump B together with the electrocatalyst 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO). In these circumstances, a 91% yield of the required acridinium **24** was isolated^{0%}[46] (Scheme 10).

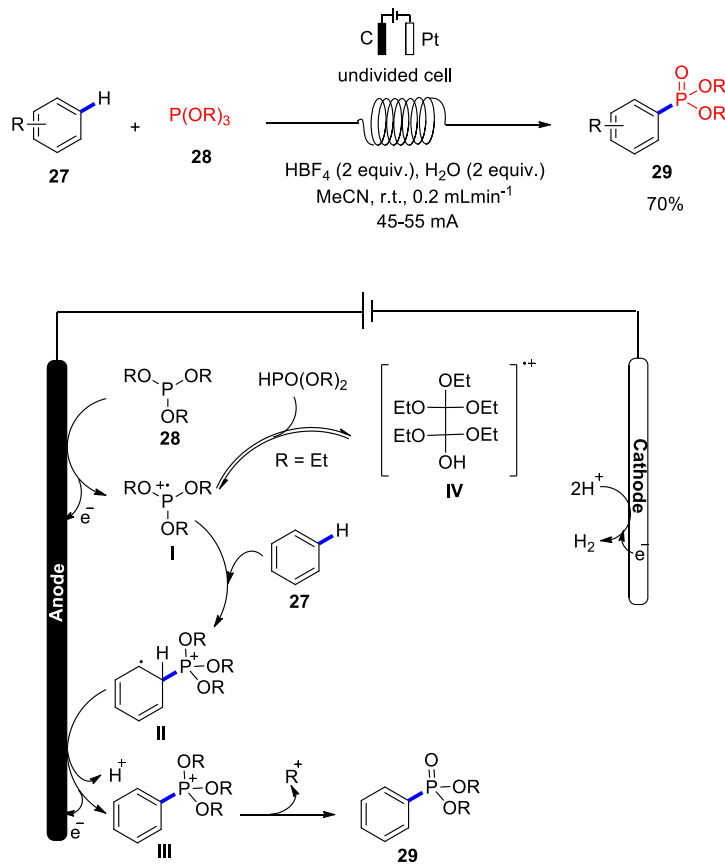


Scheme 10: Electrochemical Synthesis of 3-alkylated acridinium salts **24**, **25** and **26**

Due to the widespread use of organophosphorus compounds in chemistry, biology, and the sciences of materials, it is crucial to create effective and sustainable processes for the creation of

carbon-phosphorus bonds^[47,48]. Xu and co-workers disclose an electrochemical C–H phosphorylation reaction of arenes in continuous flow without the use of a catalyst or external oxidant for the manufacture of aryl phosphorus compounds. In spite of extensive research on P-radicals, the formation of the C–P bond involves the reaction of arenes with anodically produced P-radical cations and a class of reactive intermediates. The gentle electro-synthesis conditions and strong reactivity of P-radical cations allow for both selective late-stage functionalization of complex natural products and bioactive chemicals as well as efficient reactions of arenes with a variety of electronic characteristics. An undivided continuous flow electrochemical cell with a graphite anode, a platinum cathode, and a flow channel carved out of a fluorinated ethylene propylene spacer with a 0.25 mm thickness was used to conduct the electrolysis. When a solution of benzoate **27** (1 equiv.), trialkylphosphite P(OR)₃ (5 equiv.), HBF₄ (2 equiv.), and H₂O (2 equiv.) in MeCN was run through the flow cell at 0.2 mL/min, an ideal 70% yield of phosphonate **29** was produced^[11].

The mechanism of phosphorylation via C–H bond functionalization has been suggested (Scheme 11). Trialkylphosphite **28** is first oxidised on the anode to produce P-radical cation **I**, which then interacts with arene **27** to produce distal radical cation **II**. In order to create phosphonium **III**, the latter is further oxidised on the anode and then deprotonated. Phosphonium **III** then loses an alkyl group to a nucleophilic species in the reaction mixture, such as H₂O or alcohol created from the hydrolysis of P(OR)₃, or during the workup, in order to produce the final phosphonate product **29**. Protons, the most readily reduced component in the reaction mixture, receive electrons at the Pt cathode in these acidic circumstances to produce hydrogen gas. Acidic additive HBF₄ prevents unintended cathodic reduction of electron-deficient molecules like **III** and **29** by promoting hydrolysis of P(OR)₃ and acting as a proton source for H₂ evolution. By reversibly forming an adduct **IV** with radical cation **I**, the HPO(OR)₂ produced in situ by the hydrolysis of P(OR)₃ delays the breakdown of **I** and prolongs the time needed for its reaction with the arene.

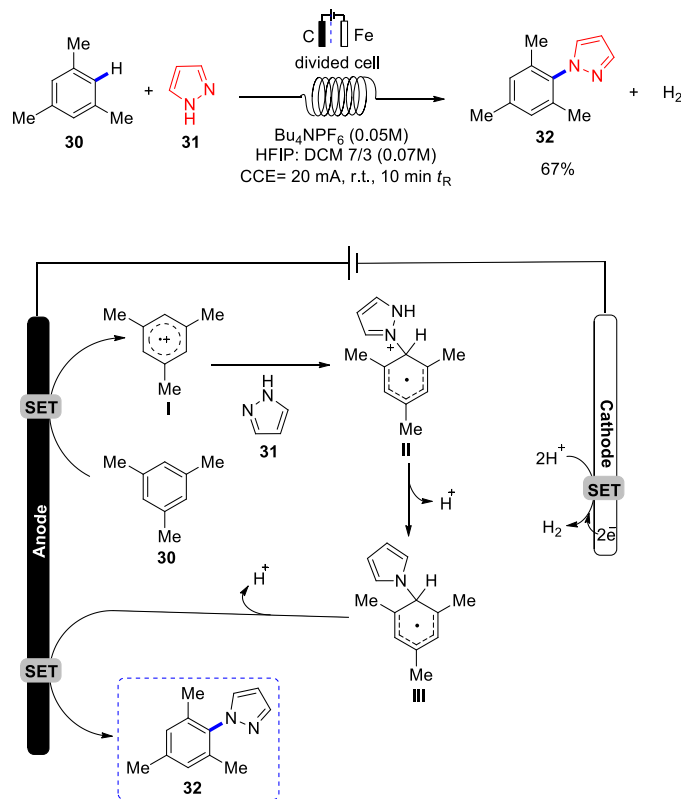


Scheme 11: Electrochemical Synthesis of phosphonate **29**.

In a microflow reactor, aryl azoles **32** were synthesised electrochemically for the first time by Noël and co-workers. Considering that the reaction depends on the anodic oxidation of the aryl derivatives, no homogeneous transition-metal-based catalysts are needed, which makes these substrates suitable to C–H functionalization with azoles **31**. It is envisaged that this electrochemical azolation technique would be used in contemporary medicinal chemistry settings due to its operational simplicity and speed-up reaction times. Carbon anode and stainless steel cathode in the electrochemical microflow reactor were separated by a Teflon gasket, resulting in an interelectrode gap of $250 \mu\text{m}$ and a volume of $700 \mu\text{L}$. A solution of pyrazole (1.0 equiv.) and 1,3,5-trimethylbenzene **30** (6 equiv.) in hexafluoro-2-propanol (HFIP)/ CH_2Cl_2 (7:3) could be subjected to the galvanostatic conditions (20 mA, equivalent to 0.71 mA cm^{-2} and 2.6 Fmol^{-1}) for just 10 minutes before 67% of the required cross-coupled product **32** could be isolated^[49].

The arene is oxidised at the graphite anode (+2.07 vs saturated calomel electrode (SCE) for mesitylene) to produce the aryl radical cation **I**, according to the mechanism that has been

hypothesised to operate in the electrochemical flow reactor (Scheme 12). The subsequent attack on this molecule by the nucleophilic azole can result in the creation of the new C–N bond. After losing a second proton and an electron, **II** will produce the radical species **III** by a deprotonation phase, which will eventually give rise to the azolated product **32**. As a synthetically advantageous consequence of the cathodic process, protons are reduced to create molecular hydrogen.



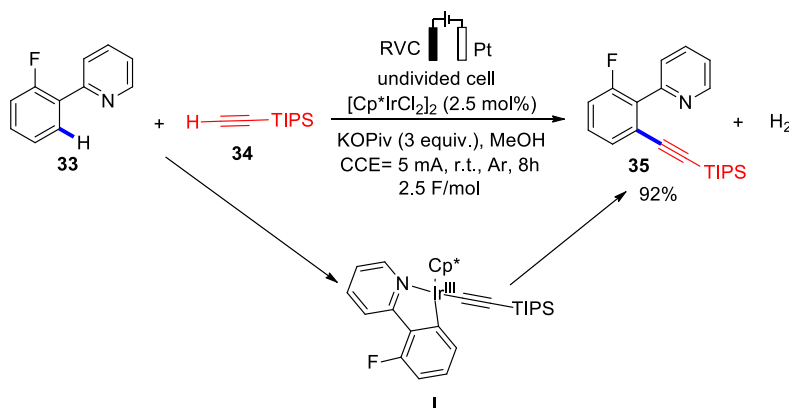
Scheme 12: Electrochemical Synthesis of aryl azole **32**

3. Arenes / Heteroarenes C–H Functionalization via Metalla-electrocatalysis

Conventional techniques primarily rely on using stoichiometric levels of harmful and costly metal and chemical oxidants, despite their overall sustainability. Unwanted by-products are being produced in the meantime, which is troublesome for the scaling up process. However, a more effective method for achieving selective functionalizations has been shown to be electrochemical C–H activation via catalyst control strategy employing metals as mediators (instead of

electrochemical substrate control approach). Thus, indirect electrolysis improves the potential range and reduces the likelihood of adverse responses. Here, we provide a summary of the metallaelectrocatalysis procedure for functionalization and activation of inert C–H bonds. These Metalla-electrocatalyzed C–H bond functionalizations are described in terms of the production of C–C and C–X bonds (where X is one of the halogens, N, O, or P)^[50]. Better chemoselectivities with a wide tolerance of sensitive functionalities are how one can describe the electrooxidative C–H transformations in the presence of metal catalysts. Additionally, metalla-electrocatalysis integration with flow and photochemistry will enable safe and efficient scale-up in the future and may potentially improve reaction kinetics, timings, and yields in order to address sustainability and green chemistry concerns ^[51].

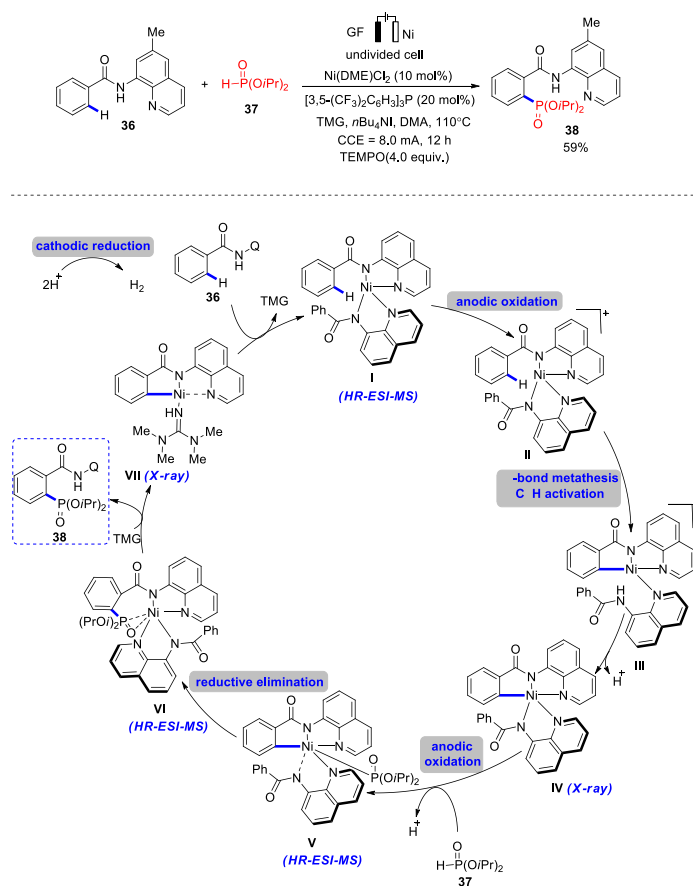
Shi and co-workers reported an electrochemical method for promoting directed C–H alkynylation with terminal alkyne by iridium catalysis. In this study, Ir(III) intermediate, which was identified by X-ray crystallography, was anodized to facilitate reductive elimination and to produce the necessary coupling products in good yields (up to 95%) without the use of any additional external oxidants. With 2.5% [Cp*IrCl₂]₂, KO₂Piv acting as the base and electrolyte in methanol under argon, the reaction's ideal conditions are made clear. The target product **35** was obtained in a 92% isolated yield when the reaction was carried out with RVC as the anode and Pt as the cathode under constant current conditions of 5mA for 8 hours at room temperature. With H₂ as the sole by-product, this transformation works well for a variety of directing groups and allows for practical oxidative C–C bond synthesis(Scheme 13) ^[52].



