A Green Approach: Vicinal Oxidative Electrochemical Alkene Difunctionalization

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Abstract: The use of electrochemistry is now regarded as one of the most efficient methodologies in which to synthesize highly functionalized moieties, such as those of the difunctionalized vicinal alkene family, from more simplistic and commercially available substrates. These vicinal transformations usually depend on transition metal catalysis, hypervalent iodine reagents or photocatalysis to form new bonds and often generate unwanted by-products. Herein, we have outline examples of electrochemical alkene difunctionalization reactions that do not require a metal catalyst incorporated into the solution and yet still proceed with excellent atom economies.

1. Introduction.

The chemical transformations in organic chemistry by applying electrical energy introduces a facile synthetic methodology. It offers an alternative clean and a green route for the in situ formation of radical cation or radical anion intermediates in organic synthesis using the electric current as the reagent, which can thus remove the requirement for expensive catalysts and ligands. In the basic setup of an electrochemical cell, organic reactions take place on the surfaces of the electrodes with the assistance of an electrolyte. These reactions serve as a powerful method in which to synthesize complicated organic molecules, since they provide the easy formation of highly reactive species and avoid the use of expensive oxidants and dangerous chemicals. Electrochemistry is generally conducted under relatively mild conditions with high chemoselectivity, making electrosynthesis in organic chemistry one of the most sustainable approaches and, therefore, presenting itself as a great candidate in which to attempt new strategies.\textsuperscript{[1]}

Electrochemical difunctionalization of alkenes has currently emerged as a new approach for olefin difunctionalization that maximises substrate generality, avoids the use of a strong oxidant, and minimises by-product formation. The anodic oxidation of heteroatom-containing anions generates radicals that can then be attached onto alkene C=C double bonds to produce a carbon radical that is the subsequently utilised in a diverse range of functionalizations reactions which include, but are not limited to, azidoiodination, aziridination, oxysulfurization and aminooxygenation. The recent developments in alkene difunctionalization will not only mediate the

design of new, green synthetic pathways using electrochemistry, but will also facilitate the use of reactor technology for an easy and facile functionalization of alkenes.

2. Vicinal Oxidative Electrochemical Alkene Difunctionalization.

1,2-difunctionalization of alkenes has received considerable attention as one of the most important and relevant chemical transformations in organic synthesis (Scheme 1). However, the incorporation of two distinct chemical bonds into alkenes via a single step construct is a difficult transformation. To perform these chemical transformation, transition metal catalysis, hypervalent iodine reagents or photocatalysis is required. The resultant products formed through 1,2-difunctionalization are of interest since they occur in many natural products and bioactive compounds, not to mention that they are also sources of important organic intermediates such as diamines, amino alcohol, diol, aziridine and oxirane compounds, etc. (Figure 1). Moreover, these difunctionalized products can then be further transformed into the specific moieties and multi-functional products. Thus, the development of a novel and mechanistically efficient strategy for expanding the oxidative alkene 1,2-difunctionalization method is an urgent need. Therefore, we hereby show that this well-defined difunctionalized strategy, using electricity as the reagent, is able to provide a powerful way to construct valuable organic and fine chemicals.

Scheme 1: General reaction scheme for 1,2-difunctionalization of alkenes.

Figure 1: Difunctionalization of alkenes.

The Lin group has reported some very interesting works on the electrochemical difunctionalization of alkenes. They used a single Mn-based electrocatalytic cycle to promote the addition to the C-C bond. Their method converts alkenes to 1,2-diazides, 1,2-dichlorides, and

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chlorotrifluoromethylated compounds. The redox-active Mn catalysts allow the initiation of radical intermediates at low potentials under mild conditions, and impart selectivity control over the alkene functionalization processes by functioning as radical group transfer agents. However, all of their work has been done under metal electrocatalysis in solution. There are only few reports in which electrochemical difunctionalization of alkenes took place completely without a metal catalyst in solution, hence, this is the main theme of this review.

2.1 C-N and C-halogen bond formation.

The azidoiridnation of alkenes reveals products that contain useful iodo and azido functional groups, which can easily be converted into useful intermediates, such as vinyl azides,[3] aziridine,[4] and tetrazoles.[5] Recently, Zeng and co-workers[6] proposed the electrochemical regioselective azidoiridnation of alkenes through constant current with NaN₃ and NaI in methanol, to provide the Markovnikov addition products (Scheme 2). Here, IN₃ is electrochemically generated in situ, without oxidants or the corrosive molecular iodine, and is performed by constant current electrolysis at 15 mA/cm² in a type H cell using graphite plates as both cathode and anode electrodes.

Scheme 2. Regioselective azidoiridnation of alkenes.

It was found that a wide range of substrates proved to be compatible with this protocol, affording the Markovnikov products in yields of up to 70%, with the substrates containing electron-rich substituents affording higher yields in comparison to those containing electron-poor groups (Scheme 2). Internal alkene derivatives were also investigated, for example cyclohexene, which afforded the trans-addition product in 30% yield.

Scheme 3: Mechanism for the azidoiridnation of alkenes.

