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# Electrosynthesis: A practical way to access highly reactive intermediates

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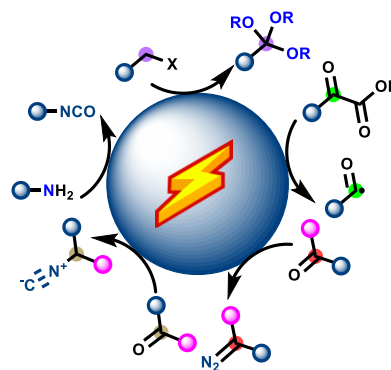
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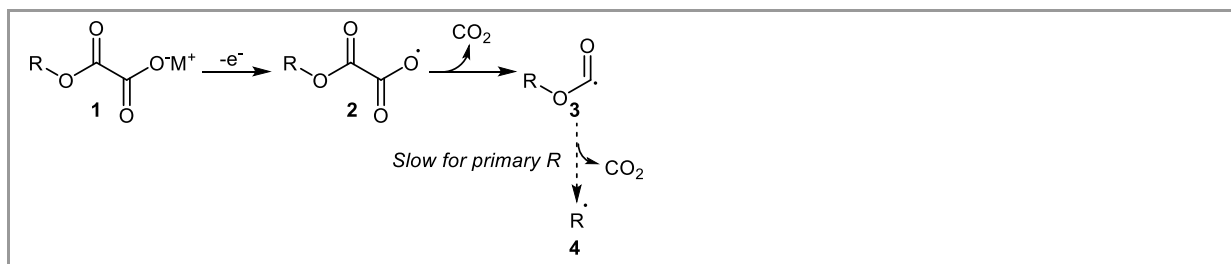
**Abstract** Electrosynthesis is undergoing a renaissance, but it is still far from being considered a standard method within the Chemists' synthetic toolbox. In this article, we will demystify organic electrochemistry by reviewing some practical methodologies developed in our laboratory to prepare highly reactive synthetic intermediates.

**Key words** electrosynthesis, lactones, orthoesters, isocyanates, isocyanides, diazo compounds, radicals, cations

Electrosynthesis has a long history taking its roots in the seminal works of Kolbe and Faraday.<sup>1,2</sup> While it experienced its hours of glory in the 60s, the general interest in the field quickly diminished over the following years.<sup>3</sup> A possible reason for the decrease in enthusiasm could lie in the fact that none of the equipment needed to perform electrosynthesis was commercially available. Having to build your own electrochemical setups was undoubtedly an important impediment for the technology to be widely adopted by the synthetic community. Nevertheless, in recent years, electrosynthesis has been undergoing a renewed interest due to the growing impetus of the chemical community for developing greener and cheaper alternatives to classical organic reactions. In the meantime, the equipment required to perform organic electrolysis has become commercially available, allowing "eCurious" an easy entry into the field.<sup>4</sup> Still, even if a plethora of electrosynthetic methodologies has been developed over the century, they are yet to be found within the Chemists' standard synthetic toolbox. Electrosyntheses are still plagued with a reputation of being black boxes, complicated to run and requiring a large amount of wasteful supporting electrolyte. Therefore, this article will challenge some of these clichés by reporting practical electrosynthetic methods developed by our group to rapidly generate highly reactive compounds that are usually difficult to access through more conventional synthetic methodologies. The electrochemical transformations discussed in this article will follow a simple "mix and electrolyse" approach. All of the reagents are mixed in an open-cell using non-pre-dried and non-degassed solvents, and no additional wasteful supporting electrolyte is added.

## Acyloxy radicals<sup>5</sup>

The chemical oxidation of hemioxalates had previously been used to generate alkyl radicals from alcohols.<sup>6</sup> While the oxidative decomposition of tertiary and secondary hemioxalates into their corresponding alkyl radicals has been extensively studied, especially under photoredox conditions, the oxidation of primary analogues remained more elusive. The oxidation of hemioxalates starts with the oxidation of the carboxylate (**1**) into an unstable carboxyl radical (**2**). This radical rapidly loses CO<sub>2</sub> and generates an acyloxy radical (**3**). For secondary and tertiary R groups, **3** rapidly loses a second molecule of CO<sub>2</sub> and forms the alkyl radical **4**. However, in the case of a primary R, the second decarboxylation is relatively slow at room temperature, which leaves enough time to use the generated acyloxy radical **3** in further chemical transformations (Scheme 1).

