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.[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

[1] E. H. Horn, B. R. Rosen, P. S. Baran, *ACS Cent. Sci.* **2016**, *2*, 302 – 308.

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**).[2] However, the incorporation of two distinct chemical bonds into alkenes via a single step construct is a difficult

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

transformation. To perform these chemical transformation, transition metal catalysis,[2b,c] hypervalent iodine reagents[2d] or photocatalysis[2e] 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.
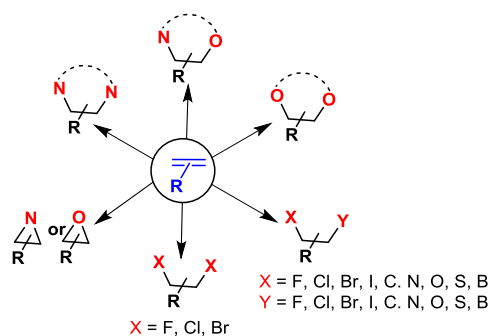

Figure 1: Difunctionalization of alkenes.

   The Lin group has reported some very interesting works on the electrochemical difunctionalization of alkenes.[2b,c,f-h] 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

[2] a) X. Zeng, *Chem. Rev.* **2013**, *113*, 6864 − 6900; b) N. Fu, G. S. Sauer, A. Saha, A. Loo, S. Lin, *Science* **2017**, *357*, 575 – 579; c) D. Cristina Silva Costa, *Arabian Journal of Chemistry* **2017**, doi. org/10.1016/j.arabjc.2017.07.017; d) U. Farid, T. Wirth, *Angew. Chem. Int. Ed.* **2012**, *51*, 3462 – 3465; *Angew. Chem.* **2012**, *124*, 3518 – 3522; e) A. Tlahuext-Aca, A. G. Garza-Sanchez, F. Glorius, *Angew. Chem. Int. Ed.* **2017**, *56*, 3708 – 3711; *Angew. Chem.* **2017**, *129*, 3762 – 3765; f) N. Fu, G. S. Sauer, S. Lin, *J. Am. Chem. Soc.* **2017**, 139, 15548–15553; g) B. M. Peterson, S. Lin, B. P. Fors, *J. Am. Chem. Soc.* **2018**, *140*, 2076 – 2079; h) K.-Y. Ye, G. Pombar, N. Fu, G. S. Sauer, I. Keresztes, S. Lin, *J. Am. Chem. Soc.* **2018**, *140*, 2438 – 2441.

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 thier 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 azidoiodination 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 azidoiodination of alkenes through constant current with NaN_3 and NaI in methanol, to provide the Markovnikov addition products (**Scheme 2**). Here, IN_3 is electrochemically generated in situ, without oxidants or the corrosive molecular iodine, and is performed by constant current electrolysis at 15 mA/cm^2 in a type H cell using graphite plates as both cathode and anode electrodes.

2a, R^1 = *p*-Me-Ph, R^2 = H, R^3 = H; 65%
2b, R^1 = Ph, R^2 = H, R^3 = H; 55%
2c, R^1 = *p*-F-Ph, R^2 = H, R^3 = H; 20%
2d, R^1 = *p*-Cl-Ph, R^2 = H, R^3 = H; 70%
2e, R^1 = Ph, R^2 = Me, R^3 = H; 44%
2f, R^1 = Ph, R^2 = H, R^3 = Me; 40%; dr: 1:1
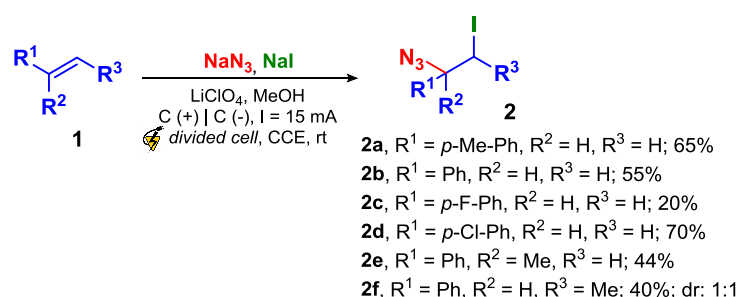
Scheme 2. Regioselective azidoiodination of alkenes.

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.
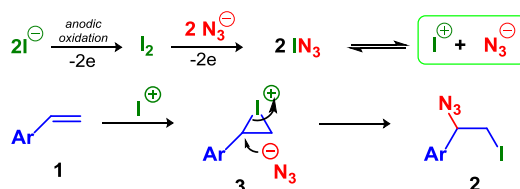
Scheme 3: Mechanism for the azidoiodination of alkenes.

[3] A.Hassner, F. W. Fowler, *J. Org. Chem.* **1968**, *33,* 2686 – 2691.
[4] S. A.Cramer, D. M. Jenkins, *J. Am. Chem. Soc.* **2011**, *133*, 19342 – 19345.
[5] H.Yoneyama, Y.Usami, S. Komeda and S. Harusawa, *Synthesis.* **2013**, *45,* 1051 – 1059.
[6] W.-q. Yan, M.-y. Lin, R. D. Little and C-C. Zeng, *Tetrahedron.* **2017**, *73*, 764 – 770.

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_4NI. In addition, Cheng and co-workers[10] proposed the first electrochemical aziridination of multisubstituted styrenes using a sulfamate as the nitrogen source (**Scheme 4**).
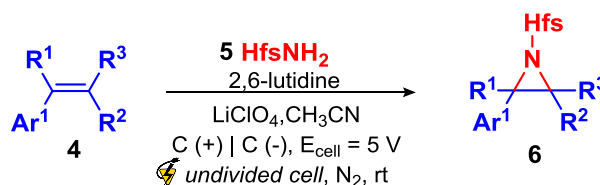
Scheme 4: Electrochemical aziridination of multisubstituted styrenes.

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_3PO_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**).

[7] a) R. S. Atkinson, B. D. Judkins, *J. Chem. Soc. Perkin Trans. 1.* **1981**, 2615 – 2619; b) N. S. Dolan, R. J. Scamp, T. Yang, J. F. Berry, J. M. Schomaker, *J. Am. Chem. Soc.* **2016**, *138*, 14658 - 14667.
[8] T. Siu and A. K. Yudin, *J. Am. Chem. Soc.* **2002**, *124*, 530 – 531.
[9] J. Chen, W.-Q. Yan, C. M. Lam, C.-C. Zeng, L.-M. Hu, R. D. Little, *Org. Lett.* **2015**, *17*, 986 – 989.
[10] J. Li, W. Huang, J. Chen, L. He, X. Cheng, G. Li, *Angew. Chem. Int. Ed.* **2018**, *57*, 5695 – 5698.
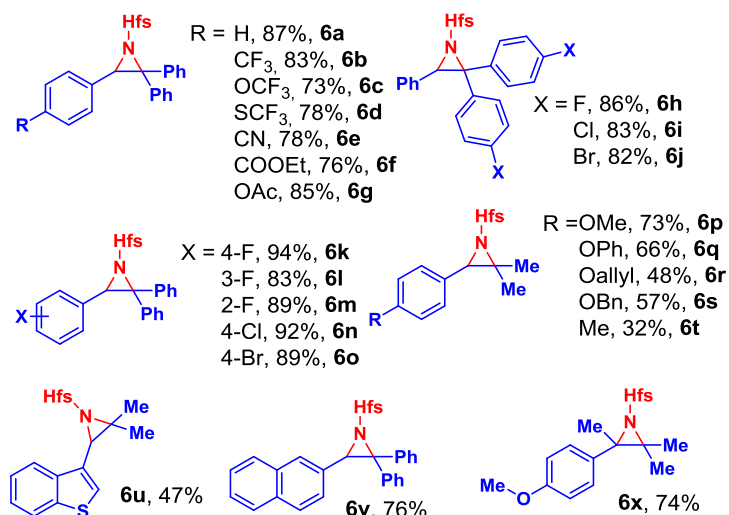
Scheme 5: Aziridination of multisubstituted styrenes.