The authors suggest that the reaction proceeds through a cyclic iodonium intermediate 3 (Scheme 3), starting with the anodic oxidation of iodine, providing the formation of molecular iodine, which reacts with the azide ion to produce IN$_3$. Consequently, IN$_3$ predominantly acts as the source of I$^+$ to form the cyclic iodonium 3 intermediate, which undergoes attack of the azide on the most substituted carbon, providing the product 2 by Markovnikov addition.

Generally, methodologies for the aziridination of alkenes involve the transfer of a metal-mediated nitrene fragment.[7] These pathways, however, produce a wide variety of waste by-products, therefore, newer, more efficient pathways are required. In 2002, Siu and Yudin were the pioneers of the electrochemical reaction of aziridination using nitrene species.[8] Recently, Little and co-workers[9] proposed an efficient electrochemical strategy for the catalytic aziridination of alkenes by a nitrogen radical, mediated by Bu$_4$NI. In addition, Cheng and co-workers[10] proposed the first electrochemical aziridination of multisubstituted styrenes using a sulfamate as the nitrogen source (Scheme 4).

Scheme 4: Electrochemical aziridination of multisubstituted styrenes.

To evaluate this protocol, the authors started from triphenylethylene and sulfamate (HfsNH$_2$) in acetonitrile as solvent, at a constant potential of 5 V using graphite felt as the electrodes, LiClO$_4$ as the electrolyte and K$_3$PO$_4$ as a base, which afforded the product 6a with 57% yield. However, with 2,6-lutidine as the base, an improvement in the reaction was obtained, with the product 6a being isolated in 87% yield, with a current efficiency of 44% (Scheme 5).

Scheme 5: Aziridination of multisubstituted styrenes.

Aziridines containing F, Cl, or Br atom (6h – o) were synthesised in excellent yields (82 – 94%) as well as the diphenyl naphthalenyl aziridine (6v, 76%). Several other substituents have been tested (Scheme 5). Cyclic voltammetry experiments have also been performed (Scheme 6).\textsuperscript{[10]}

The transfer of electrons to the anode occurred in +2.0 V, which is almost identical to the oxidation potential of A in the reaction mixture. The authors concluded that the reaction began with the activation of the alkene by an electron transfer from the molecule to the anode, leading to an alkene radical cation. The following stepwise formation of C-N bonds using a nucleophilic nitrogen source would provide aziridine products.

2.2 C-N, C-S and C-O bond formation.

Recently, Lei and co-workers\textsuperscript{[11]} proposed an electrochemical oxidative alkoxy sulfonfylolation of alkenes with alcohols and sulfonfyl hydrazides. The authors examined the scope of the substrate with a wide variety of sulfonfyl hydrazides, alkenes and alcohols (30 examples), and the products were obtained in yields of up to 97% (Scheme 7).

Scheme 7: Electrochemical oxidative alkoxy sulfonylation of olefins.

The authors performed tests with various combinations of electrodes, such as C(+)|Pt(-), C(+)|Fe(-), Pt(+)|Ni(-), however, the best reaction condition was reached with C(+)|Ni(-) and BuNBF$_4$ as a electrolyte in MeCN, at a constant current of 12 mA, affording the product 10b in 86% yield after 3 hours.

Several sulfonyl hydrazines were analyzed. It was observed that both those substituted with electron donor groups and those with electron withdrawing groups afforded the $\beta$-alkoxy sulfones in good to high yields (Scheme 8, 10a – c). In addition, several olefins were also tested. Styrene derivatives with various substituents on the aromatic ring were fruitful substrates, affording the products in good yields (10d – f). However the reaction condition was not efficient when aliphatic alkenes 10g were applied. The use of tertiary alcohols 10h was also not efficient for this synthesis.

Scheme 8: Representative examples for the oxidative alkoxy sulfonylation of olefins.

A possible mechanism was proposed (Scheme 9). First there is a deprotonation, electrochemical oxidation, and then a release of N$_2$, forming the radical 12, which reacts with the alkene 7 to provide the radical 13, which then undergoes oxidation to produce a benzylic intermediate 14, followed by the nucleophilic attack of the alcohol 9 and deprotonation, affording the product 10.
Xu and co-workers\textsuperscript{[12]} have developed a triarylamine-catalysed electrochemical dehydrogenative annulation of alkenes using diols, affording 1,4-dioxane and 1,4-dioxepane derivatives with yields of up to 85%; this is compatible with a large scope of functional groups (\textbf{Scheme 10}).

\textbf{Scheme 10}: Electrochemical dehydrogenative annulation of alkenes using diols.

The reaction scope was extensively studied, performing the synthesis of 38 examples (0 - 85%). The reaction was fructiferous with different 1,1-diphenyl alkenes, being compatible with benzene ring activating and deactivating substituents (\textbf{Scheme 11}).

\textbf{Scheme 11}: Representative examples for the synthesis of O-heterocycles.

A mechanism has been proposed (\textbf{Scheme 12}), starting from the anodic oxidation of the triarylamine catalyst 18, providing the radical cation 19, which then oxidises the substrate 15 through simple electron transfer to provide the corresponding radical cation 20, and regenerating 18. Subsequently, the addition of ethylene glycol 16 to 20, followed by deprotonation affords the

carbon-centred radical 21, which is then oxidised by 19, to provide the cation 22. The cyclisation of 22 provide the 1,4-dioxane product 17.