Scheme 13: Electrochemical Synthesis of alkynyl arene **35**

Earth-abundant nickel catalysts were used to produce C–H phosphorylation with waste-free power acting as the redox mediator. Arylphosphonates, phenylphosphine oxides, and diazaphospholidine oxides of significance to bioactive chemicals and materials were successfully obtained by the strong nickel-electrooxidative C–H activation of arenes, heteroarenes, and olefins. The electrooxidative C–P synthesis with guanidine assistance avoided chemical oxidants. By using X-ray diffraction analysis, catalytically important nickel(II) and nickel(III) intermediates were identified and thoroughly characterised. It has been documented that nickel-electrooxidative C–H phosphorylation of benzamide **36** occurs non-sequentially with an undivided cell using unmasked phosphonate **37**. The desirable product **38** was successfully obtained in high yields using a graphite felt (GF) anode and a nickel (Ni) foam cathode in the presence of the organic base 1,1,3,3-tetramethylguanidine (TMG) as an additive and Ni(DME)Cl₂ as a catalyst^[53].

In Scheme 14, a possible catalytic cycle is shown. Coordination of substrate **36** and anodic oxidation at Ni(III)**II** results in first C–H activation. Later coordination of phosphonate **37** prepares Ni(IV)**V** for an oxidation-induced reductive elimination. It is suggested that the TMG addition will help **VII** form by facilitating coordination. The phosphine is postulated to stabilise an off-cycle species rather than directly take part in an on-cycle event, hence increasing the overall electrochemical stability. Through cathodic reduction, these newly generated protons provide hydrogen gas.

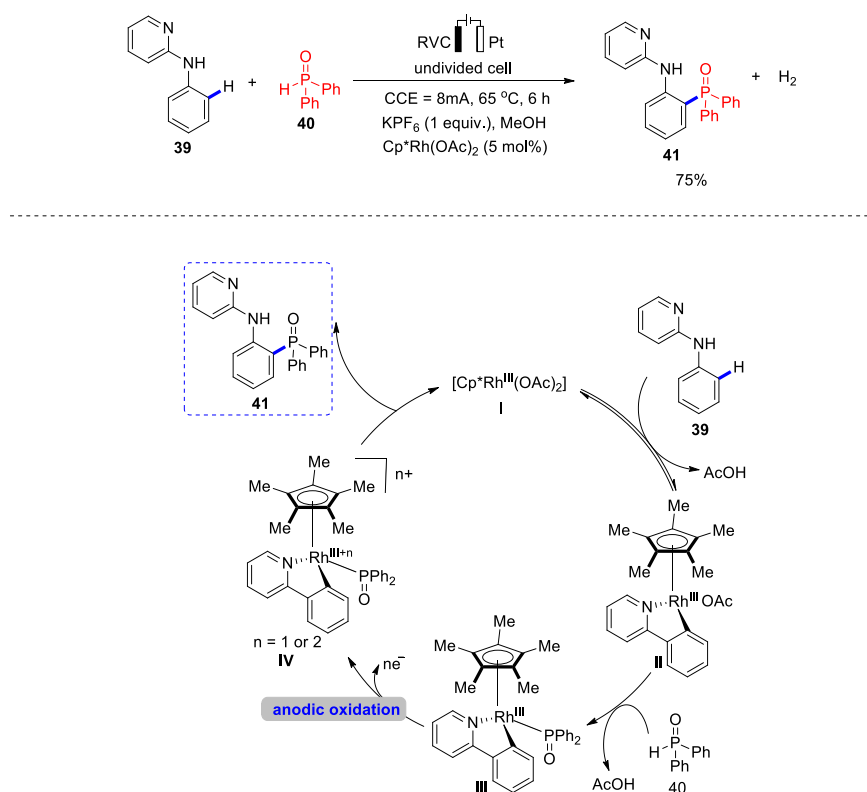


Scheme 14: Electrochemical synthesis of Arylphosphonate **38**

Aryl C–H phosphorylation under Rh^{III} catalysis without the need of stoichiometric metal oxidants was suggested by Xu and colleagues in 2020. H_2 is produced during the reaction. The method is useful for producing triarylphosphine oxides from diarylphosphine oxides, which are usually difficult coupling partners for reactions involving C–H phosphorylation that are catalyzed by transition metals. A wide range of aryl C–H and P–H coupling partners are compatible with it. In order to advance the electrochemical conditions for the previously unreported phosphorylation of N-(2-pyridyl)aniline **39**, diphenylphosphine oxide **40** is initially added in these research. For the electrosynthesis, a Pt-cathode and an RVC-anode were provided in an undivided cell. The finest outcomes were obtained when the reaction mixture of KPF_6 -supporting salt (1 equiv.), methanol-solvent, and $\text{Cp}^*\text{Rh}(\text{OAc})_2$ (5 mol%)-catalyst was run at 65°C with a constant current of 3 mA. In these conditions, 75% of the yield of the required phosphorylated product **41** was obtained^[54].

Using the production of **41**, Scheme 15 depicts a potential mechanism for the electrochemical C–H phosphorylation process. The ortho C–H bond of 2-phenylpyridine undergoes a

straightforward and reversible cyclorhodation reaction to produce the rhodacycle **II**. via exchanging ligands between **II** and **40**, the more oxidizable organometallic complex **III** is created. Depending on the oxidation state of **IV**, the Rh^{III} or Rh^{II} complex is then generated, along with the C–H phosphorylation product **41**, via oxidation-induced reductive elimination. Currently, it is unknown how many electrons **III** will lose before the reductive elimination. Since protons are reduced at the cathode to create hydrogen gas, external electron or proton acceptors are not required.

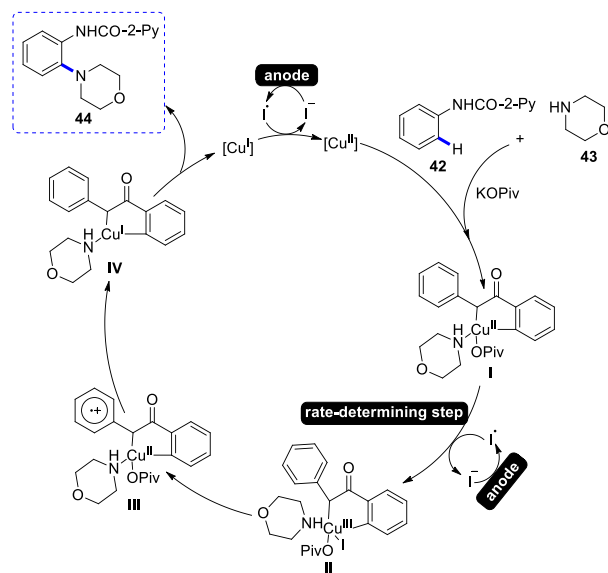
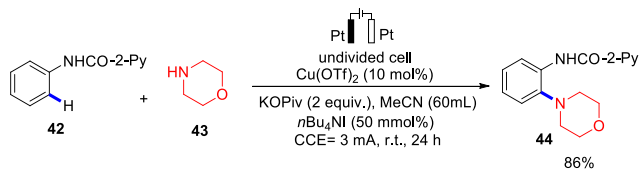


Scheme 15: Electrochemical synthesis of phosphorylated arene **41**

Metal catalyzed electrochemical C–H amination is an highly demanded transformation owing to the dominance of heteroarylamines and arylamines in pharmaceuticals and natural products. The electrochemical C–H aminations of arenes catalyzed by cobalt with secondary amines was independently developed by Ackermann^[55] and Lei group^[56]. An environmentally acceptable alternative to traditional procedures that call for caustic stoichiometric chemical oxidants is electrochemical oxidation. However, up to now, most C–H functionalizations combining transition-metal catalysis and electrochemical methods have mostly relied on precious metals and

divided cells ^[57]. The first examples of room-temperature electrochemical C–H aminations of arenes with copper as the catalyst using undivided electrochemical cells was proposed by Mei and co-workers in 2018, offering a workable solution for the production of arylamines. Scheme 16 provides up a novel route for electrochemical C–H functionalization processes mediated by transition metals. N-phenylpicolinamide**42** and morpholine**43** were initially used as reaction partners, and several reaction conditions were investigated in order to achieve the expected electrochemical C–H amination in an undivided cell with platinum electrodes. After thorough optimization, it was shown that under constant-current electrolysis at 3.0 mA, 10 mol% Cu(OTf)₂, 50 mol% *n*-Bu₄NI (redox mediator), and 2 equiv of KOPiv in MeCN for 24 hours, 86% isolated yield of the desired product **44** could be produced^[58]. The aminated products might be obtained in good to excellent yields if the arenes exhibited various functional groups which are well-tolerated such as silyl, ether, alkyl, hydroxyl, alkyne, trifluoromethyl, alkene, thioether and halogen etc.

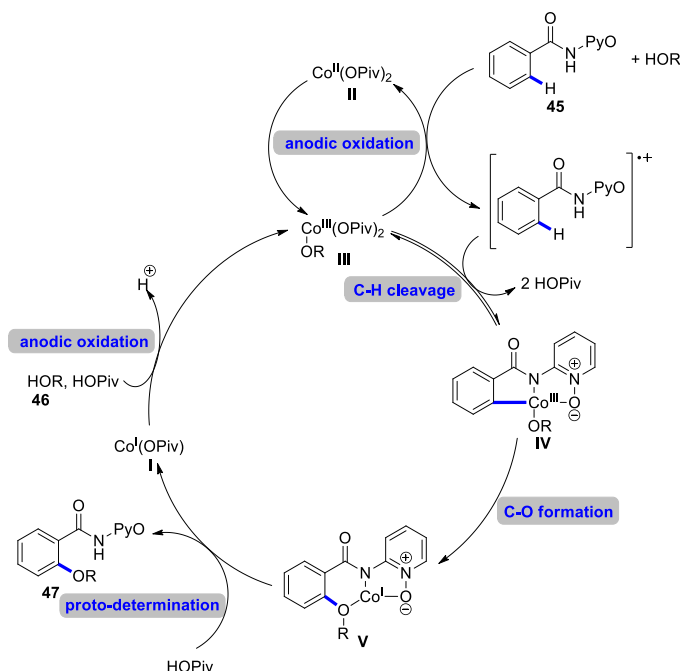
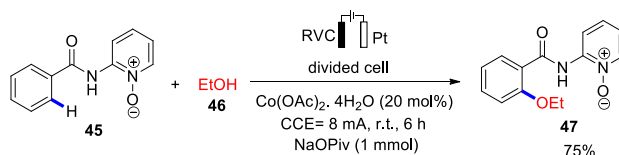
Experimental findings are used to offer a viable mechanism for the Cu(II)-catalyzed electrochemical C–H amination (Scheme 16). The copper(II) catalyst first works in conjunction with an amine and substrate**42** to produce copper(II) complex **I**. Iodine radical then oxidises copper(II) complex**I** to produce Cu(III) species **II**. According to kinetic studies, the catalytic cycle's rate-determining step is the production of Cu(III). The next step involves a single electron transfer (SET), which produces intermediate **III** from complex **II**. Species **IV** is developed by an intramolecular amine transfer to the radical-cation intermediate and a second SET event, which liberates the aminated product **44** and creates a Cu(I) species. Cu(II) catalyst is renewed following anodic oxidation, concluding the catalytic cycle.



