

Review

# Electrochemical Bromofunctionalization of Alkenes and Alkynes—To Sustainability and beyond

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**Abstract:** The electrochemical generation of highly reactive and hazardous bromine under controlled conditions as well as the reduction of surplus oxidizers and reagent waste has placed electrochemical synthesis in a highlighted position. In particular, the electrochemical dibromination and bromofunctionalization of alkenes and alkynes have received significant attention, as the forming of synthetically important derivatives can be generated from bench-stable and safe bromide sources under “green” conditions. Readily available and non-corrosive bromide salts have been utilized with a dual role as both a reagent and supporting electrolyte. However, this trend seems to change with the preparation of organobromine species. In this review, the electrochemical dibromination and bromofunctionalization of alkenes and alkynes was addressed in terms of their bromine sources and sustainability.

**Keywords:** anode; alkenes; alkynes; bromine; electrochemistry; oxidation; synthesis



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## 1. Introduction

With the increasing amount of economic, environmental and political pressure, the chemical industry faces the challenge of providing the public and the scientific community a sustainable and greener alternative to conventional chemical methods [1]. Electro-organic synthesis has become one of the most attractive research topics in recent years, providing highly versatile synthetic methodologies [2–6]. Using electrons as “traceless” redox reagents allows the elimination of the excess use of harmful redox chemicals with a high atom efficiency [7]. The electro-generation of highly reactive species in-situ allows the utilization of inherently safe surrogates and provides a simplified approach [8]. These advantages, in combination with the valorization of renewable feedstock and “green electricity”, makes electrochemical functionalization particularly attractive.

There have been many recent reviews discussing C–C [9–15], C–N [13,16–18], C–O [12,13,17], C–S [19,20] and C–P [12,21] bond formation under electrochemical conditions [22,23]. In parallel to this, the implementation of halogens in electro-organic synthesis has also received significant attention [24,25]. The highly versatile and valuable organohalides that serve as prevalent structural motifs in pharmaceuticals [26,27], natural products [28] and intermediates [29] have encouraged electrochemists to provide more sustainable methodologies for the installation of halo-substituents. The precise control of electron transfer at the electrode via constant electric current or potential without the addition of metal-catalysts or exogenous oxidants overcomes the conventional halogenation methods that burden conventional synthetic protocols [30–32]. Furthermore, the use of inexpensive and bench-stable halides allows the controlled generation of halonium species, halogen radicals or halogens in-situ. In particular, the electrochemical generation of bromine has received significant attention. Bromine can be easily generated under electrochemical conditions and equally holds its place as a direct halogenating reagent as well as a mediator [24,33,34]. A great example of electrochemically generated bromine as a mediator in organic synthesis was demonstrated via the electrooxidation of alcohols [35], as well as via the Clauson–Kaas electro-alkoxylation of furanes in the presence of bromide

and methanol [36]. The latter was also demonstrated in the preparation of the natural product hispanolone [37].

In this review, the electrochemical dibromination and bromofunctionalization of alkenes and alkynes will be discussed in terms of their bromine source and sustainability.

## 2. Bromine and Bromination Agents

Bromine is a dark brown-red, volatile, noxious liquid at room temperature. Due to its high reactivity, it is mainly found as alkali bromides in brines, minerals and the Earth's crust. One of the richest sources is the Dead Sea, which has a bromide content of ca. 5 g/L [38]. However, these sources are diminishing, and their prices are increasing steadily. Currently, bromine is produced on a global scale at 390,000 t/year, and bromine demand has been increasing over the last 5 years and is predicted to rise dramatically [39].

In particular, vicinal 1,2-dibromides are prevalent motifs used in fine chemicals and flame retardants [29]. Almost half of the globally produced bromine is used to produce the latter, which can easily leach out, posing a persistent environmental problem [40,41]. As well as its environmental toxicity, bromine's storage and transportation equally pose hazards [42,43].

The most common bromination methods include the direct use of elemental bromine or HBr, which is toxic, corrosive and creates hazardous reagent waste. Alternatively, inorganic or organic bromide salts with an external oxidant allows the in-situ generation of bromine, however, above-stoichiometric amounts of exogenous oxidizers are required under harsh conditions [44]. The utilization of inherently safe bromine surrogates such as *N*-bromosuccinimide and pyridinium tribromide allows the controlled liberation of Br<sub>2</sub>. Nevertheless, their preparation is difficult, wasteful and costly. Moreover, their recycling as well as their production requires elemental bromine, and therefore these agents are considered low-atom economic [45,46].

Oxidative electrochemistry provides a fundamentally greener alternative compared to the traditional strategies, as electricity replaces the usually harmful and surplus redox reagents. The relatively low oxidation potential of bromides has inspired extensive studies for the electro-generation of bromine in different solvent systems [47–49]. The oxidation of bromide to bromine or to its stable tribromide salt is described as a two-electron transfer process (Equation (1)), which has been extensively studied in aprotic media due to the stabilization effect of solvent, facilitating the formation of both brominating species simultaneously [47–49]. The first oxidation potential corresponds to the direct formation of bromine (0.82 V in acetonitrile at a platinum disk electrode), which simultaneously forms stable tribromide complexes in the presence of a high bromide concentration in aprotic media (Equation (2)) [47]. Via a second oxidation potential, bromine is generated from the aforementioned tribromide species (1.2 V in acetonitrile at a platinum disk electrode) (Equation (3)) [47].



Moreover, as bromine can be generated easily from its salts under electrochemical conditions, the traditional production of bromine via the chlorine oxidation process can be completely avoided.

Bromides are popular alternatives due to their proportionate pricing compared to traditional brominating agents such as HBr and Br<sub>2</sub> (Table 1). In particular, NaBr and KBr provide an economically greener choice, as the abundance of sodium (2.36%) and potassium metal (2.09%) in the Earth's crust is relatively high, with sodium being the sixth most abundant element [50]. In combination with their non-corrosive natures and long shelf-lives, they are desired substitutes for smaller research facilities that struggle with the burden of conventional brominating reagents and storage issues.

**Table 1.** Price comparison of bromide salts with classical brominating reagents [51].

Reagents <sup>1</sup>	Bulk Price <sup>2</sup>	Molar Price <sup>3</sup>
KBr	€95/kg	€11.31/mol
NaBr	€135/kg	€13.93/mol
LiBr	€294/kg	€25.53/mol
NH <sub>4</sub> Br	€220/kg	€21.55/mol
NEt <sub>4</sub> Br	€121/kg	€25.43/mol
NBu <sub>4</sub> Br	€831/kg	€267.89/mol
N-Bromosuccinimide	€140/kg	€24.92/mol
Pyridinium tribromide	€362/kg	€115.77/mol
HBr (48%)	€151/L	€8.20/mol
Bromine	€264/L	€13.57/mol *

<sup>1</sup> Prices were obtained from Sigma Aldrich website: <https://www.sigmaaldrich.com/DE/en> (accessed on 14 September 2022). <sup>2</sup> Bulk prices are given in EUR per kg or L. <sup>3</sup> Molar prices are calculated from bulk, prices are given in EUR per mol. \* Refers to molar price of Br<sub>2</sub>.

Organic bromide salts bridge the obligatory protic additive issue that is associated with alkali bromide salts, providing a simpler setup. Nevertheless, these agents are more expensive, and their preparation is elaborate and therefore low-atom economic.

Via the conscious choice of bromine substitution and the precise amendment of the electrochemical parameters, an intrinsically green, efficient and viable approach can be provided [4,52,53]. In particular, careful consideration has to be made regarding the counter electrode reactions [54–57]. In combination with sustainable electro-organic chemistry and green chemistry principles, it is highly desired that bromine from a “green source” can be generated synergically, for example under linear paired electrolysis conditions [58–62].

### 3. Electrochemical Bromofunctionalization of Alkenes

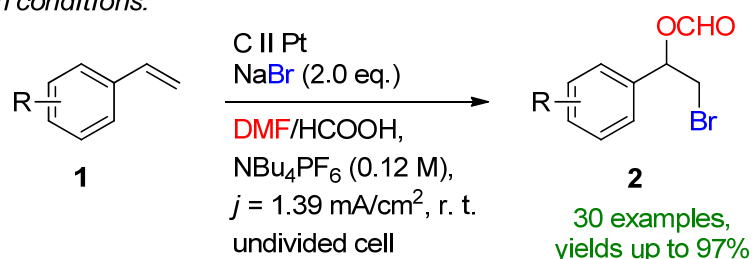
The electrochemical bromination and bromofunctionalization of alkenes are well-researched areas, as their products serve as highly valuable synthetic intermediates and important chemicals. Vicinal dibromides, bromohydrins and bromoesters serve as useful intermediates for pharmaceuticals and fine chemicals [29,63]. Moreover, the halogenated species can be simply further functionalized resulting in a plethora of elaborated products. Therefore, the simultaneous and selective installation of one or two functionalities across the alkenes has been extensively researched as the desired products can be obtained under a simplified set-up and “green” conditions. The electrochemical bromofunctionalization of alkenes is mostly represented by the utilization of bromide salt with a dual role as both a reagent and supporting electrolyte in aprotic media accompanied by a protic additive such as water or short-chained alcohols. These agents do not only provide the respective hydroxyl or ether functionalities but also compliment the cathodic reaction liberating H<sub>2</sub>, providing a “clean” by-product [54]. The employment of organobromines as halogenating agents has also become popular as it allows bromine to form as a result of an electrochemical redox process, excluding the need for the sacrificial half reaction. Nevertheless, these agents are usually harmful and therefore should be avoided.