Scheme 12: Mechanism proposal for the synthesis of saturated O-heterocycles.

Additionally, Lei and co-workers\textsuperscript{[13]} proposed a selective approach for oxysulfenylation and aminosulfenylation of alkenes using thiophenols/thiols as thiolating agents. β-alkoxy and β-amino derivatives were produced with good to excellent yields under electrochemical oxidation conditions. It was not necessary to use external oxidants or metal catalysts, which is of great advantage from a synthetic point. The methodology was shown to be general, being compatible with several alkenes, such as thiophenols/thiols, O-nucleophiles, N-nucleophiles and can also be applied for the hydroxysulfenylation and acyloxysulfenylation of alkenes (Scheme 13).

Scheme 13: Oxysulfenylation and aminosulfenylation of alkenes.

A range of styrenes containing electron donor groups were compatible with this protocol, affording the expected β-alkoxy sulfides in good yields (Scheme 14). Halo substituents were tolerated as well (27e – g, 62 – 78%). In conjunction, the indene was fruitful in this condition, and the desired β-alkoxy sulfoxide was obtained in an optimal diastereomeric ratio (27k, dr: >20:1, 71%). Aliphatic alkenes, such as cyclohexene, 2-ethyl-1-butene and 1-vinyl-2-pyrrolidone were appropriate as well, with yields of 22% (d.r: >20:1), 20% and 61%, respectively. Remarkably, aliphatic alcohols containing halogens or hydroxyl were also efficient in this transformation (27n – o, 46 – 63%). Other successful examples include sterically hindered substrates, such as tert-butyl

alcohol (27p, 37%), and O-nucleophiles, such as water (27r, 42%) and acetic acid (27q, 39%), primary aromatic amines, primary aliphatic amines, secondary aromatic amines, heteroaryl amines and amides all provided their corresponding products in good yields (28a – d, 52 – 61%). A wide range of thiophenols gave the desired products in moderate to excellent yields.

Scheme 14: Oxysulfenylation and aminosulfenylation of alkenes.

To understanding the reaction mechanism, several control experiments were performed (Scheme 15). First, the radical trapping experiment was performed with TEMPO, however, the expected product was not produced for the standard reaction of 4-chlorothiophenol 29, styrene 30 and methanol 31, with only the radical capturing compound 34 being obtained in 30% yield. The radical homo-coupling experiment was performed with 4-chlorothiophenol 29 in the absence of styrene 30, under standard reaction conditions, and the product bis-(4-chlorophenyl)disulfide 35 was obtained in 78% yield. Additionally, for the cross-coupling experiment, the reaction did not occur without the use of an electric current. However, the cross-coupling product 37 was obtained under the standard reaction conditions in 40% yield.
In 2018, Pan and co-workers,¹⁴ developed an electrochemical methodology for the 1,2-sulfonylation/alkynylation of inactive olefins via radical 1,4-alkynyl migration of alkynyl-substituted tertiary alcohols, affording α-sulfonyl-β-alkynylation products in yields of up to 92%; this being the first report for the distal radical migration reaction via electrochemistry (Scheme 16).

A broad scope of reaction conditions were evaluated. The introduction of substituents on the aromatic alkyne ring proved to be efficient for both electron-activating and electron-withdrawing groups, affording the products in good yields (68-78%). However, for strongly withdrawing groups present in sodium sulfinate phenyl, the reaction presented a disadvantage (40h, trace).

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This methodology represents the first example of an electrochemical distal radical migration reaction, providing an important opportunity for new synthetic routes while being able to offer several products in mild and green conditions.

In addition, Han and co-workers[15] described the first electrochemical oxidative oxysulfuration of olefins with thiols and other sources of nucleophilic oxygen through two cascade oxidations at the anode, at room temperature, and without a catalyst and oxidant. In addition, this reaction showed a wide range of possible substrates, broad functional group tolerance and excellent regioselectivity, even though it is a new and green strategy for the difunctionalization of olefins (Scheme 17).

![Scheme 17](image)

Scheme 17: Electrochemical oxysulfuration of alkenes.

An electrochemical oxidative oxysulfuration approach for the synthesis of thio-substituted γ-lactone derivatives was set. Several electrolytes were evaluated, including NaCl, Bu₄NBr and Bu₄NBF₄. However, it was found that Bu₄NBF₄ was the optimal choice. To prove the efficacy of the method, several carboxylic acids and thiophenols were evaluated (Scheme 18), revealing that both the donor group and the electron withdrawing group in the thiophenol ring were efficient, affording the products in good yields (58 – 87%).

![Scheme 18](image)

Scheme 18: Representative examples for the olefin oxysulfurations.

Based on previous literature and their experimental results, the authors proposed a possible mechanism (Scheme 19).

Scheme 19: Mechanism for the electrochemical oxidative radical reaction.

The reaction begins with the aromatic thyl radical 48 formation from thiophenol 43 through a single-electron transfer (SET) oxidation at the anode. In addition, this aromatic thyl radical 48 is added to the alkene 41 affording the radical intermediate 49, which is oxidised to the carbocation 50 in the anode. C-carbocation is retained by the alcoholic nucleophile to provide the ultimate oxy-sulfuration product. Concurrently, thiophenol 43 is reduced to release the anion 51 and hydrogen gas at the cathode, which reacts with the proton to regenerate thiophenol 43.