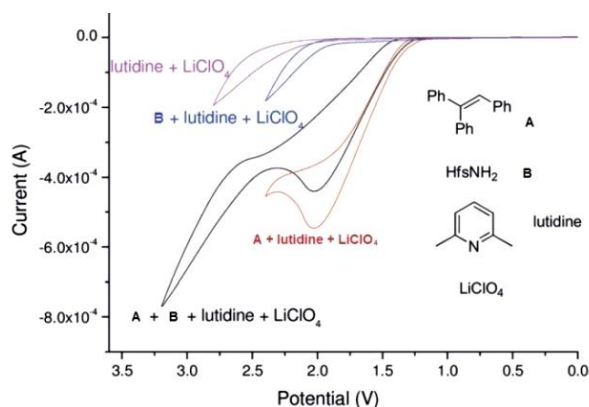Aziridines containing F, Cl, or Br atom (**6h – o**) were synthesised in excellent yields (82 – 94%) as well as the diphenyl naphthalenyl aziridine (**6v,** 76%). Several other substituents have been tested (**Scheme 5**). Cyclic voltammetry experiments have also been performed (**Scheme 6**).[10] The transfer of electrons to the anode occurred in +2.0 V, which is almost identical to the oxidation

Scheme 6: Cyclic voltammetry spectrum. Reproduced with permission from ref 10.

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[11] proposed an electrochemical oxidative alkoxysulfonylation of alkenes with alcohols and sulfonyl hydrazides. The authors examined the scope of the substrate with a wide variety of sulfonyl hydrazides, alkenes and alcohols (30 examples), and the products were obtained in yields of up to 97% (**Scheme 7**).

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[11] Y. Yuan, Y. Cao, Y. Lin, Y. Li, Z. Huang and A. Lei, *ACS Catal.* **2018**, *8*, 10871 − 10875.
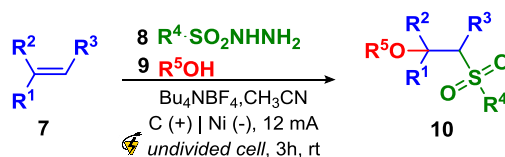
Scheme 7: Electrochemical oxidative alkoxysulfonylation of olefins.

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 *β*-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.
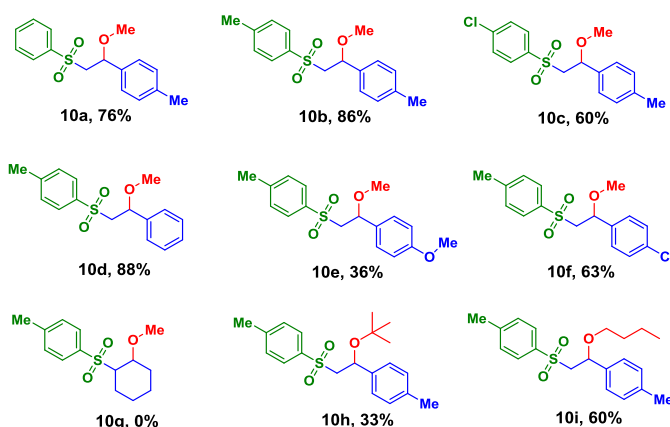
Scheme 8: Representative examples for the oxidative alkoxysulfonylation of olefins.

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**.
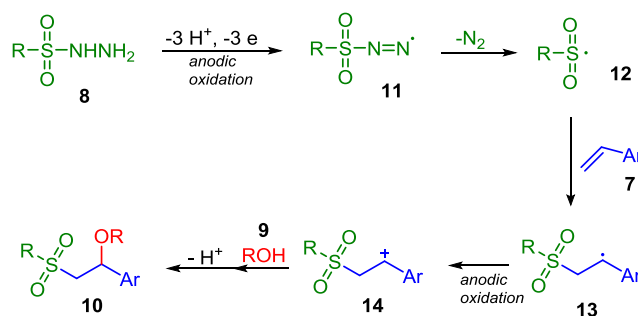
Scheme 9: Mechanism for the oxidative alkoxysulfonylation of olefins.

Xu and co-workers[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 (**Scheme 10**).
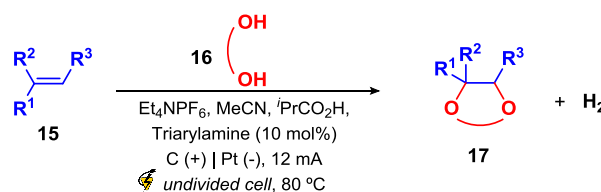
Scheme 10: Electrochemical dehydrogenative annulation of alkenes using diols.

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 (**Scheme 11**).
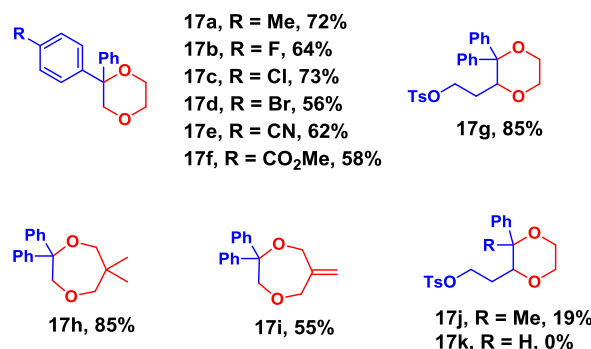
Scheme 11: Representative examples for the synthesis of O-heterocycles.

A mechanism has been proposed (**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

12 C. –Y. Cai, H. –C. Xu, *Nature Commun.* **2018**, *9*, 3551 – 3558.

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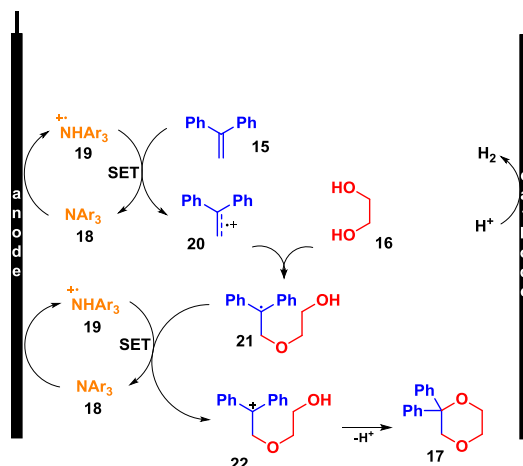
Scheme 12: Mechanism proposal for the synthesis of satured O-heterocycles.

Additionally, Lei and co-workers[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**).
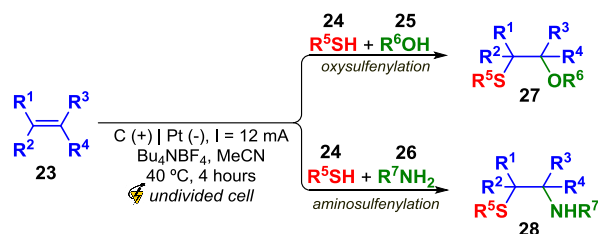
Scheme 13: Oxysulfenylation and aminosulfenylation of alkenes.

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

[13] Y. Yuan, Y. Chen, S. Tang, Z. Huang, A. Lei, *Sci. Adv.* **2018**, *4*, eaat5312.

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, heteroarylamines 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.