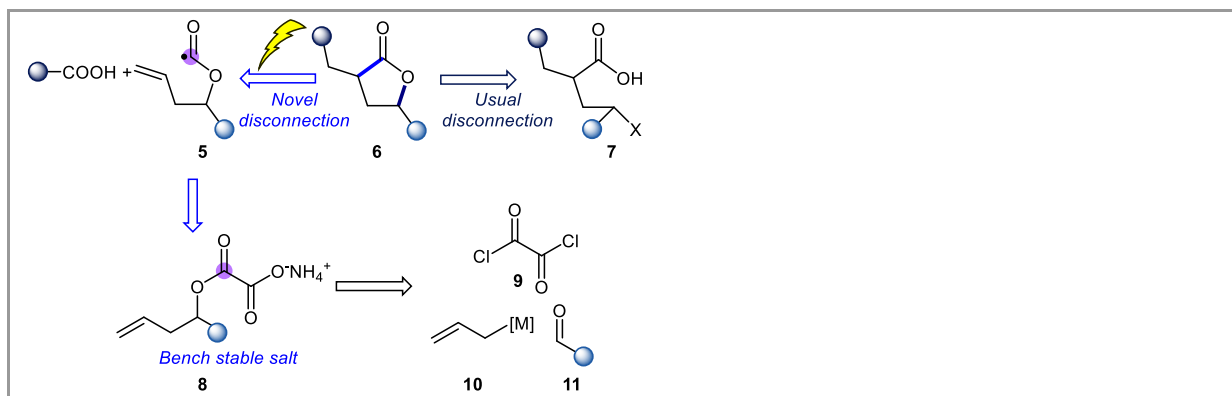


**Scheme 1** Oxidative decomposition of hemioxalates

Still, fundamental challenges remain associated with this transformation. First, traditional methodologies rely on toxic and expensive chemical oxidants or photocatalysts. Then, hemioxalic acids are unstable compounds that rapidly degrade at room temperature. Therefore, a common strategy is to neutralise them into corresponding stable carboxylates. Among the possible options, caesium hemioxalates have exhibited the highest solubility in organic solvents, even though their synthesis is often non-straightforward and can be costly and time-consuming.

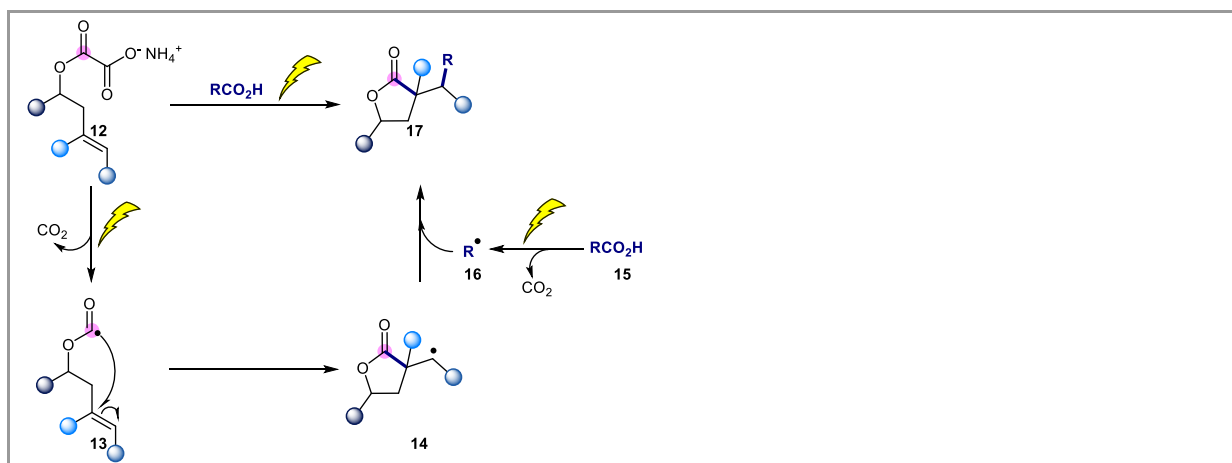
Therefore, to overcome these issues, our team has developed a practical electrochemical method based on the anodic Kolbe oxidation of carboxylic acids. Replacing the photocatalysts and chemical oxidants with a simple anode is a step forward in developing a more sustainable reaction at a lower cost. In addition, we have found that ammonium hemioxalates are readily prepared by treating hemioxalic acids with an excess of ammonia. These compounds have shown no degradation even after years of storage at room temperature. Furthermore, they are highly soluble in methanol, the solvent used in this anodic methodology.

Our electrochemical strategy is a non-traditional way to assemble functionalised lactones rapidly (Scheme 2).



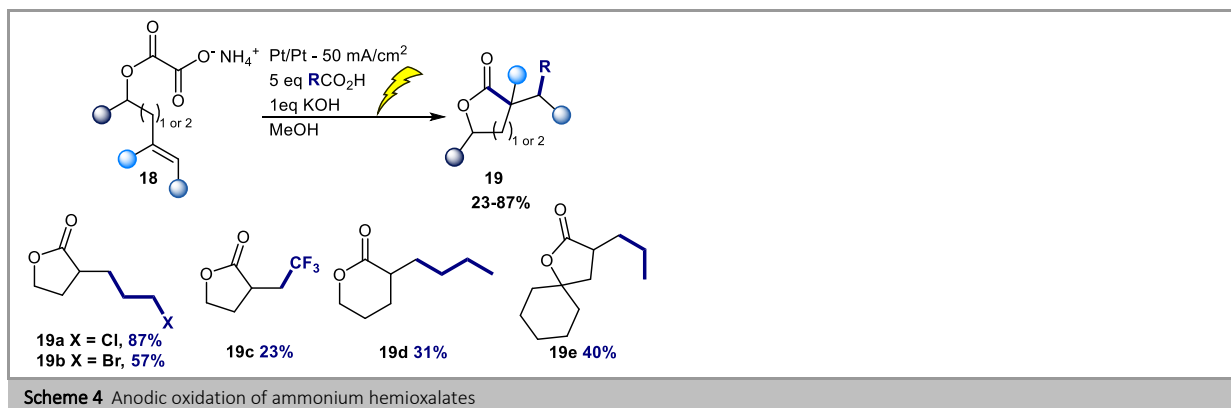
**Scheme 2** Novel electrochemical approach for the generation of oxycarbonyl radicals.

First, the hemioxalate **12** is anodically oxidised and rapidly loses a molecule of  $\text{CO}_2$  to form the acyloxy radical **13**. This radical then cyclises onto an olefin and generates a lactone and a new carbon-centred radical **14**. Finally, by taking advantage of electrochemistry's unique ability to generate high radical densities near the electrode, a unique  $\text{sp}^3\text{-sp}^3$  radical cross-coupling occurs between **14** and **16**, a radical produced by the concomitant decarboxylation of co-acid **15** present in solution. While these cross-couplings generally require the use of transition metal catalysts in classical chemistry, they can be achieved in an open flask, without any catalyst, by using electrochemistry (Scheme 3).