2.3 C-C bond formation.

One of the most challenging transformations for synthetic chemicals is the formation of new carbon-carbon bonds. Corroborating this, electrochemical reactions of carbon dioxide have attracted considerable interest, since cathodic reduction allows the introduction of CO$_2$ into alkenes, alkynes, allenes and other carbon-carbon multiple bonds. Organic halides may also provide carboxylic acids under atmospheric pressure of CO$_2$.[16] Additionally, Tokuda and co-workers[17] performed the electrochemical dicarboxylation of phenyl-substituted alkenes under atmospheric pressure of CO$_2$ with a magnesium rod anode and platinum plate cathode, which afforded the respective 1,2-dicarboxylic acids (Scheme 20).

Scheme 20: Electrochemical dicarboxylation of olefins.

The Electrochemical dicarboxylation of phenyl-substituted alkenes proceeded in high conversions, affording the respective 1,2-dicarboxylic acids 54 in excellent yields (66 - 91%). Cyclic Voltammetry of the substituted alkenes was performed, and from these results and CO\textsubscript{2} reduction potential (-2.53 V vs. Ag/Ag\textsuperscript{+}), the authors propose two possible mechanistic pathways (Scheme 21).

**Scheme 21**: Mechanism for the electrochemical dicarboxylation.

*Path a*: The alkenes generated from 52a all have a more negative reduction potential than CO\textsubscript{2} (-2.91 to <-3.00 V), therefore, the reduction of an electron from carbon dioxide occurs to generate its anionic radical. The addition of the anionic radical of CO\textsubscript{2} to alkene 52a result in intermediate. The reduction of one electron followed by the reaction with CO\textsubscript{2} gives rise to the dicarboxylate ion 59. *Path b*: In the reaction of alkene 52e whose reduction potential is slightly more positive than CO\textsubscript{2} (-2.44 to -2.58 V), a direct or CO\textsubscript{2}-mediated one-electron reduction from this occurs to generate its anionic radicals 55. This reaction with CO\textsubscript{2} gives the monocarboxylate intermediate 56. Further reduction followed by reaction with CO\textsubscript{2} leads to the formation of the dicarboxylate ion 57.

In 2018, Xu and co-workers\cite{18} proposed a first synthesis of pyrrolidines and tetrahydropyridines derivatives by N-allyl amides annulation with 1,3-dicarbonyl compounds in yields of up to 89% (Scheme 22). The N-allyl amides react with the malonate through annulation (4+1) providing pyrrolidines, or β-ketoesters to give tetrahydropyridine derivatives via annulation (4+2). Several redox catalysts derived from phenothiazine were evaluated, but the best performance was achieved with 62 and HCO\textsubscript{2}Na (0.3 equiv) as the base additive, in a mixture of the solvents tBuOMe/MeCN/H\textsubscript{2}O (20:3:1) under reflux in a current of 7.5 mA.

Scheme 22: Electrochemical synthesis of pyrrolidines.

The synthesis of the pyrrolidine derivatives were efficient for a large number of substituents present on the substrates (Scheme 23).

Scheme 23: Representative examples for the pyrrolidine synthesis.

The phenyl present on the alkenyl carbon atom could be substituted with electron donor moieties (63a-c) halogens (63d) or electron withdrawing moieties (63e). However, when the OMe group was present in the ortho-position of the phenyl group R1, a disadvantage was observed (63f, 30%). In addition, with a methyl group in place of phenyl (R1), the product was obtained in 15% yield (63g). Likewise, the substituents on the phenyl ring (R2) were also tolerant to a wide range of substituents, such as ring activating moieties, halogens or electron withdrawing moieties (63h - k). It was also found that the substitution of an alkyl group on the phenyl group R2 did not provide the desired products. In addition, the R3 group was tolerant of different steric properties (63l - m).

Scheme 24: Electrochemical synthesis of tetrahydropyridine.
For the synthesis of tetrahydropyridine derivatives (4+2), the reactivity of the substituents present in the molecule were similar to the reactions for the synthesis of pyrrolidines derivatives (4+1). However, for the tetrahydropyridine, the alkyl group present in the nitrogen (N-nPr) provided the desired product in 53%. The β-ketoester also tolerated different substituents (Scheme 25).

**Scheme 25**: Representative examples for the tetrahydropyridine synthesis.

For the synthesis of tetrahydropyridine derivatives (4+2), the reactivity of the substituents present in the molecule were similar to the reactions for the synthesis of pyrrolidines derivatives (4+1). However, for the tetrahydropyridine, the alkyl group present in the nitrogen (N-nPr) provided the desired product in 53%. The β-ketoester also tolerated different substituents (Scheme 25).