#### 3.1. HBr, MBr and Alkylammonium Bromides as Bromine Sources

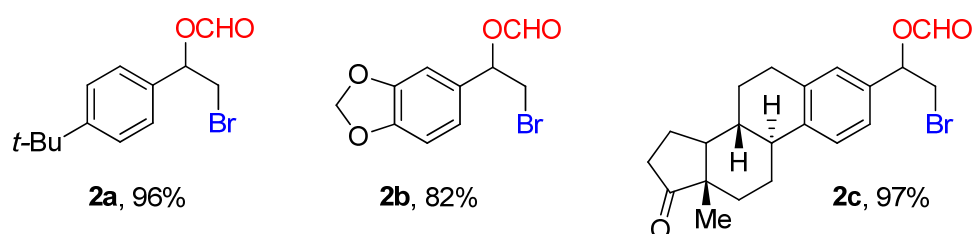
Pioneering work in the field was demonstrated by Torii in the early 80s, reporting the bromofunctionalization of alkenes in the presence of aq. NaBr, which popularized the indirect electrochemical oxidation of olefins using stable and inexpensive metal halide salts [64–68]. This form of a bromine source has received particular attention due to its ability to tame hazardous and toxic molecular bromine in-situ under controlled conditions. It is worth mentioning that the complementary half-reaction’s electrode choice is usually a low-hydrogen-overpotential material such as platinum or nickel, which supports cathodic hydrogen evolution. Nevertheless, platinum group metals are depleting, costly and highly contaminating [69–71].

In 2019 Hu, Fang and Mei reported the electrochemical radical formyloxylation–bromination of various alkenes in a regio- and chemoselective fashion [72]. The implementation of stable NaBr as a radical bromine source makes this approach sustainable. DMF serves a dual role as both the solvent and the formyloxylation reagent, while acetic acid supports the cathodic reaction. *Para*-substituted electron-rich styrene derivatives afforded excellent yields, while electron-deficient and strongly electron-withdrawing groups prolonged the reaction time. The naturally derived safrrole-type and estrone-type derivatives also readily underwent electrochemical formyloxylation, proving the possibility for the late-stage functionalization of pharmaceutical scaffolds. In total, 30 examples were reported with excellent yields up to 97%. The scalability was proved via a gram-scale experiment (6.0 mmol) resulting in an isolated yield of 90%. The method was extended to the formyloxylation–chlorination and formyloxylation–trifluoromethylation of alkenes as well. The authors suggest that bromide is oxidized at the anode to bromo-radicals, which then rapidly combine with arylalkene **1** to form the benzyl radical **I**. Via a second oxidation, the forming benzylic carbocation **II** is subjected to nucleophilic attack by DMF to iminium intermediate **III**, which is subsequently hydrolyzed resulting in the formyloxylated brominated product **2** (Scheme 1).

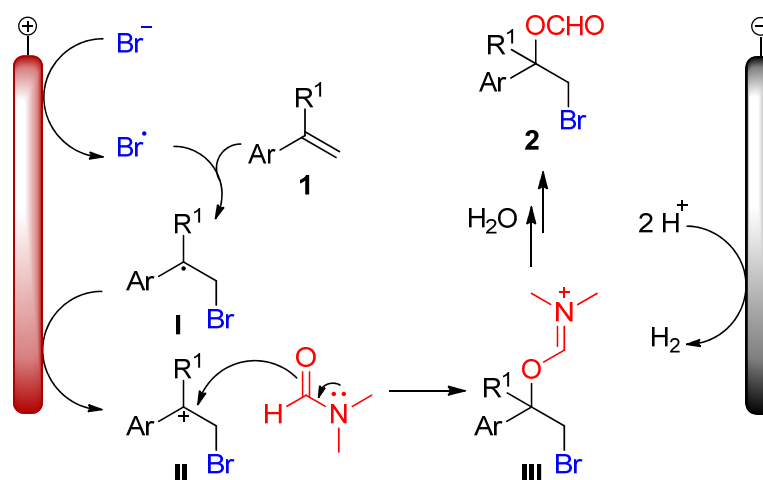
Reaction conditions:



Representative scope:



Plausible mechanism:



Scheme 1. Electrochemical radical formyloxylation bromination of alkenes [72].

The electrobiocatalytic bromolactonization was reported by Bormann and Holtmann on carbon-nanotube-modified gas-diffusion electrodes [73]. The paper reports the cathodic reduction of ambient oxygen to H<sub>2</sub>O<sub>2</sub> at a reduced overpotential in a divided cell separated via a proton exchange membrane. *Curvularia inaequalis* (CiVCPO), a vanadium-dependent chloroperoxidase enzyme converts the forming peroxide in the presence of potassium bromide into hypobromite, which leads to the bromolactonization of 5-pentenoic acid. The reaction is complimented via the oxidation of water at a platinum anode. The superiority of the reaction lies in the oxygen-enriched, modified-carbon-nanotube diffusion electrode that significantly lowers the overpotential for peroxide formation, which is a sensible factor for the enzymatic catalytic reactivity [74].

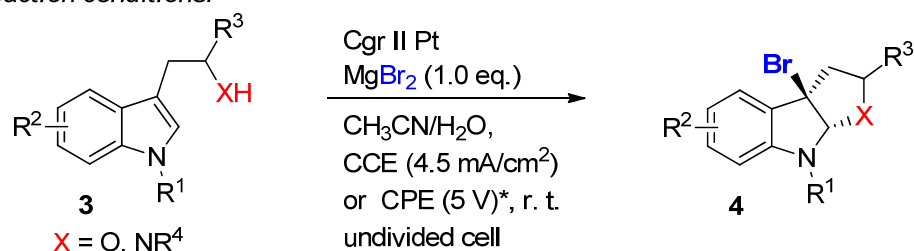
The electrochemical bromocyclization of tryptophol, tryptamine and tryptophan derivatives was recently reported by Wu and Vincent [75]. This efficient protocol features MgBr<sub>2</sub> with a dual role as a halogen source and supporting electrolyte. The reaction proceeds in an undivided cell under both constant current (CCE) and constant potential (CPE) conditions in the presence of 1 eq. MgBr<sub>2</sub>. Magnesium bromide is oxidized at the carbon anode into bromine in an acetonitrile/water solution under ambient conditions. It is worth mentioning that under CPE, the constant potential window is maintained via measuring the potential against a reference electrode. Here, the constant terminal voltage of the cell was determined via measuring the constant terminal voltage between the electrodes, which is not an adequate parameter for CPE conditions. The dearomative reaction proceeds via the formation of bromonium intermediate **IV**, followed by intramolecular cyclization to form the corresponding brominated derivatives with excellent yields (Scheme 2). This simple and environmentally friendly set up featured 22 examples with up to 96% isolated yields and a broad scope of functional group tolerance.

The synthetic utility was demonstrated via the electrochemical bromocyclization and further functionalization of *L*-tryptophan-derived diketopiperazine (**5**) to (–)-*epi*-amauromine (**7a**) and (+)-*novo*amauromine (**7b**), which was reported to be superior to the conventional procedure using stoichiometric NBS (Scheme 3) [76].

Solvent stabilizing effects have been reported in electrochemical synthesis, for example using hexafluoroisopropanol (HFIP) [77–82]. Yoshida demonstrated the formation of  $\alpha$ -bromocarbonyls and bromohydrins via a low-temperature DMSO-stabilized halogen cation pool method [83,84]. Based on these reports, a sophisticated technique for the electrochemical bromohydrin and bromohydrin ether formation was reported in a chemoselective fashion (Scheme 4) [85]. The anodic oxidation of potassium bromide on a glassy carbon electrode in the presence of 10 eq. acetic acid in DMSO/H<sub>2</sub>O allowed the corresponding bromohydrins to be produced in excellent yields. By changing the solvent system to acetonitrile/alcohol, bromohydrin ethers were obtained. The key additive of this approach is the addition of acetic acid or trifluoroacetic acid. In the absence of the additive, the yield drops dramatically. The reaction is complemented with hydrogen evolution at a platinum cathode.

Sun and co-workers reported an elegant way of on-site bromination and hydrogenation in a simultaneous fashion [86]. The paired electrolysis takes place in a H-type cell setup divided by a Nafion membrane. This method demonstrates high halogenation flexibility and functional group tolerance, as the bromination reaction is spatially separated from the electrolysis event. The key principle is the use of bench-stable NaBr as a halogen source and the utilization of cathodic hydrogen evolution to achieve a high atom economy and energy efficiency. The anodically generated bromine gas from aqueous sodium bromide in acidic media is transferred into a separate compartment, where ideal conditions for the corresponding substrates can be set up. Likewise, cathodically generated hydrogen gas is used in the presence of Pt/C, demonstrating the synergic pairing of on-site bromination and hydrogenation. This is an excellent example for the utilization of the redox properties of the electrochemical cell.

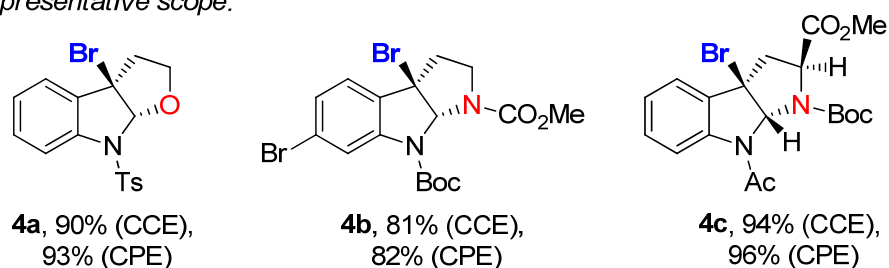
Reaction conditions:



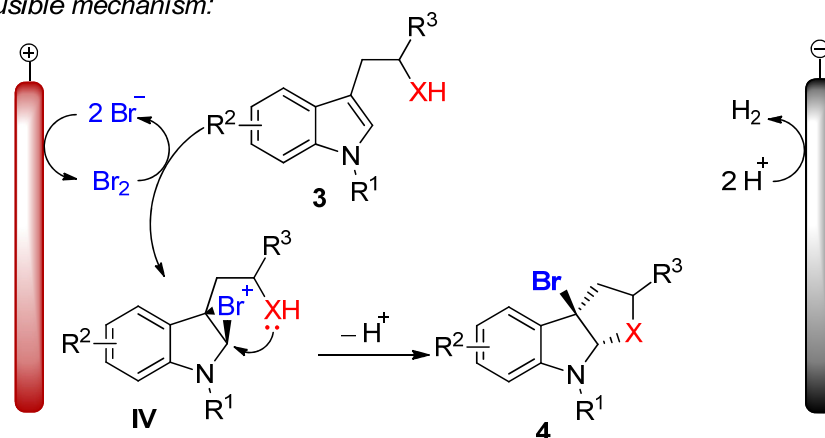
$\text{R}^1 = \text{Ac}, \text{Boc}, \text{Cbz}, \text{SO}_2\text{Ph}, \text{Ts}$      $\text{R}^3 = \text{H}, \text{CO}_2\text{Me}$   
 $\text{R}^2 = \text{H}, \text{Cl}, \text{Me}, \text{OMe}$              $\text{R}^4 = \text{Boc}, \text{Cbz}, \text{CO}_2\text{R}, \text{Ts}$

22 examples,  
yields up to 96%

Representative scope:



Plausible mechanism:



**Scheme 2.** The electrochemical bromocyclization of tryptophol, tryptamine and tryptophan derivatives utilizing  $\text{MgBr}_2$ . \* Constant terminal voltage of the cell was observed between a graphite anode and platinum plate cathode [75]. Cgr = graphite.

