

Review

Recent Progresses in the Preparation of Chlorinated Molecules: Electrocatalysis and Photoredox Catalysis in the Spotlight

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Abstract: Among halogenated molecules, those containing chlorine atoms are fundamental in many areas such as pharmaceuticals, polymers, agrochemicals and natural metabolites. Despite the fact that many reactions have been developed to install chlorine on organic molecules, most of them rely on toxic and hazardous chlorinating reagents as well as harsh conditions. In an attempt to move towards more sustainable approaches, photoredox catalysis and electrocatalysis have emerged as powerful alternatives to traditional methods. In this review, we collect the most recent and significant examples of visible-light- or current-mediated chlorination published in the last five years.

Keywords: chlorination; photoredox catalysis; electrocatalysis; visible light; halogenation



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1. Introduction

The incorporation of halogen atoms into molecules is of great importance in organic synthesis as well as in materials science and medicinal chemistry. Halogenated, and more specifically chlorinated, compounds are not only widespread in nature (Figure 1a) [1–3], but also essential intermediates in the preparation of complex molecules and active pharmaceutical ingredients.

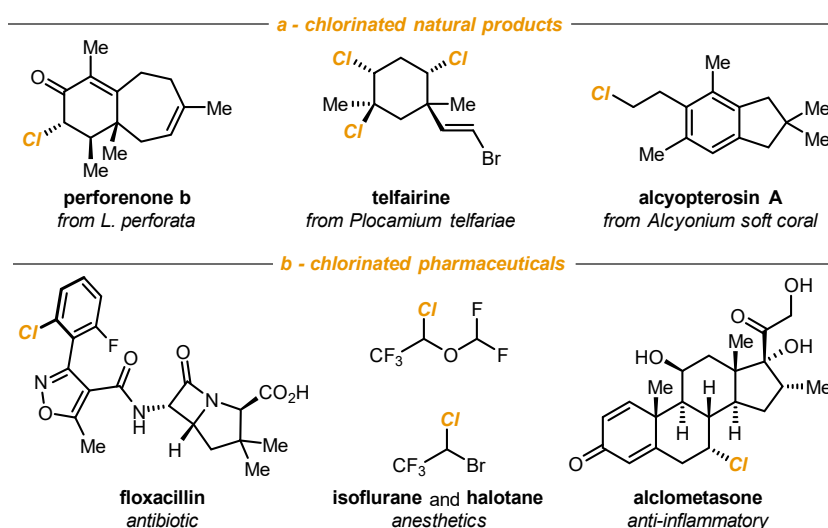


Figure 1. Selected examples of (a) chlorinated pharmaceuticals and (b) natural metabolites.

Chloroalkanes are all-round building blocks in organic chemistry. They are fundamental precursors to alcohols, ethers, amines and thioethers, which are prepared through displacement by appropriate nucleophiles. They are also used in the Finkelstein reaction to make more reactive iodoalkanes [4]. Moreover, organochlorine compounds can be converted into synthetically important organometallic species, such as Grignard and

organolithium reagents, and can produce reactive radical intermediates through halogen atom transfer (XAT) [5]. In the area of pharmaceuticals, both aromatic and aliphatic chloro compounds are key intermediates in the preparation of a large variety of drugs. Some of them are active ingredients themselves and used as antibiotics (e.g., floxacillin and dicloxacillin), anesthetics (e.g., halothane and isoflurane) and anti-inflammatory drugs (e.g., alclometasone) (Figure 1b) [6–9]. In addition, vinyl chloride, used in the plastic manufacture for the preparation of polyvinyl chloride (PVC), is among the largest petrochemicals in world production [10]. Some of them also find application as paint additives [11], and in food packaging [12]. Finally, some chlorinated hydrocarbons (e.g., dichloromethane, chlorobenzene and tetrachloroethylene) are used as solvents in organic chemistry and in cleaning applications, such as degreasing and dry cleaning.

Therefore, the continuous interest towards the development of new methods to incorporate chlorine atoms is not surprising. The formation of C-Cl bonds can be achieved via three general approaches: electrophilic addition to C-C multiple bonds, nucleophilic displacement of leaving groups or radical chlorination of C-H bonds. Alkenes are readily converted in the corresponding dichloro and monochloro derivatives upon reaction with Cl₂ or HCl, respectively. Chlorine can also be used for the chlorination of aromatic hydrocarbons. In such cases, a Lewis acid (FeCl₃, AlCl₃) is necessary to generate a strong chlorinating species able to overcome the low reactivity of the substrate. Chloroalkanes can be prepared starting from available alcohols upon conversion of the hydroxyl group into a better leaving group. This can be carried out through sulfonylation, followed by replacement with a chloride salt. Alternatively, alcohols can be activated in situ with thionyl chloride [13], or with PPh₃/CCl₄ in the Appel reaction [14]. Finally, the radical C-H chlorination is a powerful tool for the synthesis of this class of compounds, since the direct substitution of hydrogen atoms in largely available alkanes is highly desirable. This last strategy relies on the formation of a carbon-centered radical, through hydrogen atom transfer (HAT), that is quenched, for instance, by one of the several available *N*-chloroimides 1a–e (Figure 2).

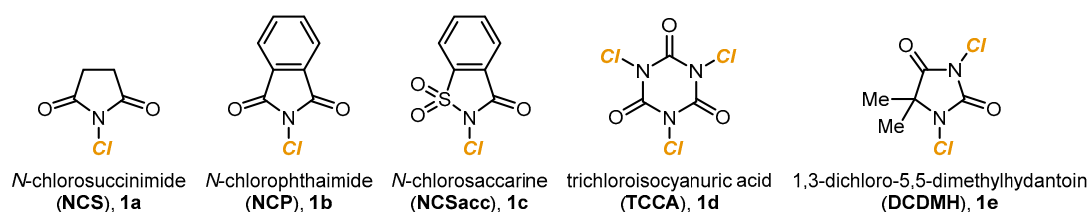


Figure 2. Common chlorinating reagents.

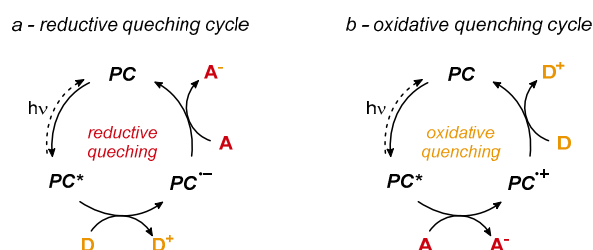
Despite the many applications of electrophilic and radical chlorination reactions, most of them require hazardous or toxic reagents, an inert atmosphere and harsh reaction conditions such as a high temperature or an excess of the chlorinating agent and initiator. These features are difficult to reconcile not only with the high chemo-, regio-, site- and stereoselectivity requirements in modern organic synthesis, but also with the present need for alternative and more sustainable processes.

In such a scenario, photoredox catalysis and electrocatalysis offer alternative ways to efficiently prepare a large variety of chlorine-containing molecules. Both approaches provide access to high-energy intermediates (e.g., radicals) under very mild reaction conditions, by promoting the movement of single electrons in redox processes. In photoredox catalysis, they are triggered by single-electron transfer (SET) events produced by a photocatalyst upon photoexcitation, while in electrocatalysis, they occur on the surface of metal electrodes connected to an external circuit. Recent reviews on the halogenation of organic molecules have shown how powerful the modern tools based on visible light [15,16] and electrochemistry are [17]. Even though photoredox catalysis and electrolysis present several differences, as recently shown by a comprehensive review by Rovis [18], they are conceptually very close. For such a reason, in this review, we collect the most recent progress in the

preparation of chloro compounds by means of electrocatalysis and photoredox catalysis, to highlight similarities and differences between the two approaches.

2. Chlorination Enabled by Visible Light Photoredox Catalysis

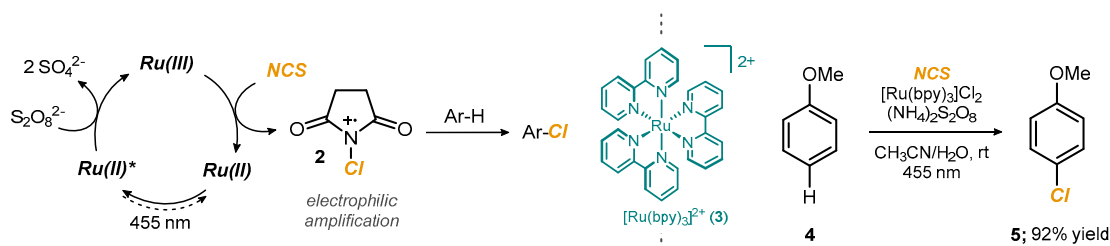
Photoredox catalysis is based on the ability of photocatalysts, transition-metal complexes or organic dyes to undergo an electronic transition from the ground state (PC) to the excited state (PC*) upon irradiation with visible light. Once produced, the excited state can be quenched by reagents through single-electron transfer in either the oxidative or the reductive quenching cycle. In a reductive quenching cycle (Scheme 1a), SET from the donor (D) to PC* results in the ground state PC•− and the oxidized donor (D+). A subsequent SET from PC•− to an acceptor (A) results in the restoration of the photocatalyst and the reduced acceptor A−. Alternatively, in an oxidative quenching cycle (Scheme 1b), SET from PC* to an acceptor (A) results in the ground state PC•+ and the reduced acceptor (A−). A subsequent SET from a donor (D) to PC•+ regenerates the photocatalyst (PC), affording the oxidized donor (D+).



Scheme 1. Illustration of (a) a reductive and (b) an oxidative quenching cycle.