27a, R[1] = H, 75%
27b, R[1] = Me, 80%
27c, R[1] = ^{t}Bu, 88%
27d, R[1] = OMe, 77%
27e, R[1] = F, 78%
27f, R[1] = Cl, 77%
27g, R[1] = Br, 62%

27h, 95%

27i, 50%

27j, 55%

27k, 71%, dr: >20:1

27l, 22%, dr: >20:1

27m, 76%

27n, R[2] = Cl, 46%
27o, R[2] = OH, 63%

27p, 37%

27q, 39%

27r, 42%

28a, 61%

28b, 61%

28c, 56%

28d, 52%
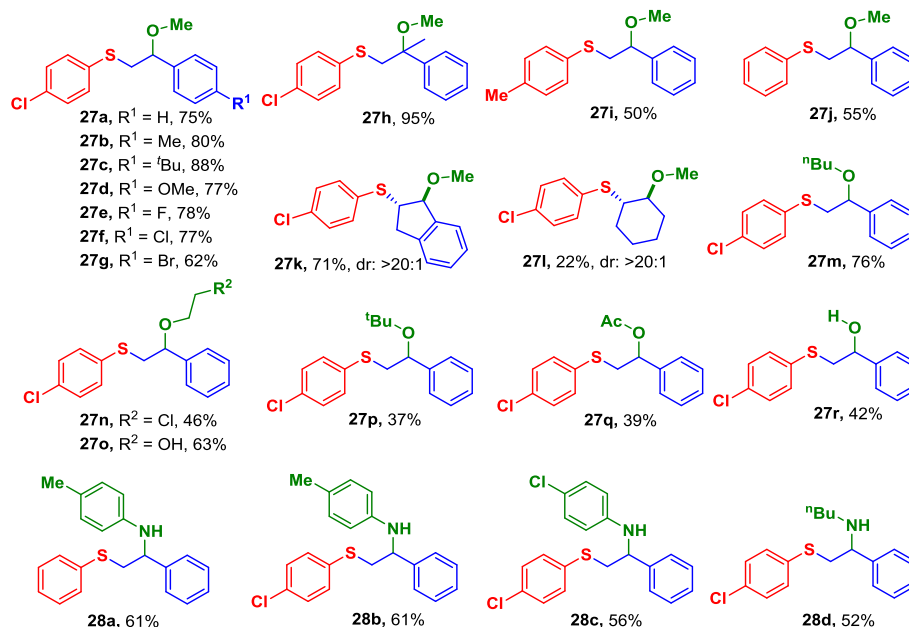
Scheme 14: Oxysulfenylation and aminosulfenylation of alkenes.

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.
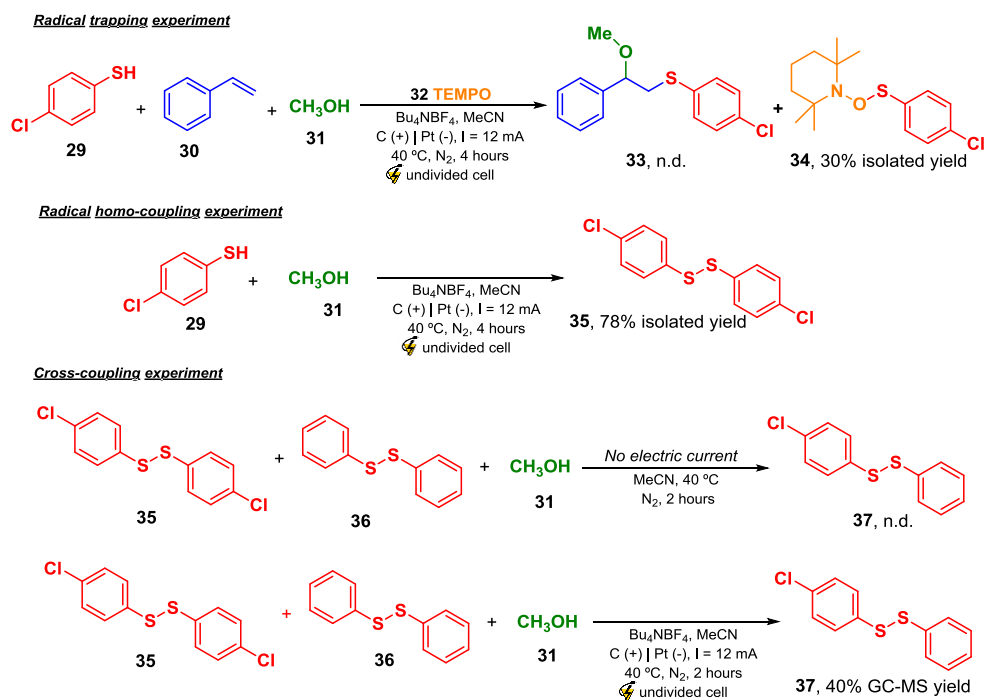
Scheme 15: Mechanistic studies.

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**).
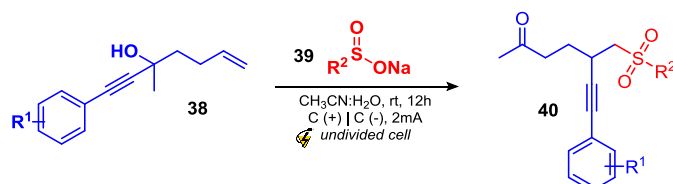
40a, R^1 = Ph, R^2 = Tol; 78%   **40f**, R^1 = Ph, R^2 = Ph; 85%
40b, R^1 = 4-Me-Ph, R^2 = Tol; 84%   **40g**, R^1 = Ph, R^2 = 3-Me-Ph; 63%
40c, R^1 = 3-Me-Ph, R^2 = Tol; 76%   **40h**, R^1 = Ph, R^2 = 4-NO$_2$-Ph; trace
40d, R^1 = 4-CN-Ph, R^2 = Tol; 68%   **40i**, R^1 = Ph, R^2 = 4-Cl-Ph; 75%
40e, R^1 = 4-Cl-Ph, R^2 = Tol; 77%   **40j**, R^1 = Ph, R^2 = Me; 92%

Scheme 16: Synthesis of α-sulfonyl-β-alkynylation products via radical 1,4-alkynyl migration of alkynyl-substituted tertiary alcohols.

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).

[14] Y. Gao, H. Mei, J. Han, Y. Pan, *Chem. Eur. J.* **2018**, doi 10.1002/chem.201804157.

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 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**).
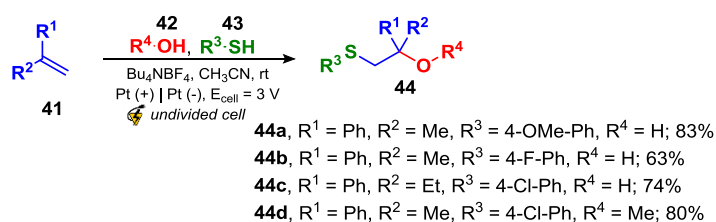
Scheme 17: Electrochemical oxysulfuration of alkenes.

An electrochemical oxidative oxysulfuration approach for the synthesis of thio-substituted γ-lactone derivatives was set. Several electrolytes were evaluated, including NaCl, Bu$_4$NBr and Bu$_4$NBF$_4$. However, it was found that Bu$_4$NBF$_4$ 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%).
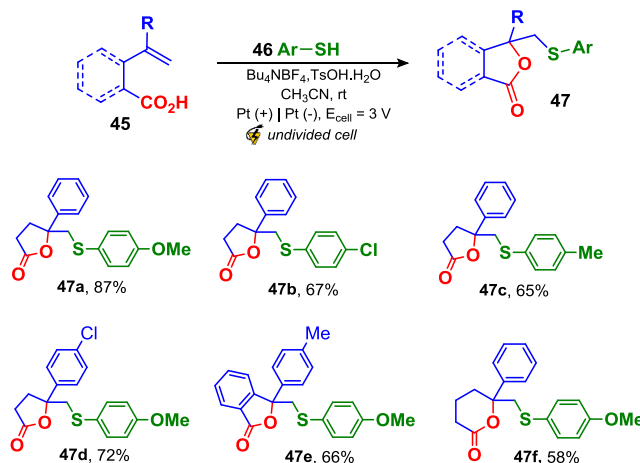
Scheme 18: Representative examples for the olefin oxysulfurations.