### 2.4 C-N bond formation by Nitrogen-centred radicals (NCRs).

Nitrogen-centred radicals have an important function as synthetic intermediates. Their use in olefin addition reactions offers an easy way to achieve biologically interesting N-heterocycles.[19]

The amidyl radicals have been drawing attention because of their electrophilic nature and respective reactivity. However, despite these advantages, a common hindrance of the aforementioned N-H activation is the requirement for a chemical stoichiometric oxidant[20] or an expensive metal reagent. On the other hand, electrochemistry has been shown to be a clean and safer method for obtaining intermediates of interest, such as radical species. Additionally, Xu and co-workers[22] have reported an efficient method in which to electrocatalytically generate amidyl radicals for the intramolecular hydrolysis of olefins for the synthesis of lactams, cyclic carbamates and ureas (Scheme 26). A wide variety of amidyl radicals containing functionalized olefins are readily obtained by using ferrocene (Fc) as a redox catalyst. Indirect electrolysis generally avoids electrode passivation, kinetic inhibition, and achieves better selectivity. Analogous to this, the authors observed a diastereomeric ratio of up to 20:1. The optimal reaction conditions consisted of 5 mol% Fc, 1 equiv Na₂CO₃ and 5 equiv 1,4-cyclohexadiene (1,4-CHD) in a Bu₄BF₄ electrolyte in THF/MeOH (5:1), under reflux. The reaction did not occur without the supply of electricity.

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Scheme 26: Amidyl radicals for the intramolecular hydrolysis of olefins.

This process gave excellent chemoselectivity, being compatible with several variables, for example, basic/acidic labile groups, such as chiral esters and Boc-protected amino esters, as well as oxidation sensitive groups such as sulfonamides, free alcohols or N-aryl carbamates (Scheme 26).

Scheme 27: Mechanism for the ferrocene-mediated redox cycle.

With the results obtained in this and previous studies by the same author,[23] a plausible mechanism was proposed (Scheme 27). The electric current promotes the anodic oxidation of FcII to FcIII and cathodic reduction of MeOH to H₂ and MeO⁻, which acts as a base, providing 69. Instead of being reduced at the cathode, the ferric catalyst FcIII quickly oxidises 69 simply by electron transfer to provide the intermediate amidyl radical 70, and regenerating FcII. The final

product 68 is formed by cyclisation of the amidyl radical 70, followed by the abstraction of a proton by 71 from 1,4-CHD or a solvent.

Xu and co-workers\cite{24} have developed a synthesis of indolines and azaindolines via intramolecular dehydrogenative annulation of arylamines with tethered alkenes using ferrocene (Fc) as a redox catalyst, with yields of up to 86% (Schemes 28 - 29). The choice of base was very important in this transformation. For the indoline derivatives, the use of NaOAc (1 equiv) afforded the best results (Scheme 28). However, for the azaindoline derivatives, the use of K₂CO₃ (1 equiv) afforded the best results (Scheme 29).

Scheme 28: Synthesis of indolines.

Several substrates were evaluated for the synthesis of the indolines (Scheme 28). The phenyl ring of the aniline proved efficient with a range of substituents, both for electron donation groups and for electron withdrawal groups alike. However, it was observed that with electron-withdrawing groups there was a decrease in the reactional diastereoselectivity (73b – d). The authors suggest that this loss most probably occurs because of the increased reactivity of the aryl ring toward the electrophilic C-radicals. With an increased number of substituents on the alkene, the product was obtained in high yield; these derivatives being of great importance, mainly because they are very difficult to construct (73e).

This protocol was also efficient for the synthesis of azaindolines derivatives (Scheme 29), providing the products of 4- (75a-b), 5- (75c), 6-azaindolines (75e), as well as 6,7-dihydro-5H-pyrrolo[3,2-d]pyrimidines (75d) in good yields. However, when attempting the synthesis of 2-aminopyridine derivatives, the reaction provided a moncyclised hydroamidation by-product (75f).

The authors suggest that the mechanism proceeds through amidyl radical 6-exo-trig cyclisation/5-ring-forming homolytic aromatic substitution (HAS) cascade to promote a C–N and C–C bond.

Additionally, Xu and co-workers[25] have reported an efficient method to generate amidyl radicals from carbamate, amide and urea substrates for the intramolecular oxidative amination reaction of tri- and tetrasubstituted alkenes (Scheme 30). The advantage of this methodology is due to the efficient amination of sterically hindered alkenes, being useful for both acyclic olefins and cyclic olefins, including steroid based structures. Another advantage is that it does not require the use of metals or oxidising reagents. The optimum reaction conditions involved a constant-current electrolysis (10 mA) using a Pt plate cathode and a reticulated vitreous carbon (RVC) anode, in an undivided cell containing a mixed electrolyte solution of Et₄NPF₆ in dimethylacetamide (DMA) and acetic acid (40:1).

Scheme 30: Amination reaction of tri- and tetrasubstituted alkenes.

The anodic oxidation of 76 leads to the amidyl intermediate 77, which undergo intramolecular cyclisation with the alkenyl moiety, to give the central carbon radical 78. The radical 78 undergoes oxidation, and its cationic derivative 79, after the proton elimination, provide the product 80 (Scheme 30). The methodology draws attention to the fact that the generation of the double bond in the elimination step occurs regioselectively at the end of the molecule, instead of the favorable product derived from thermodynamically more stable tetrasubstituted enamine.

Scheme 31: Representative examples of the intramolecular oxidative amination of alkenes.