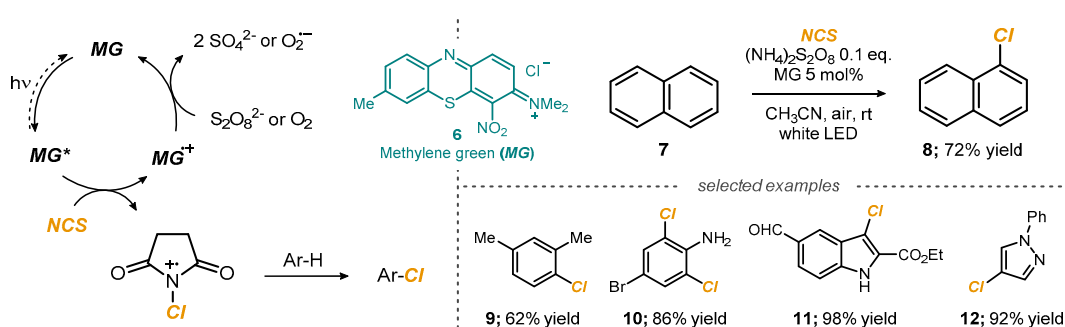
2.1. Photoredox Electrophilic Amplification of NCS and Related Reagents

In 2016, König demonstrated that photocatalysis is a valuable alternative way to activate NCS for the chlorination of arenes [19]. *N*-Chlorosuccinimide **1a** is a common chlorination reagent but requires activation. Nevertheless, it is more reactive than *N*-chloroamines, as a consequence of the two carbonyl groups on the succinimide, which reduce the electron density on the nitrogen and increase the electrophilicity of the chlorine. NCS oxidation generates an even more reactive intermediate **2**, because of the formation of a *N*-radical cation, possibly capable of giving S_EAr even on electron-poor arenes. The oxidation potential of **1a** ($E^0(C/C^+) = +1.10$ V) does not match that of the photoexcited state of $[Ru(bpy)_3]Cl_2$ **3** ($E^0(Ru^{II*}/Ru^I) = +0.77$ V). This means that its activation via the reductive quenching cycle is not possible. However, in an oxidative quenching cycle, the so-formed Ru(III) complex is a stronger oxidizer ($E^0(Ru^{III}/Ru^{II}) = +1.29$ V). Indeed, the authors reported that, in the presence of $(NH_4)_2S_2O_8$ as the sacrificial oxidant, anisole **4** was selectively chlorinated at the *para* position, affording 4-chloroanisole **5** in 92% yield (Scheme 2). Without photocatalytic activation, they did not observe any conversion after three hours, and product **5** was produced in less than 5% yield after sixteen hours, despite the complete conversion of the substrate. Nevertheless, the electrophilic amplification was not sufficient to chlorinate electron-poor arenes such as acetanilide and acetophenone.



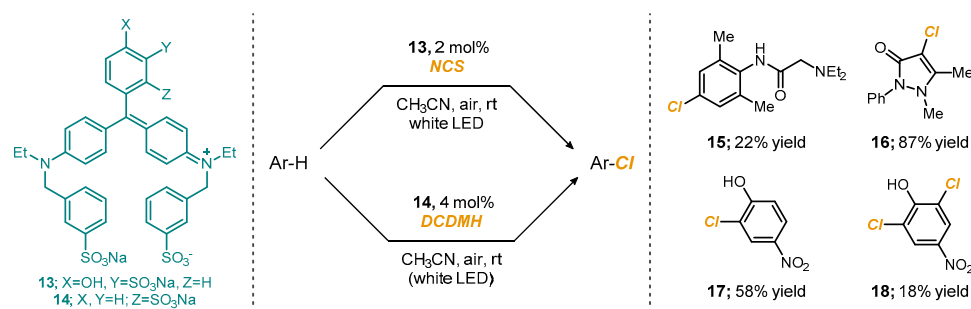
Scheme 2. Photoredox-catalyzed electrophilic amplification on NCS **1a**.

To unlock the direct electrophilic amplification of NCS without the use of sacrificial oxidizers, photocatalysts possessing a higher oxidizing photoexcited state are necessary. In 2019, Lamar et al. reported the use of organic dyes for the introduction of chlorine into aromatic substrates [20]. Choosing naphthalene **7** as the model reactant ($E^0(\text{C}/\text{C}^+) = +1.64 \text{ V}$), they extensively screened organic photocatalysts, using white LED irradiation under aerobic conditions. Methylene green **6** ended up being the best one, producing 1-chloronaphthalene **8** in 72% yield. Oxygen was responsible for the regeneration of the ground-state photocatalyst, as demonstrated by the formation of H_2O_2 . Nevertheless, in order to enhance the efficiency of the catalytic process, 10 mol% of $(\text{NH}_4)_2\text{S}_2\text{O}_8$ was also added, and the molarity of the reaction was increased from 0.1 M to 0.2 M in acetonitrile. Under the optimized conditions, a library of (hetero)aromatic molecules bearing electron-donating and withdrawing groups was chlorinated in good to excellent yields (selected products **9–12**) (Scheme 3).



Scheme 3. Aromatic chlorination using NCS **1a** and methylene green **6**.

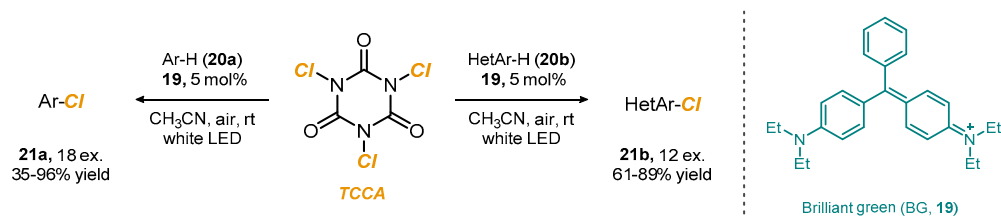
In an attempt to further evolve towards sustainable processes, Lamar and LeBlanc described two new catalytic systems based on FDA-approved food dyes (Fast Green FCF **13** and Brilliant Blue FCF **14**) capable of functionalizing aromatics and heteroaromatics under mild conditions [21]. The methodology was exploited for the chlorination of known pharmaceuticals, such as lidocaine **15** and phenazone **16**, as well as for the preparation of agrochemicals (nitrofungin **17** and chloroxylin **18**) (Scheme 4). Additionally, the two organocatalysts were employed with two distinct *N*-chloro reagents, NCS **1a** and DMDCH (1,3-dichloro-5,5-dimethylhydantoin **1e**). Mechanistic investigations of the separate systems indicated two different modes of activation. Fast Green FCF **13** indeed acted as a light-promoted photoredox catalyst oxidizing NCS **1a**, while Brilliant Blue FCF **14** served as a chlorine-transfer catalyst with DCDMH **1e**, not necessarily involving visible light.



Scheme 4. Chlorination with NCS **1a** and DCDMH **1e** with FDA-approved food colorants.

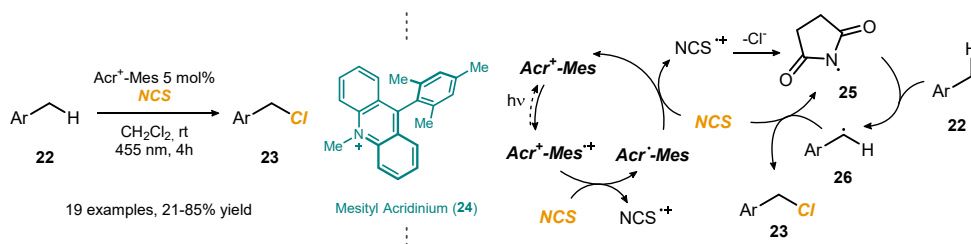
Similarly, other chlorinating reagents can undergo electrophilic amplification by exploiting visible light photoredox catalysis. Trichloroisocyanuric acid (TCCA, **1d**), for example, which usually requires activation under acidic conditions, was used to chlorinate a large group of arenes **20a** and heteroarenes **20b** under air and irradiation with white light using the inexpensive brilliant green **19** [22]. Chlorinated derivatives **21a** and **21b** were isolated with yields between 35% and 96% (Scheme 5). Noteworthy, the reported

methodology was highly efficient even on electron-poor rings, presented short reaction times, with some substrates undergoing chlorination in 5–10 min, and was scalable up to the gram scale with no erosion in the yield. In comparison to other chlorinating agents, such as Palau'chlor [23], the TCCA/BG system was proven as a valuable complementary method and, in many examples, provided a superior alternative for the chlorination of arenes and heteroarenes.



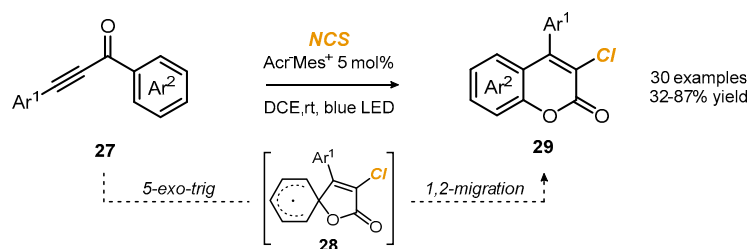
Scheme 5. Brilliant green 19-catalyzed chlorination using TCCA 1d.

N-Chlorosuccinimide 1a has not only been used in S_EAr reactions for the production of chlorinated aromatic compounds, but also to quench radical (cation) intermediates. In 2020, Wu described a visible light chlorination of benzylic C-H bonds, employing NCS 1a and Fukuzumi's dye (Acr^+-Mes , 24) [24]. The reaction, conducted in dichloromethane under argon and blue LED irradiation and described in Scheme 6, converted a library of substituted toluenes 22, affording the corresponding benzyl chlorides 23 in moderate to good yields after 4 h. The authors conducted an extensive study on the reaction mechanism, based on quenching analysis of the photocatalyst. They proposed a mechanism involving the initial oxidation of NCS 1a by the photoexcited catalyst (Acr^+-Mes^+), generating Acr^+-Mes , which can reduce a second equivalent of NCS to afford NCS^\bullet and regenerate the ground-state Acr^+-Mes . Subsequently, NCS^\bullet releases further Cl^- with the generation of succinimidyl radical 25, which abstracts a hydrogen atom from substrate 22 to give benzylic radical 26. NCS may react with radical 26, affording benzylic chloride 23 and succinimidyl radical 25, which results in chain propagation.



