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Professeur O. Riant

# Organic Electrochemistry Applied to the Kolbe Anodic Cyclization of Functionalized 2-Pyrrolidinones

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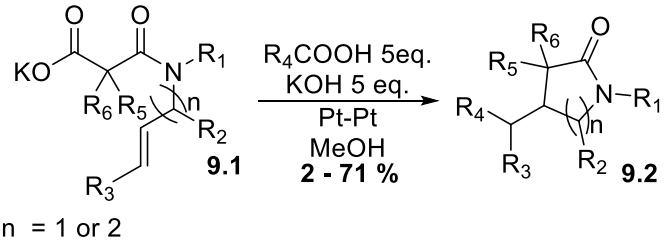
## Abstract

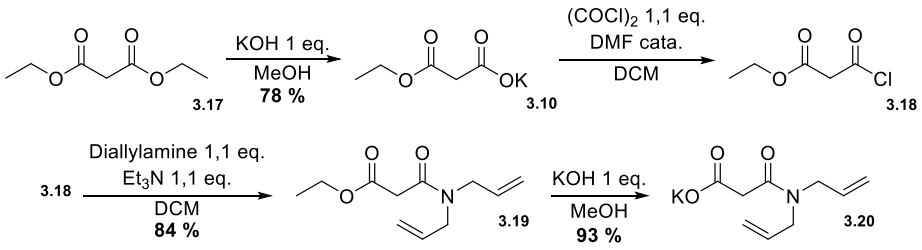
Organic electrochemistry is a scientific field which studies the behavior of organic molecules in electrolytic conditions. This methodology, which is presently experiencing a renaissance, has the advantage of being environmentally friendly, given that reduction and oxidation reactions are performed using the electron ass a mass-free reagent. Moreover, the electrolysis is economically interesting as this process uses the cheapest electron source in the world, namely the electricity. Therefore, organic electrochemistry is a very attractive method for synthetic purpose.

Among the numerous electroorganic reactions, we decided to study the Kolbe electrolysis in order to synthetize functionalized 2-pyrrolidinones. Indeed, racetams is a family of molecules sharing a 2-pyrrolidione core. This group is well-known for its positive effects on the cognitive functions. These γ-lactams have a large prescription field and are used for the treatment of central nervous system disorders, cognition and memory problems, epilepsy, seizure, and neuro-degenerative diseases, *etc.* Furthermore, the lack of knowledge on the action mode of these molecules contributes to an increasing tendency for research of new 2-pyrrolidinone derivatives in order to generate better clinical efficacy.

The first part of our research was focused on the development, optimization, and exemplification of a Kolbe electrocyclization of functionalized 2-pyrrolidinones with a pharmaceutical interest. This original and straightforward methodology enables the cyclization and the subsequent functionalization of 2-pyrrolidinones, using the adequate co-acid. This process allows to form two carbon-carbon bonds, in only one step.

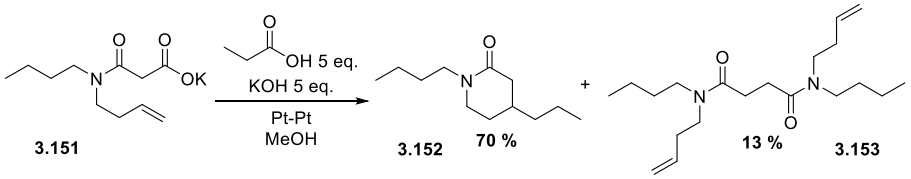



Therefore, we first synthetized an electrocyclization substrate, in only three steps, starting from the inexpensive and commercially available ethyl potassium malonate and diallylamine.

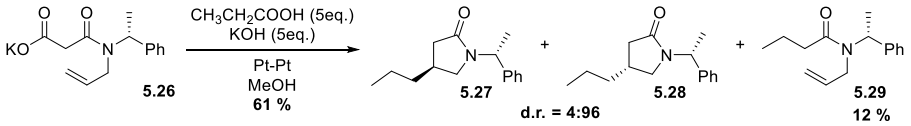



Secondly, we developed and optimized the electrocyclization of this substrate in functionalized 2-pyrrolidinones. Given that, in organic electrochemistry, a great number of parameters have a critical impact on the outcome of a reaction, the substrate concentration, current density, temperature, solvent, electrodes nature, and the number of equivalent of electrolyte were modified in order to find the most efficient conditions for our transformation.

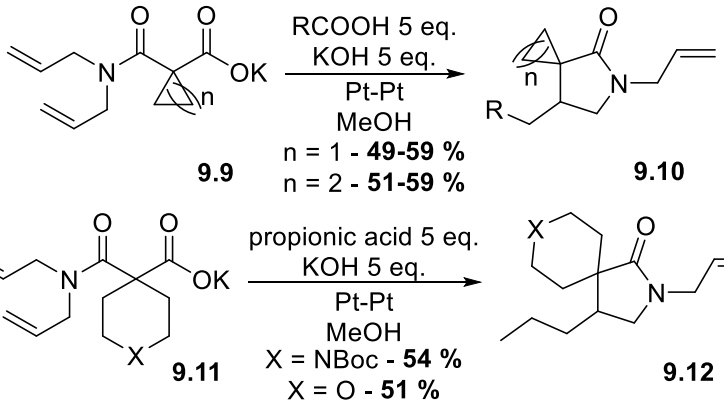
Thirdly, we focused our work on the formation of a library of diversely substituted 2-pyrrolidiones. To achieve that, several co-acids were tested; the nature of the protecting group of the nitrogen atom in the substrate structure was modified; and the double bond and malonic part of the substrate were diversely substituted.
Furthermore, the replacement of the allyl function, in the substrate structure, by a homoallyl group allowed to synthetize electrochemically a 2-piperidinone, via a *6-exo-trig* cyclization.



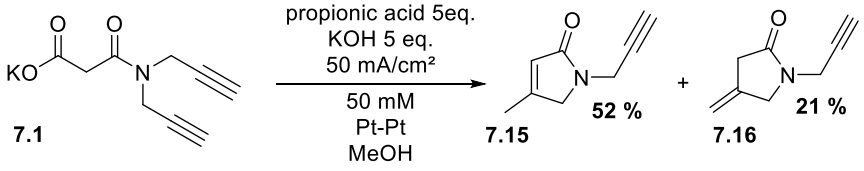

In the second phase of our research, we have focused our attention to the development of a diastereoselective electrocyclization of 2-pyrrolidinones given that our classic electrocyclization of 2-pyrrolidinones does not allow the control of the stereochemistry. The adopted strategy relied on the judicious insertion of a chiral auxiliary inside the structure of the electrocyclization substrate, in order to induce a facial selectivity during the cyclization step.



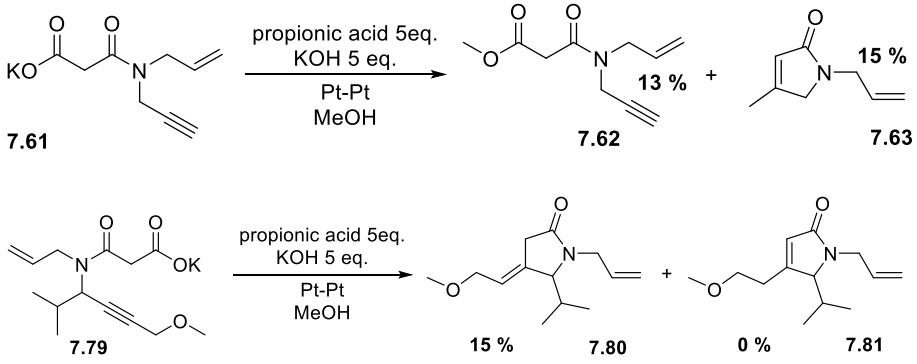

In a third phase of our work, we have attempted to synthetize various polycyclic 2-pyrrolidinones via several strategies, such as: the synthesis of linear and cyclic substrates, and the application of gold and copper catalysis to access original cyclic and polycyclic substrates. The most successful strategy was to incorporate a carbon cycle or a heterocycle inside the malonate part of the cyclization reagent. This method enabled the formation of various spiro 2-pyrrolidinones bearing a carbon 3- or 5-membered ring, a piperidine, or a tetrahydropyran moiety, with good yields; which shows the wide applicability of our brand new methodology.

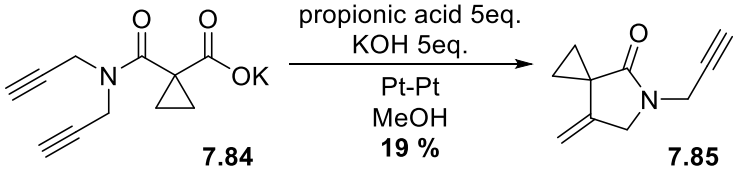



In a fourth phase of our thesis, we decided to apply our electrocyclization conditions to a propargylic substrate. Our interest in this investigation relies on the fact that the addition of an alkyl radical on an alkyne function is a highly favored process, even if the starting radical is more stable than the vinyl radical formed. Interestingly, this process allowed the formation of a pyrrolone and an α,β-unsaturated 2-pyrrolidinone, via a *5-exo-dig* cyclization. The reaction parameters and work-up procedure were then optimized such that selectivity was obtained; and thus each product was produced with only a very small amount of its isomeric product formed concurrently.

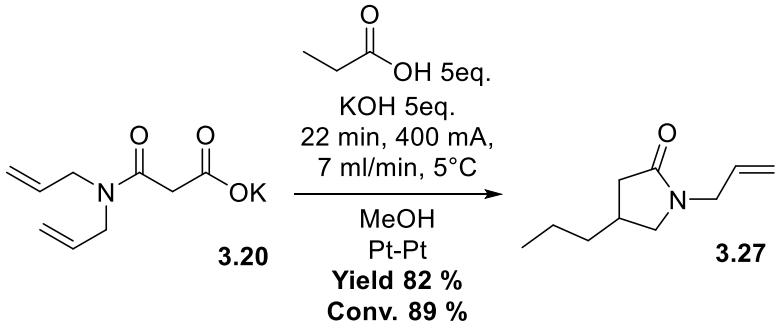


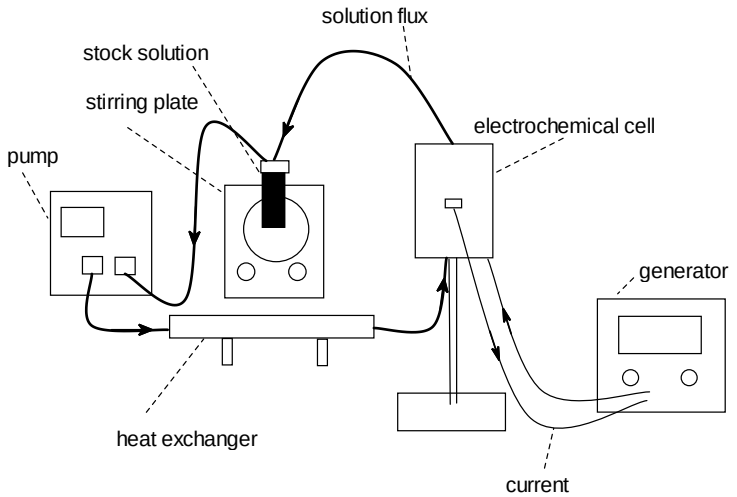

A second part of this research topic was the exemplification of the reaction. Therefore, the nature of the protecting group of the nitrogen atom in the electrocyclization substrate structure was modified. Moreover, the propargylic part of the reagent was functionalized which led to the formation of functionalized α,β-unsaturated 2-pyrrolidinones. Finally, spirocyclic α,β-unsaturated 2-pyrrolidinones were formed via the electrocyclization of a cyclic propargylic substrate.






Finally, the electrocyclization of the 1-allyl-4-propylpyrrolidin-2-one, a brivaracetam derivative, was transposed from a batch-type double jacketed cell to IKA ElectraSyn Flow cell. Therefore, the reaction parameters, which already have been optimized for the batch-type cell, were adapted in the flow cell. This transposition was a success and allowed to drastically lower the reaction time from 240 min in the batch cell to 22 min in the flow cell. Moreover, the yield was increased form 71 % in the batch-cell to 82 % in the flow cell. Furthermore, the Faradic yield was also increased from 19 % in the batch cell to 31 % in the flow cell, which proves that the flow cell promotes higher current efficiency. This excellent result derives from the characteristics of the ElectraSyn flow cell, such as: a large ratio of electrodes surface area (12 cm²) to cell volume (0.6 ml), a small inter-electrodes gap (0.5 mm), and a good temperature control thanks to the heat exchanger and to the fast flow rate. Finally, the ElectraSyn Flow cell promotes better reproducibility with its defined geometry.




**representation 1 ElectraSyn Flow reactor**

## Abbreviations

| | |
|---|---|
| Å | Ångström |
| AcOH | acetic acid |
| AcOEt | Ethyl acetate |
| AIBN | azobisisobutyronitrile |
| BASF | Badische Anilin-& Soda-Fabrik |
| $Boc_2O$ | Di-*tert*-butyl dicarbonate |
| Bu | buthyl |
| $Bu_3SnH$ | Tributyltin hydride |
| C | concentration |
| C-C | carbon electrodes |
| $C_{gr}$-$C_{gr}$ | carbon graphite electrodes |
| Cata. | catalyst |
| CGRP | calcitonin gene-related peptide |
| $cm^2$ | square centimeter |
| Conv. | conversion |
| d | debit, flow rate of the solution |
| DCC | *N,N'*-Dicyclohexylcarbodiimide |
| DCM | dichloromethane |
| $(DHQD)_2PHAL$ | hydroquinidine 1,4-phtalazinediyl diether |
| DIPEEA | *N,N*-Diisopropylethylamine |
| DMAP | 4-(Dimethylamino)pyridine |
| DMF | *N,N*-dimethylformamide |
| DMSO | dimethyl sulfoxide |
| d.r. | diastereomeric ratio |
| E | electrophile |
| E° | oxidative potential |
| $e^-$ | electron |
| *ect.* | *Et cetera* |
| e.e. | enantiomeric excess |
| EP | Petroleum ether |
| eq. | equilibrium |
| ESH | standard hydrogen electrode |
| *et al.* | *et alii* |
| $Et_3N$ | triethylamine |
| $Et_2O$ | diethyl ether |
| EtOH | ethanol |
| EtONa | sodium ethoxide |
| Exp. | experiment |
| F | Faraday constant |
| GABA | *gamma*-aminobutyric acid |
| h | hour |
| HFIP | hexafluoro-2-propanol |
| HIV | human immunodeficiency viruses |
| HMPA | Hexamethylphosphoramide |
| HPLC | high-performance liquid chromatography |
| HRMS | high resolution mass spectrometry |
| I | current |

| | |
|---|---|
| IR | Infrared |
| J | current density |
| LDA | Lithium diisopropylamide |
| LUMO | lowest unoccupied molecular orbital |
| mA | milliamps |
| MeCN | acetonitrile |
| $MeO^-$ | methoxide |
| MeOH | methanol |
| mm | millimeter |
| MS | mass |
| *n*-BuLi | *n*-butyllithium |
| NHE | normal hydrogen electrode |
| NMR | nuclear magnetic resonance |
| Nu | nucleophile |
| Ox | oxidant |
| p. | page |
| p ESI | probe electrospray ionization |
| $PGF_{2\alpha}$ | prostaglandin $F_{2\alpha}$ |
| pH | power of hydrogen |
| Ph.D | *Philosophiae doctor* |
| pKa | acid dissociation constant |
| ppm | parts per million |
| PPTS | pyridinium *p*-toluenesulfonate |
| Pt-Pt | Platinum electrodes |
| Purif. | purification |
| Q | electrical charge |
| R | faradic yield |
| Red | reductant |
| RCV | reticulated vitreous carbon electrode |
| SCE | saturated calomel electrode |
| SOMO | singly occupied molecular orbital |
| T | temperature |
| *t*-BuOH | *tert*-butanol |
| TEMPO | (2,2,6,6-tetramethylpiperidin-1-yl)oxyl |
| TFA | Trifluoroacetic acid |
| THF | tetrahydrofuran |
| TCL | Thin-layer chromatography |
| TMSCl | Trimethylsilyl chloride |
| TMSOTf | trimethylsilyl trifluoromethanesulfonate |
| TSCl | 4-Toluenesulfonyl chloride |
| UCB | union chimique belge |
| UV | Ultraviolet |
| V | volt |
| *vs* | versus |

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# 1 Introduction

## 1.1 Organic electrochemistry

Organic electrochemistry is the combination of two particular chemistry fields: organic synthesis and electrochemistry. The purpose of this discipline is to study the behavior of organic molecules in electrolytic conditions. The organic electrochemistry is not limited to the analytical aspects and the aim of this method is to generate products in sufficient quantities by electrolysis. Specifically, this approach is the combination of heterogeneous electron transfers at an electrode surface with chemical reactions. Following this electron transfer, reactive intermediates arising from dissociative mechanisms (cations, anions and radicals) and radical ions can be generated.

### 1.1.1 Principal concepts

In organic electrochemistry, organic chemists employ electrochemically generated reactive intermediates for selective synthetic reactions. Contrarily to common methods, electrochemical procedures involve electron transfer from substrates to the anode or electron transfer from the cathode to substrates. This method enables the formation of reactive intermediates from simple and ubiquitous functional groups. In the case of an oxidation reaction, the active species are expected to be radical, cation, radical cation, and dication. Moreover, radical anion, dication, and radical can be formed via a reduction process.

| Electron transfer process | Reactive species |
|---|---|
| $X \xrightarrow{-e^-} X^{+\bullet}$ | Radical cation |
| $X^{+\bullet} \xrightarrow{-e^-} X^{2+}$ | Dication |
| $X^- \xrightarrow{-e^-} X^\bullet$ | Radical |
| $X^\bullet \xrightarrow{-e^-} X^+$ | Cation |
| $X \xrightarrow{+e^-} X^{-\bullet}$ | Radical anion |
| $X^{-\bullet} \xrightarrow{-e^-} X^{2+}$ | Dication |
| $X^+ \xrightarrow{+e^-} X^\bullet$ | Radical |

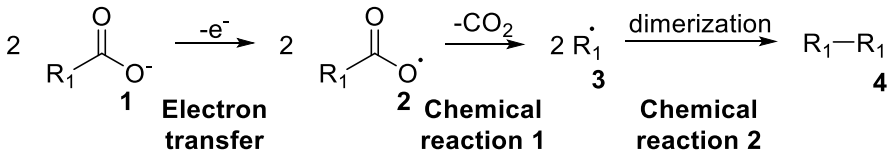
**Table 1 electron transfer process**

The reactive intermediates radical and cation are typically stemmed from carboxylates, phenolates, alcoholates, thiolates, and halides, *etc*., by one or two electron discharge at the surface of the anode. On the other hand, radical cation and

dication species commonly arise from unsaturated, aromatic, and hetero atom-containing compounds by one or two electron losses.

### 1.1.2 Electron transfer and chemical reaction

Generally, electro-oxidative reactions occur, in a stepwise fashion, through the discharge of electrons by electrolysis and the following chemical reaction. For example, the Kolbe dimerization process is divided in three parts: an electron transfer followed by two chemical reactions (see Scheme **1**). In the electronic process, it is decisive to produce the desired products selectively by controlling the potential of the cell. Contrariwise, in the chemical process, it is fundamental to control the reactivity and the reaction course of the intermediates by modifying the constituents of the electrolysis media and the electrolysis conditions. In fact, the solvents, electrolytes, additives, electrodes, current density, potential, and pH always influence the destiny of the intermediates. Therefore, even starting from the same intermediate, it is possible to achieve distinct results by adjusting the conditions of the electro-oxidation. Accordingly, a suitable choice of the electrolysis conditions and system can participate in an attractive product-selectivity.




**Scheme 1 Kolbe dimerization**

### 1.1.3 Practical aspects in electrochemistry

#### *1.1.3.1 The electrolytic cell*

An electrolytic cell drives non-spontaneous redox reactions via the application of an external power. Basically, all electrochemical circuits are composed of an electric generator connected to two electric cables terminated by connectors. Those connectors or crocodile clips are connected to the electrodes. Moreover, the two electrodes are positioned, in a solution that includes a substrate, a solvent, and an electrolyte. After the insertion of the electrodes into the reaction mixture, a voltage is applied across the gap between the anode and the cathode. Commonly, in a laboratory batch electrochemical cell, the inter-electrode gap should be kept within the range of 1 – 5 mm so the current density is maintained within 10 – 100 mA/cm$^2$. On the other hand, for industrial-scale electrolysis, the inter-electrode gap can reach 5 cm and the current density applied may be of 500 mA/cm$^2$.[1] This allows the creation of two separate processes. On the one hand, molecules are oxidized at the anode, leading to an electrons transfer from the reaction solution to the anode. On

[1] (a)Pletcher, D.; Walsh, F.C. *Industrial Electrochemistry*, Bangalore, Spinger Science + Business Media, LLC, **1984**, p. 148; (b) Wendt, H.; Kreysa, G. *Electrochemical Engineering Sceince and Technology in chemical and other industries*, Berlin, Sprigner, **1999**.

the other hand, molecules are reduced at the cathode, leading to the transfer of electrons from the cathode to the substrate adsorbed at the cathode surface. The consequence of these two processes is the transfer of electrons between the two electrodes, which enables the current to flow through the cell (see Figure **1**).

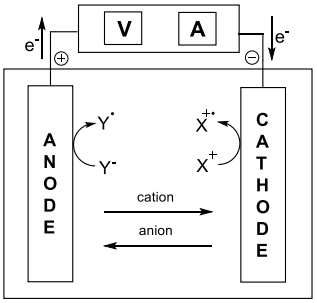



**Figure 1 electrolysis cell**

*1.1.3.1.1*<u>*Supporting electrolyte*</u>

Since organic solvents have poor conductivity, it is crucial to dissolve a conductive electrolyte into the solvent to favor the creation of a workable electrolysis mixture, which can transmit electricity. The supporting electrolyte is a salt and exhibits good conductivity. The typical electrolytes are divided in three main groups: basic, acidic and neutral electrolytes. Since the electrolyte can have an impact on the reaction outcome, it is necessary to study the effects of a large range of salts in these respects by changing both the counter anions and cations to achieve a good product-selectivity. Moreover, the decomposition potential of the electrolyte must exceed the oxidation or reduction potential of the substrate. Additionally, the substrate must be preferentially adsorbed at the surface of the electrode to favor the desired transformation. The common electrolytes regroup lithium perchlorate, potassium hydroxide, tetraethylammonium tosylate, and tetrabutylammonium tetrafluoroborate, *etc*.

*1.1.3.1.2*<u>*Solvent*</u>

For organic electrolysis, based on the interactions between the reactive intermediates and the solvent, solvents can be divided in two groups: dipolar aprotic solvents and dipolar protic solvents. The usual solvents used in organic electrosynthesis are methanol, THF, DCM, DMF, and acetonitrile. Moreover, in the case of the Kolbe reaction, it is not helpful to degas the solvent before an electroorganic reaction since the ratio between the oxygen concentration and the radical concentration, at the anode surface, is almost zero.

*1.1.3.1.3*<u>*Electrodes*</u>

The most widely used electrodes for oxidative electrolysis are generally carbon graphite and platinum ($E°_{Pt/Pt2+}$=1.19 V *vs* NHE) electrodes. The electrode material is chosen in such a way that it does not oxidatively or reductively dissolve, at the

applied potential. The product-selectivity is generally affected by the nature of the electrode material. Switching from one electrode to another, such as from carbon to platinum, can have a big impact on the product selectivity, even in an identical electrolysis mixture apart from the electrode nature. Essentially, platinum electrodes are suited for one-electron oxidation, providing radical and cation radical species, while carbon electrodes afford two-electron oxidation, furnishing cationic moieties. Platinum electrodes are hardwearing and can be refreshed multiple times by washing in nitric acid, rinsing with water and finally treating in a burner flame. Interestingly, the platinum oxidation potential ($E°_{Pt/Pt2+}$ = 1.19 V *vs* NHE) is lower than a typical carboxylate oxidation potential ($E°_{RCOO-/RCOO°}$ = 1.80 – 2.60 *vs* NHE). Nevertheless, the carboxylate oxidation takes place at the surface of a platinum anode. Indeed, a platinum oxide $PtO_2$ passivation layer is present at the surface of platinum electrodes; and this passivation layer does not impact the redox reactions. Finally, a sacrificial anode can be used in a reduction process in order to avoid oxidative side-reactions. Indeed, a sacrificial anode is made of a metal that is easily oxidized which prevent the oxidation of the molecules in the reaction mixture.

*1.1.3.1.4Cell*

In organic electrochemistry, two types of cells are commonly used. A two-compartment cell can be employed if side reactions can occur at the counter electrode. This type of cells is divided in two compartments by appropriate microporous separators, such as ion-exchange membrane, porous ceramic or fritted glass. However, some electro-oxidation reactions can be performed in an undivided cell equipped with two electrodes and a magnetic stirring bar (see Figure **2**). Finally, in a jacketed cell, the temperature of the solution can be controlled by cooling the cell with tap water, which can be extremely useful to avoid undesirable side-reactions.

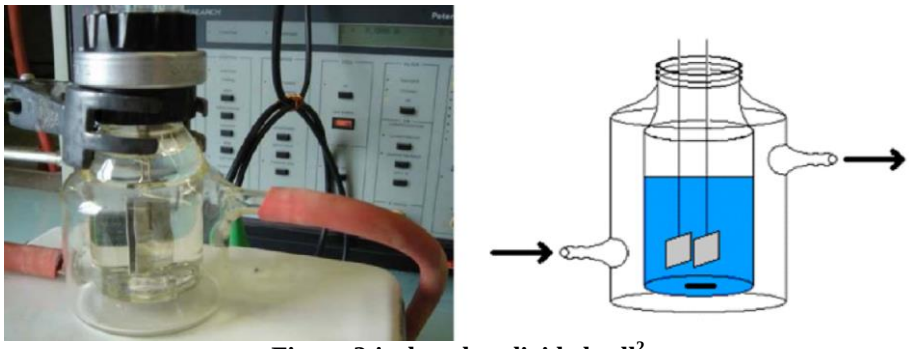


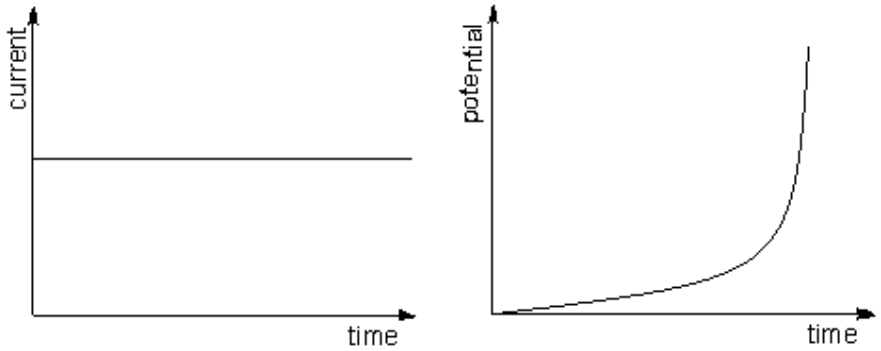
**Figure 2 jacketed undivided cell**[2]

*1.1.3.2 Electrolysis modes*

*1.1.3.2.1Constant current electrolysis*

[2] Lam, K. thèse de doctorat, Université catholique de Louvain, **2010**.

There are two ways to control electrochemical reactions. The first one is known as the constant current method. In this case, the current density, which is the current flow per unit of electrode area, is measured to express the rate of the electrolysis. This value is expressed in $mA/cm^2$ unit, and is calculated by dividing the total current by the immersed surface area of the working electrode. For a constant current electrolysis, a galvanostat is used to apply a current at a constant value while the potentials of the electrodes vary (see Graph **1**). Once the current is set, the anode potential climbs until it attains a sufficient value to oxidize the lowest oxidation potential species, in the medium. After, the potential stabilizes and the species are oxidized at a rate corresponding to the current applied. As soon as the first reactive species is mostly consumed, the electrode potential climbs until it corresponds to the value of the oxidation potential of a second species present in solution. The electrode potential stabilizes again at this second potential, and the second species is oxidized. This mechanism repeats until either the solvent is oxidized or the current is switched off. An equivalent reduction mechanism takes place at the cathode. Constant current reactions can be pushed to more than 90 % conversion if the current applied is appropriate. Thanks to its very simple reaction setup, the constant current electrolysis appears to be the most recommended one. Moreover, this technique allows the calculation of the Faradic Yield. However, this technique disadvantage is that the selectivity of the oxidation reaction decreases as the reagent is consumed, and the potential at the anode begins to climb. In most cases, the low selectivity of this process is not a big deal. As for example, when no other electroactive species is present, and the product oxidizes at a much higher potential than the reagent, then the yield of the reaction can be pushed to more than 90%.

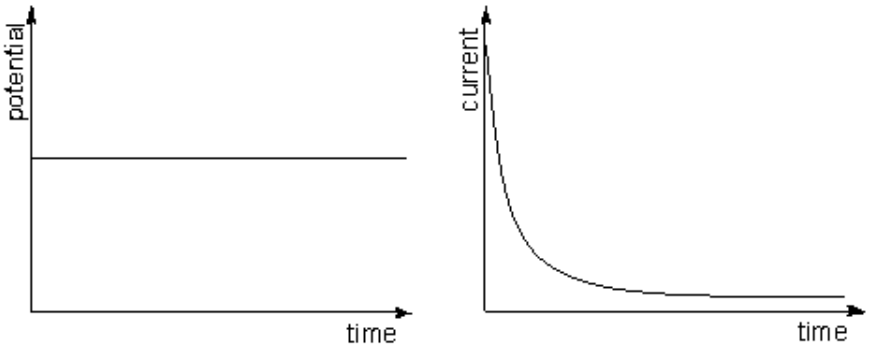



**Graph 1graphs of the evolution of the current and the potential as a function of time, in the case of a constant current electrolysis**

*1.1.3.2.2Constant potential electrolysis*

The second one is called the controlled potential electrolysis. This technique is used if the need for selectivity is really an issue. In this type of reactions, a reference electrode is added in the solution, in order to monitor the potential of the working electrode. In the case of an anodic reaction, as the potential of the working electrode is maintained stable, only substrates having an oxidation potential equal or lower

than the potential of the anode will be oxidized. This technique ensures selectivity throughout the entire reaction time. Unfortunately, this gain in selectivity brings some drawbacks. As the concentration of the reagent drops, the current density decreases (see Graph **2**). Consequently, to push a controlled potential electrolysis to high conversion is extremely time-consuming. Furthermore, the reaction set-up is more complex, as this technique requires the use of a third electrode and a potentiostat in order to set the potential of the working electrode relative to the reference electrode.




**Graph 2 graphs of the evolution of the current and the potential as a function of time, in the case of a controlled potential electrolysis**

## 1.1.4 Theoretical aspects in electrochemistry

### *1.1.4.1 The electric potential*

The electric potential is a physical value expressed in Volt, which describes the electric state of a point in space. In an electrochemical cell, the potential difference (electrical voltage) between the two electrodes is the cause of the current flow through this cell. Indeed, the current always comes down the potentials: that means that the electrical current flows the electrical circuit from the higher potential to the lower potential.

In the same trend that the temperature rise promotes endothermic reactions, the potential rise of an electrode can readily accelerate electrochemical reactions of several orders of magnitude, if the material transport is fast enough, and the electron transfer is the rate-limiting step.

To prove this point, let us consider the energy diagram of an electron transfer at an electrode: $Ox + ne^- \rightleftharpoons Red$ (see Graph **3**).

The potential energy profiles Red A and Ox are at the standard potential of the system, where by definition the reduction rate constant ($k_{Ox->Red)}$ and the oxidation rate constant ($k_{Red->Ox}$) are equal. Moreover, $\Delta G_{eq}$ is the activation energy for an electron transfer under those conditions. If this value is high, the interconversion from Red to Ox is slow at that potential.

Now assume that the electrode potential is moved from its equilibrium value of a $\Delta E$ quantity towards a favored reduction. The fact that the reduction becomes favored leads to a modification of the energy profile between Red A and Red B because an

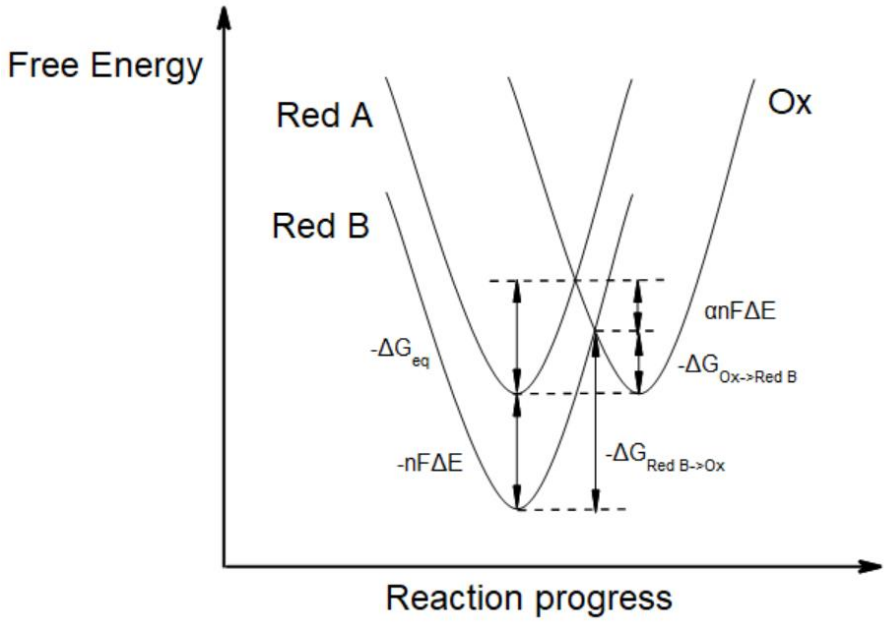
easier reduction means that the free energy of the reduced species is decreased. This free energy decrease is given by the formula: $\Delta G = nF\Delta E$. Now, the activation energy to oxidize Red to Ox and to reduce Ox to Red is expressed by:

$$\Delta G_{Ox->Red} = \Delta G_{eq} - \alpha nF\Delta E$$
$$\Delta G_{Red->Ox} = \Delta G_{eq} + nF\Delta E - \alpha nF\Delta E$$
$$\Delta G_{Red->Ox} = \Delta G_{eq} + (1 - \alpha)nF\Delta E$$

Where $\alpha$ represents the electronic transfer coefficient ($0 < \alpha < 1$) which depends on the shape of the Red and Ox energy profiles. Moreover, this charge transfer coefficient is used to describe the kinetics of electrochemical reactions. Once these expressions of activation energy are used in the Arrhenius equation, it gives the following rate constants:

$$k_{Ox->Red} = k^{Ref}_{Ox->Red} \exp(-\alpha nF(E-E_{Ref})/RT)$$
$$k_{Red->Ox} = k^{Ref}_{Red->Ox} \exp((1-\alpha)nF(E-E_{Ref})/RT)$$

Where Ref corresponds to the standard conditions. It can be seen that the speed constant of an electron transfer reaction depends exponentially on the electrode potential.




**Graph 3 Energy diagram of an electron transfer at the electrode, where : - $\Delta G_{eq}$ = activation energy of an electron transfer to convert Red A in Ox or Ox in Red A; -$\Delta G_{Ox->Red}$ = activation energy of an electron transfer to reduced Ox in Red B; -$\Delta G_{Red->Ox}$ = activation energy of an electron transfer to oxidized Red B in Ox; n = number of electrons involve in this reaction; F = the Faraday constant (96 485.33 C/mol) (F = Na*q where Na = Avogadro constant ($6.02*10^{23}$ $mol^{-1}$) and q = the fundamental electron charge ($1.602*10^{-19}$C)); ΔE = the potential difference.**

In conclusion, the electric potential has a major impact on organic electrochemical reactions because this potential enables the electronic exchanges and the current flow through the cell. Moreover, this value has a significant incidence on the kinetic of organic electrochemical reactions and a good calibration of this variable can provide excellent reaction selectivity.

*1.1.4.2 The electrical current*

The electric current refers to the motion of electrical charge carrier in a conductive material per unit of time (Q = I*T). Throughout an electrolysis, the electric current, through conductive materials (electrodes included), is operated by the electron movement. However, this current circulates in the solution via the movement of all the charged species in the reaction mixture. Thus, the positively charged species travel in the conventional current direction to the cathode, while the negatively charged species move to the anode. Three different transport modes exist and are discussed in the following section.

#### *1.1.4.3 Electrolysis transport modes*

In an electrical circuit, the current flow is operated by the movement of electrons. However, in the case of an electrolysis, at the metal-solution interface, the current flow is proceed by an electrochemical reaction, and, in the bulk solution, the current flow is ensured by the movement of the cations and ions in the solution. More specifically, in the reaction mixture, three different transport modes ensure the current flow, which is guaranteed by the motion of charged substrate and electrolyte salt, in the media.

##### *1.1.4.3.1 The diffusion*

Firstly, the diffusion is a transport mode leaded by the concentration differences. More specifically, this is the motion of the species from most concentrated regions to less concentrated areas. The diffusion only takes place at the vicinity of the electrodes and the thickness of the diffusion layer may be only few micrometers (strong stirring) to several centimeters (no stirring).

##### *1.1.4.3.2 The convection*

Secondly, convection is a motion caused by the macroscopic fluidic movements and appears in the solution and not in the diffusion layer. In the case of organic electrochemistry, the convection is forced by the motorized stirring.

##### *1.1.4.3.3 The migration*

Thirdly, the migration is a movement affected by an electrical field and occurs in all the solution. At the anode, the electrons are removed from the substrate to go through the anode, therefore the anode is positively charged. On the other hand, at the cathode, the electrons come from the cathode to react with the substrate, therefore the cathode is negatively charged. Essentially, the anions diffuse from the cathode to the anode, while the cations diffuse from the anode to the cathode.

Finally, the diffusion and convection impacts ions and non-charged molecules while the migration only affects charged moieties.

#### *1.1.4.4 The electric double layer*

In the case of conventional chemical reactions in a homogeneous solution, the distribution of the molecules in the solution is commonly uniform. Therefore, the reaction takes place homogeneously in the solution. Contrarily, in the case of an electroorganic reaction, the activation of the reactant does not take place in the bulk of solution, but rather in the vicinity of the electrode surface, which is able to give or take electrons. During an electrolysis, the anion moieties can lie in an electric double layer (inner Helmholtz layer), 10 – 15 Å thick, adjacent to the anode as desolvated species, as solvated species or adsorbed on the anode surface. In direct electro-oxidation processes, the electric double layer has a significant impact on electron transfer. Moreover, the variability of the structure of the double layer has also an impact on the oxidation potential of the substrate and the current. At the anode-solution interface, solvated anions are concentrated in parallel to the surface of the

anode, constituting a charge transfer layer. A sharp drop in potential is detected ongoing from the anode surface to the charge transfer layer. Accurately, the charge transfer layer can be splitted in two layers, the inner and outer Helmholtz layers (see Figure **3**). The inner layer constitutes the area from the electrode surface to the centers of desolvated anions adsorbed at the anode surface. While the outer Helmholtz layer represents the space portioned by the inner limit and the centers of the solvated anions. The large potential drop between the electrode and the outer Helmholtz layer causes the electron transfer from the substrate to the anode. Finally, dipolar solvent can also adopt a specific orientation, at the immediate vicinity of an electrode. For instance, various studies have shown a small but significant orientation of water dipoles at the vicinity of Hg electrode with oxygen lone-pairs oriented towards the metal.[3]

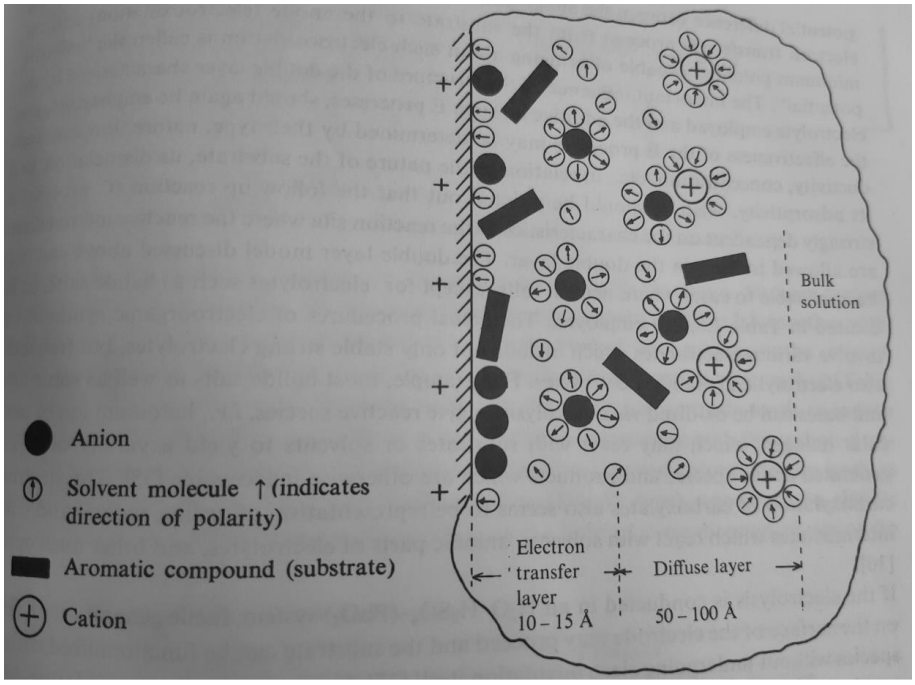



**Figure 3 electric double layer, taken from ref[4]**

## 1.1.5 Organic electrochemistry advantages and disadvantages

### *1.1.5.1 Advantages*

The synthetic organic use of electricity is presently experiencing a renaissance.[5] With a growing number of synthetically oriented laboratories working on this area,

[3] Korzeniewski Conway The electrochemical double layer. Texas: The Electrochemical Society **1997**.

[4] Torii, S. Electroorganic Syntheses Methods and Applications, Part 1: oxidation, Monographs in Modern Chemistry. Tokyo: Kondansha **1985**, p 17.

the field of application of this method is currently broadening. In the following subsections, the advantages explaining the rebirth of this technology, which was lately seen as a niche method, are listed.

*1.1.5.1.1Environmentally friendly method*

The green chemistry aims to create chemicals and processes that lower or eradicate the use and generation of hazardous substances.[6] Green chemistry actively looks for plans to produce substances in a way that is more harmless to human health and environment. Moreover, this concept searches new technologies that are cleaner and economically competitive. Therefore, electrochemistry seems to be one of the most important tools for implementing this conception. Indeed, electrochemistry offers numerous advantages, including lower energy requirement and increased selectivity. In addition, the electrolysis offers the benefit of completing reduction and oxidation reactions with the electron as a mass-free reagent, avoiding the use of metals or others toxic and expensive compounds. Finally, in the case of indirect electrolysis, catalytic quantities of electrochemically regenerable redox couple can be used for oxidation or reduction reactions instead of stoichiometric quantities of redox reagents.[7]

*1.1.5.1.2Economic method*

Additionally, even if the equipment cost is significant, the electrolysis is economically interesting as this process uses the cheapest electron source in the world, namely the electricity. This method enables chemists to do more with less. Furthermore, the redox "umpolung" saves steps because it allows the one-step coupling of two donors or two acceptors.[8,9] In comparable classic chemical conversions two or more steps are needed for that purpose.

In order to prove the inexpensiveness of the electric current, let's determine the cost of one mole of electrons. Given that the price of electricity in Belgium is 0.0554 €/kWh, we can thus calculate the cost of one mole of electrons. One mole of electrons (Q = 96 485 C), supplied by an electric circuit at 120 V, corresponds to an energy of 96 485 C *120 V = 11 578 200 J. Moreover, knowing that 3 600 000 J corresponds to 1 kWh, this energy value equals 3.21 kWh. Therefore, the cost of one mole of electrons is 3.21 kWh*0.0554 €/kWh = 0.18 €.

*1.1.5.1.3Practical method*

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[5] (a) Yan, M.; Kawamata, Y.; Baran, P.S. *Chem. Rev.* **2017**, 117, 13230; (b) Wiebe, A.; Gieshoff, T.; Möhle, S.; Rodrigo, E.; Zirbes, M.; Waldvogel, S.R. *Angew. Chem. Int. Ed.* **2018**, 57, 5594.

[6] Anastas, P.T. ; Warner, J.C. *Green Chemistry: Theory and Practice*, Oxford University Press, New York, **1998**, p. 30.

[7] Sequeira, C.A.C.; Santos, D.M.F. *J. Braz. Chem. Soc.* **2009**, 20, 387.

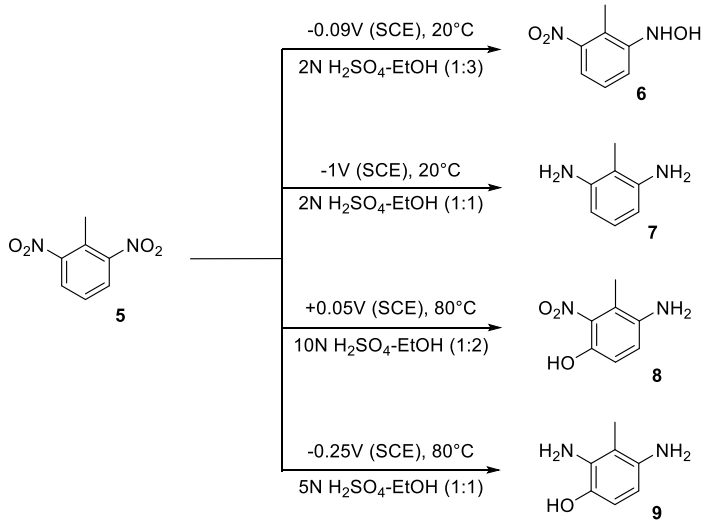
[8] Moeller, K.D.; Tinao, L.V. *J. Am. Chem. Soc.* **1992**, 114, 1033.

[9] Bowers, R.; Giese, R.W.; Grimshaw, J.; House, H.O.; Kolodny, N.H.; Kronberger, K.; Roe, D.K. *J. Am. Chem. Soc.* **1970**, 92, 2783.

Electrochemical preparations are generally easier to conduct than classic chemical transformations. First, solubility problems, which often appear with inorganic redox reagents, are not encountered. Secondly, the work-up is usually simpler, as no by-product derived from chemical oxidants or reductants must be separated. Furthermore, electroorganic reactions are performed under less aggressive process conditions, commonly room temperature, ambient air, and atmospheric pressure. Finally, the scale-up of electrochemical reactions and the transposition of those processes from a batch reactor to a flow device are typically easier than in the case of classical chemistry transformations.

*1.1.5.1.4Selective method*

The chemoselectivity of an electrochemical reaction is usually superior to that of a classical transformation. Indeed, by tuning the electrode potential, the chemoselectivity of electrochemical transformations increase dramatically, as illustrated in Scheme **2**.[10] For example, by modulating the experimental conditions, such as the temperature, the pH, the solvents, and the potential employed, the dinitrobenzene derivative **5** can be reduced selectively leading to a number of polyfunctional products.



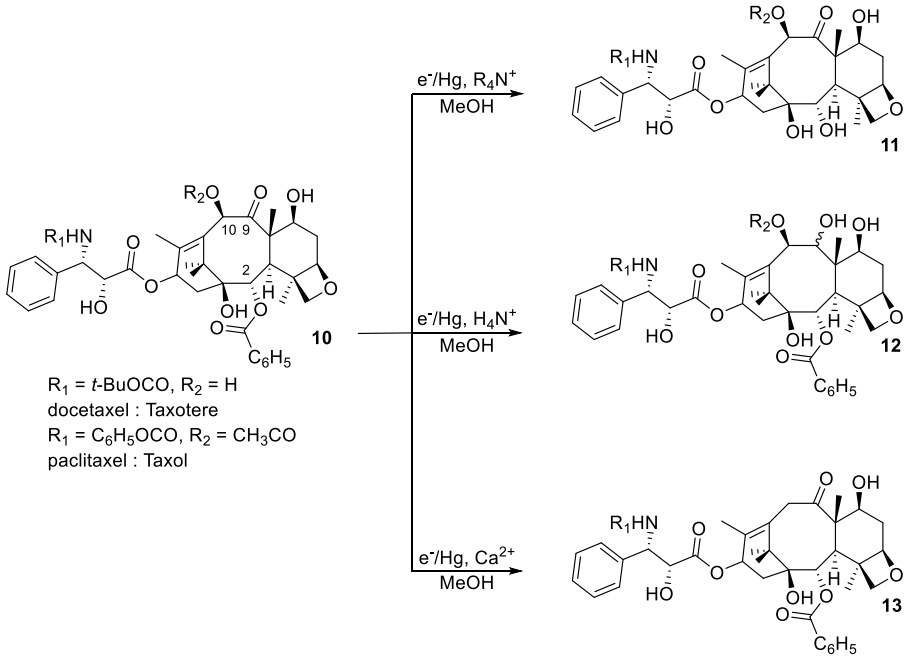

**Scheme 2 dinitrobenzene reduction under different experimental conditions**

Finally, the nature of the cation in the supporting electrolyte typically plays a major role in the selectivity of an organic electrolysis. This is beautifully illustrated in the electrosynthesis of taxanes, substances of relevant interest due to their antitumor activity (see Scheme **3**).[11] The regioselectivity of the electrochemical reduction of

[10] Fry, A.J. *Synthetic Organic Electrochemistry*; John Wiley and Sons, Inc. New York, 2nd Edition, **1989**.

[11] Pulicani, J.P.; Bourzart, J.D.; Bouchard, H.; Commerçon, A. *tetrahedron Lett.* **1994**, 35, 4999.

docetaxel, at a stirred mercury pool cathode, depends on the cation used and can takes place at three different positions in the taxane backbone. In the presence of a quaternary ammonium salt $R_4N^+$, the ester function located at $C_2$ is reduced into an alcohol **11** with a yield of 72 %. Employing $NH_4^+$, the ketone group at position $C_9$ is reduced to the alcohol **12** in 64 % yield. Finally, using $Ca^{2+}$ or $Mg^{2+}$ as supporting electrolyte leads to the reduction of the $R_2O$ group at $C_{10}$ in 43 % yield, because the cation is able to complex the α-hydroxy-ketone at $C_9$-$C_{10}$, which modifies the electronic density on the C-O alcoholic bond at $C_{10}$, and thus favors the dehydroxylation process. This approach enables regioselective reductions without any protection/deprotection steps.



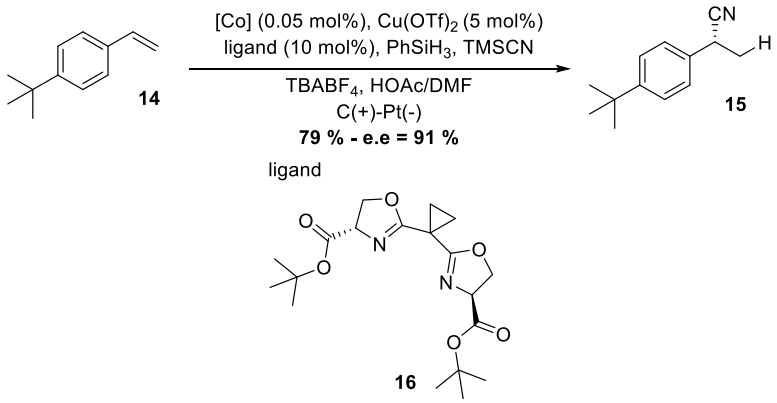

**Scheme 3 electrosynthesis of taxanes by regioselective reduction**

*1.1.5.2 Disadvantages*

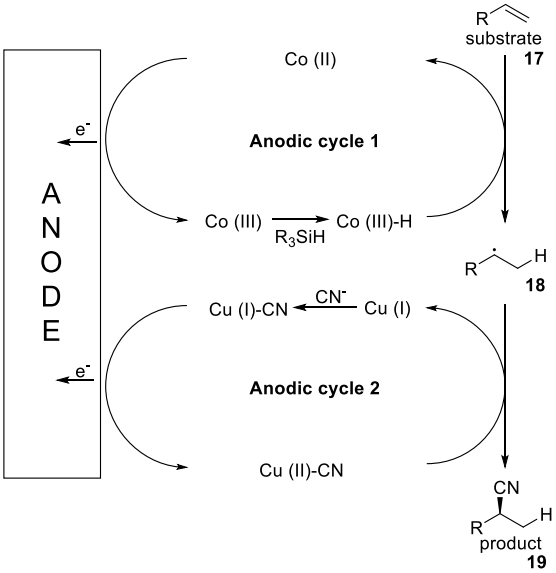
*1.1.5.2.1 Lack of stereoselectivity*

A disadvantage of electrochemistry is that the stereoselectivity is often inferior to those reached in classical transformations. An explanation of this tendency is that classical transformations involve inner sphere electron transfers, which, by nature, are more selective than outer sphere electron transfers at the electrode. Furthermore, during Kolbe electrolyzes, lower temperatures are not attainable and deeper knowledge on the control of classic reactions has been accumulated over the years. However, the potential of electrochemistry in this field remains high, and a lot of research is currently performed in order to deepen the knowledge on this area. For instance, the use of electrodes functionalized with chiral molecules allows to reach

around 50 % e.e.. Moreover, the use of a chiral mediator enables to reach excellent enantiomeric excesses via electrochemistry. For instance, Song Lin *et al.* have developed, in 2019, an enantioselective hydrocyanation of conjugated alkenes via dual electrocatalysis (see Scheme **4**).[12] This strategy combines a cobalt-mediated hydrogen-atom transfer and a copper promoted radical cyanation, without the need for stoichiometric oxidant (see Scheme **5**).




**Scheme 4 enantioselective hydrocyanation of conjugated alkenes via dual electrocatlysis**




**Scheme 5 mechanism of the enantioselective hydrocyanation of conjugated alkenes via dual electrocatalysis**

[12] (a) Song, L.; Fu, N.; Ernst, B.G.; Lee, W.H.; Frederick, M.O.; Distasio, R.A.; Lin, S. *ChemRxiv.* **2019**; (b) Fu, N.; Song, L.; Liu, J.; Shen, Y.; Siu, J.C.; Lin, S. *JACS* **2019**, 141, 14480.

*1.1.5.2.2Uncommon technique*

Moreover, organic chemists have only sparsely applied electrochemistry despite the long history of the latter. This may be due to their lack of familiarity with this method and the use of specialized equipment. In addition, even if organic electrochemistry is a synthetic method, the majority of the text-books on this area are based on an analytical physical approach, which can complicate the understanding for organic chemists. Notwithstanding, performing electrolyzes for synthesis does not require complicated material and even with a basic comprehension of this method, many reaction setups can be simplified to accomplish transformations of interest with simple battery, as a power supply, and common glassware. Finally, in recent years, organic electrochemists have developed new equipment to increase the reproducibility of experiments, which is accompanied by a variety of different parameters influencing the reaction. For instance, Baran has developed with IKA the ElectraSyn 2.0. an inexpensive and easily applicable setup for beginners, and Waldvogel has developed a sccreening system for up to eight simultaneous reactions as well as commercially available continuous flow electroorganic reactors.[13]

*1.1.5.2.3Long reaction time*

Clearly, in a batch electrolytic cell, the bidimensional character of the electrode and the heterogeneous nature of the electron transfer can extend the reaction time. To offset this problem, porous electrode (known for their larger surface) or large surface electrodes can be used. Furthermore, stirring and the use of ultrasounds can facilitate the supply of the product to the electrode. Finally, the transposition of electro-reactions to a continuous flow reactor or microreactor can drastically lower the reaction time thanks to the high ratio of electrodes surface to reactor volume.[14]

*1.1.5.2.4Conductivity requirement*

Another disadvantage is that conductivity is required in order to allow the movement of electrons through the cell. This is the reason why polar solvents and supporting electrolytes are needed to perform an electroorganic synthesis.

*1.1.5.2.5Electrodes passivation*

Finally, the passivation of the electrodes can significantly affect the outcome of an electroorganic procedure. Passivation means that the electrode become passive, which involves creation of an outer layer of shield material, at the surface of the electrode. This problem can be overcome by changing the nature of the electrolyte or the electrode material or by pulsing the voltage. For instance, the oxidation of methanol to paraformaldehyde leads to the formation of a white layer at the surface of the anode, which passivates this electrode.

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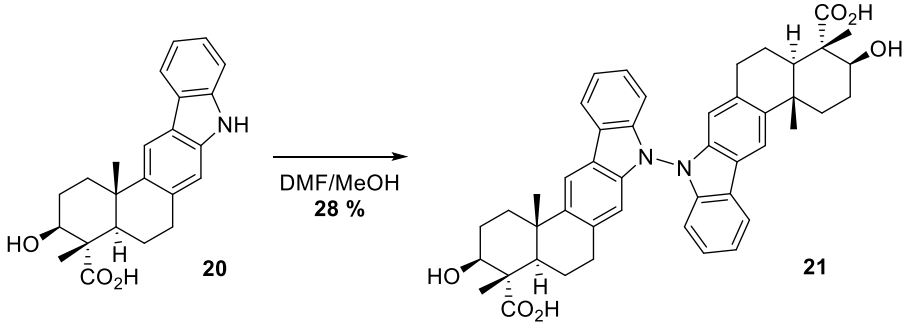
[13] Pollok, D.; Waldvogel, S.R. *Chem. Sci.* **2020**, Advance Article.

[14] (a) Watts, K.; Grattrell, W.; Wirth, T. *Belstein J. Org. Chem.* **2011**, 7, 1108; (b) Folgueiras-Amador, A.A.; Philipps, K.; Guilbauds, S.; Poelakker, J.; Wirth, T. *Angew. Chem. Int. Ed.* **2017**, 56, 15446.

### 1.1.6 Renewed enthusiasm for organic electrochemistry

Despite all the advantages of the organic electrochemistry, this technology has never been a routine tool in the armamentarium of the organic chemists working on a laboratory scale.[15] Indeed, for most organic chemists electrochemistry represents a technique used as a "last resort". The stagnation in the interest within the synthetic community may be explained by various reasons, such as the existence of analogous non-electrochemical technologies, the complex reaction setup (potentiostat, galvanostat, divided/undivided cell, electrodes, *etc.*) and the seemingly endless number of reaction variables (electrolyte, electrodes, cell type, and current density, *etc*.).[16] Moreover, this may be due to the lack of engineering research directed in this area. Actually, in order to attempt any electrochemical experiment, chemists are required to engineer their own setups. This is why many of the recent elegant literature examples employ homebuilt setups rather than commercially available equipment.[17] Finally, electrochemistry is mostly teach by physical chemists and the organic electrochemistry textbooks are mostly based on physical concepts, which seems to create a barrier to preparative organic applications.[18]

However, this last decade, the organic electrochemistry has gained a renewed interest and is seen as an emerging field. The increasing awareness of the versatility and uniqueness of electrolysis procedures in organic synthesis can be explained by several factors, such as the rich history, the useful reactivity enabled by electrochemistry, the invention of devices that cater to the specific needs of the synthetic community, and the application of electrochemistry in complex molecule synthesis. For instance, Baran has solved a synthetic problem applying the anodic oxidative dimerization to the synthesis of dixiamycin **21** (see Scheme **6**).[19]




**Scheme 6 oxidative dimerization applied to the synthesis of dixiamycin 21**

Moreover, with the appearance of the modern risks, such as the global warming, dramatic natural disasters, and limitations of fossil resources, our society is

[15] Yan, M.; Kawamata, Y.; Baran, P.S. *Angew. Chem. Int. ed.* **2018**, 57, 4149.
[16] Kingston, C.; Palkowitz, M.D.; Takahira, Y.; Vantourout, J.C.; Peters, B.K.; Kawamata, Y.; Baran, P. *Acc. Chem. Res.* **2020**, 53, 72.
[17] Horn, E.J.; Rosen, B.R.; Baran, P.S. *ACS Cent. Sci.* **2016**, 2, 302.
[18] Waldvogel, S.R. *Beilstein J. Org. Chem.* **2015**, 11, 949.
[19] Rosen, B.R.; Werner, E.W.; O'Brien, A.G.; Baran, P.S. *J. Am. Chem. Soc.* **2014**, 136, 5571.

increasingly quartered between, on one side, the concern for the economic efficiency and sustainability, and, on the other side, the need to protect the environment. This global change has created the inclusion of ecological parameters into the investment process of chemical industries. Given that industries and government are increasingly calling for technological innovations in this field, scientists are seriously concerned by this thematic. Organic electrochemistry appears to be the ideal tool for this purpose as this technology is environmentally friendly and economical.

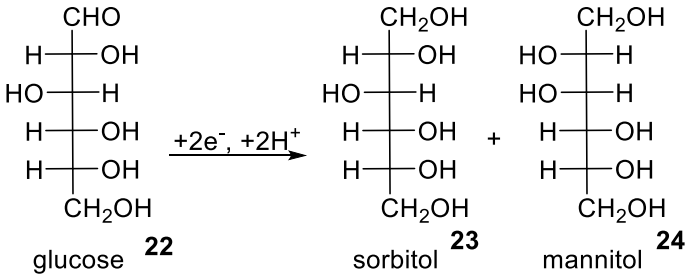
Finally, the combination of electrochemistry with other powerful techniques, such as ultrasonic treatment and flow microcells, will push electrosynthesis applications beyond current limits and make it even more attractive.

### 1.1.7 Organic electrochemistry in industry

Clearly, the best way to show the efficiency of organic electrochemistry is to present some reactions developed in industry. Indeed, even if it is a little bit downgrading, the shortcut between the interest of a reaction and its industrial exploitation remains valuable. Actually, the value of an organic reaction is defined by its utility. Therefore, some industrial electrochemical reactions are presented in the following paragraphs.

#### *1.1.7.1 Mannitol and sorbitol*

Until 1920, only a few electroorganic processes were utilized in industry, among them the production of either mannitol **24** or sorbitol **23** from glucose **22** (see Scheme **7**). In this example, the major product of electro-reduction depends upon the pH of the solution.[20] These sugar alcohols formed via electrochemistry are used as sweeteners and medications. For instance, D-mannitol is employed to reduce raised intracranial pressure; and sorbitol can be used as a laxative.




**Scheme 7 pH dependent reduction of glucose**

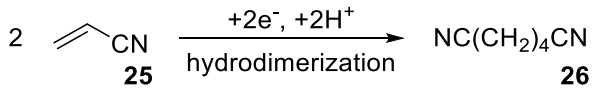
The indirect electro-oxidation of aldoses to the corresponding aldonic acids, which was carried out industrially as early as 1930, is still used today on tone scale by

[20] Creighton, H.J. *Can. Chem. Process Inds.* **1942**, 26, 690.

Sandoz.[21] Early, porcelain diaphragms were replaced with less fragile and more chemically inert polymeric membranes. Furthermore, the way to conceive the structure of the electrodes changed, in order to obtain larger surface areas. In particular, tridimensional electrodes cells were employed, and systems of forced circulation of the electrolyte were adopted.

### *1.1.7.2 Adiponitrile*

During 1955-65, great efforts pioneered by Baizer among others led to the development of the first large-scale manufacturing plant for the production of adiponitrile **26** by means of electro-reductive coupling of acrylonitrile **25** (see Scheme **8**).[22] This remains the largest volume organic electrochemical process. Adiponitrile, an intermediate to nylon, is produced by Monsanto at Decatur, Alabama, to the extent of about 200 million kg per year by electro-hydro-dimerization of acrylonitrile, using a cadmium cathode and a steel anode in aqueous phosphate buffer solution in an undivided cell of compact and sophisticated design.[23]




**Scheme 8 production of adiponitrile by hydro-dimerization**

### *1.1.7.3 Sebacic acid*

Sebacic acid is a reagent commonly used in plastic, cosmetic, lubricant, and candles industry. This chemical is produced industrially by hemi-synthesis from glycery ricinoleate, which is extracted from the castor oil.[24] Unfortunately, due to the formation of by-products, the yield of sebacic acid is low, in practice yields of 50 – 55 % are considered to be good. For that reason, an electrochemical way to produce industrially this molecule was developed. Indeed, Asahi Chemical Industry, in Japan, produced electrochemically this acid for several decades and BASF, in Germany, has also piloted this process.[25] This procedure provides high purity sebacic acid form readily available adipic acid. This process consists in three steps. Firstly, adipic acid is partially esterified into monomethyl adipate. Secondly, the potassium salt of the monomethyl adipate **27** is electrolyzed in a mixture of methanol and water, leading to the formation of dimethyl sebacate **28** (see Scheme **9**). Finally, the ester **28** is hydrolyzed into sebacic acid; the overall yields are reported to be about 85 %.

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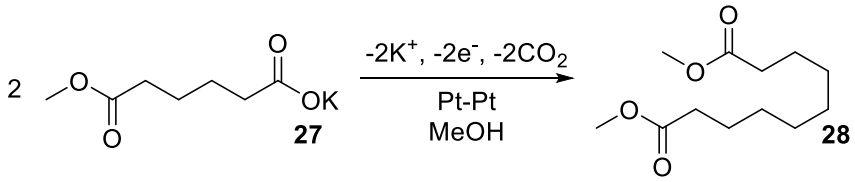
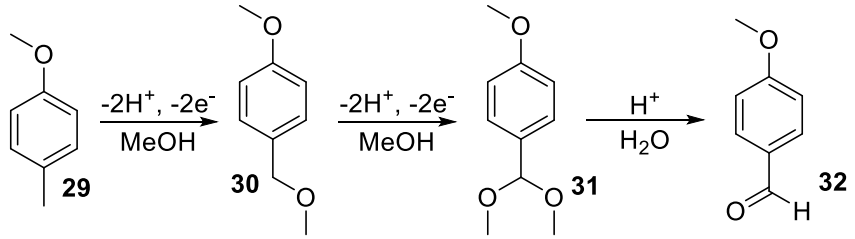
[21] Neuezüricher Zeitung, *Organische Synthese durch Elektrolyse*, 31.12.85.
[22] (a) Baizer, M.M. *J. Electrochem. Soc.* **1964**, 111, 215; (b) Baizer, M.M. *Chem. Ind.* **1979**, 435.
[23] Danly, D.E. *J. Electrochem. Soc.* **1984**, 131, 435.
[24] Gilbert, M. *Brydson's plastics materials* **2017**, p789.
[25] Seko, M.; Yomiyama, A.; Isoya, T. *Hydrocarbon Processing* **1979**, 117.




**Scheme 9 electrochemical preparation of the dimethyl sebacate 28**

*1.1.7.4 Substituted benzaldehydes*

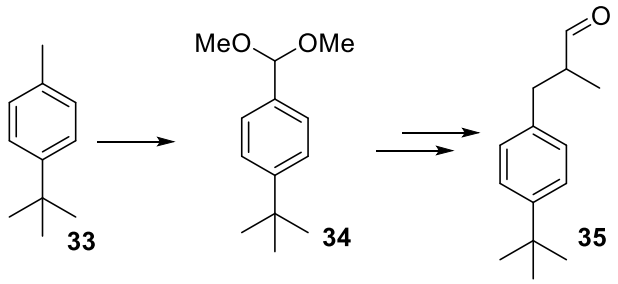
Aromatic aldehydes are mostly utilized as additives in perfumes, as flavoring additives or as intermediates for the design of pharmaceuticals. This family of compounds was first synthetized by chemical oxidation under harsh conditions. However, the low selectivity and low yields led chemists to search for an alternative synthesis road. Therefore, organic electrochemistry was used for the oxidation of alkyl aromatic reagents (see Scheme **10**). Indeed, toluene moieties can be anodically oxydated in methanol to form the corresponding dimethylacetal **31**, which is then hydrolyzed to generate the corresponding aldehyde. Thanks to this strategy, BASF produces 3500 tons per year of *p*-anisaldehyde **32** by oxidation of *p*-methoxytoluene **29**.[26]




**Scheme 10 *p*-anisaldehyde 32 electrosynthesis**

Another product of this process is the lysmeral **35**, which is a fragrance with the smell of lily of the valleys.[27] This aroma-chemical is found in several perfumes such as: Anais Anais by Cacharel, and Eternity by Calvin Klein. BASF performs the anodic dimethyloxylation of 4-*tert*-butyltoluene **33** to afford the protected benzaldehyde **34** (see Scheme **11**). The condensation of this intermediate with propanal, and a subsequent hydrogenation leads to the formation of the lysmeral **35**. Finally, the hydrogen formed via reduction of the methanol during electrolysis is used in the hydrogenation process.

[26] Cardoso, D.S.P.; Sljkic, B.; Santos, D.M.F.; Sequeira, C.A.C. *Org. Process Res. Dev.* **2017**, 21, 1213.
[27] Möhle, S.; Zirbes, M.; Rodrigo, E.; Gieshoff, T.; Wiebe, A.; Waldvogel, S.R. *Angew. Chem. Int. Ed.* **2018**, 57, 6018.



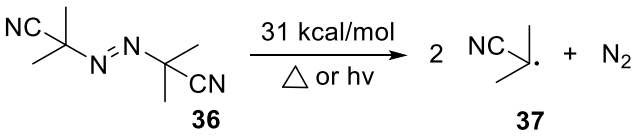

**Scheme 11 BASF lysmeral electro-production**

Nowadays, chemical manufacturing represents 26 % of the world energy demand. This is the reason why organic electrochemistry has emerged as a promising platform for the integration of renewable energy sources in chemical industry.[28] Indeed, over the past 25-30 years, the use of electrochemistry as a synthetic tool in organic chemistry has increased remarkably. More than 100 electroorganic synthetic processes have been piloted at levels ranging from a few tons up to $10^5$ tons. This number can be even higher considering that most of the electroorganic processes in synthesis are protected by industrial interest.[29] The high degree of interest for that technique is related to the fact that this method is economic, environmentally friendly, readily scalable, and selective. Moreover, this type of processes enables the direct interconversion of clean electricity into chemical energy. Finally, those last years, a wide range of new strategies have provided answers to problems that previously limited the performance of those processes, such as paired electrochemical reactions, indirect electrosynthesis, electrochemical microreactors, ionic liquids, and improvement and sophistication in the equipment, *etc*.

### 1.1.8 Radical cyclization reactions

In the same way as thermolysis and photolysis (see Scehme **12**), the Kolbe reaction is a methodology that promotes the formation of radicals. However, contrary to the first two methodologies, the radical originates from the intramolecular transfer of one electron through an oxidation process. Moreover, thermolysis and photolysis reactions are homogeneous reactions, whereas the Kolbe electrolysis only takes place at the surface of the anode, where, depending on the reaction conditions, the radical concentration can be $10^3$ to $10^6$ higher than in the case of homogeneous processes. Therefore, a radical recombination process takes place, at the surface of the anode, which is a very rare phenomenon in homogeneous reactions.

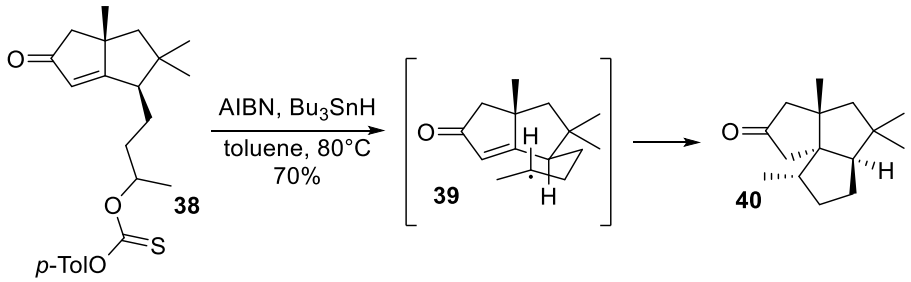
[28] Blanco, D.E.; Modestino, M.A. *Trends in Chemistry* **2019**, 1, 8.
[29] Pletcher, D.; Walsh, F.C. *Industrial Electrochemistry.* 3rd Edition; Blackie Academic & Professional: London-New York, **1993**.



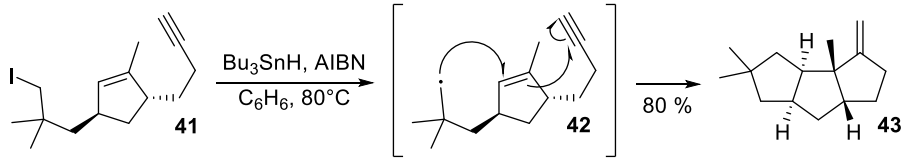

**36** **37**

**Scheme 12 thermal or photochemical decomposition of AIBN 36**[30]

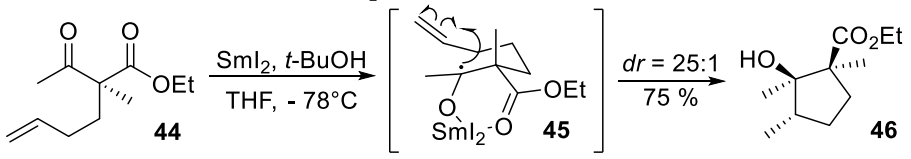
Radical cyclization reactions are powerful and have been widely applied in organic synthesis.[31] Those reactions were used by Curran[32], Molander[33], and Rao[34], who generated radicals from different functions, such as: halogens (see Scheme **14**), ketones (see Scheme **15**), xanthates[35] or carbonothioates (see Scheme **13**). The advantage of the radical chemistry is that radicals are highly reactive intermediates and can be used for the construction of hindered and strained systems. Moreover, radical cascades can be utilized for building complex polycyclic systems.




**Scheme 13 Stereospecific radical cyclization for the synthesis of silphinene, a fused tricyclopentanoid**




**Scheme 14 tandem radical cyclization strategy applied to the synthesis of the triquinane; hirsutene**




**Scheme 15 functionalized carbocycle formation by intramolecular reductive coupling reaction promoted by samarium diiodide with stereochemical control**

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[30] Engel, P.S. *Chem. Rev.* **1980**, 80, 99.