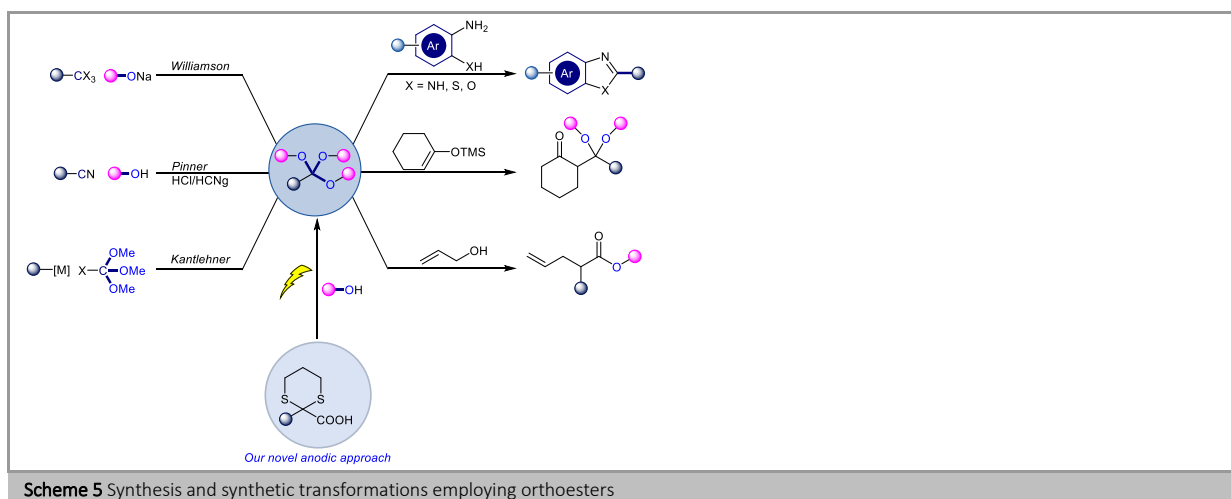
**Scheme 3** Overall mechanism for anodic lactonisation

The anodic radical transformation is robust and does not require prior degassing or drying of the solvent. The reaction can even be performed in water if the substrates are at least partially soluble in the medium. In addition, the ionic nature of the starting materials avoids the need for any wasteful supporting electrolytes. Furthermore, the transformation has been shown to tolerate a wide range of functional groups, including halides such as chlorides (**19a**) and bromides (**19b**), which are not always compatible under traditional radical conditions. Finally, using trifluoroacetic as a co-acid proved to be a rapid and economically relevant method for introducing a  $\text{CF}_3$  fragment (**19c**) (Scheme 4).



## Orthoesters<sup>7</sup>

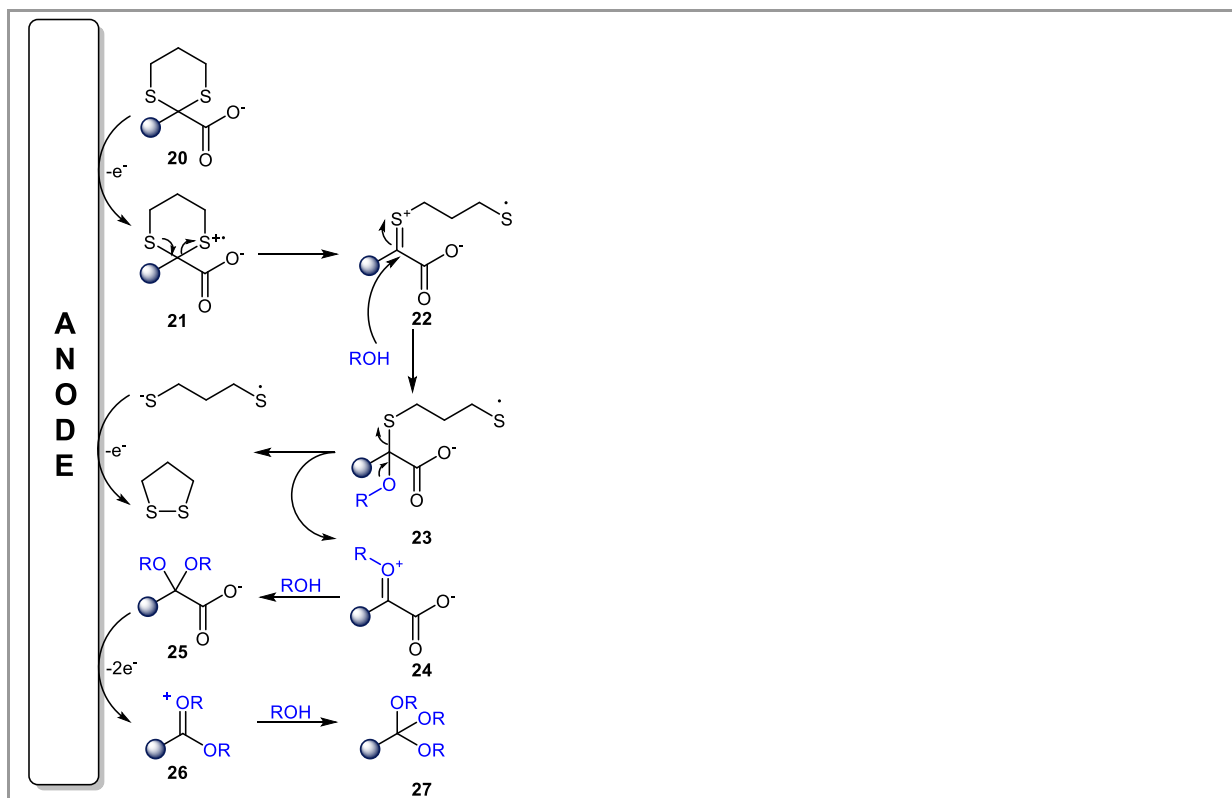
Orthoesters are attractive building blocks that could be used to access complex and highly functionalised compounds rapidly, yet their synthesis remains challenging (Scheme 5).<sup>8-10</sup> The favoured route to orthoesters, the Pinner method, requires treating a nitrile with gaseous HCl or HCN to form an extremely moisture-sensitive imidate salt. This salt is then reacted in the presence of an alcohol to provide the desired orthoester. Not only this method could require up to 6 days to get the orthoesters, but the yields remain relatively low. In addition, the use of such harsh conditions precludes the use of most of the standard functional groups. Therefore, it is unsurprising that only a handful of orthoesters are commercially available.