Scheme 6. Benzylic chlorination with Fukuzumi's salt 24.

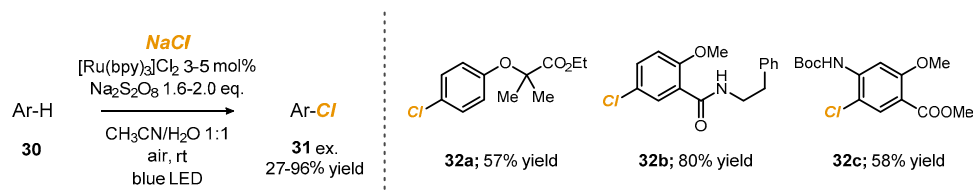
Under similar conditions, Mal and co-workers were able to develop a chlorinative cyclization of aryl alkynoates 27, to synthesize coumarins 29. Additionally, in this report, the mechanistic hypothesis was based on data coming from several techniques (Stern–Volmer, electrochemical and EPR analysis), together with on–off and radical trapping experiments. The reaction involved the oxidation of 27 by SET from the excited photocatalyst and dearomatization through cyclization to give spiro compound 28. Subsequent aryl migration and final HAT from the succinimidyl radical generated chloroisocoumarins 29 (Scheme 7).



Scheme 7. Synthesis of chloroisocoumarins **29** via chlorinative cyclization.

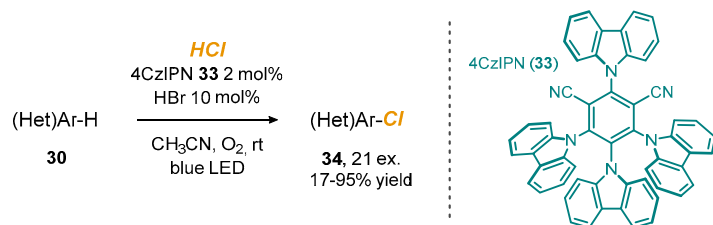
2.2. Photoredox Chlorination Using Alternative Chlorinating Reagents

Despite the excellent results obtained with NCS **1a** and related reagents, several groups have devoted great efforts towards the development of methodologies that rely on the use of alternative, more sustainable reagents capable of incorporating chlorine atoms into molecules. In 2017, Hu demonstrated that the catalytic system reported the year before by König and depicted in Scheme 2 was also effective in the activation of NaCl, a more sustainable chlorine source [25]. The oxidative quenching cycle of $[\text{Ru}(\text{bpy})_3]\text{Cl}_2$ was triggered by using $\text{Na}_2\text{S}_2\text{O}_8$ and used to oxidize Cl^- to Cl^+ or its equivalent (HClO), probably via a chlorine radical intermediate. The in situ generated electrophilic chlorine was then incorporated into several aromatic substrates, showing good yields and functional group tolerance. The authors demonstrated the potential utility of the reaction by preparing clofibrate **32a**, **32b** (precursor of glibencamide), and **32c** (precursor of metoclopramide), (Scheme 8).



Scheme 8. Chlorination of arenes **30** with NaCl.

Halogenidric acids are valuable alternatives as halogen atom sources. This concept was demonstrated by König, who used the organophotocatalyst 4CzIPN **33** to chlorinate electron-rich arenes **30** under blue light and an oxygen atmosphere, with a mixture of HBr and HCl (Scheme 9) [26]. The catalyst has a dual role, as it is able to oxidize both bromide and chloride anions to their respective radical species. Bromine radicals recombine to bromine as the active brominating agent. The in situ formed bromo arenes are subsequently attacked by chlorine radicals, yielding the desired chlorinated compounds.

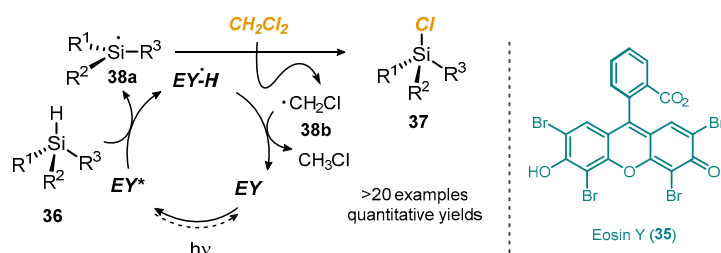


Scheme 9. Chlorination of arenes **30** with HCl via bromination–debromination.

The chloride ion (introduced in the form of a salt or HCl) was also employed for electrophilic aromatic oxidative chlorination using biomimetic or bioinspired approaches. In particular, in 2016, Hering, inspired by flavin adenine dinucleotide (FAD)-dependent halogenases, replaced the biomolecules FAD and NADH_2 with the inexpensive organic dye riboflavin tetraacetate and anisyl alcohol as the sacrificial reducing agents [27]. By irradiating at 455 nm under air, an equimolar mixture of acetic and hydrochloric acids

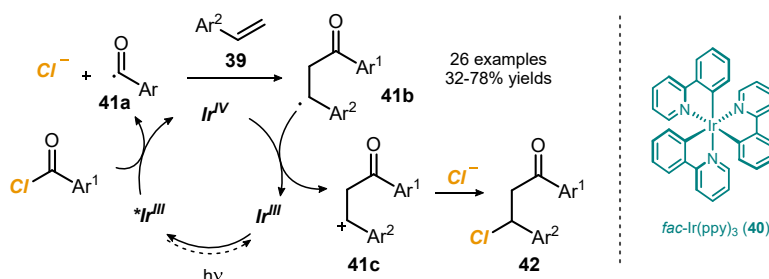
was effectively used to add a chlorine atom on aryl ethers and anilines. Similar conditions provided α -monochlorination on aceto- and propiophenone. More recently, Gulder and co-workers managed to combine photocatalysis and biocatalysis by using flavin mononucleotide (FMN) together with a vanadium-dependent haloperoxidase from *Acaryochloris marina* (*Am*VHPO) [28]. To avoid the use of sacrificial reductants, they used a redox-active buffer or even water as the electron source. In the reaction vessel, the H_2O_2 produced in situ by FMN was directly used by the peroxidase to halogenate electron-rich (hetero)aromatics using KCl.

Reaction solvents such as dichloromethane can act as chlorinating reagents as well. In 2019, Wu and Cui published a visible-light-mediated chlorination of silanes by accessing silyl radicals using photocatalytic Si-H activation promoted by neutral Eosin-Y **35**. Under simple operative conditions, more than twenty silanes **36** were quantitatively converted in the corresponding chlorosilanes **37**, widely used reagents in organic synthesis and in materials science (Scheme 10). Moreover, the strategy was also transferred from stirred reactor vessels to continuous-flow micro-tubing reactors. Under flow conditions, the chlorination was amenable to gram-scale production, and, even more importantly, the stepwise chlorination of di- and trichlorosilanes was successfully achieved in a highly selective manner. Regarding the mechanism, silyl radical **38a** was generated by the HAT between the light-activated photocatalyst **35** (EY^*) and hydrosilane **36**. The derived silyl radical subsequently abstracted the chlorine from CH_2Cl_2 to deliver the silyl chloride product **36** and the chloromethyl radical species (**38b**). A reverse hydrogen atom transfer (RHAT) between radical **37** and the catalyst (EY^*-H) regenerated the ground-state eosin Y **35** (EY) and produced chloromethane.



Scheme 10. Chlorination of hydrosilanes **36** with dichloromethane as the chlorine source.

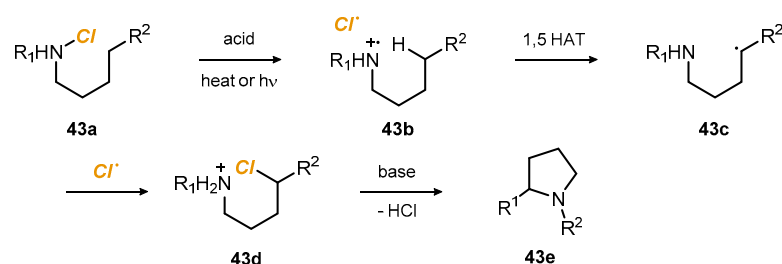
Finally, acyl chlorides can be used as well as chlorinating reagents. The chloroacylation of styrenes **39** was reported by Oh in 2020 employing *fac*-Ir(ppy)₃ **40** as the photocatalyst to cleave the C-Cl bond in the acyl chloride and produce Cl^- and a nucleophilic acyl radical **41a** [29]. Upon acylation, benzyl radical **41b** is oxidized to the corresponding cation **41c**, thus regenerating the ground-state photocatalyst. The interception of chloride from **41c** finally produces β -chloroketones **42** (Scheme 11). The authors pointed out the essential role of KHCO_3 , which prevented the dehydrochlorination of the product by keeping a neutral pH during the course of the reaction.



Scheme 11. Photoredox-catalyzed chloroacylation of styrenes **39**.

2.3. Photoredox Chlorination of Nitrogen-Containing Aliphatic Molecules

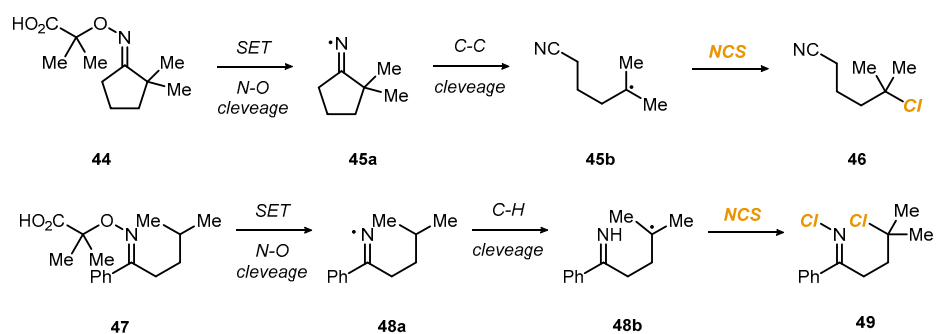
Alkane chlorination is probably one of the first reactions that undergraduate students meet during their studies, and they also learn that, because of the similar BDEs, more than one C-H bond is usually chlorinated, producing mixtures of regioisomers difficult to separate. In addition to this, the standard radical halogenation requires high temperatures, radical initiators and hazardous reagents (Cl_2). Photoredox catalysis can provide for milder reaction conditions, the choice of safer and alternative chlorinating reagents and also site selectivity, for example, when the substrate contains nitrogen atoms. One classic example of how this high regioselectivity is achieved is represented by the Hofmann–Löffler–Freytag reaction [30], producing cyclic amines, typically pyrrolidines, by the thermal or photochemical decomposition of *N*-chloroamines in the presence of a strong acid (H_2SO_4 or $\text{CF}_3\text{CO}_2\text{H}$) (Scheme 12).