[31] (a) Rossi, R.A.; Penenory, A.B. *Curr. Org. Synth.* **2006**, 3, 121; (b) Majumdar, K.C.; Basu, P.K.; Chattopadhyay, S.K. *Tetrahedron* **2006**, 63, 793; (c) Miyabe, H.; Takemoto, Y. *Chemistry – A European Journal* **2007**, 13, 7280; (d) Giese, B.; Kopping, B.; Göbel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K.J.; Trach, F. *Organic Reactions;* Vol. 48 Paquette, L.A.; John Wiley & sons, Inc. **1996**, p 301.

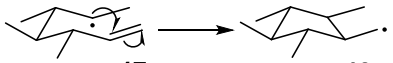
[32] Curran, D.P.; Rakiewicz, D.M. *J. Am. Chem. Soc.* **1985**, 107, 1448.

[33] Molander, G.A.; Kenny, C. *J. Am. Chem. Soc.* **1989**, 111, 8236.

[34] Rao, Y.K.; Nagarajan, M. *Tetrahedron Lett.* **1988**, 29, 107.

[35] Quiclet-Sire, B.; Zard, S.Z. *Science China Chemistry* **2019**, 62, 1450.

Many others efficient systems were developed, and theoretical and empirical researches have strengthened the practical aspect of those reactions. Indeed, many physico-chemical studies have allowed to generate some predictive rules about the capacity of a radical to cyclize, radical stability, and radical tolerance for other chemical functions. For example, Baldwin rules are empirical kinetic rules, which predict the relative facility of ring forming reactions.[36] Those rules are useful to organic chemists especially in planning synthesis. Finally, the relative stereochemistry of the substituents of a cyclization product can be rationalized using the Beckwith model (see Scheme **16**).[37]



**47** **48**

**Scheme 16 Beckwith model**

In this model, the substituents preferentially occupy the pseudo-equatorial positions, in the favored chair-like transition state. Some theoretical calculations support this model, which rationalizes the behavior of radical species on basis of simple notions concerning the way in which steric and stereoelectronic factors affect the relative stability of possible transition states.[38] Thanks to those results and extensive research in this field, radical chemistry has been developed significantly during these last decades. This is the reason why, nowadays it is common to synthesize complex molecules by radical chemistry. However, despite major progresses, the radical generation still appears problematic. Indeed, this step relies on the use of toxic and expensive compounds ($(Me_3Si)_3SiH$, tin hydrides). Therefore, the radical generation by electrochemistry, with its ecological, economical, and technical advantages, is an attractive alternative to common methodologies.

## 1.1.9 Kolbe reaction

### *1.1.9.1 Historic of the Kolbe reaction*

The history of electroorganic chemistry as a tool for organic synthesis may be traced back to the traditional Kolbe reaction (see Scheme **17**). This bicentenary reaction is probably one of the most studied electrochemical reactions. Despite its name, the Kolbe reaction was not discovered by Kolbe but by Faraday, in 1834, when he studied the acetates conductivity in solution, and reported a flammable gas formation at the anode surface.[39] However, more focused on physics than on chemistry, he did not characterize this gas, which was ethane **52**. Nevertheless, it is only in 1849 that Kolbe determined the nature and significance of this reaction.[40] The analysis of the flammable gas formed during the electrolysis enabled him to discover a dimerization process.

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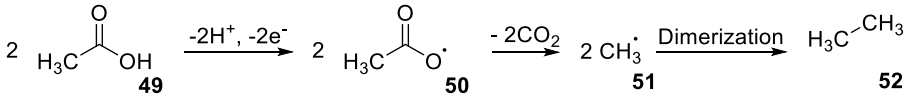
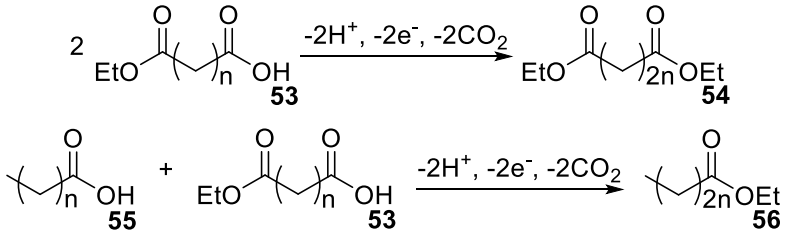
[36] Baldwin, J.E. *J.C.S. Chem. Comm.* **1976**, 734.
[37] Beckwith, A.L. *tetrahedron* **1981**, 37, 3073.
[38] Beckmith, A.L.; Schieser, C.H. *Tetrahedron* **1985**, 41, 3925.
[39] Faraday, M. *Ann. Phys.* **1834**, 109, 149.
[40] (a) Kolbe, H. *Annalen der Chemie und Pharmacis* **1848**, 64, 339; (b) Kolbe, H. *Liebigs Ann. Chem.* **1849**, 69, 257.




**Scheme 17 Kolbe dimerization reaction**

By definition, the Kolbe reaction is an electrochemical oxidation leading to the loss of an electron from a carboxylate function. The acyloxy radical **50** formed is unstable and instantly eliminates carbon dioxide to lead to the formation of the carbon centered radical **51**. Finally, this radical dimerizes generating the corresponding dimer **52**.[41]

Furthermore, the Kolbe reaction can also be performed on a mixture of two carboxylic acids. In this case, the product obtained is derived from the cross-coupling between two radicals generated from the oxidative decarboxylation of two carboxylic acids of a different nature. This process discovered in 1855, by Wurtz, is called the Kolbe cross-coupling.[42] The preferred strategy, in this type of reaction, is to introduce a large excess of the cheapest acid or the less time-consuming acid to synthetize, in order to minimize the dimerization of the most expensive carboxylic acid.[43] Indeed, the formation of dimerization side products is inevitable throughout cross-Kolbe electrolysis. Moreover, Brown and Walker have developed an effective methodology to generate electrochemically α-ω-dicarboxylic acids (see Scheme **18**).[44]




**Scheme 18 dimerization and cross-coupling of Brown and Walker**

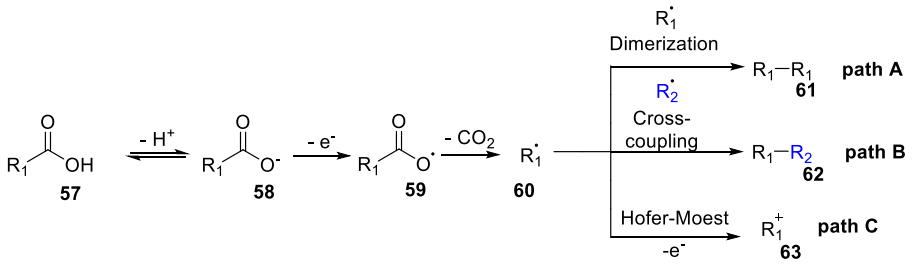
The Kolbe reaction has really taken off in the sixties, when Weedon[45], Conway[46], Eberson[47], Brennan, and Brettle[48] did a remarkable work on the mechanism and the methodology of that transformation.

### *1.1.9.2 The Hofer-Moest reaction*

However, a radical formed by oxidative decarboxylation can also lose a second electron and form a carbocation **63**. The carbocation obtained can follow different

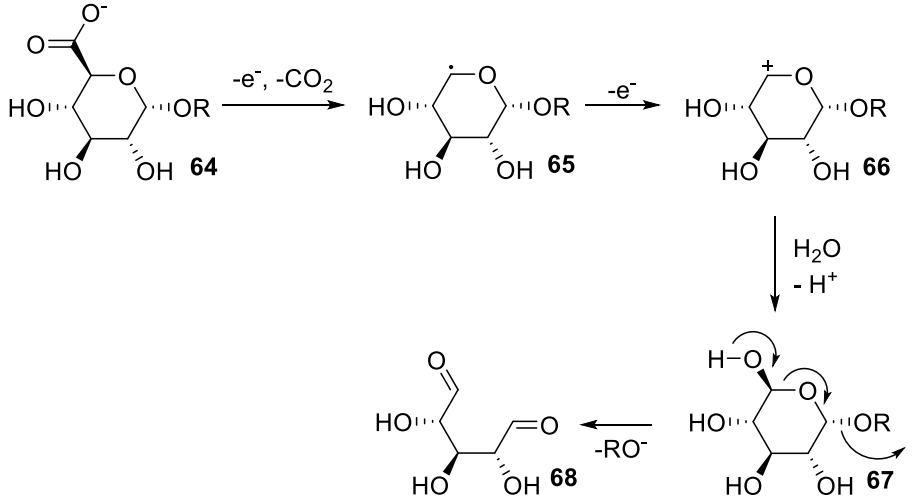
[41] Eberson, L. *Electrochimica Acta.* **1967**, 12, 1473.
[42] Wurtz, A. *Ann. Chim. Phys.* **1855**, 44, 291.
[43] Schäfer, H.-J. *Topics in current chemistry* **1990**, 152, 91.
[44] Brown, A.C.; Walker, J. *Liebigs Ann. Chem.* **1991**, 261, 107.
[45] Weedon, B.C. *Advan. Org. Chem.* **1960**, 1, 1.
[46] Vijh, K.; Conway, B. *Chem. Rev.* **1967**, 67, 623.
[47] Eberson, L. *Electrochim. Acta.* **1976**, 12, 1473.
[48] Brennan, M.P. ; Brettle, R.J. *J. Chem. Soc. Perkin Trans I* **1973**, 257.

pathways and lead to solvolysis, rearrangement or nucleophile addition products. In this case, the overall process is called a Hofer-Moest reaction.[49] The experimental parameters such as the substrate structure, electrodes nature, solvent, electrolyte, temperature, and the pH, *etc*. can be optimized to allow to reach selectivity in favor of the Kolbe or the Hofer-Moest reaction.




**Scheme 19 Kolbe dimerization, Kolbe cross-coupling, and Hofer-Moest reaction**

The following example is the application of the Hofer-Moest reaction to the oxidation of the D-glucuronic acid **64** (see Scheme **20**).[50] This reaction starts by the oxidation of this acid followed by carbon dioxide elimination, which leads to the formation of the secondary radical **65**. This radical is then oxidized into the corresponding carbocation **66**. This latter undergoes the nucleophilic attack from the solvent, whose product undergoes a spontaneous hydrolysis to yield the dialdose **68**.



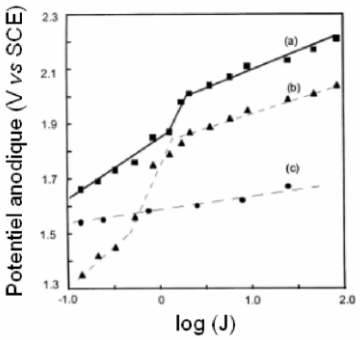

**Scheme 20 Hofer-Moest oxidation of *D*-glucuronic acid 64**

*1.1.9.3 The critical potential of a Kolbe reaction*

Some voltamperometric and mechanistic studies enabled a better understanding of the oxidation process at the electrode. When the electrolysis of a carboxylic acid is performed at a low potential, in water or methanol, the production of oxygen and

[49] Hofer, M.; Moest, M. *Liebigs Ann. Chem.* **1902**, 323, 284.
[50] Stapley, J.A.; BeMiller, J.N. *Carbohydrate Research* **2007**, 342, 610.

oxidation products of methanol (formaldehyde, paraformaldehyde, formic acid, and carbon dioxide) is mostly observed, at the anode. By contrast, the electrolysis, in water, at a potential higher than 2.00 and 1.85 V *vs* SCE enables the oxidation of carboxylic acids, as shown on the Tafel[51] diagram for platinum and iridium electrodes (see Graph **4**). It is worth noting that J symbolizes the current density applied at the electrode. What is strange and remarkable in this reaction is the ability to oxidize carboxylic acids and carboxylate salts at a potential outside the electrochemical window of the solvent ($Pt/H_2O/LiClO_4$ or $Pt/H_2O/Et_4NClO_4$: -1.10 to 1.80 [V *vs* SCE]). This phenomenon is explained by the fact that, after a critical potential, the carboxylates are preferentially adsorbed at the surface of the anode. The film formed by the carboxylates, at the anode surface, inhibits the methanol and water oxidation and enables the rise of the potential until the oxidation of the carboxylates is possible.[52] The process implies that the presence of ions, which are adsorbed preferentially to the carboxylates ($Cl^-$, $Br^-$) at the surface of the anode, inhibits the Kolbe reaction.




**Graph 4 Tafel diagram[53] (electrode: [a] platinum, [b] iridium, [c] gold)**

Finally, in order to study the oxidation of carboxylates via cyclic voltammetry, the solvent has to be an ionic liquid, such as: $[BMIM]PF_6$ (see Scheme **21**), given that those solvents have a large electrochemical window. Indeed, the oxidation of carboxylates in methanol is due to preferential adsorption phenomenon at the anode surface. The analysis of the cyclic voltammogram of a carboxylate shows that the oxidation is irreversible. Actually, only the oxidation wave is observed and no reduction wave, corresponding to the reduction of the acyloxy radical in carboxylate, is detected, even if the scanning speed is 500 mV/s. Moreover, all the tested carboxylates have a comparable oxidation potential of 2.8 V *vs* Ag/AgCl.[54]

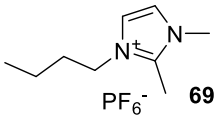
---

[51] (a) Robertson, J.B. *J. Chem. Soc.* **1925**, 127, 2057; (b) Dickinson, T.; Wynne-Jones, W.F. *Trans. Faraday Soc.* **1962**, 58, 382.

[52] (a) Fleischmann, M.; Mansfield, J.R.; Lord Wynne-Jomes *J. Electroanal. Chem.* **1965**, 10, 522; (b) Vassiliev, Y.B.; Grinberg, V.A. *Electroanal. Chem.* **1991**, 308, 1.

[53] Tafel diagram represents the exponential relationship between the applied current density at an electrode and the electrode potential of a specific metal. These graphs are used by electrochemists to predict specific corrosion related information.

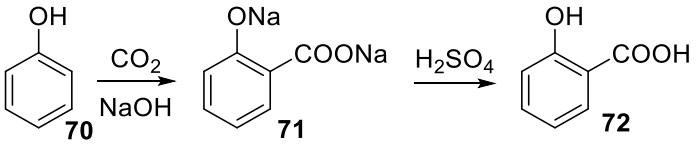
[54] Lebreux, F. Thèse de doctorat, Université catholique de Louvain, **2008**, p. 66.




**Scheme 21 [BMIM]$PF_6$**

*1.1.9.4 Adolph Wihlhem Hermann Kolbe*

Beyond the Kolbe reaction, Adolph Wihlhem Hermann Kolbe (27 September 1818 – 25 November 1884) was a great contributor in the modern organic chemistry birth. Indeed, this German chemist contributed in the development of a large number of chemical reactions, such as the Kolbe-Schmitt reaction in the preparation of the salicylic acid[55] **72** (see Scheme **22**). He also discovered, along with Edwards Frankland, that nitriles can be hydrolyzed into the corresponding carboxylic acid. He was the first person to use the word "synthesis" in its present meaning. Finally, through his synthesis of acetic acid from carbon disulfide, he contributed to the disappearance of the vitalism, which was already started by the Wöhler synthesis of urea in 1828. This doctrine holds that organic compounds can only be derived from biological compounds, as a life-force is necessary to create them.[56]




**Scheme 22 Kolbe-Schmitt reaction**

*1.1.9.5 Selectivity between radical or cationic routes*

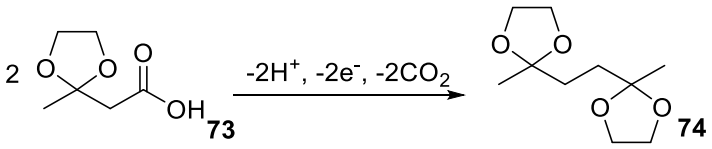
In order to give a synthetic value to this oxidative process, it is important to achieve a good selectivity between Kolbe and Hofer-Moest reactions. Through some empirical and theoretical studies, some predictive rules were highlighted. Indeed, variation of electrochemical parameters, such as temperature, concentration, pH, electrodes nature, solvent or supporting electrolyte, has an essential role in the selectivity of the reaction. Nevertheless, the substrate structure has also a leading role in the selectivity control. The following paragraphs describe those trends.

*1.1.9.5.1 <u>Substrate structure</u>*

Radicals generated by decarboxylation undergo a second oxidation only if the conversion in the corresponding carbocation is accompanied by an increase in stability. The oxidative potential of carboxylic acids is almost constant, whereas the oxidative potential of radicals is highly dependent on the substrate nature. Consequently, if the oxidative potential of a radical to a cation is higher than the oxidative potential of the carboxylate to the acyloxy radical ($E^0_{R^{\cdot}->R^+} > E^0_{RCOO^-}$-

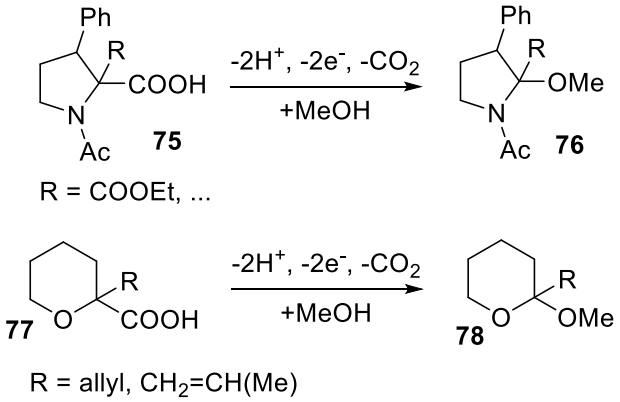
[55] Kolbe, A.W.H. *Ann. Chem. Pharm.* **1860**, 113, 125.
[56] « **KOLBE HERMANN -** (1818-1884) », *Encyclopædia Universalis* [en ligne], consulté le 22 janvier 2020. URL : http://www.universalis-edu.com/encyclopedie/hermann-kolbe/

$_{>RCOO^{\cdot}}$), the radical path is favored. This arises if the carboxylic acid is primary or if it is substituted in β-position by an electron-withdrawing group, such as an ester or a nitrile (see Scheme **23**).




**Scheme 23 primary carboxylic acid electrolysis**

By contrast, in the opposite case ($E^{0}_{R^{\cdot}->R^{+}} < E^{0}_{RCOO^{-}->RCOO^{\cdot}}$), the radical, still found close to the anode, is right away oxidized and is transformed into the corresponding carbocation. This arises if the carboxylic acid is tertiary or if an electron-donor group is found in β-position of the carboxylic acid (see Scheme **24**). Those functions can be donor by induction or mesomery.




**Scheme 24 electrolysis of a carboxylic acid in β-position of an electron-donor group**

For this reason, it is advisable to work with primary carboxylic acids or carboxylic acids substituted in β-position by an electron-withdrawing group in order to perform a Kolbe reaction. To illustrate this phenomenon, the following table **2** shows the oxidation potentials of some free radicals, which have been determined by voltammetry ($2.0 < E°_{RCOO^{-}->RCOO^{\cdot}} < 2.8$ V *vs* SCE).[57]

[57] Wayner, D.D.; Houmann, A. *Acta Chem. Scand.* **1998**, 52, 377.

**Table 2 oxidation potentials of free radicals**

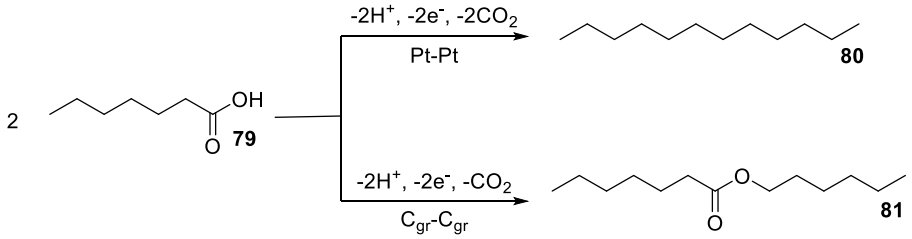
| Function | $E^{\circ}_{R^{\bullet} \rightarrow R^{+}}$ (*vs* SCE) |
|---|---|
|  | -1.03 V |
|  | -0.24 V |
|  | 0.09 V |
|  | 0.73 V |
|  | 0.99 V |
|  | 2.49 V |

*1.1.9.5.2*<u>*The electrolyte salt and substrate concentration*</u>

Under ambiguous circumstances where the electro-generated radical can follow the radical or the cationic path (as it is the case with secondary carboxylic acids), the concentration has a significant role. Indeed, the radical is adsorbed at the anode and may just as much be coupled with another radical or be oxidized in the corresponding carbocation. If the concentration or the current density is high, the number of radicals adsorbed at the anode per unit area becomes greater and the number of dimer formed increases. In contrast, the presence of an electrolyte salt can affect the Kolbe dimerization since the density in the substrate radical decreases at the surface of the anode as the anion of the electrolyte salt is also adsorbed at the anode. Therefore, the presence of an electrolyte has a tendency to promote the two electrons oxidation process.

*1.1.9.5.3*<u>*The electrodes nature*</u>

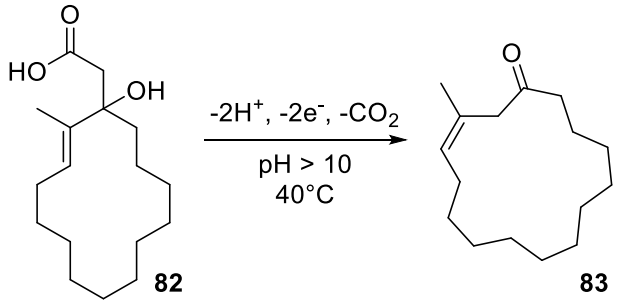
For undetermined reasons, platinum, iridium and glassy carbon (low porosity) electrodes promote the one electron process, and thus the Kolbe reaction. On the other hand, graphite carbon electrodes promote the Hofer-Moest reaction (see Scheme **25**). The most likely explanation of this process is the presence of a low bonding between the radicals and the graphite electrode. This close proximity of the radical would have the effect of making the second oxidation easier. However, these trends remain empirical.




**Scheme 25 influence of the electrode nature on the electrolysis selectivity**

*1.1.9.5.4*<u>*Temperature and pH*</u>

Usually, temperature and pH have a little influence on the selectivity between radical and cationic paths. However, in specific circumstances, some trends were identified. Indeed, at extreme temperatures and pH, the two electrons process is favored, while, at intermediate temperature and pH, the Kolbe reaction is promoted. The following example illustrates the influence of higher temperature and pH (see Scheme **26**).[58] In one hand, even if the substrate **82** structure allows a rearrangement, at intermediate temperature and pH, the carboxylic acid is oxidized, which leads to the formation of a primary radical. On the other hand, if the temperature and the pH are raised, the cationic path is followed and a rearrangement takes place.




**Scheme 26 electrolysis at higher pH and temperature**

*1.1.9.5.5*<u>*The solvent*</u>

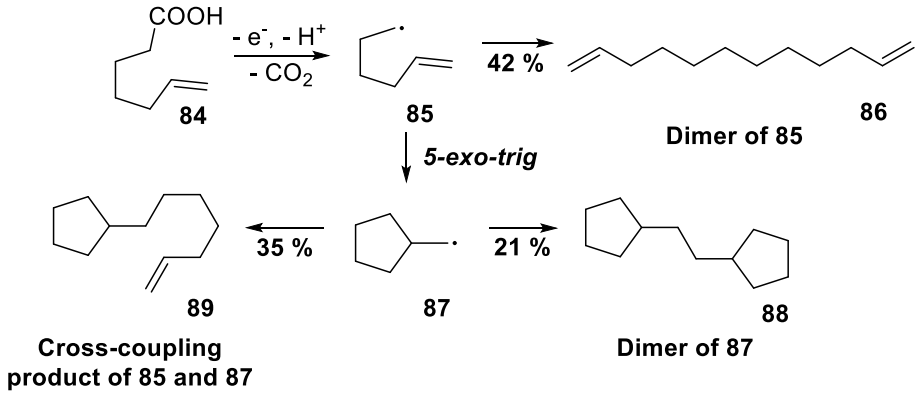
It was empirically determined that methanol, ethanol, and mixture of methanol and water are the best solvents for the Kolbe reaction. However, many different solvent conditions can be applied to the Hofer-Moest reaction, even if the methanol remains the most usual solvent for that reaction.

## 1.1.10 State of the art of the Kolbe electrocyclization reaction

It was only in 1973 that Weedon developed the first radical cyclization via Kolbe electrolysis (see Scheme **27**).[59] However, the low yields in the cyclization product **89** (around 35 %) and the formation of the side products **86** and **88** prevented the

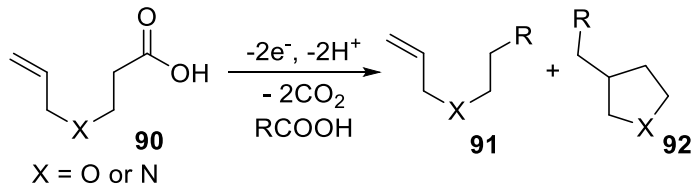
[58] Shono, T.; Hayashi, J.; Omoto, H.; Matsumura, Y. *Tetrahedron Let.* **1977**, 31, 2667.
[59] Garwood, R.F.; Weedon, B.C.L. *J. Chem. Soc. Perkins I* **1973**, 2714.

reaction to reach a real synthetic utility. In this case, the *5-exo-trig* cyclization is kinetically favored over the *6-endo-trig* cyclization. This preference is explained by stereo-electronic effects, as the 5-membered-ring is favored because of better orbitals overlap. Furthermore, this phenomenon can be explained by the more favorable entropy of activation associate with the formation of the smaller possible ring. Indeed, the entropy change associated with the loss of rotation freedom becomes increasingly unfavorable with increasing the size of the ring being formed.[60]




**Scheme 27 first Kolbe electrocyclization**

Twenty years later, Schäfer improved the reaction by adding a co-acid in excess, such as acetic acid[61], and consequently, increased the yields of the reaction (see Scheme **28**). Indeed, once cyclized, the resulting radical is quickly captured by another radical R·, mainly present in the reaction mixture. Furthermore, he introduced oxygen and nitrogen atoms, in the substrate **90** carbon skeleton with the aim of synthetizing tetrahydrofurans and pyrrolidines. Nonetheless, the yields in the range of 40 – 50 % remain modest, but acceptable.

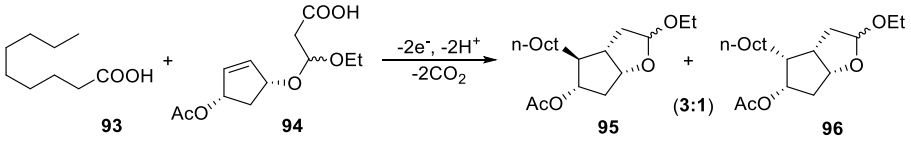



**Scheme 28 pyrrolidines and tetrahydrofurans electrocyclization**

The Schäfer's process has been exemplified during the synthesis of the prostaglandin ($PGF_{2\alpha}$) precursor; with a yield around 54 % and a diastereoisomeric ratio of 3/1 (see Scheme **29**).[62] A well-fitted current density allowed a slight improvement in yield. Indeed, the radical concentration at the anode is directly

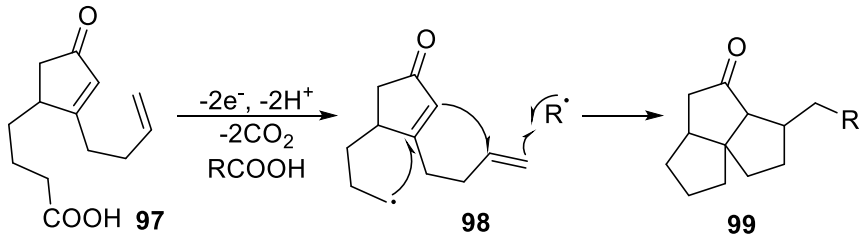
[60] Athelstan, L.; Beckwith, J. *Tetrahedron* **1981**, 37, 3073.
[61] Weiguny, J.; Schäfer, H.J. *Electroorganic Synthesis* **1993**, 57, 235.
[62] Weiguny, J.; Schäfer, H.J. *Liebigs Ann. Chem.* **1994**, 225.

related to the current density. For that reason, a high current density promotes the formation of intermolecular coupling products, while a low current density promotes intramolecular reactions.



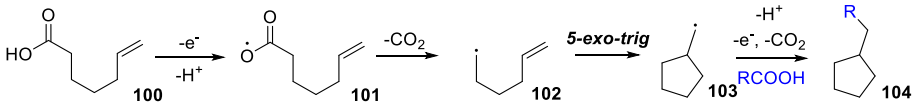

**Scheme 29 electrosynthesis of prostaglandin precursor**

Furthermore, one year later, Schäfer and Amatore developed a triquinane radical polycyclization with a yield of 45 % (see Scheme **30**).[63]




**Scheme 30 triquinane radical polycyclisation**

At the beginning of the 2000s, Markó started to work on the development of the radical cyclization of 5- and 6-membered heteroatom rings and carbon rings, by electrochemistry (see Scheme **31**).[64] This methodology, which is inspired by Weedon and Schäfer's work, involves the Kolbe oxidative decarboxylation reaction, followed by an intramolecular radical cyclization and a radical cross-coupling with a radical derived from a co-acid.

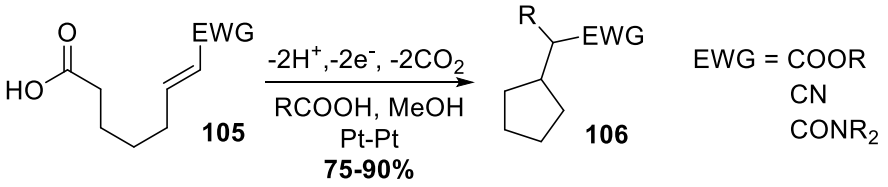



**Scheme 31 mechanism of the Kolbe radical electrocyclization**

During their PhD, F. Buzzo[65] and F. Lebreux[66] improved the efficacy of the Kolbe electrocyclization (see Scheme **32**). An important part of their work was focused on the nature of the involved olefin. In order to develop an efficient synthesis of carbon rings **106**, from acrylates, acrylonitriles, and acrylamides, they were inspired by the work of Lelandais[67], which postulates that a nucleophilic radical reacts more readily

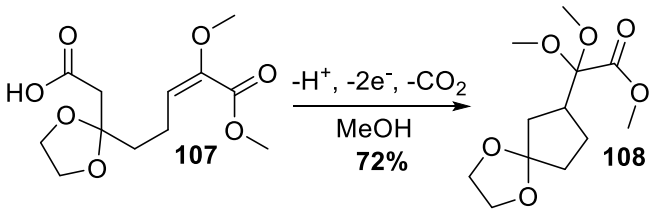
[63] Matzeit, A.; Schäfer, H.J.; Amatore, C. *Synthesis* **1995**, 1432.
[64] (a) Lebreux, F.; Buzzo, F.; Markó, I.E. *ESC Transactions* **2008**, 13, 1; (b) Lebreux, F.; Buzzo, F.; Markó, I.E. *Synlett* **2008**, 18, 2815.
[65] Buzzo, F. Thèse de doctorat, Université catholique de Louvain, **2005**.
[66] Lebreux, F. Thèse de doctorat, Université catholique de Louvain, **2008**.
[67] (a) Chkir, M.; Lelandais, D. *Chem. Commun.* **1971**, 1369; (b) Giese, B. *Angew. Chem. Int. Ed. Engl.* **1983**, 22, 753; (c) De Vleeschouwer, F.; Van Speybroeck, V.; Waroquier, M.; Geerlings, P.; De Proft, F. *Org. Lett.* **2007**, 9, 2721.

with an electron-withdrawing olefin and vice versa for an electrophilic radical. Actually, in those paths of synthesis, a nucleophilic carbon centered radical is added on an electron-withdrawing olefin, in order to form a ring.



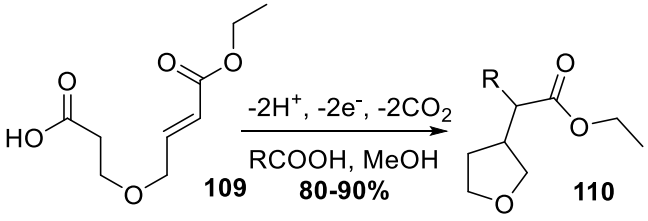

**Scheme 32 electrocyclization from acrylates, acrylonitriles and acrylamides 105**

Subsequently, they have combined a cascade of electrochemical reactions to synthetize highly functionalized carbocycles (see Scheme **33**). For example, the Kolbe oxidation of the substrate **107**, possessing a captodative olefin, which is well known for its important radicophilicity[68], allows a 5-membered ring closing and the formation of the stabilized captodative radical. The latter undergoes an electrochemical Hofer-Moest reaction, leading to the corresponding carbocation, which is captured by the solvent, generating the adduct **108** with good yield.



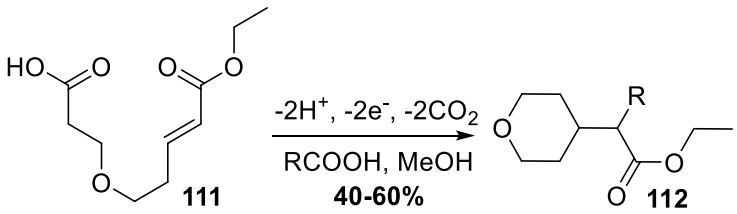

**Scheme 33 electrocyclization of a substrate having a captodative olefin 107**

In a third phase, the syntheses of the tetrahydrofurans **110** and the tetrahydropyran **112**, which are respectively substituted at the position 3 and 4, were also successfully explored (see Schemes **34** and **35**).



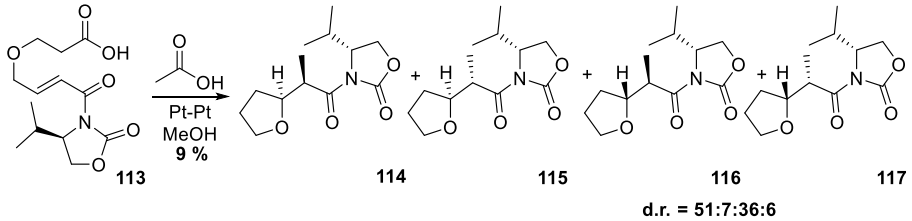

**Scheme 34 tetrahydrofurans 109 electrosynthesis**

[68] Sustmann, R.; Muller, W.; Mignani, S.; Janousek, Z.; Viene, H.G. *New J. Chem.* **1989**, 13, 557.




**Scheme 35 tetrahydropyran 111 electrosynthesis**

Finally, considering that those reactions do not allow a stereochemical control of the chiral centers formed, a diastereoselective synthesis was developed. The strategy is to introduce, inside the structure of the electrocyclization substrate **113**, a chiral auxiliary in order to favor a facial selectivity, during the cyclization step (see Scheme **36**). It is more precisely, close to the double bond that was positioned an Evans chiral auxiliary; and (S)-(−)-4-Isopropyl-2-oxazolidinone was chosen considering its high compatibility with Kolbe conditions. Despite the promising diastereoselectivity achieved (51:7:36:6), the yield obtained (9 %) remains low. Therefore, this type of reaction should be deeper investigated.




**Scheme 36 diastereoselective electrosynthesis**

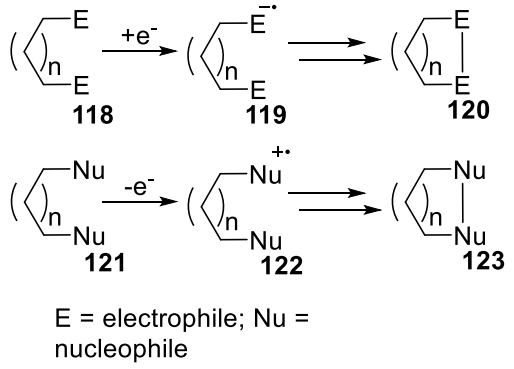
### 1.1.11 Organic electrochemistry applied to the synthesis of cyclic compounds

In this section, Intramolecular ring formation will be discussed. Heterocycles are omnipresent in organic chemistry. Moreover, most of the biologically active compounds and natural products contain heterocycles. Consequently, electrochemical routes for the design of heterocycles have always been an ongoing research field.

The conventional organic synthesis employs the interplay between species of complementary polarities (electrophiles and nucleophiles). However, in some cases, functional groups with the same polarity have the ability to react together. These couplings can be performed by the adequate use of reagents with reverse polarity "umpolung reagents".[69] This kind of polarity inversion can be readily achieved using electrochemical synthesis (see Scheme **37**). Actually, organic electrolysis enables the selective removal or introduction of electrons from organic species. It is therefore an excellent tool for reversing the polarity of functional groups and generating umpolung reactions. For instance, electron-deficient groups can be

[69] Little, R.D.; Moeller, K.D. *The Electrochemical Society Interface* **2002**, 36.

reduced, with the aim of converting them from electrophiles to nucleophiles. On the other hand, electron-rich functions can be oxidized, with the aim to converting them from nucleophiles to electrophiles.



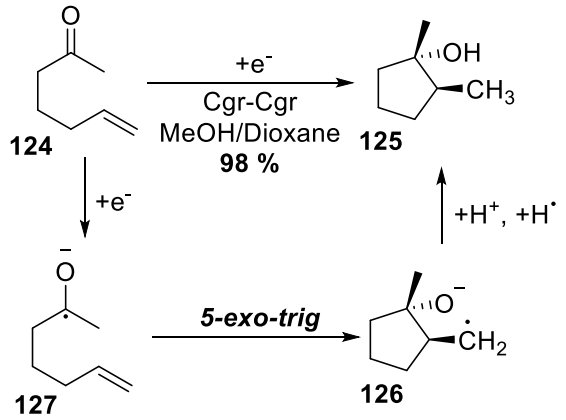

**Scheme 37 umpolung electrocyclization**

The reactive intermediate formed can then react, leading to the net coupling of either two nucleophiles or two electrophiles, in a manner which would be otherwise difficult. Such reactions give the ability to create totally new synthetic roads for the development of complex molecules.

*1.1.11.1 Imines and ketones reduction*

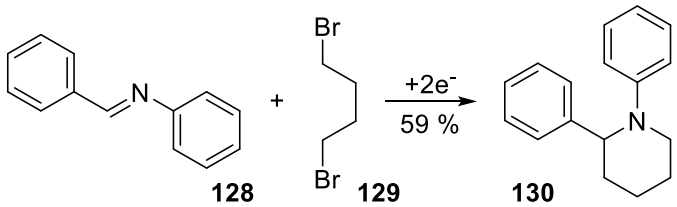
Shono was the first to report the ketyl radical - olefin electrocyclization (see Scheme **38**). This type of reactions implies the formation, via reduction of a radical anion **127**, which is able to cyclize by addition on a large variety of functions such as olefins[70], allenes[71], alkynes[72] or aromatic cycles[73]. In addition, the scope of the reaction was defined with respect to stereochemistry, ring sizes, and different substituents.

[70] (a) Shono, T.; Nishiguchi, I.; Ohmizu, H.; Mitani, M. *J. Am. Chem. Soc.* **1978**, 100, 545; (b) Kariv-Miller, E.; Maeda, H.; Lombardo, F. *J. Org. Chem.* **1989**, 54, 4022.
[71] Patenden, G.; Robertson, G.M. *Tetrahedron* **1985**, 41, 400.
[72] Shono, T.; Nishiguchi, I.; Ohmizu, H. *Chem. Lett.* **1966**, 1233.
[73] Shono, T.; Kise, N.; Suzumoto, T.; Morimoto, T. *J. Am. Chem. Soc.* **1986**, 108, 1986.




**Scheme 38 ketyl radical - olefin cyclization**

Some intermolecular cyclizations were also described with good yields. Indeed, the electrochemical reduction of unsaturated compounds (activated olefins, ketones, and imines) in the presence of dielectrophiles enables the formation of cyclic molecules (see Scheme **39**).[74]

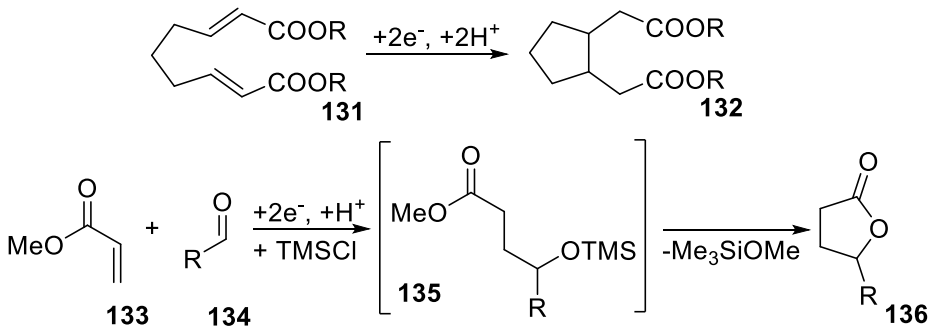



**Scheme 39 intermolecular reductive cyclization**

*1.1.11.2 Activated olefins reduction*

The reduction of activated olefins allows the formation of rings. This type of reactions, which is the source of the famous Monsanto acrylonitrile hydrodimerization, can be performed intra[75]- and inter[76]-molecularly (see Scheme **40**). In the case of the inter-molecular cyclization (see Scheme **40**), the electroreductive hydrocoupling of the activated olefin **133** is performed in the presence of trimethyl chlorosilane. The role of trimethyl chlorosilane is the activation of the carbonyl compound **134** as electrophile by coordination to the carbonyl group. The first step of the reaction is one electron reduction of the acrylic ester **133** to the corresponding radical anion. Moreover, the second step is the protonation of the anion radical to the corresponding radical and further reduction of the radical to the anion. Subsequently, the anion formed is added on the activated carbonyl to form the species **135**.

[74] Degrand, C.; Compagnon, P.; Belot, G.; Jacquin, D. *J. Org. Chem.* **1980**, 45, 1189.
[75] (a) Petrovitch, J.P.; Anderson, J.D.; Baize, M.M. *J. Org. Chem.* **1966**, 31, 3890; (b) Moens, L.; Baizer, M.M.; Little, R.D.; *J. Org. Chem.* **1986**, 51, 4497.
[76] Shono, T.; Ohmizu, H.; Kawakani, S.; Sugiry, H. *Tetrahedron Let.* **1980**, 21, 5029.

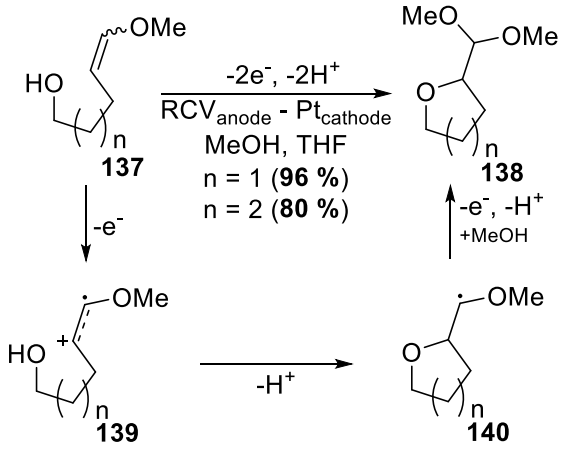



**Scheme 40 intra- and inter-molecular cyclization by reduction of activated olefins**

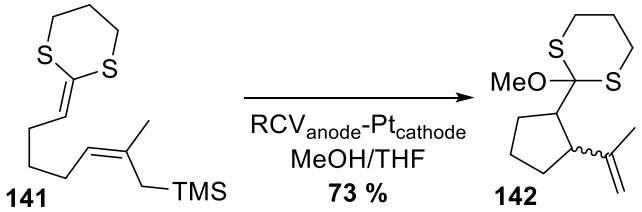
*1.1.11.3 Activated double bond oxidation involving trapping nucleophiles*

Moeller reported a wide variety of ways to trap anodically formed radical cations, which are derived from electron-rich olefins, via an intramolecular ring closure.[77] Several readily oxidized double bonds can be used in this type of reactions, such as enol ethers (see Scheme **41**), silylenol ethers, vinyl sulfides (see Scheme **42**, **43** and **44**), and ketene dithioacetals. Moreover, a large number of nucleophiles can serve as a trapping group, such as alcohols[78] (see Scheme **41**), amines (see Scheme **43**), enol ether[79], sulfonamides, allylsilanes[80] (see Scheme **42**), amides[81], aryl functions[82] (see Scheme **44**), furans, and carboxylic acids[83]. Usually, oxidation can also occur at the trapping nucleophilic function, followed by an intramolecular electron transfer or an addition of the olefin to the generated radical (see Scheme **45**). After ring closure, a second oxidation occurs and the carbocation intermediate is trapped by either the methanol solvent or another nucleophile. This process is part of the hot topics in organic electrochemistry and its enormous potential was greatly expanded by variation of the reaction variables.

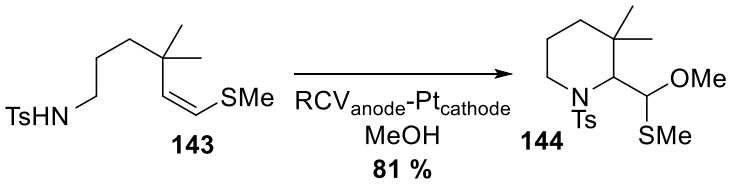
[77] (a) Duan, S.; Moeller, K.D. *J. Am. Chem. Soc.* **2002**, 124, 9368; (b) Liu, B.; Duan, S.; Sutterer, A.C.; Moeller, K.D. *J. Am. Chem. Soc.* **2002**, 124, 10101; (c) Little, R.D.; Moeller, K.D. *The electrochemical Society Interface* **2002**, 36; (d) Xu, H.C.; Moeller, K.D. *J. Am. Chem. Soc.* **2008**, 130, 13542; (e) Feng, R.; Smith, J.A.; Moeller, K.D. *Acc. Chem. Res.* **2017**, 50, 2346.
[78] Sutterer, A.; Moeller, K.D. *J. Am. Chem. Soc.* **2000**, 12, 5636.
[79] Moeller, K.D.; Tinao, L.V. *J. Am. Chem. Soc.* **1992**, 114, 1033.
[80] Tinao-Woolridge, L.V.; Moeller, K.D.; Hudson, C.M. *J. Org. Chem.* **1994**, 59, 2381.
[81] Brandt, J.D.; Moeller, K;D. *Org. Lett.* **2005**, 7, 3553.
[82] New, D.G.; Tesfai, Z.; Moeller, K.D. *J. Org. Chem.* **1996**, 61, 1578.
[83] Perkins, R.J.; Xu, X.C.; Campbell, J.M.; Moeller, K.D. *Beilstein J. Org. Chem.* **2013**, 9, 1630.



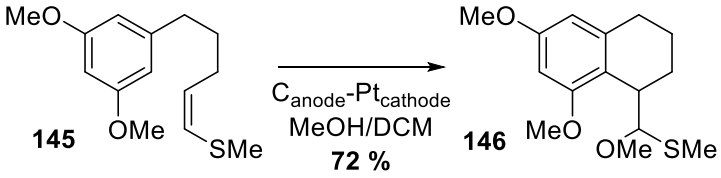

**Scheme 41 oxidative cyclization of enol ether**



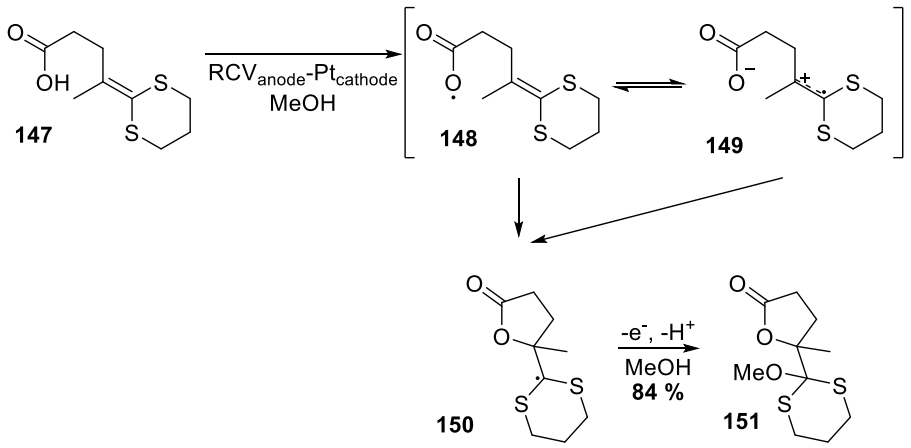

**Scheme 42 electrocyclization via ketene dithioacetal oxidation followed by a radical cation trapping by allylsilanes**




**Scheme 43 electrocyclization via vinylsulfide oxidation followed by a radical cation trapping by amine**

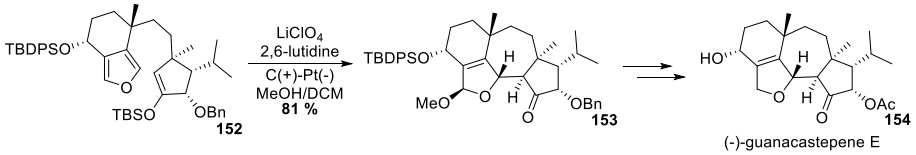



**Scheme 44 electrocyclization via vinyl sulfide oxidation followed by a radical cation trapping by an aryl function**




**Scheme 45 electrocyclization of lactones**

Finally, Trauner developed a total synthesis of (-)-guanacastepene E **154**, which contains an electrochemical step (see Scheme **46**).[84] Indeed, his synthesis is inspired by the work of Moeller and Wright, who have shown that silyl enol ethers can be coupled with furans through anodic oxidation. Consequently, the anodic oxidation of the compound **152**, under conditions described by Moeller, allowed the formation of the central seven membered ring of (-)-guanacastepene E and gave the tetracycle **153** in good yield and as a single isomer. This work highlights the usefulness of electrochemistry in the synthesis of complex target molecules.

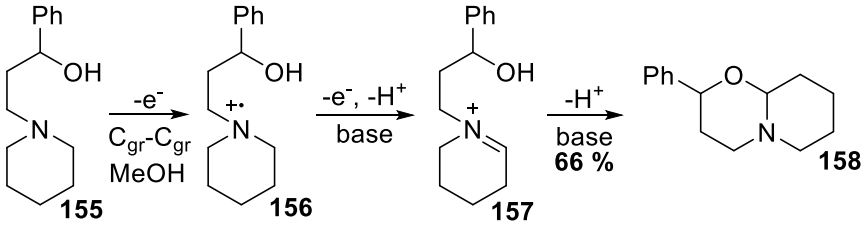



**Scheme 46 (-)-guanacastepene E total synthesis**

*1.1.11.4 Oxidation of amides and amines: Shono-type oxidation*

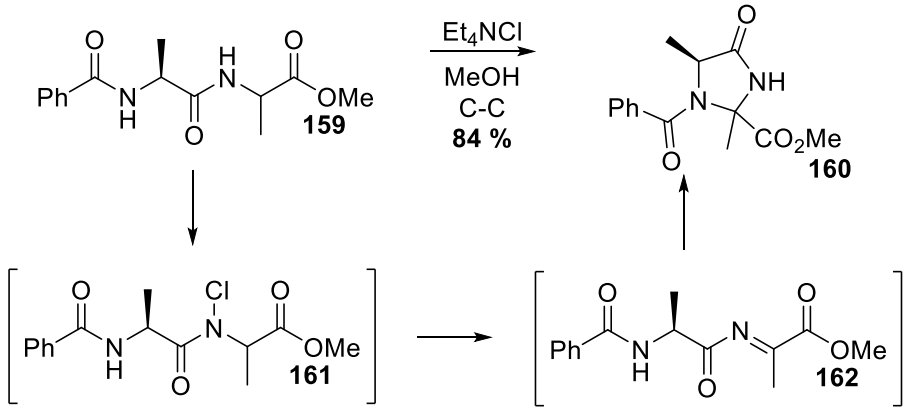
The Shono oxidation of amides and amines leads to α-functionalized products. Indeed, the anodic oxidation of alkyl amides and amines gives rise to N-centered radical cations **156**, in methanol. These reactive intermediates then readily undergo fragmentation to afford N-acyl iminium or iminium ions **157**. When a nucleophile is present in the substrate structure, the reactive intermediate can be trapped intramolecularly leading to a cyclization process (see Scheme **47**).[85]

[84] (a) Hughes, C.C.; Miller, A.K.; Trauner, D. *Org. Lett.* **2005**, 7, 3425; (b) Miller, A.K.; Hughes, C.C.; Kennedy-Smith, J.J.; Gradl, S.N.; Trauner, D. *J. Am. Soc.* **2006**, 128, 17057.
[85] Okimoto, M.; Ohashi, K.; Yamamori, H.; Nishikawa, S.; Hoshi, M.; Yoshida, T. *Synthesis* **2012**, 44, 1315.




**Scheme 47 Shono-type oxidation of amine applied to cyclization**

In addition to direct oxidation, indirect oxidation of amides and amines can be useful for cyclization reaction.[86] This kind of reactions employs a halide based electrolyte as redox catalyst that is oxidized at the anode surface to form the reactive species (see Scheme **48**). This intermediate then reacts with the nitrogen atom of an amide group. A subsequent elimination reaction leads to the desired N-acyliminium ion or iminium **162**.




**Scheme 48 chloride mediated electrooxidative cyclization using tetraethylammonium chloride as redox catalyst**

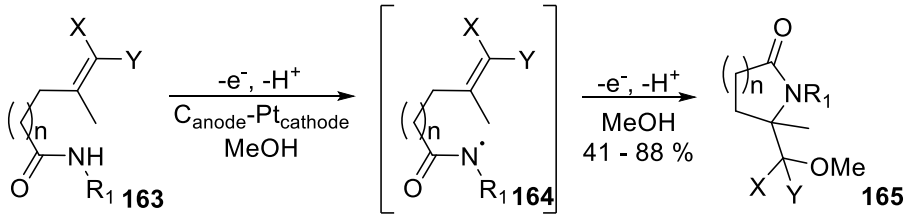
*1.1.11.5 Oxidation of amides: amidyl radical*

Moeller has showed that the synthesis of C5-functionnalized pyrrolidinones **165** can be designed by organic electrochemistry.[87] Indeed, due to their high reactivity and electrophilic nature, amidyl radicals are able to perform cyclization reaction by addition on electron-rich olefins, leading to the formation of γ- and δ-lactam structures found in a vast number of biologically active molecules (see Scheme **49**). Those radicals can be generated anodically from *O*-benzyl hydroxamates and *N*-phenyl amides under mild conditions. The benzyloxy group on the amide lowers the oxidation potential of the nitrogen while stabilizing the ensuing radical species. After cyclization, the cyclized carbon-centered radical formed undergoes further

[86] Papadopoulos, A.; Lewal, B.; Steckhan,E.; Ginzel, K.D.; Knoch, F.; Niefer, M. *Tetrahedron* **1991**, 47, 563.

[87] (a) Xu, H.-C.; Campbell, J.M.; Moeller, K.D. *J. Org. Chem.* **2014**, 79, 379; (b) Campbell, J.M. doctoral thesis, Washington University in St. Louis, **2014**.

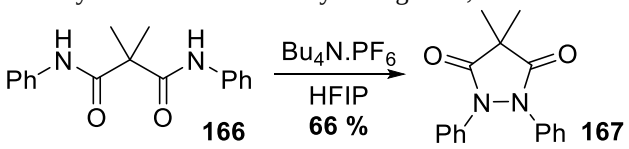
electrochemical oxidation wherein the carbocation formed can be trapped by a nucleophile, such the methanol solvent.




X = Y = -S-$(CH_2)_3$-S-; X = OMe, Y = H
X = SMe, Y = H; $R_1$ = OBn, Ph; n = 1, 2

**Scheme 49 pyrrolidinone cyclization via anodic oxidation of amide**

The oxidative formation of N-centered radicals may also lead to a N,N-dimerization process (see Scheme **50**). Indeed, Moeller and Waldvogel developed an electroorganic synthesis of pyrazolidin-3,5-diones, which are known to be an important motif in heterocyclic chemistry.[88] In this protocol, two aryl amide functions are oxidized into the corresponding amidyl radicals. This two intermediates then cyclizes intramolecularly through a N,N-dimerization **167**.

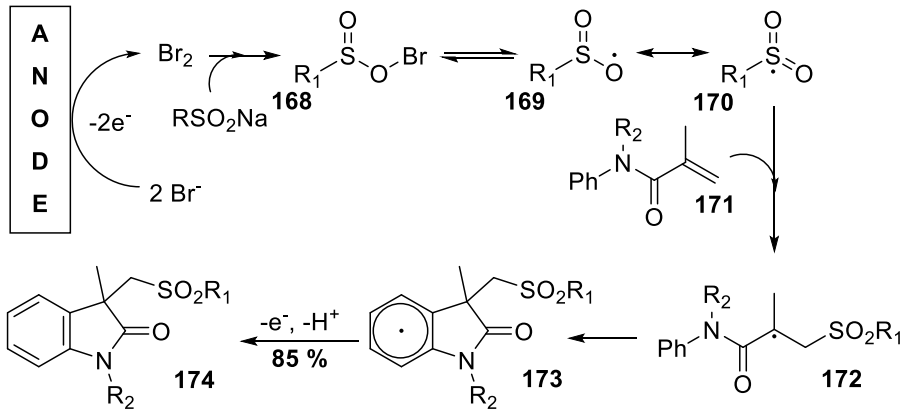



**Scheme 50 pyrazolidin-3,5-dione 167 electrocyclization**

*1.1.11.6 Oxidation of sulfuric acid salts*

Sulfinates can be readily oxidized into sulfonyl radicals via organic electrochemistry.[89] The intermediate formed can be finally cyclized by addition on an olefin. This oxidation is mediated by a catalytic amount of $NH_4Br$ (10 mol %). Indeed, in this reaction, bromide ion coming from the redox catalyst is oxidized into bromine. This latter subsequently reacts with sodium sulfonate to generate sulfonyl bromide **168**. Then, homolytic cleavage of the sulfonyl bromide **168** affords an oxygen-centered radical **169**, in equilibrium with the more stable sulfonyl radial **170**. Afterwards, the addition of sulfonyl radical **170** to acrylamide **171** generates the radical **172**. The intramolecular cyclization of this intermediate **172** leads to the radical **173**. The oxindole **174** is finally obtained through the radical **173** oxidation (see Scheme **51**).

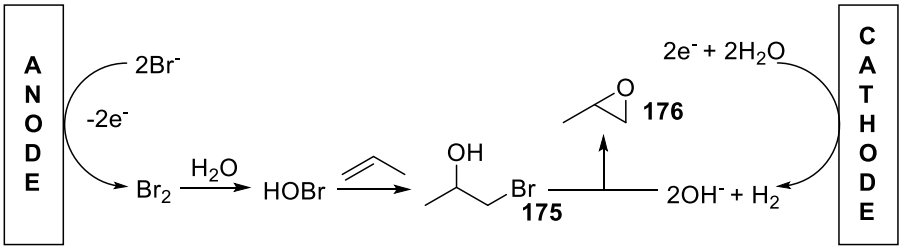
[88] (a) Gieshoff, T.; Shollmeyer, D.; Waldvogel, S.R. *Angew. Chem. Int. Ed.* **2016**, 55, 9437; (b) Gieshoff, T.; Kehl, A.; Schollmeyer, D.; Moeller, K.D.; Waldvogel, S.R.R. *J. Am. Chem. Soc.* **2017**, 139, 12317.
[89] Jiang, Y.Y.; Liang, S.; Zeng, C.C.; Hu, L.M.; Sun, B.G. *Green Chem.* **2016**, 18, 6311.




**Scheme 51 Oxindole 174 cyclization via the oxidation of sulfuric acid salt**

*1.1.11.7 Epoxidation via paired electrolysis*

The use of paired electrolysis, where two processes take place simultaneously at both the anode and the cathode, promotes energy efficiency of electroorganic chemistry. Girault developed a propylene epoxidation process via paired electrolysis (see Scheme **52**).[90]In this protocol, a bromide solution is saturated with propylene. The bromide is then anodically oxidized in bromine, which reacts consecutively with water to form hypobromous acid. This acid in turn reacts with propylene to form propylene bromohydrin **175**. The hydroxide ions produced cathodically are then used to complete the overall process.

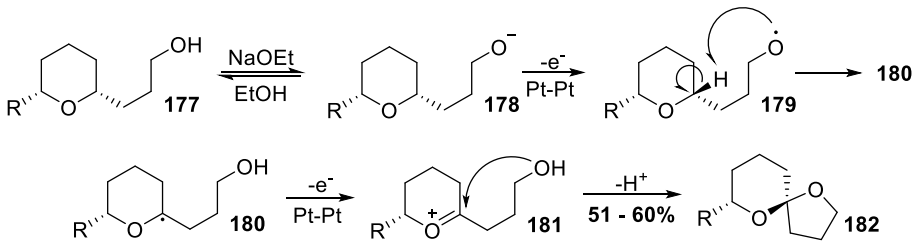



**Scheme 52 epoxidation via paired electrolysis**

*1.1.11.8 Oxidation of alcohols*

In 2000, Markó developed an electrochemical cyclization of ω-hydroxy-tetrahydropyrans to [4,5]- and [5,5]-spiroketals (see Scheme **53**).[91] This process is allowed by the anodic oxidation of an alcohol function. Specifically, the mechanism involved an initial deprotonation of the sidechain alcohol leading to the corresponding alkoxide **178**, which is then oxidized. Subsequently, the oxygen-centered radical formed **179** abstracts intramolecularly a hydrogen atom causing the formation of a carbon-centered radical **180** in α-position of the oxygen atom of the ether function. Afterwards, a second oxidation affords the cyclic oxonium **181**. Finally, the reaction is completed by an intramolecular cyclization.

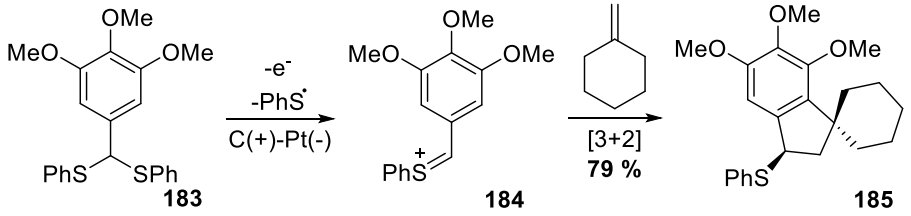
[90] Belmont, C.; Girault, H.H. *Electrochim. Acta.* **1995**, 40, 2502.
[91] Markó, I.E. *Tetrahedron Lett.* **2000**, 41, 4383.




**Scheme 53 spiroketals electrochemical cyclization**

*1.1.11.9 Oxidation of benzylic dithioacetals*

The anodic oxidation of dithio-acetals or –ketals allows the formation of thionium cations. Chiba demonstrated that the thionium species **184** formed during the anodic oxidation of benzylic dithioacetals **183** could perform [3+2] cycloaddition, leading to the design of varied aromatic derivatives (see Scheme **54**).[92]




**Scheme 54 anodic oxidation of benzylic dithioacetals**

## 1.1.12 Asymmetric synthetic organic electrolysis

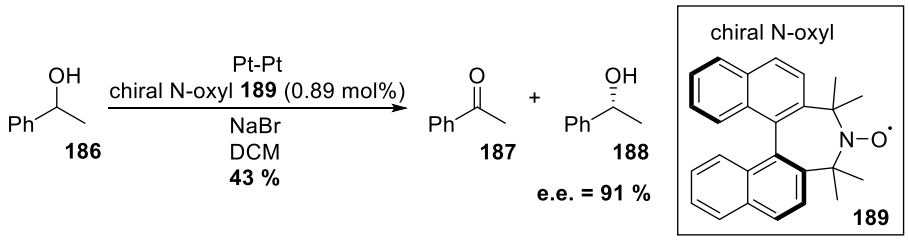
Asymmetric electrochemical synthesis is defined by electroorganic reactions giving rise to the selective introduction of one or more new elements of chirality into a target molecule structure. An analysis of the literature demonstrates that even if relatively few examples of asymmetric synthetic organic electrolysis exist, the potential of the electrochemistry in this field is nonetheless promising.[93] Indeed, the stereoselectivity can be achieved by using suitable chiral sources, such as the use of a chiral catalyst, a chiral solvent, a chiral supporting electrolyte or a chiral mediator. However, the use of a chiral solvent or a chiral supporting electrolyte has yet only shown low to moderate values of enantiomeric excess. The incorporation of a chiral auxiliary in the structure of the substrate can also lead to good diastereoselectivity. Finally, the heterogeneity of those reactions can be exploited in the design of chiral electrodes. By way of illustration, some examples of asymmetric synthetic organic electrolysis are presented.

*1.1.12.1 Chiral mediators*

Mediators refer to compounds that enable or facilitate homogeneous electron transfer from the electrode surface to the substrate. The use of this type of substances could be considered as indirect electrolysis, given that the mediator captures an electron from the electrode and carries out the organic transformation.

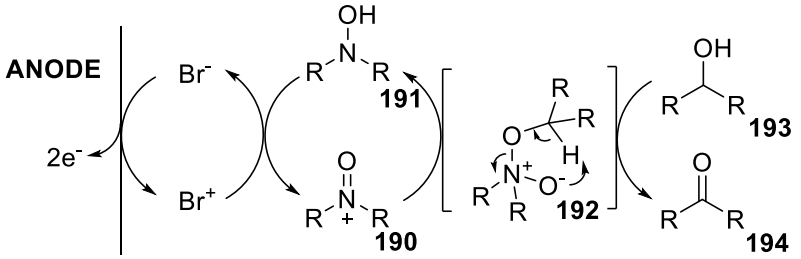
[92] Chiba, K.; Uchiyama, R.; Kim, S.; Kitano, Y.; Tada, M. *Org. Lett.* **2001**, 3, 1245.
[93] Ghosh, M.; Shinde, V.S.; Rueping, M. *Beilstein J. Org. Chem.* **2019**, 15, 2710.

Moreover, chiral mediators, besides their electrochemical role, have also the purpose to induce selectivity. Tanaka, in 2000, developed a kinetic resolution of secondary alcohols via electrochemical oxidation, in an undivided cell, under constant current, with a catalytic amount of a N-oxyl radical mediator **189** (see Scheme **55**).[94]




**Scheme 55 kinetic resolution of secondary alcohols 186 via electrochemical oxidation with a chiral N-oxyl-radical-mediator 189**

The mechanism of this electro-oxidative resolution involves bromide salt and optically active N-oxyl mediator **189** (see Scheme **56**). First, bromide ion is adsorbed at the surface of the anode and is reduced into bromine cation. The bromine oxidizes then the N-oxyl mediator to generate the nitrosonium species **190**, which finally selectively oxidizes the alcohol **193**, which leads to the formation of the desired ketone **194**.




**Scheme 56 mechanism of the kinetic resolution of secondary alcohols via electrochemical oxidation with a chiral N-oxyl-radical-mediator**

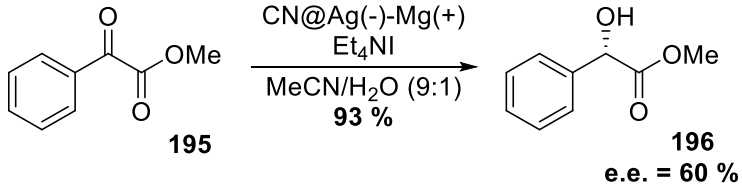
*1.1.12.2 Chemically modified chiral electrodes*

In the case of chemically modified chiral electrodes, electrodes serve as a heterogeneous catalyst. Those electrodes can be prepared through the adsorption of chiral active auxiliaries onto the surface of the electrode or by covalent bonding. This type of electrodes is useful for asymmetrical induction because they require a small amount of inducing agent. However, poor coverage of the electrode surface with the chiral species is a major disadvantage of this technique. In 2014, Wang and Lu have developed the synthesis of metallo-organic hybrid materials by means of entrapment of alkaloids within silver particles.[95] This metal was used as a cathode for the enantioselective electro-hydrogenation of **195** (see Scheme **57**).

---

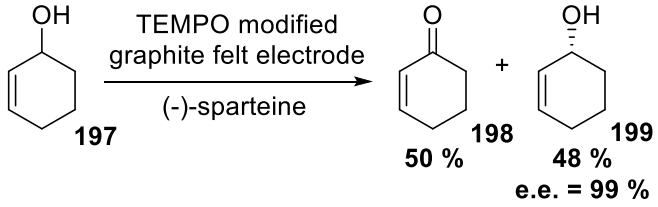
[94] Kuroboshi, M.; Yoshihisa, H.; Cortona, M.N.; Kawakami, Y.; Goa, Z.; Tahaka, H. *tetrahedron Lett.* **2000**, 41, 8131.

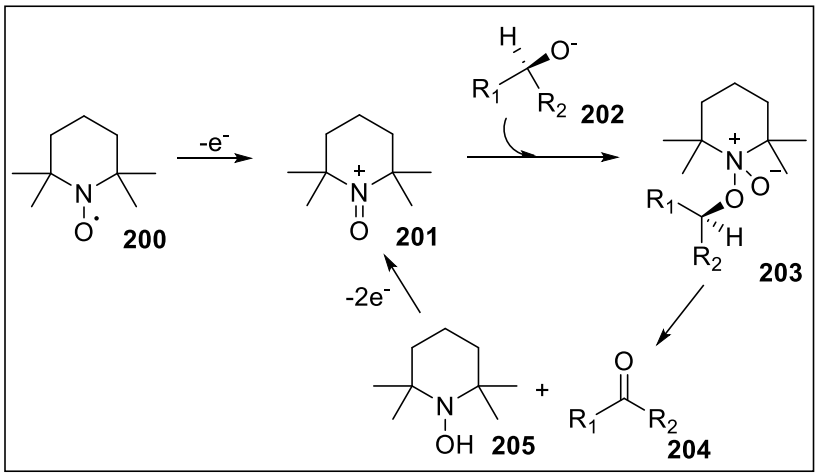
[95] (a) Yang, H.P.; Wang, H.; Lu, J.X. *Electrochem. Commun.* **2015**, 55, 18 ; (b) Yang, H.; Chi, D.; Sun. Q.; Sun, W.; Wang, H.; Lu, J. *Chem. Commun.* **2014**, 50, 8868.




**Scheme 57 enantioselective electro-hydrogenation**

In 1994, Osa developed an enantioselective method for the oxidation of racemic secondary alcohols on a graphite felt electrode modified with TEMPO in the presence of (-)-sparteine as a base (see Scheme **58**).[96] This reaction is effective and economic as the electrodes are stable and reusable a large number of times. The mechanism includes the oxidation of a nitroxyl radical **200** into an oxopiperidinium **201**, which is the intermediate that reacts with the alcohol.




**Scheme 58 asymmetric electro-catalytic oxidation of racemic alcohols on a TEMPO-modified graphite felt electrode in the presence of (-)-sparteine**

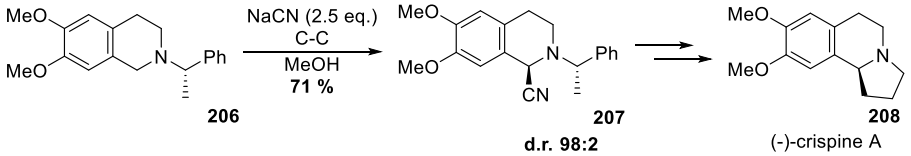
*1.1.12.3 Chiral auxiliary approach*

A chiral auxiliary can be introduced inside the structure of the electrolysis substrate in order to induce stereoselectivity. In 2011, Hurvois developed a stereoselective electrochemical total synthesis of the tetrahydroisoquinoline alkaloid (-)-crispine A **208** with excellent diastereoselectivity (see Scheme **59**).[97] The key step of this

[96] Kashiwagi, Y.; Yanagisawa, Y.; Kurashima, F.; Anzai, J.I.; Osa, T.; Bobbitt, J.M. *Chem. Commun.* **1996**, 2745.

[97] Lovafi, F.; Moreau, J.; Shahane, S.; Golhen, S.; Roishel, T.; Sinbandhit, S.; Hurvois, J.P. *J. Org. Chem.* **2011**, 76, 9720.

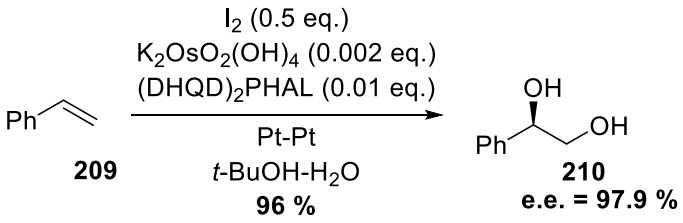
synthesis is the anodic oxidation of **206**, in the presence of NaCN, to the α-amino nitrile (+)-**207**. Finally, the compound **207** is converted into the desired product **208**, upon further alkylation, reduction, and catalytic hydrogenolysis.




**Scheme 59 (-)-crispine A 208 total synthesis**

*1.1.12.4 Chiral catalyst*

This method has been studied in greater detail than the other strategies. There are three categories of chiral catalysts: metal catalysts, enzyme catalysts, and organocatalysts. In 1996, Torri has created an electrochemical approach for the Sharpless asymmetric dihydroxylation of alkenes using a potassium osmate as a catalyst in presence of Sharpless ligand and iodine as the oxidizing mediator (see Scheme **60**).[98] In this procedure, the classic chemical oxidant is replaced by an anode that regenerates Os (VIII) to Os (VI). Thanks to this technic, olefins are converted to the corresponding dihydroxylation product **210** in excellent enantiomeric excesses and good yields. Finally, further improvements of this procedure have recently been accomplished by Moeller who conceived a photovoltaic apparatus for the efficient Sharpless dihydroxylation of styrene with outstanding enantiomeric excess.[99]




**Scheme 60 Sharpless asymmetric electrodihydroxylation of alkenes using an osmium complex**

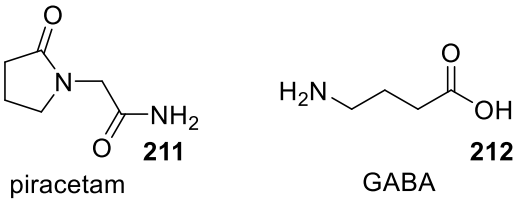
It is clear that the design of stereoselective electrochemical procedures remains a challenging task. Nonetheless, tremendous efforts have been made these two last decades by synthetic laboratories in order to achieve selectivity, resulting in a number of publications with successful stereoselective electroorganic reactions.