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

[15] Y. Wang, L. Deng, H. Mei, B. Du, J. Han, Y. Pan, *Green Chem.* **2018**, *20*, 3444 – 3449.
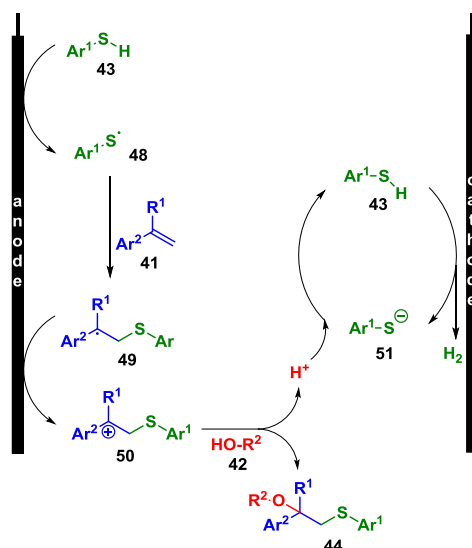
Scheme 19: Mechanism for the electrochemical oxidative radical reaction.

The reaction begins with the aromatic thiyl radical **48** formation from thiophenol **43** through a single-electron transfer (SET) oxidation at the anode. In addition, this aromatic thiyl 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. Cocurrently, 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**).

54a, R^1 = H, R^2 = H, R^3 = H; 66%; E_{red}: -2.91 V
54b, R^1 = Me, R^2 = H, R^3 = H; 68%; E_{red}: <-3.0 V
54c, R^1 = Ph, R^2 = H, R^3 = H; 91%; E_{red}: -2.58 V
54d, R^1 = H, R^2 = H, R^3 = Ph; 84%; E_{red}: -2.50 V
54e, R^1 = H, R^2 = Ph, R^3 = H; 84%; E_{red}: -2.44 V
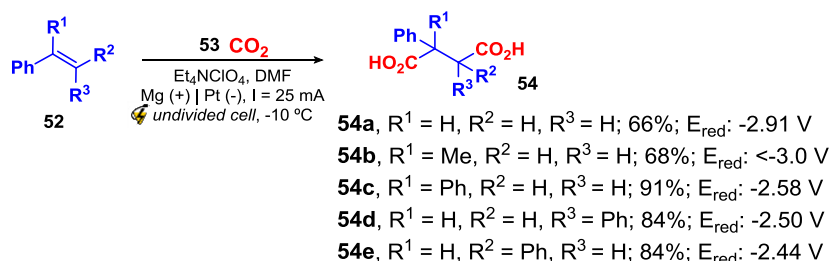
Scheme 20: Electrochemical dicarboxylation of olefins.

[16] R. Matthessen, J. Fransaer, K. Binnemans, D. E. De Vos, *Beilstein J. Org. Chem.* **2014**, *10*, 2484 – 2500.
[17] H. Senboku, H. Komatsu, Y. Fujimura, M. Tokuda, *Synlett.* **2001**, 418 – 420.

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_2 reduction potential (-2.53 V vs. Ag/Ag$^+$), the authors propose two possible mechanistic pathways (**Scheme 21**).
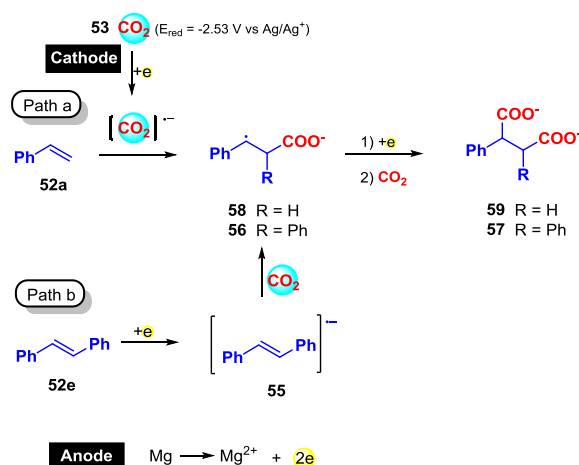
Scheme 21: Mechanism for the electrochemical dicarboxylation.

Path a: The alkenes generated from **52a** all have a more negative reduction potential than CO_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_2 to alkene **52a** result in **58** intermediate. The reduction of one electron followed by the reaction with CO_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_2 (-2.44 to -2.58 V), a direct or CO_2-mediated one-electron reduction from this **52e** occurs to generate its anionic radicals **55**. This reaction with CO_2 gives the monocarboxylate intermediate **56**. Further reduction followed by reaction with CO_2 leads to the formation of the dicarboxylate ion **57**.

In 2018, Xu and co-workers[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_2Na (0.3 equiv) as the base additive, in a mixture of the solvents *t*BuOMe/MeCN/H$_2$O (20:3:1) under reflux in a current of 7.5 mA.

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[18] Z.-J. Wu, S.-R. Li, H.-C. Xu, *Angew. Chem. Int. Ed.* **2018**, *57*, 14070 – 14074.
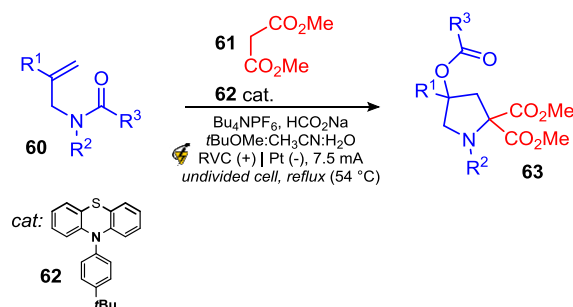
Scheme 22: Electrochemical synthesis of pyrrolidines.

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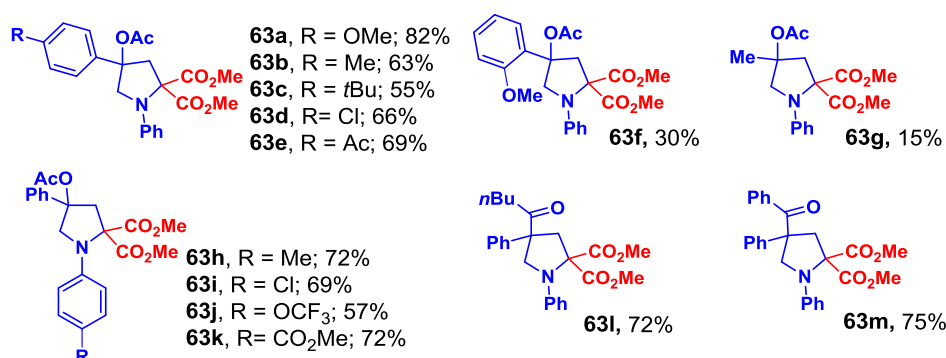
Scheme 23: Representative examples for the pyrrolidine synthesis.

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 R^1, a disadvantage was observed (**63f**, 30%). In addition, with a methyl group in place of phenyl (R^1), the product was obtained in 15% yield (**63g**). Likewise, the substituents on the phenyl ring (R^2) 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 R^2 did not provide the desired products. In addition, the R^3 group was tolerant of different steric properties (**63l - m**).
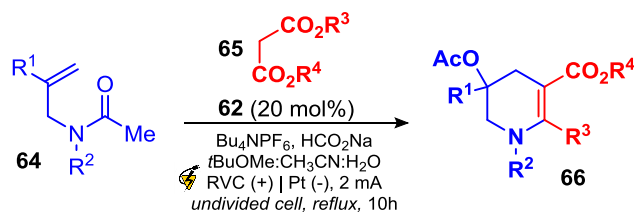
Scheme 24: Electrochemical synthesis of tetrahydropyridine.