Scheme 12. Hofmann–Löffler–Freytag reaction.

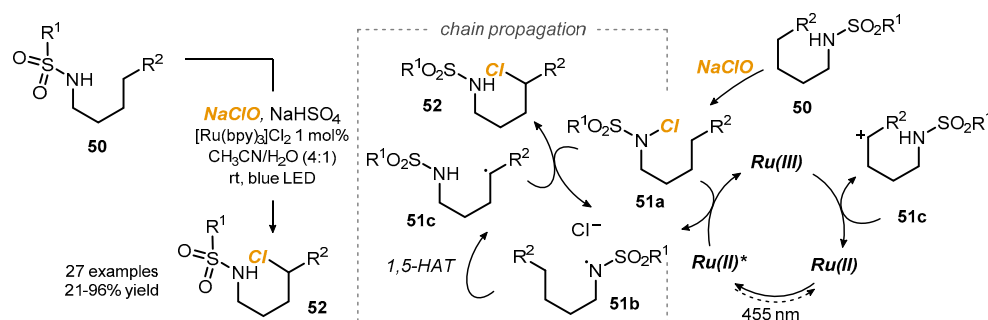
When *N*-chloroamine **43a** is protonated, the homolytic cleavage of the N-Cl bond under the influence of heat, light or other initiators affords radical cation **43b** and the chlorine radical. The ammonium radical undergoes a favored intramolecular 1,5-HAT to afford alkyl radical **43c** which, capturing a chlorine radical, forms alkyl chloride **43d**. The alkyl chloride is later cyclized under the influence of a base, producing pyrrolidine **43e**. The key to the regioselectivity relies on the site-selective hydrogen abstraction occurring on the intermediate containing the *N*-centered radical, accessible through photoredox catalysis from *N*-Cl- or *N*-OX ($X = \text{H}$ or R)-containing substrates.

In 2018, Leonori proved that the remote functionalization of cyclic and acyclic oximes **44** was indeed possible via a radical-promoted C-C and C-H bond cleavage cascade, by using the aforementioned Fukuzumi acridinium salt **24** [31]. The methodology provided access to a series of γ -chlorinated nitriles and imines, depending on the structure of the starting material. When cyclic oximes **44** were used, the formation of the corresponding imidyl radical **45a** by the excited photocatalyst triggered C-C bond cleavage to open the ring, producing a terminal cyano group and a C-centered radical **45b**. The radical was then quenched by NCS **1a** to afford chlorinated nitrile **46**. When linear oximes **47** were used instead, the imidyl radical **48a** underwent 1,5-HAT, affording radical imine **48b**. NCS **1a** was again responsible for the chlorination, this time of both the radical and the imino group, producing stable γ -Cl,*N*-Cl imines **49** (Scheme 13).



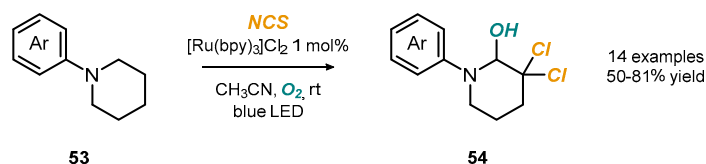
Scheme 13. Photoinduced remote functionalization by iminyl radicals to obtain chlorinated nitrile **46** and γ -Cl,*N*-Cl imines **49**.

Additionally, aliphatic amines can undergo a similar γ -chlorination. In 2020, Yu published a methodology to functionalize sulfonamides using sodium hypochlorite [32]. More than twenty sulfonamides **50** were successfully chlorinated with good to excellent yields, even at the gram scale (Scheme 14). Chlorination at the allylic or benzylic position, as well as across a cyclohexyl moiety, was not feasible. According to the mechanistic hypothesis, the reactive *N*-chloroamine **51a** was produced directly in the reaction mixture and underwent single-electron reduction to *N*-centered radical **51b** from photoexcited $[\text{Ru}(\text{bpy})_3]\text{Cl}_2$. 1,5-HAT generated radical **51c** reacting with a second equivalent of **51a**, initiating a chain reaction (as suggested by the quantum yield measurement of 3.23), and producing product **52**.



Scheme 14. Remote chlorination of aliphatic sulfonamides **50**.

To conclude this section, one example of cyclic amine chlorination is presented. Aryl piperidines **53** were functionalized under aerobic conditions, in the presence of NCS **1a**, affording 3,3-dichloro-2-hydroxy-piperidines **54** via two subsequent chlorinations of an intermediate enamine, followed by the capture of O_2 by an α -amino radical species (Scheme 15) [33].



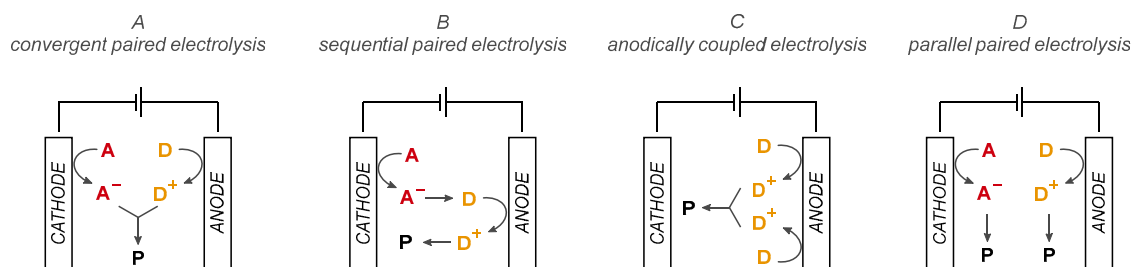
Scheme 15. Visible-light-induced $\text{C}(\text{sp}^3)\text{-H}$ functionalization of piperidines **53**.

To gain insights into the mechanism, the authors ran control experiments. When 2,2,6,6-tetramethylpiperidinoxy (TEMPO) and 2,6-di-*tert*-butyl-4-methylphenol (BHT) were added to the reaction mixture as radical scavengers, the formation of the product was completely suppressed, indicating that a free radical process was involved in the transformation. Additionally, when the model reaction was performed under a molecular oxygen ($^{18}\text{O}_2$) atmosphere, the ^{18}O -labeled **54** was isolated, confirming that the oxygen in the product was coming from the molecular oxygen in the air.

3. Chlorination Enabled by Electrocatalysis

Electrocatalysis pivots on the use of electrical energy to apply a potential across a pair of electrodes immersed into a solution of the components to be electrolyzed. In an electrolysis experiment, four key features are present: (1) an anodic oxidation, (2) a cathodic reduction, (3) conservation of the charge in the solution and (4) the presence of a soluble supporting electrolyte to ensure the low electrical resistance of the solution. Common to many organic electrochemical transformations, only one of the two electrodes (working electrode) generates a useful product, while on the counter electrode, a non-productive reaction takes place. For net-oxidative processes, proton reduction to H_2 at the counter electrode is the most common non-productive reaction. For net-reductive reactions, sacrificial oxidation of an amine or the anode itself (e.g., Zn, Mg, Al, Cu) is commonly

encountered. In this section, there are many examples in which both electrodes produce useful intermediates. Some common mechanisms in electrolysis are depicted in Scheme 16 and are those herein presented.

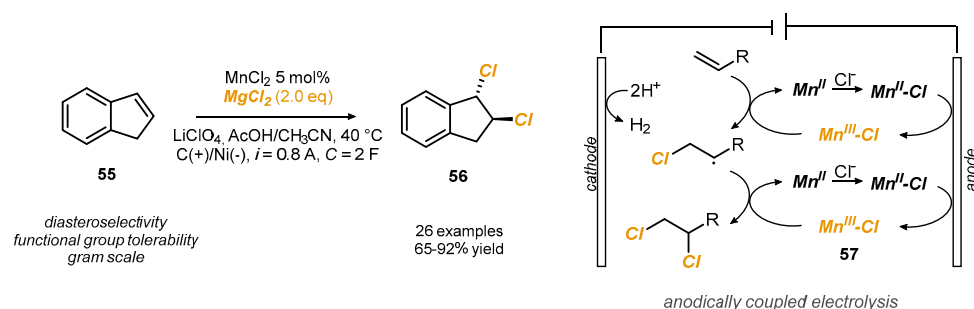


Scheme 16. Examples of electrolytic processes presented in this review.

One major difference between the two approaches is that while in photoredox catalysis, the redox events take place on the same site (i.e., the photocatalyst), in electrocatalysis, they occur on two distinct places (cathode and anode). This feature makes it possible to physically separate the two events, when necessary, via the use of a divided cell, provided that a method to accommodate the movement of ions from one half-cell to the other is employed. This is usually achieved by interfacing the two half-cells with a separator, such as a sintered-glass frit, a porous ceramic, a porous polymer sheet or a semipermeable ion-selective membrane (e.g., Nafion). The other fundamental difference is that, in direct electrolysis, redox events occur at the interface between the electrode and solution, which can produce a localized, high concentration of radicals. In contrast, redox chemistry in photoredox catalysis occurs in the solution and provides a low radical concentration. As a result, the coupling of two transient radicals is feasible in electrochemistry if they are generated at the same electrode, whereas this is more challenging in photoredox catalysis.