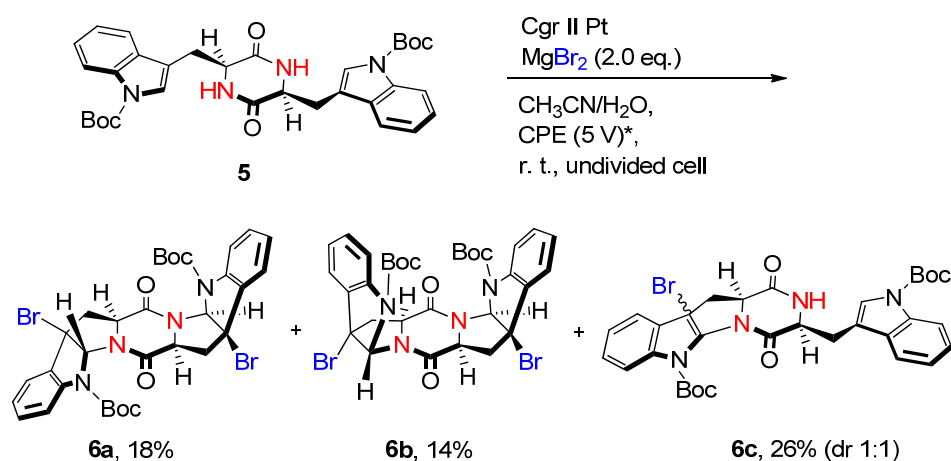
Similarly, Hilt and his group published a linear paired electrolysis for the electrochemical dibromination of alkenes with the realization of 200% current efficiency for stoichiometric transformations in the presence of oxygen [87]. The dual role supporting electrolyte and bromide source  $\text{NBu}_4\text{Br}$  is used as a brominating agent. Bromide undergoes direct oxidation at the anode to bromine and is produced mediated via reductively formed  $\text{H}_2\text{O}_2$  determining the theoretical applied charge of 1 F (Scheme 5). The stable tribromide species are the results of the stabilizing effect of acetonitrile and the high concentration of bromide. Using this method, the authors reported 13 examples with good to excellent yields, providing **11c** quantitatively with a current efficiency of 200%. The reaction proved to have a good functional group tolerance via performing the Glorius-test [88,89]. The method could be adopted to the bromination of arenes and for the iodination of alkenes as well.

A highly regioselective electrochemical protocol for the synthesis of isoxazolines from  $\beta,\gamma$ -unsaturated ketoximes via cascade C–O and C–Br annulation was reported (Scheme 6) [90]. The stable inorganic potassium bromide has a dual role of serving as a bromine source as well as a supporting electrolyte. The key features of this method are the

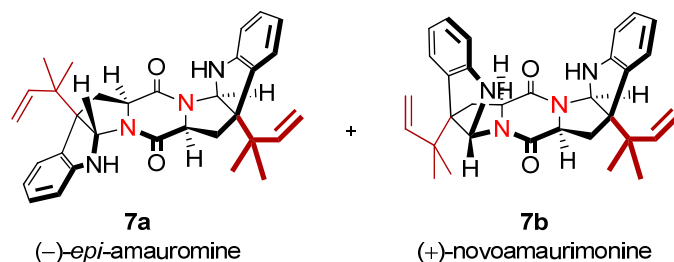


generation of DMSO-stabilized bromine in-situ and the employment of a sodium acetate base under high current density conditions to form the desired bromoethyl-substituted isoxazolines. The method demonstrated excellent functional group tolerance and a high selectivity, and the isoxazoline derivatives could be obtained with up to 81% isolated yields. The presence of the base as well as the electrode material choice is crucial to the success of the reaction. The scalability in both batch-type and flow electrolysis were demonstrated.

*Reaction conditions:*



*Subsequent functionalization (from 6a and 6b):*



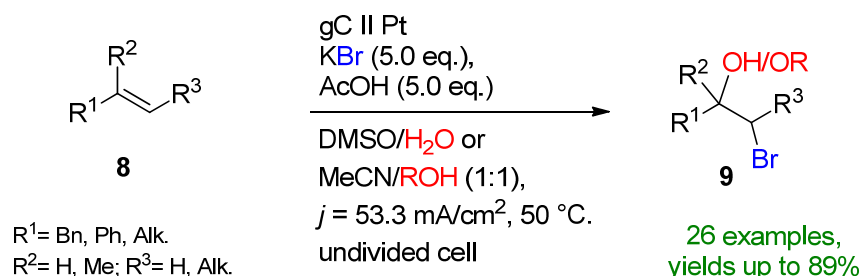
**Scheme 3.** Electrochemical formation and subsequent functionalization of **6a** and **6b** [76]. \* Constant terminal voltage of the cell was observed between a graphite anode and a platinum cathode [75]. Cgr = graphite.

Yin and co-workers introduced an oxidant- and base-free electrochemical intramolecular halo-amination of unactivated alkenes to form diverse brominated *N*-heterocycles [91]. They provide a simple electrochemical protocol using bench-stable LiBr or LiI as a halide source and a supporting electrolyte furnishing a dual role. The reaction proceeded smoothly at room temperature, providing 26 examples combined with the iodo-cyclization in excellent yields. The reaction tolerates labile functional groups such as cyclopropyl, substituted aromatics and heterocycles. Moreover, in the presence of LiI, highly challenging *N*-heterocycles such as the three-membered aziridine or six-membered piperidine could be formed (Scheme 7).

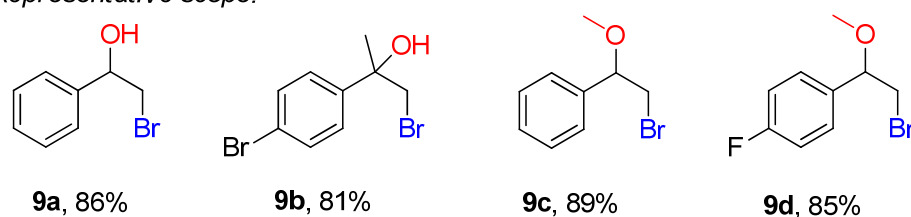
Similarly, the electrochemical oxidative bromolactonization of unsaturated carboxylic acids was reported for the first time [92]. This environmentally friendly approach features sodium bromide as the halogen source in acetonitrile, which is oxidized at the carbon rod anode to give the corresponding bromine radical, which directly reacts with the alkene of the carboxylic acid to form intermediate **V** (Scheme 8). After subsequent oxidation to the stabilized cationic intermediate **VI** and cyclization, the corresponding bromoethylated  $\gamma$ -lactones could be formed with excellent yields. Control experiments also supported the proposed mechanism, as in the presence of radical scavengers or molecular bromine,

the yield dropped dramatically. The authors propose hydrogen evolution as a cathodic counter-reaction at a nickel electrode.

*Reaction conditions:*



*Representative scope:*



**Scheme 4.** Electrochemical bromohydrin and bromohydrin ether formation [85]. gC = glassy carbon.

The electrochemical bromination of electron-deficient alkenes in quinones, coumarins, quinoxalines and 1,3-diketones has also been reported [93]. The synthetically useful organohalides could be obtained using bromides on graphite felt in combination with a platinum cathode. The key feature of this bromination method is the in-situ formation of HBr from KBr and H<sub>2</sub>SO<sub>4</sub>, which is anodically oxidized to bromine. Control experiments with 2,6-di-*tert*-butyl-4-methylphenol suggest a radical pathway by the formation of the halogen.

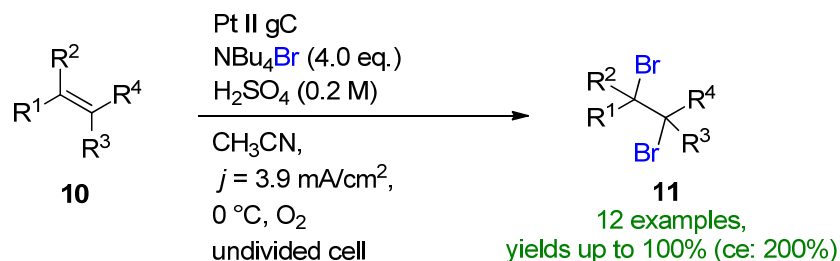
Recently, Waldvogel et al. published the selective electrochemical bromination of terpenes and naturally derived alkenes [94]. The challenging halofunctionalization of renewable feedstock was demonstrated by the employment of inexpensive and bench-stable NaBr with a dual role of being both a bromine source and supporting electrolyte. The test substrate, limonene, could be brominated selectively under ambient conditions giving the brominated derivative in a 53% yield. The optimization procedure showed that the careful consideration of the MeCN/H<sub>2</sub>O solvent system as well as the NaBr as a bromide source are important features of the method. Other inorganic or organic bromide salts resulted in a diminished yield or no conversion. The method could be successfully extended to linear and cyclic monoterpenes, terpenoids and phenylpropanoids to give 10 desired vicinal 1,2-dibromo derivatives, with the bromination of carvone representing the best yield of 82% (**20b**, Scheme 9). A slight change in the electrochemical parameters provided the tetrabrominated limonene derivative in a 74% isolated yield. The reaction proved to be scalable and a synthetic utility could be demonstrated via subsequent functionalization to the  $\alpha,\beta$ -unsaturated nitrile derivative **21a** for the first time. Cyclic voltammetry studies support the oxidative bromine formation in-situ, which is complimented by the liberation of H<sub>2</sub> at the cathode.