Scheme 16: Electrochemical synthesis of arylamine **44**

Cobalt mediated C–H oxygenation was performed by Ackermann and co-workers. Large substrate scope was a highlight of the reliable electrochemical C–H functionalization, and mechanistic analyses supported a simple C–H cleavage. By avoiding the use of stoichiometric silver(I) oxidants under ambient circumstances, the electrochemical cobalt-catalyzed C–H oxygenation was successful on arenes and alkenes with excellent degrees of positional and diastereo-selectivity. Using an RVC-anode(+) and a platinum-cathode(–), the electrochemical oxygenation was accomplished at 23°C, applying 3.6 F/mol delivering the product **45**. $\text{Co}(\text{OAc})_2$ was the best cobalt precursor out of a representative group, with NaOPiv as the preferred base^[59].

Focusing on fundamental research, a possible catalytic cycle that would start with the electrochemical SET of the aromatic benzamide **45** by anodic oxidation and end with the creation of a simple electrochemical catalyst has been proposed (Scheme 17). Following that, proximity-induced chelation aids in C–O production, ensuring high positional selectivity. The final result is the release of the desired product **47**, and anodic oxidation is used to renew the catalytically active cobalt(III) species.

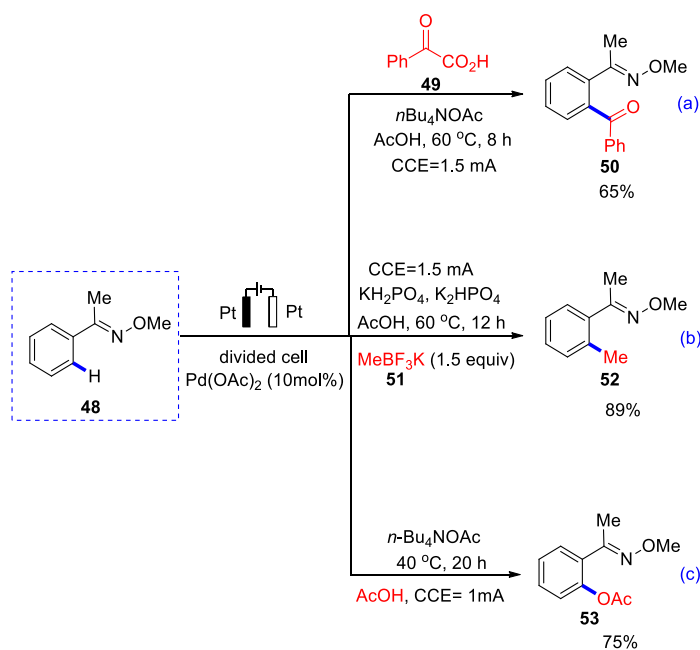


Scheme 17: Electrochemical synthesis of alkyl aryl ether **47**

For organic synthesis, the electrochemical C–H functionalization reactions catalyzed by palladium have appeared as an appealing tool. The distinct potential of electricity as a green terminal oxidant is highlighted by the fact that other regularly used chemical oxidants, such as PhI(OAc)₂, *t*-BuOOAc, or NaNO₃/O₂, delivered the desired product in noticeably lower yields. Mei and co-workers reported the oxidative C(sp²)–H methylation **52** (yield = 89%) and benzoylation **50** (yield = 65%) of oxime ether **48** with methyltrifluoroborates **51** and benzoyl acetic acids **49**, respectively, based on their preliminary findings (Scheme 18-a and 18-b). By using anodic oxidation, first instance of Pd(II)-catalyzed C(sp²)–H methylation and acylation was disclosed. This procedure represents an environmentally friendly way for cross-coupling potassium trifluoroalkylborates and α -keto acids with C(sp²)–H bonds, as opposed to traditional procedures that call for strong chemical oxidants. Oxime ether **48** was selected as the substrate for the reaction with potassium trifluoromethylborate (CH₃BF₃K) under electrochemical conditions in

order to study the formation of C(sp²)–C(sp³) bonds. The monomethylated product **52** was produced in 76% (89% GC yield) by treating **48** (0.3 mmol) with MeBF₃K (2 equiv) in the presence of Pd(OAc)₂ (10 mol%) under constant-current electrolysis conditions at 1.5 mA ($J = 0.75 \text{ mA cm}^{-2}$) [60].

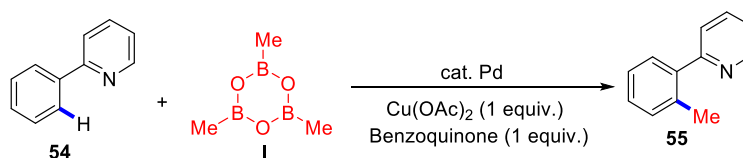
The acetoxylation of C(sp²)–H bonds with palladium has a successful electrochemical technique. The disadvantages of conventional acetoxylation techniques that use stoichiometric oxidants are overcome by this reaction, which proceeds at a low temperature without the use of harmful oxidants. Because the oxime moiety can be easily controlled and has a large amount of derivation potential, it was decided to employ oxime **48** as the substrate for the reaction under electrochemical circumstances to study the production of C(sp²)–O bonds. Fortunately, a 75% isolated yield (scheme 18-c) of the monoacetoxylated product **53** was produced by the reaction of **48** with 10 mol% Pd(OAc)₂ in the presence of 1 equiv of tetrabutylammonium acetate under constant-current electrolysis conditions at 1.0 mA ($J = 0.75 \text{ mA/cm}^2$) [61].



Scheme 18: Electrochemical synthesis of benzoyl **50**, methyl **52** and acetyloxy **53** derivatives of arenes

The first example of Pd-catalyzed aryl C–H cross coupling reaction with alkyl boron and alkyl tin reagents, reported by Yu and co-workers in 2006 (Scheme 19)^[62–64]. However, many examples

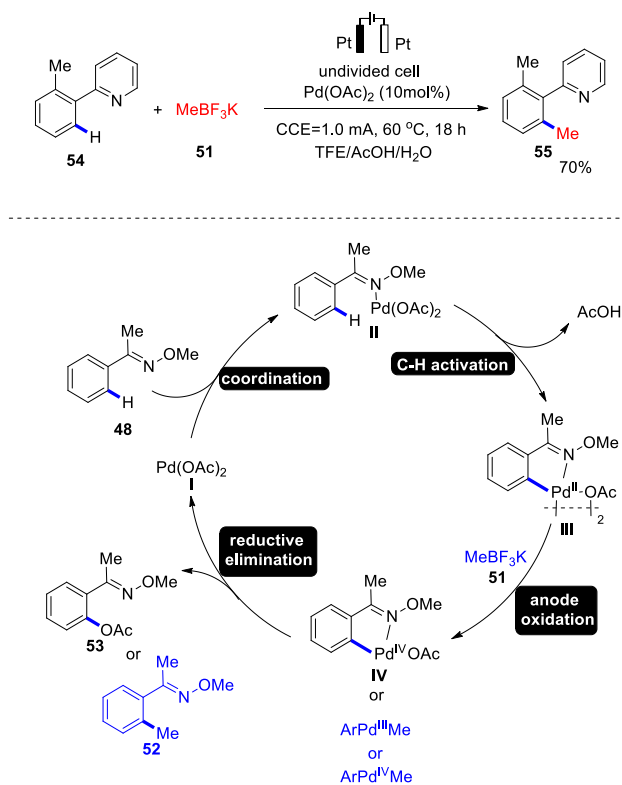
of aryl C–H couplings catalyzed by Pladium using organoboron reagents have been established. In orgnic synthesis, these tranformations possess remarkable importance in convenient construction of C–C bonds, however, in these system the practical disadvantage is the requirement of the constituents of the transition metal chemical oxidant in stoichiometric amont. Thus, there is highly demand to developed the novel oxidation set-up, so electrochemical C–H bond functionalization catalyzed by transition metal has developed as an appealing tool in organic synthesis and by-products, side reactions can be eliminated because it avoids the use of toxic and dangerous chemical oxidants^[65–66].



Scheme 19: Pioneering work on Pd-catalyzed C(sp²)–H cross-couplings

In an undivided cell, the electrochemical C–H alkylation was tested under various reaction conditions using MeBF₃K and 2-(o-tolyl)pyridine **54** as reaction partners. A TFE/AcOH/H₂O solution (2 mL/2 mL/0.5 mL) containing 10 mol% Pd(OAc)₂ and 2 equivalents of MeBF₃K was found to be capable to producing a 70% isolated yield of the target product **55** when electrolyzed at constant current at 1.0mA after considerable optimization^[67].

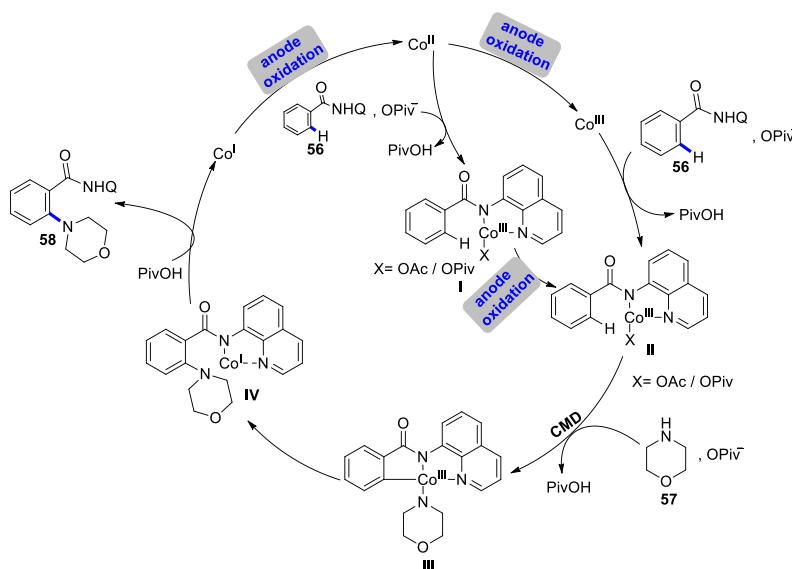
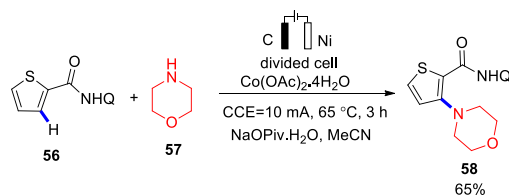
In light of the aforementioned experimental results, a plausible mechanism for the Pd(II)-catalyzed C(sp²)-H methylation through electrochemical oxidation is hypothesized (Scheme 20). The ortho-C-H bond is nearby due to the first interaction of the palladium catalyst with a nitrogen atom in substrate **48**. C(sp²)-H activation comes next, leading to palladacycle **III**. Then, **III** might either interact with a methyl radical produced in-situ from MeBF₃K or undergo a transmetallation with MeBF₃K under anodic oxidation to produce a Pd(III) or Pd(IV) intermediate **IV**. The high-valent palladium intermediate would eventually be subjected to a reductive elimination to liberate the methylated product **52** and regenerate Pd(II) species. However, at this time, we were unable to rule out the possibility that Pd(II)/Pd(0) catalyzed this alkylation. The intermediate **III** is created by a rate-determining C-H activation after the N atom of the oxime first aligns with Pd(II) to make the acetyloxy derivative. This Pd(II) complex is directly oxidized at the anode to create Pd(IV) complex **IV**. The intermediate **IV** is then reductively eliminated to produce the desired product **53**, concluding the catalytic cycle.