66a, R = H; 64%
66b, R = 4-OMe; 71%
66c, R = 4-CF₃; 43%
66d, R= 4-Br; 83%
66e, R = 3,5diOMe; 55%

66f, R = OMe; 41%
66g, R = F; 72%
66h, R = Cl; 68%
66i, R= Br; 89%
66j, R = CO₂Me; 64%

66k; 53%
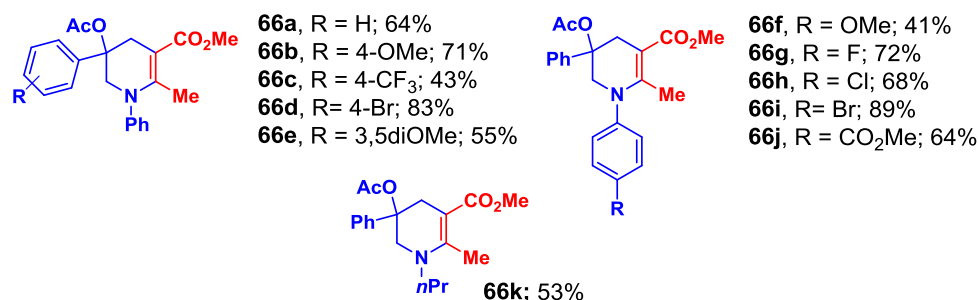
Scheme 25: Representative examples for the tetrahydropyridine synthesis.

For the synthesis of tetrahydropyridine **66** derivatives (4+2), the reactivity of the substituents present in the molecule were similar to the reactions for the synthesis of pyrrolidines **63** derivatives (4+1). However, for the tetrahydropyridine **66k**, the alkyl group present in the nitrogen (N-*n*Pr) provided the desired product in 53%. The β-ketoester **65** 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.[21] 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 Na_2CO_3 and 5 equiv 1,4-cyclohexadiene (1,4-CHD) in a Bu_4BF_4 electrolyte in THF/ MeOH (5:1), under reflux. The reaction did not occur without the supply of electricity.

[19] T. Xiong, Q. Zhang, *Chem. Soc. Rev.* **2016**, *45*, 3069 – 3087.
[20] K. C. Nicolaou, P. S. Baran, Y.–L. Zhong, S. Barluenga, K. W. Hunt, R. Kranich, J. A. Veja, *J. Am. Chem. Soc.* **2002**, *124*, 2233 – 2244.
[21] T. M. Nguyen, D. A. Nicewicz, *J. Am. Chem. Soc.* **2013**, *135,* 9588 – 9591.
[22] L. Zhu, P. Xiong, Z.-Y. Mao, Y.-H. Wang, X. Yan, X. Lu, H.-C. Xu, *Angew. Chem. Int. Ed.* **2016**, *55*, 2226 – 2229.
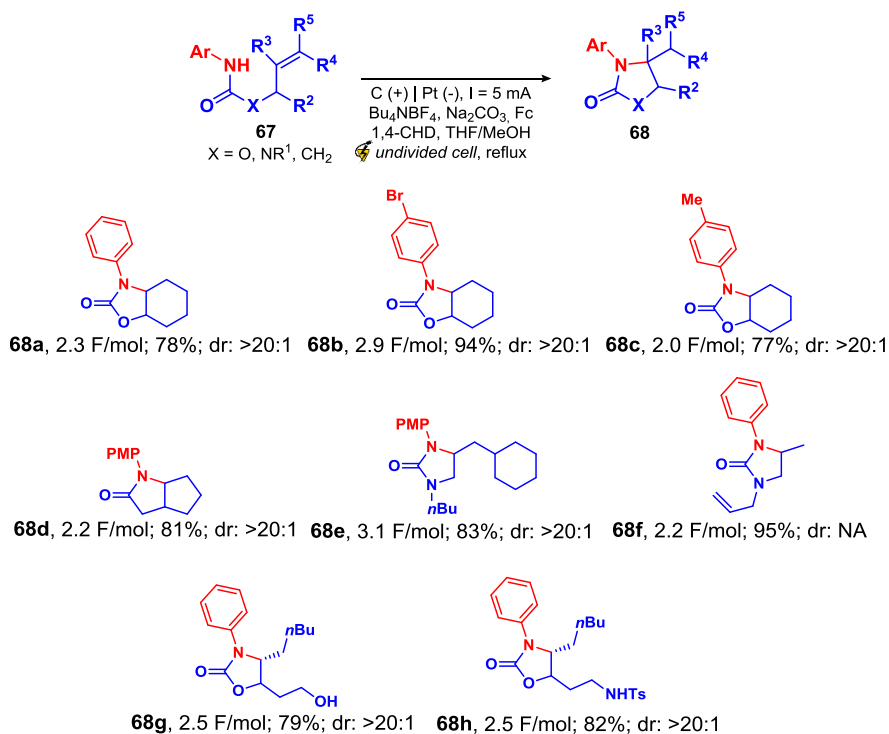
Scheme 26: Amidyl radicals for the intramolecular hydrolysis of olefins.

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 to oxidation sensitive groups such as sulfonamides, free alcohols or N-aryl carbamates (**Scheme 26**).
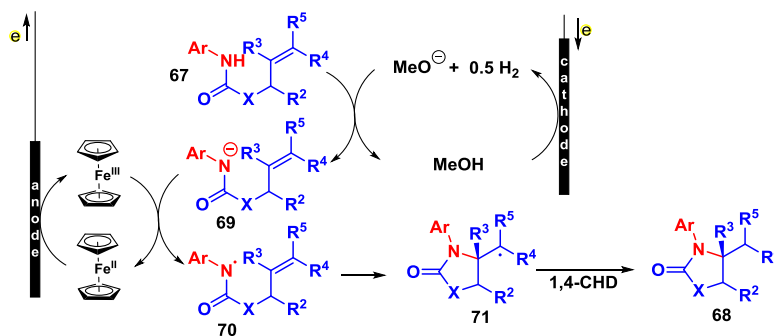
Scheme 27: Mechanism for the ferrocene-mediated redox cycle.

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 Fc^{II} to Fc^{III} and cathodic reduction of MeOH to H$_2$ and MeO$^-$, which acts as a base, providing **69**. Instead of being reduced at the cathode, the ferric catalyst Fc^{III} quickly oxidises **69** simply by electron transfer to provide the intermediate amidyl radical **70**, and regenerating Fc^{II}. The final

[23] F. Xu, L. Zhu, S. Zhu, X. Yan, H.-C. Xu, *Chem. Eur. J.* **2014**, *20*, 12740 – 12744.

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[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 K$_2$CO$_3$ (1 equiv) afforded the best results (**Scheme 29**).

73a, R = OMe; 70%; dr: >20:1
73b, R = Cl; 78%; dr: >13:1
73c, R = CN; 77%; dr: >13:1

73d, 85%; dr: 6:1

73e, 86%
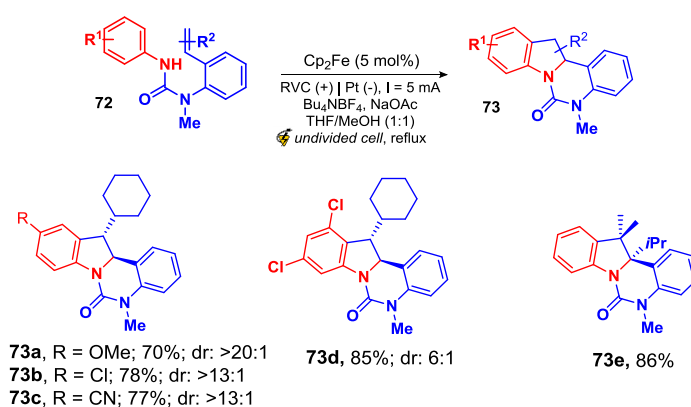
Scheme 28: Synthesis of indolines.