Another form of metal-free in-situ bromine generation is the use of HBr as a bromine source. Lei et al. reported an electrochemical oxidative clean halogenation of alkenes using HBr on a carbon anode and platinum cathode, providing 23 examples with up to 89% isolated yields under constant current conditions [95]. The method provides a general halogenation system of HX/MX including the chlorination and bromination of various heteroarenes, arenes, alkenes, aliphatic hydrocarbons and alkynes as well. Under the optimal conditions, the gram-scale synthesis of the electrochemical dibromination of

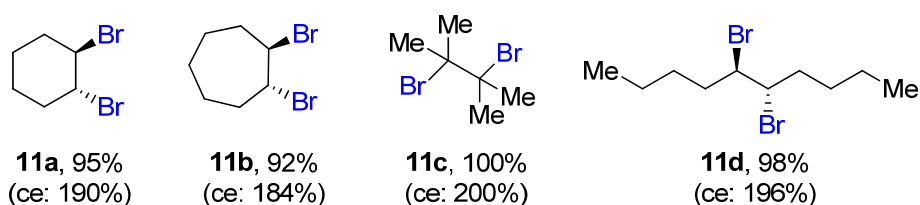


dodecane (**22**) allowed the formation of 1,2-dibromododecane (**23**) with a yield of 86% and 50.9 g isolated clean product (Scheme 10).

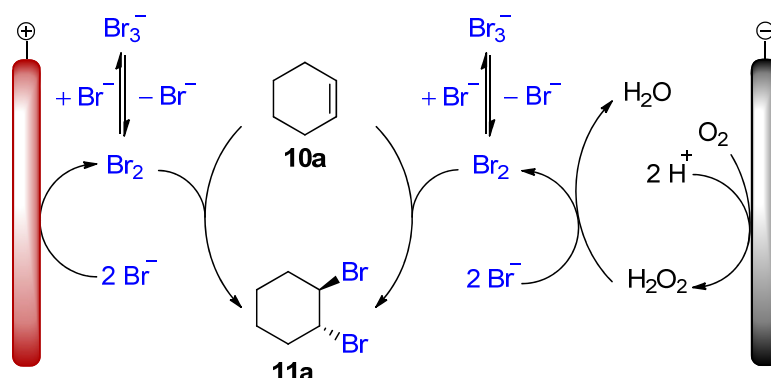
Reaction conditions:



Representative scope:

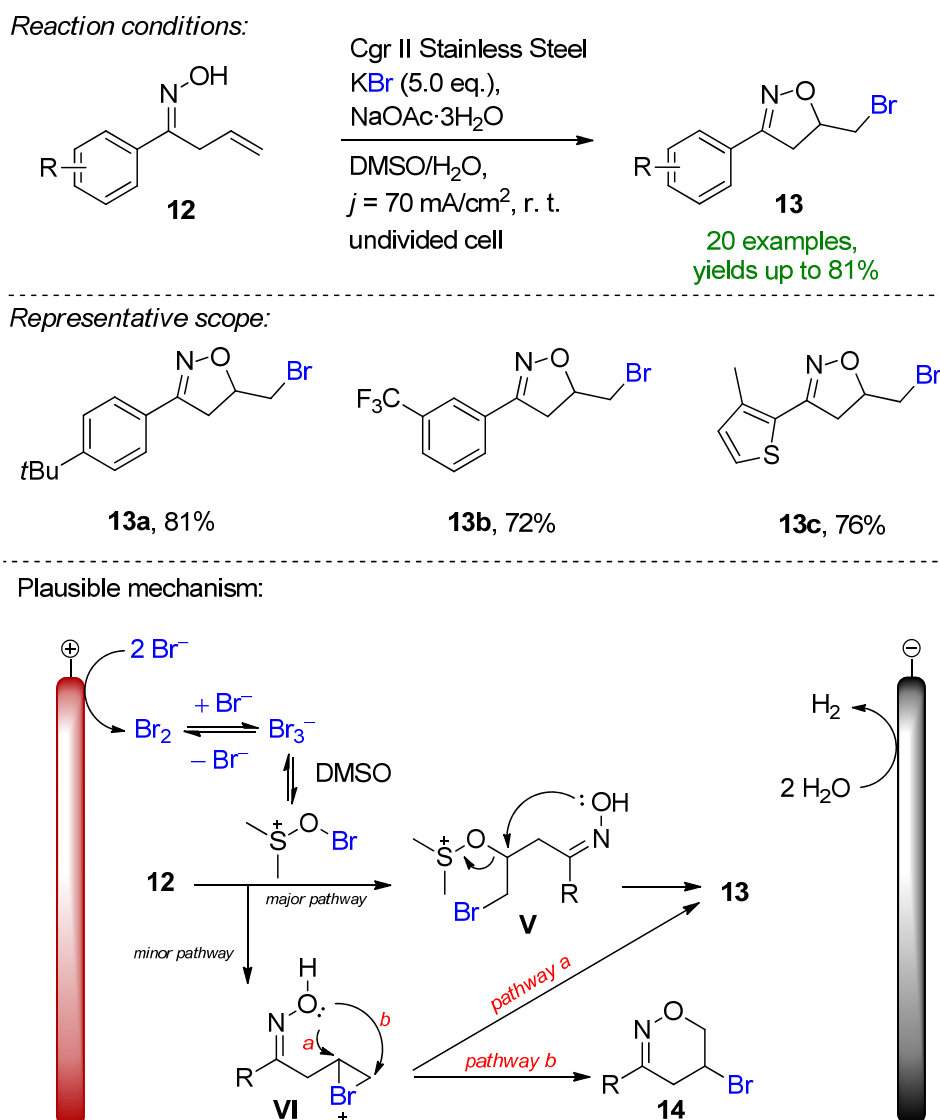


Plausible mechanism:



**Scheme 5.** Linear paired electrolysis for the dibromination of alkenes [87]. gC = glassy carbon.

Encouraged by these results, the Wirth group described the electrochemical bromination and bromofunctionalization of activated and unactivated alkenes in a flow reactor under single-pass conditions [96]. The 600  $\mu\text{L}$  reactor was equipped with platinum foil electrodes separated by a 500  $\mu\text{M}$  fluorinated ethylene propylene (FEP) spacer. The small interelectrode distance allowed the omission of the addition of water and supporting electrolyte, which was described in previous studies. The optimized conditions for the dibromination of styrene were found in the presence of 6 eq. HBr in pure acetonitrile. The combination of a 0.4 mL/min flow rate, 4  $F$  applied charge and platinum electrodes allowed the formation of **25a** in a 79% isolated yield (Scheme 11). When the optimized conditions were applied using a platinum-coated titanium cathode, **25a** could be obtained in an excellent yield of 86%. Via switching the co-solvent, the electrochemical bromohydrin formation could be also targeted. The applicability of this method was demonstrated on several aromatic and aliphatic alkenes. In total, 33 examples were provided exhibiting the formation of dibrominated, tetrabrominated, hydrobrominated and alkoxybrominated products with good to excellent yields. The scalability of the flow-procedure was also demonstrated via applying the conditions for 9.5 h providing **25a** in an isolated yield of 65% and a productivity of 413 mg/h.



**Scheme 6.** Electrochemical formation of isoxazolines with the aid of KBr [90]. Cgr = graphite.

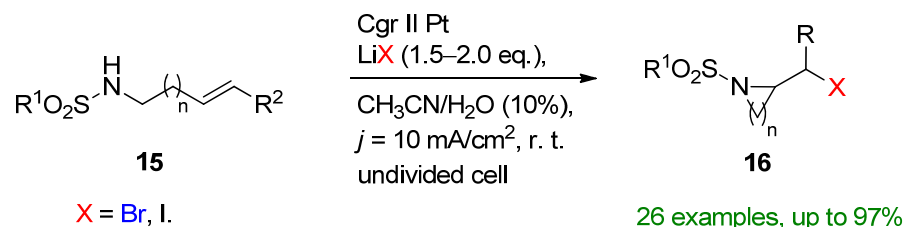
### 3.2. Organohalides as Bromine Sources

Li et al. reported a three-component, TEMPO-mediated 1,2-bromoesterification of alkenes with the aid of carboxylic acids and *N*-bromosuccinimide [97]. The method allows the simultaneous addition of a C–O and C–Br bond to form  $\beta$ -bromoalkyl esters, which are excellent intermediates for natural products and pharmaceutical agents [97,98]. The reaction proceeded well in the presence of 50 mol% TEMPO, 2 eq. of carboxylic acids and 2 eq. NBS to form **27b** in an 88% isolated yield (Scheme 12). The optimized conditions were extended to a variety of carboxylic acids and alkenes, and a total of 40 examples were provided with excellent yields. Even challenging substrates such as adamantane-1-carboxylic acid and amino acids were tolerated. The reaction is complemented via H<sub>2</sub> evolution at the cathode.

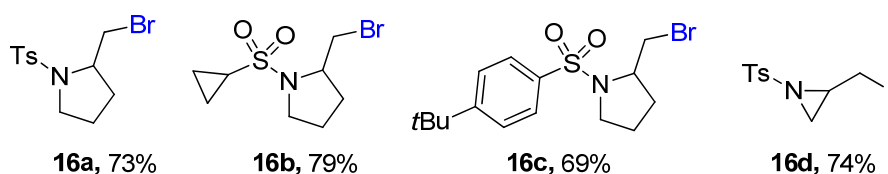
Paired electrolysis methods are generally preferred over a sacrificial approach [57]. Here, the same authors introduced electrochemical alkoxyhalogenation and organohalide dehalogenation within a convergent strategy [99]. Diethyl-2-bromomalonate (**29**) serves as the bromine source. The key promoters of this method are NBU<sub>4</sub>OH and Cp<sub>2</sub>Fe, as omitting one or both decreases the yield. The reaction mechanism was postulated via the mediated oxidation of alkene **28** by Cp<sub>2</sub>Fe<sup>+</sup>, which forms the radical cation **IX**. Intermediate **IX** is scavenged by the bromine radical or bromine that is either formed via the cathodic

reduction of bromomalonate to **XIII** or via the  $S_N2$  reaction induced by the supporting electrolyte (Scheme 13).