[98] Torii, S.; Liu, P.; Bhuvaneswari, N.; Amatore, C.; Jutand, A. *J. Org. Chem.* **1996**, 61, 3055.
[99] Nguyen, B.H.; Perkins, R.J.; Smith, J.A.; Moeller, K.D. *J. Org. Chem.* **2015**, 11, 280.

## 1.2 2-Pyrrolidinones

### 1.2.1 Discovery of piracetam

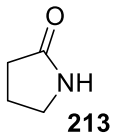
The history of every field of science provides numerous examples showing that the creation of scientific notions not always proceeds linearly, from a rational hypothesis to a validated theory. This is the case for the discovery of piracetam **211** by Corneliu Giurgea, in 1964. Originally, Giurgea wanted to synthesize a cyclic derivative of the main inhibitory neurotransmitter, *gamma*-aminobutyric acid, GABA **212**, in order to design a tranquilizer and sleeping drug, but it was found that this drug did not have this effect.[100] Indeed, piracetam did not present any type of interference with the GABA neurotransmitter and no sleep-inducing action. In turn, Giurgea tuned an apparent failure into a large success for UCB Pharma by discovering the racetams.




**Scheme 61 piracetam and GABA**

### 1.2.2 The racetams and their large prescription field

The racetams is a family of molecules that shares a 2-pyrrolidinone core **213**. This group of molecules is well-known for its positive effects on the cognitive functions. Indeed, those γ-lactams have a large prescription field and are used for the treatment of central nervous system disorders, cognition and memory problems, epilepsy, seizure, neuro-degenerative diseases, stroke, ischaemia, and to deal with stress and anxiety. There are also some researches to use those molecules as a drug for the treatment of Alzheimer[101] and Parkinson[102] diseases. Finally, those compounds have the advantage of having very low toxicity and no serious side effects.




**Scheme 62 2-pyrrolidinone core**

[100] Margineanu, D.G. *Revue des questions Scientifiques* **2011**, 1, 33.
[101] (a) Chiroma, S.M.; Taib, C.N.M.; Moklas, M.A.M.; Baharuldin, M.T.H.; Amom, Z. Jagadeesan, S. *Biomedical Research and Therapy* **2019**, 6, 2937; (b) Uddin, M.S.; Mamun, A.A.; Kabir, M.T.; Jakaria, M.; Mathew, B.; Berroto, G.E.; Asharaf, G.M. *Molecular Neurobiology* **2019**, 56, 4925.
[102] Honma, S.; Takei, A.; Fukuzawa, T.; Hamada, K.; Hamada, T. *Aging Diseases* **1995**, 8, 96.

### 1.2.3 The nootropics

The racetams have been classed in a special group of psychoactive agents, the nootropics, which are claimed to selectively enhance the higher integrative activities in the telencephalon.[103] The term nootropic[104] was created by Giurgea in 1972, from Greek *noos* (mind) and Greek *tropos* (turn) to describe these compounds with the following specific properties:

a) Enhancement of learning and memory.

b) Facilitation of the flow of information between the cerebral hemispheres.

c) Enhancement of the resistance towards chemical and physical injuries.

d) Lack of the usual psychological and general cardiovascular pharmacological activity of psychotropic drugs.

### 1.2.4 Mechanism of action of the racetams

The racetams compounds have been extensively researched and the total number of clinical publications representing all compounds exceeds 300. There are seven relevant drugs available on the market worldwide (see Table **3**) and some of them are use as dietary supplement. However, no commonly accepted mechanism of action of racetams has been established.[105] This is related to the fact that the pharmacology of racetams has been less explored than the clinical applications of these medications.[106] The nootropics can all to a certain degree pass the blood-brain barrier.[107] Furthermore, these molecules interplay with target receptors in the brain and modulate the excitatory and inhibitory processes of neurotransmitters, neuro-hormones, and post-synaptic signals, which have an impact on cognition and neurological behaviors. In addition, those molecules have an effect on the energy metabolism; indeed, they increase the oxygen utilization in the brain, the permeability of cell and mitochondrial membranes and the synthesis of cytochrome b5 and of intermediates of the Krebs cycle. Those compounds have also an action on ions channels and ions transporters in neurons. Moreover, all the racetams should have a different action mode because they have a different chemical structure but it is reasonable to expect that the compounds with minimal changes in their structure share the same mechanism of action. This lack of knowledge on the action mode of those molecules with a large prescription field contributes to an increasing tendency for research of new 2-pyrrolidinone derivatives in order to generate better clinical efficacy.

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[103] Bhattacharya, S.K.; Upadhyay, S.N.; Jaiswal, A.K.; Bhattacharya, S. *Indian Journal of Experimental Biology* **1989**, 27, 261.

[104] (a) Giurgea, C.E. *Drug Development Research* **1982**, 2, 441; (b) Giurgea, C. *ChemTech* **1980**, 10, 360; (c) Giurgea, C. *Biol. Psychiatry* **1978**, 2, 876; (d) Giurgea, C. *Actual. Pharmacof.* **1972**, 25, 115; (e) Giurgea, C.E. *Integrative Psychological Behavioral Science* **1973**, 8, 108; (f) Giurgea, C.; Salama, M. *Progress in Neuro-Pharmacology* **1977**, 1, 235.

[105] Gouliaev, A.E.; Senning, A. *Brain Research Reviews* **1994**, 19, 180.

[106] Malykh, A.G.; Sadia, M.R. *Drugs* **2010**, 70, 287.

[107] Pranav, J.C. *UJEAS* **2013**, 1, 8.

### 1.2.5 Synthetic racetams

Since the discovery of piracetam in 1964, a large number of racetams have been synthetized with the aim of treating neurologic illnesses. Several companies have worked on the development of those compounds, such as UCB Pharma, Menarini, Merck, Valenta Pharm, and Roche Pharmaceuticals, *etc*. In the following subsections, several commercialized synthetic 2-pyrrilidinones are presented, such as: piracetam, etiracetam, levetiracetam, brivaracetam, Oxiracetam, aniracetam, pramiracetam, and Phenylpiracetam (see Table **3**).

#### *1.2.5.1 Piracetam*

Piracetam, the first synthetic racetam, was discovered, in 1964; and marketed by UCB Pharma under the name of Nootropil, in 1971. Although the initial function of piracetam was as an anti-motion sickness drug[108], this active substance is prescribed for cognitive disorders, including age-related memory impairment[109] and dementia[110]. Moreover studies have shown that two weeks regime of this drug enhance verbal memory in healthy college students.[111] Additionally, this compound is also use to treat vertigo.[112] Finally, this molecule has a key importance, because it is the first of a long series of 2-pyrrolidinone moieties showing interesting pharmaceutical activities.

#### *1.2.5.2 Etiracetam and Levetiracetam*

In 1974, etiracetam appeared as a promising second generation nootropic.[113] Some years later, it emerged that only one of the two stereoisomers of etiracetam had anti-amnesic activity.[114] Indeed, the (S)-enantiomer of etiracetam, the levetiracetam, is the only one showing this activity; nevertheless this activity is too low to have a real pharmacological application. In 1992, interestingly, this molecule showed anticonvulsant activity far above piracetam.[115] Thanks to this impressive activity, this compound, commercialized by UCB Pharma under the name of Keppra, was worldwide approved as an antiepileptic drug and became blockbuster in the United States, in 2002.

#### *1.2.5.3 Brivaracetam*

Brivaracetam is a drug prescribed for epilepsy, marketed by UCB Pharma under the name of Briviact.[116] This molecule is the successor of levetiracetam. Indeed, in

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[108] Giurgea, C.; Moeyersoons, F.E.; Evraerd, A.C. *Archives Internationales de Pharmacodynamie et de Thérapie* **1967**, 166, 238.
[109] Israel, L.; Melac, M.; Milinkevitch, D.; Dubos, G. *International Psychogeriatrics* **1994**, 6, 155.
[110] Herlann, W.M.; Stephan, K. *International Psychogeriatrics* **1992**, 4, 25.
[111] Dimond, S.J.; Bfouwers, E.M.; *Pychopharmacology* **1976**, 49, 307.
[112] Rosenhall, U.; Deberdt, W.; Friberg, U.; Kerr, A.; Oosterveld, W. *clinical Drug Investigation* **1996**, 11, 251.
[113] Sara, S.J.; *Psychopharmacology* **1980**, 68, 235.
[114] Verloes, R.; Scotto, A.M.; Gobert, J.; Wülfert, E. *Psychopharmacology* **1988**, 95, 226.
[115] Gower, A.; Noyer, M.; Verloes, R.; Gobert, J.; Wülfert, E. *European Journal of Pharmacology* **1992**, 222, 193.
[116] Kenda, B.M.; Matagne, A.C.; Talaga, P.E. *Journal of Medicinal Chemistry* **2004**, 47, 530.

2008, research showed that this molecule has about 10-fold greater anticonvulsant potency than levetiracetam in animal tests.[117]

#### *1.2.5.4 Oxiracetam*

Oxiracetam is a racetam commercialized by Merck under the name of Neuromet. This drug is used for neurological disturbances and shows improvement in learning ability in normal animals[118] and rats whose cognitive functions are impaired[119]. Finally, researches prove that this molecule reduce the effects of Alzheimer's disease.[120]

#### *1.2.5.5 Aniracetam*

Aniracetam is a member of the nootropic drugs family. This molecule is commercialized, in Europe, by Menarini and Roche Pharmaceuticals, under the name of Ampamet. This active molecule is prescribed for memory decline and neurodegenerative disorders.[121] Research has shown that aniracetam has a beneficial effect on cognitive impairment due to senile dementia of the Alzheimer's type.[122]

#### *1.2.5.6 Pramiracetam*

Pramiracetam is a racetam drug marketed by Menarini under the brand name of Pramistar. This compound is prescribed for the treatment of memory and attention impairments for aging people with neurodegenerative dementia such as Alzheimer disease.[123]

#### *1.2.5.7 Phenylpiracetam*

Phenylpiracetam is a phenyl analog of piracetam developed, in 1983, at the Russian Academy of sciences.[124] This molecule was first used as a medication for cosmonauts in order to increase tolerance to extreme stress. This molecule is now commercialized, in Russia, by Valenta Pharm, under the brand name of Phenotropil. Unlike piracetam, Phenylpiracetam exhibits a specific anticonvulsant effect and thus is used as an antiepileptic drug. Finally, this compound is also prescribed to improve the cerebral functions in the case of patients with brain injuries.

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[117] Matagne, A.; Margineanu, D.G.; Kenda, B.; Michel, P.; Keitgaard, H. *British Journal of Pharmacology* **2008**, 154, 1662.
[118] Sansone, M.; Castellano, G.; Ammassari-Teule, M. *Arch. Int. Phamacodyn. Ther.* **1985**, 275, 86.
[119] Banfi, S.; Dorigotti, L.; Abbracchio, M.P.; Balduini, W.; Coen, E.; Ragusa, C.; Cattabeni, F. *Pharmacol. Res. Commun* **1984**, 16, 67.
[120] Villardita, C.; Grioli, S.; Lomeo, C.; Cattane, C.; Parini, J. *Neuropsychobiology* **1992**, 25, 24.
[121] Lee, C.R.; Benfield, P. *Drugs & Aging* **1994**, 4, 257.
[122] Sourander, L.B.; Portin, R.; Mölsä, P.; Lahden, A.; Linne, U.K. *Psychopharmacology* **1987**, 91, 90.
[123] Ennaceur, A.; Cavoy, A.; Costa, J.C. ; Delacour, J. *Behavioural Brain Research* **1989**, 33, 197.
[124] Bobkov, I.; Morozov, I.; Glozman, O.; Nerobkova, L.; Zhmurenko, L. *Biulleten' Eksperimental' noi Biologii Meditsiny* **1983**, 95, 50.

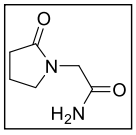
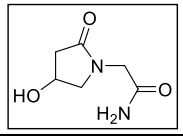
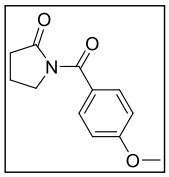
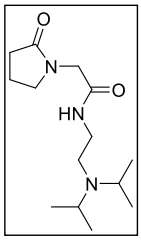
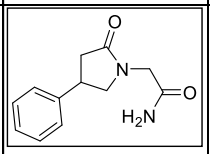
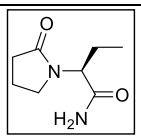
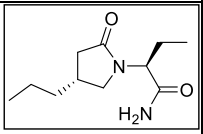
| Active compound | Chemical structure | Trade name/company | Indications |
|---|---|---|---|
| Piracetam |  | Nootropil®<br>UCB Pharma, Belgium | Neurocognitive impairements, memory decline, cortical myoclonus, cerebral circulation disorders |
| Oxiracetam |  | Neuromet®<br>ISF, Italy | Aging mental impairments |
| Aniracetam |  | Ampamet®<br>Roche Pharmaceuticals<br>Switzerland | Memory decline, neurodegenerative disorders |
| Pramiracetam |  | Neupramir®<br>Warner-Lambert, USA | Aging mental impairments, anxiety |
| Phenylpiracetam |  | Phenotropil®<br>Valenta Parmaceuticals<br>Russia | Mental function impairments central nervous system, neurotic disorders |
| Levetiracetam |  | Keppra®<br>UCB Pharma, Belgium | Epilepsy |
| Brivaracetam |  | Briviact®<br>UCB Pharma, Belgium | Epilepsy |

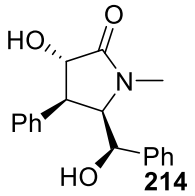
**Table 3 commercially available racetams**

### 1.2.6 Natural racetams

2-Pyrrolinone moiety is present in a large range of natural biologically active compounds. The scope of biological activities covered by this class of molecules is very broad. Moreover, some of those species have nootropic properties. In the following subsection two of them are presented: (-)-clausenamide and pyroglutamic acid.

### *1.2.6.1 (-)-Clausenamide*

The (-)-clausenamide is a naturally occurring racetam, isolated from a flowering plant, *Clausena lansium* (see Scheme **63**). This molecule, containing four chiral centers, displays several interesting pharmacological activities. Indeed, this compound has the ability to increase cognition and shows anti-dementia effects. Moreover, this promising drug is a candidate for treatment of Alzheimer's disease and other neurodegenerative disorders.[125]

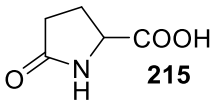



**214**

**Scheme 63 (-)-clausenamide**

### *1.2.6.2 Pyroglutamic acid*

Pyroglutamic acid is a natural amino acid derivative, found in several proteins (see Scheme **64**). This compound is formed via cyclization of the glutamic acid leading to the formation of a lactam. This molecule is classed as a nootropic agent or cognitive-enhancing agent.[126] Double blind trial shows that pyroglutamic acid improves some verbal memory functions in subjects affected by age-related memory decline.[127]




**215**

**Scheme 64 pyroglutamic acid**

## 1.2.7 Conclusion

Research is focused on the development of solutions to help patients suffering from serious illnesses of which all the types are not treated, such as epilepsy, Alzheimer disease, and other aged related illnesses. For example, there are different types of epilepsy, which means that many patients do not have access to appropriate treatment. Fifty millions of people suffer from this disease worldwide; nevertheless, one third of these persons does not receive the drug that would control their epileptic seizures in an adequate manner. Research must therefore endeavor to respond the unmet needs of those patients to provide them a normal life. This is the reason why extensive research must be done to create new and original racetam molecules in order to treat all the types of neurodegenerative diseases. Indeed, a logical progression of the complexity of the chemical structure of the synthetic racetams can be observed over the years. This thesis is focused on the electrosynthesis of innovative molecules form the so-called racetam family, differing from each other by the structure of the substituents around the 2-pyrrolidinone core.

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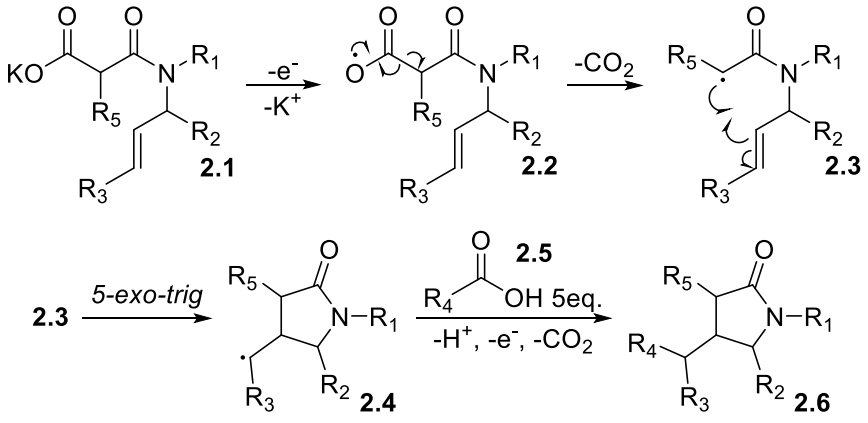
[125] Chu, S.F.; Zhang, J.T. *Acta Pharmaceutica Sinica B* **2014**, 4, 417.
[126] Barone, D.; Spignoli, G. *Drugs Under Experimental and Clinical Research* **1990**, 16, 85.
[127] Grioli, S.; Lomeo, C.; Quattropani, M.C.; Spignoli, G.; Villardita, C. *Fundamental & Clinical Pharmacology* **1990**, 4, 169.

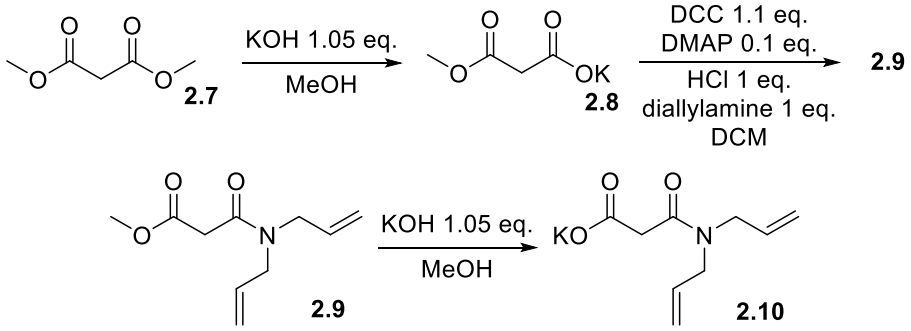
## 2 Aims of the research project

The aim of our Ph.D. research deals with the development of an electrochemical synthesis of functionalized 2-pyrrolidinones **2.6**, considering the great pharmacological interest for those molecules. This work follows the footsteps of the researches carried out by the doctors Buzzo and Lebreux, who have cyclize 5- and 6-membered rings via addition of an electrophilic radical on an electrophilic double bond. Indeed, the methodology of organic electrochemical radical cyclization developed within the laboratory of the professor Markó appears to be a practical, innovative, and efficient approach to the preparation of diversely substituted 2-pyrrolidinones **2.6**. This strategy consists in the electrochemical generation of the linear carbonated radical **2.3** through the Kolbe reaction, followed by the intramolecular cyclization of this radical and the cross-coupling of the cyclic radical formed **2.4** and a radical derived from an appropriate precursory co-acid **2.5**. Two carbon-carbon bonds are generated, in only one-step, which leads to the formation of substituted γ-lactams **2.6** of which the classical preparation usually leads to the generation of unwanted secondary products. The use of electrochemistry could offset this downside. Apart from being ecological and having a high step economy, this technology is economical and readily transposable to batch reactors as well as to continuous flow reactors.




**Scheme 65 mechanism of the electrochemical cyclization of functionalized pyrrolidinones 2.6**

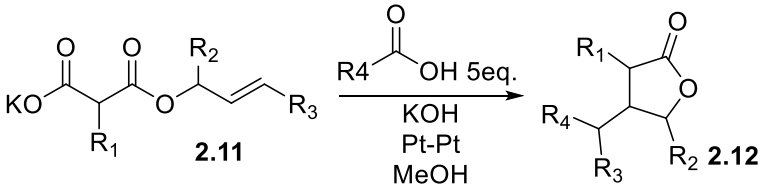
In the first instance, we will design a synthetic path for the electrocyclization substrate **2.10** formation, in only three steps starting from inexpensive and commercially available reagents (see Scheme **66**). This procedure begins with the hydrolysis of the dimethyl malonate **2.7** into the corresponding potassium salt **2.8**. This salt is then converted into the amide **2.9**, via a Steglich amidation reaction. Finally, the amide **2.9** is transformed into the substrate of electrocyclization **2.10** by hydrolysis.




**Scheme 66 electrocyclization substrat 2.10 synthesis**

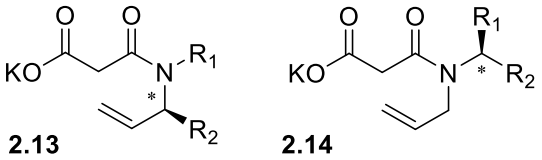
Subsequently, we would like to perform the electrocyclization reaction (see Scheme **65**) in a batch-type cell and optimize the reaction conditions by adjusting the experimental variables, such as: the current density, substrate concentration, electrodes nature, solvent, temperature, time, and the nature and concentration of the electrolyte salt, *etc.* Once the experimental variables will be determined, in order to get the best yields in the shortest possible time, the procedure will be exemplified by modifying the nature of the co-acid, the nature of the nitrogen protecting group, and by adding substituents on the carbonated skeleton of the electrocyclization substrate. In this context, we wish to synthetize readily available, easily modifiable, and diversely substituted 2-pyrrolidinones, under mild reaction conditions: ambient atmosphere, atmospheric pressure, and ambient temperature.

Subsequently, we would like to complete our study by applying our methodology to lactones electrosynthesis (see Scheme **67**), as those moieties are frequently met in the structure of natural compounds. This could be easily achieved by designing an ester substrate **2.11** analogue to the classic amide substrate.



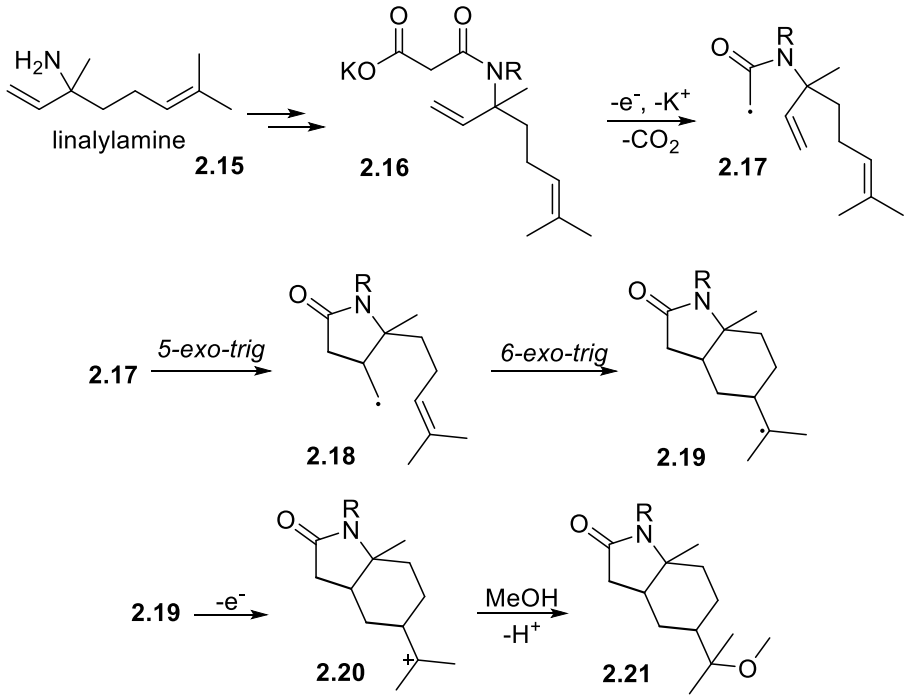

**Scheme 67 electrocyclization of lactones 2.12**

Afterwards, considering that the lacking diastereoselectivity of our method tends to limit the interest for our approach, it would be interesting to work on the development of a diastereoselective electrocyclization of 2-pyrrolidinones. The adopted strategy would rely on the judicious insertion of a chiral auxiliary inside the structure of the cyclization substrate, in order to induce a facial selectivity during the cyclization step (see Scheme **68**).



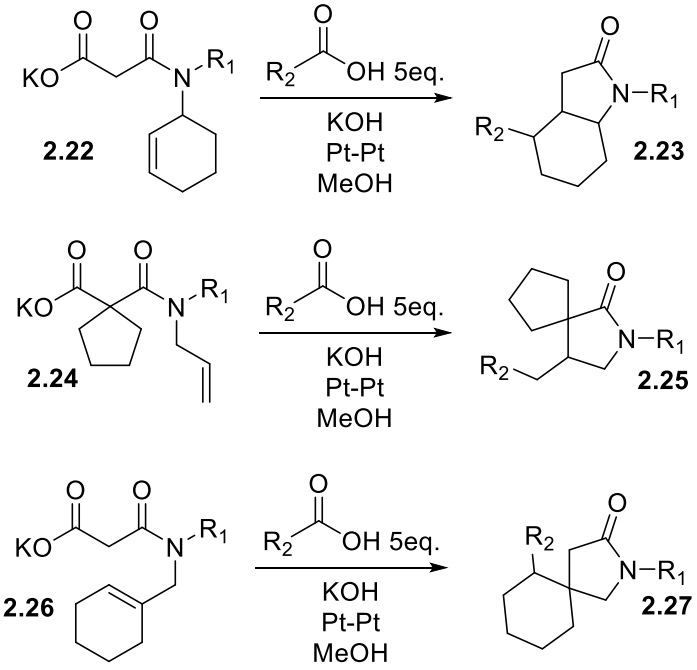

**Scheme 68 chiral substrates 2.13 and 2.14 for diastereoselective electrocyclization**

Furthermore, this methodology could become an efficient and original synthesis pathway for various fused- and spiro-bicycles containing a 2-pyrrolidinone unit. For this purpose, different strategies can be applied to access polycyclic 2-pyrrolidinones. Firstly, F. Lebreux has shown that in order to generate polycyclic molecules from linear substrates by Kolbe electrolysis, it is relevant to form primary radical intermediates to promote the cyclization reactions and not the Hofer-Moest processes. Based on the work of F. Lebreux, a linear substrate derived from the linalylamine **2.15** could be developed to generate a fused bicycle **2.21**. This synthesis would imply the oxidative decarboxylation of the substrate **2.16**, leading to the formation of the linear radical **2.17**, which could then cyclize and form the cyclic radical **2.18**. After, this latter would cyclize intramolecularly to generate the readily oxidizable tertiary alky radical **2.19**. Finally, the radical **2.19** would be oxidized to generate the carbocation **2.20**, which is subsequently trapped by methanol and produce the original bicyclic product **2.21**.



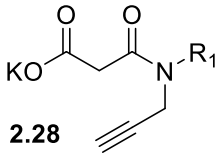

**Scheme 69 electrocyclization of polycyclic fused pyrrolidinone 2.21**

Another strategy to access polycyclic moieties would be to design cyclic substrates to perform electrocyclization reactions (see Scheme **70**). Those cyclic reagents could be synthesized by functionalizing the malonate part of the molecule or by replacing the allyl part of the substrate by a substituent containing a cyclohexene moiety.




**Scheme 70 strategies for pyrrolidinones 2.23, 2.25, and 2.27 polycyclization**

Furthermore, in order to expand the scope of the electrochemical radical cyclization process, it could be interesting to apply our methodology to substrates such as **2.28**, bearing a C-C triple bond (see Scheme **71**). Our enthusiasm for this survey relies on the fact that the addition of alkyl radicals to triple bonds is a greatly favored process, even though the starting alkyl radical is more stable than the formed vinyl radical.



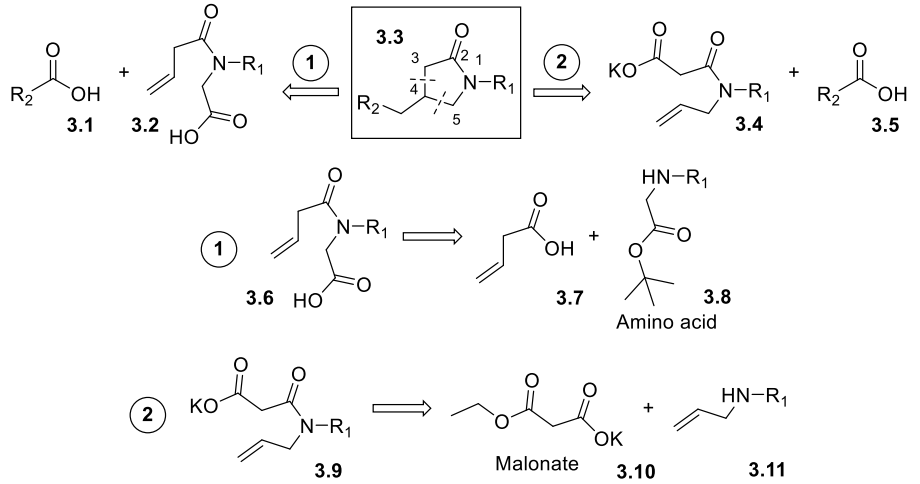

**Scheme 71 electrocyclization substrate containing a triple bond 2.28**

Finally, we would like to transpose our electrochemical cyclization of functionalized pyrrolidinones from a batch-type cell to a continuous flow-type cell, because the use of a continuous flow cell enables to get higher yields and conversions, to have better reproducibility, and to lower the reaction time. These benefits arise from the characteristics of flow reactors. Indeed, these cells have a high ratio of electrodes surface area to reactor volume, a small inter-electrodes gap, and a fixed geometry.

# 3 2-Pyrrolidinones Kobe electrocyclization

## 3.1 Strategy for the synthesis of the electrocyclization substrate

In order to develop an electrocyclization of functionalized 2-pyrrolidinones **3.3**, it is necessary to first establish a procedure to synthetize a model product. This latter is functionalized at the C4 position. Moreover, the substitution of that position has been reported to have a major effect on the biological activity for this class of compounds.[128] A retrosynthetic analysis of the 2-pyrrolidinone **3.3** shows that two disconnections can be considered (see Scheme **72**). In the first case, the disconnection is located between the carbons C4 and C5. Under this scenario, the substrate of electrocyclization is derived from an amino acid **3.8**. In the second case, the disconnection is positioned between the carbons C3 and C4. In that case, the substrate of electrocyclization is derived from a malonate compound **3.10**.



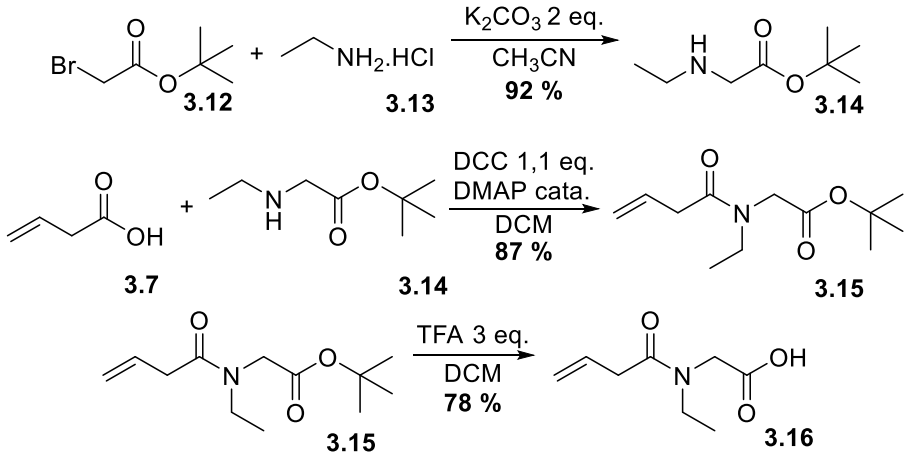

**Scheme 72 retrosynthetic analysis of functionalized 2-pyrrolidinones 3.3 formation**

### 3.1.1 Substrate derived from an amino acid

In the first case, the substrate can be derived from a protected amino acid **3.14**. The advantage of this procedure is that the reagents of the cyclization substrate are cheap and commercially available. Moreover, the substrate **3.16** can be readily functionalized in a varied manner, using different natural or synthetic amino acids. An ethyl function protects the amino group from further oxidation under the conditions of the Kolbe electrolysis. The synthetic road of the substrate **3.16** requires only three steps. First, *tert*-butylethylglycinate **3.14** is formed by nucleophilic substitution between methyl bromoacetate **3.12** and ethylamine hydrochloride **3.13**

[128] (a) Bhattacharya, K.; Upadhyay, S.; Jaiswal, A.; Bhattacharyla, S. *Indian J. Exp. Biol.* **1989**, 28, 261; (b) Winnocka, K.; Tomasiak, M.; Bielawska, A. Acta. *Poloniae Pharmaceutica – Drug Research* **2005**, 62, 405; (c) Grossman, L.; Stewart, A.; Kalueff, A. V.; Howard, H. *Brain Reseach Bulletin* **2011**, 85, 58.

in the presence of potassium carbonate. A Steglich[129] amination reaction is then performed in order to generate the *tert*-butylester **3.15** using the species **3.14** and the 3-butenoic acid **3.7**. Finally, this compound is treated with TFA, which leads to the formation of the substrate **3.16**.




**Scheme 73 synthesis of the substrate 3.16 derived from a protected amino acid 3.14**

### 3.1.2 Substrate derived from a malonate ester

An alternative synthetic road was envisaged where the substrate was derived from a malonate (see Scheme **74**). In this case, the advantage is that the substrate can be easily functionalized via malonic substitution in α-position of the two carbonyls. Considering the high instability of malonic acids[130], which are readily decarboxylated, the cyclisation substrate was isolated as the potassium salt **3.10**, which is more stable than the corresponding acid. Furthermore, given the instability of the nitrogen functions in electrolysis conditions[131], the nitrogen of the amide function in the substrate structure was protected by an allyl function. Indeed, secondary amides are unstable in oxidative conditions and are easily oxidated in the corresponding nitrogen centered amide radical. The allyl protecting group can be easily removed after the cyclization step.[132] Moreover, the fact that the substrate contains two allyl groups on the nitrogen atom results in the fact that the two rotamers are able to cyclize. The synthetic road of the substrate **3.20** began with the conversion of the diethyl malonate **3.17** into the corresponding potassium salt **3.10**. This latter was then treated with oxalyle chloride, which led to the formation of the acyl chloride **3.18**. The acyl chloride was then converted into the corresponding amide **3.19**, which was finally transformed into the electrocyclization substrate **3.20** by saponification with potassium hydroxide. The potassium salt **3.20** was purified via filtration and diethyl ether washing.

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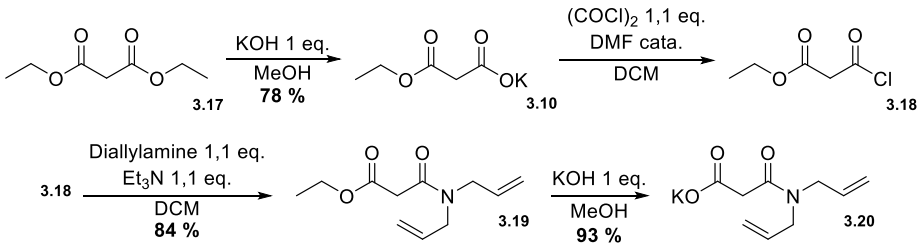
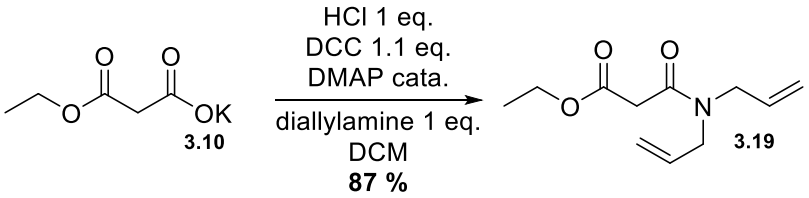
[129] Neises, B.; Steglich, W. *Angew. Chem. Int. Ed.* **1978**, 17, 522.
[130] Hall, G.A. *J. Am. Chem. Soc.* **1949**, 71, 2691.
[131] (a) Becking, L.; Schäfer, H.J. *Tetrahedron Letters* **1988**, 29, 2797; (b) Ole, H.; Lund, H. Organic Electrochemistry Fourth Edition. New-York: Marcel Dekker, **1991**.
[132] (a) Alcaide, B.; Almendos, P.; Alonso, J.M. *Tetrahedron Letters* **2003**, 44, 8693; (b) Cadierne, V.; Gimeno, J.; Nebra, N. *Chemistry – A European Journal* **2007**, 13, 6590.




**Scheme 74 synthesis of the electrocyclization substrate 3.20 derived from a malonate ester 3.17**

Another way of synthetizing this compound was to use dicyclohexylcarbodiimide (DCC) as a coupling reagent and DMAP as a catalyst to perform a Steglich amidation on the potassium salt **3.10**. In this case, as the ethyl potassium malonate **3.10** is commercially available and cheap, the electrocyclization reagent was produced in only two steps.




**Scheme 75 Steglich amidation**

## 3.2 Development and optimization of the electrocyclization process

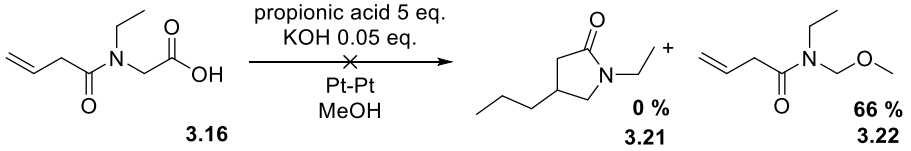
### 3.2.1 Development

With the desired precursors in hand, the electrolysis parameters were optimized, using the experimental conditions developed by F. Buzzo and F. Lebreux. In organic electrochemistry, many parameters have an impact on the reaction outcome, such as the electrode nature, temperature, substrate concentration, number of equivalent of electrolyte salt and co-acid, solvent, current density and the potential. During this optimization study, constant current electrolysis was used. This means that the current density was maintained at a constant value, while the potentials of the electrodes vary. This technic has the advantage to have a simpler setup and to be less time-consuming than the controlled potential electrolysis. Moreover, during electrolyzes at constant current, the Faradic yield of the reaction can be calculated. Finally, a jacketed undivided cell was employed as there should be no major side reactions at the cathode.

#### *3.2.1.1 Substrate derived from an amino acid*

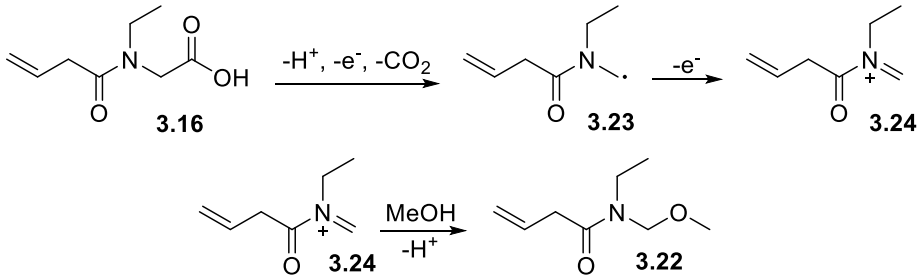
The substrate **3.16**, which was derived from an amino acid, was put in electrolysis conditions, which took their inspiration from the experimental conditions developed by F. Buzzo and F. Lebreux (see Scheme **76**). Under those reaction settings, the current density was 37.5 mA/cm², the solvent used was the methanol, and the electrodes were made of platinum. Moreover, 5 equivalents of co-acid and 0.05 equivalents of potassium hydroxide electrolyte salt, and a concentration of 0.132

mol/l of substrate were needed. The temperature of the reaction was maintained around 10°C using tap water to regulate the temperature of the jacketed reactor. Unfortunately, under those conditions, the expected 2-pyrrolidinone **3.21** was not obtained.




**Scheme 76 electrolysis of the substrate 3.16**

Actually, the electrolysis of the carboxylic acid **3.16** led to an oxidative decarboxylation and to the formation of the radical **3.23**. This carbon radical, which was situated in α of the nitrogen atom of an amide function, was readily oxidated into the corresponding N-acyliminium ion **3.24**. The latter was then trapped by a nucleophile, the methanol solvent, to finally form the hemiaminal species **3.22** (see Scheme **77**).




**Scheme 77 Hofer-Moest oxidation of 3.16**

The high rate of oxidation of the carbon radical **3.23** can be explained by the net bonding interaction between the nitrogen lone pair and the singly occupied molecular orbital (SOMO) (see Figure **4**) which makes this radical more reactive.[133] The greater orbitals overlap and the smaller orbitals energy difference result in stronger interaction. This bonding interaction is seen as a two-center three electrons bond. This interaction increases the radical energy, which makes the radical easily oxidizable.

[133] Simones, J.A.M. Energetics of organometallic species *Spinger Science + Business media Dondrecht* **1992**, 99.

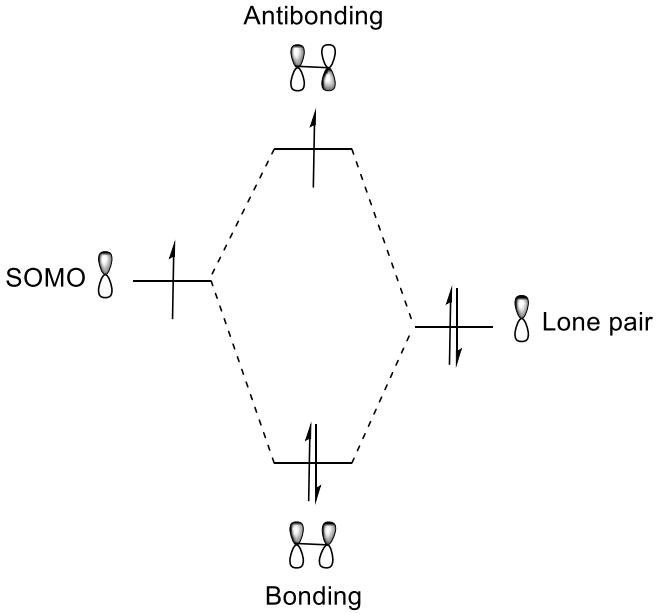
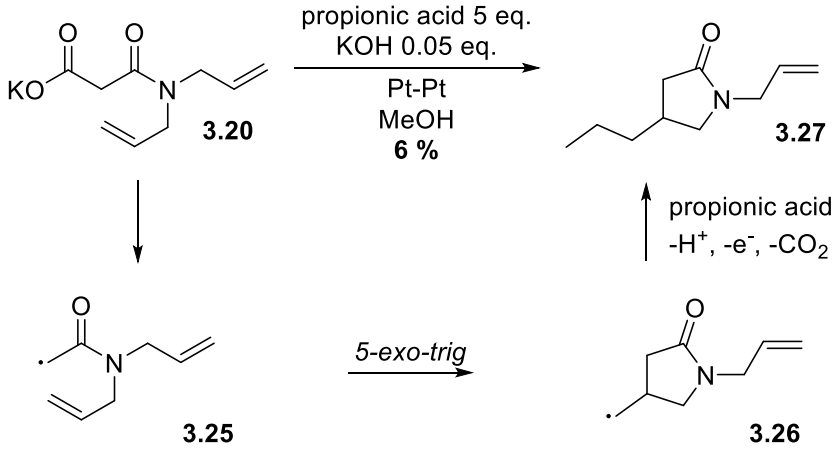



**Figure 4 three electron bonding interaction between the SOMO and lone pair**

This part of the project was finally abandoned due to the high reactivity of the α-amidomethyl radical **3.23**, which is oxidized and does not perform a *5-exo-trig* cyclization. This phenomenon could also be due to the preponderance of the s-*trans*-rotamer of the amide **3.23**, which should selectively lead to the oxidation reaction.

*3.2.1.2 Substrate derived from a malonate ester*

The reagent **3.20**, derived from a malonate ester, was tested in the same electrolysis conditions as the substrate **3.16**. In this case, a *5-exo-trig* electrocyclization took place and led to the formation of the desired 2-pyrrolidinone **3.27**, in modest yields. As a result of the fast and inexpensive preparation if this substrate **3.20**, it was then prepared, in large quantities, in order to perform an optimization of the experimental variables of this electrolysis.




**Scheme 78 electrocyclization of 2-pyrrolidinone 3.27**

Unlike the radical **3.23**, the carbon radical **3.25**, positioned in α position of a carbonyl function was stable and did not undergo a second oxidation. The stability of the radical **3.25** can be explained by the Fukui theory of frontier orbital interactions.[134] Indeed, the interaction between the SOMO and the lowest unoccupied molecular orbital (LUMO), Π* antibonding orbital, stabilizes the radical and makes it less oxidizable. This orbital interaction is favored by the dissymmetry of the LUMO π* orbital; the orbital lobe situated on the carbon atom is bigger than the one situated on the oxygen atom of the carbonyl function.

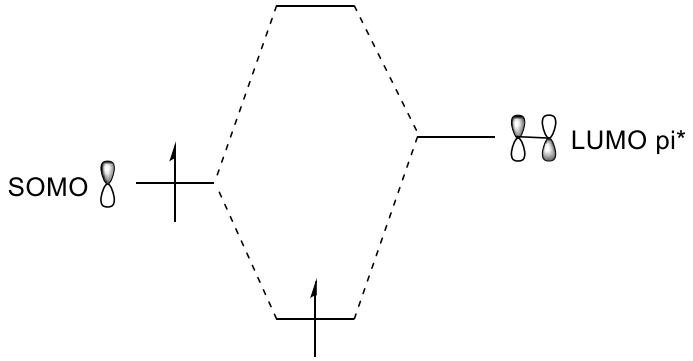


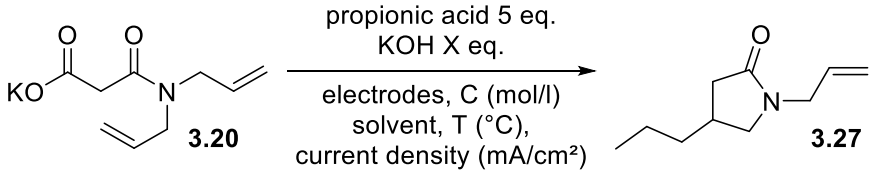

**Figure 5 frontier orbital interactions between the SOMO and the LUMO**

### 3.2.2 Optimization

The low yield (6 %) obtained during the development of the electrocyclization of 2-pyrrolidinones process was the reason why an optimization study was conducted (see Scheme **79**).[135] In order to improve the yield of the reaction, several variables were modified such as the substrate concentration, current density, temperature, solvent, electrodes nature, and the number of equivalent of supporting electrolyte (see Table **4**). Those parameters have a huge impact on the yields, reaction time and selectivity towards radicals or carbocations. This optimization study was conducted

[134] Fukui, K.; Yonezawa, T.; Shingu, H. *The Journal of Chemical Physics* **1952**, 20, 722.
[135] Quertenmont, M.; Goodall, I.; Lam, K.; Markò, I.; Riant, O. *Org. Lett.* **2020**, 22, 1771.

in an undivided jacketed cell and electrolysis reactions were performed with a constant current density. After reaction, the products were purified via silica gel chromatography and isolated yields were calculated.



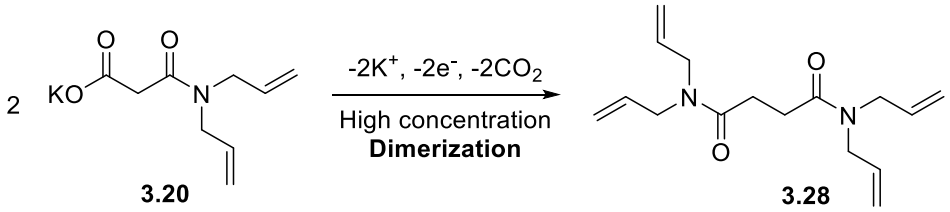

**Scheme 79 electrocyclization optimization**

| Entry | C (mol/l) | Current density (mA/cm²) | T (°C) | Electrodes | Solvent | KOH eq. | Yields (%) |
|---|---|---|---|---|---|---|---|
| 1 | 0.033 | 25 | 10 | platinum | MeOH | 5 | 68 |
| 2 | **0.066** | 25 | 10 | platinum | MeOH | 5 | 71 |
| 3 | 0.132 | 25 | 10 | platinum | MeOH | 5 | 26 |
| 4 | 0.066 | 12,5 | 10 | platinum | MeOH | 5 | 56 |
| 5 | 0.066 | **25** | 10 | platinum | MeOH | 5 | 71 |
| 6 | 0.066 | 37,5 | 10 | platinum | MeOH | 5 | 68 |
| 7 | 0.066 | 50 | 10 | platinum | MeOH | 5 | 64 |
| 8 | 0.066 | 75 | 10 | platinum | MeOH | 5 | 64 |
| 9 | 0.066 | 100 | 10 | platinum | MeOH | 5 | 61 |
| 10 | 0.066 | 25 | 0 | platinum | MeOH | 5 | 29 |
| 11 | 0.066 | 25 | **10** | platinum | MeOH | 5 | 71 |
| 12 | 0.066 | 25 | 25 | platinum | MeOH | 5 | 51 |
| 13 | 0.066 | 25 | 40 | platinum | MeOH | 5 | 37 |
| 14 | 0.066 | 25 | 10 | **platinum** | MeOH | 5 | 71 |
| 15 | 0.066 | 25 | 10 | graphite | MeOH | 5 | 7 |
| 16 | 0.066 | 25 | 10 | glassy carbon | MeOH | 5 | 0 |
| 17 | 0.066 | 25 | 10 | platinum | AcOH | 5 | 0 |
| 18 | 0.066 | 25 | 10 | platinum | DMSO | 5 | 0 |
| 19 | 0.066 | 25 | 10 | platinum | H2O | 5 | 9 |
| 20 | 0.066 | 25 | 10 | platinum | DMF | 5 | 40 |
| 21 | 0.066 | 25 | 10 | platinum | EtOH | 5 | 49 |
| 22 | 0.066 | 25 | 10 | platinum | CH3CN | 5 | 70 |
| 23 | 0.066 | 25 | 10 | platinum | $MeOH/H_2O$ | 5 | 68 |
| 23 | 0.066 | 25 | 10 | platinum | **MeOH** | 5 | 71 |
| 24 | 0.066 | 25 | 10 | platinum | MeOH | 0.05 | 54 |
| 25 | 0.066 | 25 | 10 | platinum | MeOH | 0.33 | 66 |
| 26 | 0.066 | 25 | 10 | platinum | MeOH | **5** | 71 |

**Table 4 optimization of the Kolbe electrocyclization reaction**

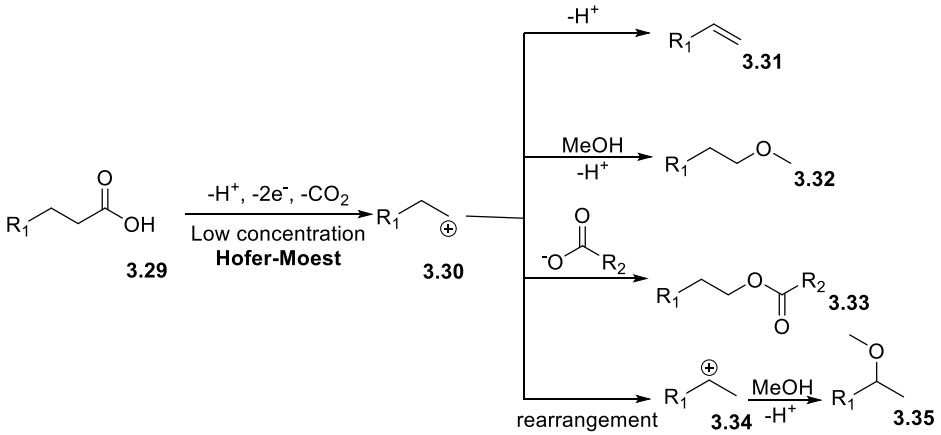
### *3.2.2.1 Substrate concentration*

In organic electrochemistry, the substrate concentration has a big influence on the reaction outcome. If an excessive concentration of the carboxylate is used, the high concentration of radical formed at the anode surface promotes the dimerization process at the expense of the cross-coupling process (see Scheme **80**). The dimer side-product **3.28** is formed instead of the desired 2-pyrrolidinone.




**Scheme 80 dimerization process**

Whereas if the concentration is too low, the low concentration of radical formed at the anode surface favors a second oxidation of that radical in the corresponding carbocation, which is called the Hofer-Moest process (see Scheme **81**).[136] This event leads to the formation of side-products. The carbocation **3.30** formed can either react with the solvent, methanol; and generate an ether moiety **3.32**, or react with a deprotonated acid to produce an ester compound **3.33** as a side-product.[137] Additionally, the obtained carbenium ion **3.30** can also react via β-elimination to form an alkene **3.31**. Finally, in the case of a straight-chain carboxylic acid such as **3.29**, the first formed primary carbenium ion **3.30** may be so unstable that it readily rearranges into a secondary carbenium ion **3.34**, which can be attacked by the solvent to form the ether **3.35**.[138] In our case, the substrate **3.20** cannot be easily oxydated in the corresponding carbocation as the interaction between the SOMO of the radical formed via oxidation and the LUMO of the carbonyl stabilizes the radical **3.25**.




**Scheme 81 Hofer-Moest process**

During our study, a concentration of 66 mmol/l of the electrocyclization substrate **3.20** appeared to be the more adapted to our electrolysis methodology (see Table **4** - Entry **2**).

### *3.2.2.2 Current density*

During a Kolbe reaction, the current density influences the yield. As the current density is directly proportional to the concentration in radical at the anode, a too

[136] Schäfer, H.J. *Topics in current Chemistry* **1990**, 152, 92.
[137] (a) Schäfer, H.J. *Topics in current Chemistry* **1990**, 152, 92; (b) Holzhäusen, F.J.; Mensah, J.B.; Palkovits, R. *Green Chem.* **2020**, 22, 286.
[138] Muck, D.L.; Wilson, E.R. *J. Electrochem. Soc.* **1970**, 117, 1358.

high current density promotes dimerization processes, while a low current density favors Hofer-Moest processes. Furthermore, at high current densities, the so-called critical potential of about 2.4 V (*vs* NHE) is reached above which the Kolbe reaction works efficiently.[139] Above the critical potential, the carboxylates are preferentially adsorbed at the anode surface and form a layer. The solvent oxidation is suppressed as the methanol is desorbed of the anode. However, there is no need for potential control during a Kolbe reaction as the critical potential is already exceeded at a current density of 1 - 10 mA/cm², which is much below the usual applied current densities. Analyzing our results, a current density of 25 mA/cm² seemed to allow the optimization of the reaction yield (see Table **4** – Entry **5**).

#### *3.2.2.3 Temperature*

According to the literature, a temperature between 10°C and 45°C favors the Kolbe electrolysis.[140] Indeed an excessive temperature leads to Hofer-Moest processes, therefore to the formation of side-products. Whereas, a too low temperature increases the solution resistance, which then increases the cell potential. In our case, a temperature of 10°C, obtained via a water flux through the jacketed reactor, allowed the optimization of the yield (see Table **4** – Entry **11**).

#### *3.2.2.4 Solvent*

As a huge variety of examples in the literature demonstrates, the methanol is the best-suited solvent for the Kolbe reaction. Indeed, this solvent has the advantage that its oxidation is drastically inhibited by the formation of a carboxylate layer at the surface of the anode, at a potential above the critical one. Furthermore, the important dipole moment of the methanol facilitates the ions flow though the solution and thus the current flow though the cell. In the course of this study, several common electrochemical solvents were tested. The methanol is the solvent that obviously gives the best results, and which has been chosen for our methodology (see Table **4** – Entry **23**). The acetonitrile also promotes good yields but its toxicity *vs* day-to-day use explains why this solvent was discarded. Moreover, the dimethylformamide is also a suitable solvent but it has the disadvantage of being readily oxidized. Furthermore, a mixture methanol/water 2/1 gives also good results. Despite the environmental benefit of using water as a solvent, this solution is less conductive than the methanol solution, which is an economic and ecologic disadvantage as the potential of the cell is increased. Nevertheless, an interesting result emerged from this research. When acetic acid was used as a solvent, the 2-pyrrolidinone **3.27** yield was zero but a yield of 85 % in the dimerization product **3.28** was obtained (see Scheme **82**). This result demonstrated that all the experimental variables have a real influence on the outcome of the Kolbe reaction.

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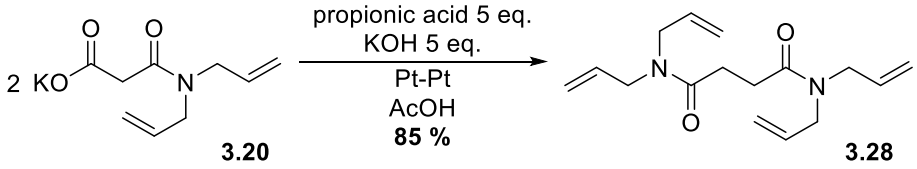
[139] Dickinson, T.; Wynne-Jones, W.F.K. *Trans. Faraday Soc.* **1962**, 58, 382.

[140] Torii, S. Electroorganic Syntheses Methods and Applications, Part 1: oxidation, Monographs in Modern Chemistry 15. Tokyo: Kondansha **1985**.




**Scheme 82 electrolysis of the substrate 3.20 with AcOH as a solvent**

*3.2.2.5 Electrode nature*

In organic electrochemistry, the knowledge on the relation between the electrode nature and the selectivity between a radial or a cationic pathway remains empirical. In the case of our methodology, the use of platinum electrodes enabled the optimization of the reaction yield (see Table **4** – Entry **14**). This result accords with the literature, in which it can be read that platinum electrodes favor Kolbe reactions. In contrast, the use of graphite electrodes promotes Hofer-Moest transformations. Gold or platinized titanium can also be used as a cathode material. Nevertheless, the nature of the cathode is not critical, as the reduction of protons and methanol is the main process at the cathode. Nevertheless, the nature of the cathode material can be chosen in order to limit the overpotential and thus maximize the faradic yield. Therefore, the electrolysis can be conducted in an undivided cell. Practically, in order to minimize the resistance and thus to lower the potential applied on the cell, the gap between the electrodes shall be as small as possible. According to the literature, the simultaneous use of acetonitrile as solvent and glassy carbon electrodes promotes the Kolbe transformation. The experiment confirmed this affirmation, but surprisingly, a yield of 61 % in the dimerization product **3.28** was obtained.

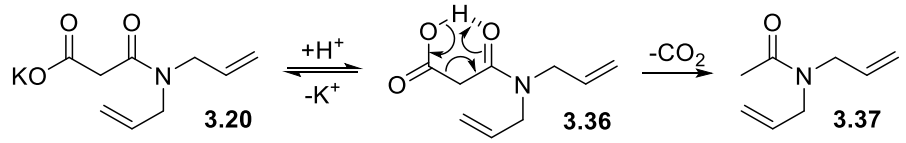
*3.2.2.6 Supporting electrolyte*

In organic electrochemistry, additives can strongly influence the outcome of a Kolbe transformation. Usually, spectator anions should be avoided, because they seem to interfere with the formation of the carboxylate layer, at the anode. The shift from a radical to a cationic road can be explained as due to blocking part of the anode surface by foreign anions, which lower the radical concentration at the anode. This phenomenon disfavors the radical coupling and promotes a second electron transfer. Moreover, foreign cations can also affect negatively the yields. This is due to the formation of oxide layers at the anode. Alkali, alkaline metals, alkylammonium ions, and also zinc and nickel cations do not affect the Kolbe process and are therefore the counter ions of choice of a supporting electrolyte. Those interactions explain why the electrolyte salt should be chosen carefully for an electroorganic process.

Our study shows that five equivalents of KOH, electrolyte salt, allowed the optimization of the reaction yields (see Table **4** – Entry **26**). The hypothesis explaining this affirmation is linked to the stability of the electrocyclization substrate **3.20**.[141] Indeed, the substrate in the form of a potassic salt is stable, while in the form of an acid **3.36** is unstable (see Scheme **83**). Therefore, in acidic conditions, when less than five equivalents if KOH are used, the yield is lower. By contrast, five equivalents of KOH and five equivalents of propionic acid enable to

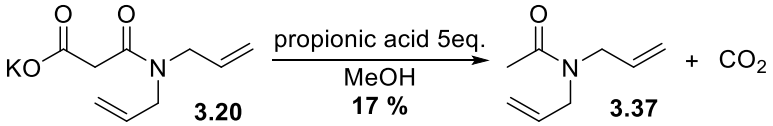
[141] Hall, G.A. *J. Am. Chem. Soc.* **1949**, 71, 2691.

work in non-acidic conditions and thus to avoid the substrate protonation, its decarboxylation, and to promote better yield.




**Scheme 83 electrocyclization substrate 3.20 decarboxylation**

In order to prove this hypothesis, a procedure was setup where the potassic salt **3.20** was stirred in acidic condition, during four hours, at room temperature, and without electric power (see Scheme **84**). After reaction, 17 % of the decarboxylation product **3.37** was isolated, which proved that the moiety **3.20** was well instable in acidic conditions.

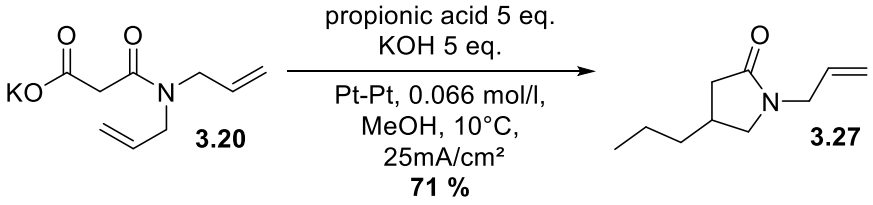



**Scheme 84 decarboxylation of the substrate 3.20 under non-electrolytic conditions**

Typically, the aim of the electrolyte salt is to increase the conductivity of the reaction mixture. However, in our case, the electrolyte salt seems to have two purposes. In one hand, it raises the conductivity of the solution; and on the other hand, it is used as a base to prevent the medium to become acidic.

### *3.2.2.7 Conclusions of the optimization of the Kolbe electrocyclization reaction*

An initial part of our research deals with the study of the electrochemical parameters, in order to find the most efficient conditions for our radical electrocyclization. We were interested in the influence of several variables, such as the current density, temperature, substrate concentration, number of equivalent of the electrolyte salt, solvent, and electrode nature. This investigation showed that to avoid homo-coupling of the radical **3.25**, the substrate should be highly diluted in methanol (66 mM in methanol) and the current density, which is a key parameter, should be kept between 25 and 37,5 mA/cm². In addition, a temperature between 10 and 20°C, the use of smooth platinum electrodes, and an excess of co-acid (5 eq.) provided the optimum results (see Scheme **85**). Finally, the use of five equivalents of supporting electrolyte, KOH, avoided the decarboxylation of the substrate by maintaining basic conditions. Under those conditions, four hours electrolysis leaded to the formation of the 2-pyrrolidinone product **3.27** in excellent yield of 71 %. Moreover, the formation of a mixture of side-products was observed. Some of them were isolated and identified; nevertheless, the structures of all of them were not determined given that we were not able to isolate all the impurities via silica gel chromatography.




**Scheme 85 electrocyclization optimized conditions**

## 3.3 Faradic yield calculation

The first electrolysis law of Faraday states that "the mass of a substance altered at an electrode during electrolysis is directly proportional to the quantity of electricity transferred at that electrode".[142] The quantity of electricity refers to electrical charge, typically measured in coulombs. The notion of Faradic yield arises from this law. The Faradic yield of the consumption of a species X throughout electrolysis refers to the ratio of the amount of electricity, which is used to consume this species for a specific time, and the total amount of electricity that crosses the cell during this time. Indeed, all the electrons crossing the cell are not involved in the oxidation of the substrate. Some are lost due to side reactions and others due to the cell resistance.

$$R = Q_x/Q$$

Where:

- ✓ R is the Faradic yield.
- ✓ $Q_x$ is the amount of electricity used to consume the species X during a specific time T.
- ✓ Q is the amount of electricity, electrical charge, crossing the cell during this time T.

When a current of an intensity I crosses the cell during a time T, the quantity of electricity involved is defined by the following relation:

$$Q = I*T$$

When, as in the case under examination, two electrochemical reactions take place simultaneously, at the surface of the anode, the total current navigating through the electrode may be defined as the sum of the partial currents corresponding to the two reactions.

$$I = I_a + I_b$$

Where:

- ✓ $I_a$ is the partial current used to consume the species a.
- ✓ $I_b$ is the partial current used to consume the species b.

[142] Faraday, M. *Experimental Researches in Electricity* Chem. Royal Institution, **1833**.

Let us now calculate the Faradic yield of our reaction if our oxidation yield was 100 %. Knowing that the current "I = 100 mA = 0.1 C/s" and that the reaction time T = 4h = 14 400 s, the total charge $Q_T$ delivered by the cell during this time T is expressed by the following expression:

$$Q_t = I*T = 0.1\ C/s*14\ 400\ s = 1\ 440\ C$$

Moreover, the Faraday constant F, whose value is 96 485 C/mol, corresponds to the product of the elementary charge of an electron e and the Avogadro's number $N_a$ ($F = N_a*e$). This value therefore represents the global charge of one mole of elementary charge. In the light of that fact, the number of mole $n_t$ theoretically consumed if the Faradic yield was 100 % is given by the following expression:

$$n_t = Q_t/F = 1\ 440\ C/96\ 485\ C/mol = 14.92\ mmol$$

Lastly, considering that, if the reaction yield was 100 %, the number of mole of the substrate $n_a$ consumed would be 0.66 mmol and the number of mole of co-acid $n_b$ consumed would be 3.3 mmol. The Faradic yield is then given by the following expression:

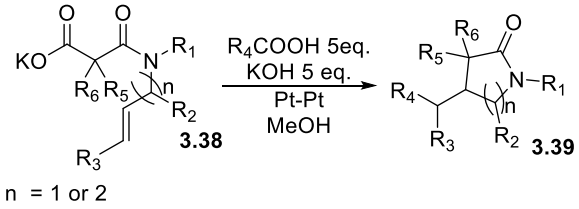
$$R = ((n_a + n_b)/n_t)*100 = ((0.66+3.3)/14.92)*100 = 27.29\ \%$$

The Faradic yield of our reaction is 19.38 % as the yield of our reaction is 71 %, which is an acceptable value according to the literature. To put this work into perspective, in order to increase the faradic yield and thus to generate as few electric loss as possible, it would be interesting to transpose our reaction in a flow reactor or micro-reactor. Indeed, the use of a continuous flow reactor allows to decrease the reaction time and to increase the yield of an electroorganic process.[143] What explains those advantages is the huge ratio of the electrode surface to the reactor volume.

## 3.4 Exemplification of the 2-pyrrolidinones electrocyclization process

With the optimized conditions ready and a large quantity of electrocyclization substrate **3.20** in hand, the scope and limitations of our methodology were investigated. This research allowed the formation of a library of diversely substituted 2-pyrrolidinones (see Tables **5** and **6**). The electrochemical reactions were carried out under the optimized conditions (section **3.2.2.7**). In order to broaden the field of substrates of our methodology, several co-acids were tested and the protecting group of the nitrogen atom was modified. Moreover, the structure of the electrocyclization reagent was changed; and the double bond part and the malonic part of that molecule were substituted. Finally, to show the versatility of this transformation, a substrate with a homoallyl function was designed to synthetize a δ-lactam.

[143] Watts, K.; Baker, A.; Wirth, T. *J. Flow. Chem.* **2014**, 4, 2.

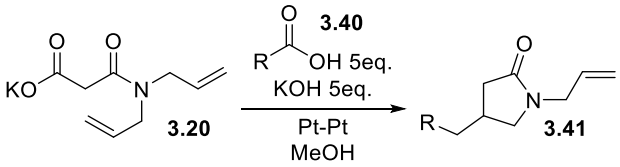



**Scheme 86 electrocyclization of lactams 3.39**

## 3.4.1 Variation of the co-acid nature

### *3.4.1.1 Carboxylic acids used as a co-acid*

First, several co-acids were tested in the electrocyclization reaction (see Tables **5** and **6**). The variation of the co-acid nature allowed the straightforward synthesis of different 2-pyrrolidinones substituted in position 4 **3.41** (see Scheme **87**). Interestingly, the substitution of that position was reported to have a major effect on the biological activity of this class of compounds. The tables **5** and **6** contain the achieved results for the electrolysis of the compound **3.20**, in the presence of various co-acids **3.40**. The yields reported are the isolated yields calculated after purification via silica gel chromatography.




**Scheme 87 electrocyclization process with variation of the co-acid 3.40 nature**

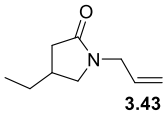
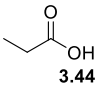
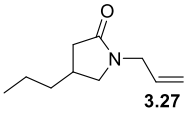
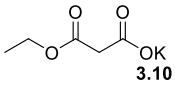
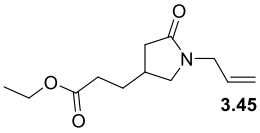
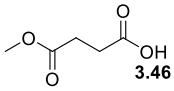
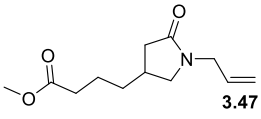
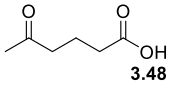
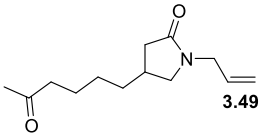
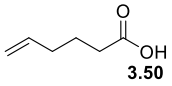
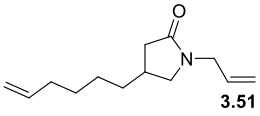
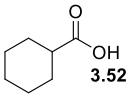
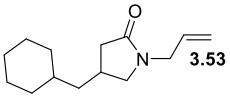
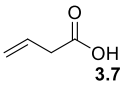
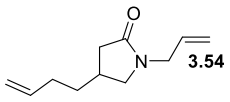
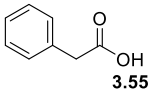
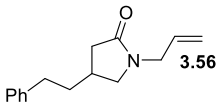
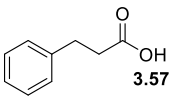
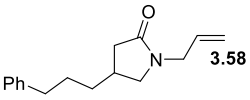
| Entry | Co-acids | Products | Yields |
|---|---|---|---|
| 1 |  **3.42** |  **3.43** | 61 % |
| 2 |  **3.44** |  **3.27** | 71 % |
| 3 |  **3.10** |  **3.45** | 70 % |
| 4 |  **3.46** |  **3.47** | 65 % |
| 5 |  **3.48** |  **3.49** | 60 % |
| 6 |  **3.50** |  **3.51** | 45 % |
| 7 |  **3.52** |  **3.53** | 36 % |
| 8 |  **3.7** |  **3.54** | 3 % |
| 9 |  **3.55** |  **3.56** | 4 % |
| 10 |  **3.57** |  **3.58** | 30 % |

**Table 5 substrate scope and limitations**

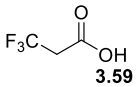
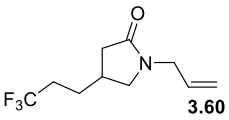
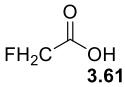
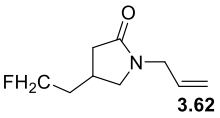
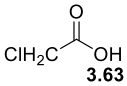
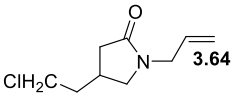
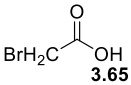
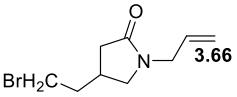
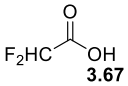
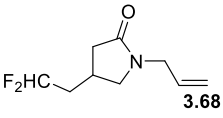
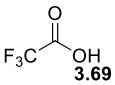
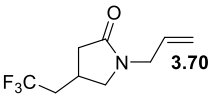
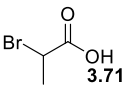
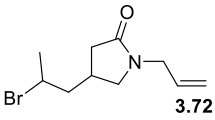
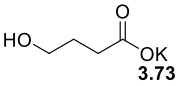
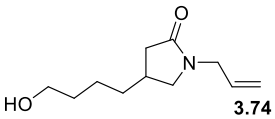
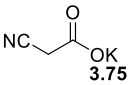
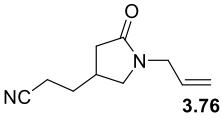
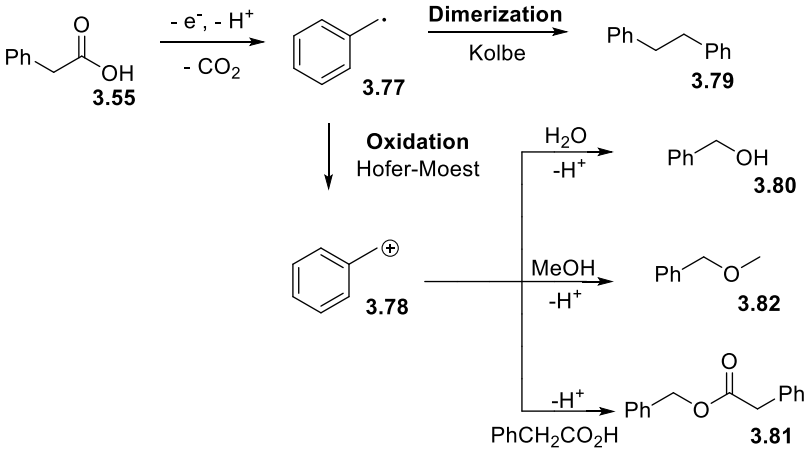
| Entry | Co-acids | Products | Yields |
|---|---|---|---|
| 11 |  **3.59** |  **3.60** | 68 % |
| 12 |  **3.61** |  **3.62** | 34 % |
| 13 |  **3.63** |  **3.64** | 27 % |
| 14 |  **3.65** |  **3.66** | 14 % |
| 15 |  **3.67** |  **3.68** | 36 % |
| 16 |  **3.69** |  **3.70** | 2 % |
| 17 |  **3.71** |  **3.72** | 0 % |
| 18 |  **3.73** |  **3.74** | 6 % |
| 19 |  **3.75** |  **3.76** | 0 % |

**Table 6 substrate scope and limitations**

The variation of the co-acid nature provided a further insight into several principles of the Kolbe reaction. In the presence of acetic acid **3.42** and propionic acid **3.44**, the electrocyclization proceeded smoothly and afforded aliphatic 2-pyrrolidinones **3.43** and **3.27** in good yields (61 – 71 %). Furthermore, the use of mono-methyl hydrogen succinate **3.46**, ethyl potassium malonate **3.10**, 5-hexenoic acid **3.50**, and 4-acetylbutyric acid **3.38** as co-acids enabled the formation of 2-pyrrolidinones **3.47**, **3.45**, **3.51** and, **3.49** in excellent yields. These good results are explained by the fact that the oxidative decarboxylation of those co-acids leads to the formation of primary radicals, which are reluctant to be oxidized in carbocations. On the flip side, the cyclohexanecarboxylic acid **3.52** and 2-bromo propionic acid **3.71** respectively generated secondary radicals prone to be rapidly oxydated, to lead to the generation of side products and lower yields. Moreover, the 2-bromo propionic acid could be fragmented because of the instability of the carbon-bromine bond in electrolytic conditions. Unfortunately, the use of potassium 2-cyanoacetate **3.75** did not lead to the formation of the expected 2-pyrrolidinone **3.76**. This result can be explain by the formation of a nitrogen centered radical via delocalization after the oxidative decarboxylation of the potassium 2-cyanoacetate **3.75**.