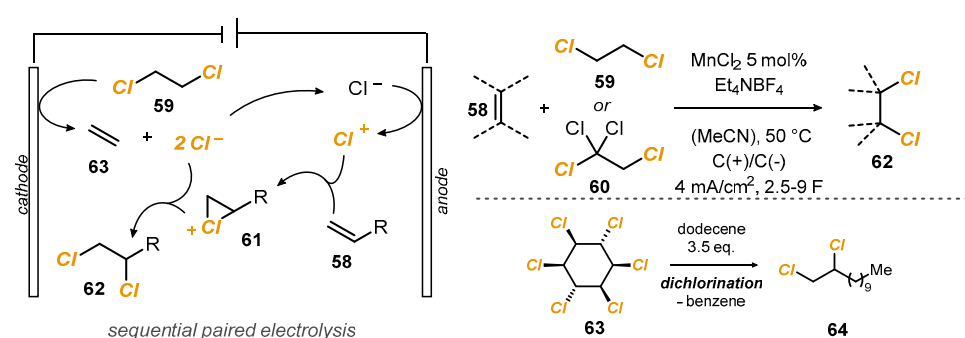
3.1. Electrocatalyzed Dichlorination of Alkenes

Just like photoredox catalysis is employed (in combination with NCS **1a** or chloride salts) to replace Cl_2 in the electrophilic chlorination of arenes, electrocatalysis is a valuable alternative to achieve alkene chlorination under mild and more sustainable reaction conditions. In 2017, Lin described a manganese-catalyzed alkene dichlorination, with MgCl_2 as the chlorine source, producing H_2 and $\text{Mg}(\text{OAc})_2$ as the sole by-products (Scheme 17) [34]. Optimizing the dichlorination of indene **55**, the authors observed that the direct electrolysis of LiCl on the Pt electrode was not satisfying, giving poor yields of **56** and no *syn:anti* selectivity. Therefore, a redox-active metal was added to impart kinetic control over the difunctionalization, and they obtained good results, in terms of diastereoselectivity, with $\text{Mn}(\text{OTf})_2$. The high diastereoselectivity came from a combination between the steric and electronic properties of the chlorine transfer agent $\text{Mn}(\text{III})\text{-Cl}$ **57**. Further improvements were observed when LiCl was replaced with MgCl_2 . The reaction was extended to several styrenes and alkenes, producing the corresponding dichloro derivatives in good yields and diastereoselectivity. Moreover, oxidatively sensitive functional groups (alcohols, aldehydes, amines) were tolerated.



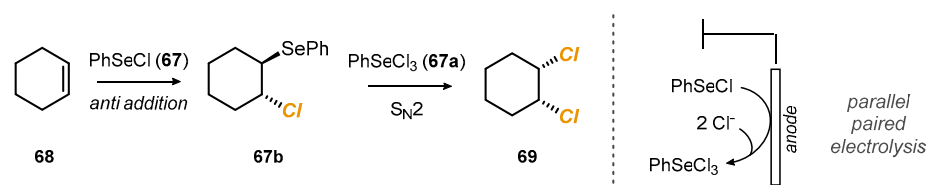
Scheme 17. Electrocatalytic radical dichlorination of alkenes **55**.

An interesting alternative for the preparation of vicinal dichlorides **62** was recently presented by Morandi. The methodology involved an electronically assisted shuttle paradigm, with inexpensive 1,2-dichloroethane (DCE) **59** used as the chlorine source [35]. In the cell, two consecutive cathodic reductions of DCE are leveraged to produce chloride anions in the reaction medium, releasing ethene **63**. Following this, the oxidation of Cl^- to Cl^+ affords an intermediate chloronium ion **61**, which is converted in the final product **62** via ring opening from Cl^- in an overall redox-neutral process (Scheme 18). Optimal reaction conditions featured graphite electrodes in an Et_4NBF_4 solution (0.1 M in DCE), at 50°C . MnCl_2 was used as the mediator. In many cases, a solution of 1,1,1,2-tetrachloroethane **60** in MeCN was used instead of neat DCE **59** to obtain better yields. Under optimized conditions, thirty alkenes were efficiently dichlorinated. Noteworthy, soil contaminated with lindane (*gamma*-hexachlorocyclohexane) **63** could also be used for the synthesis of 1,2-dichlorododecane **64**.



Scheme 18. Paired electrolysis for reversible vicinal dichlorination of alkenes **58**.

In 2021, Hilt published the first electrochemical *cis*-dichlorination of alkenes [36]. The key reagent in such a transformation was PhSeCl **67**, which has a double role (Scheme 19). On one side, it can be oxidized at the anode, in the presence of tetrabutylammonium chloride (TBAC, **66**), to form PhSeCl_3 **67a**, but on the other side, it can undergo a non-catalyzed *anti*-chloroselenation of cyclohexene **68**, affording intermediate **67b**. PhSeCl_3 , being a strong electrophile, may induce a nucleophilic chlorination on intermediate **67b**, with inversion of the configuration, producing *cis* dichlorocyclohexane **69**. The reaction could be applied to cyclic as well as linear olefins, also bearing hydroxyl and acetoxy moieties. Lower yields were observed on styrenes, and the authors attributed the result to the redox lability of the substrates.

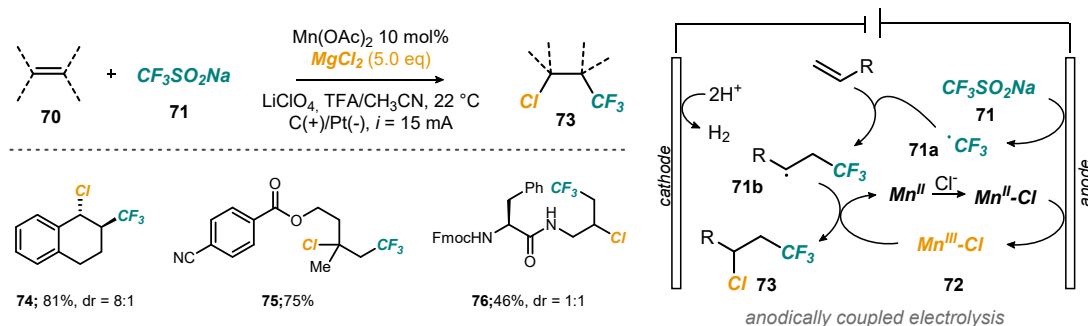


Scheme 19. Electrochemical *cis*-chlorination of alkenes **68**.

3.2. Electrocatalyzed Heterofunctionalization of Alkenes

After having developed the electrocatalyzed dichlorination of olefins **70**, Lin applied an anodically coupled electrolysis to merge two distinct oxidative events and therefore make the heterofunctionalization of alkenes possible. In particular, he developed a protocol to incorporate the trifluoromethyl moiety using Langoi's reagent **71** ($\text{CF}_3\text{SO}_2\text{Na}$) [37]. This salt is directly oxidized on the graphitic carbon to the electrophilic trifluoromethyl radical **71a** (anodic event A), capable of reacting with electron-rich alkenes, affording the alkyl radical **71b**. Concomitant oxidation of Cl^- , assisted by $\text{Mn}(\text{OAc})_2$ (anodic event B), generates the radical chlorinated reagent $\text{Mn}(\text{III})\text{-Cl}$ **72**, able to quench intermediate **71b**, giving the final product **73** (Scheme 20). The two events could be merged thanks to the

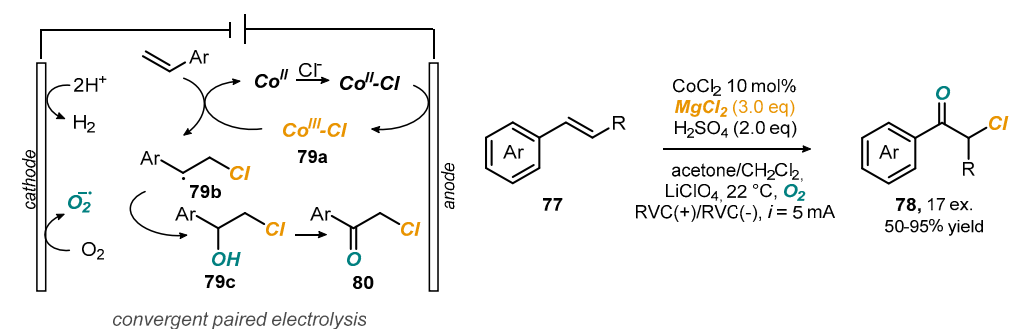
different natures of the two radical species. The alkene is indeed more likely to react with a transient free radical, such as **71a**, than with the persistent metal-based radical **71c**. The authors investigated the scope of the reaction, and several different styrenes and alkenes were efficiently trifluoromethylchlorinated (selected products **74–76**).



Scheme 20. Electrocatalyzed trifluoromethylchlorination of alkenes **70**.

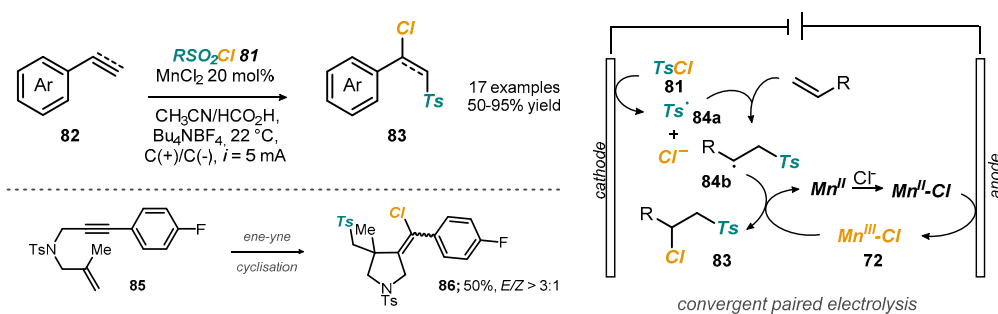
The same group later applied a similar concept to achieve alkene chloro-alkylation by anodic generation of a carbon-centered radical from malonitrile through proton-coupled electron transfer [38].