Reaction conditions:

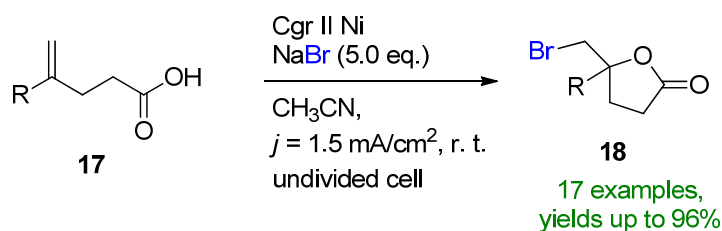


Representative scope:

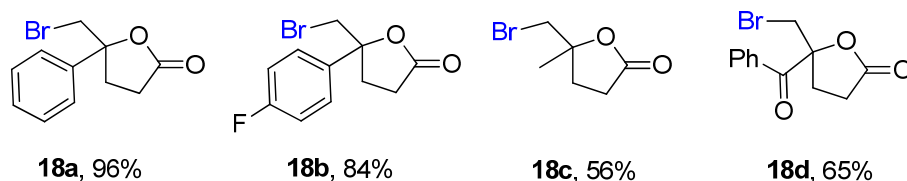


**Scheme 7.** Electrochemical intramolecular haloamination with the aid of LiBr and LiI [91]. Cgr = graphite.

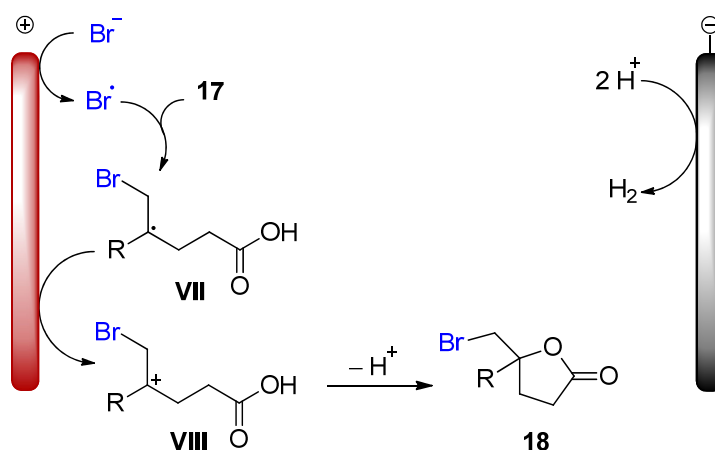
Reaction conditions:



Representative scope:

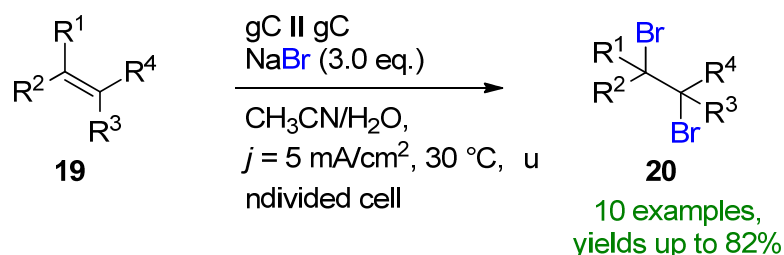


Plausible mechanism:

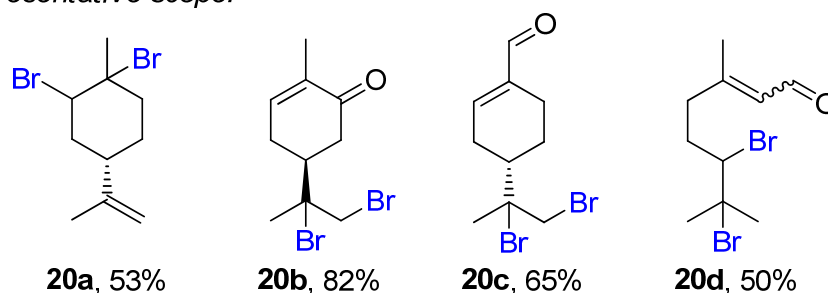


**Scheme 8.** Electrochemical bromolactonization of unsaturated carboxylic acids [92]. Cgr = graphite.

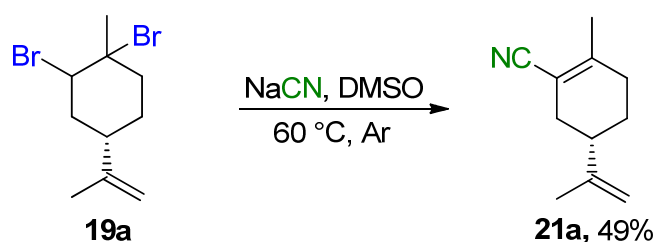
Reaction conditions:



Representative scope:

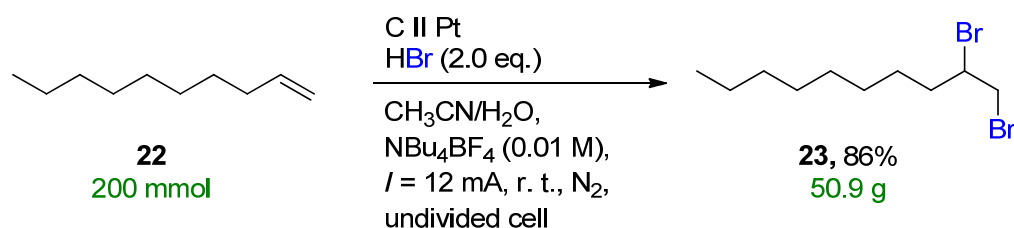


Subsequent functionalization:



**Scheme 9.** Electrochemical dibromination of terpenes and terpenoids [94]. gC = glassy carbon.

Gram-scale synthesis:

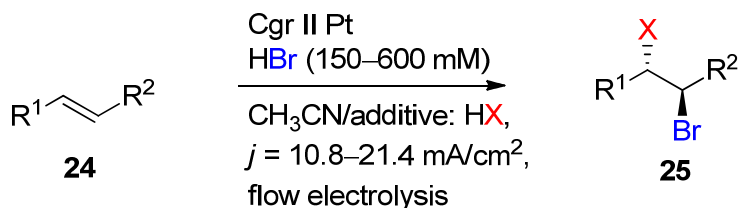


**Scheme 10.** Electrochemical dibromination of **22** on a gram scale [95]. CCE conditions were described with current ( $I$ ), as the immersed electrode area was not specified.

The bromide could also be oxidized in-situ to form bromine. The formed alkyl cation **XI** is complemented via methanol to provide the desired product. The formation of malonic ester (**31**) is depicted via GC and GC-MS. The convergent strategy was demonstrated on various aryl alkenes bearing *para*-, *meta*- or both substituents and alkyl halides. The alkoxyhalogenation of bioactive molecules such as adamantene, estrone and ibuprofen derivatives were also demonstrated. In combination, 43 examples were provided with up to a 98% yield.

A merging e-shuttle reaction for the retro-dihalogenation reaction was developed by Waldvogel and Morandi, enhancing the already existing halogenation reactions (Scheme 14) [62].

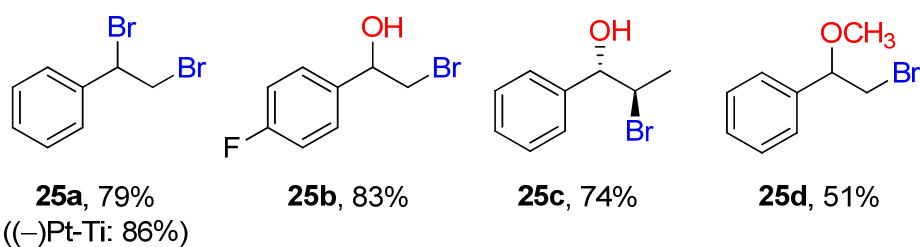
Reaction conditions:



X = Br, OH, OR<sup>3</sup>, OAr, NTsAr

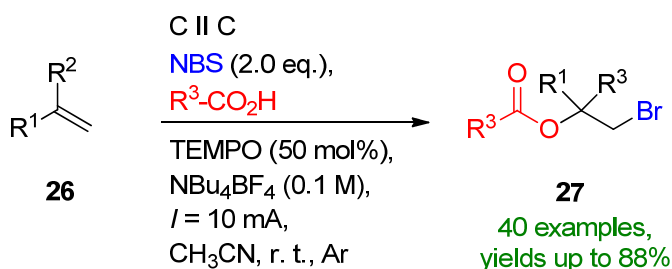
33 examples,  
yields up to 86%

Representative scope:



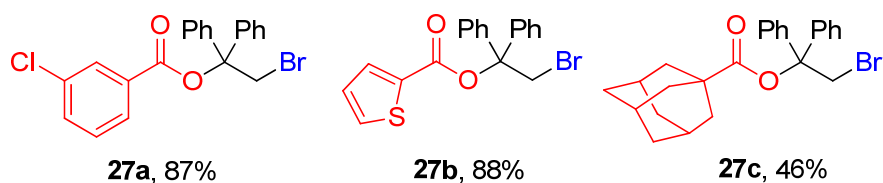
**Scheme 11.** Electrochemical bromination and bromofunctionalization of alkenes in flow electrolysis [96]. Cgr = graphite.