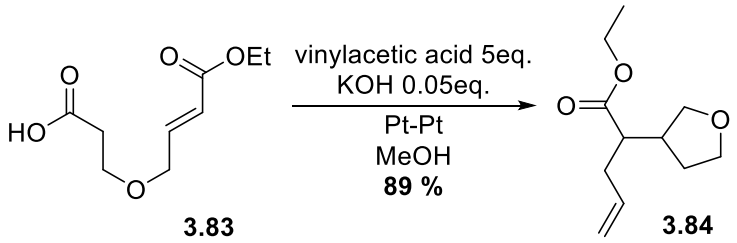
In a second phase, the project was focused on the insertion of an aromatic ring in the structure of 2-pyrrolidinones. Phenylacetic acid **3.55** was tested in the first place. Unfortunately, its electrolysis produced only 4 % of the desired product **3.56**. The reason of this poor yield can be explained by the presence of an aromatic ring in the α-position of the radical formed by oxidative decarboxylation.[144] This aromatic nucleus triggers an electron delocalization, and thus a reduction of the oxidation potential of the intermediate radical **3.77** (see Scheme **88**). This phenomenon causes the formation of the carbocation **3.78**; and thereupon the formation of miscellaneous secondary products, such as: the benzylic alcohol **3.80**, the benzylic ether **3.82** and, the benzylic ester **3.81**. In order to address this problem, the hydrocinnamic acid **3.57** was evaluated in our process. The oxidation of that reagent led to the formation of a non-delocalizable and less oxidizable radical, which generated, by cross-coupling, the 2-pyrrolidinone **3.58** in a reasonable yield of 30 %. The lower yields, compared to aliphatic acids, might be due to an adsorption trend of the homobenzyl-substituted radicals on the electrode surface.

[144] Weedon, C. *J.C.S. Perkin II* **1974**, 106.




**Scheme 88 phenylacetic acid 3.55 oxidation**

Subsequently, the vinylacetic acid **3.7** was tested under our conditions. Surprisingly, a really low quantity of the corresponding 2-pyrrolidinone **3.54** was isolated. This result did not correlate with the excellent yield achieved by F. Lebreux, in the electrocyclization of substituted tetrahydrofuran **3.84** (see Scheme **89**). An explanation of this phenomenon can be related to the instability of vinylacetic acid, as the unconjugated double bond can easily isomerize in basic condition. Furthermore, the radical formed via the oxidative decarboxylation of the 3-butenoic acid **3.7** could be easily oxidation into the corresponding carbocation which should be stabilized via resonance.




**Scheme 89 electrocyclization of tetrahydrofuran 3.84 in presence of vinyl acetic acid 3.7**

Thereafter, the use of potassium 4-hydroxybutanoate **3.73** did not lead to good yield of the corresponding 2-pyrrolidinone **3.74**. This trend can be related to the oxidation of the alcohol function. In fact, most primary and secondary alcohols can be oxidized at higher potentials than 2.3 V (vs ESH). Thus, the primary alcohol function of the co-acid **3.73** may be oxidized to the corresponding aldehyde, but under electrolysis conditions, aldehydes can be transformed to carboxylic acids by further oxidation. This latter can subsequently undergo a Kolbe-type decarboxylation, which leads to the formation of a large number of side-products. Another explanation of that phenomenon could be the fragmentation of the radical formed via the oxidative decarboxylation of the potassium 4-hydroxybutanoate **3.73** into formaldehyde and ethylene.

Finally, our exploration revolved around the incorporation of fluorinated and others halogenated groups in the structure of γ-lactams, given the pharmaceutical interest

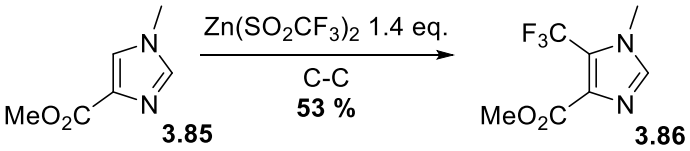
for those moieties. Indeed, the importance of the use of bioisosteric replacements in drug design explains the enthusiasm for fluorinated substituents.[145]
For that reason, fluoroacid acid **3.61**, chloroacetic acid **3.63** and, bromoacetic acid **3.65** were tested, under our conditions, and allowed the formation of halogenated 2-pyrrolidinones **3.62**, **3.64**, and **3.66** in modest but consistent yields. Those humble yields can be attributed to the acidity of those co-acids, whose respective pKa are 2.58, 2.86, and 2.86. The very low yield of 14 % obtained with bromoacetic acid **3.65** is not only correlated to the acidity of this reagent but also to the instability of the carbon-bromine bond in electrolytic conditions. Indeed, an electrooxidation of alkyl halides can happen in organic electrochemistry. The carbon-halogen bond of alkyl halides (R-X) can be oxidized by electrolysis to generate the corresponding alkyl carbocation.[146] The ease of conversion of alkyl halides into carbocations seems to coincide with the reactivity order of these halides: R-I > R-Br >> R-Cl > R-F. Nevertheless, carbon-chlorine and carbon-fluorine bonds are relatively stable under electro-oxidation conditions.
Finally, difluoroacetic acid **3.67** and trifluoroacetic acid **3.69** were tested in the optimized electrocyclization conditions. Acceptable yield of 36 % of the difluorinated 2-pyrrolidinone **3.68** was achieved. Nonetheless, extremely low yield of the trifluorinated 2-pyrrolidinone **3.70** was obtained. Two different hypotheses could justify that result.
On one hand, the strong acidity of the trifluoroacetic acid ($pk_a$ = 0.3) would induce the preferential protonation of the electrocyclization substrate **3.20**. Therefore, at the anode surface, the only carboxylate present and thus oxidizable would be the trifluoroacetic acid. The latter, after oxidative decarboxylation, would dimerize to form hexafluoroethane. To overcome this problem, the literature proposes to neutralize, before reaction, the trifluoroacetic acid with a stoichiometric quantity of base. That process was performed under our conditions but did unfortunately not lead to the formation of our product **3.70**.
On the other hand, a preferential adsorption of the trifluoroacetic acid **3.69**, which could arise from its structure or pKa, could explain the low yields. In this case, a slow addition of the strongest acid, in the electrolysis medium, should give better results, as the weakest acid is present in major concentration during the course of the reaction. Several operating modes found in the literature were applied to our methodology.[147] Finally, the only result of a $CF_3$ functionalization of 2-pyrrolidinone has only led to 2 % of product. As a consequence, the strategy has been changed.
For this reason, 3,3,3-trifluoropropionic acid **3.59** was applied to our methodology. Thanks to its low acidity, this acid allowed the formation of the trifluoro-substituted 2-pyrrolidinone **3.60** in admirable yield of 68 %.

#### *3.4.1.2 Sulfinic acids used as a co-acid*

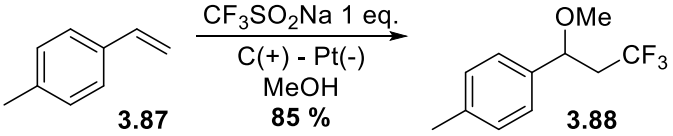
Since the great interest for the $CF_3$-function in medicinal chemistry, an alternative to the use of the trifluoroacetic acid had to be found. For this reason, the use of

[145] Patani, G.A.; LaVoie, E.J. *Chem. Rev.* **1996**, 96, 3147.
[146] (a) Becker, J.Y. *the Chemistry of Functional Groups* John Wiley & Sons, New-York **1983**, p.203; (b) Becker, J.Y.; Zemach, D. *J. Chem. Soc. Perkins Tans. II* **1981**, 336.
[147] (a) Renaud, R.N.; Champagne, P.J. *Can. J. Chem.* **1975**, 53, 529; (b) Renaud, R.N.; Sullivan, D.E. *Can. J. Chem.* **1972**, 50, 3080.

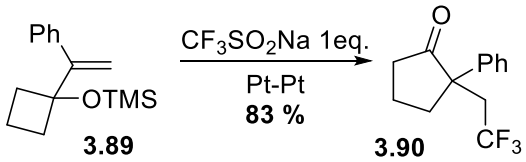
trifluoromethanesulfinate salts was also investigated. Indeed, in several recent studies, the usage of sodium Triflinate **3.91**, the Langlois reagent, and of zinc trifluoromethanesulfinate, the Baran trifluoromethylation reagent, was reported in order to perform trifluoromethylation processes by electrochemistry. Those trifluoromethylation reagents have the advantage to be inexpensive, shelf stable, and easily handled. Hereunder, several applications if the use of sulfinic acids, in organic electrochemistry, are reported. First, Baran and Blackmond developed, in 2014, an electrochemical trifluoromethylation of heteroarenes **3.85** utilizing the Baran trifluoromethylation reagent (see Scheme **90**).[148] Secondly, the Langlois reagent **3.91** was used to develop, in 2018, a methodology for the multicomponent intermolecular oxytrifluoromethylation of alkenes (see Scheme **91**).[149] Finally, in 2019, the Langlois reagent was also used for the synthesis of β-trifluoromethylated ketone derivatives via electrochemically oxidative trifluoromethylation/1,2-carbon migration sequences (see Scheme **92**).[150]




**Scheme 90 trifluoromethylation of heteroarenes**



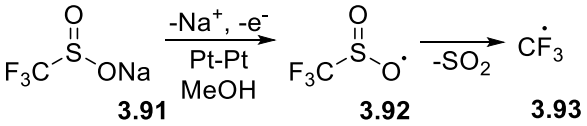

**Scheme 91 oxytrifluoromethylation of alkenes**




**Scheme 92 electrochemical synthesis of β-trifluoromethylated ketone**

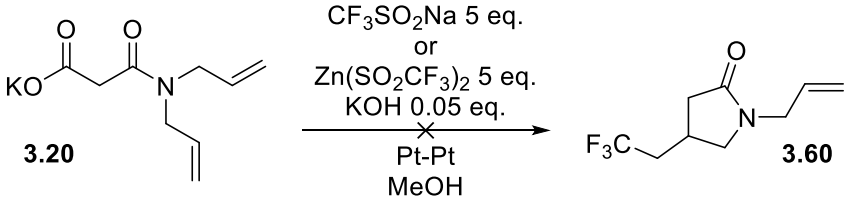
In order to perform a trifluoromethylation of 2-pyrrolidinones, sodium Triflinate and zinc trifluoromethane sulfinate were tested as co-acids, in our methodology (see Scheme **94**). Indeed, the anodic oxidation of trifluoromethanesulfinate salts leads to the generation of $CF_3$-radicals via $SO_2$ release (see Scheme **93**). Those radicals might perform a cross-coupling with the cyclic radical to form the trifluoromethylated 2-pyrrolidnone **3.60**.

[148] O'Brien, A.G.; Maruyama, A.G.; Inokuma, Y.; Fujita, M.; Baran, P.S.; Blackmond, D.G. *Angew. Chem. Int. Ed.* **2014**, 53, 11868.
[149] Zhang, L.; Zhang, G.; Wang, P.; Li, Y.; Lei A. *Org. Lett.* **2018**, 20, 7396.
[150] Jung, H.I.; Kim. Y.; Young Kim, D. *Org. Biomol. Chem.* **2019**, 17, 3319.




**Scheme 93 anodic oxidation of sodium Triflinate 3.91 leading to $CF_3$-radicals formation**

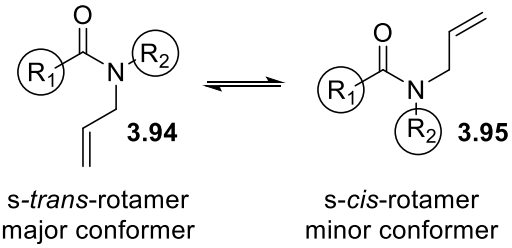
To prove that hypothesis, the electrocyclization substrate **3.20** was electrolyzed in our usual conditions using sulfinic salts as co-acids. Unfortunately, these manipulations did not lead to the formation of the expected product. Instead, a complex mixture of side-products was obtained. Unfortunately, we were not able to isolate and identify those impurities. This result may be due to the strong acidity of the co-acid or to the $CF_3$-radicals weak nucleophilicity.




**Scheme 94 electrolysis using sulfonic acids as co-acid**

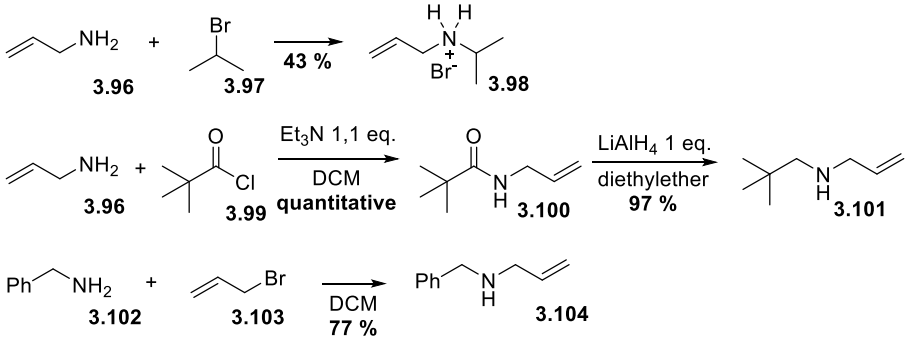
### 3.4.2 Variation of the N-protecting group nature

The electrocyclization substrate **3.20** possesses a protecting group on the nitrogen atom of the amide function. This group protects the amino function from further oxidation under the conditions of the Kolbe reaction. Moreover, this protecting group has to be a hindered function in order to promote the formation of the *trans*-rotamer, in which the allyl function is as close as possible to the carbon radical, during the cyclization step, in order to favor the cyclization (see Scheme **95**). Indeed, the rotation about the C-N bond in an amide function is restricted due to the partial double bond nature of this link. In fact, the C-N bond rotation barrier is approximately 63 – 84 kJ/mol in amides, enough so that the bond rotation is restricted at room temperature. Therefore, two amide conformers can exist: the s-*trans*-rotamer **9.94** and the s-*cis*-rotamer **3.95**. Due to repulsive steric interactions between the side chains in the s-*cis*-form, the s-*trans*-rotamer of a tertiary amide is more stable and thus present in higher concentration.




**Scheme 95 amide rotamers 3.94 and 3.95**

To fulfil the role of protecting group, four functions were chosen: allyl, benzyl and two aliphatic chains (neopentyl and isopropyl). For instance, the allyl[151] and the benzyl[152] protecting groups could be easily deprotected or further functionalized after the oxidative reaction, opening the way to more chemical diversity, which is especially important for drug design. The synthesis of these substrates began with the formation of the secondary allylamines **3.98**, **3.101**, and **3.104**. Firstly, the N-isopropyl allylammonium salt **3.98** was prepared by treatment of the allylamine **3.96** with the 2-bromopropane **3.97**. Subsequently, the N-neopentyl allylamine **3.101** originated from the reduction of the corresponding amide **3.100**, which came from the addition of allylamine **3.96** on the pivaloyl chloride **3.99**. Finally, the N-benzyl allylamine **3.104** was assembled by treatment of the allyl bromide **3.103** with an excess of benzyl amine **3.102** (2.5 eq.).

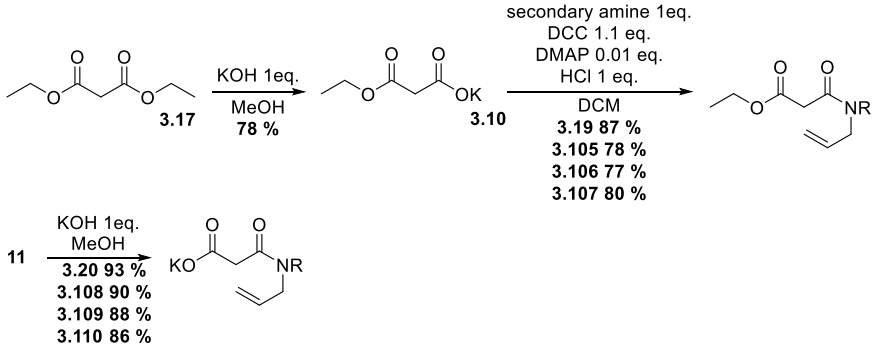



**Scheme 96 secondary allylamines 3.98, 3.101, and 3.104 synthesis**

Once the secondary amines synthetized, the potassium ethyl malonate **3.10**, which was prepared by hydrolysis of diethyl malonate **3.17**, was coupled with the secondary amines **3.98**, **3.101**, and **3.104**, via a Steglich amidation step (see Scheme **97**). The generated amides were finally hydrolyzed to form the electrocyclization substrates **3.20**, **3.108**, **3.109**, and **3.110**.

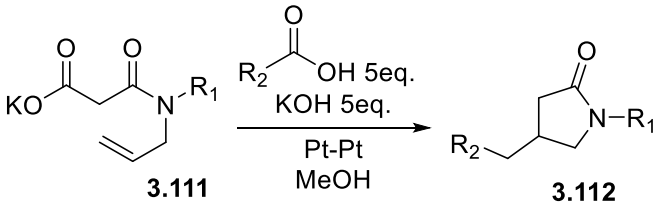
[151] (a) Alcaide, B.; Almendros, P.; Alonso, J.M. *Tetrahedron Lett.* **2003**, 44, 8693. (b) Cadierno, V.; Gimeno, J.; Nebra, N. *Chem. - Eur. J.* **2007**, 13, 6590.

[152] (a) Paik, S.; Lee, J.Y. *Tetrahedron Lett.* **2006**, 47, 1813. (b) Rombouts, F.; Franken, D.; Martinez-Lamenca, C.; Braeken, M.; Zavattaro, C.; Chen, J.; Trabanco, A.A. *Tetrahedron Lett.* **2010**, 51, 4815; (c) Ishii, K.; Sugiyama, S.; Morishita, K.; Chiba, M. *Heterocycles* **2002**, 57, 637.




**Scheme 97 electrocyclization substrates synthesis (3.19 – 3.20 diallylamine, 3.105 – 3.108 N-benzylprop-2-en-1-amine, 3.106 – 3.109 N-isopropylprop-2-en-1-amine, 3.107 – 3.110 N-neopentylprop-2-en-1-amine)**

With the electrocyclization substrates in hand, the electrocyclization step was performed on those substrates under our optimized conditions (see Scheme **98**). Comparable yields were obtained in the presence of the four protecting groups, which enabled to produce several N-substituted 2-pyrrolidinones (see Table **7**). In the presence of a benzyl protecting group, there was the formation of the side-products **3.121**, **3.122**, and **3.123**, which were generated by the cross-coupling of the radical and the radical which came from the oxidative decarboxylation of the adequate co-acid. This phenomenon might be due to the steric hindrance of substrate **3.108**, which limited the amide C−N bond rotation or absorption phenomenon of the benzyl-substituted radicals, on the electrode surface.




**Scheme 98 electrocyclization of substrates bearing different protecting groups**

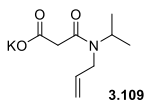
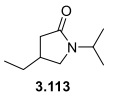
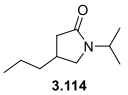
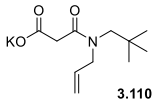
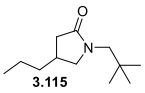
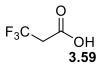
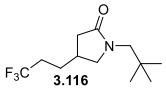
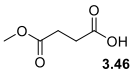
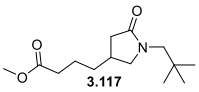
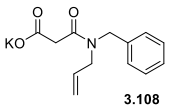
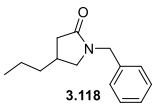
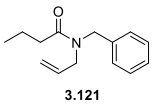
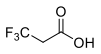
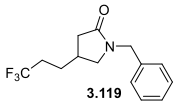
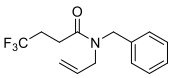
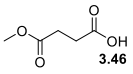
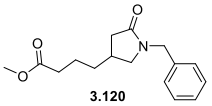
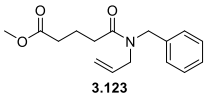
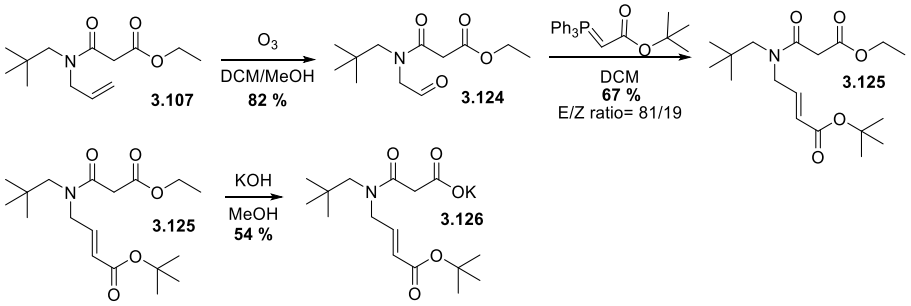
| Entry | Substrates | Co-acids | Products | | Yields |
|---|---|---|---|---|---|
| 1 |  **3.109** |  **3.42** |  **3.113** | | 50 |
| 2 | |  **3.44** |  **3.114** | | 64 |
| 3 |  **3.110** |  **3.44** |  **3.115** | | 65 |
| 4 | |  **3.59** |  **3.116** | | 69 |
| 5 | |  **3.46** |  **3.117** | | 60 |
| 6 |  **3.108** |  **3.44** |  **3.118** |  **3.121** | **3.118** 59<br>**3.121**14 |
| 7 | |  **3.59** |  **3.119** |  **3.122** | **3.119** 43<br>**3.122** 12 |
| 8 | |  **3.46** |  **3.120** |  **3.123** | **3.120** 56<br>**3.123** 11 |

**Table 7 substrates Scope and limitations**

### 3.4.3 Substitution of the double bond part of the electrocyclization substrate

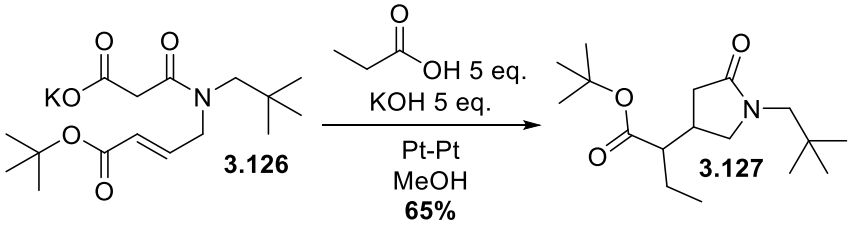
Based on the work of F. Lebreux and F. Buzzo, a substrate of electrocyclization **3.126** containing a substituent on the double bond part was synthetized in order to broaden the field of substrates of our methodology (see Scheme **99**). In this case, the protecting group on the nitrogen atom of the amide function has to be an aliphatic group because the ozonolysis of a substrate containing two allyl functions leads to the formation of a large variety of side products. Moreover, a neopentyl function was chosen to fulfil this role of protecting group as this function has a great steric hindrance. The synthesis of the substrate **3.126** began with the ozonolysis of the molecule **3.107** of which the design is detailed in the Scheme **97**. The aldehyde **3.124** underwent then a Wittig reaction, in which this moiety reacted with a

stabilized phosphonium ylide, which led us to the formation of the olefin **3.125**. Finally, this latter was hydrolyzed into the electrocyclization substrate **3.126**.




**Scheme 99 synthesis of the substrate 3.126**

The electrolysis of the molecule **3.126** was performed under our optimized conditions (see Scheme **100**). This step led to the isolation of the highly substituted 2-pyrrolidinone **3.127** in good yield. This reaction proved that a new position can be substituted on a 2-pyrrolidinone moiety using our methodology.

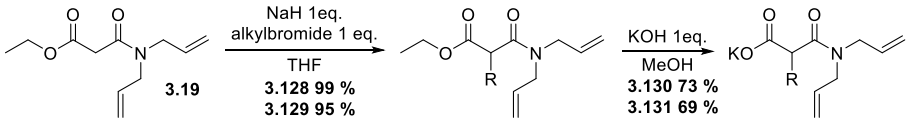



**Scheme 100 Kolbe electrocyclization of the 2-pyrrolidinone 3.127**

## 3.4.4 Substitution of the malonic part of the electrocyclization substrate

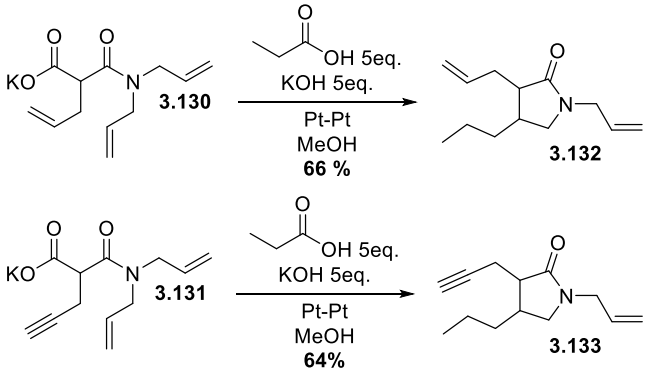
### *3.4.4.1 Monosubstitution of the malonic part of the electrocyclization substrate*

To broaden the Scope of the functionalized pyrrolidinones electrocyclization, the allylic and propargylic substrates **3.130** and **3.131** were formed in a straightforward manner, according to the sequence outlined below. First, the compound **3.19**, of which the synthesis is described in the Scheme **74**, was alkylated at the carbon in alpha of the two carbonyl functions to generate the substituted molecules **3.128** and **3.129**. Subsequently, those molecules were hydrolyzed into the electrocyclization reagents **3.130** and **3.131**.




**Scheme 101 electrocyclization substrates 3.130 and 3.131 synthesis (alkylbromide = 3.128 – 3.130 allyl bromide, 3.129 – 3.131 propargyl bromide)**

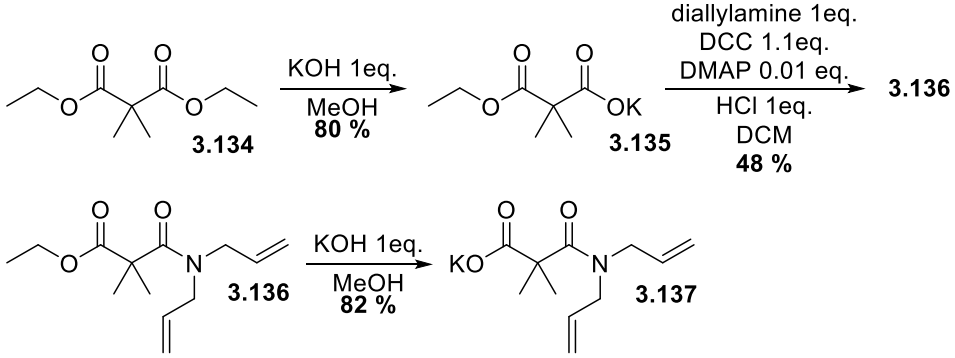
Once the electrocyclization substrates **3.130** and **3.131** in hand, the electrocyclization steps were performed and allowed the formation of the position 5-substituted pyrrolidinones **3.132** and **3.133**, in 66 and 64 % yields, which once again shows the versatility of our methodology (see Scheme **102**).




**Scheme 102 electrosynthesis of the 2-pyrrolidinones 3.132 and 3.133**

*3.4.4.2 Disubstitution of the malonic part of the electrocyclization substrate whit a gem-dimethyl group*

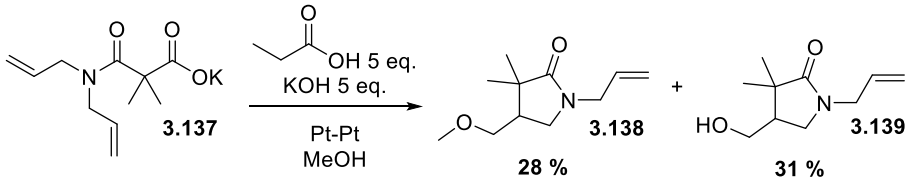
The *gem*-dimethyl group is a structural feature frequently found in plenty of natural products of clinical interest and in at least 51 drugs.[153] Inspired by this function, medicinal chemists have widely explore its utilization in the development of biologically active small molecules. This strategy can be traced back to the 1920s when the *gem*-dimethyl substituted penicilins were accidently isolated by A. Fleming from the fungus *Penicillium notatum*. Given the pharmaceutical potential of this substituent, an electrocyclization reagent containing a *gem*-dimethyl function was synthetized according to the chemical sequence described in the Scheme **103**. In this sequence, the commercially available diethyl dimethylmalonate **3.134** was first converted into the corresponding potassium salt **3.135**. This latter was then coupled with the diallylamine via a Steglich amidation step. The amide formed **3.136** was finally hydrolyzed to lead to the generation of the substrate **3.137**.




**Scheme 103 disubstituted substrate 3.137 synthesis**

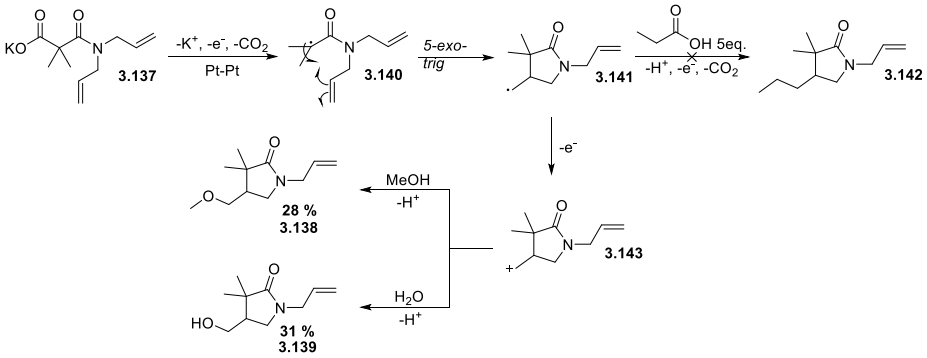
The substrate **3.137** was submitted to our optimized electrocyclization conditions (see Scheme **104**). Surprisingly, the expected product **3.142** was not formed. Instead, the alcohol substituted 2-pyrrolidinone **3.139** and the methoxy substituted 2-pyrrolidinone **3.138** were isolated, in 31 and 28 % yields.

[153] Talele, T.T. *J. Med. Chem.* **2018**, 61, 2166.




**Scheme 104 electrocyclization of the substrate 3.137**

This result can be explained by the fact that, after the cyclization step, the cyclic radical formed **3.141** was not involved in the cross-coupling process leading to the formation of the desired product **3.142**. Instead, this radical **3.141** was oxidized into the corresponding carbocation **3.143**. This latter finally reacted with methanol or water to generate the products **3.138** and **3.139**. Unfortunately, we were not able to find an explanation of that overoxidation phenomenon which should be related to the presence of a *gem*-dimethyl function in the substrate **3.137** structure.

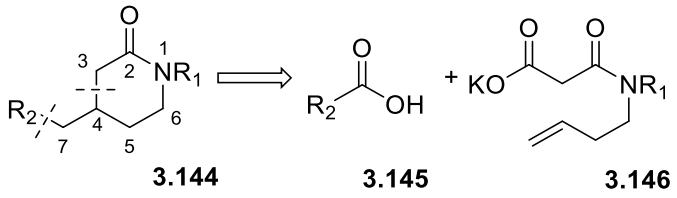



**Scheme 105 hypothetic mechanism**

## 3.4.5 Δ-lactam electrocyclization

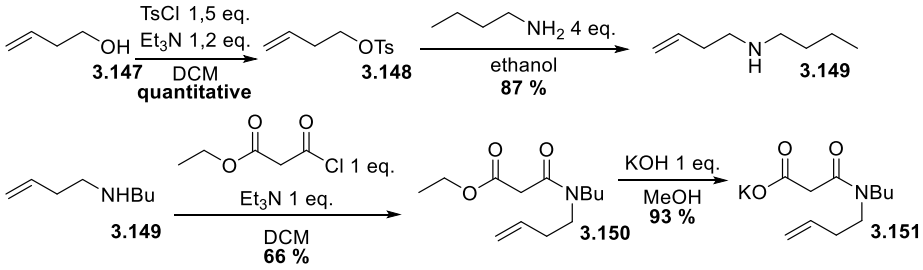
Δ-lactams are six-membered rings containing an amide function. Those molecules are known for their biological activities[154] and are also used as intermediates in the preparation of other chemicals. Therefore, we envisioned an electrochemical cyclization of those cyclic compounds. Moreover, given the strong similarity between the γ-lactams and the δ-lactams, this new methodology could be easily derived from our γ-lactams Kolbe electrocyclization. First, the synthesis of the electrocyclization substrate **3.151** had to be elaborated. A retrosynthetic analysis of the adduct **3.144** shows that it is possible to apply two disconnections to this molecule, those match the two bonds formed during the electrochemical step (see Scheme **106**). Specifically, the first disconnection is placed on the cycle, between the carbons C3 and C4, while the second disconnection is placed between the carbon C7 and the substituent $R_2$. Therefore, the substituted δ-lactam **3.144** may be electrochemically obtained from the co-acid **3.145** and the substrate **3.146**.

[154] (a) De Lucas, G.V. *Bioorganic & Medicinal Chemistry Letters* **1997**, 7, 501; (b) Han, G. *J. Med. Chem.* **2007**, 50, 2735.



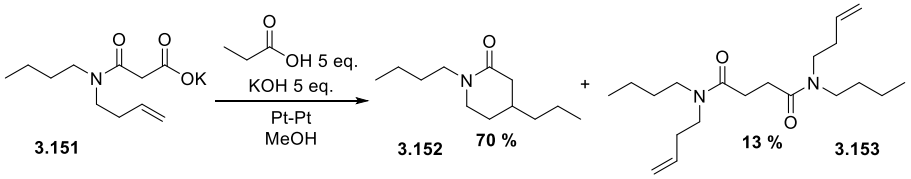

**Scheme 106 retrosynthesis of the substrate 3.146**

With the aim of designing the electrocyclization reagent **3.151**, the but-3-ene-1-ol **3.147** was first converted into the corresponding tosylate **3.148**. This latter then underwent the nucleophilic attack of the butan-1-amine, which led us to the formation of the secondary amine **3.149**. A following step of amidation supplied the amide **3.150**. Finally, this latter was deprotected under basic conditions to form the electrocyclization substrate **3.151** (see Scheme **107**).




**Scheme 107 electrocyclization substrate 3.151 synthesis**

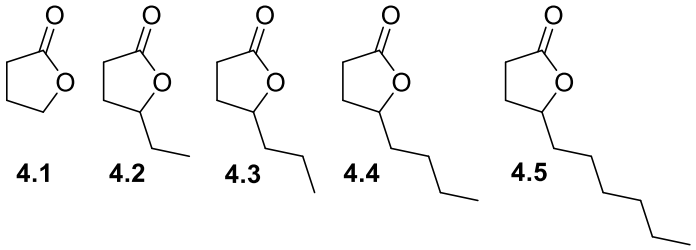
The electrolysis step was performed under our optimized conditions of γ-lactam electrocyclization (see Scheme **108**). The δ-lactam **3.152** was obtained in a good yield of 70 %. However, as the *6-exo*-cyclization is known to proceed at a lower speed, compared to *5-exo*-cyclization, the primary radical can then dimerize and we observed the formation of the side-product dimer **3.153**, along with the desired piperidinone **3.152**. In conclusion, the application of our methodology to a substrate bearing a homoallyl function enabled to broaden the field of substrates of our reaction to the formation of 2-piperidinones. This state-of-the-art electrosynthesis of functionalized 2-piperidinones puts emphasis on the fantastic applicability of our cyclization methodology.




**Scheme 108 electrocyclization of the δ-lactam 3.152**

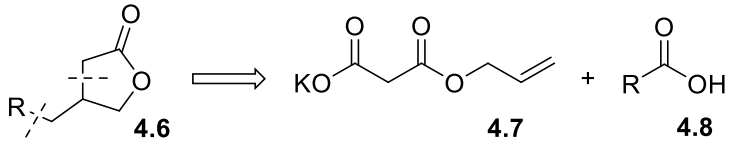
# 4 Towards an electrosynthesis of lactones

Lactones are cyclic esters found in many different natural products and used as intermediates in the production of other chemicals. Those compounds are widely employed in the food industry and the cosmetic industry. Indeed, lactones are used as fragrances and as aroma compounds in food and beverages. For instance, butter contains 26 distinct lactones and dozens of lactones are found in peach, apricot, papaya, and strawberry.[155] They are also present in cheese[156], tea, coffee, and wine.[157] For example, the γ-hexalactone **4.2** has an herbaceous aroma; the γ-heptalactone **4.3** smells like caramel and hazelnut; the γ-octalactone **4.4** has a coconut flavor; and the γ-decalactone **4.5** is an aroma with an intense peach flavor. Beside their aromatic properties, those moieties have also medicinal applications. Due to its structure very similar to the neurotransmitter, γ-hydroxybutiric acid, the γ-butyrolactone **4.1** is used as a prodrug and is rapidly converted in the neurotransmitter *in vivo*.[158]




**Scheme 109 γ-butyrolactone 4.1, γ-hexalactone 4.2, γ-heptalactone 4.3, γ-octalactone 4.4, γ-decalactone 4.5**

Regarding those applications and the similarities between the γ-lactams structure and the γ-lactones structure, a strategy to design the electrosynthesis of γ-lactones was investigated. A retrosynthetic analysis of the γ-lactone **4.6** shows that this molecule could be formed electrochemically from the allyl potassium malonate **4.7** and the co-acid **4.8** (see Scheme **110**).



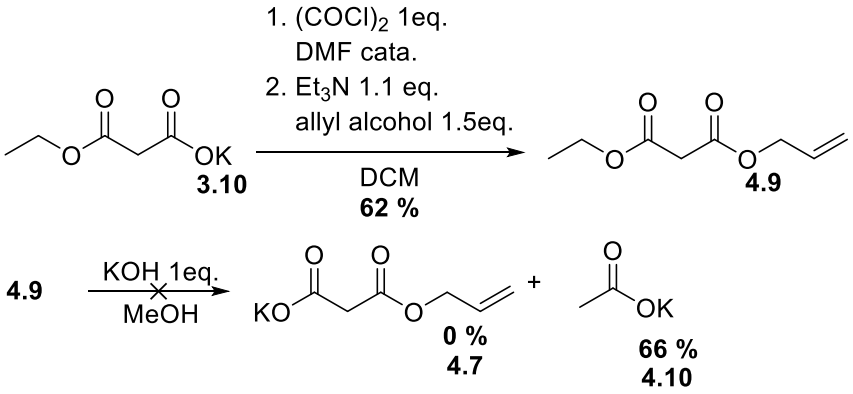

**Scheme 110 retrosynthetic analysis of the substrate 4.7 formation**

## 4.1 Synthesis of the substrate **4.12** of the lactones electrocyclization

In order to prepare the electrocyclization substrate **4.7**, commercially available ethyl potassium malonate **3.10** was converted into the corresponding acyl chloride and then treated with allyl alcohol to lead to the generation of the allyl ethyl malonate

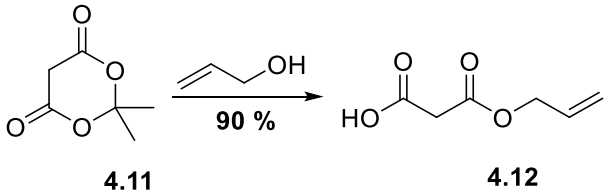
[155] Dufossé, L. *Sc. Aliments* **1994**, 14, 17.
[156] Fross, D.A. *Journal of Dairy Science* **1969**, 52, 832.
[157] Maga, J.A. *Crit. Rev. Food Sci. Nutrit.* **1976**, 8, 1.
[158] Lettieri, J.; Fung. H.L. *Research communications in Chemical Pathology and Pharmacology* **1978**, 22, 107.

**4.9**. Subsequently, the allyl ethyl malonate **4.9** was treated with potassium hydroxide to generate the potassic salt **4.7**. Unfortunately, this reaction did not lead to the formation of the desired product but to the generation of potassium acetate **4.10** (see Scheme **111**).




**Scheme 111 attempt to synthetize of the substrate 4.7**

In the literature, the carboxylic acid **4.12** is described as a stable compound and its synthesis counts only one step.[159] Indeed, this carboxylic acid **4.12** can be generated, in a good 90 %yield, by treatment of Meldrum's acid **4.11**, 2,2-dimethyl-1,3-dioxane-4,6-dione, with allyl alcohol, at reflux.



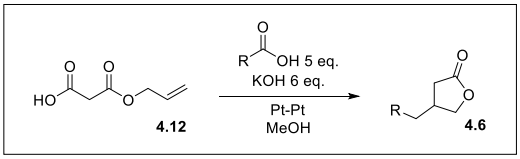

**Scheme 112 substrate 4.12 synthesis**

## 4.2 Electrocyclization of the substrate **4.12**

With the electrocyclization substrate **4.12** in hand, several electrolyzes were accomplished with different co-acids, in our optimized conditions of electrocyclization (see Table **8**). Unfortunately, those reactions led to the formation of only traces of the functionalized γ-lactone products **4.13**, **4.14**, and **4.15**. Furthermore, three various side-products **4.16**, **4.17**, and **4.18** were isolated.

[159] Navarro, I.; Basset, J.F.; Hebbe, S.; Major, S.M.; Werner, T.; Howsham, C. *J. Am. Chem. Soc.* **2008**, 130, 10293.

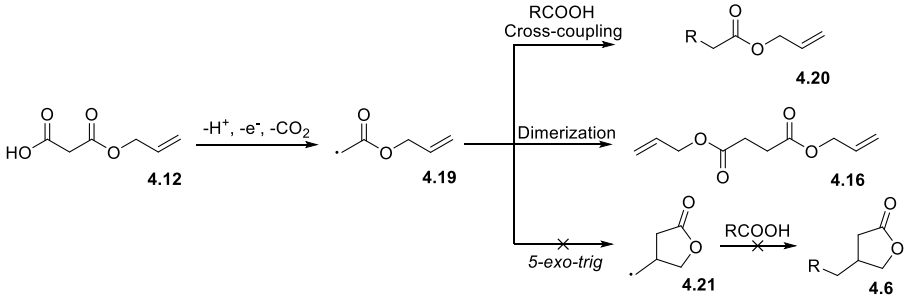
**Table 8 electrolysis of the substrate 4.12 in presence of various co-acids**




| co-acid | product | side-products | Yield |
|---|---|---|---|
| 3.44 | 4.13 | 4.16 | **4.13** traces<br>**4.16** 15 % |
| 3.57 | 4.14 | 4.17<br>4.16 | **4.14** 4 %<br>**4.17** 47 %<br>**4.16** 11 % |
| 3.48 | 4.15 | 4.18<br>4.16 | **4.15** traces<br>**4.18** 36 %<br>**4.16** 12 % |

## 4.3 Analysis of the results of the substrate **4.12** electrolyzes

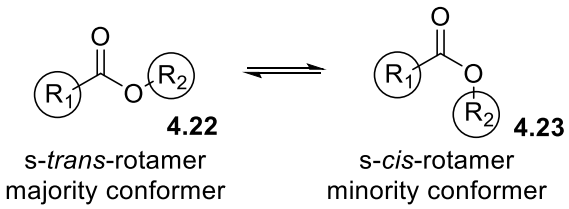
The analysis of the structures of the side-products shows that the compound **4.16** originated from the dimerization of the radical **4.19** derived from the oxidative decarboxylation of the substrate **4.12**. Moreover, the molecules **4.17** and **4.18** came from the cross-coupling of the radical **4.19** with the radicals generated by the oxidative decarboxylation of the co-acids **3.57** and **3.48**. This result can be explained by the fact that the *5-exo-trig* cyclization of the radical **4.19** is slower than the cross-coupling and dimerization processes. Given that those unwanted processes are irreversible, the expected products are unfortunately not formed (see Scheme **113**).




**Scheme 113 analysis of the products formed during the electrolysis of the substrate 4.12**

The geometry of the radical **4.19** can explain the slowness of the *5-exo-tirg* cyclization. Indeed, the esters are present in two major conformer forms: the s-*trans*-rotamer and the s-*cis*-rotamer (see Scheme **114**). Due to the steric hindrance, dipole-dipole interaction, hydrogen bond, and the hyperconjugation of the oxygen lone pair

in the carbonyl antibonding orbital σ*, the s-*trans*-rotamer is the predominant conformer of esters. For instance, in the case of the methyl acetate, the s-*trans*- and s-*cis*-rotamers energy difference was reported to be 8.5 kcal/mol.[160] This means that, in the structure of the radical **4.19**, the double bond is too far away from the carbon radical to allow a correct cyclization. For those reasons, the research on the electrocyclization of lactones was discarded. In future research, it could be interesting to increase the reaction temperature in order to make the rotation around the amide C-O bond faster, and thus to try to facilitate the cyclization.




**Scheme 114 ester rotamers 4.22 and 4.23**

[160] Wiberg, K.B.; Laidig, K.E. *J. Am. Chem. Soc.* **1987**, 109, 5935.

# 5 Diastereoselective electrosynthesis of 2-pyrrolidinones

## 5.1 Strategy to develop a diastereoselective electrocyclization

The two enantiomers of a chemical drug can have different biological activities. In "Through the looking-glass", Lewis Carrol makes a specific reference to this phenomenon, even if little was known about chemical chirality in his time. In this book, Alice asks a feline friend: "How would you like to live in Looking-Glass House, Kitty? I wonder if they would give you milk in there? Perhaps Looking-Glass milk isn't good to drink?".[161] Alice's speculation regarding the potability of Looking-Glass milk makes reference to the chemical chirality. Moreover, after her return from the mirror world, her body was mirror-flipped down to the molecular level; therefore she was unable to digest food anymore.

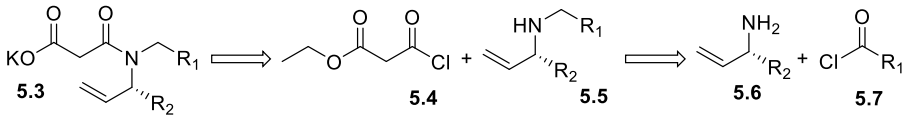
Due to the importance of being able to control the chirality while developing bioactive molecules, we decided to investigate the possibility to develop a diastereoselective electrocyclization of 2-pyrrolidinones. In organic electrochemistry, the stereocontrol of reactions is a hot topic and a promising research field. The stereoselectivity can be achieved by several strategies, such as: the use if a chiral catalyst, a chiral solvent, a chiral supporting electrolyte or chiral electrodes. Inspired by the work of F. Lebreux, our strategy relied on the judicious insertion of an enantiopure function inside the structure of our cyclization substrate, in order to induce a facial selectivity, during the cyclization step. Indeed, F. Lebreux developed a diastereoselective cyclization of tetrahydrofuran (see section 1.1.10). Nonetheless, this methodology needs to be deeper investigated as the diastereoselective ratio is promising (51:7:36:6) but the yield remains really low (9 %) (see Scheme **36**). In our case, two approaches were investigated (see Scheme **115**). In the first case, an enantiopure chiral center was introduced in α position of the allyl group, which is attacked during the cyclization step. For this purpose, a chiral allyl amine needed to be synthetized. In the second case, a chiral auxiliary was incorporated in the substrate structure **5.2**. To this end, a chiral methyl benzyl was used as a protecting group of the nitrogen atom. In the following paragraphs, those plans of action are detailed.


**Scheme 115 Substrates of diastereoselective electrocyclization**

## 5.2 Substrate **5.18** containing a chiral allyl amine

Our first strategy was to insert a chiral center in α position of the allyl group in the structure of the electrocyclization substrate **5.18**. A retrosynthetic analysis of the molecule **5.3** shows that this compound could be easily assembled from the acyl chloride **5.4** and the enantioenriched secondary amine **5.5**. This latter can be formed using the chiral allylamine **5.6** and the acyl chloride **5.7**.

[161] (a) Carroll Lewis **1872** *Through the Looking-Glass and What Alice found there* Philadelphia, Henry Altemus Company; (b) O'Leary, J.S.B. *Victorian Network* **2010**, 2, 70.

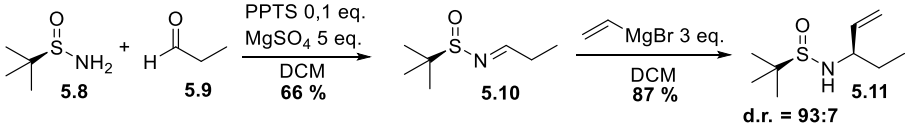


**Scheme 116 retrosynthesis of the substrate 5.3**

The Ellman chiral auxiliary, the *tert*-butanesulfinamide **5.8**, was chosen for the purpose of preparing the chiral allylamine **5.14**. Given that more than 80 % of all drugs and drug candidates contain amine functionality and that many of these amine-containing molecules are also chiral and can be challenging to prepare, Ellman has developed an asymmetric synthesis of α-branched amines from aldehydes and ketones.[162] The Ellman *tert*-butanesulfinamide **5.8** is a versatile and extensively used chiral reagent.

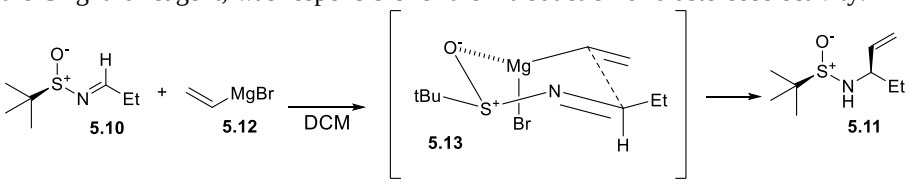
### 5.2.1 Synthesis of the substrate **5.18** of the diastereoselective electrocyclization of 2-pyrrolidinones

In order to design the reagent **5.18** for the diastereoselective electrocyclization of 2-pyrrolidinones, the enantiopure α-branched allylamine **5.14** was first synthetized according to the following procedure. In the first place, the direct condensation of the *(R)-tert*-butanesulfinamide **5.8** with the propionaldehyde **5.9** took place leading to the formation of the *tert*-butanesulfinyl imine **5.10**. This latter was then converted with good yields and excellent diastereocontrol into the sulfonamide **5.11** via the nucleophilic addition of the vinyl Grignard reagent **5.12**. The diastereomeric ratio of 93:7 was determined via $^{1}$H-NMR analysis (see Scheme **117**).



**Scheme 117 two first steps of the synthesis of the substrate 5.18**

During the addition step of the vinyl Grignard reagent **5.12** on the *(R)-tert*-butanesulfinyl imine **5.10**, a Zimmermann Traxler transition state, in which the oxygen atom of the *(R)-tert*-butanesulfinyl imine **5.10** is coordinated to the metal of the Grignard reagent, was responsible for the introduction of diastereoselectivity.

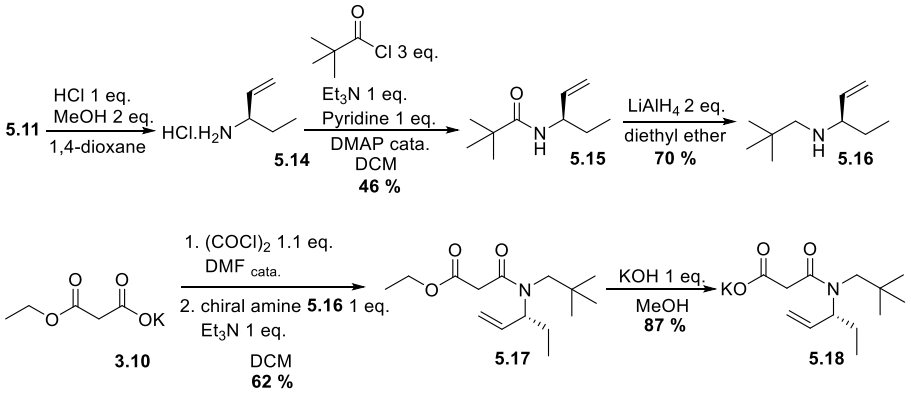


**Scheme 118 Zimmermann Traxler transition state 5.13**

The chiral α-branched allylamine **5.14** was then deprotected in acidic conditions. Subsequently, the amide **5.15** was formed by nucleophilic addition of the amine **5.14** on the commercially available acyl chloride. The amide **5.15** was consecutively reduced into the chiral secondary amine **5.16** with two equivalents of the reducing

[162] (a) Liu, G.; Cogan, D.A.; Owens, T.D.; Tang, T.P.; Ellman, J.A. *J. Org. Chem.* **1999**, 64, 1278; (b) Brog, G.; Cogan, D.A.; Ellman, J.A. *Tetrahedron Letters* **1999**, 40, 6709; (c) Tang, T.P.; Ellman, J.A. *J. Org. Chem.* **1999**, 64, 12.

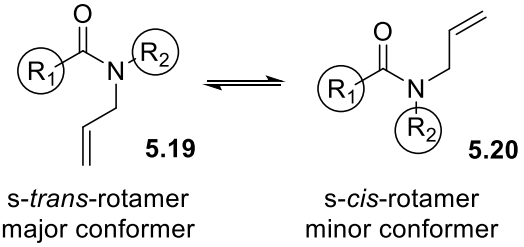
agent $LiAlH_4$. Afterwards, the ethyl potassium malonate **3.10** was converted into the corresponding acyl chloride, which was then attacked by the chiral amine **5.16** to generate the amide **5.17**. Finally, the ester **5.17** was deprotected in basic conditions to form the electrocyclization substrate **5.18**.




**Scheme 119 synthesis of the substrate 5.18**

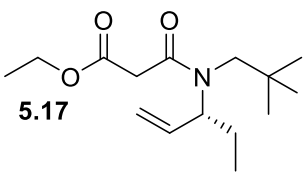
## 5.2.2 Identification of three rotamers using variable-temperature $^1$H-NMR

Usually, the $^1$H-NMR signals of our amide compounds are doubled. This phenomenon is due to the presence of two predominant amide conformers: the s-*trans*-rotamer and the s-*cis*-rotamer (see Scheme **120**). Indeed, the partial double bond nature of the C-N amide bond, which is due to the resonance of this functional group, is responsible for an increased rotation barrier, and thus a restricted rotation around that bond. This leads to the presence of two rotation isomers, which are visible on a $^1$H-NMR spectrum.

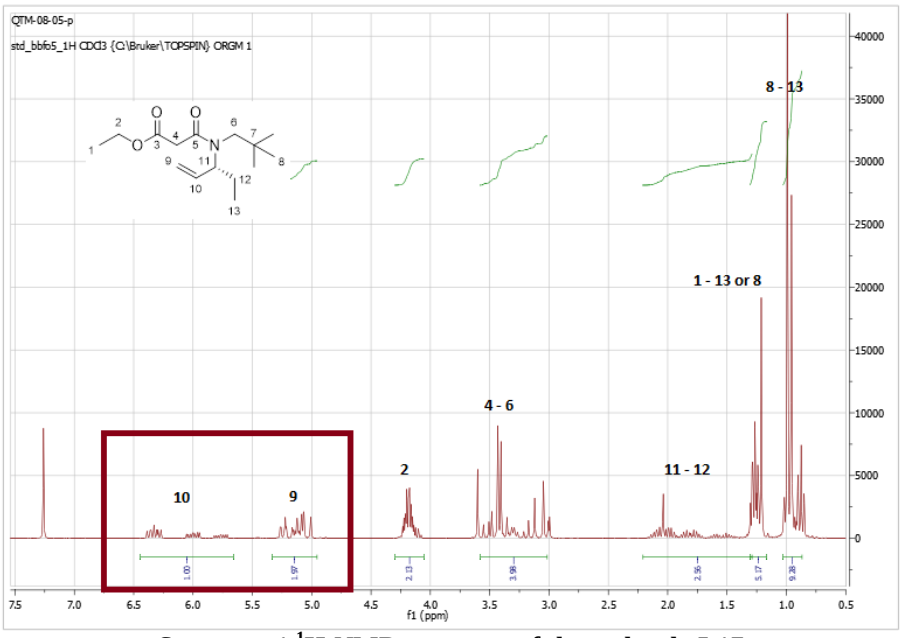



**Scheme 120 amide cis- and trans-rotamers**

Nevertheless, the signals of the molecule **5.17**, which was synthetized during the diastereoselective electrocyclization study, were not doubled but tripled.




**Scheme 121 molecule 5.17**




**Spectrum 1 $^{1}$H-NMR spectrum of the molecule 5.17**

Two hypotheses allow explaining that phenomenon. The first hypothesis states that the presence of new signals can be related to the existence of impurities inside the sample, even if this sample was beforehand purified by silica gel chromatography.

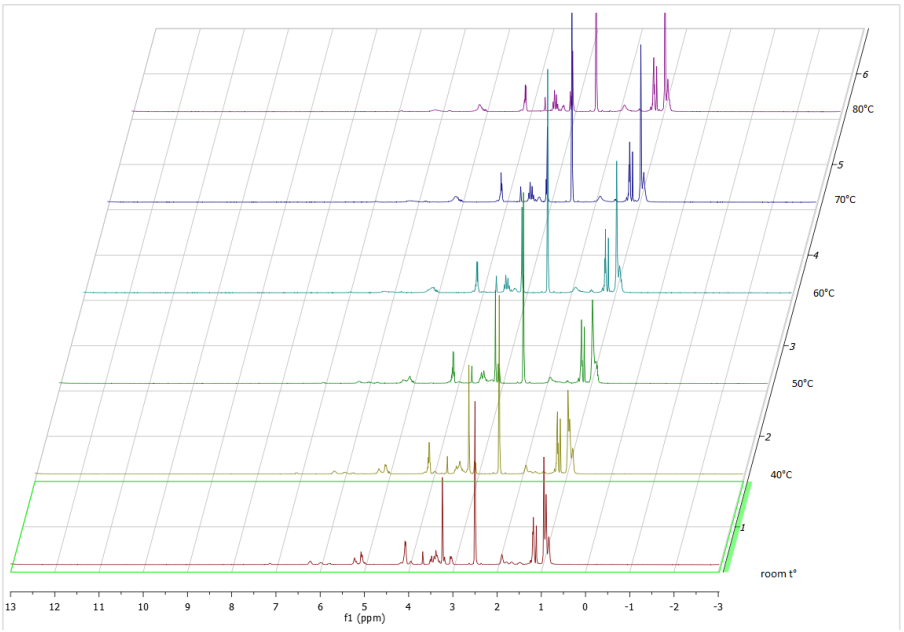
The second hypothesis states that the presence of three rotamers can explain the formation of tripled signals on the $^{1}$H-NMR spectrum. Actually, the complex structure of the amide **5.17** could even more restrict the rotation around the C-N amide bond. In the literature, several examples highlight the formation of three majority rotamers of amides compounds with a complicated structure.[163] In such cases, the complex structure around the amide bond increases the number of conformational states by decreasing the free energy difference between the *cis*- and *trans*-amide rotamers. At the same time, this hindrance around the amide C-N bond limits the number of low energy conformers by constraining adjacent torsion angles.

It is important to refute the first hypothesis because the presence of impurities in the sample can lead to the formation of a large number of side-products, under electrolysis conditions. In order to prove that the presence of tripled signals on the $^{1}$H-NMR spectrum is due to the presence of three rotamers, variable-temperature NMR was performed. This technique allows to distinguish equilibrating species, such as rotamers, from non-equilibrating species, such as impurities. Actually, nuclear magnetic resonance spectroscopy is one of the most commonly used tools for studying dynamic processes such as conformational changes.[164] Examples of conformational studies using variable-temperature NMR are the boat-chair interconversion in cyclohexanes and the *cis-tans* isomerization of amides. Indeed, when rotamers have an important rotation barrier in solution and that the sample is

[163] Deng, S.; Taunton, J. *J. Am. Chem. Soc.* **2002**, 124, 916.
[164] Hu, D.X.; Grice, P.; Ley, S.V. *J. Org. Chem.* **2012**, 77, 5189.

at room temperature, a division of the NMR peaks is observed. In contrast, when the temperature rises, the interconversion between the rotamers is accelerated and a coalescence phenomenon is noticed. The coalescence is the rapprochement between the NMR signals and then the addition of the NMR signals of the rotamers, which takes place at a certain temperature, known as coalescence temperature.

The variable-temperature NMR study was conducted by means of a 500 MHz NMR Bruker device and deuterated DMSO was used as a solvent as its boiling point is 189°C. Six spectra were measured: one at ambient temperature and five others were recorded from 40°C to 80°C in 10°C steps. The rapprochement between the NMR signals was properly observed (see Table **9**). Nevertheless, for technical reasons, the coalescence temperature was not reached because our spectrometer did not allow to work at a temperature higher than 80°C. In conclusion, this study highlighted the presence of three rotamers in solution. Actually, at ambient temperature, $^{1}$H-NMR spectrum of the compound **5.17** revealed tripling of signals, this nonequivalence results from the protons being in magnetically nonequivalent environments, which is due to the presence of three rotamers.




**Spectrum 2 variable-temperature NMR spectra of the compound 5.17**

In the Table **9**, a zoom on the $^{1}$H-NMR signals of the olefin protons was made in order to facilitate the visualization of the rapprochement between the NRM signals. Moreover, the Spectrum **3** shows the superposition of the variable-temperature NMR spectra of the molecule **5.17** in order to further facilitate the observation of the pics rapprochement.

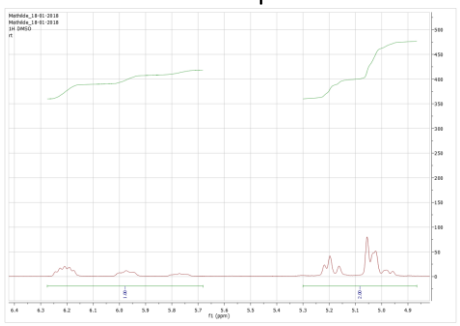
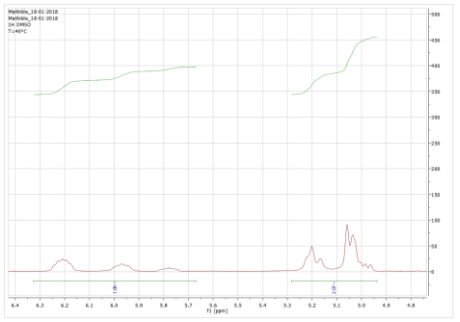
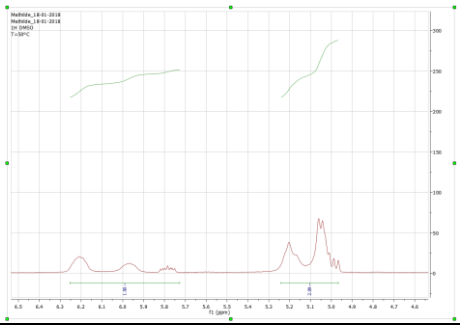
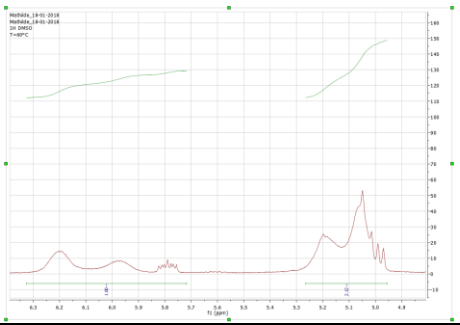
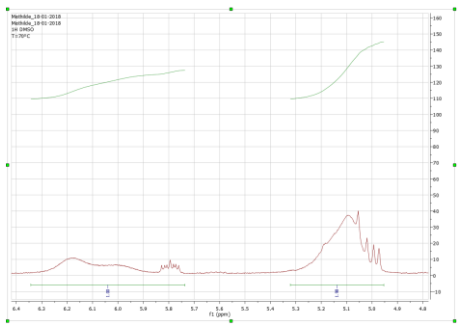
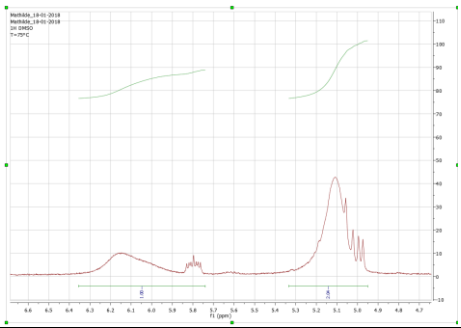
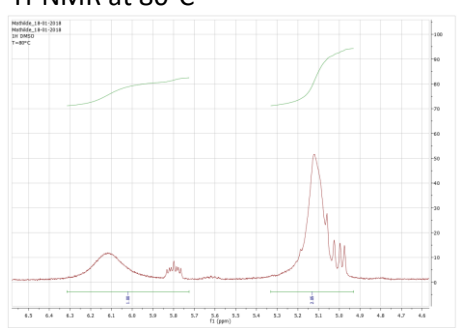
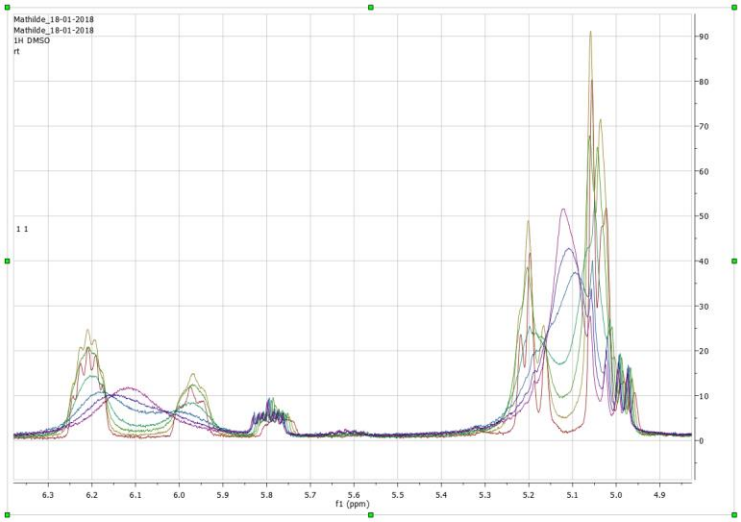
| | |
|---|---|
| $^{1}$H-NMR at room temperature | $^{1}$H-NMR at 40°C |
|  |  |
| $^{1}$H-NMR at 50°C | $^{1}$H-NMR at 60°C |
|  |  |
| $^{1}$H-NMR at 70°C | $^{1}$H-NMR at 75°C |
|  |  |
| $^{1}$H-NMR at 80°C | |
|  | |

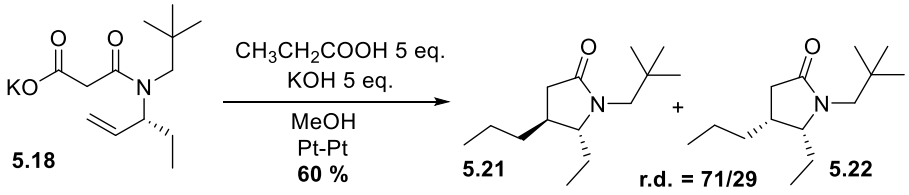
**Table 9 zooms of the variable-temperature NMR spectra of the compound 5.17**




**Spectrum 3 superposition of the variable-temperature NMR spectra of the compound 5.17**

### 5.2.3 Diastereoselective electrocyclization of the 2-pyrrolidinones **5.21** and **5.22**

Once the electrocyclization substrate **5.18** was synthetized, the electrolysis of this compound was performed under our optimized conditions of reaction (see Scheme **122**). Eventually, a chiral HPLC analysis of our sample, which was beforehand purified via silica gel chromatography, exhibited an interesting diastereoselectivity. Indeed, an encouraging diastereoselective ratio of 71/29 and a good yield of 60 % were obtained. Given this promising result, a second strategy was investigated in the following paragraphs in order to develop a diastereoselective cyclization of functionalized 2-pyrrolidinones. Nevertheless, the attribution of the *cis*- and *trans*-diastereoisomers was not done. In order to attribute the *cis*- and *trans*-diastereoisomers, the commercial analogues of the *cis*- and *trans*-diastereoisomers could be used via chiral HPLC to determine the retention time of the two diastereoisomers and thus their proportionality. Finally, another strategy to do this attribution would be to crystalize the two diastereoisomers and then to determine the molecular structure of the crystal via X-ray crystallography.




**Scheme 122 diastereoselective electrocyclization of the 2-pyrrolidinones 5.21 and 5.22**

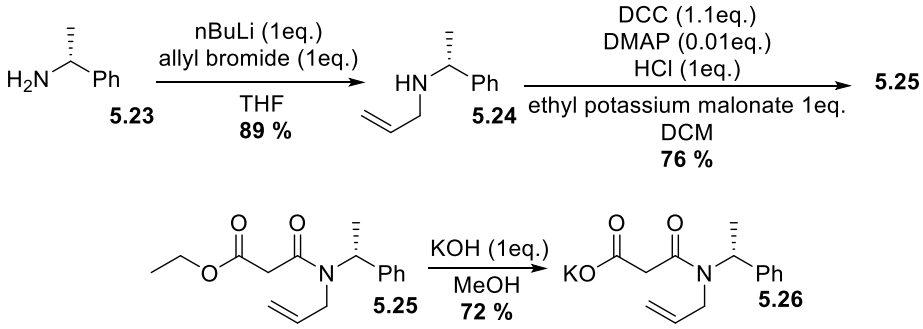
## 5.3 Substrate **5.26** containing a chiral benzyl as chiral auxiliary

Since we obtained promising results with our first strategy, the investigation of the diastereoselective electrocyclization of functionalized 2-pyrrolidinones was

extended. Our second strategy consisted in introducing chirality in the structure of the electrocyclization substrate by protecting the nitrogen atom of the amide function with a chiral benzyl function used as a chiral auxiliary. In this case, the main advantage of this method compared to the previous strategy is that the chiral auxiliary can be easily removed after the electrochemical process by catalytic hydrogenation[165], catalytic transfer hydrogenation[166], and other reactions[167]. Finally, the synthesis of the substrate **5.26** offers the advantage to be much shorter and simpler than the synthesis of the previous reagent **5.18** derived from the Ellman chiral auxiliary.

### 5.3.1 Enantiopure electrocyclization substrate **5.26** synthesis

In order to test this approach, the enantiopure substrate of electrocyclization **5.26** was synthetized (see Scheme **123**). The inexpensive and commercially available *(R)*-(+)-α-methylbenzylamine **5.23** was chosen as chiral inducer. First, this molecule **5.23** was deprotonated with *n*-butyllithium and the anion formed then attacked allyl bromide to generate the enantiopure secondary amine **5.24**. Furthermore, Steglich amidation was performed between the amine **5.24** and ethyl potassium malonate which led us to the generation of the amide **5.25**. Finally, the amide ester was treated with potassium hydroxide to form the enantiopure electrocyclization substrate **5.26** in only three steps and good yields.




**Scheme 123 substrate 5.26 synthesis**

### **5.3.2** Electrocyclization of the enantiopure substrate **5.26**

With the enantiopure electrocyclization substrate **5.26** in hand, the electrolysis of this species was performed using the previously optimized electrocyclization conditions (see Scheme **124**). Thereafter, the product was analyzed by HPLC-MS.

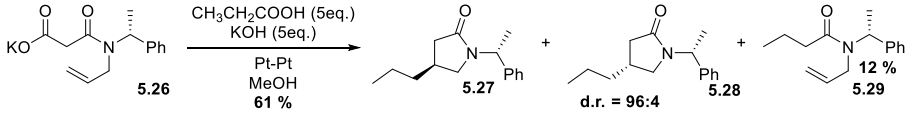
---

[165] (a) Stanchev, G.; Milenkov, B.; Dimitrov, V. *Heterocycles* **1986**, 24, 1825; (b) Vazquez, E.; Galindo, A.; Gnecco, D.; Bernes, S. *Tetrahedron: Asymmetry* **2001**, 12, 2099; (c) Tararov, V.I.; Kadyrov, R.; Kadyrova, Z.; Dubrovina, N.; Borner, A. *Tetrahedron: Asymmetry* **2002**, 13, 25; (d) Couture, A.; Deniau, E.; Grandclaudon, P.; Lebrun, S. *Tetrahedron: Asymmetry* **2003**, 14, 1309.