Terminal and internal alkenes, including the tetrasubstituted product were obtained (Scheme 31). Substrates derived from urea and unsaturated amides were fruitful, as well as the carbamates with less electron-rich groups, such as \( p\)-Br-Ph (80e, 71%). Surprisingly, no products were obtained with the substrate p-CN-Ph (80h, NR). However, a variety of functional groups have been well tolerated, including ester, imide, thiazole, pyridine, thiophene, alkyne, alcohol and silyl ether.
Additionally, Xu and co-workers\textsuperscript{[26]} conducted an electrochemical approach for the intramolecular aminooxygenation of non-activated alkenes. The difunctionalization of olefins with readily available amides, carbamates and TEMPO as a trapping group afforded aminooxygenation products in high yields, providing trans products with excellent selectivity (dr. up to > 20:1). According to mechanical studies, there is the formation followed by addition of the nitrogen-centered radicals in the double bond, providing the new radical 83 generated by electrochemical oxidation to alkenes, which is captured by TEMPO, a trapping group (Scheme 32).

\[ \text{Scheme 32: Electrochemical aminooxygenation of alkenes.} \]

The reaction was performed at 60 °C in a constant current of 10 mA using a reticulated vitreous carbon anode (RVC) and a platinum wire cathode (Figure 2). A solution of 0.1M Bu$_4$NBF$_4$ in H$_2$O/CH$_3$CN (1:19) was used as a support electrolyte along with two equivalents of TEMPO. Several bases were also tested, such as Na$_2$CO$_3$, LiOH and Cs$_2$CO$_3$. It was observed that completely consumption of the starting material, while the reaction was being performed at the lowest possible current, was possible with the use of Na$_2$CO$_3$.

\[ \text{Figure 2: Pt wire cathode and RVC anode. Reproduced with permission from ref 26, Wiley.} \]

Several substituents were evaluated (Scheme 33). The N-phenyl ring was modified to investigate their effects on the aminooxygenation of the alkene. The authors observed a broad spectrum of substituents, including electron donor groups, such as Me (84a, 97%), OMe (84b, 94% - 84k, 90%), F (84c, 88%), and electron withdrawing groups, such as CF$_3$ (84d, 83%), Ac (84e, 86%) and CN (84f, 87%). Carbamates with a 2,6-disubstituted phenyl group also proved to be

efficient substrates (84g, 85%). This methodology was also efficient for trisubstituted olefins, providing stereogenic tetrasubstituted centres (84i, 81%). However, the introduction of a nitro group resulted in unsatisfactory results (84h, 51%).

Very recently, Ahmed and Khatoon\[27\] developed an efficient and economical electrochemical system for the difunctionalization of amine-tethered alkenes, providing cyclic ureas in high yields (up to 85%). The reaction was conducted at 60 °C under a constant current of 10 mA using a reticulated vitreous carbon (RVC) anode and a platinum wire cathode. A solution of 0.1M Bu₄NBF₄ in CH₃CN/H₂O (19:1 v/v) as support electrolyte, 1.1 equivalents of Na₂CO₃ and 1.5 equivalents of TEMPO was used (Scheme 34).

Several substituents were evaluated (Scheme 35), including Me (86d, 80%), MeO (86e, 85%), CF₃ (86b, 85% - 86h, 79%), NO₂ (86c, 83%) and fluoro groups (86i, 77%), all of which proceeded

smoothly in the electrochemical system. However, the tosyl (86f, traces) and naphthyl group (86g, 25%) led to unsatisfactory results, the respective difficulty in forming the nitrogen radical being indicated as the cause.

Scheme 35: Examples for the synthesis of cyclic ureas.

A possible mechanism was proposed (Scheme 36). The process originates from the anodic oxidation of TEMPO to the oxoammonium ion and the cathodic reduction of water (H₂O) to the hydroxide (OH) and H₂, which promotes deprotonation of the substrate 85, leading to an anion containing nitrogen 87. Single-electron transfer (SET) between the nitrogen-containing substrate 87 and the oxoammonium ion provides the nitrogen-centred radical 88, regenerating the TEMPO radical molecule. The nitrogen radical 88 after cyclisation may form another carbon radical 89, which then reacts with TEMPO to afford the product 86.

Scheme 36: Proposed mechanism for the difunctionalization of amine-tethered alkenes.

This study showed that a non-stabilised primary radical can be generated and captured in the reaction, which is uncommon in radical chemistry.

Moeller and co-workers²⁸ demonstrated that amidyl radicals can also be generated anodically from O-benzyl hydroxamates and N-phenyl amides. The reaction depends on the control of the energy of the cyclisation relative to the competing routes of radical dimerisation and the H-abstraction. To direct the formation of one or another product, the reaction can be influenced by

modulating the relative energy of the reaction by appropriate selection of the olefin and amide substituents; the ketene dithioacetal groups have been shown to be the most effective (Scheme 37).

Scheme 37: Anodic intramolecular coupling of O-benzyl hydroxamates and N-phenyl amides.