Although a few attempts have been made at developing an electrochemical way of accessing orthoesters, none offered a general route to functionalised orthoesters.

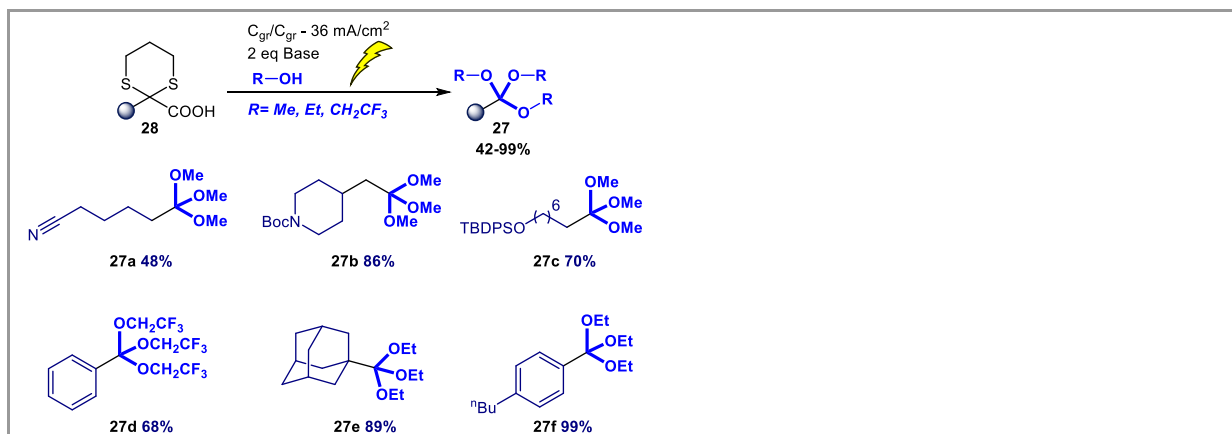
We, therefore, sought to develop the anodic oxidation of dithianecarboxylic acid derivatives as an expedient, practical and general method to access functionalised orthoesters.

A possible mechanism for this transformation is depicted in Scheme 6. First, the dithiane carboxylate **20** undergoes an anodic oxidation on one of the sulfur centres. This leads to the opening of the dithiane and the formation of the thionium **22**, which is then attacked by the alcoholic solvent to form an *S,O*-acetal **23**. Then, as it is the case during the usual deprotection of dithiane, the mixed acetal eliminates the sulfur group to form the oxonium **24**, and undergoes a second attack from the solvent. Finally, the acetal **25** is anodically decarboxylated to generate a novel oxonium **26**, which, once trapped by the solvent, leads to the formation of the desired orthoester **27**.



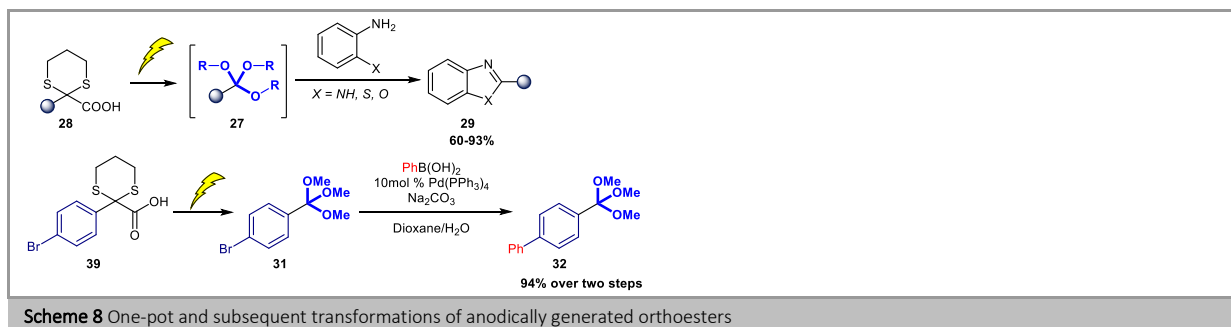
**Scheme 6** Plausible mechanisms for the anodic generation of orthoesters.

Much to our delight, this novel electrochemical approach allowed us to prepare functionalised orthoesters in high yield with no other purification than a rapid basic workup. Moreover, for the first time, some orthoesters bearing acid-sensitive functional groups (nitrile, *N*-Boc, alkynes, alkenes, etc.) were obtained using this novel approach. In addition, by varying the nature of the solvent, we have been able to make fluorinated orthoesters (**27f**), a class of compound which was unknown until now (Scheme 7).