[166] (a) Daga, M.C.; Taddei, M.; Varchi, G. *Tetrahedron Lett.* **2001**, 42, 5191; (b) Volk, F.J.; Wagner, M.; Frahm, A.W. *Tetrahedron: Asymmetry* **2003**, 14, 497; (c) Meyer, U.; Breitling, E.; Bisel, P.; Farhm, A.W. *Tetrahedron: Assymetry* **2004**, 15, 2029.

[167] (a) Arvanitis, E.; Motevalli, M.; Wyatt, P.B. *Tetrehedron Lett.* **1996**, 37, 4277; (b) Baussanne, I.; Travers, C.; Royer, J. *Tetrahedron: Asymmetry* **1998**, 9, 797; Paik, S.; Lee. *Tetrahedron Lett.* **2006**, 47, 1813.

Those analyses have shown an excellent diastereoselective ratio for this electrochemical transformation. As a result, the use of *(R)*-(+)-α-methylbenzylamine as chiral inductor has led to the formation of the enantioenriched pyrrolidinones **5.27** and **5.28** with an excellent diastereoselective ratio of 96:4. However, an impurity **5.29**, which was generated by the cross-coupling of the radical and the radical which came from the oxidative decarboxylation of the co-acid, was formed in 12 % yield. This phenomenon may be due to the steric hindrance of substrate **5.26**, which limits the amide C−N bond rotation or to absorption phenomenon of the benzyl-substituted radicals on the electrode surface. In conclusion, an attractive diastereoselective electrocyclization process was developed.



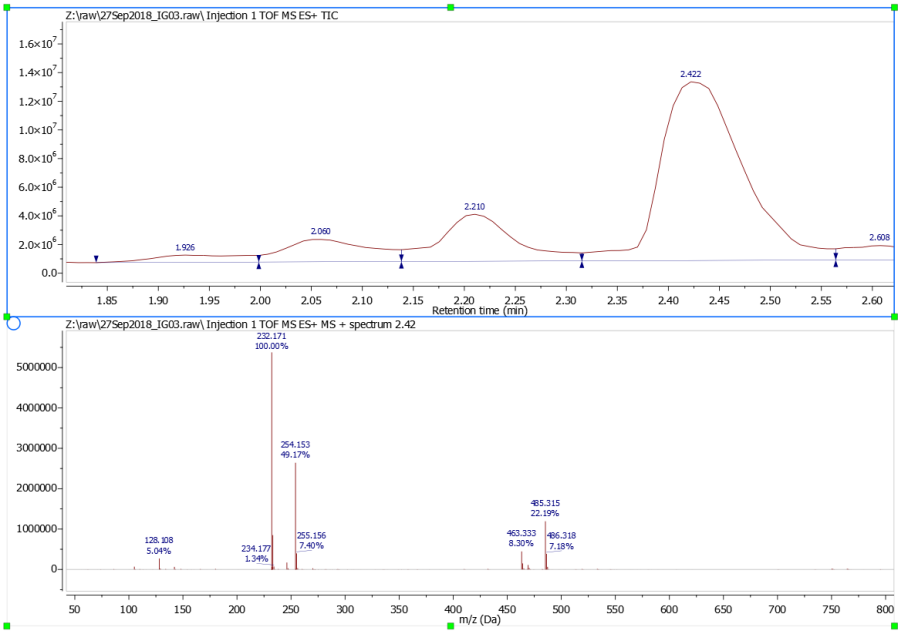

**Scheme 124 diastereoselective electrocyclization of the 2-pyrrolidinones 5.27 and 5.28**

In the future, it could be interesting to perform some computational studies in order to have a better understanding on the transition state conformation, which leads to this excellent diastereoselectivity.

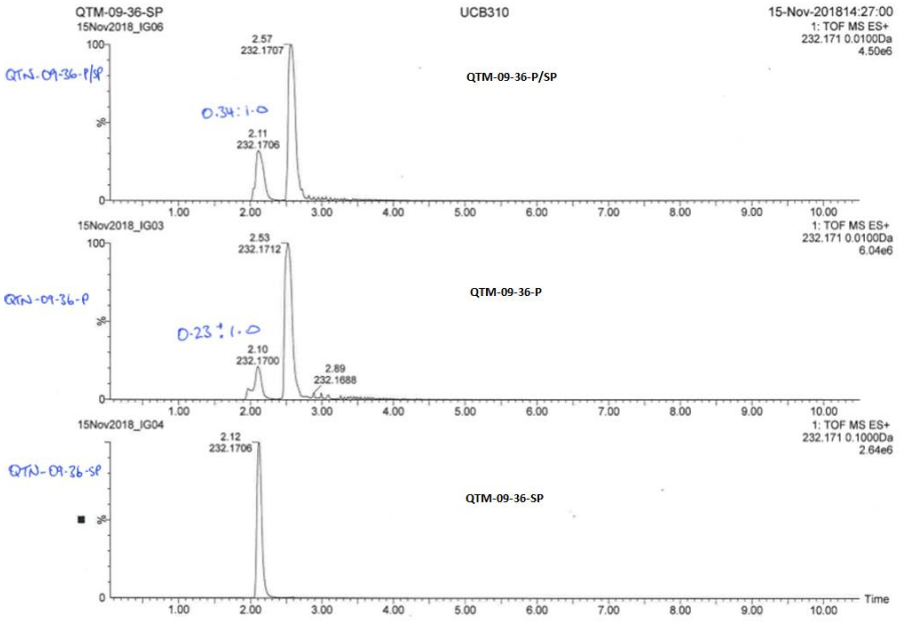
### 5.3.3 HPLC-MS analyses of the diastereoisomers of the pyrrolidinone **5.27** and **5.28**

HPLC-MS analyses were performed in order to determine the diastereoisomeric ratio of our electrocyclization reaction. Unfortunately, the impurity **5.29** had the same mass as the diastereoisomers of the 2-pyrrolidinone **5.27** and **5.28**, and a structure very similar to the structure of those diastereoisomers. Therefore, after silica gel chromatography, a small quantity of the impurity remained in the product sample. Moreover, only one HPLC-MS analysis was not enough to determine the diastereoselective ratio of this reaction. Actually, on the HPLC-MS spectrum of the product sample, three peaks corresponding to a molecule with a mass of 232.171 g/mol were observed. These peaks corresponded to the two diastereoisomers of the pyrrolidinone **5.27** and **5.28** and to the impurity **5.29**. In order to Scheme out which peak corresponded to which molecule, three HPLC-MS analyzes were accomplished. QTM-09-36-sp is the HPLC-MS analysis of the impurity **5.29**, which was beforehand isolated via silica gel chromatography. QTM-09-36-p is the analysis of the pyrrolidinones **5.27** and **5.28** sample. QTM-09-36-P/SP is the HPLC-MS analysis of the contaminated pyrrolidinones **5.27** and **5.28** sample with the impurity **5.29**. This latest analysis allowed us to determine which peaks corresponded to the diastereoisomers of the pyrrolidinone **5.27** and **5.28**, and to Scheme out the diastereoselective ratio of the reaction (92:8).

Even if we were able to determine the diastereomeric ratio of the reaction, the attribution of the absolute configuration of the new asymmetric carbon was not determined. Indeed, we were not able to obtain mono-crystals of our product which explains why we were not able to resolve the absolute configuration of the major product via X-ray crystallography. Finally, we could not propose a stereoinduction model for this diastereoselective radical cyclization because the absolute configuration of the product was not determined.




**Spectrum 4 HPLC-MS of the products 5.27 and 5.28 sample**

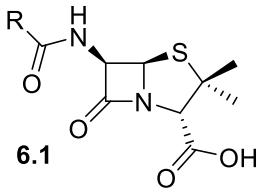



**Spectrum 5 HPLC-MS: QTM-09-36-P/SP, QTM-09-36-P, QTM-09-36-SP**

# 6 Electropolycyclization of 2-pyrrolidinones

## 6.1 Fused polycyclic lactams

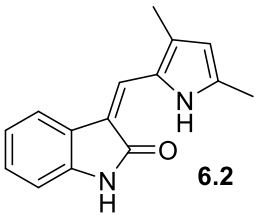
Fused polycyclic compounds are molecules that contain two rings sharing two adjacent atoms. Fused polycyclic lactams are found in many natural compounds, and display interesting biological activities, as illustrated by the examples hereunder. The first example is related to the most well-known class of fused polycyclic lactams: the penicillins. The penicillins form a family of antibiotics, which contains a β-lactam as nucleus. In 1928, Alexander Fleming accidentally discovered this class of molecules.[168] Returning from holiday, Fleming sorted through petri dishes containing colonies of *Staphylococcus*, bacteria that cause abscesses, sore throats and boils. He noticed an unusual phenomenon on one dish. This latter was dotted with colonies, save for one area where a patch of mold was spreading. The zone immediately around the mold, which was later identified of *Penicillium notatum*, was clear, as if the mold has secreted a substance that inhibited bacterial growth. This substance was then identified as penicillin (see Scheme **125**). This class of molecules has been used as one of the first medication for many bacterial infections and is still widely used today even if many types of bacteria have developed resistance due to extensive use.




**6.1**

**Scheme 125 Penicillins**

A further example is the fused γ-lactam, Semaxanib, which is a tyrosin kinase inhibitor drug (see Scheme **126**).[169] This molecule is a cancer therapeutic and is an experimental drug.



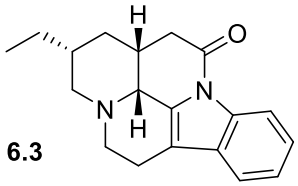

**6.2**

**Scheme 126 Semaxanib**

The final example is the fused δ-lactam, tacamonine, which is an indole alkaloid extracted in 1984 by Van Beek from the *Tabernaemontana eglandulosa*, a plant that has traditionally been used for the treatment of snake bites (see Scheme **127**).[170] This molecule is currently studied for its promising biological activities due to its

[168] Fleming, A. *British Journal of Experimental Pathology* **1929**, 10, 226.
[169] O' Donnell, A.; Pahani, A.; Hayes, C.; Kakkar, A.J.; Leach, M.; Trigo, J.M.; Scurr, M.; Raynaud, F.; Phillips, S. *Journal of cancer* **2005**, 93, 876.
[170] Van Beek, T.A.; Verpoorte, R.; Svendsen, B. *Tetrahedron* **1984**, 40, 737.

resemblance with vincamine alkaloids, which are cerebral vasodilators and antihypertensive drugs.[171]




**6.3**

**Scheme 127 Tacamonine**

Considering the interesting properties of fused-polycyclic lactams and given the structural similarities between fused polycyclic γ-lactams and the functionalized γ-lactams that we have electrochemically synthetized, we have tried to develop a new electrochemical road for the design of fused-polycyclic γ-lactams. This new synthetic path was inspired by our new Kolbe electrocyclization process applied to the synthesis of functionalized 2-pyrrolidinones.

## 6.1.1 Linear substrate

Based on the remarks made by F. Lebreux following his attempt to synthetize electrochemically bicyclic tetrahydrofurans we planned to synthetize the bicyclic γ-lactam **6.15** using electrochemistry. These remarks made the subsequent observations.

- First, the oxidative decarboxylation of the carboxylate reagent must generate a primary radical or a radical situated in α of an electron-withdrawing group, in order to promote the radical path and thus the first cyclization process.
- Secondly, the first cyclization must lead to the formation of a primary radical poorly oxidizable, and thus lead to a second cyclization process and not to the oxidation of this radical in a carbocation.

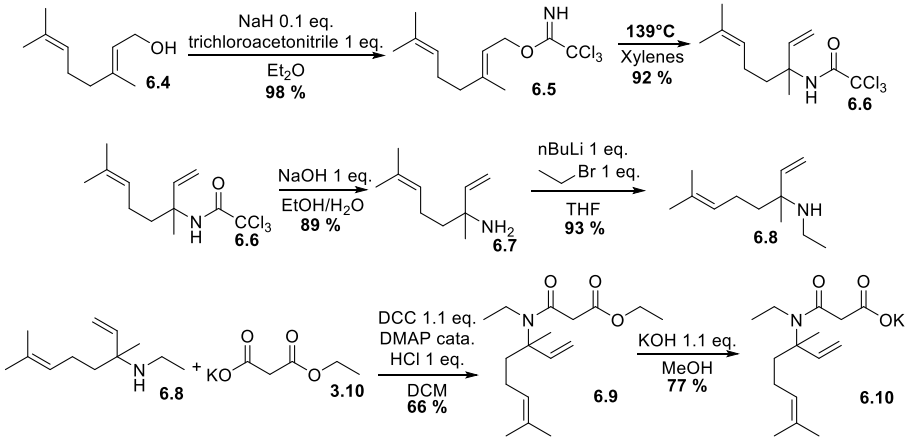
Based upon these remarks, the synthesis of a linear electrocyclization substrate **6.10** derived from the linalylamine **6.7** was developed.

### *6.1.1.1 Synthesis of the electropolycyclization substrate 6.10*

In order to test our strategy, we designed the cyclization substrate **6.10** according to the following procedure (see Scheme **128**). First, linalylamine **6.7** or 3,7-dimethyl-1,6-octadien-3-amine was synthetized in three steps from commercially available and inexpensive geraniol **6.4** and trichloroacetonitrile.[172] This procedure started by the treatment of the geraniol **6.4** with sodium hydride, which led to the formation of the corresponding alcoholate. This latter reacted then with trichloroacetonitrile to generate the trichloroacetimidate **6.5**. The acetimidate **6.5** was subsequently diluted into xylene and refluxed for 8 hours, to promote the sigmatropic rearrangement into the 3,7-dimethyl-3-trichloroacetamide-1,6-octadiene **6.6**. Afterwards, the octadiene **6.6** was converted into linalylamine **6.7** via a treatment with sodium hydroxide. Linalylamine was then protected by alkylation to generate the secondary amine **6.8**. This latter was then coupled with ethyl potassium malonate via a Steglich amidation to form the amide **6.9**. Finally, this amide **6.9** was converted into the

[171] Smith, M.W.; Ferreira, J.; Hunter, R.; Venter, G.A.; Su, H. *Org. Lett.* **2019**, 21, 8740.
[172] Clizbe, L.A.; Overman, L.E. *Organic Synthesis* **1978**, 58, 4.

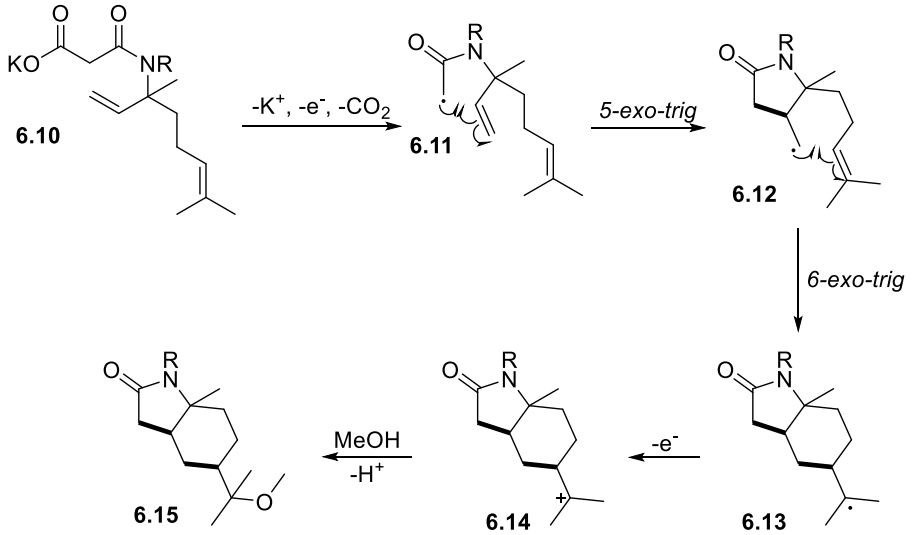
electrocyclization substrate **6.10** by hydrolysis of the ester function with potassium hydroxide.




**Scheme 128 synthesis of the electrocyclization substrate 6.10**

### *6.1.1.2 Expected mechanism of the electrobicyclization of the substrate **6.10***

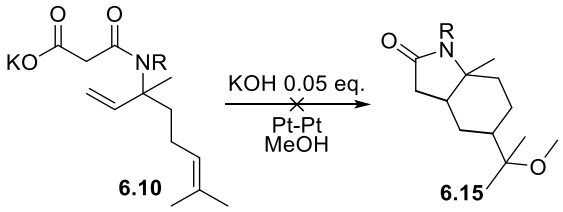
The expected mechanism of the electrobicyclization of the substrate **6.10** is the following (see Scheme **129**). First, the reagent **6.10** should be oxidated and decarboxylated to generate the linear radical **6.11**. This latter then should undergo a *5-exo-trig* cyclization, which should lead to the formation of the cyclic radical **6.12**. Subsequently, the radical **6.12** should form the bicyclic radical **6.13** via a *6-exo-trig* cyclization. The tertiary radical **6.13** is extremely oxidizable and should then be converted into the corresponding carbocation **6.14**. Finally, this latter should be trapped with methanol to form the fused bicyclic γ-lactam **6.15**. In this case, no co-acid should take action, in the reaction mechanism, because the final radical **6.13** is no enough stable to be coupled with the radical which is derived directly from the co-acid oxidative decarboxylation. Instead, a carbocation should be formed and coupled with the methanol solvent to form a methyl ether function.




**Scheme 129 expected mechanism of the electrocyclization of the substrate 6.10**

### *6.1.1.3 Electrolysis of the linear substrate **6.10***

The linear substrate **6.10** derived from the linalylamine was electrolyzed into the conditions determined during the optimization part of our work (see Scheme **130**). Unfortunately, the expected product **6.15** was not isolated from the crude. Instead, a complex mixture of side products was formed. No molecule could be isolated from the crude mixture, given that the structures of the side-products seem too similar to be separated via silica gel chromatography.

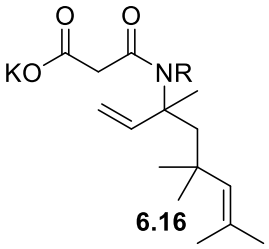



**Scheme 130 substrate 6.10 electrolysis**

### *6.1.1.4 Perspectives*

In the future, it could be interesting to add a *gem*-dimethyl group in the structure of the substrate **6.10**. For example, this group could be introduced on the carbon situated in α of the terminal double bond, which should be attacked during the *6-exo-trig* cyclization process. The presence of this substituent should promote a Thorpe-Ingold effect[173] and thus favor the second ring closure over side-reactions. This should limit the formation of side-products and accelerate the second cyclization mechanism.

[173] Beesley, R.M.; Ingold, C.K.; Thorpe, J.F. *J. Chem. Soc.* **1915**, 105, 1080.



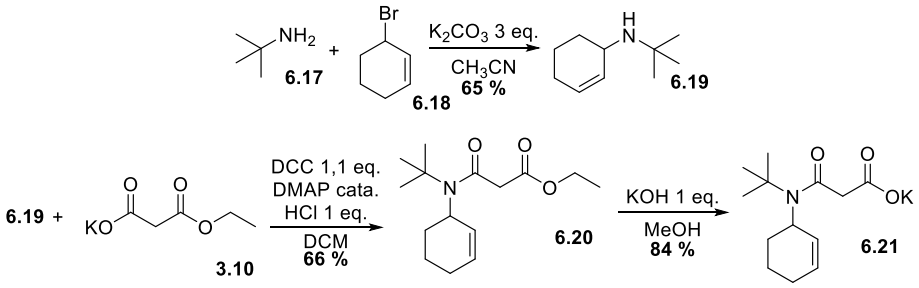

**Scheme 131 electrocyclization substrate 6.16 containing a *gem*-dimethyl substituent**

## 6.1.2 Cyclic substrate

Considering the failure of the electrobicyclization of the linear substrate **6.10**, we then decided to adapt our strategy for the electrosynthesis of bicyclic fused 2-pyrrolidinones. For this purpose, the cyclic substrate **6.21** was synthetized in order to facilitate the formation of bicyclic fused γ-lactam, since; in this case, only one cyclization operation should take place to lead to the formation of a desired bicyclic product.

### *6.1.2.1 Synthesis of the electrobicyclization substrate **6.21***

The cyclic electro-bicyclization substrate **6.21** was synthetized, in three steps, according to the next straightforward procedure (see Scheme **132**). First, *tert*-butylamine **6.17** was alkylate with 3-bromocyclohexene **6.18**, to yield the secondary amine **6.19** in a 65 % yield. This latter was then coupled with ethyl potassium malonate **3.10** via a Steglich amidation reaction. Finally, the ester **6.20** was converted into the corresponding potassium salt **6.21** via basic treatment.

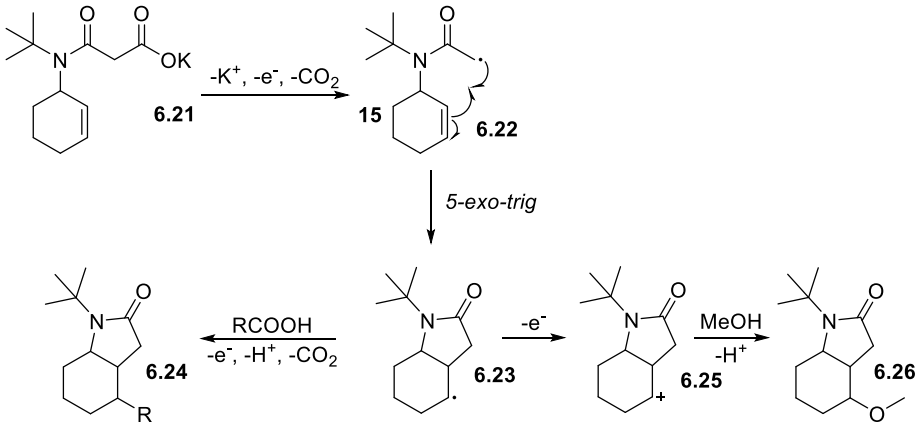



**Scheme 132 synthesis of the electrobicyclization substrate 6.21**

### *6.1.2.2 Expected mechanism of the electrobicyclization of the substrate **6.21***

The expected mechanism of the electrobicyclization of the substrate **6.21** is the following. The potassic salt **6.21** should be first oxidized and decarboxylated to generate the corresponding radical **6.22**. This radical **6.22** should then perform a *5-exo-trig* cyclization to form the secondary radical **6.23**. This species may lead to the formation of two products **6.24** and **6.26** depending on the speed of those irreversible steps. Actually, the secondary radical **6.23** is more easily oxidized into the corresponding carbocation **6.25** than a primary radical is. Therefore, this species **6.23** could either be oxidized into the corresponding carbocation **6.25** and trapped to

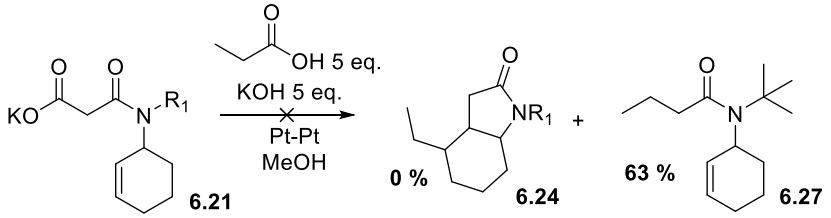
form the compound **6.26** or be coupled with the radical, which comes from the oxidative decarboxylation of the co-acid and generate the product **6.24**.




**Scheme 133 expected mechanism of the electrolysis of the substrate 6.21**

### *6.1.2.3 Electrolysis of the cyclic substrate **6.21***

With the electrobicyclization substrate **6.21** in hand, the electrolysis process was conducted in the conditions determined during the optimization study (see Scheme **134**). Unfortunately, the expected bicyclic product **6.24** was not isolated from the crude mixture. Instead, the side-product **6.27** was isolated in good yield via purification by chromatography on silica gel. This compound is derived from the cross-coupling between the radical coming from the co-acid oxidative decarboxylation and the radical generated by the oxidative decarboxylation of the compound **6.21** into the radical **6.22**. This phenomenon means that the speed of this cross-coupling process is higher than the speed of the *5-exo-trig* cyclization. Therefore, the cyclization did not occur, as the speed of this step is too low.



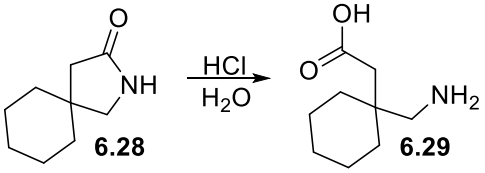

**Scheme 134 substrate 6.21 electrolysis**

The formation of the side-product **6.27** might be due to the steric hindrance of the molecule **6.21**, which limits the amide C-N bond rotation, or to adsorption phenomenon of the hindered radical **6.22** on the electrode surface. For those reasons, this strategy was discarded and we then decided to focus our attention on the formation of spirocyclic γ-lactams via electrochemistry.

## 6.2 Spirocyclic-lactams

Bicyclic-spiro-compounds are composed of two rings connected through a defining single common quaternary carbon atom. The one mutual atom connecting the two rings distinguishes spiro-compounds from other bicyclic products. A large number of natural molecules contain spiro-cycles, such as simple spiroketals which are

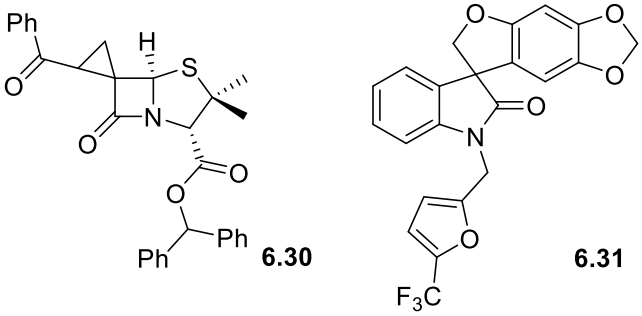
known insect pheromones. Several spiro compounds have been used to provide chemicals for medicinal studies and to serve as scaffolds for the synthesis of new therapeutic agents. Moreover, spirocyclic scaffolds have been increasingly used in drug discovery.[174] Actually, spiro containing molecules not only have greater three-dimensionality than flat aromatic compounds, but also offer structural innovation for patentability. For example, the gabapentine **6.29** is an antiepileptic drug and an analgesic, marketed by Pfizer under the designation of Neurotin®.[175] This active substance is derived from the spiro-γ-lactam **6.28** via acidic treatment (see Scheme **135**).



**6.28** **6.29**

**Scheme 135 synthesis of gabapentine 6.29 from the spiro-γ-lactam 6.28**

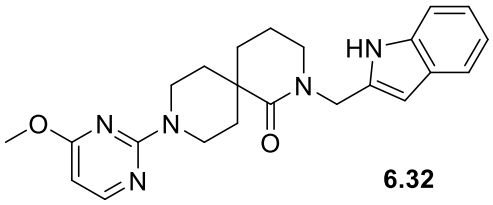
Another example of the medicinal applications of the spiro-lactams is the spiro-β-lactam **6.30**, which has anti-HIV activity.[176] Furthermore, XEN402 **6.31** is a spiro-oxindole, which inhibits the $Na_v1.7$ ion channel and is in clinical trials for the treatment of pain in patients with congenital erythromelalgia.[177] Finally, the spiro δ-lactam **6.32** from Novartis is a sleep inducer (see Scheme **137**).[178]



**6.30** **6.31**

**Scheme 136 spiro β-lactam with anti-HIV activity 6.30 and XEN402 6.31**

[174] Zheng, Y.; Tice, C.M.; Singh, S.B. *Bioorganic & Medicinal Chemistry Letters* **2014**, 24, 3676.
[175] Dipak, V.; Deepak, P.; Vidyadhar, *J. Chemical Science Transactions* **2016**, 5, 442.
[176] Alves, A.J.S.; Alves, N.G.; Caratao, C.C.; Esteves, M.I.M.; Fontinha, D.; Bartolo, I.; Soares, M.I.L.; Lopas, S.M.M.; Prudencio, M; Taveira, N. Pinho e Melo, T.M.V.D. *Current topics in Medicinal Chemistry* **2020**, 20, 13.
[177] Goldberg, Y.P.; Price, N.; Namdari, R.; Cohen, C.J.; Lamers, M.H.; Winters, C.; Price, J.; Young, C.E.; Verschoof, H.; Sherrington, R.; Pimstone, S.N.; Hayden, M.R. *Pain* **2012**, 153, 80.
[178] Betschart, C.; Hintermann, S.; Behnke, D.; Cotesta, S.; Fendt, M.; Gee, C.E.; Jacobson, L.H.; Laue, G.; Ofher, S.; Chaudhari, V.; Badiger, S.; Pandit, C.; Wagner, J.; Hoyer, D. *J. Med. Chem.* **2013**, 56, 7590.

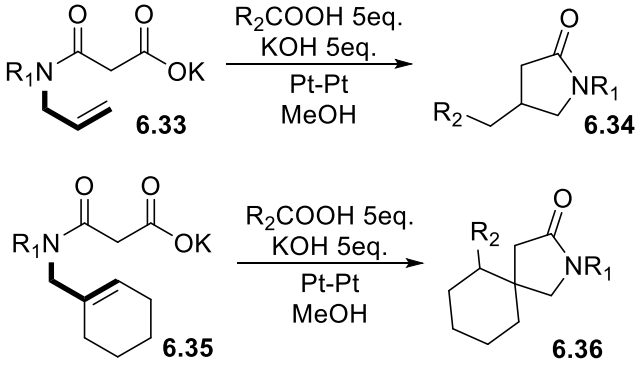



**Scheme 137 spiro δ-lactam 6.32 and sleep inducer**

Spirocyclic compounds represent an unique synthetic challenge. Due to their valuable properties, chemists have paid special attention to find various and efficient methodologies to access this class of molecules. Therefore, we have focused our work on the electrosynthesis of spirocyclic γ-lactams. In the following subsections, the strategies developed to this end are outlined.

## 6.2.1 2-azaspiro[4.5]decan-3-one

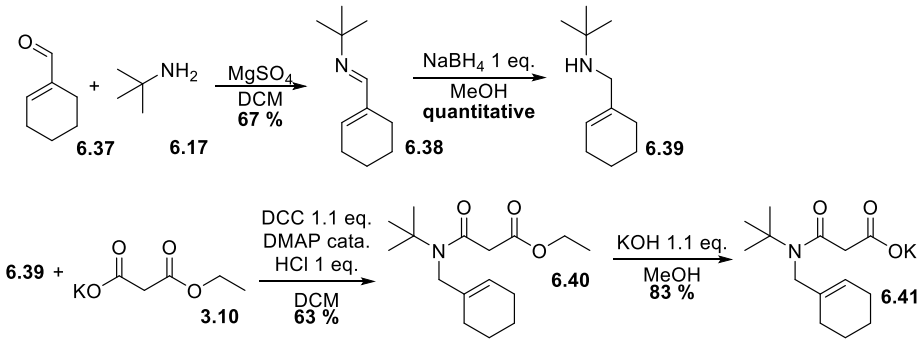
Our first strategy was to replace the allyl function in the substrate **6.33** structure by a cyclohexene moiety in order to promote a spiro cyclization process (see Scheme **138**). Actually, in this case, the olefin attacked during the cyclization step is situated on a six membered ring; therefore, the cyclization product should be a spirocyclic compound.




**Scheme 138 substrate 6.33 and substrate 6.35 electrolysis**

### *6.2.1.1 Electrobicyclization substrate **6.41** synthesis*

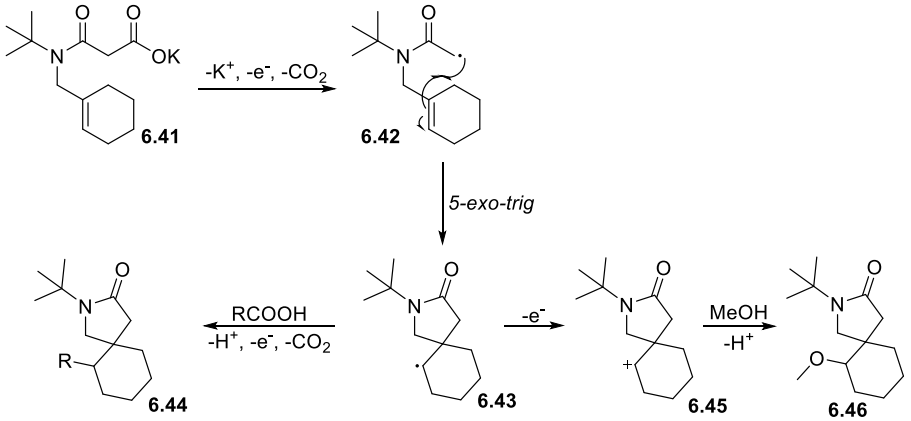
With the goal of providing a new method for the electro-spiro-cyclization of 2-pyrrolidinones, the substrate **6.41** was synthetized in four steps (see Scheme **139**). Firstly, 1-cyclohexene-1-carboxaldehyde **6.37** was condensed with *tert*-butylamine **6.17** to form the imine **6.38**. This latter was then reduced in the allylic secondary amine **6.39**. Subsequently, the amine **6.39** was coupled with potassium ethyl malonate **3.10**, via a Steglich amidation, to generate the amide **6.40**. Finally, the amide ester **6.40** was hydrolyzed, which leads to the formation of the electro-spiro-cyclization substrate **6.41**.




**Scheme 139 electro-spiro-cyclization substrate 6.41 synthesis**

### *6.2.1.2 Expected mechanism of the electro-spiro-cyclization of the compound **6.41***

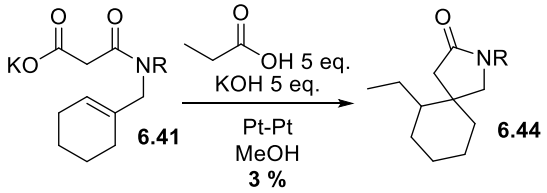
We expected that the electrolysis of the substrate **6.41** could lead to the formation of two different products **6.44** and **6.46**. Those products are interesting targets as their structures are very similar to the structure of the precursor of gabapentine known for its antiepileptic activity. This reaction should begin with the oxidative decarboxylation of the substrate **6.41**, which should lead to the formation of the radical **6.42**. Subsequently, this latter should perform a *5-exo-trig* cyclization to lead to the formation of the spirocyclic radical intermediate **6.43**. During this step, a quaternary carbon, which is typical of spirocyclic molecules, should be formed. The radical chemistry should help this process to take place given that radicals are highly reactive intermediates, and can be used for the design of hindered or strained molecules. Afterwards, two different mechanisms could take place, depending on the kinetic of those irreversible reactions. On one hand, the spirocyclic radical **6.43** could undergo a cross-coupling process with a radical coming from the oxidative decarboxylation of the co-acid (RCOOH), leading to the formation of the spirocyclic product **6.44**. On the other hand, the spirocyclic secondary radical **6.43** could be oxidized into the corresponding carbocation **6.45**, given that secondary radicals are more oxidizable than primary radicals. Finally, this carbocation **6.45** should be trapped by methanol. Finally, this should lead to the formation of the product **6.46** (see Scheme **140**).




**Scheme 140 expected mechanism of the electrolysis of the substrate 6.41**

### *6.2.1.3 Electrobicyclization of the substrate **6.41***

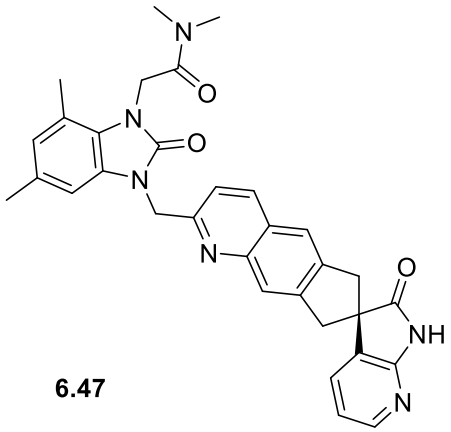
With the electrobicyclization reagent **6.41** in hand, the electrochemical step was performed, in the conditions determined during our optimization study. This electrolysis led to the formation of the desired spirocyclic 2-pyrrolidinone **6.44**. Nevertheless the yield was only 3 %. This very low yield might be due to the steric hindrance of the molecule **6.41**, which should limit the amide C-N bond rotation, or to adsorption phenomenon of the hindered radical **6.42,** on the electrode surface. Moreover, a mixture of side-products was obtained. Those side-products were not identified given that their structures are too similar to allow their separation via chromatography on silica gel. Having regard to those results, we had to adapt our approach in order to design electrochemically spirocyclic 2-pyrrolidinones in significant yields. The formation of side-products could be related to the formation of the secondary radical **6.43** which could be oxidized into the corresponding carbocation **6.45**.




**Scheme 141 substrate 6.41 electrolysis**

## 6.2.2 2-azaspiro[4.4]nonan-1-one

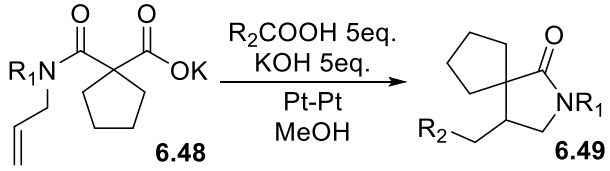
2-azaspiro[4.4]nonan-1-one derivatives are known to display interesting biological activities. For instance, the spiro compound **6.47** acts as CGRP antagonist; and CGRP (calcitonin gene-related peptide) is a naturally occurring peptide distributed in the central and peripheral nervous system.[179] Therefore, the spiro 2-pyrrolidinone **6.47** is a useful pharmacological agent for disorders that involve GCRP in humans, such disorders include: migraine, chronic pain, pain, brain trauma, stroke, epilepsy, and neurodegenerative diseases.




**Scheme 142 CGRP antagonist 6.47**

[179] Bell. I.M.; Selnick, H.G.; Stump, C.A.; Theberge, C.R.; Zartman, C.B. PCT Int. Appl., 2007061696, 31 May 2007.

Having regard to the previous results and the promising biological activities of 2-azaspiro[4.4]nonan-1-one derivatives, we adapted our methodology to generate spirocyclic 2-pyrrolidinones (see Scheme **143**). Actually, our new strategy was to incorporate a cycle inside the malonate part of the cyclization substrate structure. To this end, the model substrate **6.48** containing a cyclopentane core was synthetized according to the procedure outlined in a following subsection.




**Scheme 143 electro-spiro-cyclization substrate 6.48**

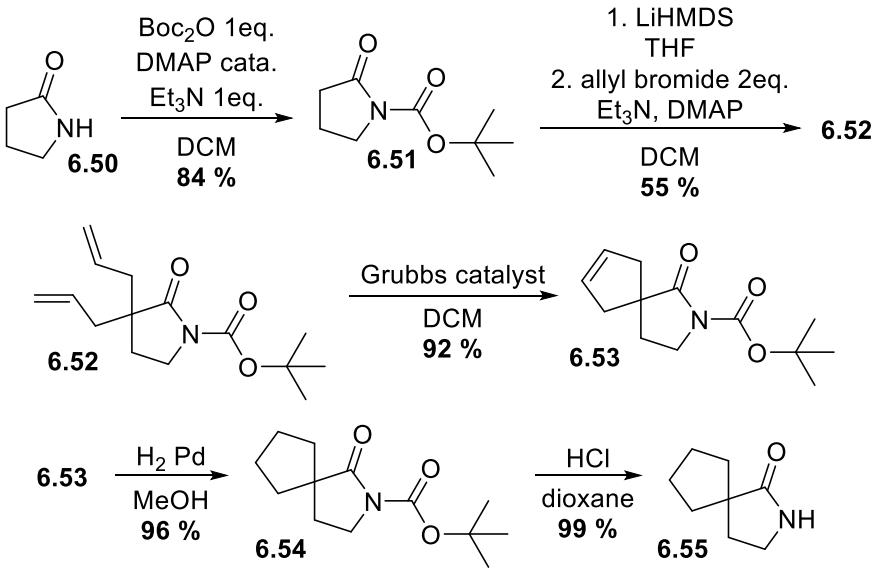
*6.2.2.1 State of the art of 2-azaspiro[4.4]nonan-1-one synthesis*

Given the interesting biological activities of 2-azaspiro[4.4]nonan-1-one derivatives, several synthetic roads, leading to the formation of that scaffold, are presented, in the scientific literature. In the following subsections, two different methodologies of formation of spiro 2-pyrrolidinone moieties are illustrated. The first example is based on an olefin metathesis cyclization process, while the second example implies a radical cyclization.

*6.2.2.1.1 Synthesis of 2-azaspiro[4.4]nonan-1-one via olefin metathesis*

In 2018, Baowei *et al.* reported a synthesis of 2-azaspiro[4.4]nonan-1-one via an olefin metathesis cyclization, in five steps, with a global yield of 40 % (see Scheme **144**).[180] This procedure began with the protection of 2-pyrrolidinone **6.50** whit Boc anhydride. The protected 2-pyrrolidinone **6.51** was then di-alkylated using allyl bromide and LiHMDS, as a base. Subsequently, the diallyl compound **6.52** was cyclized using a Grubbs catalyst, to yield the spirocyclic compound **6.53**. Consecutively, the catalytic hydrogenation of the olefin **6.53** was performed. Finally, a deprotection step led to the formation of the spiro 2-pyrrolidinone **6.55**.

[180] Baowei, Z.; Mingming, Z.; Hangping, Y.; Shuqun, Y.; Zhui, C.; Yaochang, X. PCT Int. Appl. 2018, WO 2018214867 A1 Nov 29, 2018.

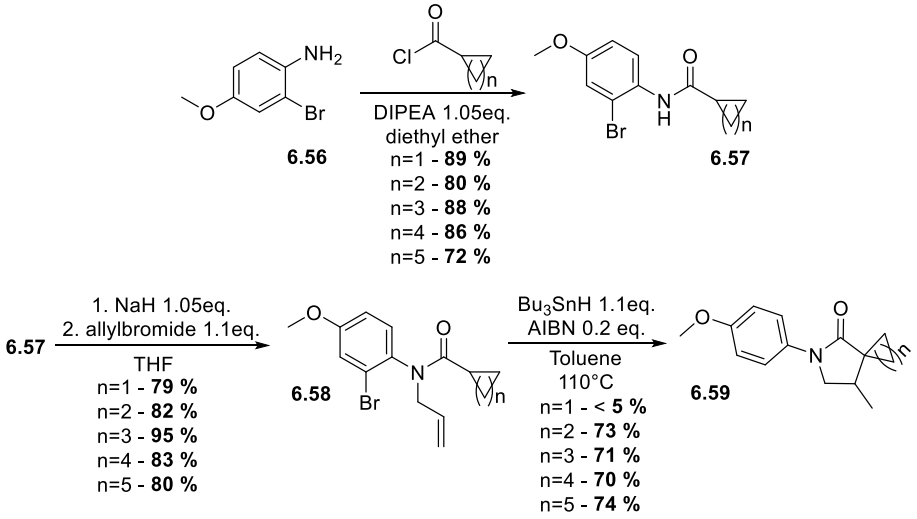



**Scheme 144 Synthesis of 2-azaspiro[4.4]nonan-1-one 6.55 via olefin metathesis**

*6.2.2.1.2Synthesis of 2-azaspiro[4.4]nonan-1-one via a [1,5]-radical translocation followed by a radical cyclization*

In 2000, Storey *et al.* reported a synthesis of 2-azaspiro[4.4]nonan-1-one moieties, which proceeds via an initial [1,5]-radical translocation followed by a radical cyclization (see Scheme **145**).[181] This procedure began with the coupling of the appropriate acid chloride with 2-bromo-4-mehylaniline **6.56** to form the secondary amide species **6.57**. Afterwards, the amide **6.57** was alkylated to yield the cyclization precursor **6.58**. Finally, treatment of the compound **6.58** with tributyltin hydride gave good yields of spiro 2-pyrrolidinones **6.59**. The final product resulted from intramolecular hydrogen atom transfer reaction followed by a *5-exo-trig* cyclization.

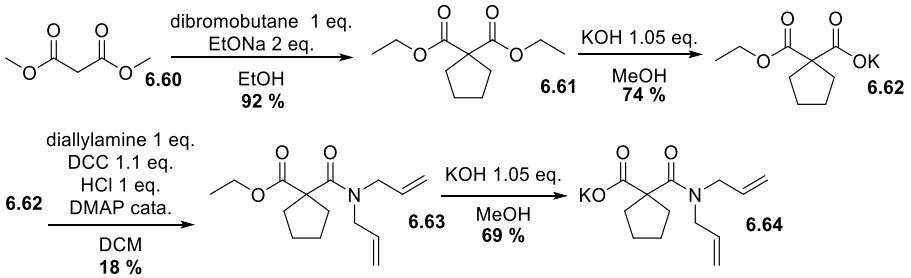
[181] Storey, J.M.D. *Tetrahedron Letters* **2000**, 41, 8173.




**Scheme 145 Synthesis of 2-azaspiro[4.4]nonan-1-one 6.59 via a [1,5]-radical translocation followed by a radical cyclization**

*6.2.2.2 Electrobicyclization substrate **6.64** synthesis*

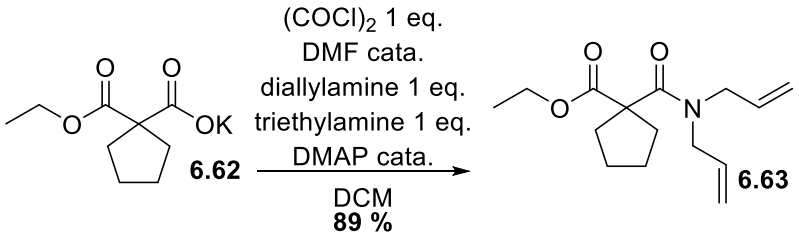
In order to produce electrochemically spirocyclic 2-pyrrolidinones, the substrate **6.64** was synthetized as reported in the following procedure (see Scheme **146**). First, commercially available and inexpensive dimethyl malonate **6.60** was substituted with dibromobutane to form the cyclic malonate **6.61**. This latter was then converted into the potassic salt **6.62,** given that the corresponding carboxylic acid is thermally unstable.[182] This potassic salt **6.62** was subsequently coupled with diallylamine via a Steglich amidation to generate the species **6.63**. This latter was finally hydrolyzed to form the electro-spiro-cyclization reagent **6.64**.




**Scheme 146 electrobicyclization substrate 6.64 synthesis**

As shown in the Scheme **146**, the Steglich amidation of the bulky cyclic carboxylate **6.62** led to the formation of the amide **6.63** in a low yield of 18 %. Indeed the Steglich reaction reached a limit with sterically hindered carboxylic acids.[183] Therefore, the Steglich amidation reaction was abandoned in favor of the treatment of the carboxylate **6.62** with oxalyl chloride and the consecutive nucleophilic attack of the acyl chloride formed with the diallylamine, leading to the formation of the amide **6.63** in a good yield (see Scheme **147**).

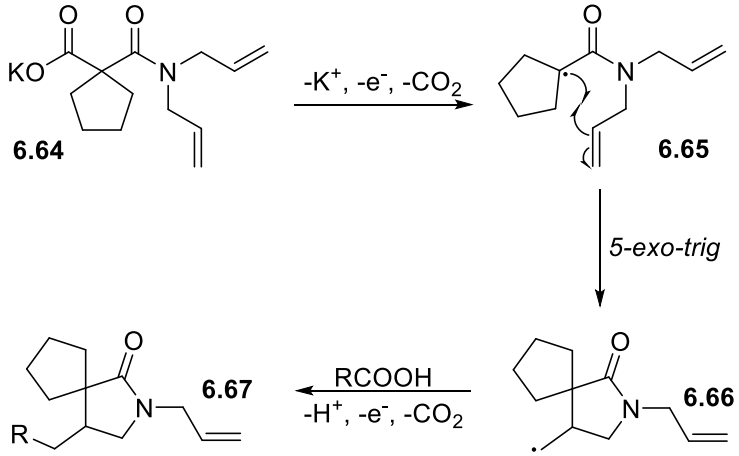
[182] Mazzocchi, P.H.; Tamburin, H.J. *J. Am. Chem. Soc.* **1975**, 97, 555.
[183] Neises, B.; Steglich, W. *Angew. Chem. Int. Ed. Engl.* **1978**, 17, 522.




**Scheme 147 amidation via acyl chloride and nucleophilic attack by diallylamine**

### *6.2.2.3 Expected mechanism of the electrobicyclization of the substrate **6.64***

The expected mechanism of the electrobicyclization of the molecule **6.64** is the following. The substrate **6.64** should be first oxidatively decarboxylated into the tertiary radical **6.65**. Given that the tertiary radical is situated in α-position of an electron withdrawing group, this tertiary radical is hardly oxidized into the corresponding carbocation. Instead, a *5-exo-trig* cyclization process should take place leading to the formation of the spirocyclic radical **6.66**, and the creation of a quaternary carbon typical of the spirocycles. This cyclization mechanism should be possible thanks to the high reactivity of the radical species. The spirocyclic radical **6.66** should finally undergo a cross-coupling with a radical derived from the oxidative decarboxylation of the co-acid, which should lead to the functionalized spiro 2-pyrrolidinone **6.67**.

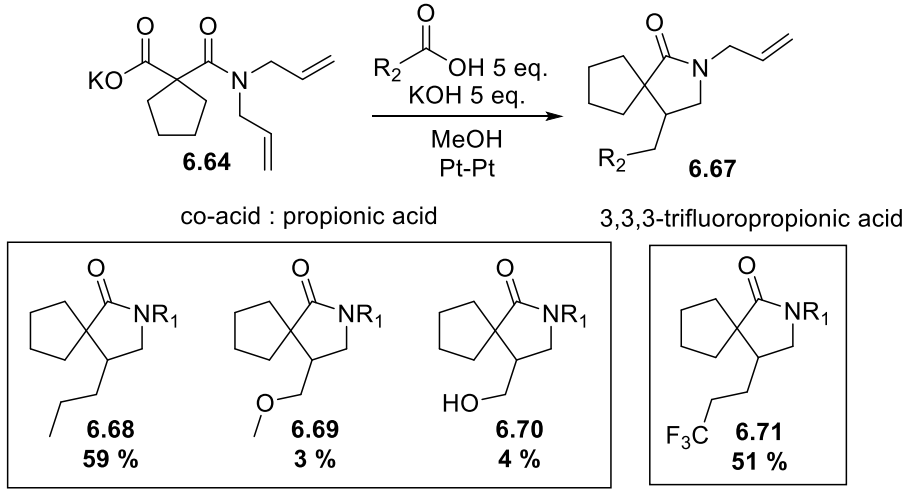



**Scheme 148 expected mechanism of the electrobicyclization of the substrate 6.64**

### *6.2.2.4 Electrobicyclization of the substrate **6.64***

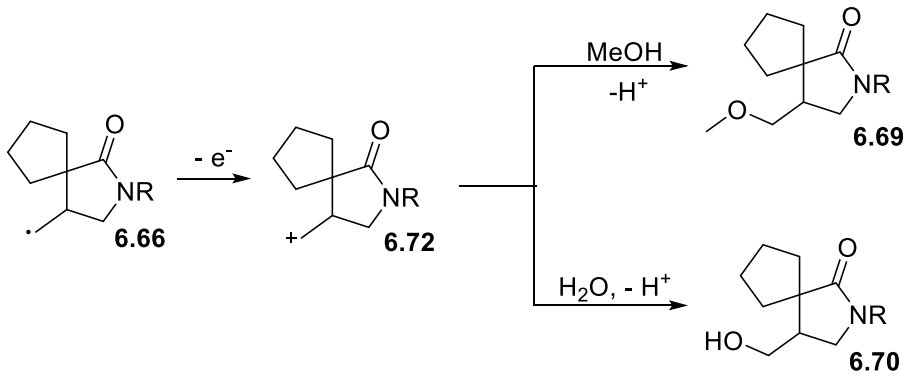
Once the electrobicyclization reagent **6.64** synthetized and purified, the electrolysis of this compound was carried out, in the conditions setted up during our optimization investigation (see Scheme **149**). This reaction was conducted twice with two different co-acids: propionic acid and 3,3,3-trifluoropropionic acid. Those reactions have led to the formation of two functionalized spirocyclic 2-pyrrolidinones **6.68** and **6.71** in good yields. Interestingly, in only one electrolysis step, two carbon-carbon bonds were formed and a spirocycle was created and

functionalized in a versatile way with a radical coming from the oxidative decarboxylation of the adaptable co-acid. Given those promising results, we decided to explore this approach of electrochemical synthesis of spiro 2-pyrrolidinones by modifying the nature of the cyclic electrolysis reagent, in order to show the versatility of this brand-new methodology.




**Scheme 149 electro-spiro-cyclization substrate 6.64 electrolysis**

Nevertheless, in the experiment with propionic acid as co-acid, two side-products **6.69** and **6.70** were formed in low yields. Those two impurities originate from the oxidation of the cyclic radical **6.66**, which led to the formation of the carbocation **6.72** (see Scheme **150**). This latter was trapped by methanol or water to generate the methoxy and alcohol functionalized 2-pyrrolidinones **6.69** and **6.70**. Finally, we were not able to find an explanation of the overoxidation of the primary radical **6.66** into the corresponding carbocation **6.72** which should be related to the presence of cyclopentane substituent in the structure of the substrate **6.64**.



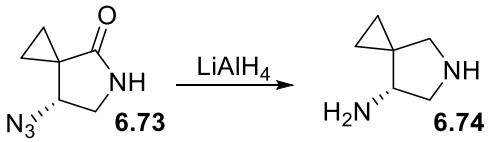

**Scheme 150 formation of the impurities 6.69 and 6.70**

In comparison with the examples found in the literature (see sections 6.2.2.1.1. and 6.2.2.1.2.), our electrochemical methodology has the advantage to proceed in five steps, starting from a cheap starting material, dimethyl malonate **6.60**. Moreover, in comparison with the synthesis of spiro 2-pyrrolidinones by Baowei *et al.*, in 2018, our electrosynthesis does not require the use of metal catalysts, which are expensive

and make the purification of pharmaceutical products more difficult. Furthermore, our procedure is performed under air and at atmospheric pressure. Additionally, in comparison with the synthesis of spiro 2-pyrrolidinones by Storey, in 2000, our methodology does not require high temperatures, and the use of electricity as oxidant, prevents the utilization of tributyltin hydride as a radical generating reagent, which is toxic and requires complicated work-up. Finally, radical reactions are easier to control via electrochemistry given that to stop the radical reaction; you only have to switch of the current.

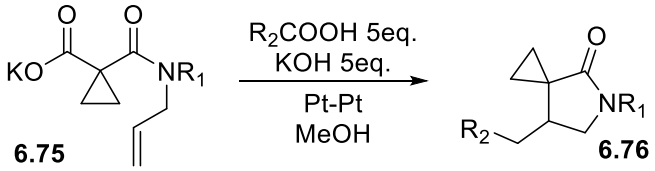
### 6.2.3 5-azaspiro[2.4]heptanone

5-azaspiro[2.4]heptanone derivatives are precursors of several interesting biologically active compounds. For instance, the spiro 2-pyrrolidinone **6.73** can be readily reduced using $LiAlH_4$ into the spiro pyrrolidine **6.74** displaying a broad spectrum of antibacterial activities.[184]




**Scheme 151 reduction of the spiro 2-pyrrolidinone 6.73 into the spiro pyrrolidine 6.74**

Given the potential of 5-azaspiro[2.4]heptanone derivatives in organic synthesis, an electrochemical synthesis of those compounds was developed. This procedure implies the oxidation of a cyclic reagent **6.75** in the Kolbe conditions (see Scheme **152**). Before going into the details of this brand new methodology, some examples of the synthesis of 5-azaspiro[2.4]heptanone found in the literature are presented in the following subsection.




**Scheme 152 electrochemical synthesis of functionalized 5-azaspiro[2.4]heptanone derivatives 6.76**

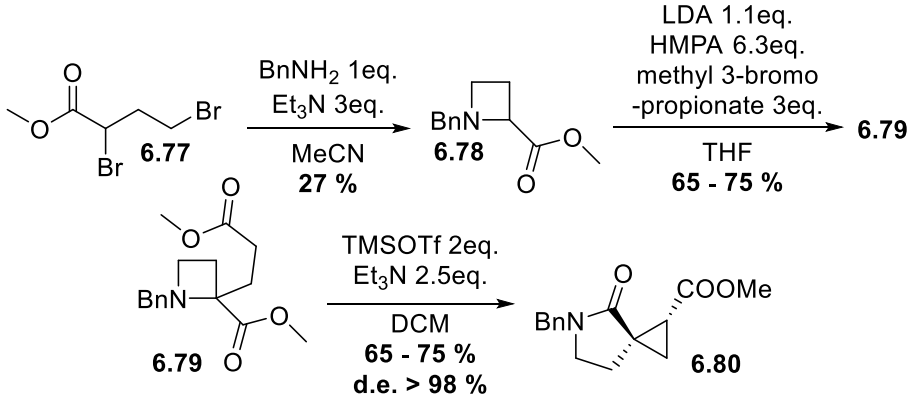
#### *6.2.3.1 State of the art of 5-azaspiro[2.4]heptanone synthesis*

As it is illustrated in the section 6.2.2.1.2., 5-azaspiro[2.4]heptanone species can be synthetized via [1,5]-radical translocation followed by a radical cyclization, in a low yield of 5 %, as described by Storey *et al.*, in 2000. Moreover, another example of the synthesis of this kind of compounds was found in the literature and is presented in the following subsection.

##### *6.2.3.1.1 Synthesis of 5-azaspiro[2.4]heptanone via tandem intramolecular azetidine ring-opening/closing cascade reaction*

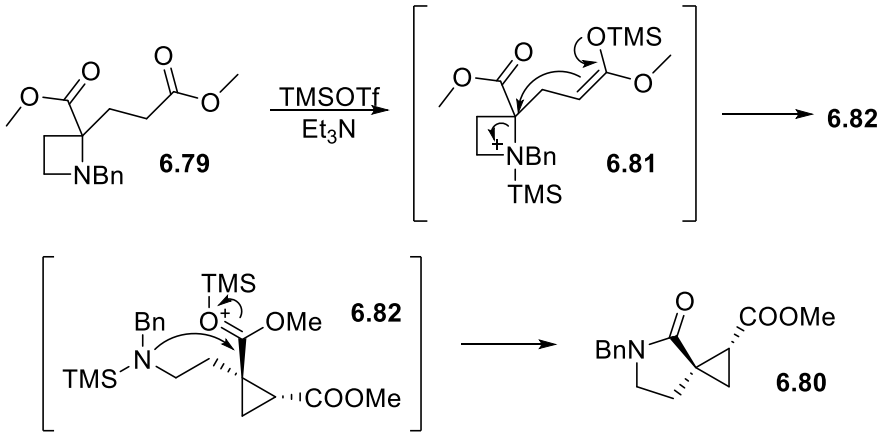
[184] Satoh, K.; Imura, A.; Miyadero, A.; Kanai, K.; Yukimoto, Y. *Chem. Pharm. Bull.* **1998**, 46, 587.

In 2011, Nocquet *et al.* reported a synthesis of 5-azaspiro[2.4]heptanone **6.80** via tandem intramolecular azetidine ring-opening/closing cascade reaction, in three steps and a global yield of 11 – 15 % (see Scheme **153**).[185] This procedure began with the cyclization if methyl 2,4-dibromobutyrate in the azetidine **6.78**. Subsequently, the azetidine **6.78** was alkylated using methyl 3-bromo-propionate. Finally, azetidine **6.79** was transformed into the spiro 2-pyrrolidinone **6.80**, using trimethylsilyl trifluoromethanesulfonate and triethylamine.




**Scheme 153 synthesis of spirocyclopropyl 2-pyrrolidinone 6.80 by highly stereoselective tandem intramolecular azetidine ring-opening/closing cascade reaction**

The key step of this process is a ring opening of the TMSOTf-activated azetidine ring by the silyl ketene acetal formed via treatment with TMSOTf and triethylamine (see Scheme **154**). The amino ester formed **6.82** then undergoes an intramolecular cyclization to yield the spiro 2-pyrrolidinone **6.80** by reaction of the amine function with the ester substituent in the γ position.

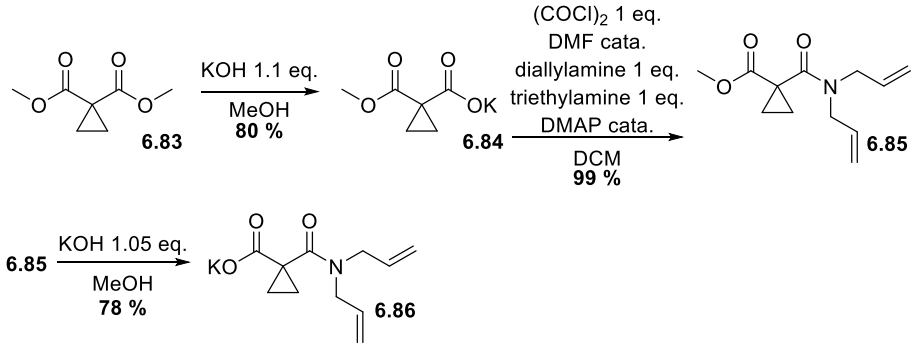



**Scheme 154 mechanism of the key step of the synthesis of spirocyclopropyl 2-pyrrolidinone 6.80 by highly stereoselective tandem intramolecular azetidine ring-opening/closing cascade reaction**

[185] Nocquet, P.A.; Hazelard, D. ; Compain, P. *Eur. J. Org. Chem.* **2011**, 6619.

*6.2.3.2 Electrobicyclization substrate **6.86** synthesis*

In order to show the generality of our new electrochemical synthesis of spiro 2-pyrrolidinones, the substrate **6.86** containing a cyclopropane moiety was prepared, in only three steps, according the following sequence see Scheme **155**. First, the affordable and commercially available dimethyl cyclopropane-1,1-dicarboxylate ester **6.83** was converted into the corresponding mono-potassic salt **6.84**. This latter was subsequently coupled with the diallylamine to generate the amide **6.85**. Finally, the product **6.85** was hydrolyzed into the electrobicyclization substrate **6.86**.



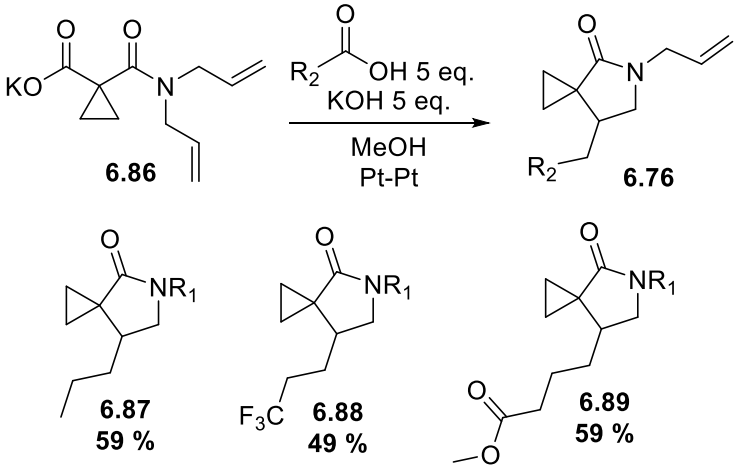

**Scheme 155 synthesis of the electro-spiro-cyclization substrate 6.86**

The dimethyl cyclopropane-1,1-dicarboxylate **6.83** originated from a commercial source; nevertheless, this reagent can be produced via an electrochemical way.[186] Indeed, this molecule **6.83** can be generated via a cyclic condensation of dihaloalkane whit activated methylene of malonic acid ester, using an electrogenerated superoxide ion as a base.

***6.2.3.3** Electrolysis of the electro-spiro-cyclization substrate **6.86***

With the electrochemical reagent **6.86** in hand, the electrolysis of this latter was performed according to our optimized conditions (see Scheme **156**). This procedure was done three times with different co-acids: propionic acid, 3,3,3-trifluoropropionic acid, and mono-methyl hydrogen succinate. Three spiro 2-pyrrolidinones **6.87**, **6.88**, and **6.89** were synthetized in good yields, which shows the adaptability of our methodology.

[186] Ojima, F.; Matsue, T.; Osa, T. *Chemistry Letters* **1987**, 2235.




**Scheme 156 electro-spiro-cyclization substrate 6.86 electrosynthesis**

In comparison with the syntheses of spiro 2-pyrrolidinones of Storey *et al.* (see section 6.2.2.1.2.), which has a global yield below 5 %, and Nocquet *et al.* (see section 6.2.3.1.1), which has a global yield of 11 % - 15 %; our methodology presents the advantage to be more efficient with a global yield of 30 – 37 %. Moreover, the synthesis of 5-azaspiro[2.4]heptanones via tandem intramolecular azetidine ring-opening/closing cascade reaction uses the expensive methyl 2,4-dibromobutyrate (50 ml – 596.0 €) as starting material, whereas our procedure requires the inexpensive dimethyl malonate (1kg – 96.5 €) or dimethyl 1,1-cyclopropanedicarboxylate (50 ml – 62.4 €) as reagent.[187]

### 6.2.4 2,8-diazaspiro[4.5]decan-1-one

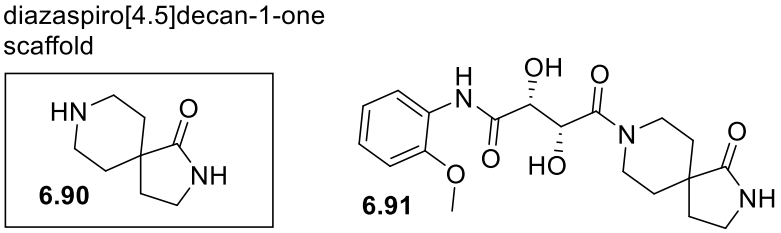
For the purpose of showing the versatility of our electrochemical methodology for the functionalized spiro δ-lactams synthesis, we have explored the electrochemical synthesis of 2,8-diazaspiro[4.5]decan-1-one **6.90**. Actually, the spiropiperidine scaffold has emerged as a privileged scaffold in drug discovery. Indeed, it has been regularly demonstrated that these moieties inherently possess drug-like properties in preclinical models.[188] For example, the diazaspiro[4.5]decan-1-one derivative **6.91** is an antifungal agent.[189] Moreover, small changes within their structure have a huge impact on their biological properties.[190] Therefore, the organic electrochemistry seems to be a really attractive way to design those medicinal targets considering our state-of-the-art polyvalent methodology.

[187] Retrieved April 27, 2020 from https://www.sigmaaldrich.com/belgium-francais.html.

[188] (a) Desimone, R.W.; Currie, K.S.; Mitchell, S.A.; Darrow, J.W.; Pippin, D.A. *Comb. Chem. High Throughput Screening* **2004**, 7, 473; (b) Kraff, E.A.; Kurt, A.; Maier, A.; Thomas, A.W.; Zimmerlis, D. *Synthesis* **2005**, 19, 3245.

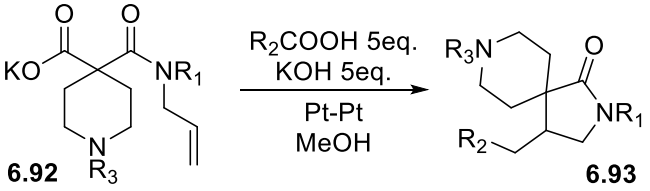
[189] Li, B.; Wang, K.; Zhang, R.; Li, B. ; Shen, Y. ; Ji, Q. *European Journal of Medicinal Chemistry* **2019**, 18, 111669.

[190] Guo, T.; Hobbs, D.W. *Assay Drug Dev. Tech.* **2003**, 1, 579.




**Scheme 157 diazaspiro[4.5]decan-1-one scaffold 6.90 and the antifungal agent 6.91**

In order to develop an electrochemical synthesis of 2,8-diazaspiro[4.5]decan-1-one derivatives, the cyclic substrate **6.92** had to be oxidated in Kobe conditions (see Scheme **158)**. In the following subsections, classic syntheses of this kind of spiro 2-pyrrolidinones are presented, with the aim to compare those methodologies with the one, which we have developed.



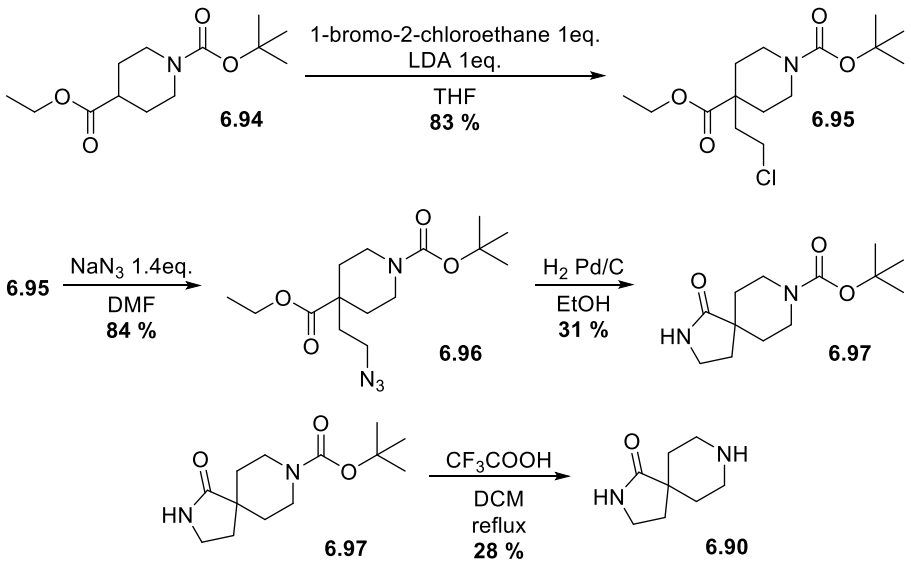

**Scheme 158 electrosynthesis of 2,8-diazaspiro[4.5]decan-1-one derivatives 6.92**

*6.2.4.1 State of the art of 2,8-diazaspiro[4.5]decan-1-one derivatives synthesis*

*6.2.4.1.1 Synthesis of 2,8-diazaspiro[4.5]decan-1-one derivative via azide reduction followed by 5-exo-trig cyclization*

In 2000, Dabbs *et al.* developed a synthesis of 2,8-diazaspiro[4.5]decan-1-one derivative **6.90** via azide reduction followed by 5-exo-trig cyclization, in four step and with a global yield of 6 % (see Scheme **159**).[191] This molecule was synthetized to treat microbial infections on animals and humans. This procedure began with the alkylation of the protected piperidine **6.94** with 1-bromo-2-chloroethane. The piperidine **6.95** was then treated with sodium azide to generate the azide moiety **6.96**. The reduction of the azide **6.96** to the corresponding primary amine, through catalytic hydrogenation with $H_2$ over Pd/C, took then place and led to the formation of the spirocyclic 2-pyrrolidinone **6.97**. Finally, the species **6.97** was deprotected to form the final product **6.90**.

[191] Dabbs, S.; Davies, S.; Dean, D.K.; Frydrych, C.H.; Gaiba, A.; Howard, S.; Hunt, E.; King, F.D.; Naylor, A.; Takle, A.K. PCT Int. Appl. (2000), WO 2000027790 A1 May 18, 2000.

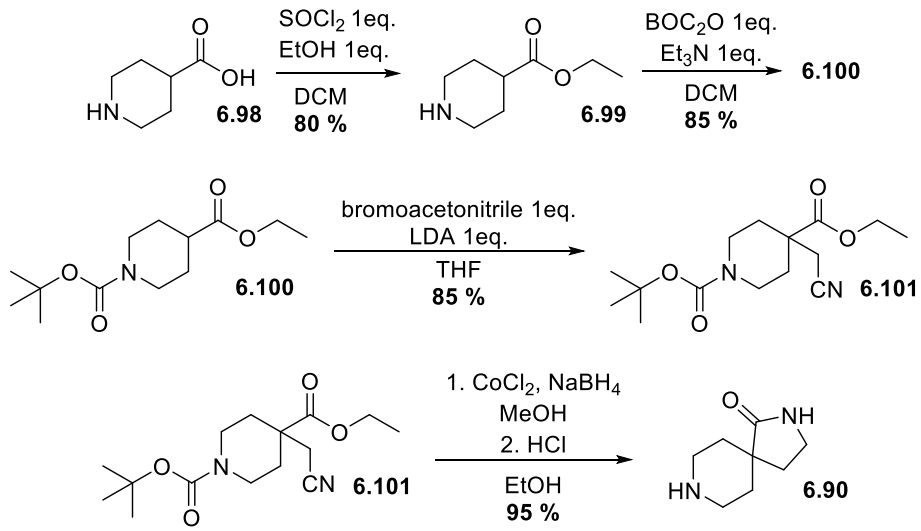



**Scheme 159 Synthesis of 2,8-diazaspiro[4.5]decan-1-one derivative via azide reduction followed by 5-exo-trig cyclization**

*6.2.4.1.2Synthesis of 2,8-diazaspiro[4.5]decan-1-one derivative via nitrile reduction followed by 5-exo-trig cyclization*

In 2019, Li *et al.* developed a synthesis of 2,8-diazaspiro[4.5]decan-1-one derivative **6.90** via nitrile reduction followed by 5-exo-trig cyclization, in five steps and with a global yield of 55 % (see Scheme **160**).[192] Their goal was to synthetize a derivative of 2,8-diazaspiro[4.5]decan-1-one for its antifungal activity. The first step of this procedure was the esterification of isonipecotic acid **6.98**, using ethanol and thionyl chloride, to yield the ester **6.99**. Subsequently, the piperidine **6.99** was protected with di-*tert*-butyl dicarbonate, which led to the formation of the protected piperidine **6.100**. Additionally, this compound **6.100** was alkylated, using LDA and bromoacetonitrile, to form the nitrile compound **6.101**. The nitrile function of the moiety **6.101** was then reduced in primary amine in presence of $CoCl_2$ and $NaBH_4$. In this sequence, $Co^{2+}$ is coordinate to the nitrile function, which enables its reduction using $NaBH_4$. A subsequent *5-exo-trig* cyclization took place and yielded to the final spirocyclic 2-pyrrolidinone **6.90**.