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**).

[24] Z. -W. Hou, H. Yan, J. Song, H.-C. Xu, *Chin. J. Chem,* **2018**, *36*, 909 – 915.
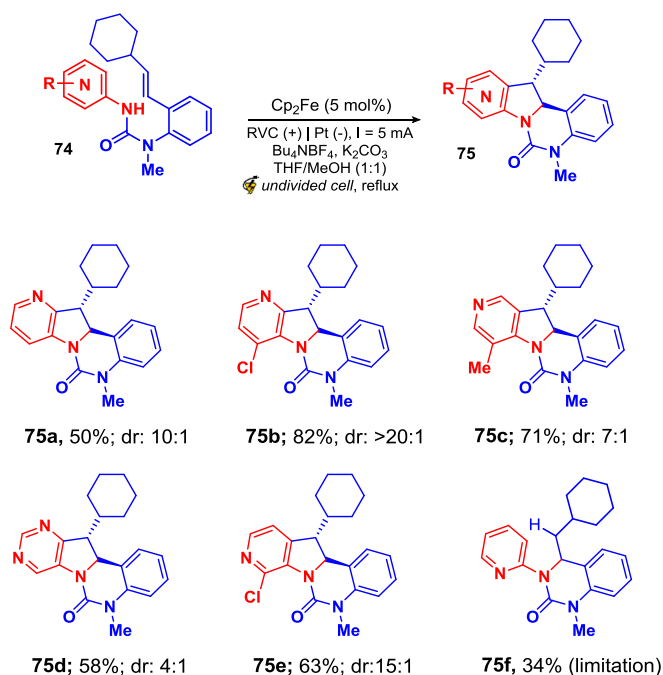
Scheme 29: Synthesis of azaindolines.

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 Et_4NPF_6 in dimethylacetamide (DMA) and acetic acid (40:1).

[25] P. Xiong, H.-H. Xu, H.-C. Xu, *J. Am. Chem. Soc.* **2017**, *139*, 2956 – 2559.
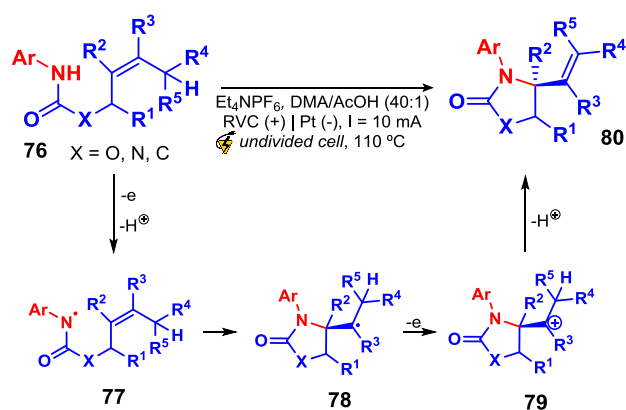
Scheme 30: Amination reaction of tri- and tetrasubstituted alkenes.

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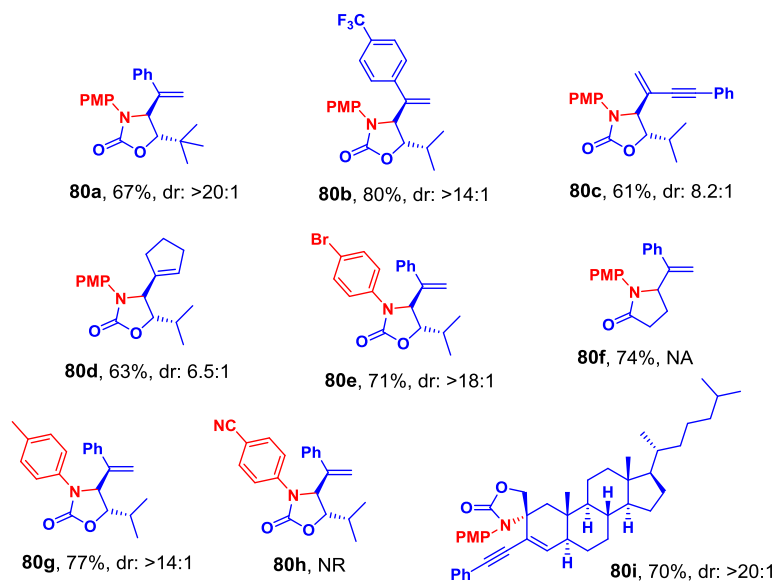
Scheme 31: Representative examples of the intramolecular oxidative amination of alkenes.

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[26] conducted an electrochemical approach for the intramolecular aminoxygenation of non-activated alkenes. The difunctionalization of olefins with readily available amides, carbamates and TEMPO as a trapping group afforded aminoxygenation 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**).

Scheme 32: Electrochemical aminooxygenation of alkenes.

The reaction was performed at 60 ^{0}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$_3$.

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 aminoxygenation 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

[26] F. Xu, L. Zhu, S. Zhu, X. Yan, H.-C. Xu, *Chem. Eur. J.* **2014**, *20*, 12740 – 12744.

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

84a, R = 4-Me-Ph, 97%, 3.0 Fmol^{-1}, d.r. >20:1
84b, R = 4-OMe-Ph, 94%, 2.2 Fmol^{-1}, d.r. >20:1
84c, R = 4-F-Ph, 88%, 2.1 Fmol^{-1}, d.r. >20:1
84d, R = 4-CF$_3$-Ph, 83%, 1.4 Fmol^{-1}, d.r. >20:1
84e, R = 4-Ac-Ph, 86%, 1.5 Fmol^{-1}, d.r. >20:1
84f, R = 4-CN-Ph, 87%, 2.0 Fmol^{-1}, d.r. >20:1
84g, R = 2,6-Me$_2$-Ph, 85%, 2.5 Fmol^{-1}, d.r. >20:1
84h, R = 4-NO$_2$-Ph, 51%, 4.1 Fmol^{-1}, d.r. >20:1

84i, 81%, 3.4 Fmol^{-1}, d.r. >20:1

84j, R = Ph, 95%, 2.5 Fmol^{-1}, d.r. >20:1
84k, R = 4-OMe-Ph, 90%, 1.4 Fmol^{-1}, d.r. >20:1

84l, 81%, 3.4 Fmol^{-1}, d.r. >20:1

84m, R = H, 90%, 2.3 Fmol^{-1}
84n, R = Bn, 86%, 2.8 Fmol^{-1}, d.r. >20:1

84o, R = H, 86%, 1.4 Fmol^{-1}, d.r. >20:1
84p, R = Me, 81%, 3.0 Fmol^{-1}, d.r. >4:1

84q, R^1 = nPr, R^2 = H, 89%, 4.2 Fmol^{-1}, d.r. >1.4:1
84r, R^1 = H, R^2 = Et, 97%, 1.4 Fmol^{-1}, d.r. >1.4:1

Scheme 33: Substituents from the aminooxygenation of alkenes.