Scheme 20: Electrochemical synthesis of alkyl arene **55**

In comparison to other noble metals, cobalt metal demonstrated a number of advantages, including special catalytic reactivity, low toxicity, and affordability. Cobalt-catalyzed C–H alkoxylation, arylation, and amination reactions have recently received a lot of attention. The necessity for an effective oxidant-free cobalt catalytic system arises because substrates may be directly or indirectly oxidized at the anode under electrolytic conditions. However, the majority of metal catalysts are designed to be reduced at the cathode, losing their catalytic reactivity in the process. Continuous efforts have been made to advance the transition-metal-catalyzed electrooxidative C–H functionalization using divided cells^[68–69]. Making valuable arylamines using an environmentally acceptable electrochemical approach has been developed as cobalt-catalyzed C–H amination of arenes. To produce C–N formation products without the requirement for external oxidants, various arenes and alkylamines are studied in divided cells. This eliminates the creation of unwanted by-products and exhibits great atom economy. The reaction may be effectively prolonged to the gram level, which is significant. N-(quinolin-8-yl)thiophene-2-carboxamide**56** and morpholine**57** are utilized as typical substrates. Constant-current electrolysis at 10 mA for three hours was able to produce a 74% isolated yield of the target molecule**58** in acetonitrile at 65°C in the presence of 20 mol% Co(OAc)₂·4H₂O and 1 equivalent of NaOPiv·H₂O^[56].

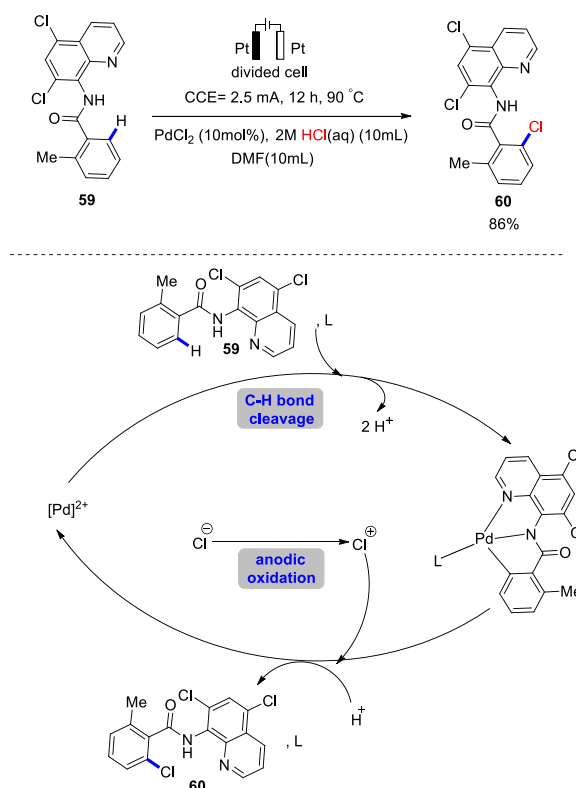
On the basis of literature findings, two potential processes have been investigated^[70–72]. Path-a, in which Co(II) was converted to Co(III) at the anode, resulted in the production of Co(III)-complex**II**. Co(III) then acted in concert with N-(quinolin-8-yl)benzamide**56**. Path-b: In the absence of a base, Co(II) coordinated to **56** to form Co(II)-complex **I** before electrolysis. This Co(II)- complex **I** underwent oxidation at the anode to create Co(III)- complex **II**. Morpholine attacked Co(III)-complex **II** in the presence of base, creating Co(III)-complex **III**, which was then reductively removed to release the desired output and Co(I) species. The Co(I) species was re-oxidized to Co(II) at the anode in order to complete the whole catalytic cycle of Co (scheme 21).



Scheme 21: Electrochemical synthesis of arylamine **58**

Jutand and co-workers in 2007 reported the first Pd-catalyzed electrooxidative C(sp²)-H alkenylation^[73]. So, there is a demand to develop economically transition metal catalysed electrooxidative C–H functionalization. Under anodic oxidation conditions, ortho-selective chlorination of N-quinolinylnbenzamide derivatives **59** with hydrochloric acid was accomplished. The selective chlorination was successful when the directing group 5,7-dichloro-8-quinolinyln was used. Vismodegib was also successfully synthesised in two steps utilising the electrochemical C–H chlorination with palladium as the catalyst. Then, it was looked at how the *o*-methylbenzamide derivative **59** reacted. The ortho chlorination product **60** was produced via the reaction of 0.20 mmol of **59** with 10 mL of DMF over a 12 hours period at 2.5 mA in an isolated yield of 86%^[63].

According to proposed mechanism (Scheme 22), the palladium-catalyzed electrochemical C–H chlorination is thought to happen by first selectively cleaving the ortho C–H bond of benzamide **59** and then reacting with electrochemically produced chlorinating species (Cl^+ or an analogous species).

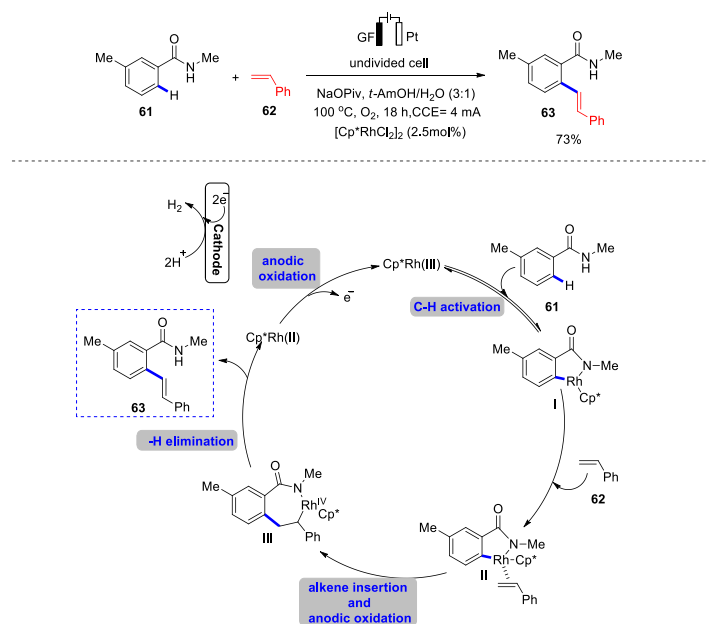


Scheme 22: Electrochemical synthesis of *o*-chlorinated N-quinolinybenzamide derivatives **60**

It has become clear that metal-catalyzed chelation-aided C–H olefinations are effective methods for creating functionalized alkenes. Here, benzamide **61** and styrene **62** were subjected to a Rhoda-electrocatalyzed C–H activation/alkenylation process in the presence of [Cp^{*}RhCl₂]₂ (2.5 mol%) and NaOPiv in *t*-AmOH/H₂O (3:1), which produced product **63** with a 73% isolated yield in an undivided cell. The product **63** was purified in an 85% yield when the alkenylation procedure was carried out at a scale of 1 mmole. Thus, the olefinations of difficult electron-poor benzamides were carried out under electrochemical conditions in a totally dehydrogenative manner, avoiding stoichiometric chemical oxidants, and with hydrogen gas as the only by-product. This adaptable alkenylation reaction uses electricity as a green oxidant and has a wide range of substrates ^[74].

Rhodacycle **I** is formed, as shown in scheme 23, by directed cyclorhodation at the ortho-position after the N-atom of amide **61** is coordinated to Cp^{*}Rh^{III}. Then, alkene **62** insertion takes place to produce intermediate **II**, which proceeds through β- hydrogen elimination to create **63** along with a rhodium(II) species that is created after the N-atom in **III** is broken up. The catalytic cycle is

finished when the rhodium(II) species is reoxidized to rhodium(III) at the anode, producing molecular hydrogen(H_2) as a byproduct at the cathode.

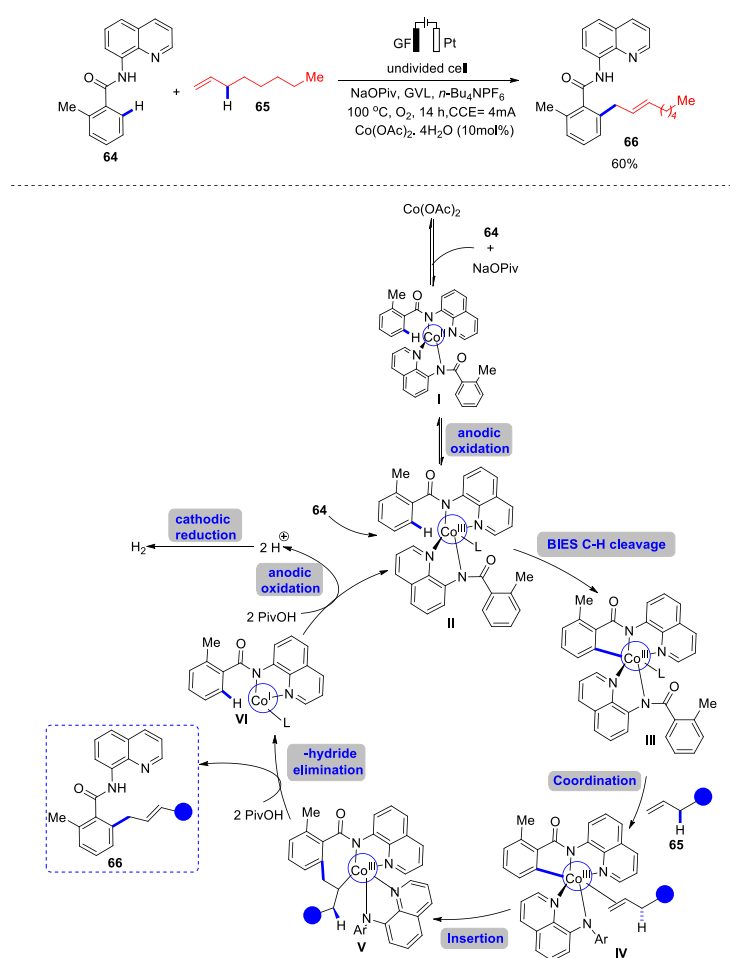


Scheme 23: Electrochemical synthesis of alkenyl arene **63**

The electrochemical C–H allylation with non-activated alkenes was made possible by versatile and powerful cobalt catalysis. Ackermann and co-workers described an electro-oxidatively C–H allylate benzamide **64** with unactivated alkene **65** in a very user-friendly undivided cell setup. NaOPiv emerged as the best additive among many others. As a result, in the solvent γ -valerolactone (GVL) formed from biomass, allylated benzamide **66** was produced with high degrees of chemo-, position-, and regio-selectivity in 60% output. With H_2 as the sole byproduct, the cobalt electro-catalysis generally accomplished resource economy by eliminating the usage of stoichiometric chemical oxidants^[75].

A base-assisted internal electrophilic-type substitution mechanism for the crucial C–H activation step was strongly supported by thorough mechanistic analyses. A possible catalytic cycle for the cobalt-catalyzed electrochemical C–H allylation has been provided in scheme 24 based on mechanistic findings. The 5-membered cobaltacycle **III**, which in a competition experiment may have a heteroleptic coordination environment, is formed first by anodic cobalt oxidation, which prepares the way for an effective BIES C–H scission with carboxylate assistance.

To create the conformationally stiff 7-membered metallacycle **V**, 1,2-migratory insertion of **IV** with the non-activated alkenes **65** is made possible by alkene co-ordination. Third, in order to produce the desired allylated product, the seven-membered metallacycle **V** primarily undergoes β -hydride removal from the allylic proton. Eventually, anodic oxidation is used to regenerate the active cobalt(III) catalyst **II**. H_2 generation is the only stoichiometric by-product of the cathodic half-reaction.