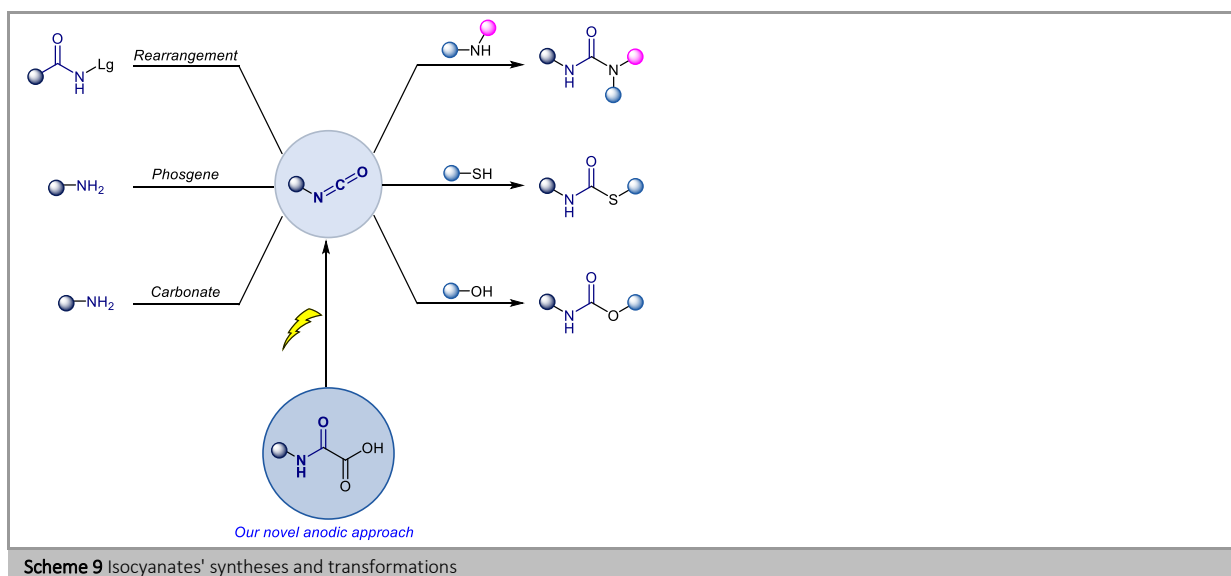
**Scheme 7** Anodic generation of orthoesters

The orthoesters have been successfully condensed into pharmaceutically relevant benzimidazoles, benzoxazoles and benzothiazoles (**29**) in a one-pot procedure, by adding the amino coupling partner post electrolysis, removing the need to isolate the sometimes volatile orthoester intermediates. Finally, we demonstrated that anodically generated orthoesters could be used in subsequent metal-mediated transformations without fear of the catalyst being poisoned by potential remaining traces of sulfur byproduct (Scheme 8).

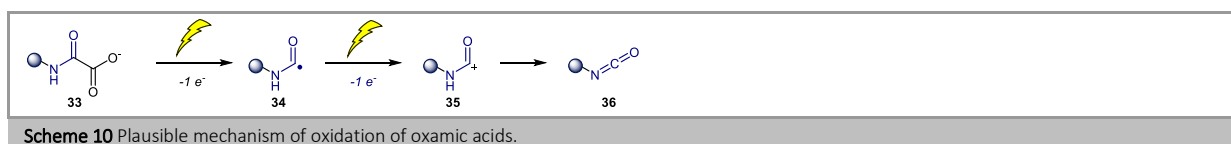


## Isocyanates<sup>11</sup>

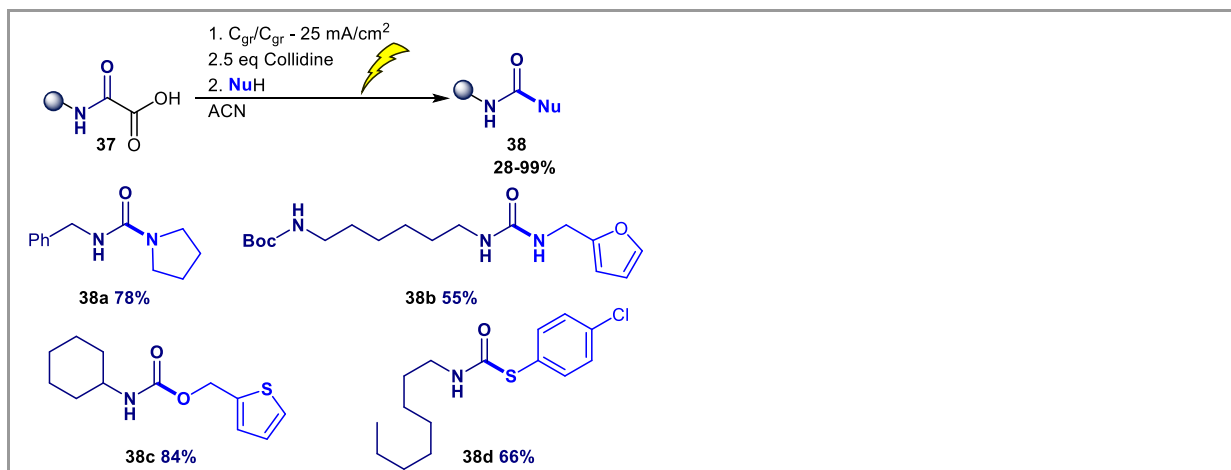
Isocyanates are essential building blocks commonly used across synthetic fields, from material to medicinal chemistry.<sup>12</sup> Yet, their synthesis often relies on using toxic reagents such as phosgene and its derivatives. In addition, isocyanates are themselves highly toxic and carcinogenic, which is exceedingly problematic if they need to be isolated (Scheme 9).