Reaction conditions:



40 examples,  
yields up to 88%

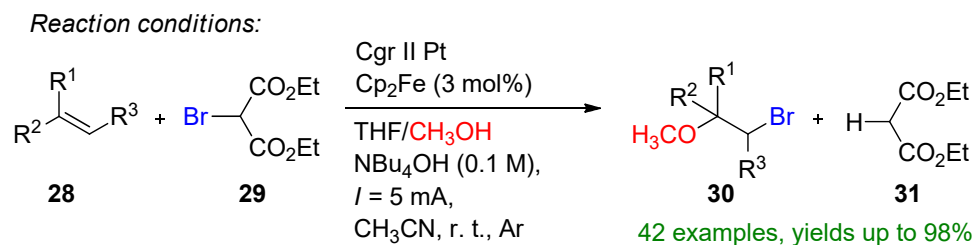
Representative scope:



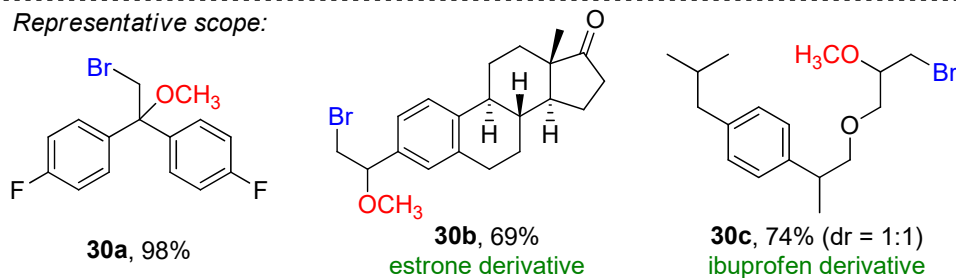
**Scheme 12.** The three-component, TEMPO-mediated 1,2-bromoesterification of alkenes [97]. CCE conditions were described with current ( $I$ ), as the immersed electrode area was not specified.

The attraction of this elegant, electrochemically promoted shuttle reaction is the use of non-corrosive vicinal 1,2-organodihalides as halogen promoters, which eliminate the use of low-atom-efficient halogenating agents and surrogates. Readily available, inexpensive, non-oxidizing 1,2-dibromoethane serves as the bromine source. The aforementioned organohalide undergoes reductive dehalogenation at the cathode and is transferred to an acceptor alkene, providing a convergent application for the reductive dehalogenation and formation of fine chemicals in one step. The reaction proceeds readily on cheap graphite electrodes in the presence of 1 v/v% HFIP in acetonitrile. The additive suppresses the oxidation of alkene and promotes dehalogenation at the cathode. Via this method, the dibromination, dichlorination, thiobromination and thiochlorination of alkenes was facilitated. The method demonstrates an extensive functional group tolerance as alkenes

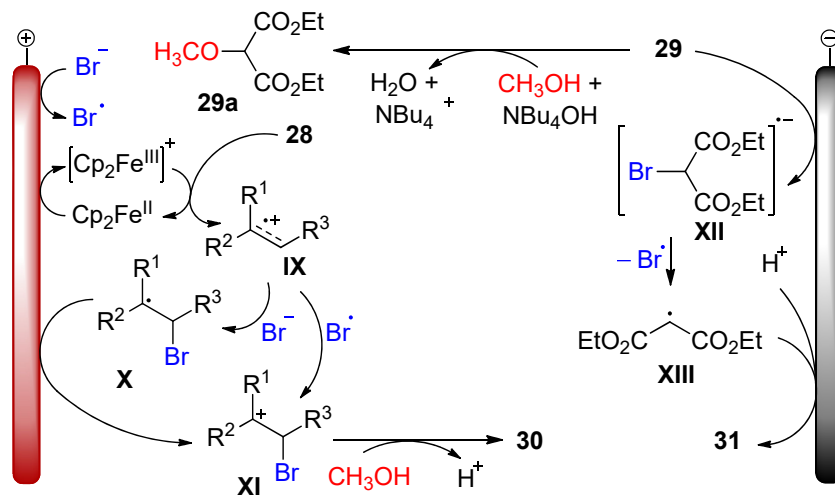
with alcohols, ethers, silylethers, sulfones, phosphones, aromatics and alkyne functional groups equally remained intact. Moreover, the electrochemical dehalogenation of persistent and toxic hexachlorocyclohexane (HCH) to benzene was also described. Various lindane-contaminated soil samples were subjected to the optimized conditions to yield the corresponding benzene and vicinal 1,2-dichloride in excellent yields.



**Representative scope:**



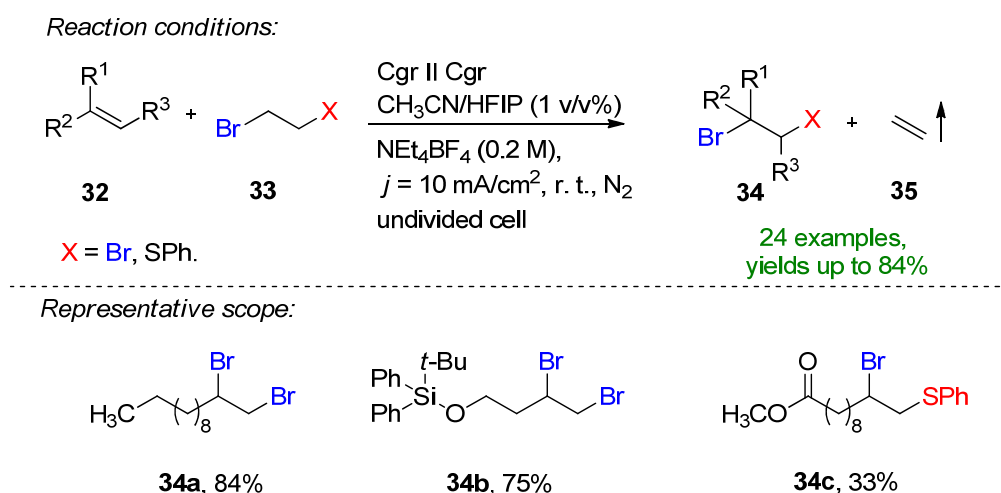
**Plausible mechanism:**



**Scheme 13.** The electrochemical alkoxyhalogenation of alkenes within a convergent paired electrolysis method [99]. CCE conditions were described with current (*I*), as the immersed electrode area was not specified. Cgr = graphite.

While the electrochemical dibromination and bromofunctionalization of alkenes are mainly characterized by the application of metal bromide salts as potential bromine sources, there are more and more methods that provide the electrochemical generation of bromine in a synergistic operation. The advantage of the former is the utilization of bench-stable and safe bromide salts. These, unfortunately, usually require an obligatory protic additive for solubility reasons and, except for organic salts, are not metal-free. Replacing the alkali bromide salts with usually toxic organobromine compounds overcomes the solubility issues, providing a simpler setup. These procedures allow the elimination or the utilization of the sacrificial half-reaction as bromine can be generated in a linear-paired fashion [62,87].





**Scheme 14.** Merging e-shuttle for the retro-dibromination and bromofunctionalization of alkenes [62]. Cgr = graphite.

#### 4. Electrochemical Bromofunctionalization of Alkynes

Although there have been substantially less protocols reported, alkynes still represent a popular electrochemical target functionality [100]. In terms of halofunctionalization, they have also received significant attention, as the forming organohalides are excellent synthons for heterocyclic molecules and other synthetic intermediates [101,102].

##### 4.1. HBr, MBr and Alkylammonium Bromides as Bromine Sources

Wang et al. reported the electrochemical oxyhalogenation of alkynes in the presence of KBr or HCl to form the corresponding  $\alpha,\alpha$ -dihaloacetone derivatives [103]. The reaction proceeds readily in a divided cell equipped with a cation exchange membrane to form the desired products in good to excellent yields. LiClO<sub>4</sub> serves as an additional supporting electrolyte and platinum electrodes promote the oxidation of halides at the anode and the liberation of hydrogen at the cathode. The authors suggest the in-situ formation of HOBr and HOCl as powerful halogenating agents.

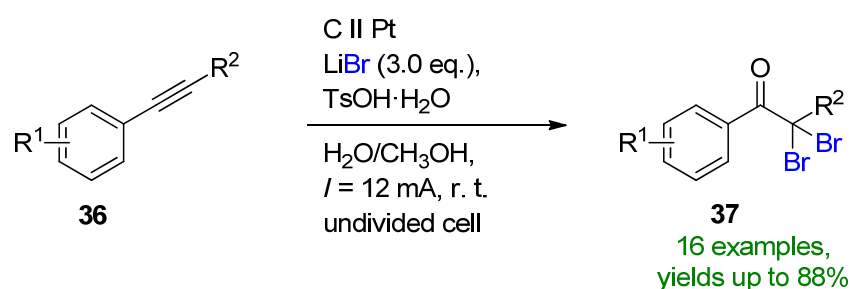
An improved electrochemical method for the oxidative functionalization of arylalkynes was published under undivided cell conditions [104]. The desired  $\alpha,\alpha$ -dibromoacetophenone derivatives readily formed in the presence of 3 eq. LiBr and *p*-toluenesulfonic acid monohydrate in aqueous media including 10% methanol. H<sub>2</sub>O (100%) as well as H<sub>2</sub>O/MeOH (50%) resulted in reduced yields, suggesting that water had a significant role in the reaction and the co-solvent was beneficial as it promoted the solvation of phenylacetylene. The combination of LiBr and *p*-TsOH·H<sub>2</sub>O was obligatory to the success of the reaction as switching either the bromide salt or the acid resulted in diminished yields. Under the optimized conditions, 16 different  $\alpha,\alpha$ -dibromoacetophenones were presented with yields up to 88%. The reaction proved to be scalable both in a batch and in-flow setup, and the synthetic applicability of the products were presented in the synthesis of three different heterocyclic compounds (Scheme 15).