Very recently, Ahmed and Khatoon[27] developed an efficient and economical electrochemical system for the diffunctionalization 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 Bu$_4$NBF$_4$ in CH$_3$CN/H$_2$O (19:1 v/v) as support electrolyte, 1.1 equivalents of Na$_2$CO$_3$ and 1.5 equivalents of TEMPO was used (**Scheme 34**).
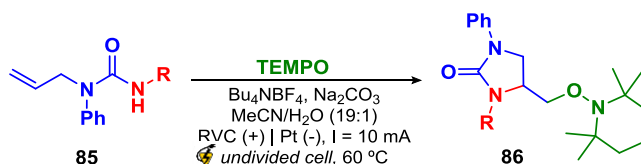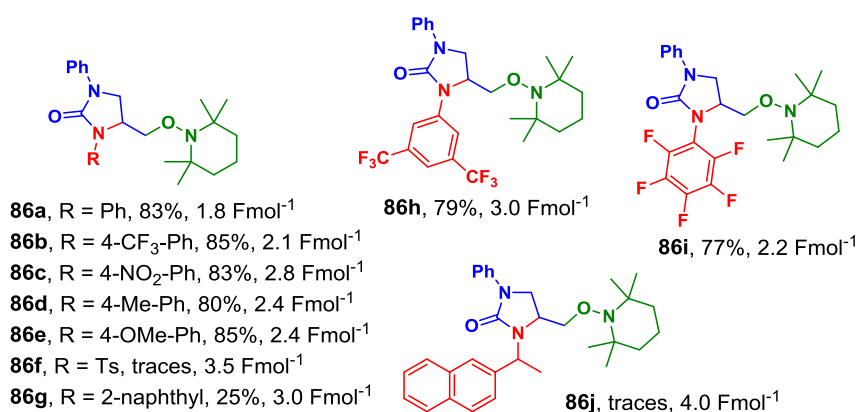

Scheme 34: Intramolecular electrochemical amination of olefins.

Several substituents were evaluated (**Scheme 35**), including Me (**86d**, 80%), MeO (**86e**, 85%), CF$_3$ (**86b**, 85% - **86h**, 79%), NO$_2$ (**86c**, 83%) and fluoro groups (**86i**, 77%), all of which proceeded

[27] N. Ahmed, S. Khatoon, *ChemistryOpen*. **2018**, *7*, 576 – 582.

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.

86a, R = Ph, 83%, 1.8 Fmol^{-1}
86b, R = 4-CF$_3$-Ph, 85%, 2.1 Fmol^{-1}
86c, R = 4-NO$_2$-Ph, 83%, 2.8 Fmol^{-1}
86d, R = 4-Me-Ph, 80%, 2.4 Fmol^{-1}
86e, R = 4-OMe-Ph, 85%, 2.4 Fmol^{-1}
86f, R = Ts, traces, 3.5 Fmol^{-1}
86g, R = 2-naphthyl, 25%, 3.0 Fmol^{-1}

86h, 79%, 3.0 Fmol^{-1}

86i, 77%, 2.2 Fmol^{-1}

86j, traces, 4.0 Fmol^{-1}

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 (H$_2$O) to the hydroxide ($^{-}$OH) and H$_2$, 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**.
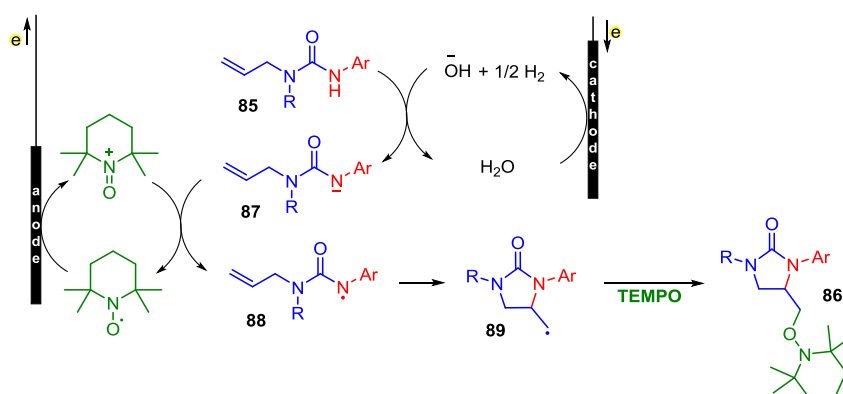

Scheme 36: Proposed mechanism for the difunctionalization of amine-tethered alkenes.

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-workers[28] 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

[28] H-C. Xu, J. M. Campbell, K. D. Moeller, *J. Org. Chem.* **2014**, *79*, 379 – 391.

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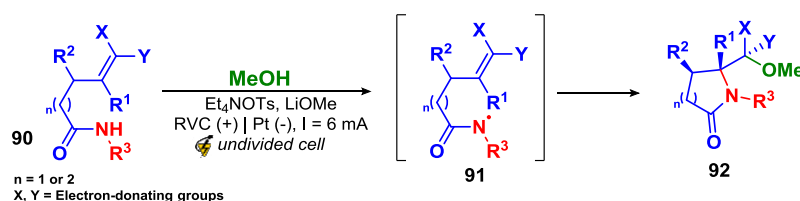
Scheme 37: Anodic intramolecular coupling of *O*-benzyl hydroxamates and *N*-phenyl amides.

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

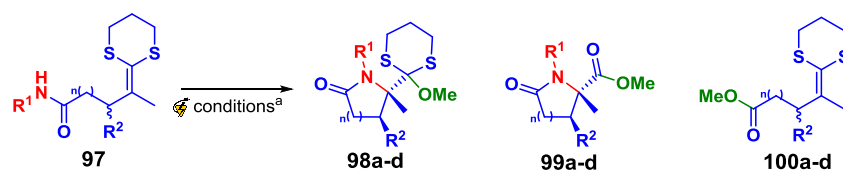| Entry	Substrate	Product, Yield (%)		
1	R = OBn	**94a**, 80	**95a**, 8	**96a**, ND[b]
2[c]	R = OBn	**94a**, 81	**95a**, 3	**96a**, ND
3[d]	R = OBn	**94a**, ND	**95a**, ND	**96a**, 88
4	R = Ph	**94b**, 87	**95b**, ND	**96b**, ND
5	R = H	**94c**, ND	**95c**, ND	**96c**, ND
6	R = Me	**94d**, ND	**95d**, ND	**96d**,75

[a]Reticulated vitreous carbon anode, platinum wire cathode, MeOH, 0.1 M Et$_4$NOTs, 0.5 equiv of LiOMe, 6 mA, 2.0−2.2 F/mol, room temperature. [b]Not detected. [c]A 6-V lantern battery was used as the power source. [d]2,6-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 N_2, methyl ester, benzyl alcohol and **100c**. *N*-phenylamide oxidation provided a complex mixture of by-products (Entry 4).

Entry	Substrate	Product, Yield (%)		
1	**97a**, $n = 1$, $R^1 = OBn$, $R^2 = Me$	**98a**, 78	**99a**, 8	**100a**, ND
2	**97b**, $n = 2$, $R^1 = OBn$, $R^2 = H$	**98b**, 73	**99b**, 10	**100b**, ND
3	**97c**, $n = 3$, $R^1 = OBn$, $R^2 = H$	**98c**, ND	**99c**, ND	**100c**, 74
4	**97d**, $n = 2$, $R^1 = Ph$, $R^2 = H$	**98d**, ND	**99d**, ND	**100d**, ND

[a]Reticulated vitreous carbon anode, platinum wire cathode, MeOH, 0.1 M Et$_4$NOTs, 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.[29] Recently, Wirth and co-workers[30] developed a flow microreator for reactions in electrochemistry, composed of two aluminum bodies (75x75x25 mm) with a square space in the centre (50x50 mm^2), 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

[29] a) J. Yoshida, *Electrochem. Soc. Interface.* **2009**, 40 – 45; b) J. Kuleshova, T. Cousins-Hill, P. R. Birkin, R. C. D. Brown, D. Pletcher, T. J. Underwood, *Electrochim. Acta* **2011**, *56*, 4322 – 4326; c) C. Gütz, A. Stenglein, S. R. Waldvogel, *Org. Process. Res. Dev.* **2017**, *21*, 771 – 778; d) T. Hardwick, N. Ahmed, *RSC Adv.* **2018**, 8, 22233 – 22249.
[30] A. A. Folgueiras-Amador, K. Philipps, S. Guilbaud, J. Poelakker, T. Wirth, *Angew. Chem. Int. Ed.* **2017**, *56*, 15446 – 15450.