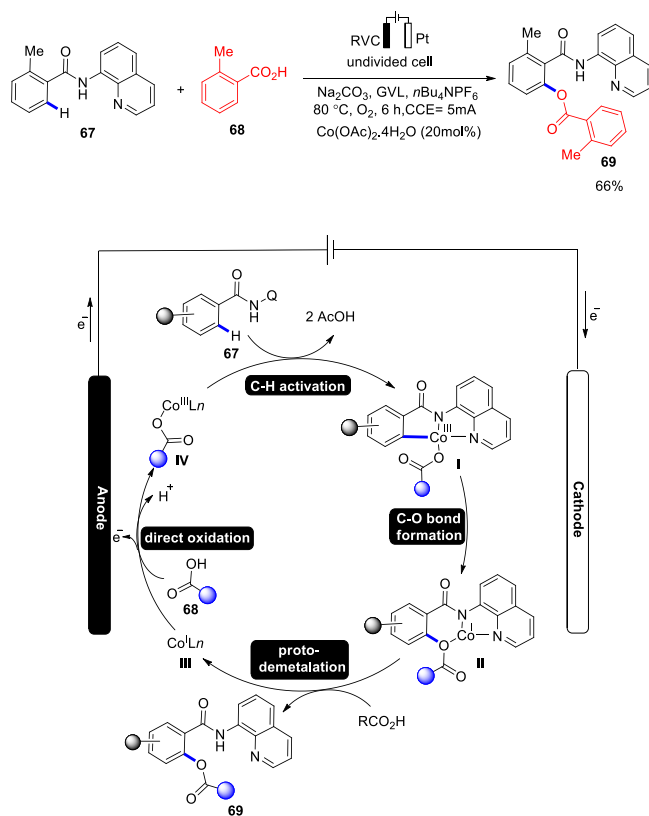


Scheme 24: Electrochemical synthesis of allylated benzamide **66**

Additionally, the same author reported an electrochemical cobalt-catalyzed C–H acyloxylation. Because there were no expensive silver oxidants present, flexible cobalt electrocatalysis allowed for long-lasting C–H oxygenations of substituted benzamides **67**, with the only waste being molecular hydrogen. The C–H acyloxylation reaction was characterised by broad applicability in

γ -valerolactone, a renewable solvent generated from biomass. Using affordable cobalt(II) salts and Na_2CO_3 as the preferred base, the required benzoxylation product **69** with a 66% yield was produced in an undivided cell arrangement at 80°C ^[76].

A catalytic cycle that is thought to be started by the electrochemical production of the catalytically competent cobalt(III) species **IV** via anodic oxidation has been postulated based on mechanistic results (Scheme 25). Following that, salt metathesis with carboxylic acid **68** results in the cobalt(III) intermediate **III**, whereas carboxylate-assisted C–H activation yields the cyclometalated complex **I**. Reductive elimination creates a cobalt(I) species **II** and yields the desired product **69**. By anodic oxidation, the catalytically active cobalt(III) complex **IV** is ultimately replenished.



Scheme 25: Electrochemical synthesis of benzoxylation product **69**

4. Arenes / Heteroarenes C–H Functionalization via photo-electrocatalysis

It is well known that photoelectrochemical (PEC) cells are a critical element for energy and environmental applications. PEC cells have also been aimed towards pollutant degradation, carbon

dioxide reduction, and the creation of solar fuels. They are most frequently employed to manufacture hydrogen fuel from water splitting. Nonetheless, their use in organic synthesis is still in its early stages. The union of photochemistry and electrochemistry is envisioned to become a new strategy to assist modern organic chemists, driven by the quest for green and sustainable synthesis processes. PEC cells are appealing due to the sun's abundance, practicality, affordability, and cleanliness, the wide variety of photoelectrode materials and redox mediators, and their capacity to operate under mild reaction conditions. This section discusses some recent advancements in photoredox catalysis and electrochemistry combined in a single system for PEC-driven chemical synthesis. It has been specifically focused on reactions involving C–H activations, which result in the formation of new chemical bonds, whether they are for the late-stage functionalization of intriguing compounds or the union of two molecular building blocks. With high atom- and step-economies, this combination is proving to be a potent system that can perform reactions that would be challenging or impossible to do using more traditional methods^[77].

For the conversion of solar energy into chemical fuels, the photoelectrochemical (PEC) cells are widely examined^[76]. This protocol is effectively applied in several pharmaceutical molecules for late-stage functionalization owing to broad scope of this method. Usually, a photoanode is used for the oxidation of water to produce oxygen and photocathode is used for the reduction of water to produce hydrogen (Figure 2). On light illumination, a high oxidizing or reducing power might be generated under mild conditions using PEC cell and they are well appropriated to catalyse the redox transformations of organic molecules to produced value-added chemicals (Figure 2). Recently, for the oxidation of benzylic alcohol^[78], cyclohexane^[79], furan^[80], 5-hydroxymethylfurfural^[81] and tetralin^[82], the oxidizing power of photoanodes like WO₃ and BiVO₄ was exploited. However, the broad scope for the synthetic methodologies of functional organic molecules utilizing PEC cells remains unexplored and further in this field more efficient organic transformations are possible^[83].

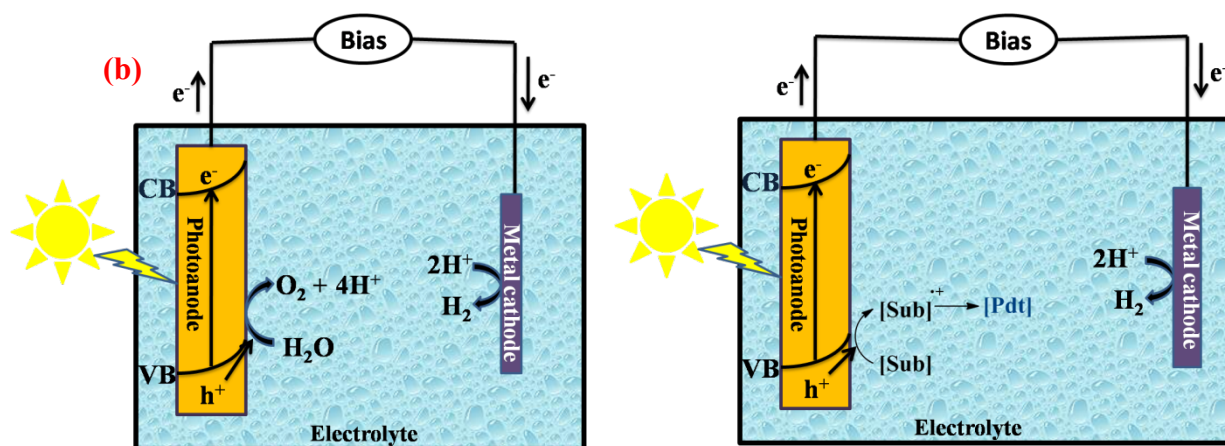


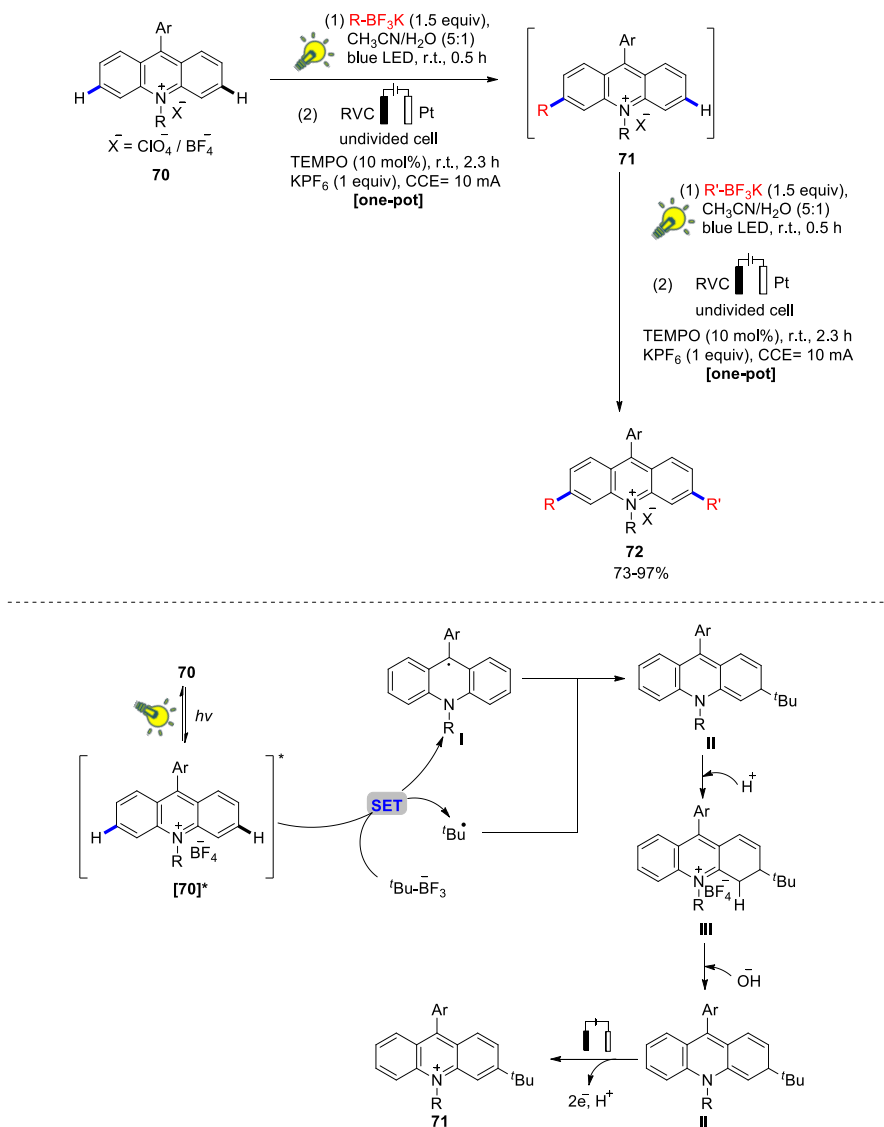
Figure 2: PEC cells: (a) Water oxidation, (b) Oxidative transformations of organic molecules, CB: conduction band, VB: valence band.

Building on the groundwork laid by early pioneers in the fields of radical chemistry and photochemistry, so-called visible light, or photoredox catalysis has become a potent tool in organic synthesis. The quick construction of complicated products on the road to new regions of chemical space is made possible by photoredox chemistry, which also creates new bonds via open shell pathways. Through a variety of synthetic transformations, including but not limited to cross-coupling, C–H functionalization, alkene and arene functionalization, and trifluoromethylation, photocatalysts can open up access to completely new, previously inaccessible bond formations in the presence of visible light. Academic research teams, industrial chemists, and academic-industrial partnerships have all used photocatalysis with success. These efforts have led to new synthetic disconnections, inventive techniques, and a better mechanistic understanding of photoredox processes^[84].

The synthesis of several 3,6-functionalized acridinium photocatalysts via site-selective late-stage C–H alkylation has been demonstrated. Following 0.5 hours of blue LED irradiation, the addition of 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) as the redox catalyst and KPF₆ as the supporting electrolyte induced the addition of organotrifluoroborate to **70** to occur. The intended 3-alkylated acridinium product **71** was obtained in high to excellent yields (73-97%) during electrolysis of the resulting reaction mixture at a constant current of 10 mA without the presence of any other regioisomers. The 3,6-dialkylated acridinium product **72** can be produced in a good yield by repeating these settings. These reactions exhibit high scalability as well as broad functional group

suitability. By adding a variety of electrically and sterically varied substituents to the cores of acridinium dyes, a synthetic technique makes it simple to adjust the photocatalytic capabilities of these dyes. The advantages of the structural variation in improving photocatalytic efficiency are revealed by the catalytic uses of the newly produced acridinium dyes in a benchmark process^[85].

The C–H alkylation of acridinium dyes was hypothesised as a possible process (Scheme 26). When excited acridinium **70** reacts with *t*Bu-BF₃K in a SET reaction, it produces the radicals *t*Bu• and **I**, which go via cross-coupling to produce 3,10-dihydroacridine **II**. Due to its smaller conjugation system and lack of reactivity, 3,4-dihydroacridinium **III** is produced by protonating **II**. It does not go through additional alkylation. While **II** ($E_{1/2} = 0.27$ V vs SCE) is considerably easier to oxidise than **III** ($E_{1/2} = 2.10$ V), **III** can revert to **II** by deprotonation by HO[−], which is produced by cathodic reduction of solvent H₂O. The electrocatalytic process results in the synthesis of alkylated acridinium product **71** by the TEMPO-mediated oxidation of **II**.