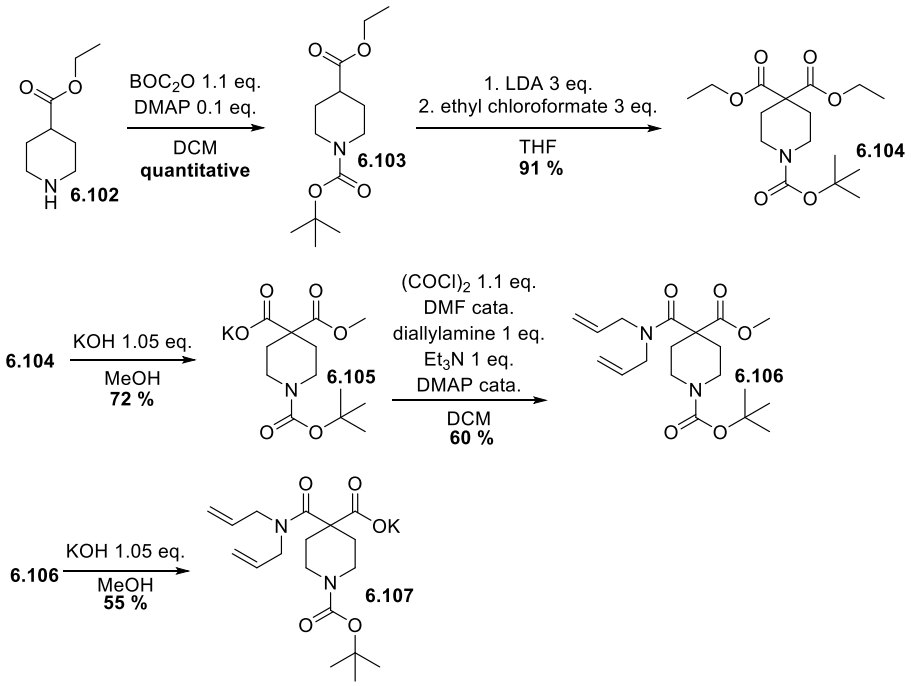
[192] Li, B.; Wang, K.; Zhang, R.; Li, B.; Shen, Y.; Ji, Q.; *European Journal of Medicinal Chemistry* **2019**, 182, 111669.




**Scheme 160 Synthesis of 2,8-diazaspiro[4.5]decan-1-one derivative 6.90 via nitrile reduction followed by 5-exo-trig cyclization**

### *6.2.4.2 Synthesis of the electro-spiro-cyclization substrate **6.107***

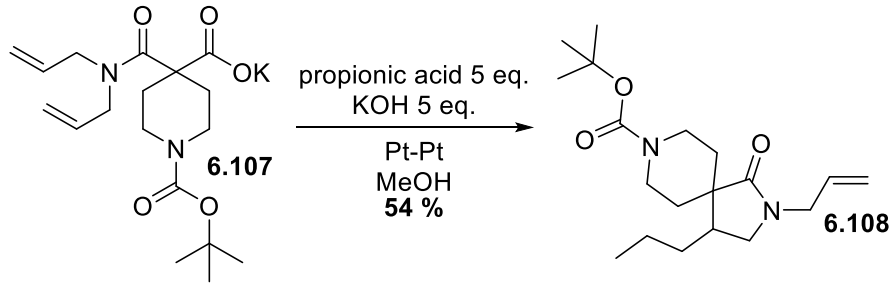
The synthesis of the substrate **6.107** began with the protection of commercially available ethyl isonipecotate **6.102** with di-*tert*-butyl dicarbonate. Subsequently, this product **6.103** was converted into the corresponding cyclic diethyl malonate **6.104** in good yields. This latter was then treated with potassium hydroxide to deliver the malonic salt **6.105**. Afterwards, this salt **6.105** was coupled with diallylamine to generate the amide **6.106**. Finally, the amide ester **6.106** was converted into the electrocyclization reagent **6.107**, via hydrolysis, using potassium hydroxide.




**Scheme 161 synthesis of the electro-spiro-cyclization substrate 6.107**

*6.2.4.3 Electro-spiro-cyclization of the substrate **6.107***

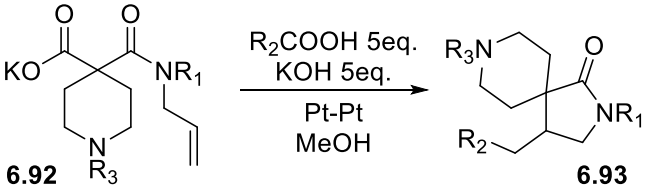
With the electro-spiro-cyclization substrate **6.107** in hand, the electrolysis of this reagent was conducted, using propionic acid as co-acid, in our optimized conditions. Successfully, the spiro 2-pyrrolidinone **6.108** was produced in excellent yield. We have thus developed a state-of-the-art synthetic route to access 4-substituted diazaspiropiperidine derivatives of pharmaceutical interest.




**Scheme 162 electro-spiro-cyclization of the substrate 6.107**

In comparison with the synthesis found in the literature (see sections 6.2.4.1.1. and 6.2.4.1.2.), our methodology has some advantages. First, our methodology does not require high temperature or high pressure; and the electrochemical step is done under air. Additionally, our procedure does not need the use of metal catalysts, which are complicate to purify industrially. Indeed, the synthesis of Dabbs *et al.* implies the use of palladium on carbon catalyst to reduce an azide function in a primary amine; and the synthesis of Li *et al.* involves the use of a combination of sodium borohydride and cobalt (II) to reduce a nitrile function, which is inert to

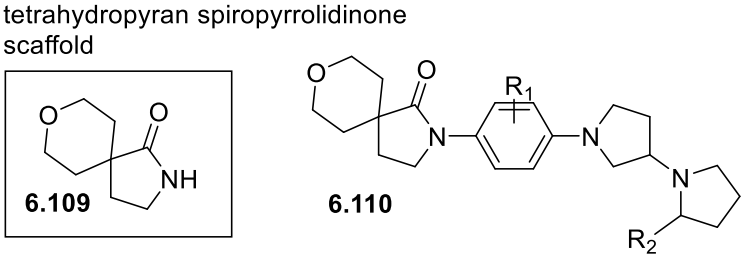
$NaBH_4$ alone. Finally, our methodology allows introducing three different functions in the structure of the spiro-piperidine, via variation of the nature of the co-acid ($R_2$), the amide protecting group ($R_1$), and the secondary amine protecting group ($R_3$) (see Scheme **163**). Moreover, the scope of the nature of those substituents is broad given that our electrolysis conditions are compatible with a large variety of functional groups. Therefore, our methodology seems promising for drug discovery since small changes, within the structure of 2,8-diazaspiro[4.5]decan-1-one scaffold, have a huge impact on the biological properties of those compounds.




**Scheme 163 electrosynthesis of spiro 2-pyrrolinones 6.93**

### 6.2.5 8-oxo-2-azaspiro[4.5]decan-1-one

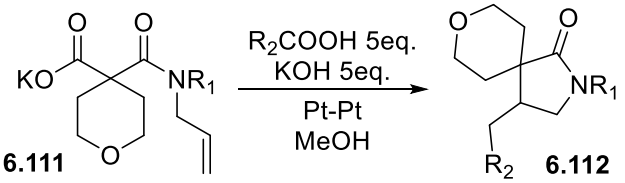
We continued our investigation by developing an electrochemical synthesis of substituted tetrahydropyran spiro 2-pyrrolidinones **6.109**. In the literature, it is illustrated that those moieties have promising biological activities. For instance, the family of molecules **6.110** is known to be useful pharmaceutical agents, as those compounds can have a benefic impact on diseases associated with the central nervous system.[193] Actually, those active substances are modulators of histamine $H_3$ receptors in the central nervous system. Those receptors inhibit the release and synthesis of the histamine neurotransmitter, which has an action on various biological processes, such as: sleep-wake regulation and gastric release, *etc*. For these reasons, 8-oxo-2-azaspiro[4.5]decan-1-one moieties seem to be an attractive target for our methodology.




**Scheme 164 tetrahydropyran spiro-pyrrolidinone scaffold 6.109 and family of molecules 6.110**

In order to develop an electrochemical synthesis of diversely functionalized tetrahydropyran spiro-pyrrolidinones, the cyclic substrate **6.111** has to be formed and electrolyzed in our optimized electrolysis conditions (see Scheme **165**). In the following subsection, a synthesis of tetrahydropyran spiro-pyrrolidinone is presented in order to compare this procedure with our brand new methodology.

[193] Gao, Z.; Hartung, R.; Stefany, D. US8217052B2 **2009**



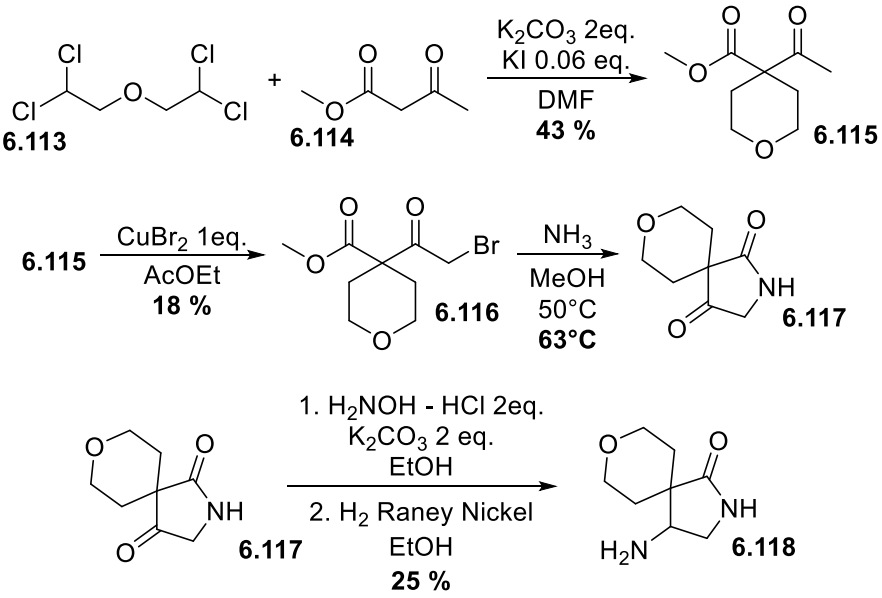

**Scheme 165 electrosynthesis of tetrahydropyran spiro 2-pyrrolidinones 6.112**

*6.2.5.1 State of the art of tetrahydropyran spiro 2-pyrrolidinones synthesis*

*6.2.5.1.1 Synthesis of tetrahydropyran spiro 2-pyrrolidinone via a selective bromination followed by an amination and a final 5-exo-trig cyclization*

In 2013, Steeneck *et al.* patented a synthesis of tetrahydropyran spiro 2-pyrrolidinone via a selective bromination, followed by an amination, and a final 5-exo-trig cyclization, in four steps and a global yield of 1 % (see Scheme **166**).[194] This procedure began with the alkylation of methyl 3-oxobutanoate **6.114** using 2,2-dichloroethyl ether **6.113** and potassium iodide, as a nucleophilic catalyst. The formed tetrahydropyran **6.115** was then selectively brominated with copper (II) bromide, which resulted in the formation of the α-bromo-ketone **6.116**. This latter was then treated with ammonia in methanol, which led to the formation of a primary amine and a subsequent *5-exo-trig* cyclization process. Finally, Hydroxylamine reacted with the ketone **6.117** producing an oxime species; and the ketoxime was subsequently reduced in the tetrahydropyran spiro 2-pyrrolidinone **6.118**.

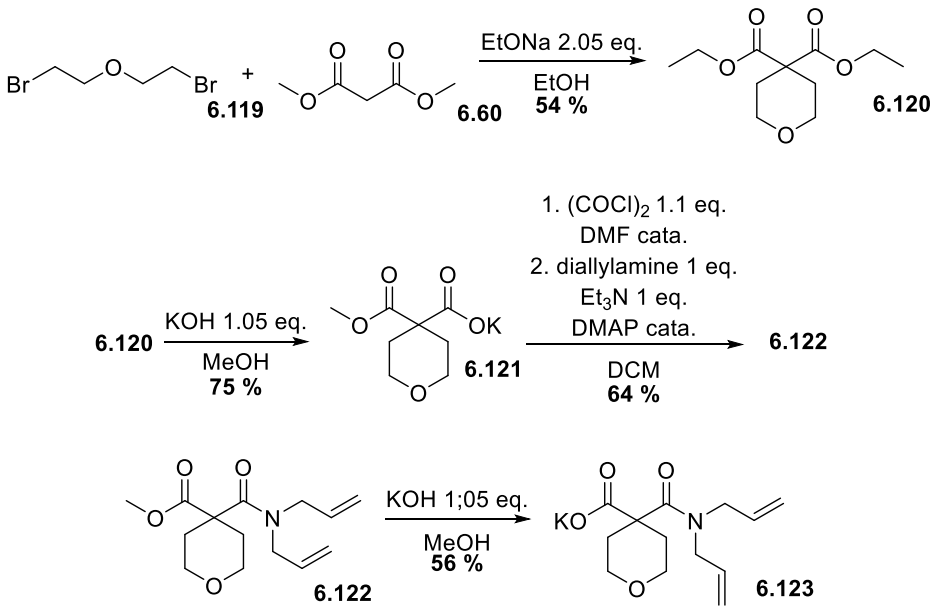
[194] Steeneck, C.; Kinzel, O.; Gege, C.; Kleymann, G.; Hoffmann, T. PCT Int. Appl. (2013), WO 2013079223 A1 June 06, 2018.




**Scheme 166 Synthesis of tetrahydropyran spiro 2-pyrrolidinone 6.118 via a selective bromination followed by an amination and a final 5-exo-trig cyclization**

### *6.2.5.2 Synthesis of the electro-spiro-cyclization substrate **6.123***

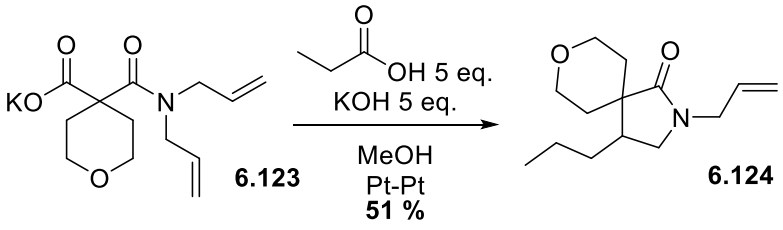
In order to design the electro-spiro-cyclization substrate **6.123**, dimethyl malonate **6.60** was substituted with the bis(2-bromoethyl)ether **6.119** to form the malonate substituted with a tetrahydropyran **6.120** (see Scheme **167**). This latter was then converted into the corresponding potassic salt **6.121**. Subsequently, this salt was coupled with diallylamine to generate the amide **6.122**. Finally, this molecule **6.122** was hydrolyzed into the corresponding potassic salt **6.123**, which is the electro-spiro-cyclization substrate.




**Scheme 167 synthesis of the electro-spiro-cyclization substrate 6.123**

### *6.2.5.3 Electrolysis of the electro-spiro-cyclization substrate **6.123***

The substrate **6.123** was electrochemically spiro-cyclized to generate the tetrahydropyran spiro 2-pyrrolidinones **6.124** in excellent yields (see Scheme **168**). This methodology is based on a straightforward addition of a carbon radical on a double bond, which leads to the formation of a quaternary center typical of the spirocyclic compounds.



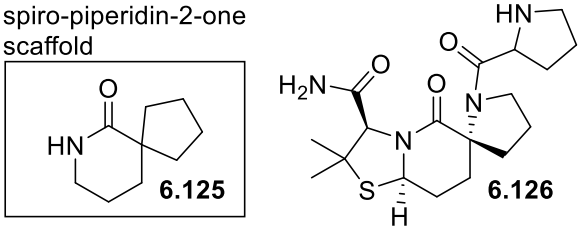

**Scheme 168 electro spiro cyclization of the substrate 6.123**

In comparison with the tetrahydropyran spiro 2-pyrrolidinone synthesis of Steeneck *et al.* with a global yield of 1 % (see section 6.2.5.1.1.), our methodology seems more efficient with a global yield of 8 %. Moreover, our procedure does not require the use of inflammable and toxic ammonia.

## 6.2.6 7-azaspiro[4.5]decan-6-one

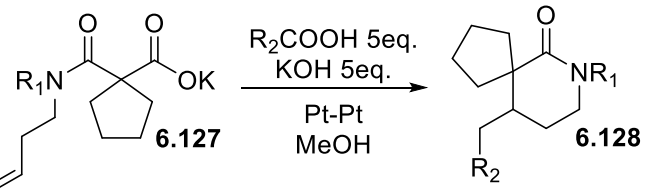
Given the outstanding results of the spiro γ-lactams electrosynthesis study, we focused our research on the electrogeneration of spiro δ-lactam scaffold. Based on our knowledge on the electrosynthesis of spiro 5-membered rings, we envisioned to design spiro 6-membered rings using our Kolbe based electro-spiro-cyclization

methodology (see Scheme **170**). Actually, the spiro-piperidin-2-one **6.125** is a unique scaffold found in many natural products and showing considerable potential in drug discovery.[195] For example the spiro scaffold **6.126** is a negative allosteric modulator of dopamine D2 receptor.[196] This compound shows promising biological activities as several important diseases of the central nervous system are associated with dysfunctions of the dopamine system, such as Parkinson's disease and schizophrenia. For these reasons, the spiro-piperidin-2-one scaffold seems to be an attractive target for our electro-spiro-cyclization methodology.




**Scheme 169 spiro-piperidin-2-one scaffold 6.125 and molecule 6.126**

In order to develop the electrosynthesis of functionalized 7-azaspiro[4.5]decan-6-ones **6.128**, a cyclic substrate bearing a homoallyl function **6.127** has to be produced and electrolyzed in our optimized electrolysis conditions.

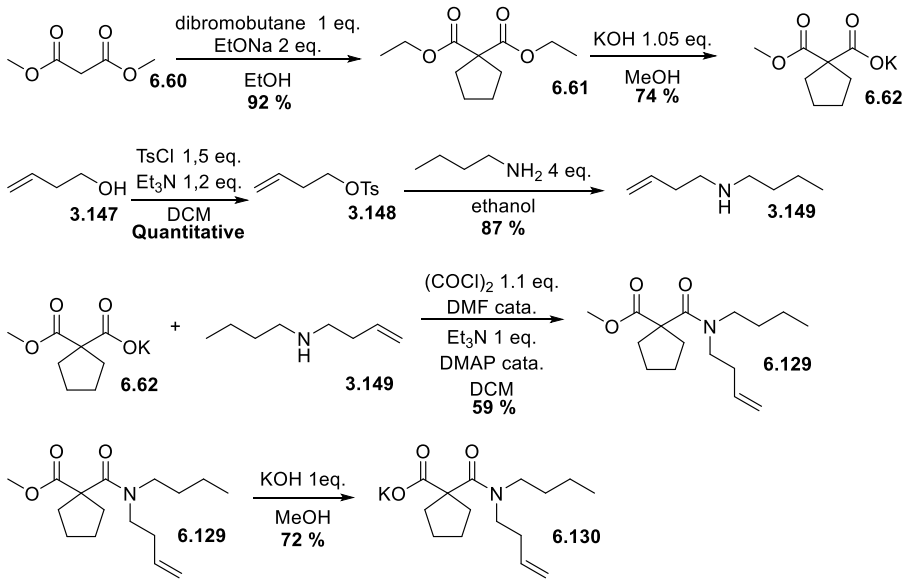



**Scheme 170 electrosynthesis of functionalized spiro-piperidin-2-ones 6.128**

*6.2.6.1 Synthesis of the electro-spiro-cyclization substrate 6.130*

In order to form electrochemically spiro δ-lactams, our strategy was to design a substrate bearing a homoallyl function contrary to our usual spiro γ-lactam substrates, which contain an allyl function (see Scheme **171**). To this end, the easily accessible starting material dimethyl malonate **6.60** was first functionalized with a cyclopentane moiety. Subsequently the cyclic malonate formed **6.61** was treated in basic conditions to generate the potassic salt **6.62**. In parallel, the homoallyl alcohol **3.147** was converted into the corresponding tosylate **3.148**, and then transformed into the secondary amine **3.149**. Afterwards, the secondary amine **3.149** and the potassic salt **6.62** were coupled to lead to the formation of the amine **6.129**. Finally, this latter was hydrolyzed to produce the electro-spiro-cyclization substrate **6.130**.

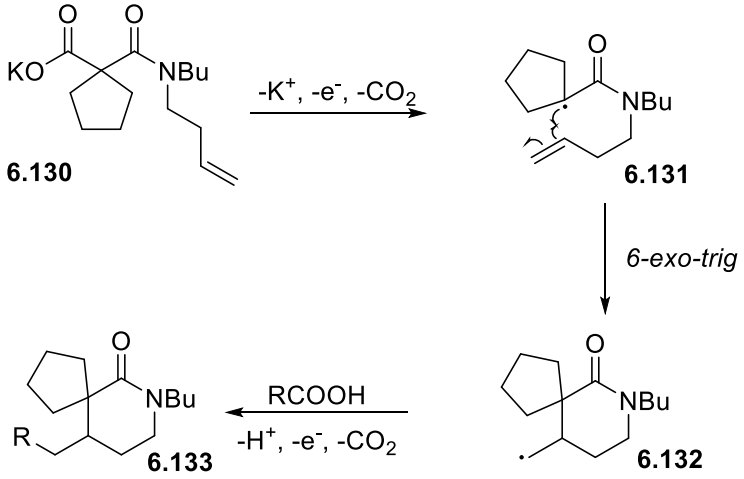
[195] Zhang, K.; Meazza, M.; Docekal, V.; Light, M.E.; Vesely, J.; Rios, R. *Eur. J. Org. Chem.* **2017**, 13, 1.
[196] Bhagwanth, S.; Mishro, S.; Daya, R.; Mah, J.; Mishro, R.K. *Chem. Neurosci.* **2012**, 3, 274.




**Scheme 171 synthesis of the electro-spiro-cyclization substrate 6.130**

*6.2.6.2 Expected spiro-cyclization mechanism*

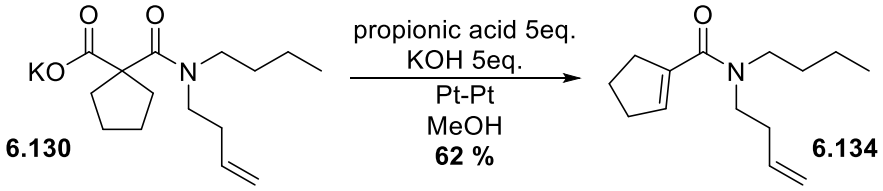
The expected mechanism of the electro-spiro-cyclization is the following. First, the reagent **6.130** should be oxidatively decarboxylated to form the linear radical **6.131**. Subsequently, the radical **6.131** should perform an intramolecular *6-exo-trig* cyclization, which should lead to the formation of the six-membered ring radical **6.132**. Finally, a cross-coupling mechanism should take place to generate the functionalized spiro δ-lactam **6.133**. This reaction has the advantage to promote the formation of two new bonds in only one step.




**Scheme 172 expected mechanism of the electro-spiro-cyclization of the substrate 6.130**

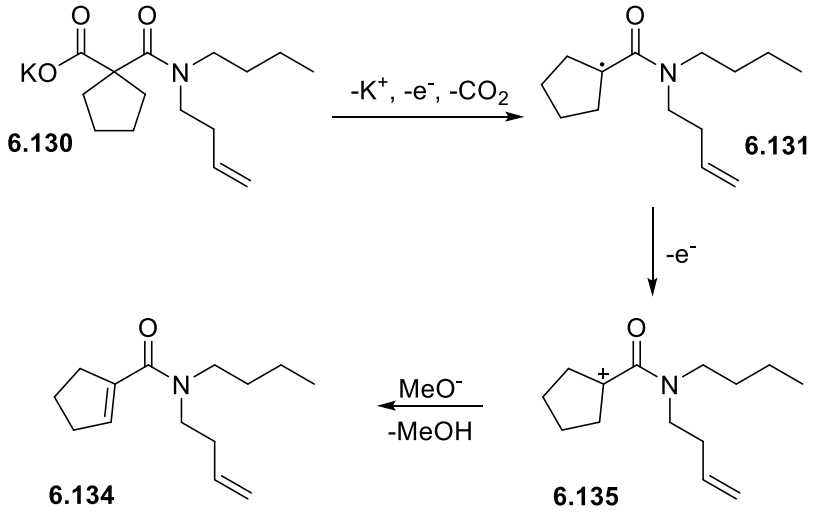
### *6.2.6.3 Electrolysis of the substrate **6.130***

Once the electro-spiro-cyclization reagent **6.130** synthetized, the electrolysis of this latter was performed in our optimized conditions of electrocyclization, using propionic acid as co-acid (see Scheme **173**). Unfortunately, the desired product was not formed; and the cyclopentene substance **6.134** was predominantly produced in good yield.




**Scheme 173 electrolysis of the substrate 6.130**

Our hypothesis to explain this phenomenon is that the *6-exo-trig* cyclization of the radical **6.131** is slower than the oxidation of this radical **6.131**, which is kinetically favored. As those two processes are irreversible, the oxidation is accomplished and the side-product **6.134** is predominantly formed. However as the *6-exo-trig* cyclization is known to proceed at a lower speed compared to the *5-exo-trig* cyclization, the spiro cyclization of spiro γ-lactams is achieved but not the spiro cyclization of spiro δ-lactams. This study sets a limit on our methodology, which can be applied to the formation of many functionalized spiro γ-lactams but not to the production of spiro δ-lactams.

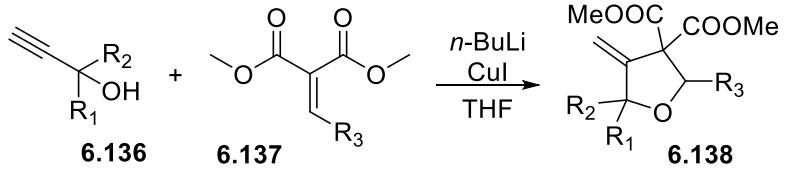



**Scheme 174 mechanism of the electrolysis of the substrate 6.130**

## 6.2.7 Knoevenagel reaction and copper catalysis applied to the synthesis of original cyclic reagents for the electro spiro cyclization of complex spiro-2-pyrrolidinones

Copper is a versatile and inexpensive transition metal that has been utilized as a building material by civilizations for over 6000 years. Nevertheless, it is only since

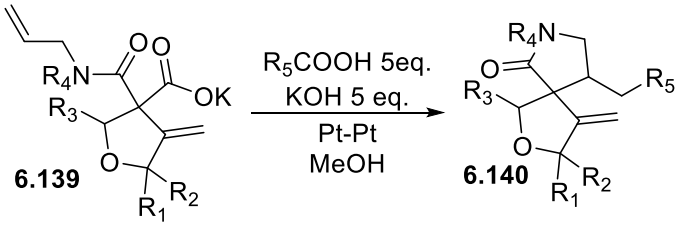
1988, that the huge potential of copper in catalysis has been increasingly studied.[197] Actually, the copper catalysis appears as an attractive method for the synthesis of original small heterocycles, which is of great interest for the pharmaceutical industry. For instance, a large library of tetrahydrofurans can be synthetized via copper catalysis using propargyl alcohols **6.136** and alkylidene-malonates **6.137** (see Scheme **175**).[198] This reaction is catalyzed by copper iodide, which is removed, at the end of the reaction, via simple filtration, to yield the desired heterocycle **6.138** in high yield and excellent purity.




**6.136** **6.137** **6.138**

**Scheme 175 synthesis of diversely functionalized tetrahydrofurans 6.138 via copper catalysis**

This procedure appears as a straightforward and inexpensive way to construct a library of original heterocyclic substrates **6.139** for our electro-spiro-cyclization of 2-pyrrolidinones methodology. Indeed, the copper iodide catalyst is inexpensive and easily removed after reaction. Moreover, this reaction is performed in mild conditions and is widely exemplified in the scientific literature. Finally, the Michael acceptor reagent is readily accessible via classical Knoevenagel reaction.[199] Specifically, in order to synthetize an original heterocyclic substrate of electro-spiro-cyclization, a copper catalyzed cyclization will be applied to an α,β-unsaturated reagent. The heterocyclic compound obtained will subsequently be converted into the electro-spiro-cyclization reagent **6.139** with the aim to form the original spiro 2-pyrrolidinone moiety **6.140**. According to this strategy, the combination of the copper catalysis, the century-old Knoevenagel reaction, and our electroorganic methodology appears as a promising and straightforward synthetic road for the formation of original spiro-2-pyrrolidinones.




**6.139** **6.140**

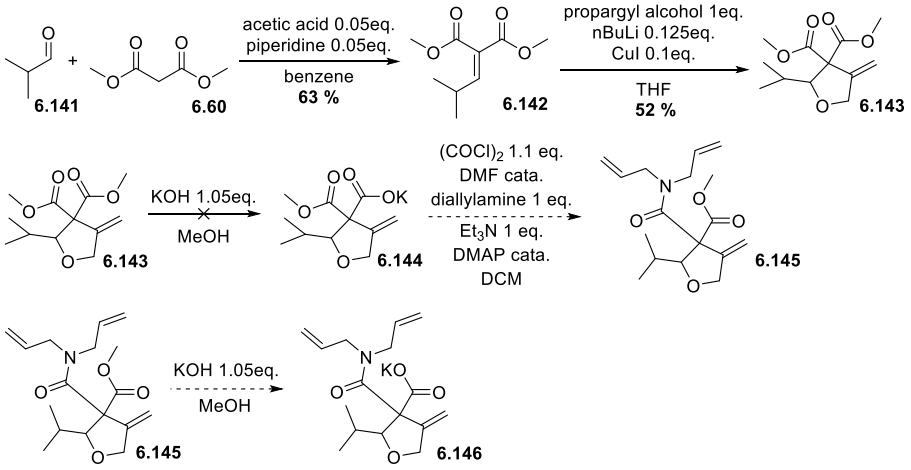
**Scheme 176 electrolysis of the substrate 6.139 synthetized via copper catalysis**

### *6.2.7.1 Synthesis of the electrocyclization substrate **6.146***

In order to design the electrocyclization substrate **6.146**, the following procedure was performed. First, dimethyl malonate **6.60** was converted into the corresponding enol intermediate. In this Knoevenagel reaction, the piperidine acts as organocatalyst and reacts with isobutyraldehyde **6.141** to from the corresponding iminium

[197] Chemler, S.R. *Beilstein J. Org. Chem.* **2015**, 11, 2252.
[198] Cavicchioli, M.; Marat, X.; Monteiro, N.; Hartmann, B.; Balme, G. *Tetrahedron Letters* **2002**, 43, 2609.
[199] Knoevenagel, E. *Berichte der deutschen chemischen Gesellschaft* **1898**, 31, 2596.

intermediate. Subsequently, the enol reacted with the iminium intermediate acceptor and a consecutive base-induced elimination occurred to yield α,β-unsaturated compound **6.142**. This latter consecutively underwent a copper catalyzed cyclization to give the heterocyclic compound **6.143**. Afterwards, the cyclic diester **6.143** was treated in basic conditions. Unfortunately, the desired molecule **6.144** was not obtained and a mixture of side-products was generated. This last reaction was performed several times with the same result. For that reason, this synthetic road was abandoned. In the following subsections, others original synthetic roads for the formation of spirocyclic 2-pyrrolidinones are studied.



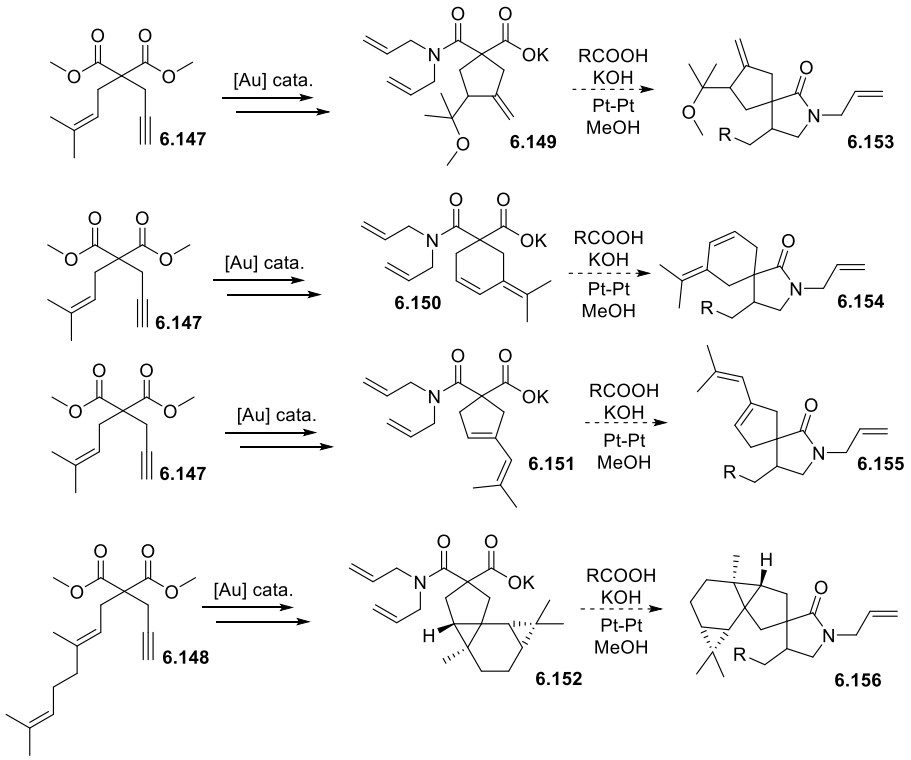

**Scheme 177 electrocyclization substrate 6.146 synthesis**

## 6.2.8 Gold catalysis applied to the synthesis of cyclic substrates for the electro spiro cyclization of complex spiro-2-pyrrolidinones

For centuries, gold has been considered as a precious, purely decorative, inert metal.[200] It was not until the eighties that the gold potential in homogeneous catalysis was discovered. For example, the gold catalyzed cyclizations of enynes are ideal procedures to design complex cyclic skeletons, under mild conditions and in short reaction times.[201] Indeed, gold is a soft transition metal that shows a strong electrophilic affinity for alkynes. Therefore, gold catalyzed cyclization reactions involve the activation of an alkyne by gold (I) followed by an attack of a pendant nucleophile, which leads to the creation of original cycles and polycycles.[202] For that reason, we have envisioned applying those reactions to the synthesis of complex cyclic and polycyclic reagents **6.149**, **6.150**, **6.151**, and **6.152** for the electro spiro cyclization of complex spiro 2-pyrrolidinones (see Scheme **178**). First, the cyclic substrates **6.153**, **6.154**, **6.155**, and **6.156** will be designed via gold catalysis. Subsequently, in a second step, the electrolysis of those substrates will be performed, under our optimized reaction conditions, to construct complex spiro

[200] Dorel, R.; Echavarren, A.M.; *Chem. Rev.* **2015**, 115, 9028.
[201] Ma, S.; Yu, S.; Gu, Z. *Angew. Chem. Int. Ed.* **2006**, 45, 200.
[202] Nieto-Oberhuber, C.; Paz Munoz, M.; Bunuel, E.; Nevado, C.; Cardenas, D.J.; Echavarren, A.M. *Angew. Chem. Int. Ed.* **2004**, 43, 2402.

molecular architectures via electrochemistry (Scheme **178**). In this study, the gold (I) catalyst, which will be used, is the [bis(trifluoromethanesulfonyl)imidate](PPh$_3$)gold(I) (2:1) toluene adduct. This latter was chosen for its robustness and good reactivity, due to the bistriflimide counteranion.




**Scheme 178 gold catalyzed synthesis of electro-spiro-cyclization substrates 6.149, 6.150, 6.151, and 6.152 and electrocyclization of those substrates**

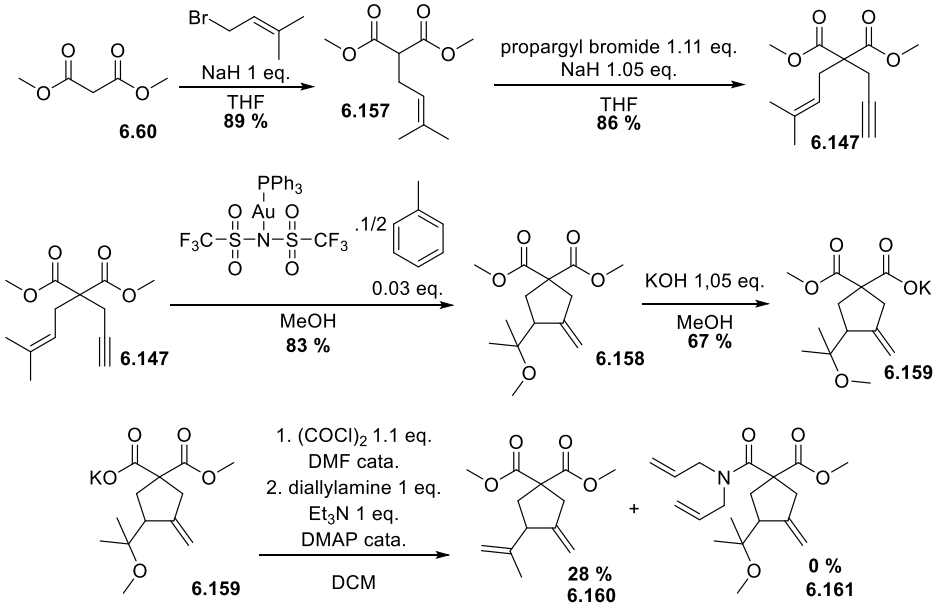
### *6.2.8.1 Spiro 2-pyrrolidinone **6.153***

*6.2.8.1.1 Substrate **6.149** synthesis*

In order to broaden the field of substrate of our electro-spiro-cyclization methodology, we attempted to synthetize the electrocyclization substrate **6.149** via a gold catalyzed cyclization of enyne (see Scheme **178**). First, dimethyl malonate **6.60** was functionalized using 3,3-dimethylallyl bromide. The mono-functionalized malonate **6.157** formed was then propargylated by means of propargyl bromide. The enyne **6.147** assembled was subsequently cyclized via gold catalysis to generate the cyclic malonate **6.158**.[203] The mechanism of this step is discussed in the following paragraph. Afterwards, this product was converted into the corresponding potassic salt **6.159**. Unfortunately, the treatment of the product **6.159** with oxalyl chloride and diallylamine did not lead to the formation of the expected amide **6.161**, which

[203] Nieto-Oberhuber, C.; Munozn M.P.; Lopez, S.; Jimenez-Nunez, E.; Nevado, C.; Herrero-Gomez, E.; Raducan, M.; Echavarren, A.M. *Eur. Chem. J.* **2006**, 12, 1677.

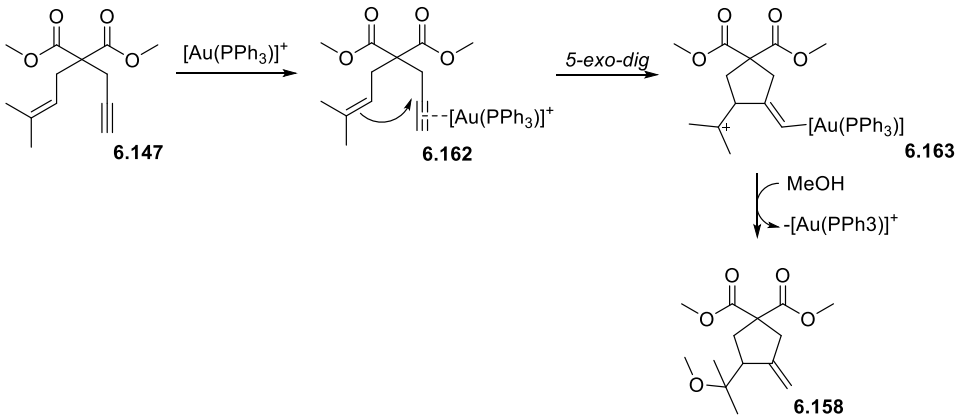
could have been converted, in only one step, into the electro spiro cyclization reagent **6.149**. Instead, the cyclic dimethyl malonate **6.160** was formed via an initial elimination of a methoxy group, which liberated a methanolate, nucleophile, which finally attacked the acyl chloride to yield this diester compound. Given that this synthesis did not lead to the formation of the desired product **6.149**, the formation of this target substrate **6.149** was abandoned in favor of the synthesis of the electro spiro cyclization substrates **6.150** and **6.151**, which can be synthetized from the enyne **6.147** formed in this first synthesis attempt.




**Scheme 179 attempt to the synthesis of the substrate 6.149**

#### 6.2.8.1.1.1 Mechanism of the gold catalyzed enyne 6.147 cyclization to form the cyclic compound 6.149

The gold cyclization of enyne **6.147** begins with the coordination of the gold catalyst to the alkyne function, which forms an alkyne metal complex. This process increases the electrophilicity of the unsaturated group and leads to a Markovnikov-type addition of the alkene nucleophile, affording a vinyl gold species **6.163** via a *5-exo-dig* cyclization reaction. Finally, as the methanol solvent is a nucleophilic species, the tertiary carbocation **6.163** is trapped with methanol, which promotes the formation of the alkoxycyclization product **6.158**.



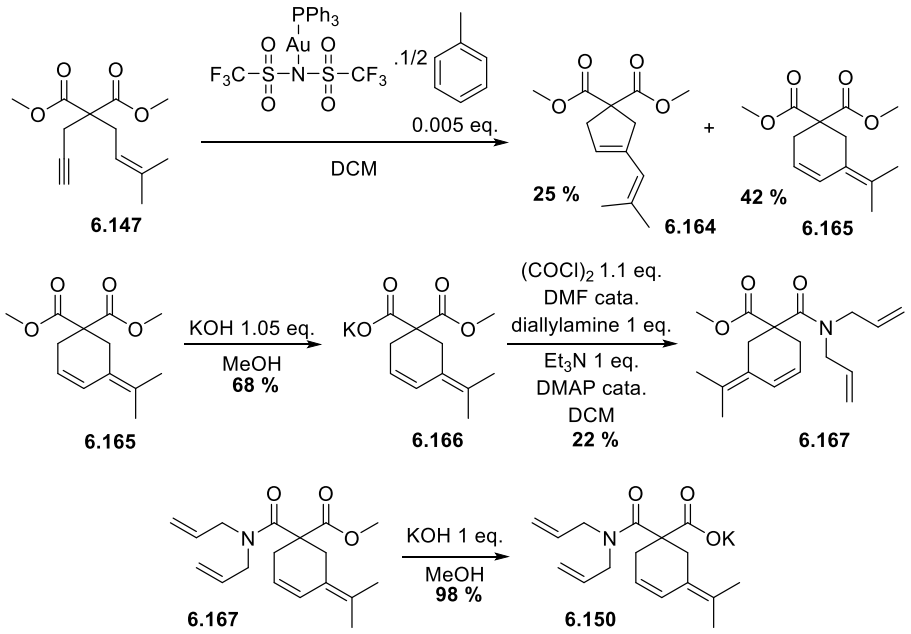

**Scheme 180 mechanism of the gold catalyzed enyne 6.147 cyclization to form the cyclic compound 6.158**

### *6.2.8.2 Spiro 2-pyrrolidinone **6.154***

*6.2.8.2.1 Substrate **6.150** synthesis*

In order to produce the electrocyclization reagent **6.150**, the enyne **6.147,** of which the synthesis was preliminarily discussed, was placed under conditions find in the literature (see Scheme **181**).[204] Those conditions should promote the formation of the six-membered ring compound **6.165**. Nevertheless, the five-membered ring compound **6.164** was also formed. The mechanisms of those catalytic cyclization processes are discussed in the next subsection. Subsequently, the cyclic compound **6.165** was hydrolyzed to form the potassic salt **6.166**, which was then converted into the amide **6.167** via an oxalyl chloride treatment. Finally, the amide ester **6.167** was hydrolyzed which enabled the production of the substrate **6.150** in excellent yield.

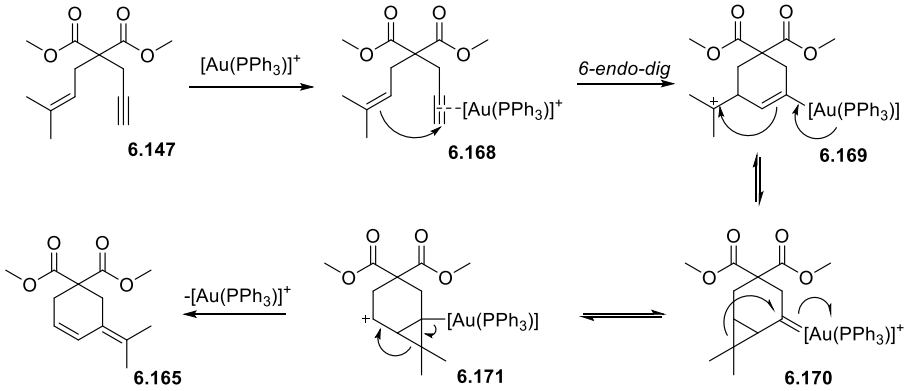
[204] Ma, S.; Yu, S.; Gu, Z.; *Angew. Chem. Int. Ed.* **2006**, 45, 200.




**Scheme 181 Substrate 6.150 synthesis**

#### 6.2.8.2.1.1 Mechanism of the gold catalyzed enyne 6.147 cyclization to form the cyclic compounds 6.164 and 6.165

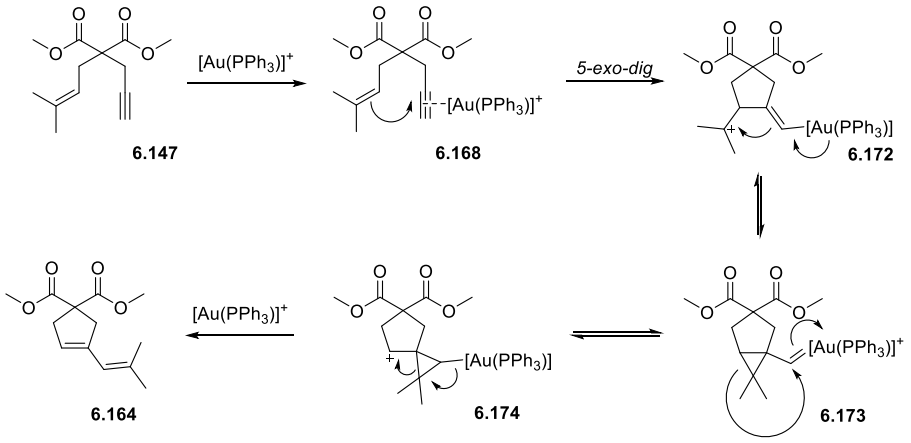
The six-membered ring species **6.165** synthesis begins with the Lewis acid activation of the alkyne bond, which results in a *6-endo-dig* cyclization leading to the formation of the cyclic species **6.169**. Finally, several skeletal rearrangements promote the formation of the 6-membered ring **6.165**.




**Scheme 182 *6-endo-dig* skeletal rearrangement mechanism**

In the case of the formation of the five-membered ring compound **6.164**, the mechanism starts with the same steps as the previous mechanism (Scheme **183**). Nevertheless, the *6-endo-dig* cyclization does not take place. In contrast, a *5-exo-dig* cyclization occurs. Subsequently, several skeletal rearrangements proceed, via the metal cyclopropyl carbene complex **6.173**, to form the conjugated diene **6.164**. The formation of the two cyclization products **6.164** and **6.165** reveals that this

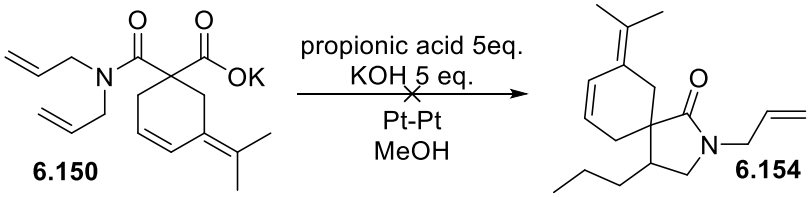
cycloisomerization reaction is not really selective. Nevertheless, the second product form is not useless and can be used to form the electro-spiro-cyclization substrate **6.151**.




**Scheme 183 *5-exo-dig* skeletal rearrangement mechanism**

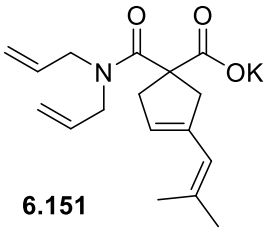
***6.2.8.2.2****Electrolysis of the substrate **6.150***

With the electrocyclization substrate **6.150** in hand, the electrolysis of this reagent was conducted in our optimized reaction conditions (see Scheme **184**). Unfortunately, the expected product **6.154** was not isolated and a mixture of side-products was formed. Moreover, the structures and retention times of those side-products were too similar. Therefore, these impurities could not be isolated for further structure analyses, via silica gel chromatography. The hypothesis explaining this phenomenon is based on the fact that the presence of four double bonds and a carbonyl function, in the structure of the substrate, promotes radical side-reactions leading to the generation of a complex mixture of impurities.




**Scheme 184 electrolysis of the substrate 6.150**

Since the structure of the substrate **6.151** also contains four double bonds, the electrolysis study of this molecule was abandoned because of the apprehension of the formation of a great number of side products. Instead, in the next subsection, the original electrolysis of a tetracyclic reagent into a pentacyclic spiro 2-pyrrolidinone is discussed.




**6.151**

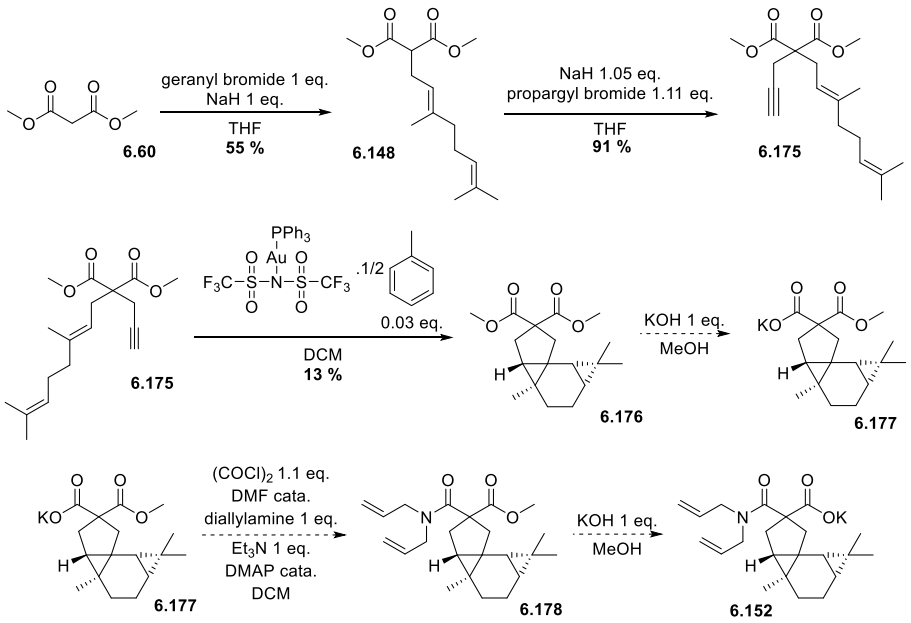
**Scheme 185 substrate 6.151**

*6.2.8.3 Spiro 2-pyrrolidinone **6.156***

*6.2.8.3.1 Substrate **6.152** synthesis*

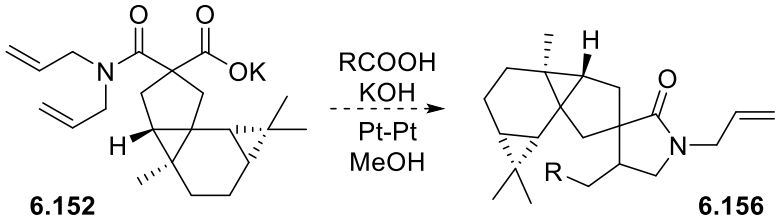
In order to design electrochemically an original pentacyclic spiro 2-pyrrolidinone **6.156**, we attempted to design the tetracyclic electrocyclization substrate **6.152** (see Scheme **186**).[205] This synthesis path began with the functionalization of the dimethyl malonate **6.60** with geranyl bromide. Subsequently, the mono-substituted malonate **6.148** was substituted a second time to generate the di-substituted propargylic malonate **6.175**. This latter was then treated with a gold (I) catalyst. The gold (I) complex selectively activated the $\pi$-bond of the alkyne in the complex molecular structure of the substrate **6.175**, which led to the formation of the tetracyclic dimethyl malonate **6.176** in very low yields and many side-products. Due to time limitations and the necessity of optimizing the gold catalyzed tetracyclization step, this synthesis was abandoned.

[205] Nieto-Oberhuben, C.; Lopez, S.; Munoz, M.P.; Jiménez-Nunez, E.; Bunuel, E.; Cardenas, D.J.; Echavarren, A. *Chem. Eur. J.* **2006**, 12, 1694.




**Scheme 186 substrate 6.152 synthesis**

In future researches, it could be interesting to end the synthesis of the tetracyclic substrate **6.152** and study the electrochemical formation of functionalized pentacyclic-spiro-pyrrolidinones **6.156**. In conclusion, the combination of organogold chemistry and organic electrochemistry is a promising tool for the construction of complex and original architectures under mild conditions.

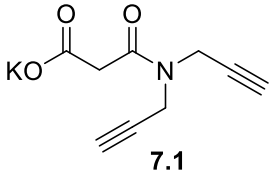



**Scheme 187 electrolysis of the substrate 6.152**

# 7 Pyrrolones and 2-pyrrolidinones featuring an exocyclic alkene electrocyclization

## 7.1 Propargylic substrate **7.1**

In order to expand the scope of application of our new methodology, it was decided to apply our electrocyclization conditions to a propargylic substrate **7.1**. Our interest in this investigation relies on the fact that the addition of an alkyl radical on an alkyne function is a highly favored process, even if the starting radical **7.6** is more stable than the vinyl radical **7.7** formed (see Scheme **188**).

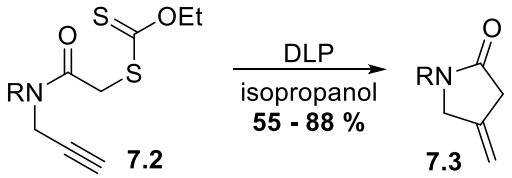



**7.1**

**Scheme 188 propargylic electrocyclization substrate 7.1**

### 7.1.1 Radical cyclizations onto alkyne functions

The radical cyclizations via addition of an alkyl radical on an alkyne function represent an important difference between radical, cationic, and anionic cyclizations. Actually, compared to cyclizations, which proceed at the expense of single or double bond, cyclizations of alkynes remain rather underrepresented. This may be in part due to the fact that it is simpler to manipulate the reactivity of alkenes via substitution. Indeed, alkynes clearly cannot bear the same number of substituents as alkenes. Therefore, few examples of radical cyclization via addition on an alkyne function can be found in the literature, such as: a xanthate-based radical cyclization onto alkynes leading to the formation of β,γ-unsaturated pyrrolidinones (see Scheme **189**).[206] An additional example is the treatment of bromoamides with $Bu_3SnH$ and AIBN resulting in an efficient *5-exo-dig* radical cyclization to 4-methylenepyrrolidinone **7.5** (see Scheme **190**).[207] For those reasons, the electrocyclization via alkyl radical addition on alkyne appears as an appealing and intriguing research topic.




**7.2** **7.3**

**Scheme 189 xanthate-based radical cyclization onto alkynes**

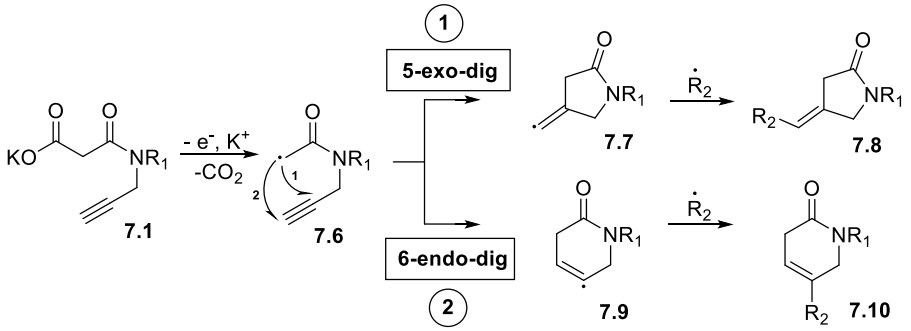
[206] (a) Kaim, L.E.; Grimaud, L.; Miranda, L.D.; Vieu, E.; Caho-Herrera, M.A.; Perez-Labrada, K. *Chem. Commun.* **2010**, 46, 2489 ; (b) Quiclet-Sire, B.; Zard, S. Z. *Proc. R. Soc.* **2017**, 473, 2200.

[207] (a) Pattenden, G.; Rescourio, G. *Org. Biomol. Chem.* **2008**, 6, 3428; (b) Clough, J.M.; Pattenden, G.; Wight, P.G. *Tetrahedron Letters* **1989**, 30, 469.


**Scheme 190 radical cyclization of propargyl bromoamide**

### 7.1.2 Expected cyclization mechanism of the propargylic substrate **7.1**

Under electrochemical conditions, the propargylic substrate **7.1** should be oxidatively decarboxylated to form the primary radical **7.6**. According to the Baldwin's rules, this linear radical **7.6** could perform two types of cyclizations. Actually, the *5-exo-dig* and the *6-endo-dig* cyclizations are allowed by the Baldwin's rules (see Scheme **191**).[208] Therefore, the electrolysis of the substrate **7.1** could lead to the formation of two products via electrocyclization followed by a cross-coupling in the presence of a co-acid. Specifically, a 2-pyrrolidinone featuring an exocyclic alkene **7.8** and piperidine-2-one bearing an endocyclic double bond **7.10** could be generated.

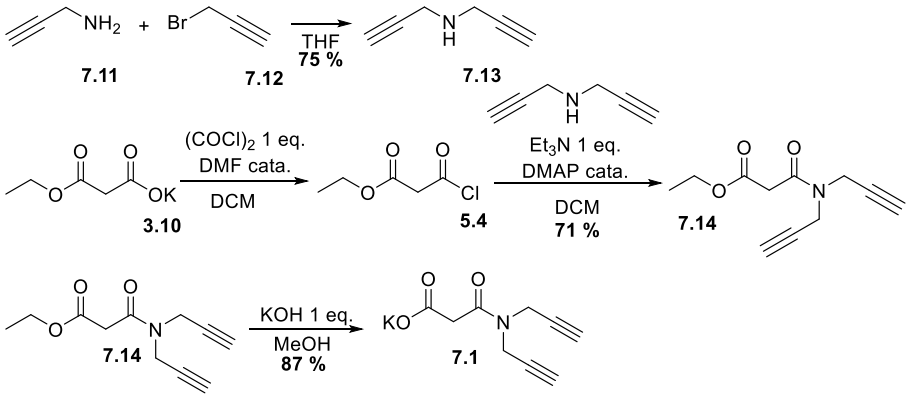



**Scheme 191 expected cyclization mechanism**

## 7.2 Synthesis of the propargylic substrate **7.1** of electrocyclization

In order to study the electrolysis of propargylic reagents, the substrate **7.1** was synthetized, in three steps, according to the following procedure (see Scheme **192**). First, the dipropargylamine **7.13** was prepared using propargyl bromide **7.12** and an excess of propargylamine **7.11**. Subsequently, the amide **7.14** was formed via coupling between dipropargylamine **7.13** and ethyl potassium malonate **3.10**. Finally, the amide ester **7.14** was hydrolyzed in basic conditions to yield the electrolysis substrate **7.1**.

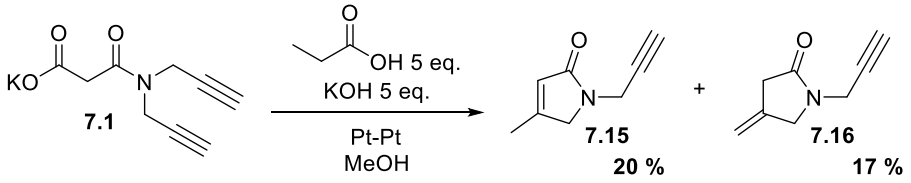
[208] Gilmore, K.; Alabugin, I.; *Chem. Rev.* **2011**, 111, 6513.




**Scheme 192 synthesis of the electrocyclization substrate 7.1**

## 7.3 Electrolysis of the propargylic substrate **7.1**

With the desired electrocyclization substrate 7.1 in hand, the electrolysis of that propargylic reagent **7.1** was performed under our usual electrolysis conditions (see Scheme **193**). Specifically, the substrate concentration was 66 mM, the current density was 22 mA/cm² and the reaction time was four hours. The reaction was performed, at 10°C, in methanol and with 5 eq. of propionic acid (co-acid) and 5 eq. of KOH (electrolyte salt). Surprisingly, two unexpected products were obtained: pyrrolone **7.15** and β,γ-unsaturated 2-pyrrolidinone **7.16**. Finally, the co-acid did not take place in the reaction, and thus no cross-coupling, leading to functionalization, was performed.

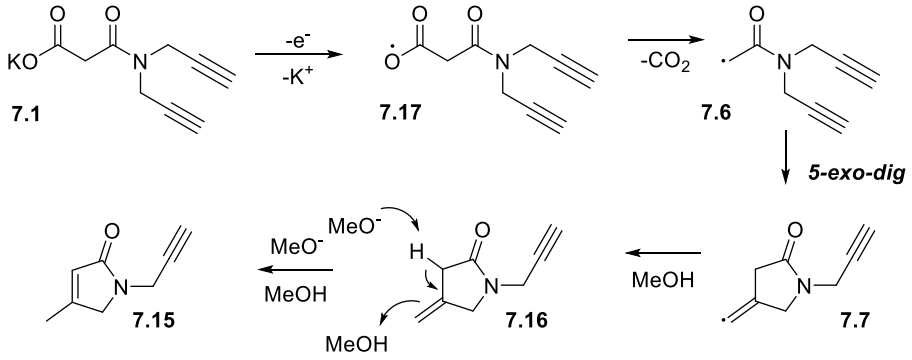



**Scheme 193 electrolysis of the substrate 7.1**

## 7.4 Mechanistic hypotheses of electrosynthesis of pyrrolone **7.15** and β,γ-unsaturated 2-pyrrolidinone **7.16**

In order to gain clearer understanding of the electrosynthesis of pyrrolone **7.15** and β,γ-unsaturated 2-pyrrolidinone **7.16**, the following mechanistic hypotheses were postulated. First, the substrate should be converted into the corresponding carboxylate, which should then be adsorbed, at the surface of the anode, and oxydated into the corresponding acyloxy radical **7.17**. This intermediate **7.17** is highly unstable and should instantly decarboxylate to generate the linear carbon radical **7.6**. Subsequently, the linear radical **7.6** should intramolecularly cyclize, via addition on an alkyne function, to form the cyclic vinyl radical **7.7**. This latter should then abstract a radical hydrogen from the solvent to generate the β,γ-unsaturated 2-pyrrolidione **7.16**. The 2-pyrrolininone bearing an exocyclic alkene is not stable in basic or acidic conditions and should be converted into the pyrrolone **7.15**, under the action of methanolate, which should be formed via reduction of the

solvent at the cathode. The pyrrolone **7.15** is more stable than the β,γ-unsaturated 2-pyrrolidinone **7.16**, because this molecule **7.15** is stabilized via resonance.



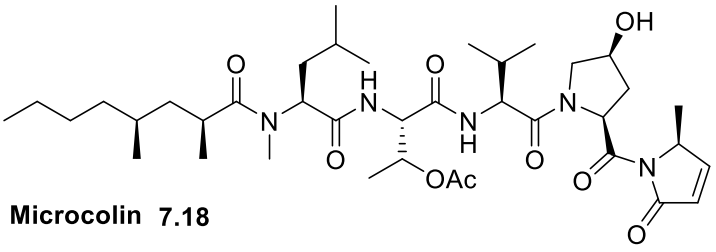

**Scheme 194 Mechanistic hypotheses of electrosynthesis of pyrrolone 7.15 and β,γ-unsaturated 2-pyrrolidinone 7.16**

Firstly, given that this reaction leads to the formation of two interesting products, the establishment of strategies to improve the selectivity of that reaction was a key part of our work, during further research explorations. Secondly, regarding the modest yields obtained during this electrolysis reaction; an optimization study was carried out to ensure the optimum results. Finally, we found that the co-acid did not take place in this mechanism, and thus no cross-coupling was observed. Therefore, other strategies must be established to ensure a varied functionalization of the products.

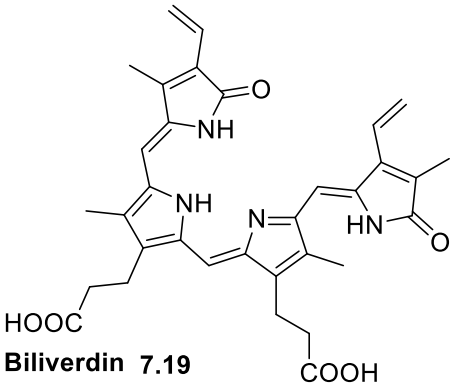
## 7.5 Pyrrolones

The electrocyclization of the propargylic substrate **7.1** led to the formation of a pyrrolone moiety **7.15** (see Scheme **193**). This is a relevant result and deeper investigations were conducted because those molecules have interesting properties and are organic synthesis targets. Specifically, pyrrolones are five-membered heterocyclic lactams and are also known as pyrrolin-2-ones and α,β-unsaturated γ-butyrolactams. This scaffold exists as a structural unit in many biologically active natural products. For example, the biliverdin **7.19** is a natural product of heme catabolism containing pyrrolones moieties, found in the human bile.[209] This compound is a green pigment and is responsible for the greenish color seen in contusions. In addition to this, dysidin[210] **7.20**, a unique halogenated marine natural product, and microcolin[211] **7.18**, a marine lipopeptide with immunosuppressive properties, contain also a pyrrolone core (see Scheme **195**).

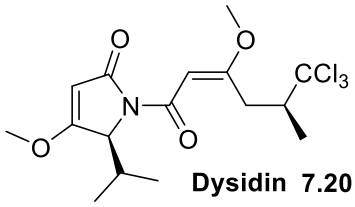
[209] Lehner, H.; Braslavsky, S.E.; Schaffner, K. *Angew. Chem. Int. Ed. Engl.* **1978**, 17, 948.
[210] Williard, P.G.; de Laszlo, S.E. *J. Org. Chem.* **1984**, 49, 3489.
[211] (a) Zhang, L.H.; Longley, R.E. *Life Sciences* **1997**, 62, 751; (b) Andrus, M.B.; Li, W.; Keyes, R.F. *J. Org. Chem.* **1997**, 62, 5542.




**Microcolin 7.18**



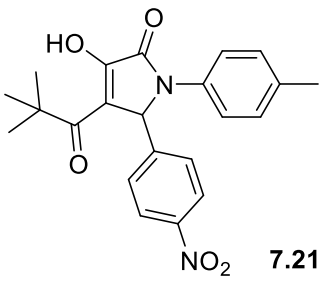

**Biliverdin 7.19**



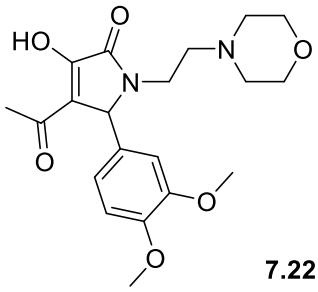

**Dysidin 7.20**

**Scheme 195 natural pyrrolones**

Moreover, pyrrolones remain therapeutic targets for the development of new leads in medicinal chemistry, given that those compounds exhibit a broad spectrum of biological activities.[212] Specifically, pyrrolones and pyrrolones derivatives are reported to have antifungal, antibacterial, anti-inflammatory, anticancer, antiviral, and anti-HIV activities. For example, the compound **7.21** exhibits antitumor activity and inhibits the growth of lung cancer and central nervous system cancer.[213] Additionally, the molecule **7.22** is part of the nootropic family and is found to have antiamnesic activity.




**7.21**



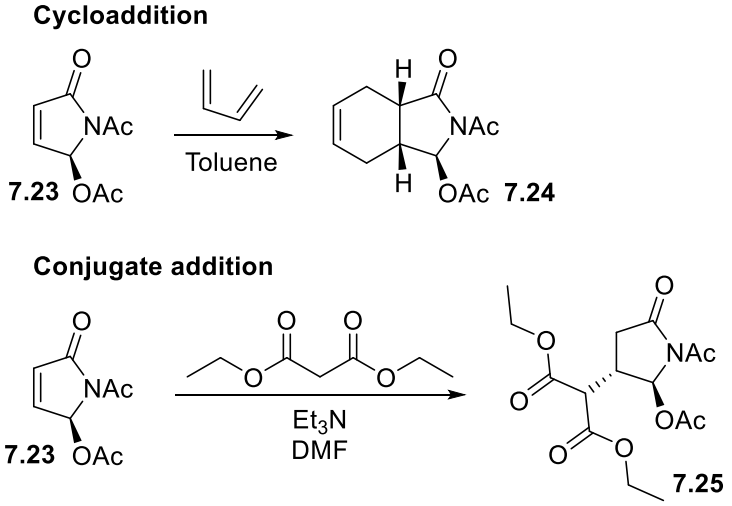

**7.22**

**Scheme 196 pyrrolones 7.21 and 7.22 with biological activities**

Furthermore, pyrrolones are important synthons used in the preparation of a variety of bioactive compounds. Indeed, α,β-unsaturated lactam moieties can be used as a Michael acceptor of a large variety of nucleophiles.[214] Additionally, the heterocycle double bound is susceptible to both hydroxylation and epoxidation. Finally, the use

[212] Ali, Y.; Alam, M.S.; Hamid, H.; Hussain, A. *Orient. J. Chem.* **2014**, 30, 1.
[213] Koz'minykh, V.D.; Lgidov, N.M.; Zykova, S.S. *Pharma. Chem. J.* **2002**, 36, 188.
[214] Jimenez, M.D.; Ortega, R.; Tito, A.; Forina, F. *Heterocycles* **1988**, 27, 73.

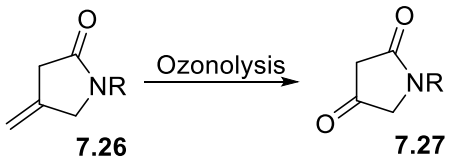
of pyrrolones as substrates in cycloaddition reactions allows the formation of more elaborated compounds (see Scheme **197**).[215] For all these reasons, the synthesis of such building blocks is nowadays receiving considerable attention.[216]




**Scheme 197 examples of reactivity of pyrrolones**

## 7.6 β,γ-unsaturated 2-pyrrolidinone

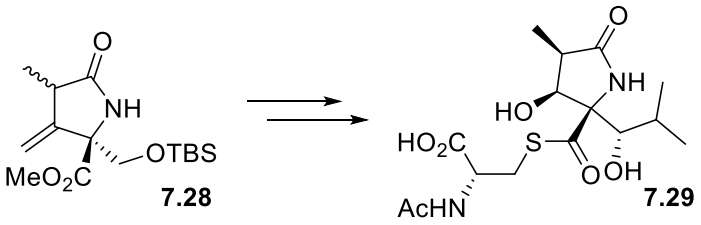
During the electrolysis of the propargylic substrate **7.1** a β,γ-unsaturated 2-pyrrolidinone **7.16** is formed (see Scheme **193**). Those molecules are also known as 4-methylene pyrrolidinones and 2-pyrrolidinones featuring an exocyclic alkene. These moieties can be transformed into interesting synthetic targets via chemical reactions, such as ozonolysis, and hydrogenation, *etc.*[217] For instance, β-methylene γ-lactams are ideal reagents for the synthesis of tetramic acids, the key structural features of a large variety of bioactive natural products.[218] Indeed, tetramic acids are known to possess antibiotic and antiviral activities[219], and a simple ozonolysis of β,γ-unsaturated 2-pyrrolidinone moiety leads to the formation of this pharmaceutical target (see Scheme **198**).




**Scheme 198 ozonolysis of β,γ-unsaturated 2-pyrrolidinone 7.26 in tetramic acid 7.27**

[215] Koot, W.J.; Hiemstra, H.; Speckamp, W.N. *J. Org. Chem.* **1992**, 57, 1059.
[216] Merino, P.; Castillo, E.; Franco, S.; Merchan, F.L.; Tejero, T.; *Tetrahedron: Asymmetry* **1998**, 9, 1759.
[217] Pattenden, G.; Rescourio, G. *Org. Chem.* **2008**, 6, 3428.
[218] Xu, C.P.; Huang, P.Q.; Py, S. *Org. Lett.* **2012**, 14, 2034.
[219] Athanasellis, G.; Igglessi-Markopoulou, O.; Markopoulos, S. *Bioinorganic Chemistry and Applications* **2010**, 11.