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**).
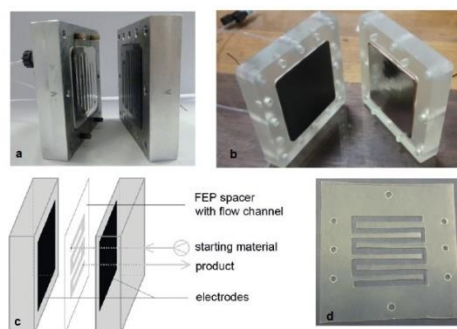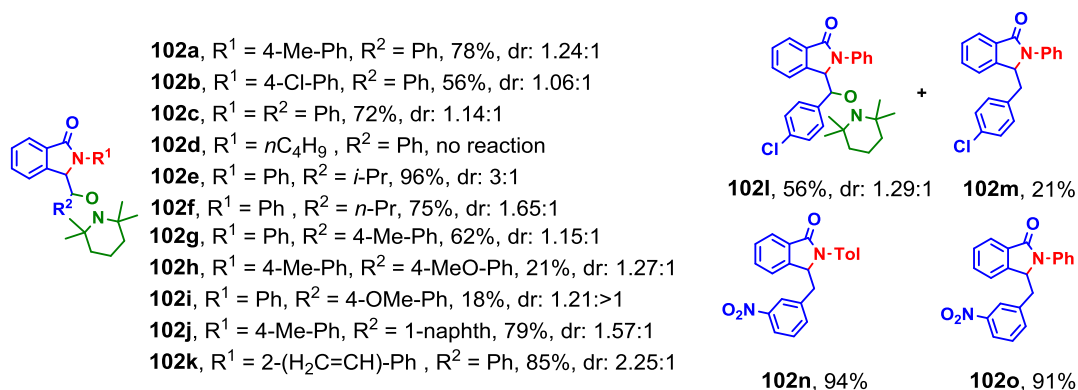

Figure 3: Electrochemical flow microreactor. a) Aluminum reactor. b) Additive Manufacturing (AM) 3D printer reactor. c) Schematic diagram. d) Spacer with flow channel. Reproduced with permission from ref 30, Wiley.

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.
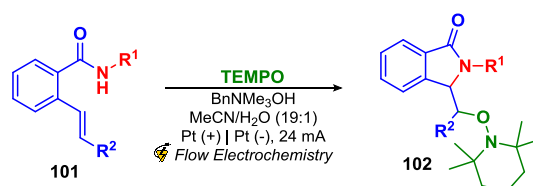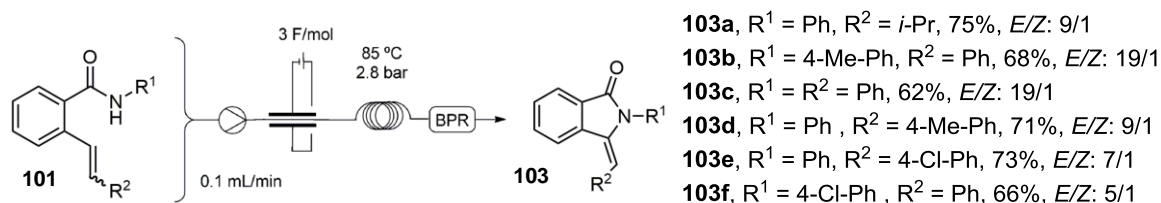

Scheme 38: Synthesis of isoindolinone.

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%).

102a, R^1 = 4-Me-Ph, R^2 = Ph, 78%, dr: 1.24:1
102b, R^1 = 4-Cl-Ph, R^2 = Ph, 56%, dr: 1.06:1
102c, R^1 = R^2 = Ph, 72%, dr: 1.14:1
102d, R^1 = nC$_4$H$_9$, R^2 = Ph, no reaction
102e, R^1 = Ph, R^2 = i-Pr, 96%, dr: 3:1
102f, R^1 = Ph , R^2 = n-Pr, 75%, dr: 1.65:1
102g, R^1 = Ph, R^2 = 4-Me-Ph, 62%, dr: 1.15:1
102h, R^1 = 4-Me-Ph, R^2 = 4-MeO-Ph, 21%, dr: 1.27:1
102i, R^1 = Ph, R^2 = 4-OMe-Ph, 18%, dr: 1.21:>1
102j, R^1 = 4-Me-Ph, R^2 = 1-naphth, 79%, dr: 1.57:1
102k, R^1 = 2-(H$_2$C=CH)-Ph , R^2 = Ph, 85%, dr: 2.25:1

102l, 56%, dr: 1.29:1   **102m**, 21%

102n, 94%   **102o**, 91%

Scheme 39: Representative examples for the synthesis of isoindolinone.

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.

103a, R^1 = Ph, R^2 = i-Pr, 75%, *E/Z*: 9/1
103b, R^1 = 4-Me-Ph, R^2 = Ph, 68%, *E/Z*: 19/1
103c, R^1 = R^2 = Ph, 62%, *E/Z*: 19/1
103d, R^1 = Ph , R^2 = 4-Me-Ph, 71%, *E/Z*: 9/1
103e, R^1 = Ph, R^2 = 4-Cl-Ph, 73%, *E/Z*: 7/1
103f, R^1 = 4-Cl-Ph , R^2 = Ph, 66%, *E/Z*: 5/1

Scheme 27: Examples for the flow functionalization of isoindolinone. BPR: backpressure regulator.

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 CHF$_2$ and CF$_3$ 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**).
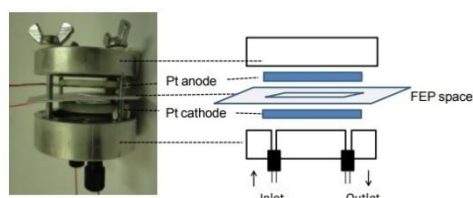
Figure 4: Electrochemical microreactor developed by the Wirth group. Reproduced with permission from ref. 32, Wiley.

[31] K. Uneyama, *Tetrahedron.* **1991**, *47*, 555 – 562.
[32] K. Arai, K. Watts, T. Wirth, *ChemistryOpen*, **2014**, *3*, 23 – 28.

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**).
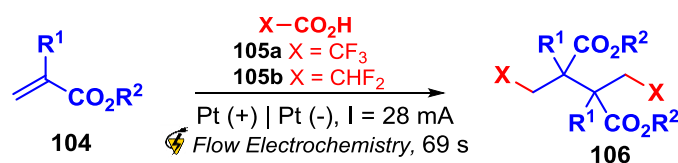

Entry	Acid	Alkene	Product	DL:meso[a]	Yield (%)
1	105a	**104a**, R^1 = H, R^2 = Me	**106a**	5:3	52
2	105b	**104a**, R^1 = H, R^2 = Me	**106b**	1:1	38
3	105a	**104b**, R^1 = H, R^2 = Et	**106c**	1:1	45
4	105b	**104b**, R^1 = H, R^2 = Et	**106d**	1:1	40
5	105a	**104c**, R^1 = H, R^2 = tBu	**106e**	1:1	45
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

[a]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**).
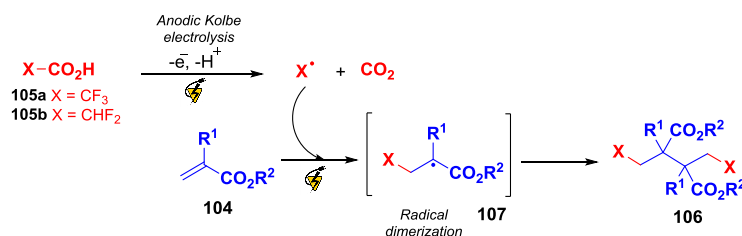
Scheme 41: Proposed mechanism for the dimerization.

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 azidoiodination, aziridination, oxysulfenylation, aminosulfenylation, dicarboxylation, generation of amidyl radical for oxidative aminations and aminooxydations 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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