When anodic and cathodic events are combined, the chloro-chalcogenation of alkenes is possible (Scheme 21). This was demonstrated by Chen, who reported a cobalt-catalyzed electrochemical oxychlorination of styrenes **77** to α -chloroacetophenones **78** [39]. To obtain reproducibility, reticulated vitreous carbon (RVC) electrodes were used. Despite prolonging the reaction times, due to the lower current density, they provided better results. Like manganese in the previous examples, cobalt was fundamental in mediating the anodic oxidation of MgCl_2 to a Co(III)-Cl radical species **79a**. Oxygen was directly reduced on the cathode to a persistent radical superoxide ion, capable of quenching the transient benzyl radical **79b**, affording alcohol **79c**. β -Chloroketone **80** was formed by the oxidation of **79c**, but the author did not investigate whether the process was electrochemical or not.



Scheme 21. Electrochemical oxychlorination of styrenes **77**.

With excellent atom economy, Lei used sulfonyl chlorides **81** as bifunctional reagents to produce β -chloro(vinyl)sulfones **83** via a redox-neutral chlorosulfonylation of alkenes and alkynes **82**, Scheme 22 [40]. In the designed reaction, the cathodic reduction of sulfonyl chloride **81**, followed by the cleavage of the S-Cl bonds, produces Cl^- and the sulfur-centered radical **84a**, which reacts with the substrate to give intermediate **84b**. Chloride anions are not wasted, but oxidized at the anode, with the assistance of MnCl_2 , to give Mn(III)-Cl **72**. Final radical coupling produces the chlorinated product **83**, regenerating the manganese catalyst. The reaction was extended to several styrenes and aryl acetylenes. Moreover, a radical ene-yne cyclization was attempted on propargyl amine **85**, and pyrrolidine **86** was isolated in 50% yield.

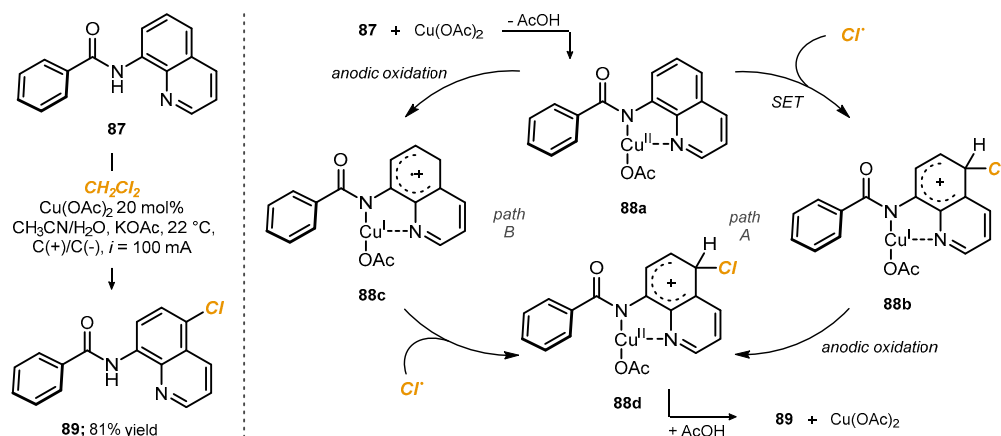


Scheme 22. Chlorosulfonylation of terminal alkenes and alkynes **82**.

3.3. Electrocatalyzed Arene Chlorination

As highlighted in the Introduction, photocatalysis and electrochemistry are closely related, despite some differences: one among all seems to be the choice of the substrates. Indeed, photoredox catalysis has mostly been used as an alternative mode of activation for aromatic electrophilic substitution, thus affording chloroarenes, with few methodologies applied to alkenes. The opposite trend appears when looking into electrochemistry. The methodology reported thus far in this review is the addition of one of two chlorine atoms to olefins. Nevertheless, there are some recent examples of aromatic chlorination performed under electrochemical conditions.

For example, in 2021, Fang and Guo reported a C-5 selective chlorination of 8-aminoquinoline **87**, catalyzed by copper acetate [41]. Dichloromethane was used as the source for chlorine radicals, being formed at the anode by the oxidation of small amounts of Cl^- released in the electrolytic cell upon DCM heterolysis, according to the authors' hypothesis. Aminoquinoline **87** is able to coordinate copper by the two nitrogen atoms, and intermediate **88a** can evolve towards product **89** through two different catalytic cycles. One possibility involves the direct addition of the chlorine radical to produce chlorinated intermediate **88b**, with the concomitant reduction of the metal center to Cu(I). Anodic oxidation produces arenium ion **88d** (Scheme 23, path B). Alternatively, the same species can be formed from complex **88a** after anodic oxidation to radical cation **88c** and the subsequent interception of the chlorine radical. In such a catalytic cycle, there is no change in the oxidation state of copper. Wheland intermediate **88c** evolves to the final product **89**, regenerating the metal catalyst. Protons are reduced at the cathode to equilibrate the overall anodic process. A fairly high current of 100 mA was essential for obtaining satisfying results.

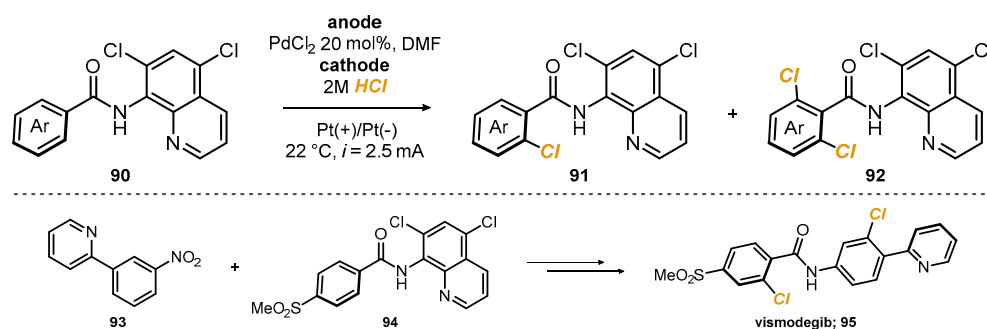


Scheme 23. Electrocatalytic chlorination of 8-aminoquinolines **87**.

The substrate scope of the reaction was explored, and moderate to excellent yields were obtained when substituted benzamides bearing electron-donating or electron-withdrawing groups were employed. Electron-rich substrates exhibited higher reactivity compared with electron-deficient ones. The different positions of the substituents on the benzene ring

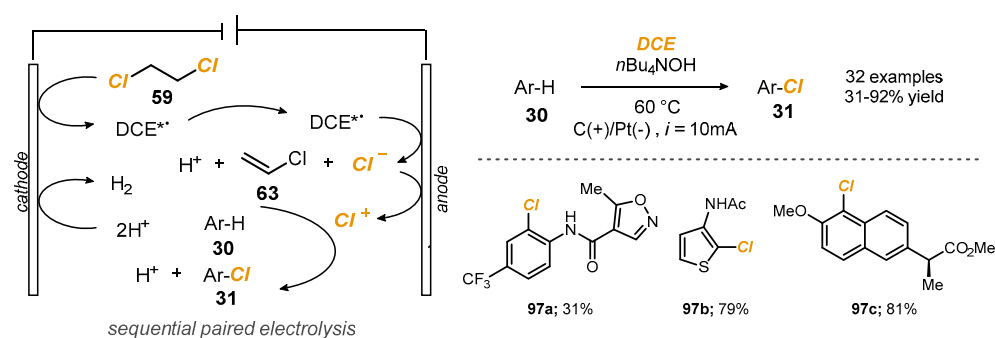
did not remarkably affect the reaction efficiency. In addition, alkyl amides were smoothly chlorinated in good yields. The preparation of **89** was also scaled up to the gram scale using a flow electrolytic cell, allowing the synthesis of 1.19 g of product **89** in 24 h (91.2% yield).

8-Aminoquinolines are peculiar heteroaromatic rings, and due to the distance between the two nitrogen atoms, they have been extensively used as the directing group for the *ortho*-functionalization of benzoic acids. The process takes advantage of the proximity between the dicoordinated metal center and the C-H bond, which can undergo metalation, producing a reactive metallacycle. In such a context, palladium is among the most used metals, and an electrochemical version of the process has been reported for the synthesis of *ortho*-chlorobenzamides, by Kakiuchi and co-workers [42]. After the initial screening of the reaction conditions, they observed that unsubstituted 8-aminoquinoline **87** was not the ideal bidentate ligand, since it could undergo chlorination itself, probably by a mechanism similar to the one later exploited by Fang. To avoid such a side reaction, a 5,7-dichloro-8-quinolinyl group was chosen as the directing unit. After testing several conditions, they optimized the process which occurred at 90 °C, with a 100 mA current, in the presence of 10 mol% PdCl₂. Crucial for the success of the reaction was the setup, consisting of a divided cell, which prevented the reduction of palladium at the cathode. Cl⁺ or synthetically equivalent species were generated in the anodic semi-cell, with chloride coming from the cathodic reduction of HCl. The reaction was applied to several substituted benzamides **90**, and the corresponding chlorinated products **91** were recovered in good to excellent yields (Scheme 24). In all cases, dichlorination occurred to some extent, producing around 10% of the undesired product **92**, with the only exception of *meta*-bromo and -CF₃ substituents, which strongly deactivated the aromatic ring toward a second substitution. Finally, palladium-catalyzed C–H chlorination under anodic oxidation conditions was applied to the convergent synthesis of vismodegib **95** from pyridine **93** and benzamide **94**.