An investigation with the purpose of identifying suitable amides for this cyclisation was carried out (Table 1).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product, Yield (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>R = OBn</td>
<td>94a, 80, 95a, 8, 96a, ND²</td>
</tr>
<tr>
<td>2²</td>
<td>R = OBn</td>
<td>94a, 81, 95a, 3, 96a, ND</td>
</tr>
<tr>
<td>3⁴</td>
<td>R = OBn</td>
<td>94a, ND, 95a, ND, 96a, 88</td>
</tr>
<tr>
<td>4</td>
<td>R = Ph</td>
<td>94b, 87, 95b, ND, 96b, ND</td>
</tr>
<tr>
<td>5</td>
<td>R = H</td>
<td>94c, ND, 95c, ND, 96c, ND</td>
</tr>
<tr>
<td>6</td>
<td>R = Me</td>
<td>94d, ND, 95d, ND, 96d,75</td>
</tr>
</tbody>
</table>

²Reticulated vitreous carbon anode, platinum wire cathode, MeOH, 0.1 M Et₄NTOs, 0.5 equiv of LiOMe, 6 mA, 2.0−2.2 F/mol, room temperature. ³Not detected. ⁴A 6-V lantern battery was used as the power source. ²²,6-Lutidine (6 equiv) was used as base.

Table 1. Determination of suitable amides for anionic cyclisations.

Oxidation of N-phenylamide afforded the desired lactam 94b in 87% yield (Table 1, entry 4) under the same conditions used for the entry 1. Cyclisation using other substituents on amidyl nitrogen was not fruitful. In addition, with the unsubstituted amide as the substrate, a complex mixture of by-products was obtained (Table 1, entry 5). Oxidation of N-methylamide gave iminolactone 96d in 75% yield (entry 6). The authors discovered the need for amide deprotonation during electrolysis. When lithium methoxide was exchanged for 2,6-Lutidine, to give less basic conditions, the electrolysis did not proceed to the desired lactam 94a. Instead, iminolactone 96a was isolated in 88% yield (Table 1, entry 3). During the electrolysis, the acid was produced at the anode. Because of the reduction of the solvent MeOH, an equal amount of base (methoxide) was produced at the cathode, this allowed the reaction to remain at the initial basic pH set by the excess LiOMe.

The authors also explored the diastereoselectivity and ring size limitations by placing a methyl group in the chain linking the amide and the electron-rich olefin (Table 2). O-benzyl hydroxamate was cyclised to form six-membered ring products (entries 1 and 2). The seven-membered ring
product was not observed (entry 3, 98c, 99c). However, the N-alkoxyamidyl radical provided a hydrazide derivative, which under decomposition, led to N₂, methyl ester, benzyl alcohol and 100c. N-phenylamide oxidation provided a complex mixture of by-products (Entry 4).

![Chemical structures](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product, Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>97a, n = 1, R¹ = OBn, R² = Me</td>
<td>98a, 78 99a, 8 100a, ND</td>
</tr>
<tr>
<td>2</td>
<td>97b, n = 2, R¹ = OBn, R² = H</td>
<td>98b, 73 99b, 10 100b, ND</td>
</tr>
<tr>
<td>3</td>
<td>97c, n = 3, R¹ = OBn, R² = H</td>
<td>98c, ND 99c, ND 100c, 74</td>
</tr>
<tr>
<td>4</td>
<td>97d, n = 2, R¹ = Ph, R² = H</td>
<td>96d, ND 99d, ND 100d, ND</td>
</tr>
</tbody>
</table>

*Reticulated vitreous carbon anode, platinum wire cathode, MeOH, 0.1 M Et₄NTOs, 0.5 equiv of LiOMe, 6 mA, 2.0–2.2 F/mol.*

Table 2. Exploration of ring size and diastereoselectivity limitations.

With DFT calculations (UB3LYP / 6-31G (d, p)) the authors studied the reactivity of the double bonds to form the respective five- and six-membered rings, corroborating with the results obtained experimentally.

### 2.5 Flow reactors in electrochemistry

Despite the advantages of organic electrochemistry shown thus far, there are some limitations in batch reactions processes. One of the main characteristics present in the electrolytic solutions is its greater or lesser capacity of conduction of the electric current. The factor that is directly related to this is the conductivity of the solvents. Common organic solvents generally have low conductivity, requiring the use of organic salts that will act as electrolytes, however these salts can lead to unwanted products. Additionally, the large distance between the electrodes results in large current gradients. However, flow reactors incorporating electrochemistry can solve this problem due to the small distance between the electrodes, which allows the formation of the products in low conductivity solvents, or without the use of support electrolytes. Recentely, Wirth and co-workers developed a flow microreactor for reactions in electrochemistry, composed of two aluminum bodies (75x75x25 mm) with a square space in the centre (50x50 mm²), within which the electrode sheet is allocated, and can be easily suitable for any type of electrode, such as graphite, platinum, nickel, etc. Between the electrode sheets is a thin film spacer of fluorinated ethylene

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propylene (FEP), providing a path for solution flow. The authors also proposed the construction of this flow system using the Additive Manufacturing (AM) 3D printer, to obtaining the bodies of the microreactor (Figure 3).

![Figure 3: Electrochemical flow microreactor. a) Aluminum reactor. b) Additive Manufacturing (AM) 3D printer reactor. c) Schematic diagram. d) Spacer with flow channel. Reproduced with permission from ref 30, Wiley.]