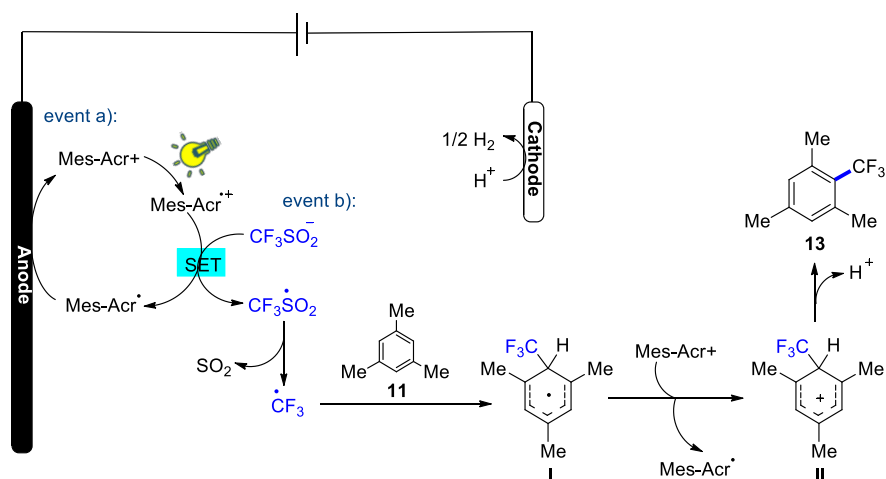
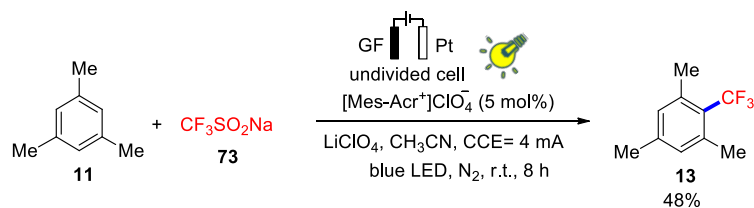


Scheme 26: Electrochemical synthesis of 3,6-dialkylated acridinium product 72

The trifluoromethylated compounds exhibit inimitable lipophilicity as well as bioactivity and thus highly demanded in pharmaceutical industries and medicinal chemistry^[57]. Moreover, in contrast to conventional methods these trifluoromethylations have made the modifications to electrosynthesis and photoredox catalysis^[85]. Additionally, Schefold used vitamin B₁₂ as an electro-photo catalyst and explained the nucleophilic acylation of Michael olefins. A refined example of electrophotocatalytic transformations were described very recently by the researchers Stahl^[86-87], Lambert^[88] and Hu^[89] on the sustainability of C–H activation persuaded through photocatalysis. Arene C–H trifluoromethylation with the Langlois reagent $\text{CF}_3\text{SO}_2\text{Na}$ (2 equiv.) has been made

possible by electro-photochemistry under benign reaction conditions. The CF_3 radical was produced without the need of chemical oxidants thanks to the combination of electrosynthesis and photoredox catalysis. Undivided cells were used for the electrophotochemistry, which made it possible to tackle difficult C–H trifluoromethylations of inactive arenes and heteroarenes like the easily available mesitylene **11**. A broad range, encompassing electron-rich and electron-deficient benzenes as well as naturally occurring heteroarenes, highlighted the robustness of the electrophotochemical manifold. A platinum plate cathode and a graphite felt (GF) anode were used in the orientation investigations, along with a cost-effective LiClO_4 additive and $[\text{Mes-Acr}^+] \text{ClO}_4^-$ as a photocatalyst (PC) in acetonitrile at 23°C room temperature^[38,60,90].

A potential mechanism was presented in Scheme 27 based on mechanistic discoveries. The oxidised excited state Mes-Acr^{+*} is produced when the organic dye Mes-Acr^+ is first exposed to radiation. The acridinyl radical and the CF_3SO_2 radical are produced by a SET reaction between Mes-Acr^{+*} and the sulfinate anion. The ground state catalyst Mes-Acr^+ is then renewed by anodic electrooxidation of the acridinyl radical. The trifluoromethyl radical attacks substrate **11** simultaneously, creating aradical **I** that then undergoes SET oxidation to create the cationic Wheland complex **II**. **I** might also undergo direct oxidation at the anode in the interim. In the end, proton abstraction produces the desired product **13**, whereas at the cathode, protons are reduced to produce H_2 .

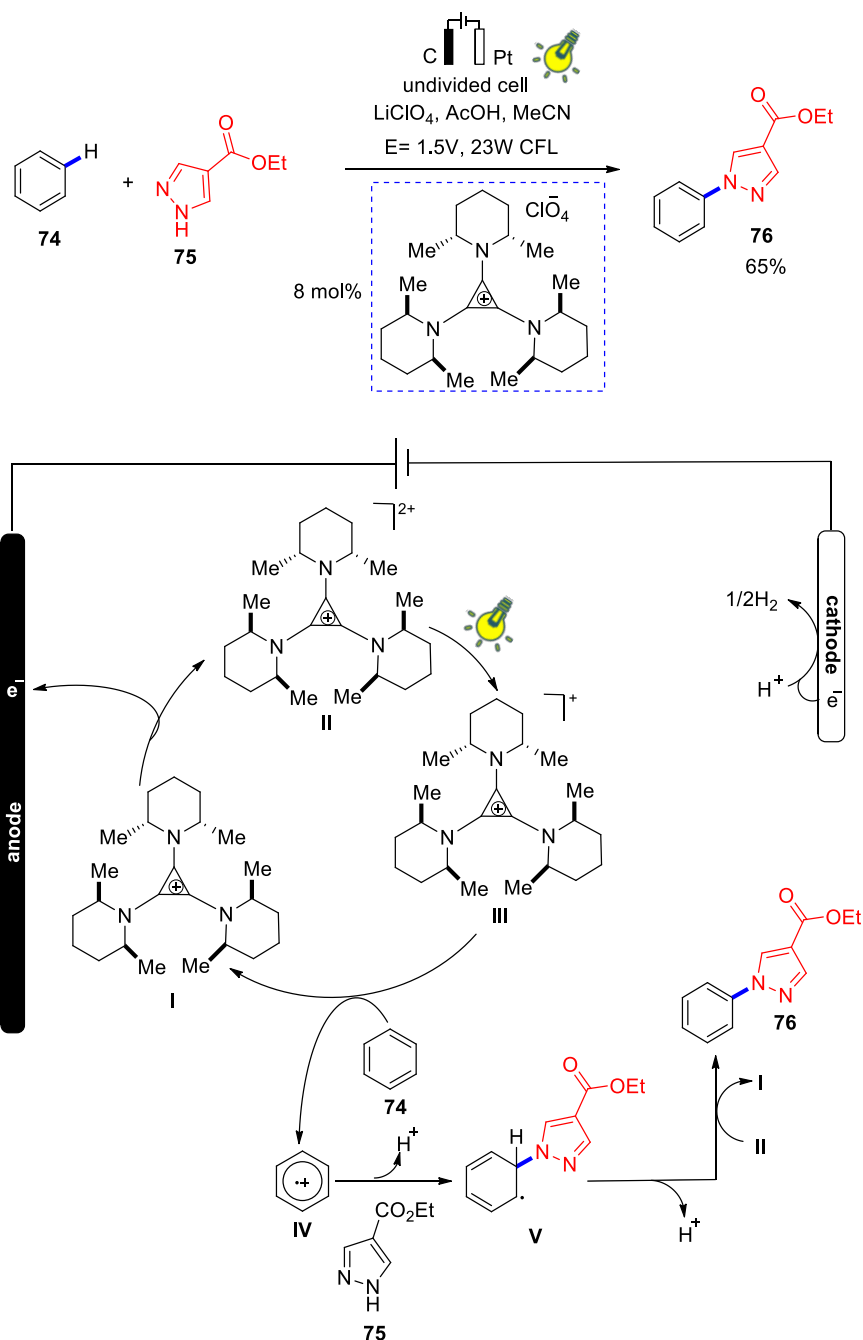


Scheme 27: Electrochemical synthesis of trifluoromethyl arene **13**

C–H functionalizations of truly unactivated arenes and even de-activated e-poor arenes for heterofunctionalization is possible by a molecular photoelectrochemical strategy. Trisaminocyclopropenium (TAC) ion catalyst is used in this process, and it is electrochemically oxidised to create cyclopropenium radical dication intermediate. By photoexcitation with visible light, the radical dication is able to oxidise benzene and halogenated benzenes via single-electron transfer (SET), which leads to C–H/N–H coupling with azoles **75**. This excited-state species has an oxidising power of 3.33 V vs. SCE. Platinum cathode and graphite anode are used. The product **76** is produced with a 65% yield under the parameters listed below. The stability of the catalyst is explained by a specific conformation of the cis-2,6-dimethylpiperidine moieties, and a reason for the significantly oxidising activity of the photoexcited species is given^[91].

A bicatalytic system made of acridinium dye and (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO)^[92] and tri(para-substituted)biarylamines (TPA)^[93] catalyst are two more electrophotocatalytic techniques that have been developed for the dehydrogenative cross coupling of arenes **74** with azoles **75**.

Scheme 28 depicts a mechanistic explanation for these electrophotocatalytic processes. The radical dication **II** is produced by the electrochemical oxidation of the colourless TAC cation **I**. The reactive intermediate **III** that results from photoexcitation can then oxidise benzene **74** through SET to form the radical cation **IV** and concurrently direct regenerate **I**. The radical **V** results from the nucleophilic entrapment of **IV** by pyrazole **75** and subsequent deprotonation. The linked product **76** is revealed by further oxidising this radical by **II** or directly at the anode, followed by re-aromatization by proton loss.

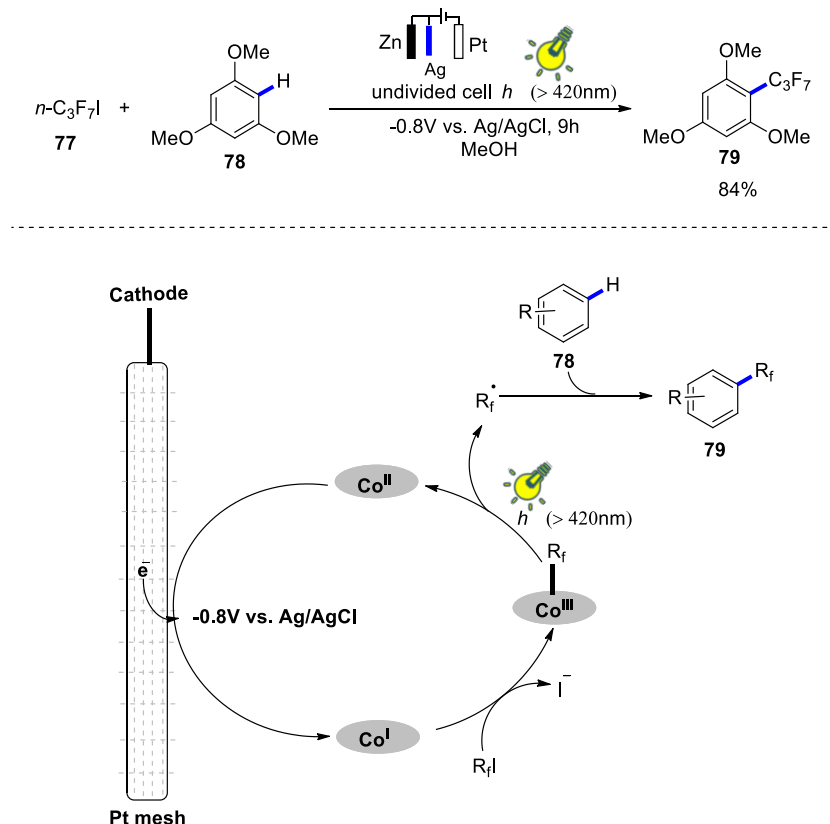


Scheme 28: Electrochemical synthesis of linked product 76

It has been created to trifluoromethylate and perfluoroalkylate aromatic compounds electrochemically using a vitamin B₁₂ derivative as a cobalt-based catalyst. An effective technique for adding trifluoromethyl and perfluoroalkyl groups to aromatic compounds that works by creating radical intermediates in an electrocatalytic process when there is a catalytic amount of 77. Fluoroalkylating reagents (R_fI) such as heptafluoropropyl iodide, trifluoroiodomethane,

nonafluorobutyl iodide, henicosafuorodecyl iodide, and heptadecafluorooctyl iodide which are easy to use and affordable, are employed in this reaction. The 1,3,5-trimethoxybenzene **78** and *n*-C₃F₇I model reaction in this work has been revealed utilising an electrochemical approach. In an undivided electrolysis cell, three electrodes namely a platinum mesh cathode, a Zn-plate sacrificial anode, and an Ag/AgCl reference electrode were included. To get a greater yield, the reaction conditions were improved. When exposed to visible light at ambient temperature, after 9 hours, 100% substrate conversion at a potential of -0.8 V vs. Ag/AgCl was achieved, yielding the desired product **79** in 84% of the cases^[94].