Moreover, in 2008, Pattenden *et al.* developed the synthesis of (+)-lactacystin **7.29**, a natural compound produced by bacteria of the genus *Streptomyces*, via ozonolysis of an β,γ-unsaturated 2-pyrrolidinone (see Scheme **199**).[220]

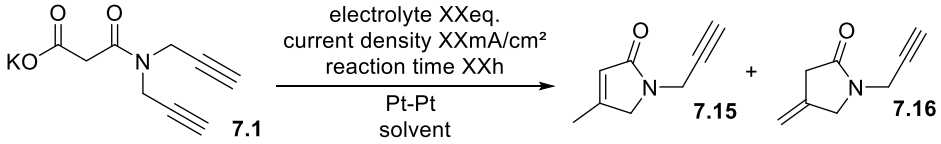



**Scheme 199 synthesis of (+)-lactacystin 7.29 from an β,γ-unsaturated 2-pyrrolidinone 7.28**

## 7.7 Optimization of the electrosynthesis of pyrrolone **7.15** and β,γ-unsaturated 2-pyrrolidinone **7.16**

In this present study, the optimization of the experimental variables of the electrochemical synthesis of pyrrolone **7.15** and β,γ-unsaturated 2-pyrrolidinone **7.16** is conducted, in order to increase the conversion and selectivity of this process. The first part of this work was to choose carefully the experimental variables, which can be numerous and thus make the optimization challenging. The substrate **7.1** concentration, current density, electrolysis time, solvent, electrolyte nature, and the number of equivalent of electrolyte were selected as operation variables. Moreover, during the optimization, all experiments were conducted in a batch mode of operation, and the desired current density was maintained constant. The setup used in this study contains a jacketed undivided cell, a constant current power supply, and platinum anode and cathode. Additionally, in each experimental run, the reaction mixture was rigorously stirred to avoid concentration gradients; and tap water was used to control the temperature inside the double walled reactor. Furthermore, following each run, the electrodes were washed with HCl solution (37%), dried, and used again. Finally, the effect of the six independent variables is shown in Table **10** and is analyzed in the following subsections.

[220] Pattenden, G.; Rescourio, G. *Org. Biomol. Chem.* **2008**, 6, 3428.



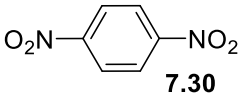

**Scheme 200 electrolysis of the substrate 7.1**

**Table 10 optimization of reaction conditions of the pyrrolone 7.15 and β,γ-unsaturated 2-pyrrolidinone 7.16 electrosynthesis**

| Entry | C (mM) | Current density (mA/cm²) | Time (h) | Solvent | Electrolyte nature | Electrolyte equiv. | Pyrrolone Yields (%) | Pyrrolidinone Yields (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | 66.0 | 25.0 | 4 | MeOH | $CH_3COOK$ | 5 | 25 | 10 |
| 2 | 66.0 | 25.0 | 4 | MeOH | KOH | 0.05 | 11 | 9 |
| 3 | 66.0 | 25.0 | 4 | MeOH | $CH_3CH_2COOH$/KOH | 5/5 | 20 | 17 |
| 4 | 66.0 | 25.0 | 4 | MeOH | $KPF_6$ | 0.05 | 5 | 3 |
| 5 | 25.0 | 50.0 | 4 | MeOH | $CH_3CH_2COOH$/KOH | 5/5 | 22 | 11 |
| 6 | 37.5 | 50.0 | 4 | MeOH | $CH_3CH_2COOH$/KOH | 5/5 | 21 | 22 |
| 7 | 50.0 | 50.0 | 4 | MeOH | $CH_3CH_2COOH$/KOH | 5/5 | 52 | 21 |
| 8 | 62.5 | 50.0 | 4 | MeOH | $CH_3CH_2COOH$/KOH | 5/5 | 22 | 22 |
| 9 | 75.0 | 50.0 | 4 | MeOH | $CH_3CH_2COOH$/KOH | 5/5 | 15 | 19 |
| 10 | 50.0 | 12.5 | 4 | MeOH | $CH_3CH_2COOH$/KOH | 5/5 | 18 | 11 |
| 11 | 50.0 | 25.0 | 4 | MeOH | $CH_3CH_2COOH$/KOH | 5/5 | 34 | 19 |
| 12 | 50.0 | 37.5 | 4 | MeOH | $CH_3CH_2COOH$/KOH | 5/5 | 28 | 24 |
| 13 | 50.0 | 42.5 | 4 | MeOH | $CH_3CH_2COOH$/KOH | 5/5 | 26 | 23 |
| 14 | 50.0 | 50.0 | 4 | MeOH | $CH_3CH_2COOH$/KOH | 5/5 | 52 | 21 |
| 15 | 50.0 | 62.5 | 4 | MeOH | $CH_3CH_2COOH$/KOH | 5/5 | 18 | 6 |
| 16 | 50.0 | 50.0 | 3 | MeOH | $CH_3CH_2COOH$/KOH | 5/5 | 26 | 17 |
| 17 | 50.0 | 50.0 | 4 | MeOH | $CH_3CH_2COOH$/KOH | 5/5 | 52 | 21 |
| 18 | 50.0 | 50.0 | 5 | MeOH | $CH_3CH_2COOH$/KOH | 5/5 | 13 | 13 |
| 19 | 50.0 | 50.0 | 6 | MeOH | $CH_3CH_2COOH$/KOH | 5/5 | 5 | 10 |
| 20 | 50.0 | 50.0 | 4 | MeOH | $CH_3CH_2COOH$/KOH | 5/5 | 52 | 21 |
| 21 | 50.0 | 50.0 | 4 | EtOH | $CH_3CH_2COOH$/KOH | 5/5 | 12 | 13 |
| 22 | 50.0 | 50.0 | 4 | $H_2O$/MeOH | $CH_3CH_2COOH$/KOH | 5/5 | 1 | 36 |
| 23 | 50.0 | 50.0 | 4 | MeCN | $CH_3CH_2COOH$/KOH | 5/5 | 1 | 43 |

## 7.7.1 Quantitative $^1$H-NMR spectroscopy

The nuclear magnetic resonance (NMR) spectroscopy is an attractive tool for the quantitative analysis of small molecules in their crude forms and in mixtures. Therefore, the quantitative $^1$H-NMR spectroscopy was chosen as analytic method in order to determine the yields of the two reaction products, using an internal standard.[221] This technique will help us save time, considering that no purification via silica gel chromatography is going to be needed. In the case of this study, the use of this analytical technique is possible because the products sample dissolves completely in the NMR deuterated solvent, chloroform. Moreover, the NMR spectra of these molecules are simple and contain singulet signals. Specifically, these singulet peaks have no overlap with other signals (see Spectra **7** and **8**).



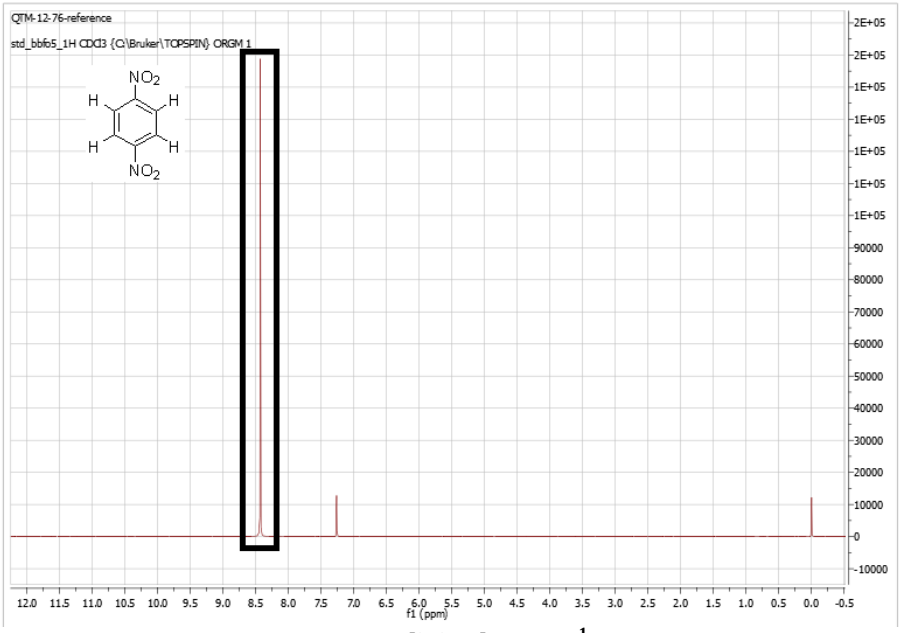

**7.30**

**Scheme 201 1,4-dinitrobenzene 7.30 standard**

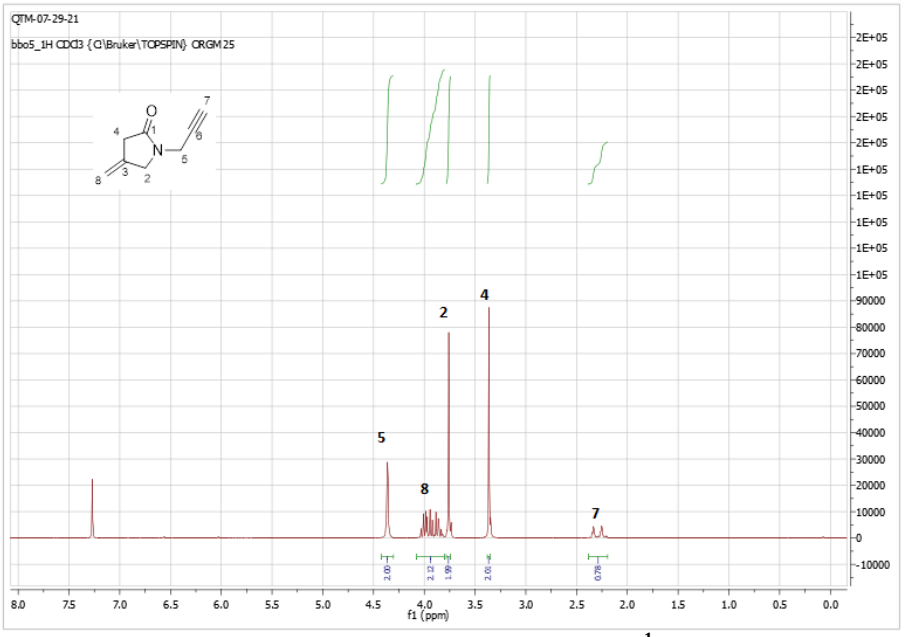
1,4-dinitrobenzene **7.30** was chosen as calibrant and its presence during the NMR analyses will allow the determination of the yields of the two electrolysis products. Indeed, the area of an NMR signal is directly proportional to its concentration, and

[221] Bharti, S.K.; Roy, R. *Trends in Analytical Chemistry* **2012**, 35, 5.

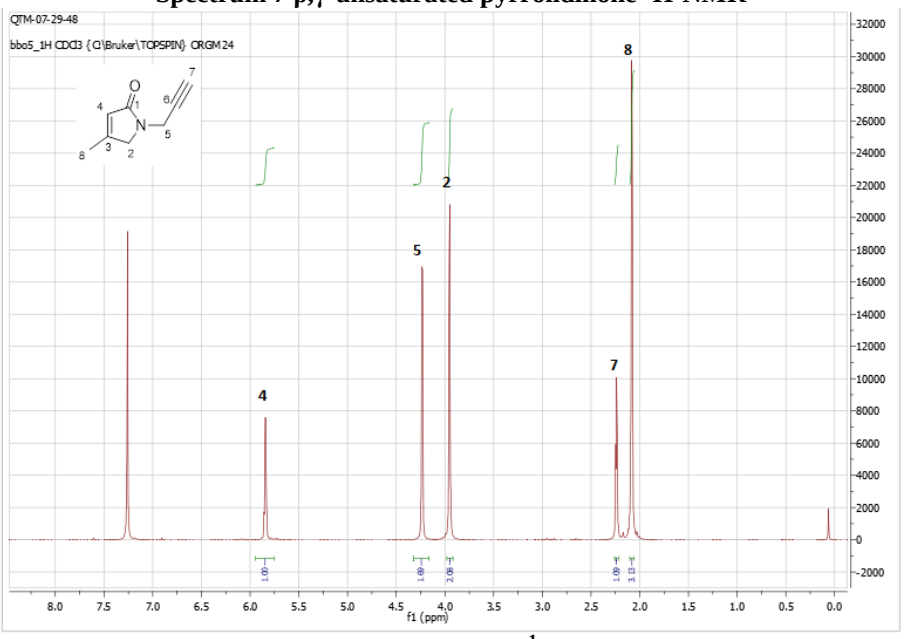
thus the concentrations of the two products are going to be determined against that calibrant of known concentration. This internal standard was selected because its resonances do not overlap with those of the analytes. Additionally, this calibrant produces a simple NMR spectrum, with only one singulet at 8.43 ppm in the deuterated chloroform (see Spectrum **6**). Furthermore, this compound is chemically inert, highly soluble in the NMR solvent and has no excessively long relaxation times. Finally, the internal standard exists in a pure form and is readily weighable.




**Spectrum 6 1,4-dinitrobenzene $^{1}$H-NMR**




**Spectrum 7 β,γ-unsaturated pyrrolidinone $^{1}$H-NMR**




**Spectrum 8 pyrrolone $^{1}$H-NMR**

### 7.7.2 Supporting electrolyte nature

This optimization study began with the selection of the electrolyte salt, in order to increase the conductivity of the solution. To this end, several electrolyte salts were tested, in our electrolysis conditions. The electrolytes, that were selected, are: potassium acetate, potassium hydroxide, potassium hexafluorophosphate, and a

combination of propionic acid and potassium hydroxide. Surprisingly, the combination of propionic acid and potassium hydroxide gave the best results. This inert electrolytes mixture was used, during the first experiment, believing that propionic acid was going to act as a co-acid. Given those results, this supporting electrolytes mix was picked to optimize our electrolysis process.

### 7.7.3 Substrate **7.1** concentration

The substrate concentration is a significant parameter in the optimization of an electrochemical transformation. Throughout a classic Kolbe reaction, if the substrate concentration is too low, the significant distance between the radicals, at the anode surface, lies at the origin of a Hofer-Moest oxidation process. In other words, an overoxidation mechanism takes place, leading to the formation of a large number of side-products. However, if the concentration is too high, the considerable concentration in radicals, at the anode surface, promotes a dimerization process. An analysis of our optimization results reveals that a concentration of 50 mM is optimal to improve the yields of our procedure.

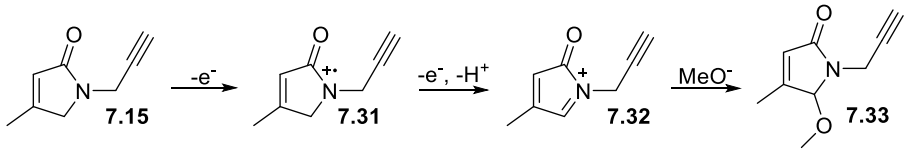
### 7.7.4 Current density

A detailed analysis of our results reveals that, at 12.5 mA/cm², the current density is too low and thus the electrons speed, inside the circuit, is too slow to ensure an optimum oxidation of the substrate **7.1**. Moreover, between 25.0 and 42.5 mA/cm², the reaction yields remain pretty steady. Nevertheless, at 50.0 mA/cm², the current density value seems to be ideal, and allows to reach the good global yield of 73 %. Finally, at 62.5 mA/cm², the yields drop probably due to the appearance of side-reactions of oxido-reduction. Indeed, a too high current density leads to the substrate dimerization. In contrast, a too low current density value is responsible for Hofer-Moest side-reactions.

### 7.7.5 Electrolysis time

According to our optimization research, the optimal electrolysis time seems to be four hours. Below this value, the electrolysis duration is not enough long to achieve a satisfying result. Nevertheless, if the reaction time exceeds four hours, the products yields drop considerably. This phenomenon can be explained by the degradation of the electrolysis products into side-products. Unfortunately, the structures of those impurities were not identified because, even after purification via silica gel chromatography, the side-products were not isolated and remained as a complex mixture of molecules. A hypothetical explanation of the product degradation is a possible Shono reaction.[222] Actually, the amide products **7.15** and **7.16** may be oxidated into the corresponding *N*-acyliminium ion **7.32**, which can be captured by methanol, solvent. This phenomenon leads to the formation of α-oxomethylated products **7.33**.

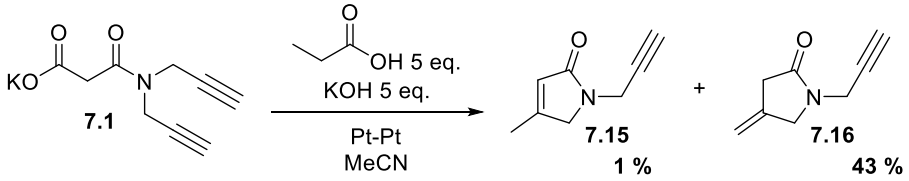
[222] Shono, T.; Matsumura, Y.; Tsubata, K.; *J. Am. Chem. Soc.* **1981**, 103, 1172.




**Scheme 202 Shono reaction**

### 7.7.6 Solvent

As confirmed in the literature, the methanol was the solvent that gave the best results, in the case of our Kolbe electrocyclization via addition of a radical on an alkyne function. Actually, the methanol is the most used solvent for Kolbe electrolyzes. The ethanol and the combination of water and methanol (1:1) were also tested, during our study. Even if those solvents present the advantage to be less toxic, and thus more attractive for pharmaceutical application, the yields obtained with the use of these solvents were lower than with methanol. A truly interesting selectivity result was achieved using acetonitrile as solvent. Indeed, the β,γ-unsaturated 2-pyrrollidinone **7.16**, which is instable in methanol, seemed to be stable in acetonitrile and was the predominant product of reaction. The hypothesis explaining this result is that the aprotic nature of acetonitrile, and the absence of formation of methanolate base, in the reaction mixture, prevent the isomerization of β,γ-unsaturated 2-pyrrollidinone **7.16** in pyrrolone **7.15**.




**Scheme 203 electrolysis of the substrate 7.1 in acetonitrile**

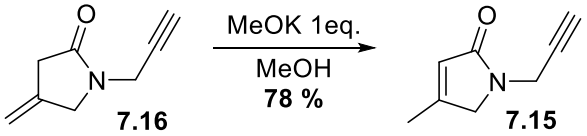
### 7.7.7 Stability study of the β,γ-unsaturated 2-pyrrolidinone **7.16**

According to the literature, the β,γ-unsaturated 2-pyrrolidinone moieties are not stable and tend to isomerize into the corresponding pyrrolones. This statement was demonstrated, during our research. First, it was noted that the ratio of pyrrolone **7.15** and β,γ-unsaturated 2-pyrrolidinone **7.16** was different before and after purification via silica gel chromatography. Indeed, the acidity of the silica gel tends to promote this isomerization process and to lead to a larger proportion of the thermodynamically favored product, the pyrrolone **7.15**. According to our research, the proportion of the pyrrolone **7.15** increased by 19 % on average, after purification via silica gel chromatography.

**Table 11 ratio of the pyrrolone 7.15 and pyrrolidinone 7.16 before and after purification via silica gel chromatography**

| Entry | Ratio of pyrrolone before purif. | Ratio of pyrrolidinone before purif. | Ratio of pyrrolone after purif. | Ratio of pyrrolidinone after purif. |
|---|---|---|---|---|
| **1** | 72 % | 28 % | 87 % | 13 % |
| **2** | 55 % | 45 % | 73 % | 27 % |
| **3** | 69 % | 31 % | 92 % | 8 % |

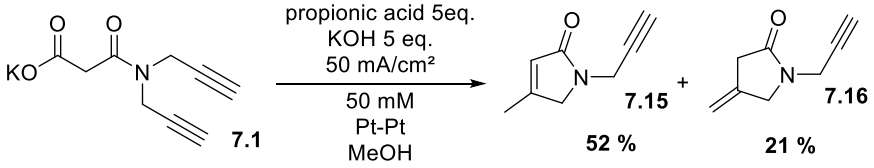
In a second phase, the stability of the 2-pyrrolidinone **7.16** was tested in basic conditions. Therefore, this product was isolated via silica gel chromatography, and then diluted into methanol and treated with potassium methoxide. This procedure has led to an excellent yield in the pyrrolone **7.15**, which confirmed the instability of the β,γ-unsaturated 2-pyrrolidinone **7.16**, in basic conditions.




**Scheme 204 treatment of the molecule 7.16 in basic conditions**

## 7.7.8 Conclusions of the optimization study

In conclusion, this investigation hallowed to find the optimal conditions of electrolysis of the substrate **7.1** leading to the formation of the pyrrolone **7.15** and the β,γ-unsaturated 2-pyrrolidinone **7.16** via cyclization through radical addition on an alkyne function. In order to achieve the best yields, the concentration in substrate should be 50 mM and 5 eq. of propionic acid and potassium hydroxide should be introduced in the reaction mixture. The best solvent for that electrolysis was methanol, four hours was the best reaction time, and the ideal current density applied during that procedure was 50 mA/cm². Finally, this electrolysis procedure was conducted in an undivided jacketed reactor, in batch mode, and the reaction temperature was controlled thanks to tap water (see Scheme **205**).




**Scheme 205 optimal electrolysis conditions**

By controlling the electrolysis conditions, the work-up, and purification conditions, the reaction selectivity can be dramatically increased. Indeed, if the solvent used is acetonitrile, the main product is 2-pyrrolidinone **7.16**. In other words, the use of this aprotic solvent allows to gain a good selectivity for the less stable product. Nonetheless, in the optimal electrolysis conditions, the pyrrolone **7.15** usually is the major product. Moreover, a good selectivity for that product can be achieved in acidic or basic conditions, given that the 2-pyrrolidione **7.16** tends to isomerized into the pyrrolone **7.15**, which leads to an excellent selectivity for the most stable product.

In conclusion, this research provided a good optimization of our electrolysis reaction and allowed achieving an excellent selectivity for each of the products. The following subsections are focused on the functionalization of those reaction products, in order to show the large applicability and increase the versatility of this transformation.

## 7.8 Exemplification of the electrosynthesis of pyrrolones and β, γ-unsaturated 2-pyrrolidiones

In the following subsections, the electrolysis of propargylic substrates leading to the formation of pyrrolones and β,γ-unsaturated 2-pyrrolidinones was diversely exemplified, in order to show the versatility of this methodology. As a first step, the variation of the protecting group, on the nitrogen atom, in the substrate structure, was explored. Secondly, the terminal alkyne function of the electrolysis substrate was functionalized, in order to extend the scope of this methodology. Finally, the creation of spirocyclic compounds starting from a propargylic substrate was investigated to show the potential of this type of reactions.

### 7.8.1 Modification of the nature of the protecting group of the nitrogen atom in the electrocyclization substrate **7.1** structure

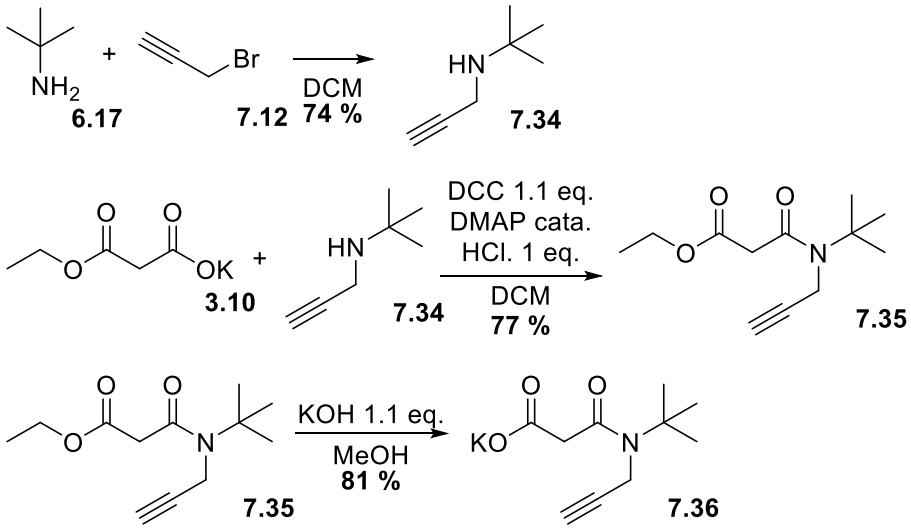
In order to show the versatility of our methodology, the nature of the protecting group of the nitrogen atom, in the electrolysis substrate structure, was modified. Indeed, the nitrogen atom of the amide function of the electrolysis substrate needs to be protected against further oxidation reactions. Moreover, the presence of a non-reactive protecting group will facilitate the functionalization of the terminal alkyne of the electrocyclization reagent.

#### *7.8.1.1 Tert-butyl protecting group*

First, the propargyl protecting group of the electrolysis substrate **7.1** was replaced by a *tert*-butyl group. The inert nature of this protecting group should facilitate the functionalization of the terminal alkyne function. Furthermore, the important steric hindrance of the *tert*-butyl protecting group should promote the formation of the *trans*-rotamer, in which the alkyne function is as close as practicable of the carbonated radical, during the cyclization step.

##### ***7.8.1.1.1*** *Synthesis of the tert-butyl protected electrolysis substrate* ***7.36***

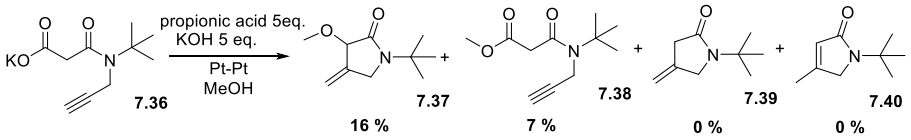
The *tert*-butyl substrate **7.36** was synthetized, in three steps, according to the subsequent straightforward procedure (see Scheme **206**). First, the secondary propargyl amine **7.34** was produced, using propargyl bromide **7.12** and *tert*-butyl amine **6.17** in excess. Subsequently, ethyl potassium malonate **3.10** and the secondary amine **7.34** were coupled via a Steglich amidation. The amide ester **7.35** generated was finally treated in basic conditions to form the electrolysis substrate **7.36**.




**Scheme 206 synthesis of the *tert*-butyl protected substrate 7.36**

*7.8.1.1.2*<u>*Electrolysis of the tert-butyl protected substrate **7.36***</u>

The *tert*-butyl protected substrate **7.36** was electrolyzed, in our optimized electrocyclization conditions. Unfortunately, this procedure did not lead to the formation of the desired substrates **7.39** and **7.40**. Instead, several side-products were formed and two of them, the side-products **7.37** and **7.38**, were purified and isolated.

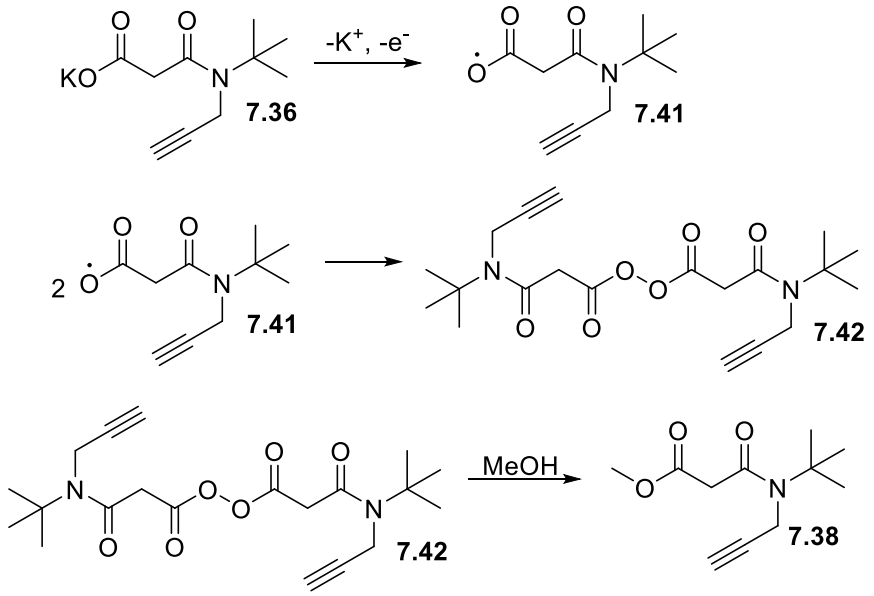



**Scheme 207 electrolysis of the *tert*-butyl protected substrate 7.36**

***7.8.1.1.3***<u>*Mechanistic hypothesis of the formation of the side-products **7.37** and **7.38***</u>

#### 7.8.1.1.3.1 Impurity 7.38 formation

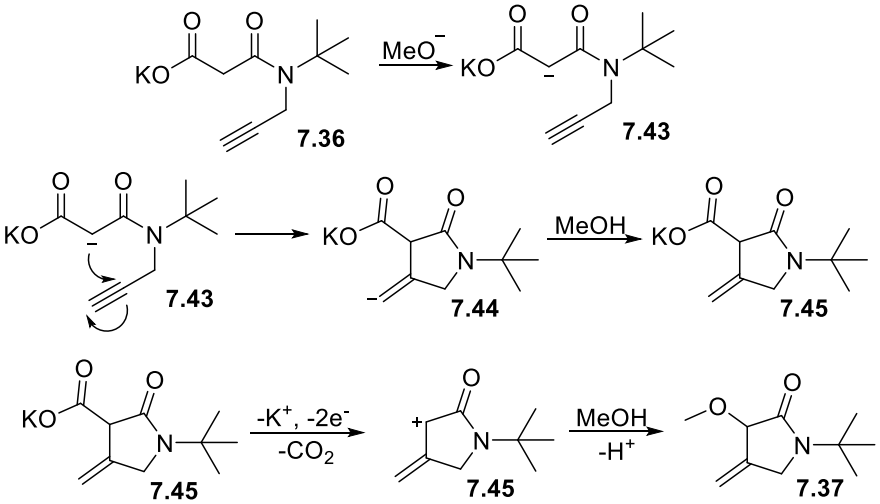
Surprisingly, the impurity **7.38** was formed as a result of the electrolysis of the substrate **7.36**. Our mechanistic hypothesis explaining the formation of this compound is the following (see Scheme **208**). First, the potassium salt **7.36** should be converted into the corresponding carboxylate, adsorbed at the surface of the anode and oxidized into the acyloxy radical **7.41**. Subsequently, the acyloxy radical **7.41** should do a homo-coupling which should lead to the formation of the corresponding peroxide **7.42**. Finally, the nucleophilic attack of the peroxide **7.42** by methanol should allow the formation of the ester **7.38**.




**Scheme 208 mechanistic hypothesis of the formation of the impurity 7.38**

#### 7.8.1.1.3.2 Impurity 7.37 formation

Curiously, the side-product **7.37** was formed, during the electrolysis of the substrate **7.36**. We tried to explain the formation of this impurity according to the subsequent mechanistic hypothesis (see Scheme **209**). First, the potassic salt **7.36** should be deprotonated to form the anion **7.43**. Subsequently, the anion **7.43** should cyclize intramolecularly via the addition of the anion on the triple bond to generate the vinyl anion **7.44**. Additionally, the anion **7.44** should abstract a proton from the solvent to form the unsaturated pyrrolidinone **7.45**. Afterwards, the carboxylate **7.45** is oxidatively decarboxylated and further oxydated to form the carbocation **7.46**. Finally, the addition of the methanol on the carbocation **7.46** should lead to the formation of the impurity **7.31**.



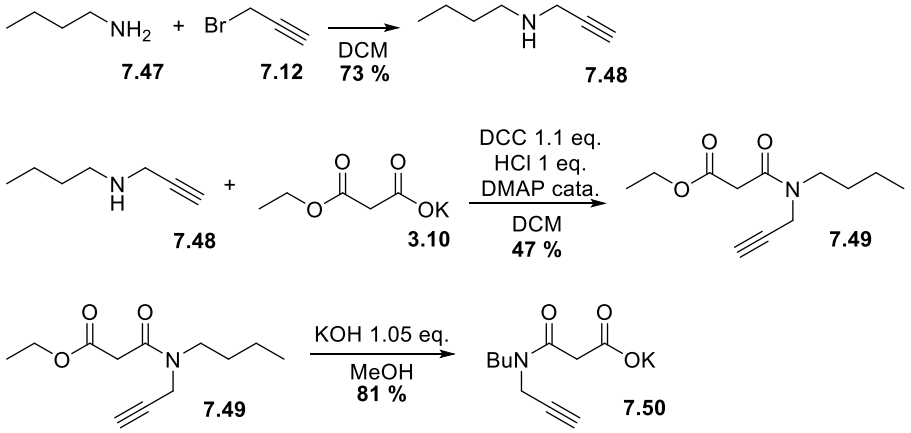

**Scheme 209 mechanistic hypothesis of the formation of the impurity 7.37**

*7.8.1.2 Butyl substituent*

In this section, a butyl function was used, in order to protect the nitrogen atom of the amide function, in the substrate **7.50** skeleton. Indeed, nitrogen functions are prone to oxidation into contact with platinum electrodes.

***7.8.1.2.1*** *Synthetis of the butyl substituted electrolysis substrate **7.50***

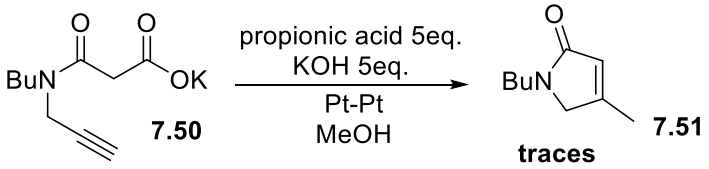
The butyl substituted electrocyclization substrate **7.50** was synthetized according to the following method (see Scheme **210**). The secondary amine **7.48** was first produced using propargyl bromide **7.12** and an excess of butyl amine **7.47**. Consecutively, this secondary amine **7.48** was coupled with ethyl potassium malonate **3.10** to form the amide **7.49**. Finally, this latter has been converted into the electrolysis substrate **7.50** in good yield.




**Scheme 210 synthesis of the butyl substituted electrolysis substrate 7.50**

***7.8.1.2.2*** *Electrolysis of the butyl substituted substrate **7.50***

Once the electrolysis substrate **7.50** was ready, its oxidation was conducted according to our optimized electroreaction conditions (see Scheme **211**). Unfortunately, this reaction was fruitless and only traces of the compound **7.51** were isolated from the crude mixture. Therefore, the investigation was proceeded with alternative protecting groups.



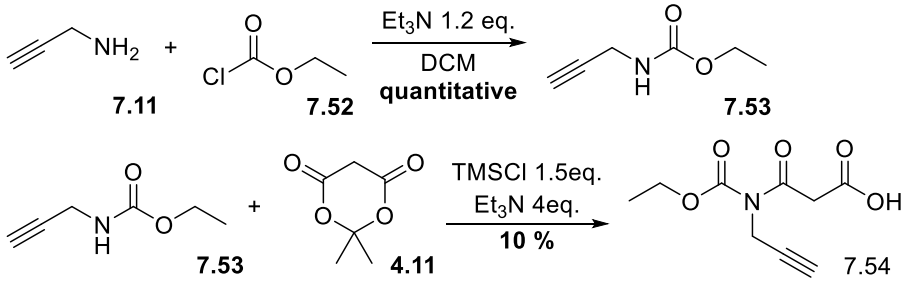

**Scheme 211 electrolysis of the butyl protected substrate 7.50**

*7.8.1.3 Ethyl carbamate protecting group*

An ethyl carbamate protecting group was inserted, in the structure of the electrocyclization substrate **7.54**, in order to test the compatibility between this protecting group and our electrolysis conditions.

*7.8.1.3.1 Synthesis of the electrolysis substrate **7.54***

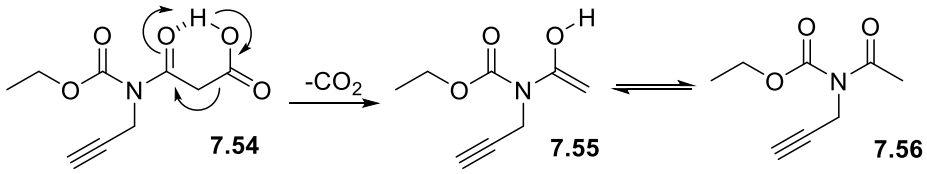
The reagent **7.54** was synthetized according to the subsequent straightforward procedure (see Scheme **212**). Indeed, the synthesis of this molecule only counts two steps. Firstly, the carbamate **7.53** was prepared using propargyl amine **7.11** and ethyl chloroformate **7.52**. Finally, the carbamate **7.53** reacted with Meldrum's acid **4.11** to lead to the generation of the electrolysis substrate **7.54**. Unfortunately, only 10 % of this chemical product was isolated via silica gel chromatography. Nevertheless, the amount of reagent was sufficient to perform an electrolysis reaction, with this molecule.




**Scheme 212 synthesis of the electrolysis substrate 7.54**

*7.8.1.3.2 Degradation mechanism of the electrolysis substrate **7.54***

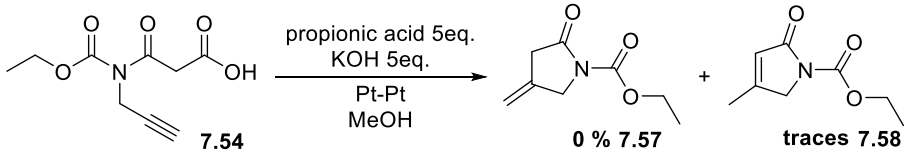
Unsuccessfully, the electrolysis substrate **7.54** was not stable and tended to decarboxylate, which led to the formation of the impurity **7.56** and to the release of $CO_2$. In fact, one of the oxygen of the molecule acted as a Lewis base, which led to the formation of a six-membered ring transition state (see Scheme **213**). An aromatic character arises from this structure **7.54**, given that three electronic pairs are able to move in this entity. This phenomenon led to a decarboxylation process and a consecutive tautomerization mechanism allowed the formation of the impurity **7.56**.




**Scheme 213 substrate 7.54 degradation mechanism**

***7.8.1.3.3****Electrolysis of the substrate **7.54***

With a sufficient quantity of electrolysis reagent **7.54** in hand, the electrolysis of that molecule was conducted, in our optimized reaction conditions (see Scheme **214**). Unfortunately, this reaction led to only traces of the products **7.57** and **7.58**, and a complex mixture of impurities.



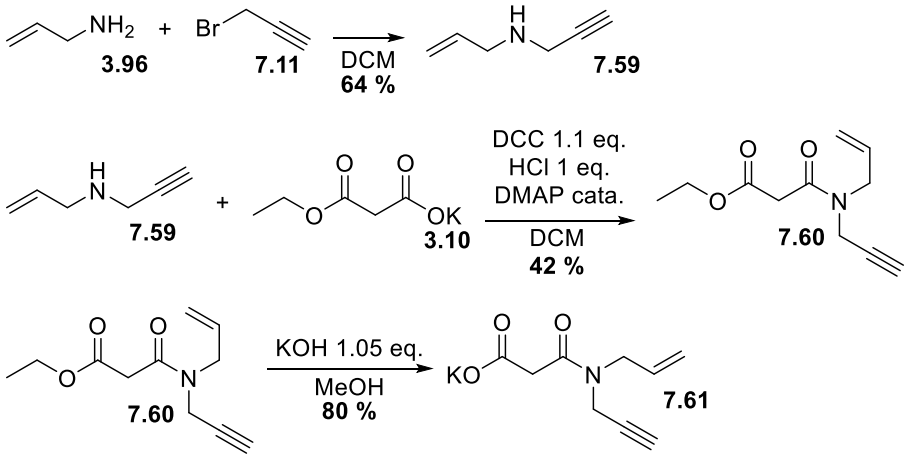

**Scheme 214 electrolysis of the substrate 7.54**

*7.8.1.4 Allyl protecting group*

A substrate bearing an allyl protecting group was synthetized in order to show the versatility of our methodology. This protecting group has the advantage of being readily deprotected after the electrocyclization step.

***7.8.1.4.1****Synthesis of the allyl protected electrocyclization substrate **7.61***

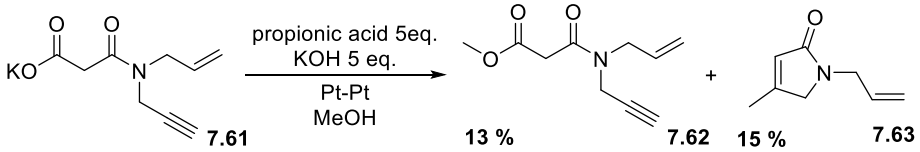
In order to design the allyl protected substrate **7.61**, the following procedure was performed (see Scheme **215**). First, the allyl propargyl amine **7.59** was synthetized with propargyl bromide **7.11** and an excess of allyl amine **3.96**. This secondary amine was then coupled with ethyl potassium malonate **3.10** to form the amide ester **7.60**. Finally, the amide ester **7.60** was hydrolyzed into the corresponding potassic salt **7.61**.




**Scheme 215 synthesis of the allyl protected substrate 7.61**

***7.8.1.4.2****Electrolysis of the allyl protected substrate* ***7.61***

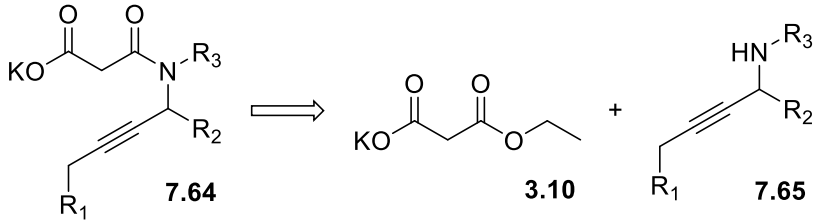
With the electrolysis reagent **7.61** in hand, the electrolysis of this compound was performed under our optimized electrolysis conditions (see Scheme **216**). As in the case of the *tert*-butyl protected substrate **7.36**, the side-product **7.62** was formed, in moderate yield. Remarkably, the pyrrolone **7.63** could be isolated, albeit in a modest yield. This low yield can be related to the formation of various side-products, during this electro-reaction.




**Scheme 216 electrolysis of the substrate 7.61**

## 7.8.2 Functionalization of the terminal alkyne in the electrocyclization substrate **7.1** structure

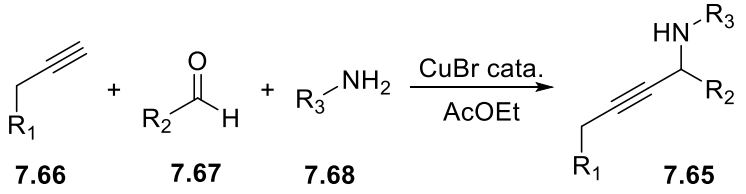
For the purpose of broadening the scope of product of our electrosynthesis of pyrrolones and β,γ-unsaturated 2-pyrrolidinones, we then decided to develop the electrocyclization of substrates bearing a substituted alkyne function. Indeed, the substituents located on the alkyne function, in the substrates structure, will decorate the carbonated skeleton of the pyrrolones and 2-pyrrolidinones formed, via electrocyclization of those substrates. A retrosynthetic analysis shows that this type of substrates **7.64** can be formed via coupling between ethyl potassium malonate **3.10** and a substituted propargyl secondary amine **7.65** (see Scheme **217**).




**Scheme 217 retrosynthesis of the substrate 7.64**

Furthermore, this type of amines **7.65** can be synthetized using copper catalysis (see Scheme **218**).[223] Specifically, an aldehyde **7.67**, a primary amine **7.68**, and a mono-functionalized alkyne **7.66** can be submitted to an A3-coupling reaction under CuBr catalysis, giving strategically a functionalized propargyl amine. This multicomponent reaction is an interesting strategy to prepare highly substituted building blocks, in high yields and in a straightforward way. Finally, this type of transformations is extremely attractive since the whole mechanism is intrinsically energy-, atom- and step-economical. In the following subsections, the synthesis and electrolysis of two various reagents bearing a substituted alkyne function are described.

[223] Carmona, R.C.; Wendler, E.P.; Sakae, G.H.; Comasseto, J.V.; Dos Santos, A.A. *J. Braz. Chem. Soc.* **2015**, 26, 117.



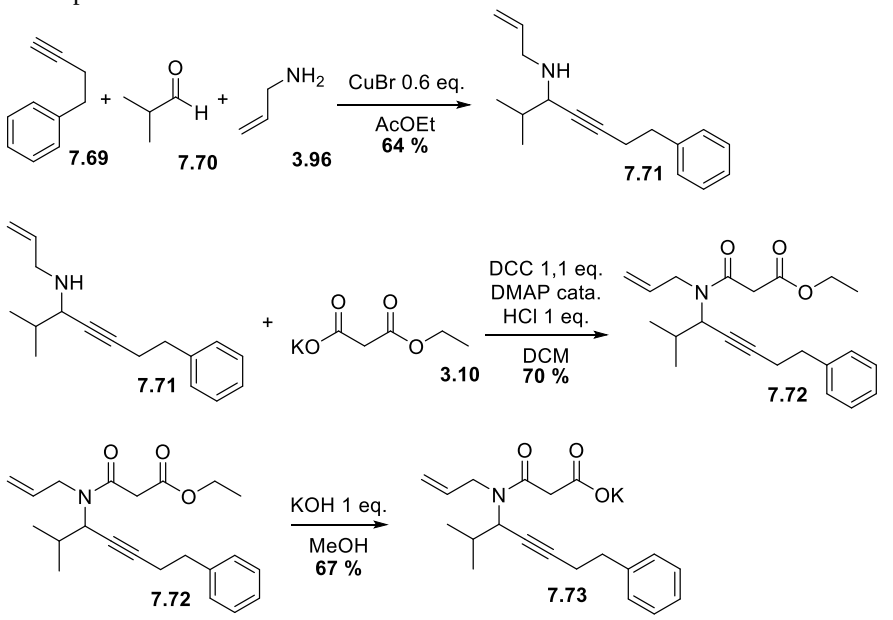

**Scheme 218 copper catalysis applied to the formation of functionalized propargyl amines 7.65**

*7.8.2.1 Electrocyclization of the substrate **7.73** bearing ethyl benzene substituted alkyne*

First, the substrate **7.73** was synthetized and electrolyzed in order to substitute pyrrolones and 2-pyrrolidinones with an aromatic function, and thus broaden the field of substrates of our reaction.

*7.8.2.1.1 Synthesis of the substrate **7.73** bearing an alkyne function substituted with an ethyl benzene*

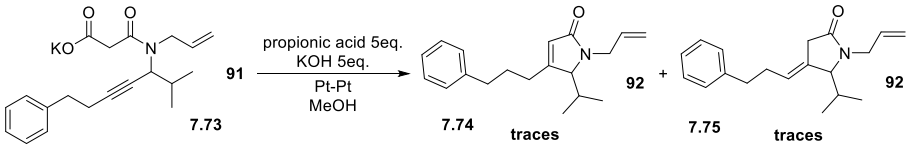
The electrolysis substrate **7.73**, bearing an alkyne function substituted with ethyl benzene, was prepared according to the following procedure, in only three steps (see Scheme **219**). First, the functionalized secondary amine **7.71** was synthetized via a multicomponent reaction catalyzed by CuBr, using allylamine **3.96**, 4-phenyl-1-butyne **7.69**, and isobutyraldehyde **7.70**. Consecutively, the propargylic amine **7.71** formed was coupled with ethyl potassium malonate **3.10**, via a Steglich amidation reaction. Finally, the electrolysis substrate **7.73** was produced via basic treatment of the compound **7.72**.




**Scheme 219 synthesis of the electrolysis substrate 7.73**

*7.8.2.1.2Electrolysis of the substrate **7.73** bearing an alkyne function substituted with an ethyl benzene*

The electrolysis of the aromatic substrate **7.73** was performed, under our optimized electrocyclization conditions (see Scheme **220**). Unfortunately, only traces of the substrates **7.74** and **7.75** were isolated via silica gel chromatography. The causes of failure could be attributed to the presence of an aromatic function in the substrate **7.73** structure or to the strong steric hindrance of the substrate. Indeed, the presence of an aromatic ring, in the structure of a molecule, or an important steric hindrance may have a direct impact on the phenomenon of adsorption, at the surface of the platinum electrode, which has a huge impact on the outcome of an electrochemical reaction.



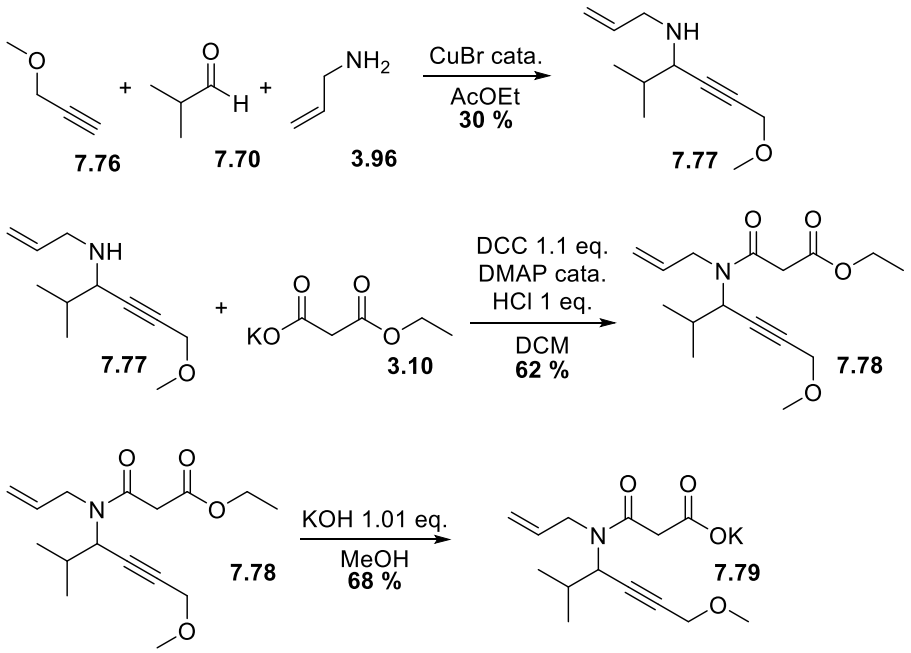

**Scheme 220 electrolysis of the substrate 7.73**

*7.8.2.2 Electrolysis of the substrate **7.79** bearing a methoxymethane substituted alkyne*

In a second stage, a substrate **7.79** containing an alkyne substituted with methoxymethane was synthetized and electrolyzed with the aim of broadening the scope of our pyrrolones and β,γ-unsaturated 2-pyrrolidinones electrosynthesis methodology.

*7.8.2.2.1Synthesis of the substrate **7.79** bearing an alkyne substituted with methoxymethane*

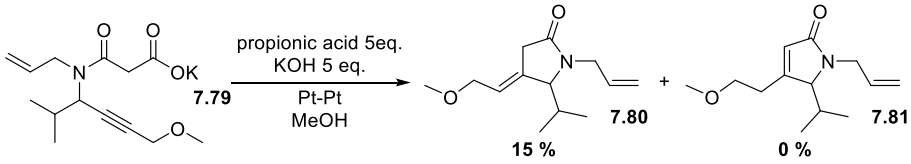
The substrate **7.79** containing an alkyne substituted with methoxymethane was designed according to the subsequent straightforward procedure, in only three steps (see Scheme **221**). First, the highly functionalized secondary amine **7.77** was synthetized via a multicomponent reaction catalyzed via copper catalysis, using allylamine **3.96**, methyl propargyl ether **7.76**, and isobutyraldehyde **7.70**. This propargylic amine was consecutively coupled with ethyl potassium malonate **3.10** to form the amide ester **7.78**. Finally, the electrolysis substrate **7.79** was produced via basic treatment of the amide ester **7.78**.




**Scheme 221 synthesis of the electrolysis substrate 7.79**

*7.8.2.2.2Electrolysis of the substrate **7.79** bearing an alkyne substituted with a methoxymethane*

With the electrolysis substrate **7.79** in hand, the electrolysis of this reagent was conducted under our optimized reaction conditions (see Scheme **222**). Successfully, the desired β,γ-unsaturated 2-pyrrolidinone **7.80** was produced in modest yield. Furthermore, the pyrrolone **7.81** was not isolated, after chromatography on silica gel. This result demonstrates that highly substituted 2-pyrrolidinones can be produced via our state-of-the-art methodology. In the future, it could be interesting to optimize this type of reaction because the yield remains quite low.

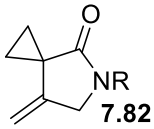



**Scheme 222 electrolysis of the substrate 7.79**

## 7.8.3 Synthesis of spirocyclic β,γ-unsaturated 2-pyrrolidinones

In this section, the electrosynthesis of β,γ-unsaturated 2-pyrrolidinones is explored with a view to apply our methodology to the formation of highly functionalized spirocyclic heterocycles. Indeed, the 5-azaspiro[2.4]heptan-4-one **7.82** is an attractive synthetic target (see Scheme **223**). This carbonated skeleton is a motif found in diverse biologically active compounds including antibacterial and

antiautoimmune agents.[224] Furthermore, the formation of this moiety via electrolysis should be more selective than our usual electrocyclizations of propargylic substrates. Actually, the present of a quaternary center situated in α-position of the carbonyl function, in the substrate structure, should make impossible the isomerization of the 2-pyrrolidinone into the corresponding pyrrolone. Finally, the presence of the olefin function inside the structure of this product makes it an interesting reagent for various reactions, such as ozonolysis, hydrogenation, electrophilic addition, and osmium tetroxide hydroxylation, *etc*.

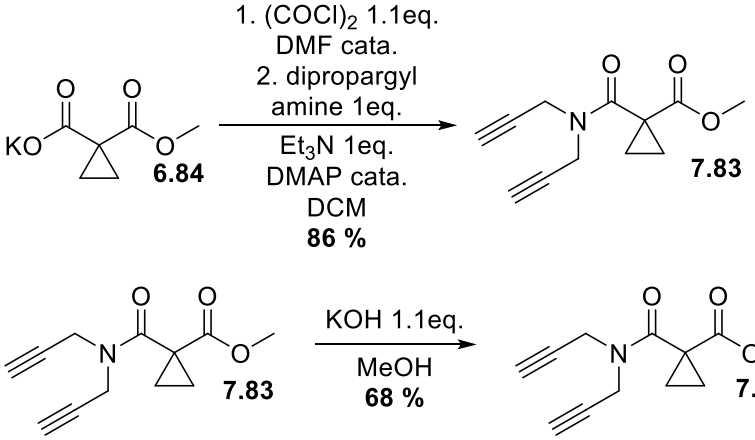



**7.82**

**Scheme 223 7-methylene-5-azaspiro[2.4]heptan-4-one 7.82**

### *7.8.3.1 Synthesis of the propargylic spiro-electro-cyclization substrate 7.84*

The synthesis of the propargylic spiro-electro-cyclization substrate **7.84** began with the amidation of cyclopropane functionalized methyl potassium malonate **6.84**. Consecutively, the compound **7.83** was transformed into electrolysis reagent **7.84** via basic treatment. Interestingly, this product was obtained, in only two steps, via a straightforward procedure (see Scheme **224**).

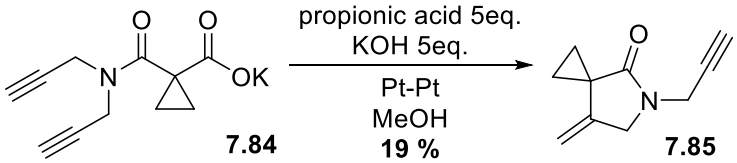



**Scheme 224 synthesis of the propargylic spiro-electro-cyclization substrate 7.84**

### *7.8.3.2 Electrolysis of the propargylic spiro-electro-cyclization substrate 7.84*

With the desired electrocyclization substrate **7.84** in hand, the electrolysis of this reagent was performed in our optimized conditions (see Scheme **225**). Successfully, the spirocyclic product **7.85** was obtained in moderate yield. The modest yield of this reaction should be related to the formation of various side-products, which were not isolated via silica gel chromatography. Given this promising result, an optimization study could be done, in the future, in order to improve the yield of that appealing transformation.

[224] Nocquet, P.A.; Hazelard, D.; Compain, P. *Eur. J. Org. Chem.* **2011**, 6619.




**Scheme 225 electrolysis of propargylic spiro-electro-cyclization substrate 7.84**

# 8 Continuous flow electrochemistry applied to the Kolbe cyclization of functionalized 2-pyrrolidinones

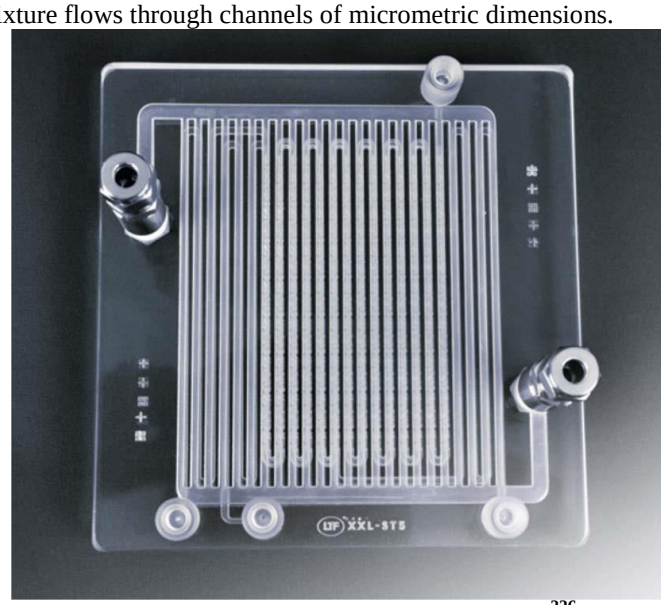
## 8.1 Continuous flow chemistry

### 8.1.1 Definition

By definition, a continuous flow reactor is a reactor where substrates are introduced on an ongoing basis. The reaction takes place while the reacting mixture circulates through the reactor. Those reactors can contain liquids, gases, and sometimes suspended solids. However, in most cases, the use of solids constitutes a major limitation of continuous flow chemistry.[225]

Continuous flow chemistry is commonly employed in heavy chemistry industries, such as: in petrochemistry, and polymer chemistry. In the context of the pharmaceutical industry, where smaller quantities are implemented, and an important variety of reactions are employed, the continuous flow chemistry is more rarely used. However, this technology can in certain cases be an attractive alternative to batch chemistry.

Besides continuous flow reactors, there are also continuous flow micro-reactors (see Picture **1**). These reactors were developed, in the nineties, thanks to progresses in the area of micro-manufacturing and micro-fluidic. In a continuous micro-reactor, the reacting mixture flows through channels of micrometric dimensions.




**Picture 1 continuous flow micro-reactor**[226]

[225] Hartman, R.L.; Jensen, K.F.; McMullen, J.P. *Angew. Chem. Int. Ed.* **2011**, 50, 7502.
[226] http://www.amarequip.com/continuous-flow-glass-microreactors/

### 8.1.2 Characteristics of the continuous flow chemistry

Continuous flow reactors owe their amazing efficiency to two of their features: an improved heat exchange and defined reaction geometry.

First, the important surface to volume ratio, coming from their micrometric dimensions, gives to those reactors an important exchange surface area. This one ensures an excellent control of the reaction temperature, much higher than what may offer a batch reactor. This improved heat exchange limits the formation of side-reactions and enables improvement of the purity of the final product. By contrast, in a batch reactor, the exchange surface area is more limited and a greater temperature gradient is observed, leading to side-reactions and energy losses.[227]

Secondly, the defined reaction geometry ensures that the reaction always starts at a defined point and finishes at another precise point. As a result, the reaction always takes place in a constant time. Moreover, the mixing geometry being also defined, the material exchanges are faster and more reproducible. For instance, the reaction can be stopped via a precise and rapid addition of a quenching reagent. The quality of the production is thus constant.

Finally, continuous flow reactors offer the possibility to handle reactions in harsh conditions, such as: high temperature, high pressure, high concentration, and explosive conditions. Indeed, the excellent transport properties of the continuous flow reactors allow to reach safely harsh reaction conditions.[228]

## 8.2 Combination of continuous flow chemistry and organic electrochemistry

Organic electrosynthesis has a huge potential to offer to organic chemists given the large array of transformations possible via electrolysis. However, classical electrolysis in batch glass reactors suffers from several limitations that can be overcome using a continuous flow electro-reactor. Indeed, over the past five years, the development of continuous flow electrochemical cells has enabled the combination of organic electrosynthesis and continuous flow chemistry.[229] Furthermore, this alliance has made selective syntheses with high yields possible, and more often with a single pass through the devise, and thus a shorter reaction time. In the following subsections, the advantages of the association of those two techniques are listed.

First, batch electrochemical reactions suffer from a lack of reproducibility. Indeed, in the literature, the exact description of the electrochemical apparatus is usually not properly described. Even if electrodes material is given, the reactor geometries, dimensions, and positioning are not. Nevertheless, the use of a continuous flow electrochemical reactor enables to overcome this problem. Absolutely, with their

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[227] (a) Roberge, M.D.; Ducry, L.; Bieler, N.; Cretton, P.; Zimmermann, Z. *Chem. Eng. Technol.* **2005**, 28, 3; (b) Roberge, M.D.; Zimmermann, B.; Rainone, F.; Gottsponer, M.; Eyholzer, M.; Kockmann, N. *Organic Process Research & Development* **2008**, 12, 905.

[228] Hessel, V.; Kralisch, D.; Kockmann, M.; Noël, T. *ChemSusChem* **2013**, 6, 746.

[229] Electrochemistry made easy with continuous flow chemistry techniques, Mansfield, A. **2018** *Flow chemistry, the flow chemistry collection.*

precise geometry, this type of reactors eliminates a lot of problems with reproducing experimental procedures.

Secondly, organic electrochemical reactions are surface phenomenon; the heterogeneous electron transfers only take place at the surface of the electrodes. This means that a large electrodes surface area to reactor volume is required to ensure the best reaction yield and the shortest reaction time. Additionally, flow reactors dispose of a large electrodes surface area to reactor volume compared to equivalent volume batch reactors. Therefore, continuous flow reactors are more adapted to electrochemical processes.

Thirdly, in batch electrochemical apparatus, electrodes are separated by a larger gap than in continuous flow device. This larger distance between the electrodes leads to a loss of control of the current passing between the electrodes, and thus to an electron gradient. Indeed, the resistivity of the electrolytic solution causes the loss of electric energy in heat via a joule heating phenomenon. In order to minimize the loss of electric energy, continuous flow electrochemical reactors are based on parallel electrodes set-up in which the electrodes are divided by a really small gap (1 mm – 0.1 mm) using a gasket that creates a flow pathway.

Fourthly, in batch mode, the utilization of an electrolyte salt is mandatory given that common organic solvents have a low conductivity. However, in continuous flow electrochemical microreactors, the distance between electrodes is very small; and therefore, the two diffusion layers of the electrodes can overlap.[230] In this case, the ions formed at the electrodes surface play the role of supporting electrolyte; and thus, the need for supporting electrolyte is eliminated. That makes continuous flow electrochemical processes less expensive and enables easier purification.

Moreover, in contrast to batch electrochemical reactors, which require a long reaction time, continuous flow electrochemical reactors enable to reach high yields in a short reaction time.[231] This is due to the excellent electrodes surface area to reactor volume ratio of flow reactors. Additionally, this short residence time in flow reactors is also advantageous form a viewpoint of the control of highly reactive radical intermediates.

Furthermore, due to the smaller volumes handled in flow reactors, transfers and removals of heat are more effective than in batch electrochemical reactors.[232] Therefore, the control of side-reactions is better in continuous flow reactors.

Finally, with the need for environmentally friendly chemistry, a large number of electrochemical transformations were developed at a laboratory scale. Nevertheless, the green advantage of organic electrochemistry has only a real impact if the electrochemical process is employed on an industrial scale. Therefore, the scale-up of organic electrochemistry reactions is a critical step. Moreover, the application of

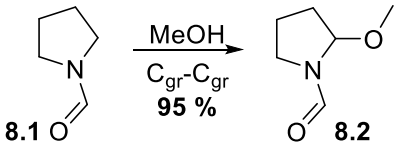
[230] Watts, K.; Gattrell, W.; Wirth, T.; *Beilstein J. Org.* **2011**, 7, 1108.
[231] (a) Moinet, C. *Journal de Physique III* **1994**, 4, 175; (b) Tolgueiras-Amador, A.A.; Philipps, K.; Guilbaud, S.; Poelakker, J.; Wirth, T. *Angew. Chem. Int. Ed.* **2017**, 56, 15446.
[232] Folgueiras-Amador, A.A.; Wirth, T. *J. Flow. Chem.* **2017**, 7, 94.

continuous flow electrolysis is of major importance for scaling-up an organic electrochemical transformation. Indeed, continuous flow electrochemical processes are easy to scale-up. The scale-up can be done either by enlarging the electrodes surface or by numbering-up.[233]

## 8.2.1 Laboratory applications

### *8.2.1.1 Shono oxidation*

In 2015, Pletcher *et al.* reported a beautiful example of the combination of continuous flow chemistry and organic electrochemistry applied to the Shono reaction (see Scheme **226**).[234] In this study, they proved that micro-flow electrolysis cells can be used for multigram scale synthesis in laboratory. Indeed, a micro flow reactor made of two circular electrodes, a spiral electrolyte flow channel, and 0.5 mm inter-electrodes gap was used to perform Shono reactions with 100 % conversion in a single pass, more than 95 % yield, and an excellent product formation rate of 20 g/h (see Figure **6**). This fantastic example shows that if the electrolysis cell architecture is well designed, the combination of the continuous flow chemistry and electrochemistry has a huge potential.




**Scheme 226 Shono oxidation**

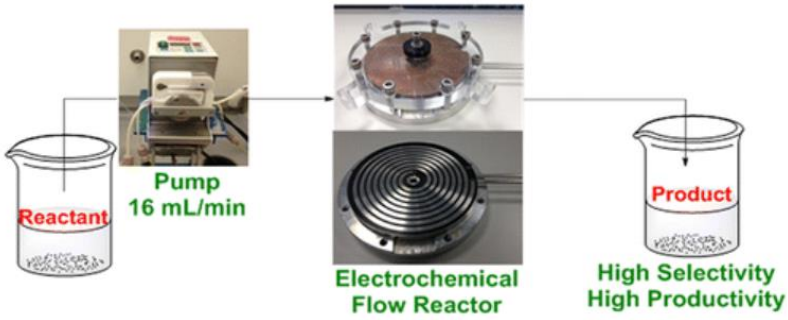



**Figure 6 micro-flow electrolysis cell**

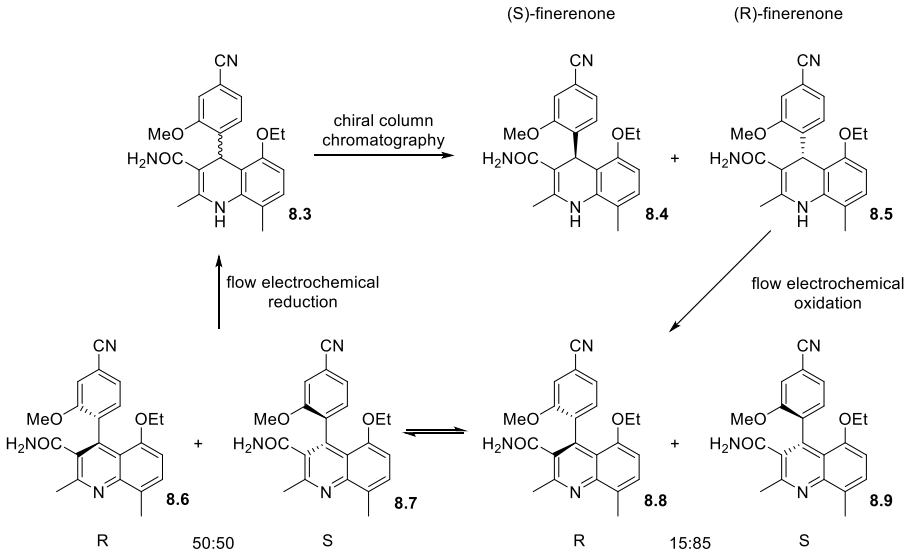
## 8.2.2 Industrial applications

### *8.2.2.1 (S)-finerenone*

In 2017, Bayer employed continuous flow electrochemistry in order to synthetize (S)-finerenone **8.4**, a molecule used as an active substance to minimize the progression of kidney disease in patients with type 2 diabetes (see Scheme **227**).[235] This procedure involved synthesis of the finerenone **8.3** as a racemic mixture, followed by chiral column chromatography to give the required S-enantiomer **8.4**.

[233] Gütz, C.; Stenglein, A.; Waldvogel, S.R. *Org. Process. Res. Dev.* **2017**, 21, 771.
[234] Green, R.A.; Brown, R.C.D.; Pletcher, D. *Org. Process. Res. Dev.* **2015**, 19, 1424.
[235] Hughes, D.L. *Org. Process Res. Dev.* **2018**, 22, 13.

Furthermore, the unwanted R-enantiomer **8.5** was recycled via conversion back to the racemic compound by an oxidation/reduction process. Therefore, a continuous flow electrochemical procedure was developed for both the oxidation and reduction steps. Remarkably, this continuous flow electrochemical process was employed to produced 200 kg of (S)-finerenone **8.4** for clinical trials.[236]

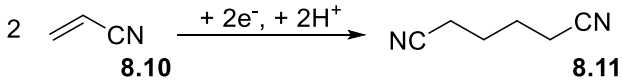



**Scheme 227 (S)-finerenone synthesis**

*8.2.2.2 Adiponitrile*

In 1984, Monsanto developed the "new Monsanto process", which dimerizes acrylonitrile **8.10** to adiponitrile **8.11** via reduction in a continuous flow electro-reactor (see Scheme **228**).[237] The new synthesis of this precursor to hexamethylene diamine for the production of nylon 6-6 was found to give higher current efficiency, less complex product extraction, and simpler cell design than the classical batch electro-production of this compound. Moreover, this process was selected for the expansion of adiponitrile in both the UK and the USA, and it is thanks to that that the output of adiponitrile by electrolysis exceeds now 300 000 ton/year.[238] This second generation process uses an emulsion of acrylonitrile in water, and a low concentration of quaternary ammonium salt, as supporting electrolyte. Furthermore, the product separation is straightforward: the organic and aqueous layers are separated; the organic phase is washed with water, and finally distilled. Additionally, 0.5 % of EDTA is used as an additive to reduce anode corrosion, and it also complexes metal ions in solution and thus reduces the rate of cathodic metal deposition, which reduces the rate of passivation of the cathode. Finally, in this continuous flow reactor, the solution circulates across the parallel inter-electrode gaps at a flow velocity of 1-2 m/s (see Figure **7**). Simultaneously, the emulsion is recycled through the cell from a reservoir; and a portion of the organic layer is continuously extracted for isolation of the final product.

[236]Platze, K.J.; Gottfried, K.; Assmann, J.; Lolli, G. WO 2017/032678 A1, March 2, 2017.
[237] Danly, D.E. *Electrochem. Soc.* **1984**, 131, 4135.
[238] Degner, D. *Electrochemistry III* **2005**, 1.




**8.10** **8.11**

**Scheme 228 reduction of acrylonitrile 8.10 to form adiponitrile 8.11**

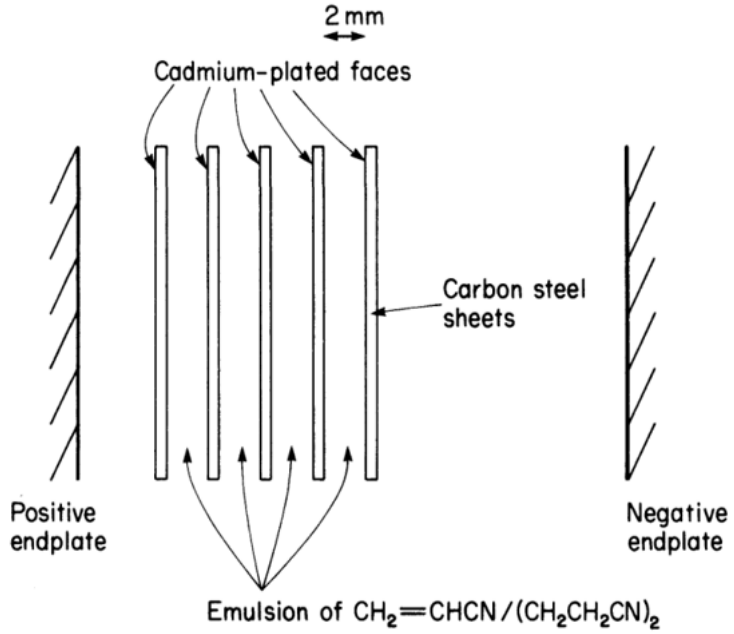
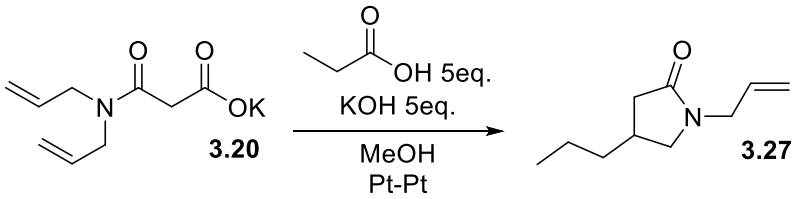



**Figure 7 continuous flow electro-reactor for the production of adiponitrile**

## 8.3 Objectives of the industrial collaboration

An industrial collaboration was created between the Université catholique de Louvain and UCB Pharma to transpose the electrocyclization of functionalized 2-pyrrolidinones from a batch electrochemical reactor to a continuous flow electrochemical reactor. Indeed, an electrochemical transformation has only a real ecological interest if the reaction is performed at an industrial scale. Therefore, the scale-up of an electrochemical transformation is a very important step. To do the scale-up of an electrochemical reaction, the reaction has to be transposed in a continuous flow electrochemical cell, because continuous flow electrochemical transformations are readily scaled-up. Moreover, given its precise geometry, short inter-electrodes gap, and high surface of electrodes to cell volume ratio, the use of an electrochemical flow cell should offer good reproducibility, short reaction time, and better yields.