With this electrochemical flow reactor, a new method through the formation of nitrogen-centred radicals for the synthesis of N-heterocycles was proposed, being obtained by the electrochemical oxidation and subsequent addition to olefins in an intramolecular cyclisation reaction (Scheme 38). Several reaction conditions were evaluated, such as different electrode species, flow, current, and concentrations of solvents, substrates and bases.

![Scheme 38: Synthesis of isoindolinone.](image)

In order to stabilise the radical nitrogen, aromatic derivatives are required in the amide nitrogen (102d - Scheme 39). However, it was observed that the substituents on the alkene portion may be varied widely. With electron withdrawing substituents attached to N-aryl, such as chloride, a low yield was observed (102b, 56%). In addition, with the same substituent attached to the ring adjacent to the double bond, a mixture of products was observed (102l and 102m) with formation of the expected product 102l in only 56% yield. Interestingly, with a strongly electron withdrawing group attached to the adjacent ring double portion, such as 3-nitro, there was a single product in high yield (102n, 94% - 102o, 91%). Activating groups in this portion were not fruitful for transformation (102g, 62% - 102h, 21% - 102l, 18%).
In order to extend the reaction scope, the respective carbamates were cyclised in electrochemical flow and then, by eliminating the TEMPO portion under flow heating in a single flow system, the products (103a–f, Scheme 40) were obtained in good yields. A residence time of 25 minutes at 85 °C / 2.8 bar were required for complete conversion of starting material into products.

Scheme 39: Representative examples for the synthesis of isoindolinone.

In 1991, Kenji Uneyama[31] reported an electrooxidation of trifluoroacetic acid in the presence of olefins, affording trifluoromethyl compounds. Additionally, Wirth and co-workers[32] have also developed a rapid and efficient way in which to allow the addition of CHF₂ and CF₃ radicals to various electron-deficient alkenes, however via an electrochemical microreactor. The electrochemical microreactor developed by the group has a thin film flow channel of fluorinated ethylene propylene (FEP) embedded between two platinum sheets (Figure 4).

Figure 4: Electrochemical microreactor developed by the Wirth group. Reproduced with permission from ref. 32, Wiley.

The electrolysis was performed in the microreactor with a water/ acetonitrile solution containing acrylates derivatives, trifluoroacetic acid and triethylamine in constant current at room temperature (Table 3).

\[
\text{Entry} & \quad \text{Acid} & \quad \text{Alkene} & \quad \text{Product} & \quad \text{DL:meso}^a & \quad \text{Yield (%)} \\
1 & 105a & 104a, R^1 = H, R^2 = Me & 106a & 5:3 & 52 \\
2 & 105b & 104a, R^1 = H, R^2 = Me & 106b & 1:1 & 38 \\
3 & 105a & 104b, R^1 = H, R^2 = Et & 106c & 1:1 & 45 \\
4 & 105b & 104b, R^1 = H, R^2 = Et & 106d & 1:1 & 40 \\
5 & 105a & 104c, R^1 = H, R^2 = tBu & 106e & 1:1 & 45 \\
6 & 105b & 104c, R^1 = H, R^2 = tBu & 106f & 1:1 & 40 \\
7 & 105a & 104d, R^1 = Me, R^2 = Me & 106g & 10:1 & 11 \\
8 & 105b & 104d, R^1 = Me, R^2 = Me & 106h & 6:5 & 16 \\
\]

* Determined by $^{13}$C NMR spectroscopy.

**Table 3.** Di and trifluoromethylation of acrylates.

The dimer 106a was obtained in 52% yield (entry 1). Similarly, electrolysis of trifluoroacetic acid 105a in the presence of 104b, 104c and 104d afforded the 106c, 106e and 106g derivatives as a mixture of isomers in 45, 45 and 11% yield (entries 3, 5, 7), respectively. The 104a – d were subjected to the electrolysis using difluoroacetic acid 105b. As a result, the similar difluoromethylated dimers 106b, 106d, 106f and 106h derivatives were obtained as a mixture of isomers in 38, 40, 40 and 16% yield (entries 2, 4, 6, 8), respectively.

The addition of the radical 105 to alkenes 104 is followed by dimerization of the radical intermediates 107 to afford products 106 in 69 seconds (**Scheme 41**).

**Scheme 41:** Proposed mechanism for the dimerization.
3. CONCLUSIONS

In summary, electrochemistry allows reactions that would otherwise require harsh environments, such as dangerous chemicals and expensive catalysts, to be conducted under relatively mild conditions while still affording desired products in high chemoselectivity, making electrosynthesis one of the most sustainable approaches in modern organic chemistry. Herein, we have manifested that selective vicinal oxidative electrochemical alkene difunctionalization is a powerful and versatile chemical pathway that can readily build complex molecules without the use of external chemical oxidants, providing products in high yield, such as the use of alkenes for azidiodination, aziridination, oxysulfonylation, aminosulfonylation, dicarboxylation, generation of amidy radical for oxidative aminations and aminoxydations as well as the use of electrochemical flow microreactors. Despite this the electrochemical alkene functionalization has been addressed in key chemical transformations.[33] However, the recent developments in alkene difunctionalization explained in this review, not only mediate to design new green synthetic pathways using electrochemistry, will also facilitate the use of reactor technology for an easy and facile functionalization of alkenes.

4. ACKNOWLEDGEMENTS

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