Co(I) was first obtained from Co(II) via controlled-potential electrolysis at -0.8 V vs. Ag/AgCl, and Co(I) then interacted with R_fI to swiftly produce the Co(III)-R_f complex (Scheme 29). The compound then emitted an R_f radical when exposed to visible light. In order to deliver the desired product **79**, the produced R_f- Trimethoxybenzene radical then reacted with non-activated substrates such arenes and heteroarenes. This reaction was followed by a one-electron oxidation and proton loss. This is the first report of catalytic trifluoromethylation and perfluoroalkylation processes employing vitamin B₁₂ derivatives, despite the fact that trifluoromethyl- and fluoroalkyl-cobalamines have been created and described by Geremia and co-workers.

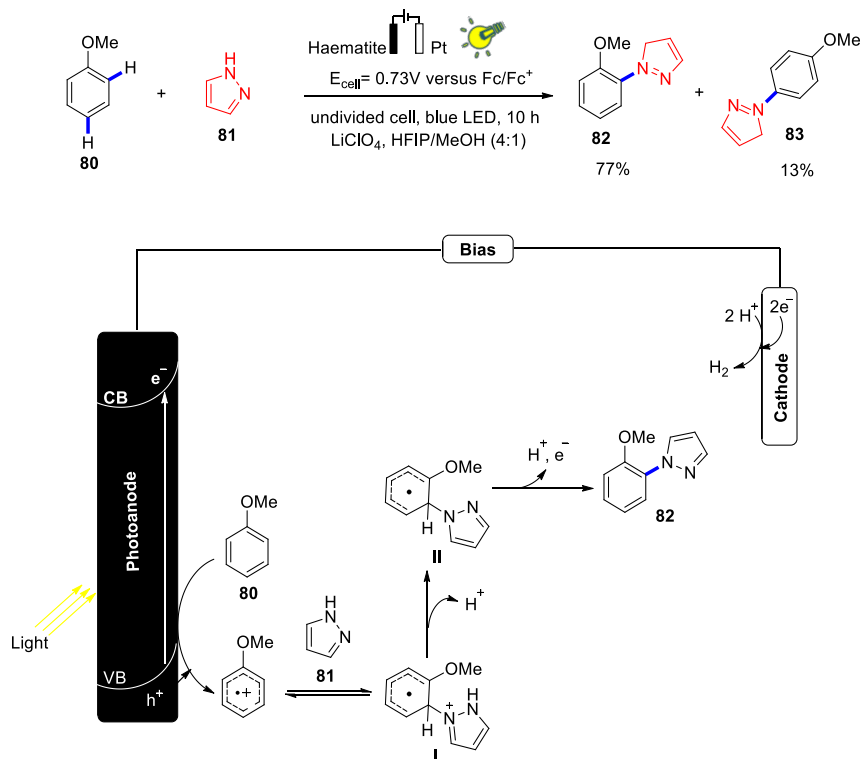


Scheme 29: Electrochemical synthesis of 2-heptafluoropropyl 1,3,5-trimethoxybenzene **79**

Now a days, for the synthesis of organic compounds through photoelectrocatalytic approach to non-directed arene C–H amination has an attractive method^[94]. To conduct the C–H amination in PEC set-up, involves the use of haematite (α -Fe₂O₃) which is an earth abundant and strong photoanode (Figure 2). For the solar-driven water oxidation, haematite has been broadly investigated due to its high stability, appropriate band gap of 2.1 eV for strong light absorption and low cost^[95]. The heterogenous nature of photoelectrocatalysis and the stability of haematite in a PEC cell suggest impending advantages in the separation of product and life time of catalyst. Due to light ingathering the photoelectrocatalysis consumes less amount of energy, if compared it with direct electrocatalysis. Consequently, this presented method is operationally simple and thus might be utilized in the synthesis of wide range of nitrogen-containing heterocycles which are considered to be advantageous in the discovery of drug. Remarkably, for many substrates reverse selectivity is attained in contrast to previously described electrochemical and photoredox methods^[96–97]. For late-stage functionalization of pharmaceuticals molecules, the utility of this method is broadly exercised by several examples.

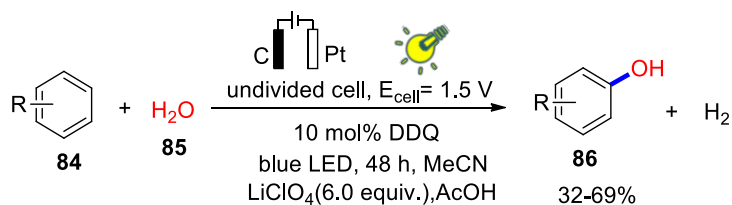
For C–H amination reaction, the C–H/N–H coupling of anisole with pyrazole was investigated using nanostructured haematite^[98] and under a blue light emitting diode (LED) the reaction was performed with a constant potential. With the photocurrent at about 2~3mA cm⁻², the potential was set at 0.73V against a ferrocene/ferrocenyl (Fc/Fc⁺) after some investigation and the reaction time period was set to about 10 hours. The tetrabutylammonium hexafluorophosphate (TBAPF₆) was initially used as electrolyte. Various organic solvents were experienced which benefit the organic media for the PEC oxidation, inspired after the work of Berlinguette and co-workers. In direct electrochemical oxidation^[99], the choice of solvent acetonitrile (CH₃CN) was found to be ineffective. The yield and selectivity were increased using LiClO₄ as the electrolyte and HFIP/methanol(4:1) as the solvent. The achievement of unusual ortho selectivity was most likely made possible by a hydrogen-bonding interaction between the substrates and the co-solvent, hexafluoroisopropanol. From this profile, the analysis of the rate order was convoluted by mass transfer to the photoanode, it was apparently observed that reaction began to down after about 6 hours. After ten hours of time period the substrate anisole remained about 10% only but improving the reaction time beyond ten hours had partial impact on the yield. Without prefunctionalizing the substrates, a variety of heterocycles having an aryl C–N moiety can be made from basic arenes and azoles. The test reaction for the C–H amination was the C–H/N–H coupling of anisole**80**(0.2mmol) with pyrazole**81**(2 equiv)^[83].

The photoelectrocatalysis has been explained by a reasonable mechanism (Scheme 30). Holes are produced at the valence band when haematite is illuminated. An electron-rich arene is converted by the holes into a radical cation that interacts electrophilically with an azole to produce intermediate **I**. Proton loss from **I** results in the intermediate **II**, which, after being oxidised and having one proton removed, produces the amination product. **II** may be oxidised at the photoanode either by the photogenerated holes or by a methoxy radical that may also be produced there. When photoexcited electrons migrate from the haematite's conduction band to the counter electrode and reduce protons into dihydrogen gas, the photoelectrocatalysis is said to be complete.



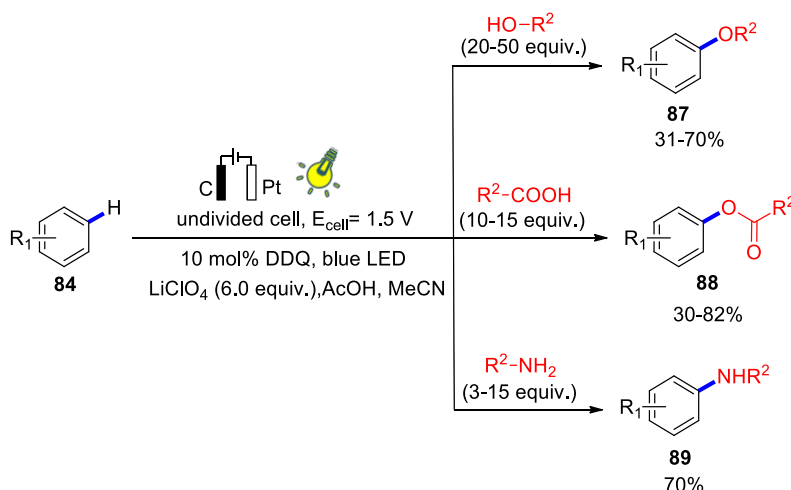
Scheme 30: Electrochemical synthesis of arene C–H amination products **82** and **83**

Lambert and co-workers proposed a heterofunctionalization of arenes via electrophotocatalysis, arenes undergo hydroxylation, amination and alkoxylation free of oxidants (Scheme 31). First, the electrophotocatalytic coupling of benzene **84** and water **85** (50 equiv.) provided phenol **86** by applying 10 mol% of 2,3-dichloro-5,6-dicyanoquinone (DDQ) at a controlled potential of 1.5 V in a undivided cell (carbon cathode, Pt anode), under visible light irradiation (blue LED strip), in the presence of LiClO_4 and acetic acid. Different yields are obtained in the presence of different arenes^[100].



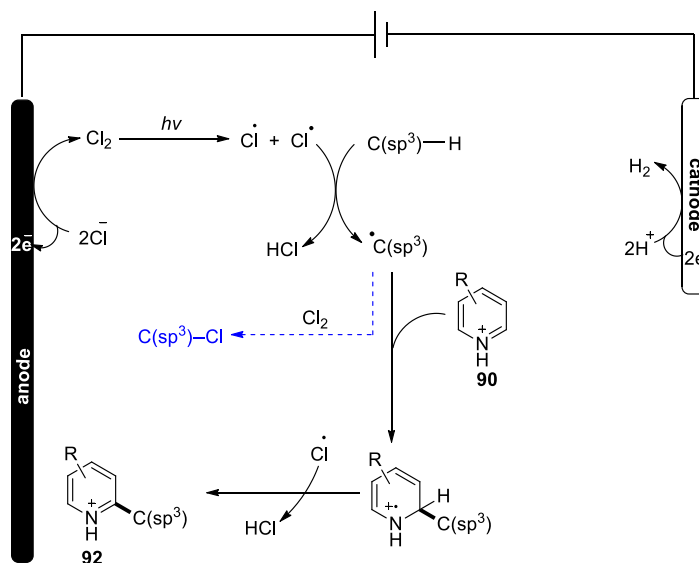
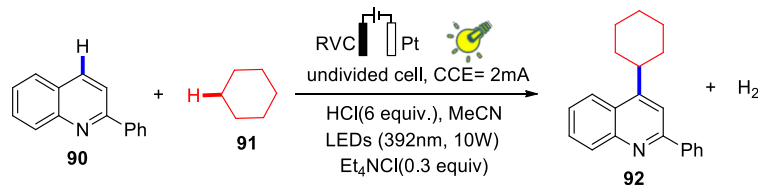
Scheme 31: Electrochemical synthesis of phenol **86**

Additionally, reactions of benzene **84** (0.4 mmol) with different alcohols, amines, and carboxylic acids produced the aryl ether **87**, aryl amines **89**, and ester **88** products, respectively (Scheme 32) [100].



Scheme 32: Electrochemical synthesis of aryl ether **87**, ester **88** and aryl amine **89** products

Proposed mechanism for schemes 31 and 32 is illustrated (Scheme 33). The photoexcited DDQ causes single electron transfer (SET) oxidation of an arene **84** to produce a radical cation **IV** that is capable of nucleophilic capture. The main distinction is that DDQ **I** would be produced by anodizing the reduced DDQH₂ **III**, and the electrochemical reaction would be finished by cathodizing protons to produce H₂. Therefore, the use of a conventional oxidant like TBN is not necessary with this electrophotocatalytic arrangement.