Therefore, we have developed a simple approach for their anodic generation from easily accessible oxamic acids. The mechanism is very similar to the oxidation of hemioxalates. First, the oxamate **33** undergoes an anodic decarboxylation to generate the corresponding carbamyl radical **34**. Then, the presence of the electron-donating nitrogen favours a second oxidation into the cation **35**, which, after a loss of a proton, forms the desired isocyanate **36** (Scheme 10). The electrogenerated isocyanate can then be trapped *in situ* by a suitable nucleophile avoiding the need for its isolation.

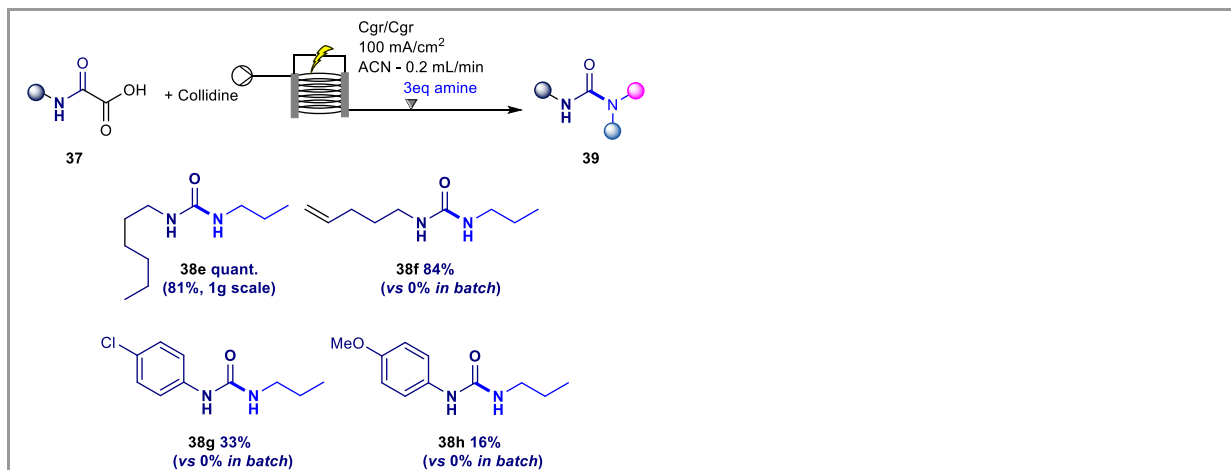


Using this novel methodology, we have successfully prepared ureas, carbamates and thiocarbamates (Scheme 11). Furthermore, the transformation has shown to be compatible with a wide variety of functional groups, such as benzylic groups (**38a**), *N*-Boc amides (**38b**) and heteroaromatics (**38b and c**).



**Scheme 11** Anodic generation of (thio)ureas and carbamates.

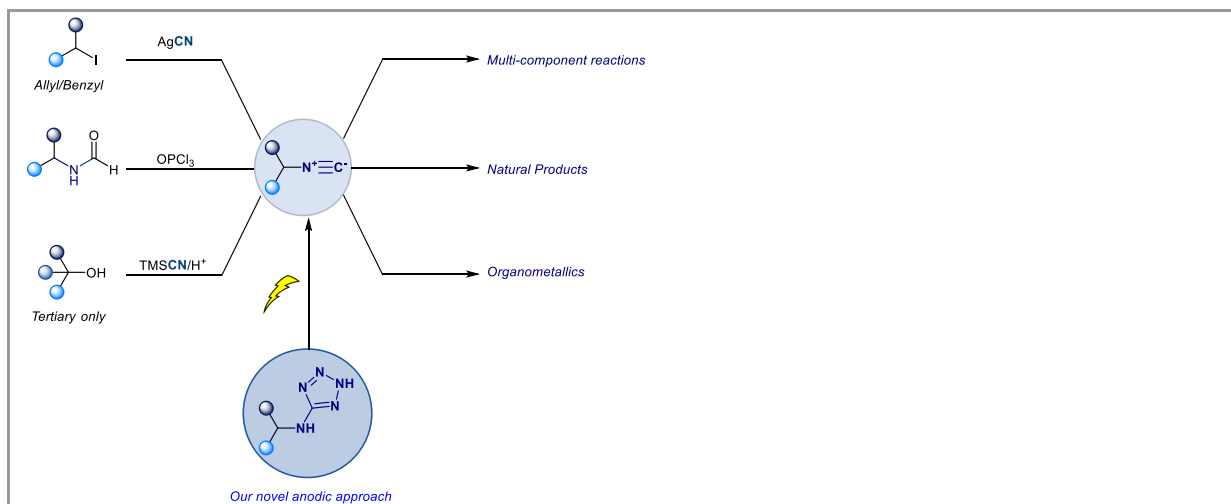
Interestingly, using collidine as a base is essential to obtain the final ureas and (thio)carbamates in good yields. Besides deprotonating the starting material, its exact role in the reaction remains to be elucidated. Finally, the reaction was rapidly scaled-up employing flow electrochemistry (Scheme 12). Again, in this case, no additional supporting electrolyte is required due to the ionic nature of the starting material.