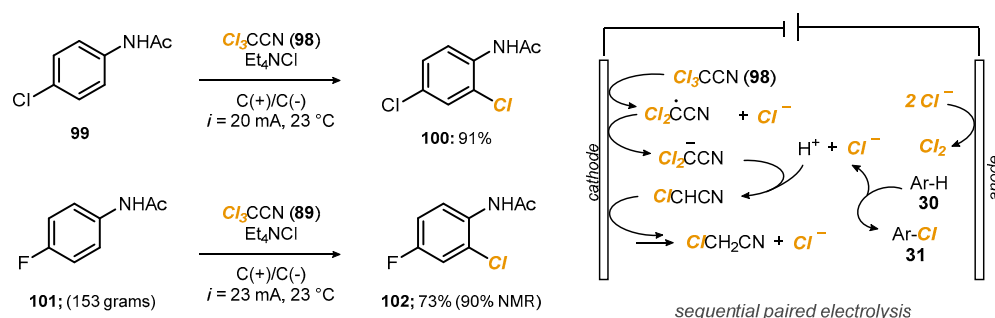
Scheme 24. Palladaelectrocatalyzed *ortho*-chlorination of benzamides **90**.

Prior to the alkene dichlorination using dichloroethane as the source of Cl⁺ species reported by Morandi and previously described in this review, Jiao and co-workers explored bifunctional electrocatalysis as a possible way to perform aromatic chlorination, decomposing DCE **59** to vinyl chloride **96** and hydrochloric acid [43]. They initially investigated the viability of the electrolytic dehydrochlorination of dichloroethane **59**, and they observed that a 100 mA current in a solution of *n*-Bu₄NOH in DCE **59** led to the formation of vinyl chloride **96** (48%), ethylene **63** (46%) and HCl. Since chloride oxidation to Cl⁺ could be coupled at the anode, they tested and demonstrated the possibility of a one-pot aromatic chlorination. Under optimized conditions, they were indeed able to efficiently chlorinate various anilides, bioactive compounds and heterocycles (selected examples **97a–c**) (Scheme 25).



Scheme 25. Electrocatalytic preparation of (hetero)aryl chlorides **97a–c** with 1,2-dichloroethane.

In the Introduction of this review, we highlighted how the chlorination reaction is among the most straightforward approaches to introduce chloride into molecules, but it comes with several drawbacks when excess chlorine gas is used, such as handling Cl_2 itself and the highly corrosive HCl that is generated. Electrocatalysis could be helpful in this scenario, assuming that chlorine is generated in situ. First, the rate of Cl_2 generation could be regulated by electrochemical parameters, leading to minimum escape from the reaction and facilitating reaction handling under ambient conditions. Second, the presence of an excess of the chloride source could be feasible, avoiding the generation of HCl . In 2021, Cheng et al. published the first example of an electrochemical aromatic chlorination with in situ generated chlorine. The authors identified trichloroacetonitrile **98** as the optimal Cl_2 source, being decomposed on a graphite felt cathode, in the presence of tetraethylammonium chloride as the supporting electrolyte. In optimizing the chlorination of *para*-chloroacetamide **99**, other solvents were tested (CCl_4 , CHCl_3 and DCE), but only traces of product **100** were observed. Moreover, without CCl_3CN , no product was formed, thus excluding a mechanism involving the direct oxidation of the electrolyte. The existence of chlorine was confirmed by the tetrachlorination of *N*-tosyl diallylamine, as previously reported by Fu [34], which excluded a radical pathway. In addition to this, they demonstrated that CCl_3CN **98** could donate all three chlorine atoms, producing acetonitrile. Product **100** was in fact produced in 91% yield after three hours when 0.67 equivalents of CCl_3CN **98** were used. In addition to this, the reaction could also be scaled up, and 153 g (1 mole) of *para*-fluoroacetamide **101** gave product **102** in 90% NMR yield and 73% isolated yield (Scheme 26).

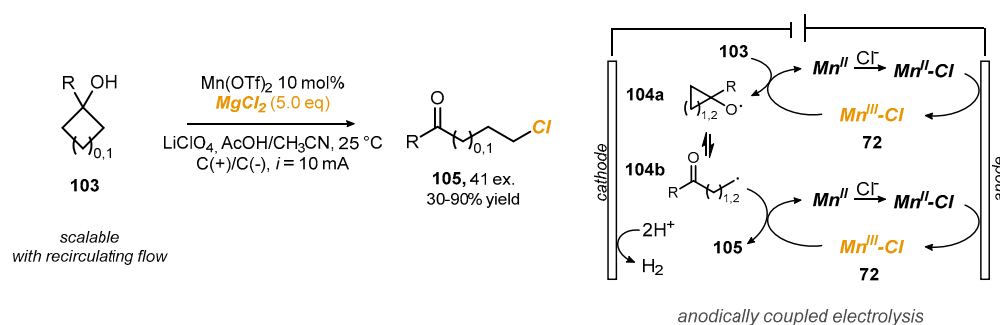


Scheme 26. Chlorination of benzamides **99** and **101** with chlorine on demand.

3.4. Electrocatalyzed Miscellaneous Reactions

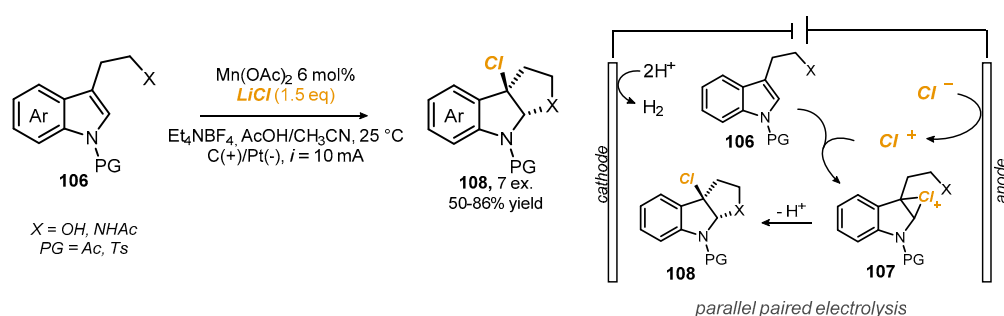
In the section dedicated to the photochemical functionalization of nitrogen-containing substrates, the C-C bond cleavage on cyclic oxime esters was presented. A similar strategy can be used in electrolysis to access chlorinated products from alcohols, again via ring opening. The concept was presented for the first time by Browne and Morrill, who reported in 2019 the electrochemical deconstructive chlorination of cycloalkanols **103**, to synthesize γ - and β -chloroketones **105** [44]. Additionally, they demonstrated that by employing micro-reactor technology and a recirculating flow, the method could be performed at the

gram scale, with incorporated purification. The reaction pivots on the formation of alkoxy radicals directly by O-H homolysis, not a trivial process to achieve under mild reaction conditions, due to the high BDE of RO-H bonds (~105 kcal/mol). The formation of radical **104a** does not occur on the electrode surface, but by means of the Mn(III)-Cl species **72**, which is also used as an active chlorinating species. The formation of the alkoxy radical also produces HCl, with protons being reduced to hydrogen on the cathode surface. In a similar process to that described by Leonori with oxime esters, alkyl radical **104b** is formed upon β -scission from alkoxy radical **104a** and, similar to other electrochemical processes, undergoes chlorination by a second equivalent of Mn(III)-Cl **72** (Scheme 27). The full scope of the electrochemical process was explored starting with the deconstructive chlorination of cyclobutanols. It has been observed that 1-arylcyclobutan-1-ols containing aromatic systems with electron-donating groups at the *ortho* or *para* positions underwent decomposition. This instability was attributed to the ionization of the C–OH bond in the presence of Brønsted and/or Lewis acids, forming unproductive stabilized carbocations. In such cases, the issue was overcome by employing a syringe pump addition of the substrate over two hours and using tetrabutylammonium acetate as the supporting electrolyte. With a choice of two suitable reaction conditions in hand, they converted a variety of 1-arylcyclobutan-1-ols **103** into the corresponding γ -chlorinated ketones **105** in good to excellent isolated yields. In addition, a representative selection of 1-aryl- and 1-alkylcyclopropan-1-ols **103** could be readily transformed to β -chlorinated ketones **105**. Furthermore, to demonstrate scalability, the batch process was translated to a recirculating flow electrochemical setup. Not only did switching from batch to flow allow for a gram-scale synthesis, but also, due to the decreased distance between the electrodes in the flow, the supporting electrolyte was not required, thus making the overall process even more efficient from a sustainability perspective.



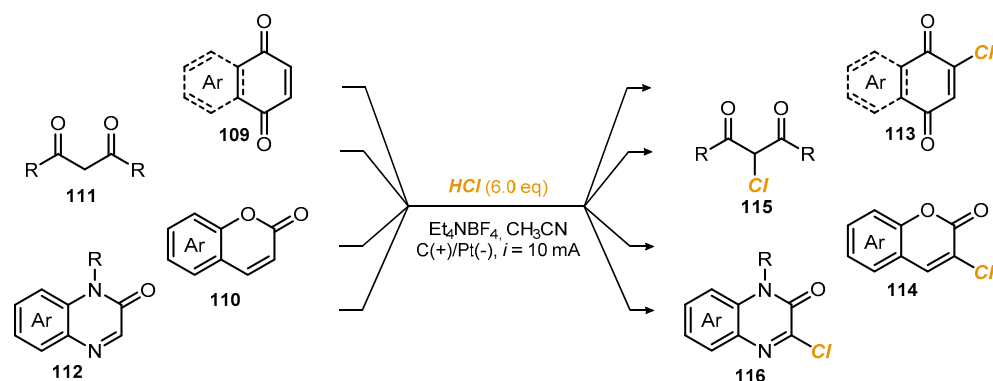
Scheme 27. Electrochemical deconstructive chlorination of cycloalkanols **103**.