A highly stereoselective, three-component annulation–sulfonylation method of 1,6-enynes to 1-indanones was reported in the presence of NaI or NaBr [105]. The test substrate, 1,6-enyne 39 was readily converted to the corresponding bromosulfonylated product 40 in the presence of 2 eq. of NaBr and 3 eq. of 4-methylbenzenesulfonylhydrazine as the sulfonyl donor (Scheme 16). The halide salts play a triple role of an electrolyte, redox catalysts and halogenating reagents. The reaction performed best at platinum electrodes in a solvent mixture consisting of THF/H<sub>2</sub>O (1:1). The highly selective nature of the reaction was postulated to rise from the electrochemically formed arylsulfonyl halide intermediate, that undergoes homolytic fission to the arylsulfonyl radical and bromine radical. The latter is oxidized at the anode to a bromonium ion. The resulting arylsulfonyl radical is

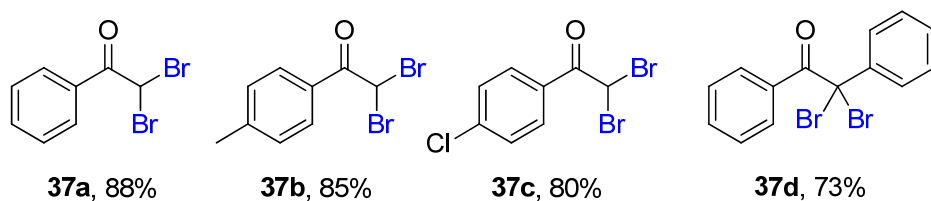
scavenged by **39** to form intermediate **XIV**, which then, due to steric hindrance, selectively forms the *Z* isomer.

The direct halogenation of *o*-arylkynylanilines to C3-halogenated indoles using  $\text{NH}_4\text{Br}$  both as electrolyte and the halogen source was reported [106]. The reaction proceeded smoothly on platinum electrodes in undivided cell conditions using ethanol as solvent. The reaction also proceeded to yield to corresponding 3-iodoindoles in the presence of ammonium iodide, providing access to skeletally diverse indole derivatives with yields up to 92%. Slightly changing the electrochemical parameters allowed the formation of unexpected indole derivatives. Changing the halide source to KI favored the generation of pentacyclic indole (**43**), while in the presence of  $\text{NH}_4\text{I}$  in acetone solvent, **44** was formed establishing the diverse applicability of the electrochemical method (Scheme 17).

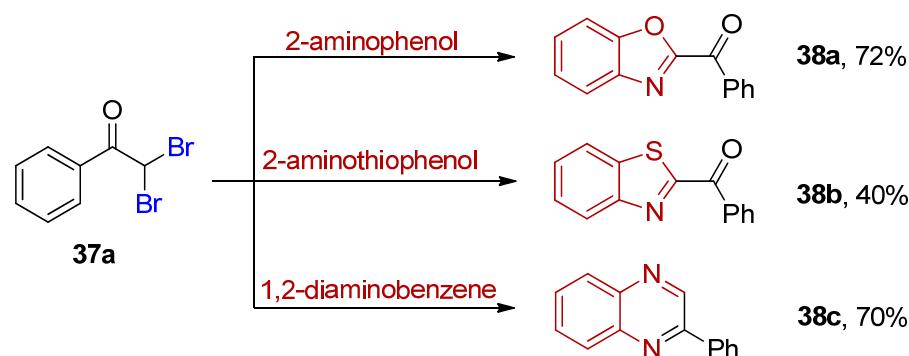
Reaction conditions:



Representative scope:



Subsequent functionalization:



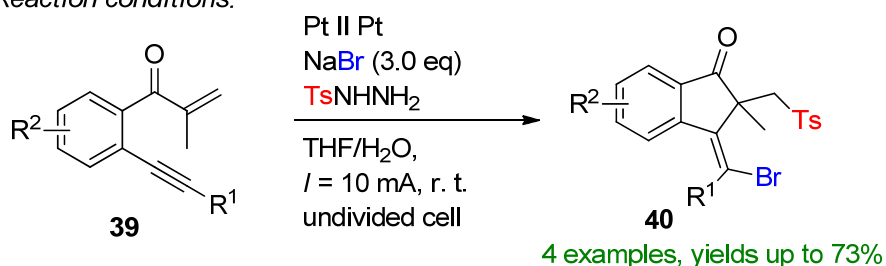
**Scheme 15.** Electrochemical  $\alpha,\alpha$ -dibromoacetophenone formation with the aid of LiBr in an undivided cell [104]. CCE conditions were described with current (*I*), as the immersed electrode area was not specified.

The oxidative *5-exo-dig-oxo*-cyclization of *o*-alkynylbenzamides for the synthesis of isobenzofuran-1-imines using NaBr was reported (Scheme 18) [107]. Using additional  $\text{LiClO}_4$  as an electrolyte at platinum electrodes at room temperature gave the brominated derivatives with up to a 77% isolated yield. The choice of additional supporting electrolyte as well as the solvent were the key features of this electrochemical method. Changing  $\text{LiClO}_4$  or the absence of the supporting electrolyte had detrimental effect on the reaction. Using 1.5 eq. NaI as a halogen source gave the corresponding 3-iodo-isobenzofuran-1-

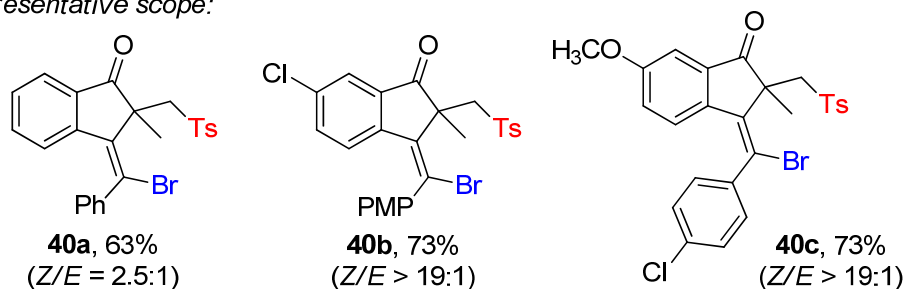
imines with excellent yields. The combined halogenation process provided 33 examples with up to an 84% isolated yield.

The electrochemical dearomative spirocyclization of *N*-aryl alkynamides to the corresponding spiro[4,5]trienones was reported [108]. The highly selective reaction was catalyzed by inexpensive and bench-stable lithium halides on graphite electrodes. The model substrate showed high affinity in the presence of 2 eq. LiBr to form the 3-bromoderivative. Extension of the scope provided 20 different brominated examples with up to a 98% isolated yield. Substitutions both on the nitrogen as well as the aniline were tolerated with only noticeable changes in the yield in the presence of electron-withdrawing groups on the nitrogen. In absence of the methoxy group as well as the halogen, no formation of the desired product was detected. Similarly, the chloro- and iodo-derivatives could be also obtained with moderate to good yields. The synthetic utility was proved by a 32-fold scale-up to provide **48** with a yield of 80% (Scheme 19).

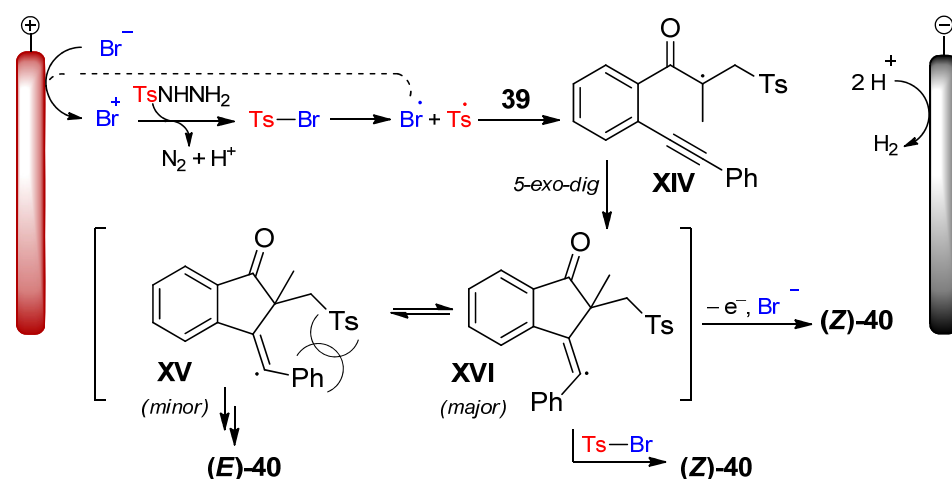
Reaction conditions:



Representative scope:



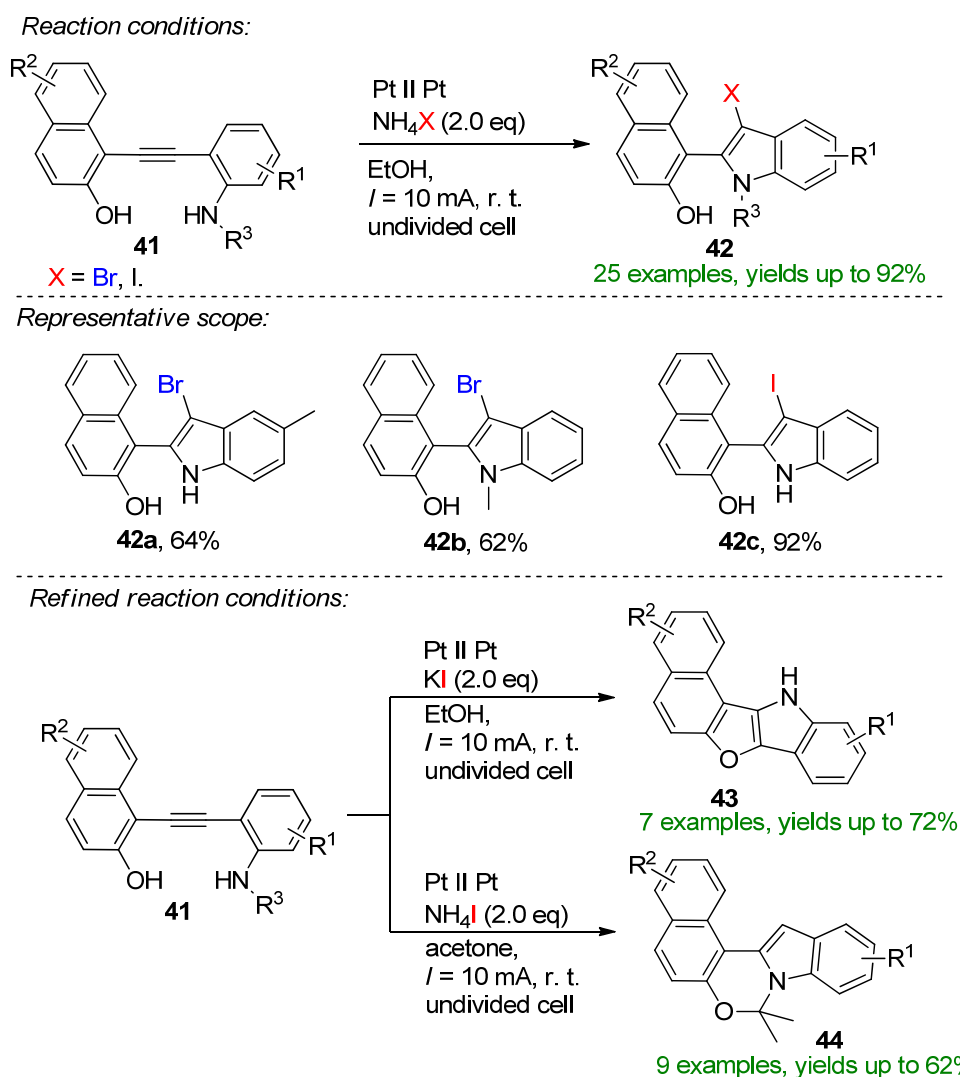
Plausible mechanism:



**Scheme 16.** Electrochemical three-component annulation-sulfonylation of 1,6-enynes to 1-indanones [105]. CCE conditions were described with current (*I*), as the immersed electrode area was not specified.

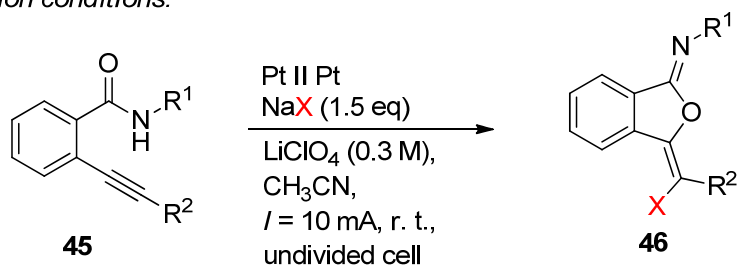
#### 4.2. Organohalides as Bromine Sources

The first electrocatalytic oxydihalogenation of alkynes using organohalides ( $\text{CH}_2\text{Br}_2$ ,  $\text{CHCl}_3$ ,  $\text{CH}_2\text{Cl}_2$ ,  $\text{Cl-CH}_2\text{-CH}_2\text{-Cl}$ ) with water as an eco-friendly oxygen source and  $\text{NBu}_4\text{I}$  as a catalyst was reported [109]. The reaction also worked for the formation of dichloroacetophenone using different organochlorine sources. The mechanism was envisioned by the  $\text{S}_{\text{N}}2$  substitution of the  $\text{CH}_2\text{Br}_2$  by iodide, which then underwent oxidation at the anode to a bromine radical that was subsequently trapped by the alkene **49** (Scheme 20). The resulting intermediate **XVII** was oxidized to carbocation **XVIII**, which then, upon reaction with water, formed the corresponding enol, and further combination with bromoradical and subsequent oxidation resulted in the product **50**. The procedure could be extended to provide 13 examples with up to 84% isolated yields.



**Scheme 17.** Electrochemical halogenation of arylalkylanilines to C3-halogenated indoles [106]. CCE conditions were described with current ( $I$ ), as the immersed electrode area was not specified.

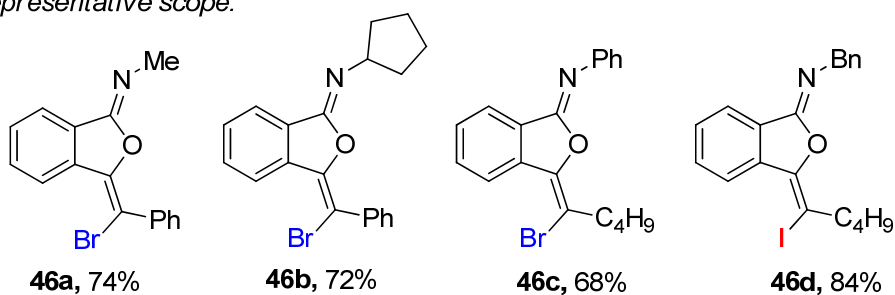
Reaction conditions:



X = Br, I.

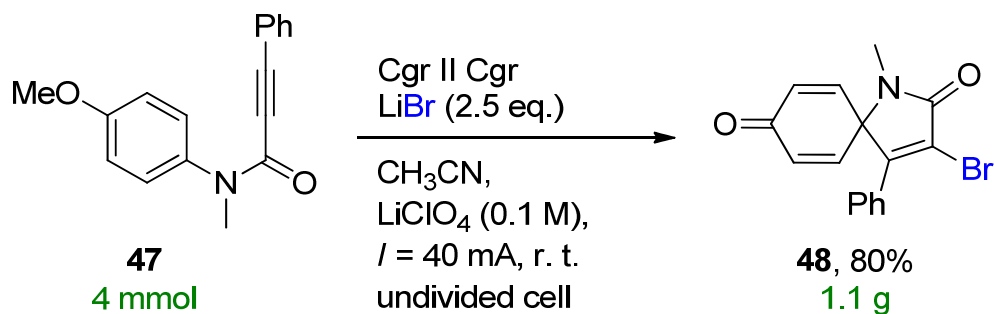
33 examples, yields up to 84%

Representative scope:



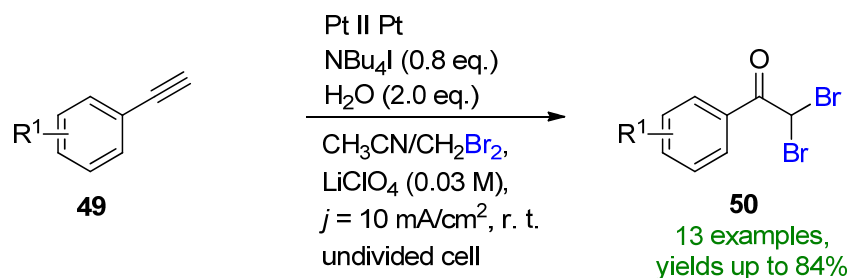
**Scheme 18.** The oxidative 5-*exo-dig*-oxo-cyclization of *o*-alkynylbenzamides to isobenzofuran-1-imines using NaBr and NaI [107]. CCE conditions were described with current (*I*), as the immersed electrode area was not specified.

Gram-scale synthesis:

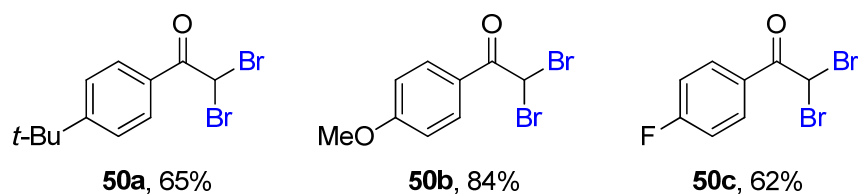


**Scheme 19.** Gram-scale synthesis of spiro[4,5]trienone **48** [108]. CCE conditions were described with current (*I*), as the immersed electrode area was not specified. Cgr = graphite.

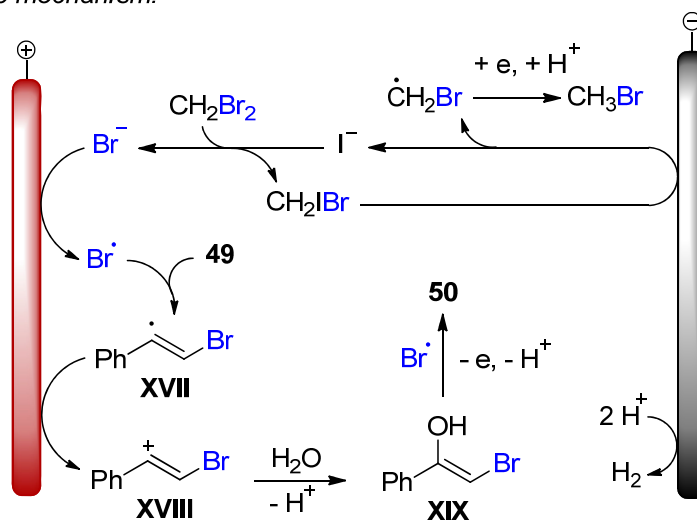
Reaction conditions:



Representative scope:



Plausible mechanism:



**Scheme 20.** Electrocatalytic oxydihalogenation of alkynes in the presence of dibromoethane [109].

## 5. Conclusions

The electrochemical bromination and bromofunctionalization of alkenes and alkynes have proved to be emerging hot topics in the last years. Via the anodic oxidation of readily available and bench-stable bromides, bromine can be generated under controlled parameters to form the desired brominated products and intermediates in a highly sustainable fashion without the use of catalysts or exogenous oxidants. The utilization of alkali bromide salts in a dual role as both a reagent and supporting electrolyte augments electrochemical bromination protocols over the traditional ones, providing a greener and accessible alternative for the scientific community. Furthermore, their non-toxic and non-corrosive nature provides a solution for the handling and storage issues that are indispensable requirements for  $\text{Br}_2$  or  $\text{HBr}$ , thus opening a more sustainable and atomically economic way for the electrochemical generation of bromine and bromofunctionalization reactions.

While the electrochemical methods are represented via the utilization of metal bromide as brominating agents, there are more and more procedures that use organobromines in a paired electrolysis fashion, replacing the usual  $\text{H}_2$  evolution as a cathodic counterpart. Although the exchange of bench-stable and safe bromide salts to organobromine compounds might raise questions, this approach could potentially open a field and draw interest for the elimination of persistent halogenated organic pollutants, such as hexachlorocyclohexane or



hexabromocyclododecane. Since the cathodic removal of bromo substituents is a common synthetic tool, which has even been applied to pharmaceutical intermediates, the basis for an electrically driven circular economy for bromine has been virtually established [110–112].

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