**Scheme 12** Flow electrochemistry of ureas

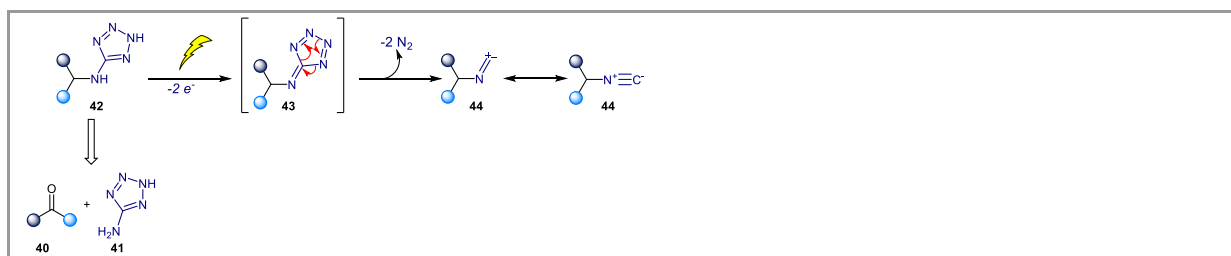
## Isocyanides<sup>13</sup>

Isocyanides represent another class of well-known compounds commonly found in natural products, used as ligands in organometallic chemistry and coupling partners in multi-component reactions.<sup>14-16</sup> As for the previously discussed types of compounds, the chemical synthesis of isocyanides remains challenging. The favoured route to access them being the dehydration of an unstable formamide using harsh and toxic reagents such as phosphorus oxychloride (Scheme 13).



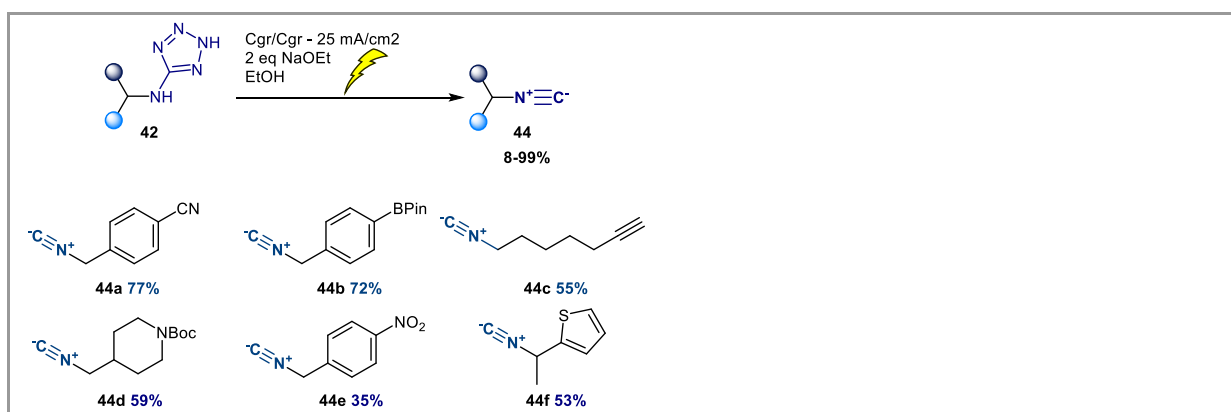
**Scheme 13** Synthesis and uses of isocyanides

We developed a novel and practical approach to preparing isocyanide by the electrochemical oxidation of aminotetrazole derivatives. Our method virtually allows the transformation of any carbonyl into its corresponding isocyanide.



**Scheme 14** Mechanism of oxidation of aminotetrazoles

Aminotetrazole (**41**), a cheap and readily available reagent, can easily undergo a reductive amination in the presence of a carbonyl compound (**40**) to provide the corresponding *N*-alkylated aminotetrazole (**42**). The anodic oxidation of **42** leads to the formation of a fulvene-type structure (**43**) that rapidly loses two molecules of nitrogen and forms the isocyanide (**44**) (Scheme 14).



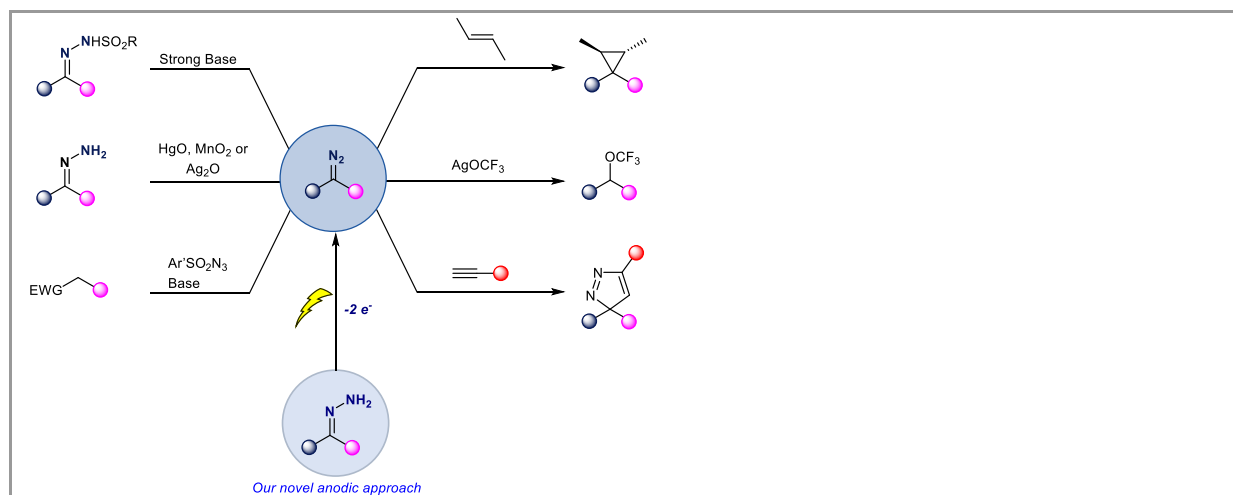
**Scheme 15** Anodic oxidation of aminotetrazoles

Again, no supporting electrolyte is required nor prior drying or degassing of the solution. The anodic oxidations have proven highly efficient in yielding clean functionalised isocyanides (Scheme 15). No other purification than a rapid basic workup was required in most cases. Finally, The transformation is exceptionally mild and has shown to be compatible with a wide variety of functional groups such as nitriles (**44a**), boronates (**44b**), alkynes (**44c**), carbamates (**44d**), nitros (**44e**) and easily oxidisable heteroaromatics (**44f**). Some of these groups would have been incompatible with the usual formamide dehydration approach.