Electrochemistry can be exploited not only to achieve synthetically relevant ring-opening processes, but also for the opposite purpose. Indeed, if a nucleophilic group is tethered to the substrate being chlorinated, it is not surprising that a cyclization can be promoted by a careful design of the reaction. One example, from 2020, is the electrochemical dearomative chlorocyclization on tryptamine and tryptophols **106**, leading to biologically and pharmaceutically relevant hexahydropyrroloindolines **108** [45]. Without the help of any metal catalyst, LiCl is oxidized at the anode to an electrophilic Cl^+ species, capable of giving an electrophilic addition to the electron-rich indolic substrate **106**, leading to the dearomatized chloronium intermediate **107**. The tethered hydroxyl or acetylated amino group is then able, by nucleophilic ring opening, to afford the final tricyclic product **108**. Hydrogen evolution at the cathode, from the supporting acetic acid, ensures redox neutrality (Scheme 28). The method was developed more specifically to obtain brominated derivatives; for such a reason, the scope was restricted to seven chlorinated products. The authors hypothesized the direct anodic oxidation of chloride ions by comparing the yield of chloro (spanning from 50 to 86%) and bromo derivatives (higher than 90%). According to Lei and co-workers, the result was consistent with the higher oxidation potential for Cl^- .



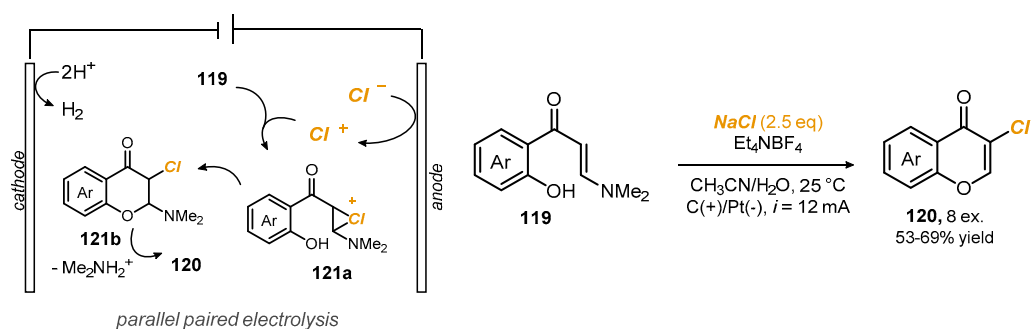
Scheme 28. Electrochemical dearomative chlorocyclization of **106**.

To conclude this section on electrolysis, three examples of non-aromatic C(sp²)-H chlorination, all from 2021, are reported. The first one, by Liu, is a chlorination of electron-deficient C-H bonds in quinones **109**, coumarins **110**, 1,3-diketones **111** and quinoxalines **112** using six equivalents of HCl [46]. The reaction occurred under simple experimental conditions, in an undivided cell, with a graphite felt anode and a platinum cathode, using a solution of Et₃NBF₄ in acetonitrile, affording chlorinated products **113–116** with moderate to good yields (Scheme 29). Despite the non-aromatic nature of both the starting material and products, the reaction should actually be considered an aromatic chlorination, at least according to the mechanism hypothesized by the authors to explain the chlorination of benzoquinone **109**. Cathodic reduction of benzoquinone **109** may easily generate the corresponding aromatic hydroquinone **117**, which undergoes electrophilic chlorination with chlorine from the anodic oxidation of Cl⁻. Anodic oxidation of the chlorinated hydroquinone **118** gives the desired product. This was not indicated by the authors, but H₂ should be generated at the cathode to ensure redox neutrality.



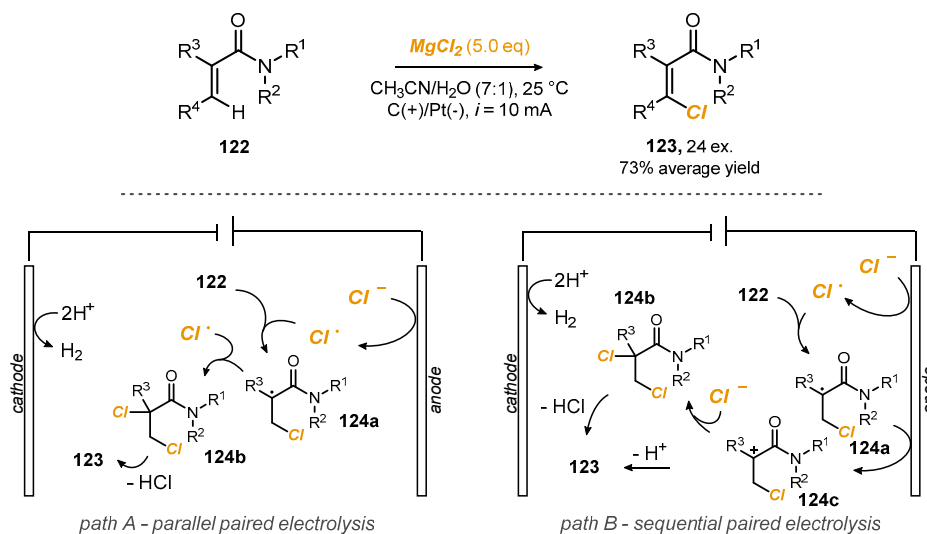
Scheme 29. Electrochemical chlorination of quinones **109**, coumarins **110**, 1,3-diketones **111** and quinoxalines **112**.

Liu et al. prepared a series of 3-chlorochromones **120** by the electrochemical chlorination of enamminones **119** [47]. The reaction was based on a cascade process, initiated by the formation of chloronium intermediate **121a** upon the addition of Cl₂ to the electron-rich enamminone group. Chlorine is electrochemically generated on the anode from the oxidation of NaCl. The tethered phenolic moiety opens the chloronium ion by intramolecular formation of a new C-O bond, affording α-chloro emiaminal ether **121b**. Elimination of Me₂NH₂Cl produces the final chromone. Additionally, in such a process, protons were reduced on the cathode (Scheme 30). The scope was restricted to eight examples, but in the same paper, they also applied the reaction to the synthesis of bromo- and iodochromones. The presented method was also scaled up, although a dramatic drop in the yield was already observed on a two-millimole scale.



Scheme 30. Electrochemical C-H chlorination of enaminones **119**.

As the last example, Morrill et al. published a method for the oxidative Z-selective C(sp²)-H chlorination of tertiary acrylamides **122**, providing access to a broad range of synthetically useful Z-β-chloroacrylamides **123** in good yields, Scheme 31 [48]. They optimized a reaction based on MgCl₂ as both the chloride source and electrolyte in MeCN:AcOH (7:1) using galvanostatic conditions (i = 10 mA), a graphite anode and a platinum cathode at 25 °C for 2 h under N₂. More than 20 products were isolated in good to excellent yields (average yield 73%). They observed that several substituents could be incorporated into the C(2)-aromatic unit, including electron-donating, electron-withdrawing and halogen substituents. Additionally, the introduction of sterically demanding groups into the acrylamide starting materials **122** did not negatively impact upon product **123** formation (Scheme 23). The reaction should initiate with anodic chloride oxidation to form a chlorine radical, which regioselectively adds to the electron-deficient acrylamide **122** to furnish the tertiary C-centered radical **124a**. One possibility is then to have a parallel paired electrolysis, with **124a** being intercepted by a chlorine radical (path A) to form the dichlorinated intermediate **124b**. The final loss of HCl should give acrylamide **123**. Alternatively, in a sequential paired electrolysis, radical **124a** could be further oxidized to form carbocation **124b**, with subsequent deprotonation providing access to the observed product **123**, or it could be intercepted by Cl⁻ to form dichlorinated compound **124c**, which could also generate **123** in such a hypothesis via hydrochloric acid loss. In all cases, hydrogen gas should be generated at the cathode.



Scheme 31. Electrochemical oxidative chlorination of acrylamides **122**.

To demonstrate product utility, the authors succeeded in a palladium-catalyzed Suzuki cross-coupling and in amide hydrolysis. In addition to this, to demonstrate scalability, the batch process was translated to a flow electrochemical setup, employing a syringe pump in combination with a commercially available Ammonite8 flow electro-reactor.

4. Conclusions

At this point, we would like to stress, one more time, how profoundly the recent developments in photo- and electrochemistry are changing the way we synthesize molecules. Every day, they are disclosing new intriguing retrosynthetic disconnections that can be helpful for the late-stage, problematic functionalization of complex molecular structures. Additionally, and maybe more importantly, they are providing us with more sustainable and safer alternatives to perform “easier” transformations with respect to traditional methods, at least at a laboratory scale, generating radicals or cations under mild and controlled reaction conditions. The formation of carbon–chlorine bonds, via direct chlorination, is a perfect example of this improvement. At the same time, we should point out some differences between these two techniques, such as the preference for aromatic chlorination in photocatalysis versus the difunctionalization of alkenes in electrocatalysis. Photoredox catalysis might present some limitations in the design of the reaction. First, there are plenty of photocatalysts that can be tested before finding the best one. Even though it can be helpful to look at redox potentials, these sometimes fail, due to the reaction conditions being far from the ideal ones used in cyclic voltammetry. Second, most of the visible-light-promoted aromatic substitutions presented here need NCS or a related reagent, much safer than Cl_2 , but less efficient in an atom economy perspective, producing a stoichiometric amount of side products that must be separated from the main product. Electrochemical chlorination usually takes advantage of chlorides or hydrochloric acid, which results in low- to zero-waste processes. Moreover, many of them are successfully scaled up, usually with the help of flow reactors. A limitation of applying electrocatalysis is the experimental setup because it requires more specialized devices to control the intensity of the current or the voltage, and expensive electrodes. This, at the moment, makes it easier for many research groups to start working on photoredox catalysis, for example, with household lights or LED strips and irradiating whatever the reaction vessel elected. In conclusion, photoredox catalysis and electrocatalysis are surely taking a leading role in the preparation of organochlorine compounds, and it is expected that even more efficient methodologies will be developed in the near future, potentially capable of overcoming the present issues with selectivity or scalability, thus making it possible to introduce such techniques to the chemical industry.

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