Scheme 34: Electrochemical synthesis of alkylarene **92**

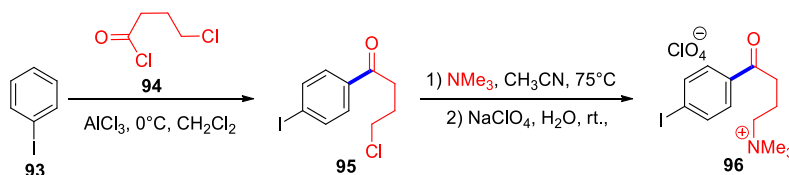
5. Arenes / Heteroarenes C–H Functionalization via organo-electrocatalysis

In developing novel and challenging organic transformations, the revitalization of photo-redox catalysis and organocatalysis, both areas individually experienced enormous success, even in the greatly stereoselective manners. For the successful implementation of α -functionalization of amines and carbonyl compounds, the merger of visible light catalysis by asymmetric organocatalysis has turned out as an operative strategy. Newly, organocatalysis have revealed extraordinary compatibility with electrochemistry to yield stimulating organic transformations, which appears challenging to realize in the absence of catalytic systems. Several practical problems in terms of organic synthesis could be resolved with the applications of photoredox, organo- and electrocatalysis which offers several advantages and could lead to the development of novel organic transformations^[102].

In the development of electrolysis, the toxic and dangerous redox reagents can be substituted by electric current or produced in situ, it is acknowledged as an environmentally friendly and safe

methodology. This is all due to the fact that the need for excess amounts of supporting electrolytes comprises a severe drawback. From the reaction mixture the supporting electrolyte must be separated as the completion of reaction takes place, unless it is reused and recovered, thus it constitutes a cause of leftover. The tetraalkylammonium salts are often used, due to their good solubility in organic solvents and maximum electrochemical stability. However, as the reaction has completed, the good solubility of an electrolyte often leads to difficulties with the separation of the salts from the products. By the use of redox mediators, further separation issue is initiated. The electron transfer between substrate and electrode is facilitated by the use of such mediators, thus also influence the selectivity of the electrochemical methodology. As both the mediators and supporting electrolyte represent an expense factor and source of waste, therefore for industrial applications their reuse and recovery in terms of various cycle is highly demanded.

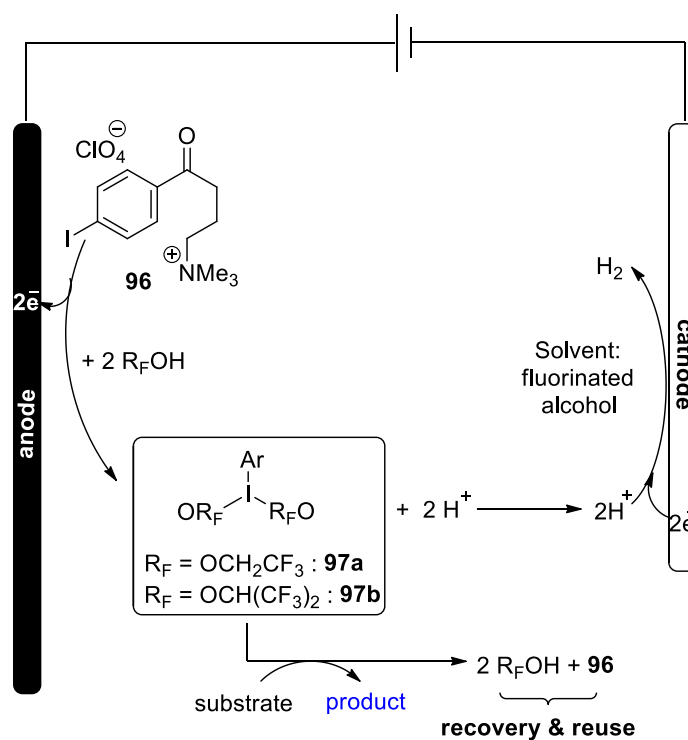
With regard to electrosynthesis thus by unlocking the potential of iodine(I)/iodine(III) redox couple, Francke and co-workers developed a mediator based on compound **93** (Scheme 35), containing a redox active unit of 4-iodopheny moiety, which is joined to a quaternary ammonium group and serves as a supporting electrolyte^[103].



Scheme 35: Synthesis of the Redox-active supporting electrolyte **96**

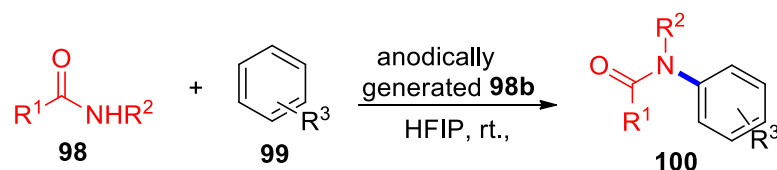
After complete transformation with a substrate, it facilitates the reuse and separation of redox active salt as shown in scheme 36. For the mediated electrochemical processes, fluorinated alcohols were targeted as solvents. Due to the excellent electrochemical properties such as anodic stability and high conductivity, the first fluorinated solvents such as 1,1,1,3,3,3,2,2,2-trifluoroethanol (TFE) or hexafluoroisopropanol (HFIP) are renowned. In the electrochemical generation of active form of mediator, alcohol is expected to play an active role by stabilizing iodine(III) (Structure **97** in Scheme 36). Additionally, due to the positive influence of fluorinated alcohols on the selectivity of transformations and rate containing ionic or radical intermediates, thus it frequently employed in iodine(III) mediated reactions. At the end, as cathodic half reaction

the selective proton reduction is feasible due to the rather low pK_a values of fluorinated alcohols, thus during electrochemical process produced H_2 as by-product.



Scheme 36: Concept for the electrochemical generation of an Iodine(III) species and the subsequent use for chemical Transformations

The concentration of **96**, current density, and electrolysis conditions have been optimised for the electrode material. It was discovered that using a glassy carbon working electrode in conjunction with a platinum counter electrode in an undivided cell while using a current density of 15 mA/cm² results in an optimum Faradaic efficiency of 70% (0.2 M solution of **96** in HFIP). With these refined parameters at hand, research into potential applications began with direct oxidative C–N bond forming reactions that had previously been reported in the context of other hypervalent iodine reagents. Through the intramolecular cyclization of 2-(N-acetylamino)-biphenyls **97**, N-acetyl carbazoles **100** have been created^[103].



Scheme 37: Electrochemical synthesis of N-acetyl carbazoles **100**

Related to the previous point, the use of fluorinated solvents TFE (tetrafluoroethylene) and HFIP (hexafluoroisopropanol) is often mentioned for their excellent properties in electrosynthesis reactions^[104–105]. These solvents are known for their high polarity, low viscosity, and ability to dissolve a wide range of organic and inorganic compounds. Additionally, they can improve the selectivity and yield of the reaction. However, it is important to note that the high cost, toxicity, and sustainability issues associated with these solvents have limitations that need to be considered. Fluorinated solvents are known for their high cost, as they are often difficult and expensive to produce. They are also highly toxic and can pose a significant risk to human health and the environment if not handled properly. Moreover, the production and disposal of these solvents can have negative sustainability impacts, such as contributing to greenhouse gas emissions and polluting water sources. Therefore, while the use of TFE and HFIP can offer certain advantages in electrosynthesis reactions, researchers must consider the limitations and strive to find alternative solvents or methods that are more cost-effective, less toxic, and more sustainable. This can help to reduce the environmental impact of electrosynthesis and ensure the safety and well-being of those involved in the process.

Conclusion & Perspective

a. Advantages of electrosynthesis compared to traditional methods

Electrosynthesis has several benefits, one of which is that it is environmentally benign. There are various factors that should persuade chemists to employ organic electrosynthesis from the perspective of practical operation. For instance, electrochemical processes typically show strong functional group tolerance in the absence of exogenous oxidants or reductants. Electrochemical reactions are typically carried out in milder conditions compared to traditional procedures, which frequently proceed at elevated temperature or pressure, offering an energy-saving alternative. Due to their high reaction efficiency, electrochemical processes typically have quick reaction times. Further reducing the reaction time is possible by tuning the current. The electrochemical system's capacity for oxidation or reduction can be optionally changed by adjusting the current or voltage, enabling processes that aren't possible with chemical oxidants or reductants. Electrochemical

processes can be quickly stopped at any time by flipping the power switch, unlike conventional reactions that typically need quenching. Last but not least, the majority of electrochemical reactions may be readily scaled up and have enormous potential for commercial applications. For instance, the industrialization of the electrochemical synthesis methods for 1,4-dicyanobutane, sebacic acid, etc. has been effective^[5].

The application of electrosynthesis proposes overcoming some limitations of the directed C–H functionalizations. For example, in molecules containing nitrogen or sulphur that will coordinate strongly with metallic catalysts, possibly poisoning the catalyst or functionalizing C–H in an unwanted position^[101–102]. The use of electrosynthesis provides greater control of the reaction medium by electrical voltage, allowing the acceleration or stabilization of synthetic intermediates. In electrosynthesis, substrates can undergo redox processes directly at the electrodes, or even better redox control of the reaction mediators can be achieved by controlling the applied electrical potential. We can also mention a better control of the substrate with fluorinated solvents, allowing the modulation of the nucleophilicity and stabilization of the intermediates^[104]. Additionally, reactions in photoelectrochemistry and flow chemistry are two promising techniques in electrochemistry. Photoelectrochemistry involves the use of electrical charges through the absorption of light and concomitantly through a source of electrical energy, while flow chemistry is characterized by the use of flow of reactants to promote electrochemical reactions in a continuous system. The environmental friendliness, high surface-to-volume ratio, and appealing mass transfers between phases make flow electrochemical technology beneficial in organic synthesis^[42]. Sunlight is abundant, convenient, affordable, and clean. A wide range of photoelectrode materials and redox mediators are also available, and PEC cells may make use of moderate reaction conditions^[77]. The combination of these approaches presents great potential for applications in solar energy and energy conversion technologies. Furthermore, these approaches have wide application in sectors such as chemical, pharmaceutical and food production, where the synthesis of chemical compounds is a critical step in the process.

b. Practical limitations of electrosynthesis

Despite many benefits, there are some disadvantages to using electrosynthesis in organic chemistry. For instance, a whole electrochemical device is required, and both its cost and maintenance are often expensive. Additionally, a supporting electrolyte must typically be used to

facilitate the transmission of electrons in solution, and because solvents like tetrahydrofuran, toluene, etc. are poorly conductive, choosing a solvent for electrosynthesis can occasionally be challenging. The use of metal catalysts in electrochemical reactions under readily accessible undivided cells is relatively limited because most metal cations are readily reduced at the cathode to zero-valent metals, and when electrochemical reactions are carried out in divided cells, expensive ion exchange membranes are required for separating anode and cathode^[5]. The flow electrochemical technique has several advantages, but due to the setup's complexity and cost, it is only used in a few chemical and pharmaceutical industries. The production of insoluble solids as a byproduct may obstruct uniform flow and limit the application of this strategy in the industrial setting. The product's quality is further impacted by the nitrogen and hydrogen gases produced during electrochemical synthesis^[42].

c. Use of enabling tools in arenes/(hetero)arenes C–H functionalization

The arenes/(hetero)arenes C–H functionalization has emerged as an elegant strategy in organic synthesis, and with technological advances as new tools, the perspective is of greater achievements for synthetic chemistry. Currently, it is observed that laboratories are being gradually updated with equipment to absorb these demands, such as flow systems, electrochemical, photochemical, ultrasound and microwave reactors, automation, etc. For this, a growing collaboration with engineers, computer scientists, electrical technicians, software developers and other areas of chemistry is required.

The modern world and its sustainable development trends are forcing the chemical industry to improve in an environmentally friendly direction and meet the requirements of “green chemistry.” Additionally, it is worth mentioning the various advantages of electrochemical reactions, such as high yields, higher selectivity and mild reaction conditions provide an environmentally friendly route. In this sense, the electrochemical arenes/(hetero)arenes C–H functionalization methods in batch reactions, continuous flow, metallacycles, photo and organo-electrocatalysis were widely discussed in this review.

Acknowledgment

Support from the Cardiff University to Dr. Nisar Ahmed is gratefully acknowledged.

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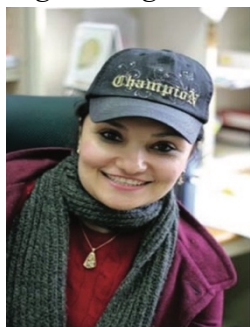
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