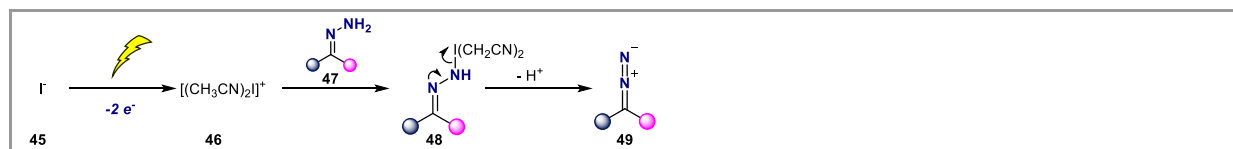
## Diazo compounds<sup>17</sup>

Although diazo compounds are highly versatile building blocks, synthesising these high-energy compounds remains challenging.<sup>18,19</sup> A few chemical methods are commonly used to generate diazo compounds (Scheme 16). Unfortunately, they often rely on hazardous conditions and offer a poor atom economy. The most attractive route to diazo compounds is the oxidation of hydrazones. Although, in this case, the atom economy is high, the problem comes from the toxic and expensive chemical oxidants routinely used to achieve this transformation.

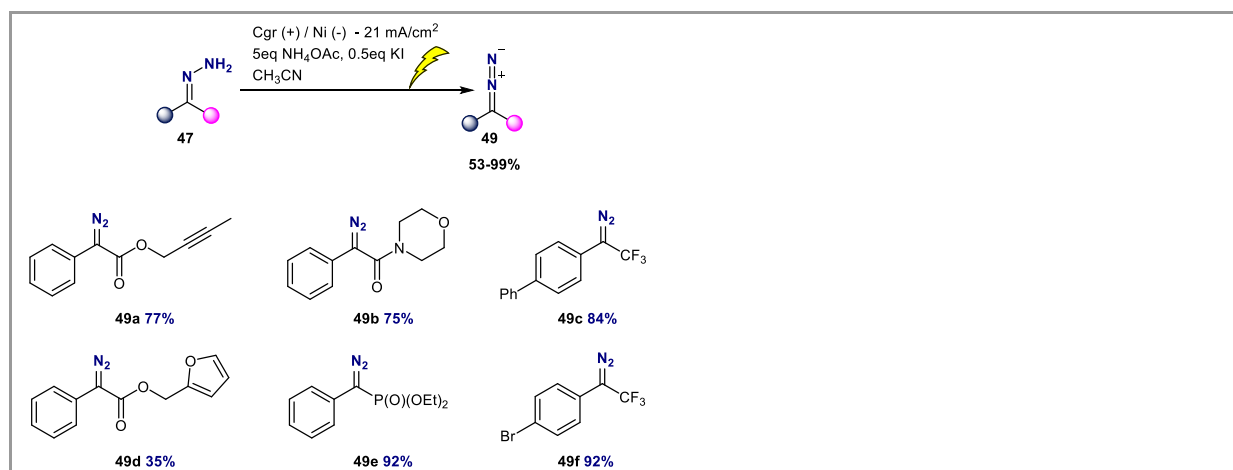


**Scheme 16** Synthesis and use of diazo compounds.

We decided to replace the toxic chemical oxidants with a simple and more ecologically friendly anodic oxidation. Although possible, the direct oxidation of hydrazones on an anode led to mediocre yields in the desired diazo compound as well as numerous side products. However, the oxidation of a hydrazone by  $[(\text{CH}_3\text{CN})_2\text{I}]^+$ , generated by anodic oxidation of KI in acetonitrile, led cleanly to the formation of the desired diazo compound in good to excellent yields. In this anodic reaction, a hypervalent iodonium (**46**) is electrogenerated by the oxidation of iodide. The iodonium then reacts with a hydrazone (**48**) to form the corresponding iodo hydrazone (**48**) which rapidly loses a proton to form the desired diazo compounds (**49**) (Scheme 17).



In this transformation, the combination of a nickel cathode with ammonium acetate is essential. Indeed, nickel has a low hydrogen overvoltage and therefore favours the reduction of a proton (from  $\text{NH}_4^+$ ) over the reduction of the anodically generated diazo compound. Besides serving as a base, the exact role of acetate still remains to be fully elucidated, yet using other bases led to lower yields in diazo compounds, as well as in the formation of numerous undesired side-products.



**Scheme 18** Anodic oxidation of hydrazones.

The method is practical and does not require the solution's degassing or rigorous drying. The anodic oxidation of hydrazones allowed to rapidly access diazoesters (**49a and d**), ketones, amides (**49b**) and phosphonates (**49e**) in good to excellent yields. Finally, trifluoro diazo compounds (**49e and f**) were also easily prepared in excellent yields (Scheme 18)

In conclusion, our laboratory has developed practical electrosyntheses to generate high-energy intermediates that are of interest to the synthetic community. In most cases, the electrochemical methods are not only more practical than the chemical methods but also cheaper and greener.

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### Conflict of Interest

The author declare no conflict of interest.

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