**3.20** **3.27**

**Scheme 229 electrocyclization of 1-allyl-4-propylpyrrolidin-2-one 3.27**

The collaboration was performed in a Chemical Process Research and Development team specialized in continuous flow chemistry. During the collaboration, we worked on the optimization and transposition of the electrocyclization of 1-allyl-4-propylpyrrolidin-2-one **3.27** using the IKA ElectraSyn Flow electrochemical reactor (see Scheme **229**).

## 8.4 Continuous flow electrochemical reactor: IKA ElectraSyn Flow

In order to optimize the electrocyclization of functionalized 2-pyrrolidinones, we had to transpose this reaction from a batch electrochemical cell to a continuous flow electrochemical cell. Therefore, the IKA ElectraSyn Flow reactor was used. This reactor is a modular parallel plate electrochemical cell. The flow cell is formed from two half cells (13 cm* 4.6 cm* 4 cm, see Picture **5**), which are assembled between two stainless steel plates using eight screws. The ElectraSyn Flow cell (see Pictures **3** and **4**) enables high modularity because, with a wide range of Teflon half-cells with various electrode materials, different anode-cathode combinations are possible. Indeed, there are Teflon half-cells with electrodes (12 $cm^2$ = 2 cm* 6 cm) made of graphite, glass-carbon, nickel, copper, lead, bronze, and platinum. A spacer with a thickness of 0.5 mm allows to separate the two half-cells, which creates a cell volume of 0.6 ml. The spacer slightly overlaps the electrodes, which seals the gap between the Teflon and the electrodes. The full set-up is composed of a pump, E36100 series DC power supply, tubing, cables, an electrochemical cell, a receptacle for the stock solution, and a stirring plate (see Picture **2**).
Additionally, a heat exchanger (see Picture **6**) was constructed and added to the set-up, in order to cool the solution before its entry into the electrochemical cell. Indeed, temperature control is really important; it is noteworthy that a significant part of the electric power is converted in heat due to resistivity, gas evolution on the surface of the electrodes, and overpotentials. And all of this can lead to a huge temperature rise, which makes an adequate cooling system mandatory in order to limit side-reactions.

In the course of continuous flow electrolysis, the stock solution is pumped through a hose by means of a pump (see Figure **8**). First the solution is cooled using the heat-exchanger, and then the solution flow through the electrochemical cell, where the reaction takes place. The electrochemical cell contains two parallel electrodes a small distance apart. These electrodes are connected to the outlet socket of a DC power supply via two power lines. The solution containing the product produced leaves the cell via a hose, together with any side product produced, and unreacted substrate. Finally, the solution goes back into the stock receptacle; and the cycle is repeated until completion of the reaction.

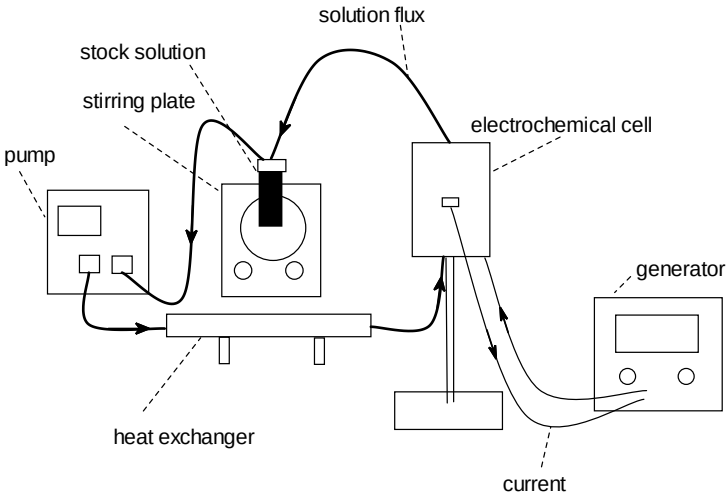
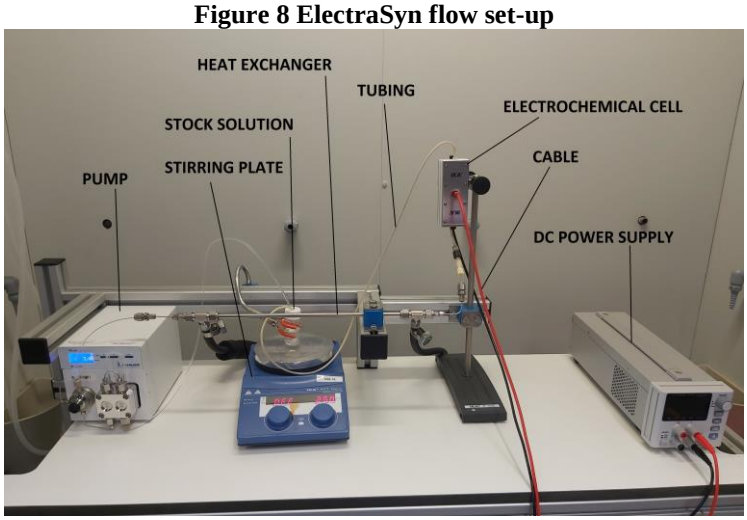
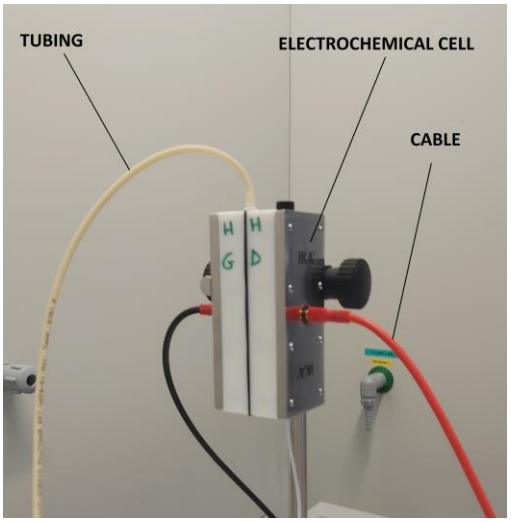


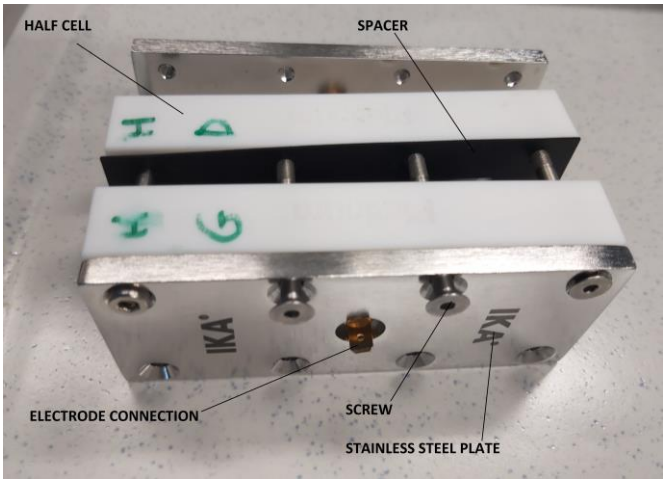

**Figure 8 ElectraSyn flow set-up**



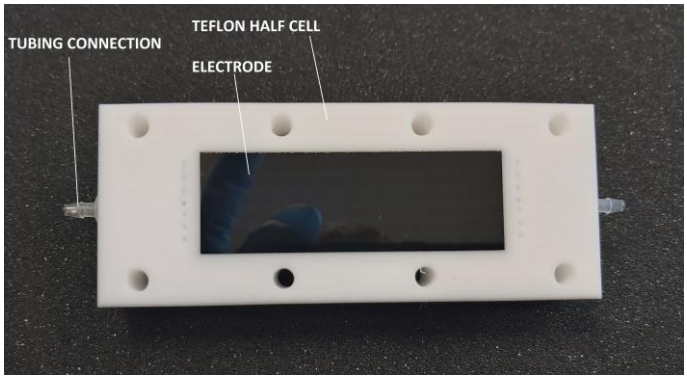

**Picture 2 ElectraSyn Flow set-up**




**Picture 3 electrochemical cell**




**Picture 4 electrochemical cell**




**Picture 5 half cell**

**Picture 6 heat exchanger**

## 8.5 Determination of the reactor volume

In order to determine the yields and conversions of the continuous flow electrolyzes via gas chromatography (GC) and ultra-performance liquid chromatography-tandem mass spectrometer (UPLC-MS), the total volume of the electrochemical reactor had to be calculated. Therefore, GC analysis was used to calculate this total volume.

Let's consider an electrochemical continuous flow reactor constituted of a stock solution, tubing, an electrochemical cell, a heat exchanger, and a pump. V1 corresponds to the volume of the stock solution and is known; and V2 is the combined volumes of the pump, tubing, heat exchanger, and electrochemical cell and is to determine. Moreover, $V_{tot}$ is the total volume of the electrochemical continuous flow reactor, and $V_{tot} = V1 + V2$. At a time T0, the electrochemical set-up is filled with methanol.

In order to calculate the volume V2, a mass X of hexanoic acid is introduced in the volume V1, at T0. Subsequently, the solution is homogenized in the flow reactor. After homogenization, the time is T1.

If Y is the mass of hexenoic acid in V1 at T1; and Z is the mass of hexenoic acid in V2 at T1:

$$X = Y + Z$$
$$Z = X - Y$$

Furthermore, at T1, after homogenization:

$$C1 = C2$$

Where C1 is the concentration in hexenoic acid in V1 and C2 is the concentration in hexenoic acid in V2.

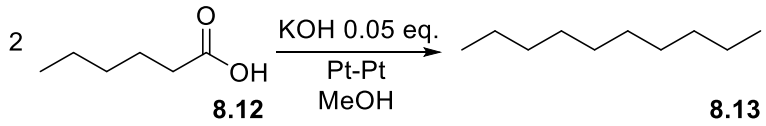
Therefore: $Y/V1 = Z/V2$
$Y/V1 = (X-Y)/V2$

$$V2 = ((X1-Y)*V1)/Y$$

Given that Y can be determined via GC analysis at T1 using a calibration curve, V2 can be calculated. V2 has a value of 9.17 ml, which means that the combined volume of the tubing, electrolysis cell, pump, and heat exchanger is 9.17 ml.

## 8.6 Familiarization with the IKA ElectraSyn Flow reactor

Once the IKA ElectraSyn Flow reactor was constructed, a familiarization study was carried out in order to have a better understanding of the use of this reactor, and in the interest of not wasting the electrocyclization substrate, which is synthetized beforehand. To perform this familiarization study, the simple Kolbe dimerization of the commercially available hexanoic acid **8.12** into decane **8.13** was chosen (see Scheme **230**). Furthermore, gas chromatography analysis was used to determine the conversions of electrolyzes using a calibration curve established beforehand. The reactions were performed without heat exchanger and with platinum plated electrodes.




**8.12** **8.13**

**Scheme 230 Kolbe dimerization of hexenoic acid 8.12 into decane 8.13**

First, five reactions were performed in order to determine the conversion after a single pass in the electrochemical cell (see Table **12**). For this reason, samples were taken just at the end of the electrochemical cell. The reactions were done at constant current; and 0.5 mol/l of hexanoic acid was dissolved in methanol with 0.05 eq. of KOH as supporting electrolyte. An analysis of the results shows that, for the same debit value, a higher current density promotes better conversions. Moreover, for the same current density value, a higher debit gives better conversions.

**Table 12 dimerization of the hexenoic acid 8.12 into decane 8.13**

| n° exp | J (mA/cm²) | d (ml/min) | Conv. (%) |
|---|---|---|---|
| 1 | 8.33 | 1 | 6.7 |
| 2 | 8.33 | 3 | 8.1 |
| 3 | 16.67 | 2 | 14.8 |
| 4 | 25.00 | 1 | 14.4 |
| 5 | 25.00 | 3 | 15.8 |

Secondly, the conversion of the Kolbe dimerization of the hexanoic acid **8.12** into decane **8.13** was determined, after a certain time, while the solution continuously flows through the electrochemical cell, tubing, pump, stock solution, and heat exchanger (see Table **13**). Electrolyzes were performed with a flow rate of 1 ml/min, at a concentration in substrate of 0.5 mol/l. Results show that excellent conversion (98 %) were obtained after 30 minutes, at a current density of 36.66 mA/cm². Moreover, working at a current density of 208.33 mA/cm², for 15 minutes, without electrolyte salt gave also excellent conversion (99 %). This means that, given the small inter-electrodes gap, the resistance is so small that the use of an electrolyte salt

is not necessary to perform a Kolbe dimerization in the ElectraSyn Flow. Finally, higher current density value and longer electrolysis time give better conversions.

**Table 13 dimerization of the hexenoic acid into decane**

| n° exp | T (min) | J (mA/cm²) | KOH (eq.) | Conv. (%) |
|---|---|---|---|---|
| 1 | 15 | 33.33 | 0.05 | 16 |
| 2 | 15 | 45.83 | 0.05 | 42 |
| 3 | 15 | 208.33 | 0.00 | 99 |
| 4 | 30 | 36.66 | 0.05 | 98 |

Considering the excellent conversions obtained for the Kolbe dimerization, in the IKA ElectraSyn Flow reactor, we started to optimize the electrocyclization of functionalized 2-pyrrolidinones in the ElectraSyn Flow reactor.

## 8.7 Optimization and transposition of the electrocyclization of 1-allyl-4-propylpyrrolidin-2-one in the IKA ElectraSyn Flow reactor

### 8.7.1 Design of experiments with three factors

First, a design of experiments with three factors was conducted for the purpose of optimizing the electrocyclization of 1-allyl-4-propylpyrrolidin-2-one **3.27**, a brivaracetam derivative (see Figure **9**). Moreover, in the case of an organic electrochemical reaction, the transposition of electrolysis from a batch reactor to a continuous flow cell is an important step in the scale-up of this reaction. Therefore, this optimization study in the IKA ElectraSyn Flow cell should help us to prove the industrial interest of the electrolysis that we have developed at a laboratory scale. We have chosen a design of experiments with three factors and in which each factor has three values; the factors have a direct influence on the results of the reactions: yields, purity, and conversions (Conv.). Those three factors are: the substrate concentration (C), the current density (J) or current (I), and the flow rate of the solution (d). Furthermore, the values of flow rate are 2, 3, and 4 ml/min; the values of concentration are 33, 66, and 99 mmol/l. Additionally, the values of current are 500, 750, and 1000 mA; which corresponds to values of current density of 41.66, 62.50, and 83.33 mA/cm² given that the electrodes area is 12 cm². This experimental plan allowed us to study the effect of those three independent variables on the yield and the conversion of the electrocyclization of 1-allyl-4-propylpyrrolidin-2-one, because in many cases, several factors may be interdependent, and thus it is impractical to attempt to analyze the effect of one variable at a time.

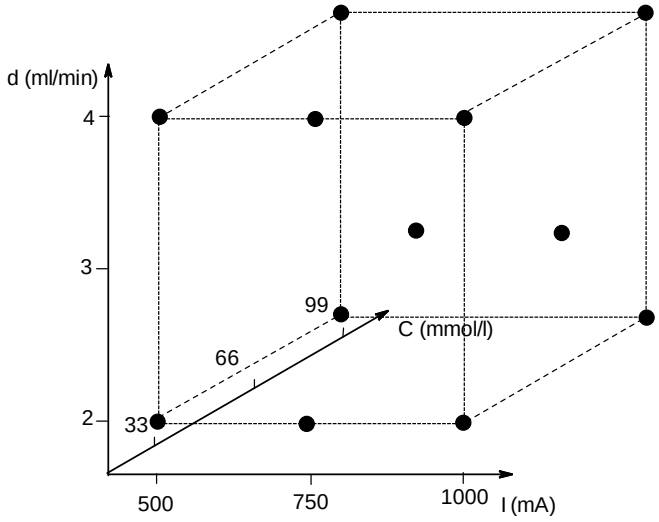
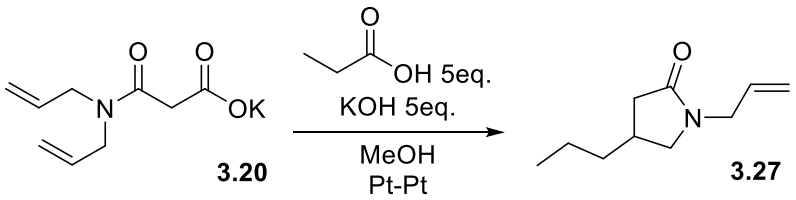



**Figure 9 design of experiments with three factors**

In order to do this design of experiments, several electrolyzes were conducted to form 1-allyl-4-propylpyrrolidin-2-one **3.27**, a brivaracetam derivative (see Scheme **231**). Those reactions were performed in the IKA ElectraSyn flow, for 30 minutes, with a heat exchanger temperature of 5°C, and with platinum electrodes. Moreover, the three factors were varied for each reaction as you can see from the Table **14**. After 30 minutes of reaction, the stock solutions were filtered using syringe filters and analyzed via UPLC-MS to determine the yields and conversions (Conv.) of the electrolyzes using some calibration curves. This study should allow us to estimate the optimum conditions for this transformation. After each electrolyzes, the flow cell set-up was washed with water, acetone, and methanol; and the electrodes were washed with an aqueous solution of HCl 37 %, if impurities remain at the electrodes surface.




**Scheme 231 electrocyclization of 1-allyl-4-propylpyrrolidin-2-one 3.27**

**Table 14 design of experiments with three factors**

| exp | I (mA) | C (mmol/l) | d (ml/min) | Conv. (%) | Yield (%) |
|---|---|---|---|---|---|
| 1 | 1000 | 66 | 3 | 60 | 34 |
| 2 | 750 | 33 | 2 | 15 | 10 |
| 3 | 750 | 33 | 4 | 95 | 38 |
| 4 | 500 | 33 | 2 | 82 | 36 |
| 5 | 750 | 66 | 3 | 76 | 34 |
| 6 | 1000 | 33 | 2 | 36 | 4 |
| 7 | 750 | 66 | 3 | 65 | 64 |
| 8 | 1000 | 33 | 4 | 99 | 16 |
| 9 | 1000 | 99 | 4 | 74 | 72 |
| 10 | 500 | 33 | 4 | 96 | 73 |
| 11 | 1000 | 99 | 2 | 56 | 44 |
| 12 | 500 | 99 | 2 | 11 | 1 |
| 13 | 500 | 99 | 4 | 61 | 55 |

*8.7.1.1 Analysis of the effect of the substrate concentration on the yields and conversions*

An analysis of the effect of the substrate concentration on the conversions and yields of the electrocyclization of 1-allyl-4-propylpyrrolidin-2-one **3.27** shows that, in comparable conditions, a lower concentration usually leads to higher conversions (see Table **15**). Moreover, no trend is observed regarding the effect of the substrate concentration on the yields of the reaction. This may be due to the interactions between the factors that have an impact on the conversions and yields.

**Table 15 effect of the substrate concentration on the yields and conversions**

d = 2 ml/min - I = 500 mA

| C (mmol/l) | Conv. (%) | Yield (%) |
|---|---|---|
| **33** | 82 | 36 |
| **99** | 11 | 1 |

d = 2 ml/min - I = 1000 mA

| C (mmol/l) | Conv. (%) | Yield (%) |
|---|---|---|
| **33** | 36 | 4 |
| **99** | 56 | 44 |

d = 4 ml/min - I = 500 mA

| C (mmol/l) | Conv. (%) | Yield (%) |
|---|---|---|
| **33** | 96 | 73 |
| **99** | 61 | 55 |

d = 4 ml/min - I = 1000 mA

| C (mmol/l) | Conv. (%) | Yield (%) |
|---|---|---|
| **33** | 99 | 16 |
| **99** | 74 | 72 |

*8.7.1.2 Analysis of the effect of the flow rate of the solution on the yields and conversions*

An analysis of the effect of the flow rate of the solution on the conversions and yields of the electrocyclization process shows that, in comparable reaction conditions (constant current density and substrate concentration), a faster flow rate leads to better yields and higher conversions (see Table **16**). Two hypotheses enable to explain this phenomenon. First, a fast flow rate makes the residence time in the cell shorter, which means that the product formed spends less time in the cell, and thus is less prone to side-reactions. Secondly, given that the solution is cooled upstream from the electrochemical cell, a faster flow rate allows to better control the temperature inside the cell. Indeed, the solution is less prone to be heated, which should lead to less side-reactions. Actually, at the cell outlet, the solution is warmer than at the cell inlet since a part of the electric energy is lost as heat. Therefore, it is important to be able to regulate the temperature correctly.

**Table 16 effect of the flow rate of the solution of the yields and conversions**

I = 500 mA - C = 33 mmol/l

| d (ml/min) | Conv. (%) | Yield (%) |
|---|---|---|
| **2** | 82 | 36 |
| **4** | 96 | 73 |

I = 1000 mA - C = 33 mmol/l

| d (ml/min) | Conv. (%) | Yield (%) |
|---|---|---|
| **2** | 36 | 4 |
| **4** | 99 | 16 |

I = 500 mA - C = 99 mmol/l

| d (ml/min) | Conv. (%) | Yield (%) |
|---|---|---|
| **2** | 11 | 1 |
| **4** | 61 | 55 |

I = 1000 mA - C = 99 mmol/l

| d (ml/min) | Conv. (%) | Yield (%) |
|---|---|---|
| **2** | 56 | 44 |
| **4** | 74 | 72 |

*8.7.1.3 Analysis of the effect of the current on the yields and conversions*

An analysis of the effect of the current intensity on the conversions and yields of the electrocyclization of 1-allyl-4-propylpyrrolidin-2-one **3.27** shows that a higher current density globally leads to higher conversions (see Table **17**). Moreover, with a substrate concentration of 33 mmol/l, a lower current density usually leads to better yields. Indeed, higher current density should lead to more electron transfers, and thus to a higher reagent consumption. Moreover, working at a high current density leads to higher electrodes potentials, and therefore to more potential side-reactions.

**Table 17 effect of the current on the yields and conversions**

d = 2 ml/min - C = 33 mmol/l

| I (mA) | Conv. (%) | Yield (%) |
|---|---|---|
| **500** | 82 | 36 |
| **750** | 15 | 10 |
| **1000** | 36 | 4 |

d = 4 ml/min - C = 33 mmol/l

| I (mA) | Conv. (%) | Yield (%) |
|---|---|---|
| **500** | 96 | 73 |
| **750** | 95 | 38 |
| **1000** | 99 | 16 |

d = 2 ml/min - C = 99 mmol/l

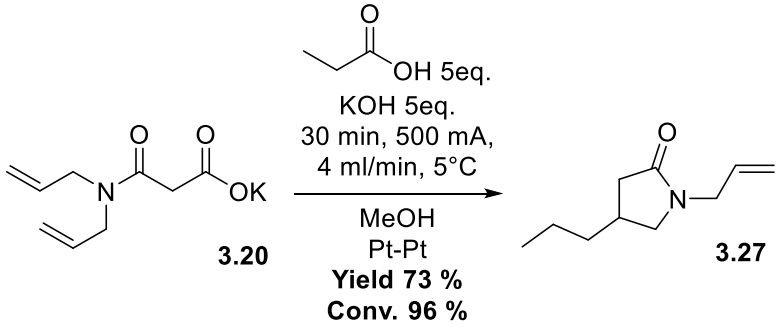
| I (mA) | Conv. (%) | Yield (%) |
|---|---|---|
| **500** | 11 | 1 |
| **1000** | 56 | 44 |

d = 4 ml/min - C = 99 mmol/l

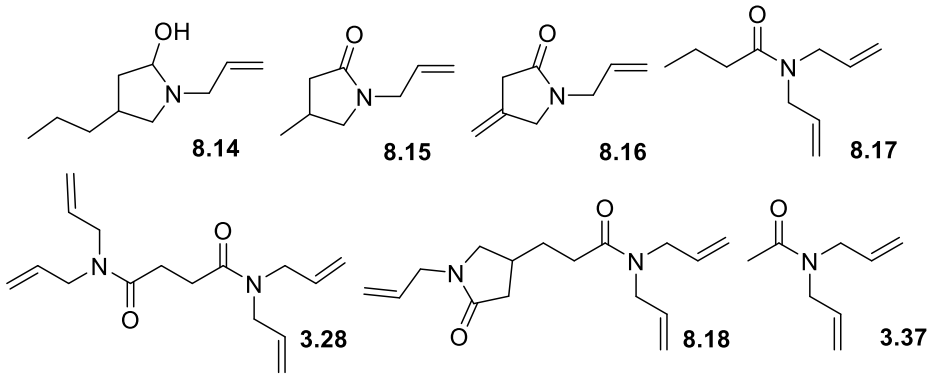
| I (mA) | Conv. (%) | Yield (%) |
|---|---|---|
| **500** | 61 | 55 |
| **1000** | 74 | 72 |

*8.7.1.4 Conclusion of the design of experiments with three factors*

In conclusion, this design of experiments enabled to see the effect of interactions between factors on the yields and conversions of the electrocyclization of 1-allyl-4-propylpyrrolidin-2-one. The optimum conditions are a current value of 500 mA, a substrate concentration of 33 mmol/l, and a solution flow rate of 4 ml/min; these conditions lead to a good yield of 73 % and an excellent conversion of 96 %, in only 30 minutes (see Scheme **232**). Finally, the UPLC-MS analyzes showed that side-products are formed during the electrolysis and that optimization of the reaction conditions is mandatory to limit the formation of these impurities (see Scheme **233**).



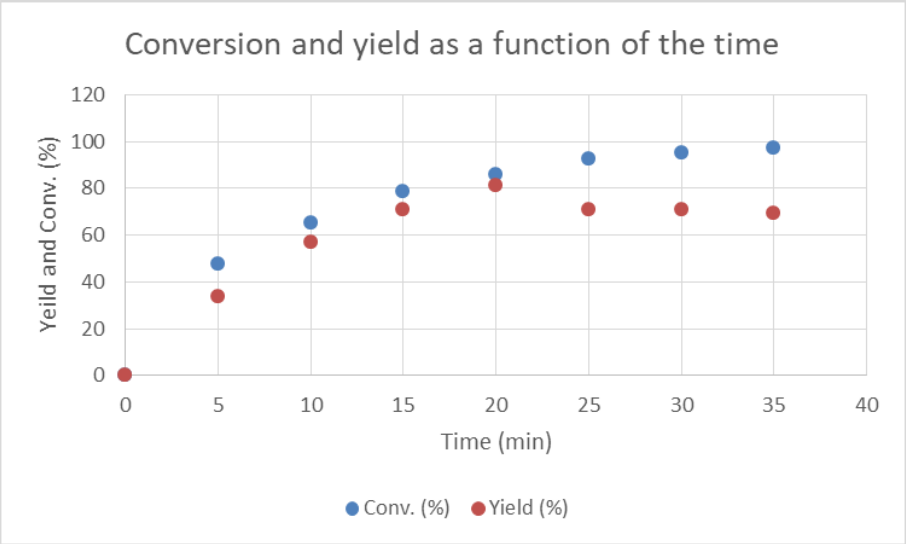

**Scheme 232 optimum conditions of the design of experiments with three factors**



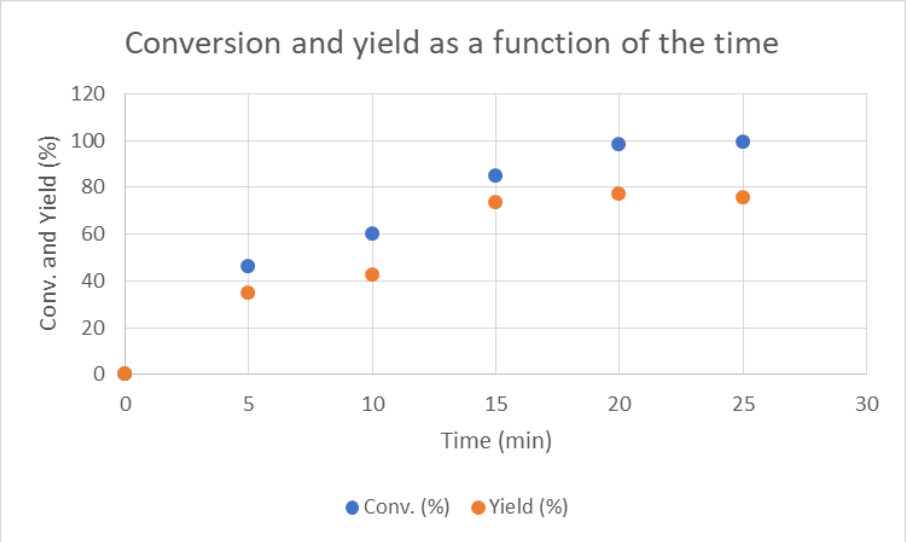

**Scheme 233 impurities formed during the electrocyclization of 1-allyl-4-propylpyrrolidin-2-one**

### 8.7.2 Kinetic study

With the optimized conditions in hand, two kinetic studies were conducted in order to continue optimizing the reaction and to have a better understanding of the process in the IKA ElectraSyn Flow reactor. Those electrolyzes were performed at a substrate concentration of 33 mmol/l, and at a constant current of 500 mA. Moreover, considering that a solution flow rate of 4 ml/min gave the best results, two higher solution flow rates were studied: 6 ml/min (see Graph **5**), and 10 ml/min (see Graph **6**), to see if higher flow rates gave better results. Therefore, the two electrolyzes were conducted and samples were taken every 5 minutes inside the stock solution and analyzed via UPLC-MS. The graphs of the surface area of the reagent (R) **3.20** and the product (P) **3.27** as a function of time were finally plotted.



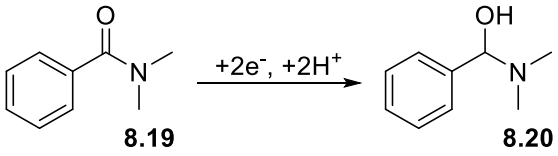

**Graph 5 kinetic study of the electrocyclization of 1-allyl-4-propylpyrrolidin-2-one 3.27 with a flow rate of 6 ml/min**




**Graph 6 kinetic study of the electrocyclization of 1-allyl-4-propylpyrrolidin-2-one 3.27 with a flow rate of 10 ml/min**

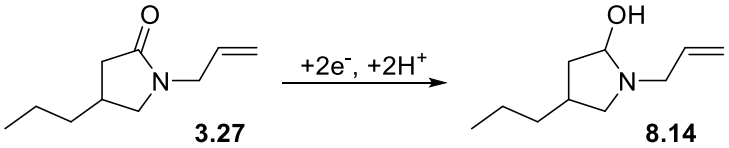
An analysis of the Graphs **5** and **6** shows that, after 20 minutes, the maximal yields were reached: 81 % yield at flow rate of 6 ml/min and 77 % at a flow rate of 10 ml/min. Furthermore, after 20 minutes of reaction, the product appears to be degraded. Indeed, the UPLC-MS analyzes show the presence of an impurity with a mass of 169 g/mol, which could correspond to the product of the reduction of the amide-type carbonyl in the product structure. In other words, a small quantity of the product formed **3.27** could be reduced into the corresponding hemiaminal **8.14** (see Scheme **235**). In the literature, reductions of amide into hemiaminal are described. For instance, the *N*,*N*-dimethylbenzamide **8.19** can be reduced into the

corresponding hemiaminal **8.20**, using a boron-doped diamond or lead cathode (see Scheme **234**).[239] Finally, if this hypothesis is true, the use of a divided cell should allow to prevent the formation of this impurity, as the product is formed at the anode and the impurity at the cathode.




**8.19** **8.20**

**Scheme 234 reduction of the *N,N*-dimethylbenzamide 8.19 into the corresponding hemiaminal intermediate 8.20**




**3.27** **8.14**

**Scheme 235 reduction of the 1-allyl-4-propylpyrrolidin-2-one 3.27 into the corresponding hemiaminal 8.14**

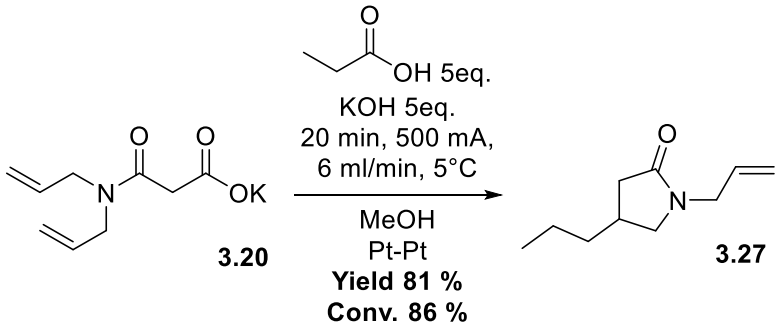
*8.7.2.1 Conclusion of the kinetic study*

In conclusion, if we compare the two best results of the kinetics study (see Table **18** entries **2** and **3**) and the best result of the design of experiments with 3 factors (see Table **18** entry **1**), we can see that a flow rate of 10 ml/min allows to get the best conversion (98 %) after only 20 minutes. Nevertheless, a flow rate of 6 ml/min enables to get the best yield (81 %) in only 20 minutes. This kinetics study allowed us to shorten the reaction time (20 min) and increase the yield (81 %) (see Scheme **236**). Indeed, after 20 minutes, a small part of the product is degraded, and thus electrolyzes should not last more than 20 min in these conditions.

**Table 18 three optimum conditions**

| exp | d (ml/min) | T (min) | Conv. (%) | Yield (%) |
|---|---|---|---|---|
| 1 | 4 | 30 | 96 | 73 |
| 2 | 6 | 20 | 86 | 81 |
| 3 | 10 | 20 | 98 | 77 |

[239] Rix, K. thèse de doctorat, Imperial College London, **2013**.




**Scheme 236 Optimum conditions of the kinetic study**

### 8.7.3 Design of experiment with 2 factors

A second design of experiments was conducted in order to further optimize the electrocyclization reaction. This time a design of experiments with two factors was constructed around the optimum result of the kinetic study (6 ml/min, 500 mA, 33 mmol/l) (see Figure **10**). The two factors that vary are the flow rate of the solution (d) and the current intensity (I). The values of flow rate are 5, 6, and 7 ml/min, and the values of the current are 400, 500 and 600 mA. Moreover, every electrolyze were done inside the IKA ElectraSyn Flow reactor, with a substrate concentration of 33 mmol/l, and the temperature of the heat exchanger was 5°C. Finally, samples were taken after 18, 20 and 22 minutes of reaction to determine precisely when the maximal yield is reached.

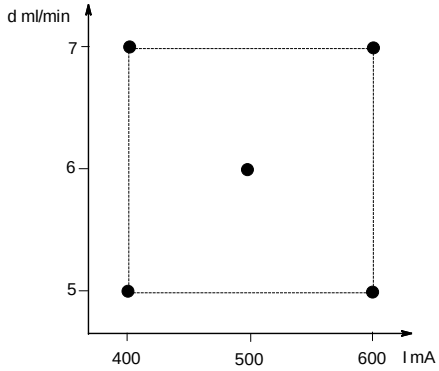



**Figure 10 design of experiments with two factors**

An analysis of the results of this design of experiments with two factors shows that a current intensity of 600 mA leads to better conversions than a current of 400 mA and 500 mA, which can be explained by a more important electron transfer. Furthermore, a current of 400 mA leads to better yields than currents of 500 and 600 mA, which can be explained by the lower electrode potential that is less likely to cause side-reactions. Moreover a flow rate of 7 ml/min leads to better yields and better conversions than a flow rate of 5 ml/min, which can be related to a better temperature control and a shorter residence time of the product in the electrochemical cell, and thus to less degradation of the product.

**Table 19 design of experiments with two factors**

I = 400 mA – d = 5 ml/min

| T (min) | Conv. (%) | Yield (%) |
|---|---|---|
| **18** | 61 | 42 |
| **20** | 76 | 44 |
| **22** | 77 | 46 |

I = 400 mA – d = 7 ml/min

| T (min) | Conv. (%) | Yield (%) |
|---|---|---|
| **18** | 76 | 67 |
| **20** | 88 | 75 |
| **22** | 89 | 82 |

I = 600 mA – d = 5 ml/min

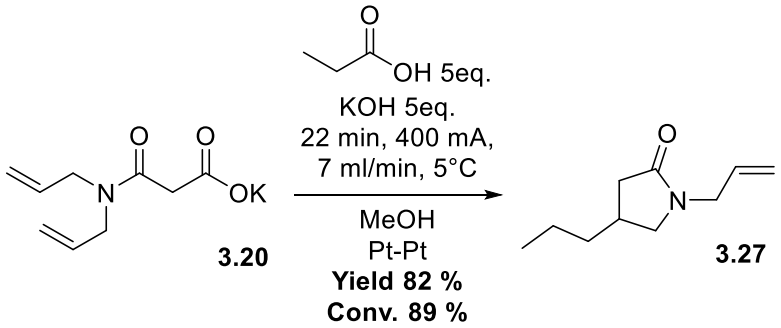
| T (min) | Conv. (%) | Yield (%) |
|---|---|---|
| **18** | 84 | 41 |
| **20** | 92 | 44 |
| **22** | 98 | 42 |

I = 600 mA – d = 7 ml/min

| T (min) | Conv. (%) | Yield (%) |
|---|---|---|
| **18** | 87 | 68 |
| **20** | 95 | 67 |
| **22** | 100 | 70 |

*8.7.3.1 Conclusion of the design of experiments with two factors*

In conclusion, this design of experiments with two factors allow us to determine the optimum conditions, where the maximal yield (82 %) is obtained, after 22 min of electrolysis, at 400 mA, with a flow rate of 7 ml/min, and a substrate concentration of 33 mmol/l (see Scheme **237**).




**Scheme 237 optimum conditions of the design of experiments with two factors**

## 8.7.4 Temperature study

In a Kolbe reaction, temperatures higher than 40°C should be avoided because they favor unwanted side-reactions, such as esterification of the carboxylic acid.[240] Therefore, the control of the temperature in an electrochemical cell is of upmost importance. Indeed, in the IKA ElectraSyn Flow, with the enlargement of the electrode surface (12 cm²), the electric power fed into the cell increases likewise, and a significant part of the electric energy is lost as heat in the system. This phenomenon can lead to a massive temperature rise, which makes an efficient cooling system mandatory. Therefore we constructed a heat exchanger and added it in the ElectraSyn Flow set-up. This cooling system was placed at the upstream of the electrochemical cell in order to properly cool the solution before it enters in the

[240] Schäfer, H.J. *Comprehensive Organic Synthesis* **1991**, 3, 633.

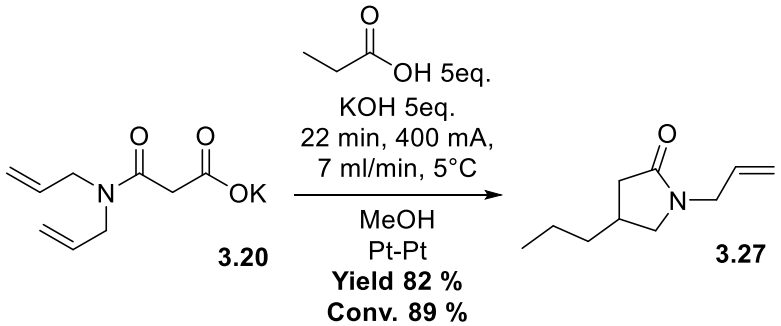
cell. A study was then carried out to determine the optimum temperature of the heat exchanger and study the impact on the yields and conversions (see table **20**). For this purpose, three electrolyzes were run, for 30 minutes, at a constant current of 500 mA, a flow rate of 4 ml/min, and a concentration in substrate of 33 mmol/l. During these three experiences, the temperature (T) of the heat exchanger was setted at 0, 5, and 20°C. The effect of the cooling system was immediately apparent. This resulted in a higher conversion of 99 %, at 0°C (see Table **20** entry **1**). Moreover, higher yield of **73** % was reached, at 5°C (see table **20** entry **2**), showing the significance of the heat exchanger in the ElectraSyn Flow setup.

**Table 20 temperature study**

| Exp | T (°C) | Yield (%) | Conv. (%) |
|---|---|---|---|
| 1 | 0 | 48 | 99 |
| 2 | 5 | 73 | 96 |
| 3 | 20 | 35 | 76 |

### 8.7.5 Conclusions and perspectives of the optimization and transposition of the electrocyclization of 1-allyl-4-propylpyrrolidin-2-one in the IKA ElectraSyn Flow reactor

In conclusion, the electrocyclization of the 1-allyl-4-propylpyrrolidin-2-one was transposed from a batch-type double jacketed cell to IKA ElectraSyn Flow cell. Therefore, the reaction parameters, which already have been optimized for the batch-type cell, were adapted in the flow cell. This transposition was a success and allowed to drastically lower the reaction time from 240 min in the batch cell to 22 min in the flow cell (see Scheme **238** and Table **21**). Moreover, the yield was increased form 71 % in the batch-cell to 82 % in the flow cell. Furthermore, the Faradic yield was also increased from 19 % in the batch cell to 31 % in the flow cell, which proves that the flow cell promotes higher current efficiency. This excellent result derives from the characteristics of the ElectraSyn flow cell, such as: a large ratio of electrodes surface area (12 cm²) to cell volume (0.6 ml), a small inter-electrodes gap (0.5 mm), and a good temperature control thanks to the heat exchanger and to the fast flow rate. Finally, the ElectraSyn Flow cell promotes better reproducibility with its defined geometry.




**Scheme 238 Optimal conditions of the electrocyclization of 1-allyl-4-propylpyrrolidin-2-one**

**Table 21 comparison of the electrocylization of 1-allyl-4-propylpyrrolidin-2-one in a continuous flow cell and in a batch cell**

| Electrolysis | Continuous flow electrolysis | Batch electrolysis |
|---|---|---|
| reactor | IKA ElectraSyn Flow | Batch double-jacketed cell |
| Cell | undivided cell | undivided cell |
| Electrodes | Pt-Pt | Pt-Pt |
| Cell volume | 0.6 ml | 25.0 ml |
| Inter-electrodes gap | 0.5 mm (constant) | 10.0 - 3.0 mm (variable) |
| solvent | MeOH | MeOH |
| cooling system | heat-exchanger | double-jacket |
| T cooling system | 5°C (constant) | 10°C (variable-tap water) |
| C in substrate | 33 mmol/l | 66 mmol/l |
| current density | 33.33 mA/cm² | 25 mA/cm² |
| duration | 22 min | 240 min |
| yield | 82% | 71% |
| Faradic yield | 31% | 19% |

In order to improve our continuous flow electrochemical reactor, the cooling system could be enhanced. Indeed, the use a heat-exchanger does not allow a perfect control of the temperature in the cell; and at the cell outlet, the solution is warmer than, at the cell inlet, since a part of the electric current is lost as heat. Therefore, in order to allow an accurate heat management, we could use the thermoregulated continuous flow cell developed by Waldvogel *et al.*.[241] The temperature of this cell can be readily controlled from the back side of the electrodes via an external cooling circuit.

Moreover, given that Kolbe cross-coupling reactions require low concentrations and thus a large volume of solvent, it would be important to recycle the solvent throughout electrolyzes to industrialize this process. Therefore, perevaporation could be a good way to recycle the methanol. By definition, perevaporation is a process technique for the separation of mixtures of liquids via partial vaporization through a membrane. This technique should allow us to concentrate the solution mixture at the outlet of the electrochemical cell, and to reinject the recycled methanol at the inlet to the electrochemical cell.

Furthermore, in order to further improve the reaction yield and shorten the reaction time, it would be interesting to study the impact of the spacer thickness and thus to vary the inter-electrodes gap.

To improve the ElectraSyn Flow setup, the platinum plated electrodes should be replaced by solid platinum electrodes. Indeed, the platinum plated electrodes are not

[241] Gütz, C.; Stenglein, A.; Waldvogel, S.R. *Org. Process Res. Dev.* **2017**, 21, 771.

of a good quality. After several electrolyzes, the platinum coating disappeared and the metal underneath the coating was deposited on the electrode surface.

In future research, the scale-up of this reaction in the IKA ElectraSyn Flow could be performed. Indeed, the application of flow electrolysis is of major importance for scaling-up organic electrolyzes. Moreover, scaling-up is crucial regarding the implementation of industrial electroorganic syntheses, and thus to show the real environmental benefit of these transformations.

Finally, the use of larger electrodes could be done to allow total conversion in a single pass.

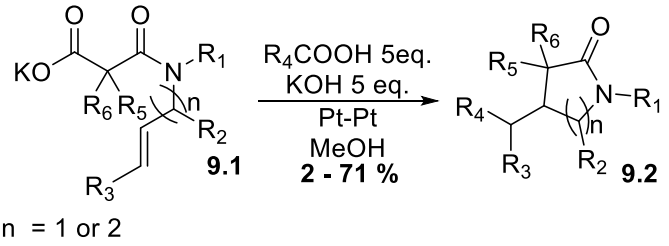
# 9 Conclusions and perspectives

## 9.1 General overview

During this PhD thesis, we have focused our work on the elaboration of an electrosynthesis of functionalized 2-pyrrolidinones with pharmaceutical interest. This work was based on the researches of Prof. Weedon, Prof. Schäfer, Dr. Buzzo, and Dr. Lebreux; who have worked on the development of a Kolbe electrosynthesis of carbon five- and six-membered rings, tetrahydrofurans, tetrahydropyrans, and pyrrolidines. We have chosen to use the organic electrochemistry because this methodology has the advantage of being ecological, economical, step-economical, selective, and easily transposable to batch and continuous flow reactors. In the following subsections, the general considerations and perspectives of all the chapters of this thesis are presented.

## 9.2 General considerations and perspectives about the Kolbe electrocyclization of 2-pyrrolidinones

The first part of our work was focused on the development, optimization, and exemplification of an electrocyclization of functionalized 2-pyrrolidinones, considering the great pharmacological interest for those molecules. This original and straightforward methodology, based on the Kolbe reaction, enables the cyclization and the subsequent functionalization of 2-pyrrolidinones, using the adequate co-acid; in only one step, two bonds are formed (see Scheme **239**).




**Scheme 239 electrosynthesis of functionalized 2-pyrrolidinones**

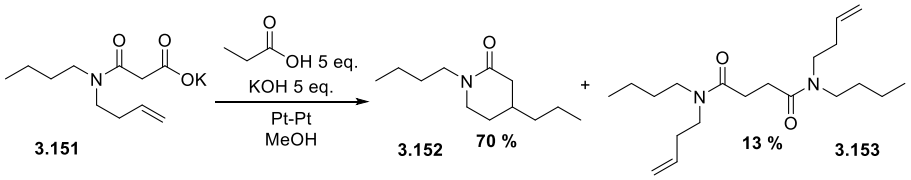
First, we synthetized an electrocyclization substrate **3.20** starting from inexpensive and commercially available ethyl potassium malonate **3.10** and diallylamine. Secondly, we developed and optimized the electrocyclization of this substrate in a functionalized 2-pyrrolidinone. Given that, in organic electrochemistry, a great number of parameters have a critical impact on the outcome of a reaction, the substrate concentration, current density, temperature, solvent, electrodes nature, and the number of equivalents of electrolyte were modified in order to optimize our transformation.

Thirdly, we tackled the formation of a library of diversely substituted 2-pyrrolidiones. To achieve that, several co-acids were tested; the nature of the protecting group of the nitrogen atom in the substrate structure was modified; and the double bond and malonic part of the substrate were diversely substituted. This exemplification study has shown the fantastic applicability of our process since 2-pyrrolidinones were functionalized with various chemical groups, such as: alkyl

chains, esters, ketones, olefins, aromatic rings, alcohols, propargyls, heterocycles, *gem*-dimethyl, halogens, and $CF_3$ functions.

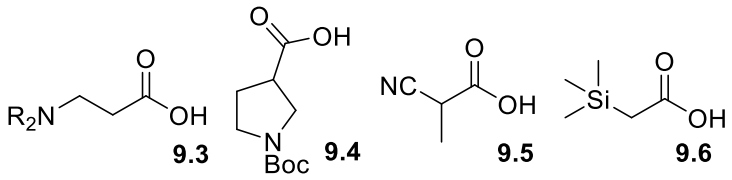
However, some limitations were noted during our optimization study. First, the use of trifluoroacetic acid as a co-acid gave bad results; we think that this may be due to the strong acidity or the high oxidability of this compound. Moreover, the formation of 2-pyrrolidinones bearing an alcohol or an aromatic function gave low yields; redox side-reactions and adsorption processes may explain these results. Finally, we were not able to use sulfinic acids as co-acid in our protocol.

Finally, the replacement of the allyl function, in the substrate structure, by a homoallyl group allowed to expand the scope of our method to the electrosynthesis of 2-piperidinones **3.152**, via a *6-exo-trig* cyclization (see Scheme **240**). Moreover, in future research, it would be interesting to optimize and exemplify the electrosynthesis of 2-piperidinones in order to broaden the field of substrate of our methodology.



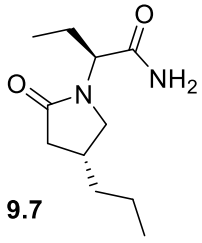

**Scheme 240 electrocyclization of the 2-piperidinone 3.152**

In perspectives, we would like to extend further the scope of our method by introducing amine, nitrile or silyl functions in the product structure by using different co-acids, such as: protected β-alanine **9.3**, pyrrolidine-3-carboxylic acid **9.4**, 2-cyano-2-methylaceic acid **9.5**, and (trimethylsilyl)acetic acid **9.6**.




**Scheme 241 protected β-alanine, pyrrolidine-3-carboxylic acid, 2-cyano-2-methylaceic acid, and (trimethylsilyl)acetic acid**

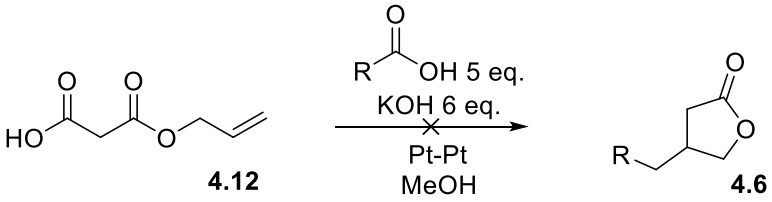
Finally, it is important to prove the usefulness of our reaction by applying it to the synthesis of natural products or commercial drugs, such as Brivaracetam **9.7**.




**Scheme 242 Brivaracetam**

## 9.3 General considerations about the electrosynthesis of lactones

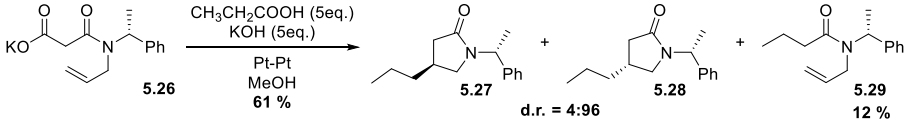
In a second phase of our work, we studied the application of our methodology to the development of a lactones electrosynthesis without success (see Scheme **243**). This result may be due to the geometry of the electrocyclization substrate. Indeed, the s-*trans*-rotamer is the major conformer of the substrate and seems unable to cyclize in electrolytic conditions.




**Scheme 243 attempt to synthetize electrochemically lactones 4.6**

## 9.4 General considerations and perspectives about the diastereoselective electrocyclization of 2-pyrrolidinones

In the third phase of our work, we have focused our attention to the development of a diastereoselective electrocyclization of 2-pyrrolidinones given that our classic electrocyclization of 2-pyrrolidinones does not allow the control of the stereochemistry of the chiral center formed during the cyclization step. The adopted strategy relied on the judicious insertion of a chiral auxiliary inside the structure of the electrocyclization substrate in order to induce a facial selectivity during the cyclization step. Following this study, it appeared that the use of (R)-(+)-α-methylbenzylamine as chiral auxiliary gave the excellent diastereoselective ratio of 96:4. The advantage of this group is that it can be readily removed after reaction via a Birch debenzylation.[242]




**Scheme 244 diastereoselective electrocyclization of 2-pyrrolidinones 5.27 and 5.28**

In future research, the scope of this diastereoselective process could be extended using various co-acids. Moreover, this chiral auxiliary could be applied to the electrogeneration of the commercially available drug, Brivaracetam (see Scheme **244**).

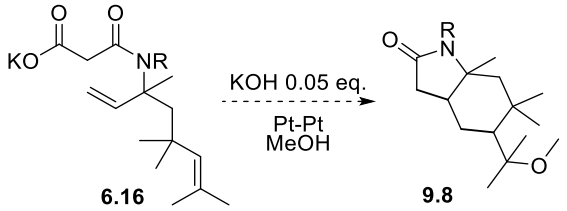
## 9.5 General considerations and perspectives about the electropolycyclization of 2-pyrrolidinones

In a fourth phase of our work, we have attempted to synthetize polycyclic 2-pyrrolidinones via various strategies.

First, we have tried to design a fused 2-pyrrolidinone using a linear substrate derived from linalyl amine. Unfortunately, this strategy did not lead to the formation of the desired product. In the future, it could be interesting to add a *gem*-dimethyl group in

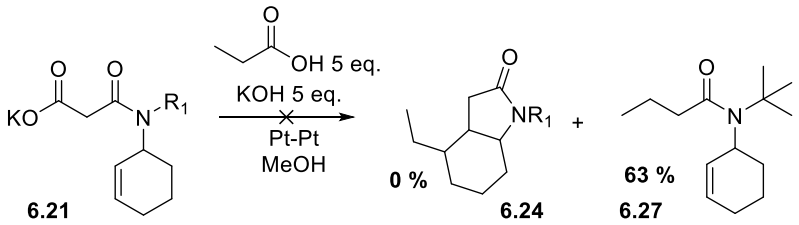
[242] Rodriguez, V.; Sanchez, M.; Quintero, L.; Sartillo-Piscil, F. *Tetrahedron* **2004**, 60, 10809.

the structure of the electrocyclization substrate **6.16**; the presence of this substituent should promote a Thorpe-Inglod effect and thus favor the second ring-closure over side-reactions (see Scheme **245**).



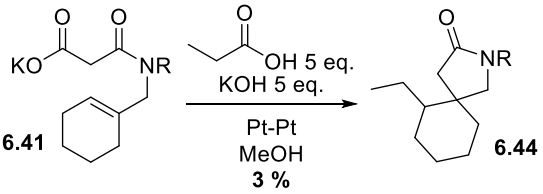

**Scheme 245 electrocyclization of the substrate 6.16 bearing a *gem*-dimethyl substituent**

Secondly, we have tried to synthetize fused 2-pyrrolidinones starting from a cyclic substrate **6.21**. Unfortunately, this strategy did not enable the formation of the desired product (see Scheme **246**). This result may be due to the steric hindrance of the substrate **6.21**, which limits the amide C-N bond rotation or to adsorption phenomenon.



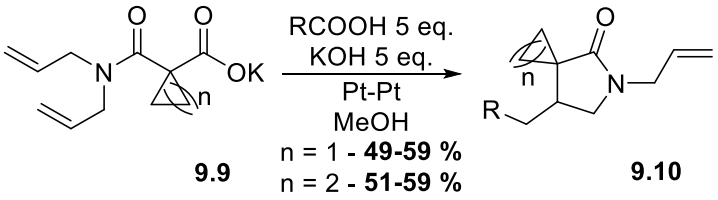

**Scheme 246 attempt to synthetize a fused 2-pyrrolidinone starting from a cyclic substrate**

Given our failures in the synthesis of fused 2-pyrrolidinones, we decided to focus our attention on the formation of spiro 2-pyrrolidinones. Our strategy was to incorporate a cyclohexene moiety in the structure of the electrocyclization substrate (see Scheme **247**). Unfortunately, the desired product **6.44** was obtained in the low yield of 3 %, via electrolysis. This result forced us to adapt our strategy in order to form spiro 2-pyrrolidinones.

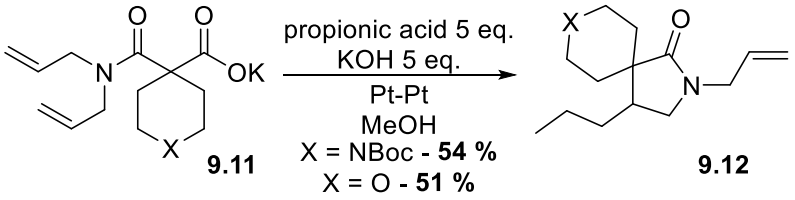



**Scheme 247 electrocyclization of spiro 2-pyrrolidinone 6.44**

In order to electrochemically synthetize spiro 2-pyrrolidiones, our new strategy was to incorporate a carbon cycle or a hetero cycle inside the malonate part of the cyclization substrate (see Schemes **248** and **249**). This strategy enabled the formation of various spiro 2-pyrrolidines bearing a carbon 3- or 5-membered ring, a piperidine or a tetrahydropyran moiety, with good yields; which shows the versatility of our brand-new methodology.

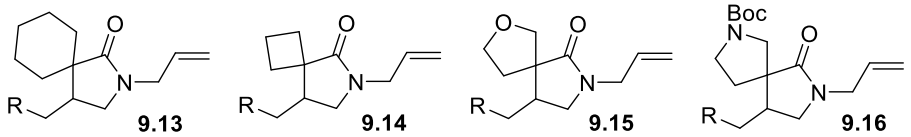



**Scheme 248 electrocyclization of spiro 2-pyrrolidinones 9.10**



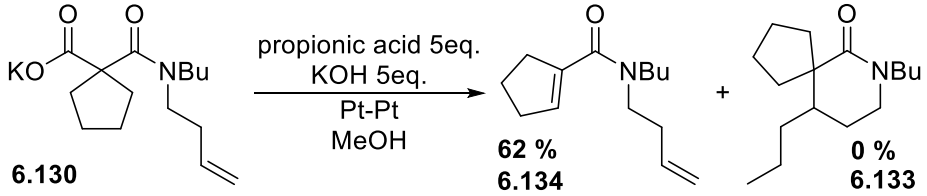

**Scheme 249 electrocyclization of spiro 2-pyrrolidinones 9.12**

Moreover, we can envision the possibility to incorporate new types of cycles inside the structure of the spiro 2-pyrrolidinones, such as: cyclohexane, tetrahydrofuran, pyrrolidine, and cyclobutane (see Scheme **250**).



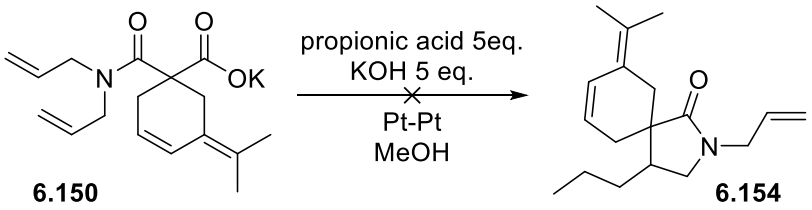

**Scheme 250 perspectives spiro 2-pyrrolidinones**

In view of the good results of the spiro-electrocyclization of 2-pyrrolidinones, we decided to apply our methodology to the synthesis of spiro 2-piperidinones (see Scheme **251**). To this end, a cyclic substrate bearing a homoallyl group **6.130** was formed and electrolyzed under our optimized conditions. Unfortunately, the desired product **6.133** was not formed given that the *6-exo-trig* cyclization process is slower than the formation of the side-product **6.134**. This sets a limit to our methodology, which is not applicable to the formation of spiro-2-piperidinones.



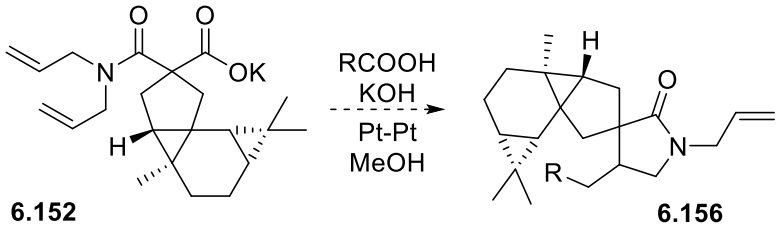

**Scheme 251 electrolysis of the homoallyl substrate 6.130**

Finally, we continued to investigate deeper the exemplification of our spiro-electrocyclization of 2-pyrrolidinones. Our strategy was to apply the gold and copper catalysis to easily access small heterocycles and carbon cycles, in order to synthetize original substrates for the electrosynthesis of various exotic spiro 2-pyrrolidiones. For instance, the substrate **6.150** was synthetized via gold cyclization of enyne, and subsequently electrolyzed. Unfortunately, the desired product **6.154** was not formed; and the presence of four double bonds in the substrate structure promoted radical side-reactions leading to the formation of a complex mixture of impurities (see Scheme **252**).



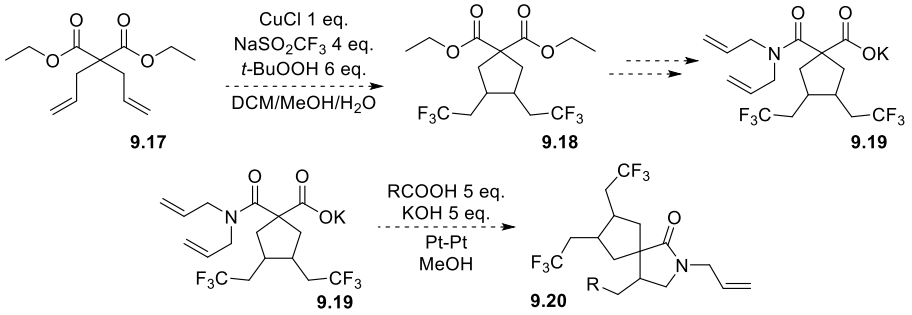

**Scheme 252 electrolysis of the substrate 6.150**

Afterwards, we studied the formation of a tetracyclic substrate **6.152** via gold catalysis in order to electrochemically synthetized a pentacyclic 2-pyrrolidinone **6.156**. Unfortunately, for lack of time and the need to optimize the catalytic tetracyclization step, this transformation was abandoned. In future research, it could be interesting to study the formation of this pentacyclic 2-pyrrolidinone via organic electrochemistry. Indeed, the combination of organogold chemistry and organic electrochemistry is a promising tool for the construction of complex and original architectures, under mild conditions.




**Scheme 253 electrocyclization of a pentacyclic 2-pyrrolidinone 6.156**

Finally, another perspective could be to apply copper catalysis to the formation of trifluoromethylated substrates **9.19** in order to form original spiro 2-pyrrolidinones **9.20** via electrochemistry (see Scheme **254**).

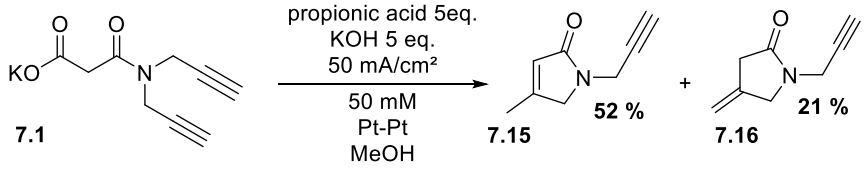



**Scheme 254 formation of substrate containing trifluoromethyl substituents and formation of the trifluoromethylated spiro 2-pyrrolidinone 9.20**

## 9.6 General considerations and perspectives about the electrosynthesis of pyrrolones and β,γ-unsaturated 2-pyrrolidinones

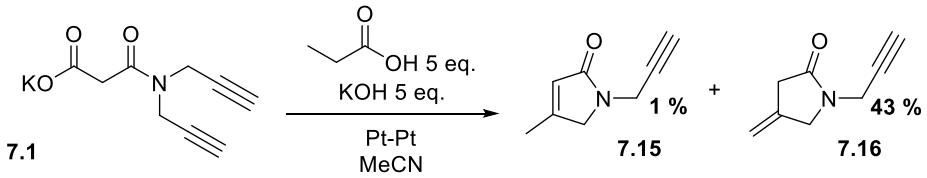
In a fifth phase of our work, we have focused our attention to the application of our methodology to the electrocyclization of propargylic substrates **7.1**. Interestingly, this process enabled the formation of a pyrrolone **7.15** and a β,γ-unsaturated 2-pyrrolidinone **7.16**, via a *5-exo-dig* cyclization (see Scheme **255**). The reaction parameters and work-up procedure were then optimized such that selectivity was

obtained; and thus each product was produced with only a very small amount of the isomeric product formed concurrently. Moreover, we proved that, in basic and acidic conditions, β,γ-unsaturated 2-pyrrolidinone **7.16** isomerized to form the more stable pyrrolone **7.15**.



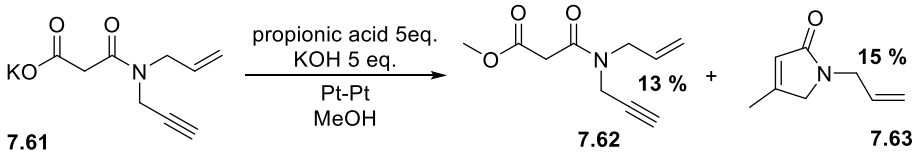

**Scheme 255 electrocyclization of the substrate 7.1 in methanol**

Interestingly, in acetonitrile, the electrolysis of the propargylic substrate **7.1** is selective and the β,γ-unsaturated 2-pyrrolidinone **7.16** is formed predominantly (see Scheme **256**). We think that the aprotic nature of the solvent prevents the isomerization of the product **7.16** into the pyrrolone **7.15**.



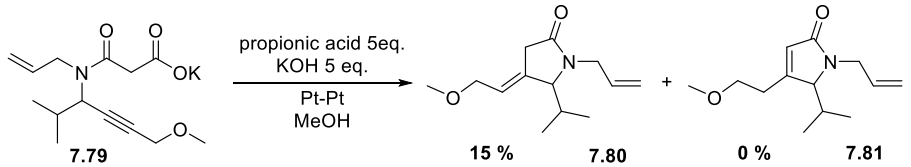

**Scheme 256 electrocyclization of the substrate 7.1 in acetonitrile**

A second part of this research topic was the exemplification of the reaction. Therefore, the nature of the protecting group of the nitrogen atom in the electrocyclization substrate structure was modified; and an allyl protecting group allowed the formation of the allyl protected pyrrolone **7.63** with 15 % yield (see Scheme **257**). In future research, we envisioned to optimize this transformation by modifying the reaction parameters.




**Scheme 257 electrocyclization of the allyl protected pyrrolone 7.63**

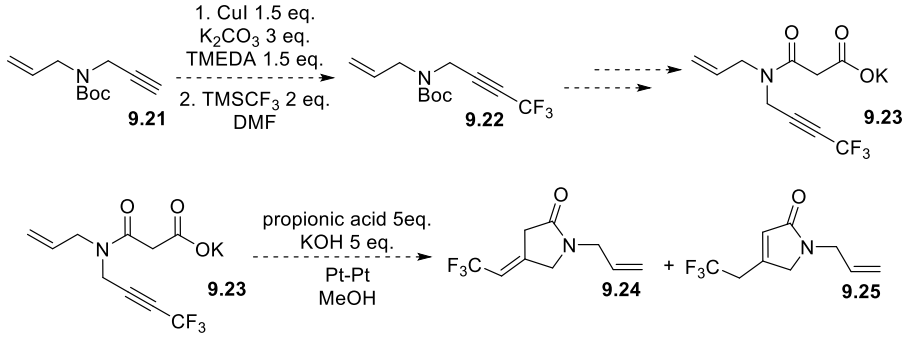
Moreover, we synthetized a propargylic substrate functionalized with an ether function **7.79** via copper catalysis. The electrolysis of this substrate led to the formation of the functionalized β,γ-unsaturated 2-pyrrolidinone **7.80** in 15 % yield (see Scheme **258**). This transformation broadens the field of substrate of our methodology.




**Scheme 258 electrolysis of the substrate 7.79 leading to the formation of the substituted β,γ-unsaturated 2-pyrrolidinone 7.80**

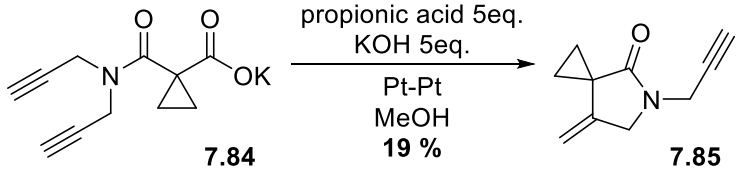
Furthermore, in future research, we envision to optimize this transformation and apply this reaction to the formation of diversely substituted 2-pyrrolidinones using

various propargyl substrates. For instance, the trifluoromethylated propargylic amine **9.22** could be synthetized via copper-mediated trifluoromethylation[243] in order to generate original trifluoromethylated products **9.24** and **9.25** via electrochemistry.

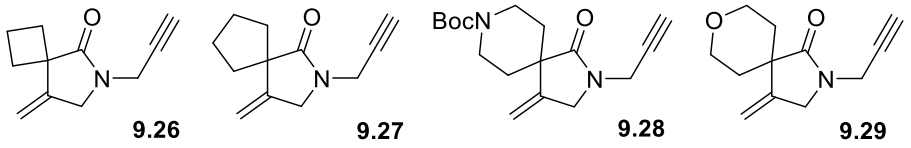



**Scheme 259 formation of trifluoromethylated substrates 9.24 and 9.25 via electrochemistry**

Finally, our methodology was transposed to the electrosynthesis of β,γ-unsaturated spiro 2-pyrrolidinone **7.85**; this complex bicyclic architecture was obtained with 19 % yield (see Scheme **260**). Given this promising result, an optimization study could be done, in order to improve the yield of that appealing transformation. Furthermore, this reaction could be exemplified by modifying the nature of the cycle inside the substrate structure; such as: cyclopentane, cyclobutane, piperidine and tetrahydropyran, *etc* (see Scheme **261**).




**Scheme 260 electrocyclization of the β,γ-unsaturated spiro 2-pyrrolidinone 7.85**



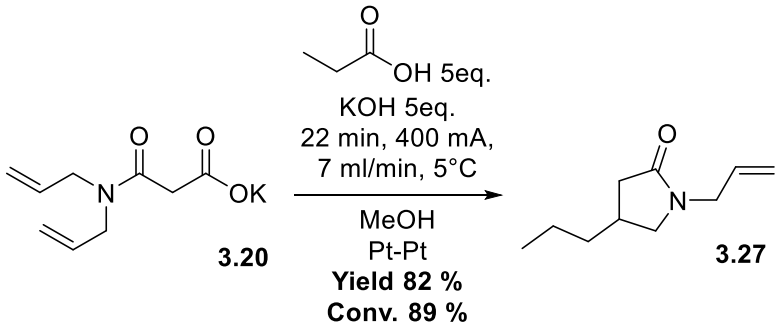

**Scheme 261 spiro β,γ-unsaturated 2-pyrrolidinones**

## 9.7 General considerations about the continuous flow electrochemistry applied to the Kolbe cyclization of functionalized 2-pyrrolidinones

In conclusion, the electrocyclization of the 1-allyl-4-propylpyrrolidin-2-one **3.27** was transposed from a batch-type double jacketed cell to IKA ElectraSyn Flow cell. Therefore, the reaction parameters, which already have been optimized for the batch-type cell, were adapted in the flow cell. This transposition was a success and allowed to drastically lower the reaction time from 240 min in the batch cell to 22 min in the flow cell (see Scheme **262**). Moreover, the yield was increased form 71 % in the batch-cell to 82 % in the flow cell. Furthermore, the Faradic yield was also

[243] Guissart, C.; Dolbois, A.; Tresse, C.; Saint-Auret, S.; Evano, G.; Blanchard, N. *Synlett* **2016**, 27, 2575.

increased from 19 % in the batch cell to 31 % in the flow cell, which proves that the flow cell promotes higher current efficiency. This excellent result derives from the characteristics of the ElectraSyn flow cell, such as: a large ratio of electrodes surface area (12 cm²) to cell volume (0.6 ml), a small inter-electrodes gap (0.5 mm), and a good temperature control thanks to the heat exchanger and to the fast flow rate. Finally, the ElectraSyn Flow cell promotes better reproducibility with its defined geometry.




**Scheme 262 optimal conditions of the electrocyclization of 1-allyl-4-propylpyrrolidin-2-one**

# 10 Experimental part

## 10.1 General experimental section

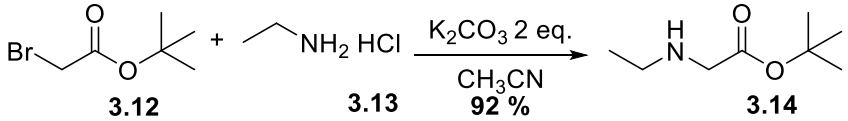
- ✓ All experiments were performed in flame dried glass apparatus and under an argon atmosphere with magnetic stirring. Nonetheless, the electrolysis reactions were performed in a jacketed undivided cell under air with magnetic stirring.
- ✓ Commercial grade solvents were dried and purified by standard procedures.[244]
- ✓ Thin layer chromatography was performed on prepared thin layers precoated plates: Silicagel Merck 60 F254. The visualization of spots on TLC plates was effected by exposure to UV, KMnO4 solution, Vanillin solution or ninhydrin solution.
- ✓ Column chromatography was performed over ROCC Silica gel 60 (40 – 63µ mesh) using relevant eluent.
- ✓ $^{1}H$ (300 MHz), $^{13}C$ (75 MHz), $^{19}F$ (282 MHz) spectra were recorded on Bruker AC-300 Avance II UltraShield or on Bruker 500 Avance UltraShield at room temperature in $CDCl_3$ or DMSO. Chemical shifts are reported in ppm downfield to $CDCl_3$ ($\delta$ = 7.26 ppm) or DMSO-d6 ($\delta$ = 2.50 ppm) for $^{1}H$-NMR and CDCl3 ($\delta$ = 77.2 ppm) or DMSO-d6 ($\delta$ = 39.5 ppm) for $^{13}C$-NMR. Coupling constants are reported and expressed in Hz, splitting patterns are designated as br (broad), s (singlet), d (doublet), dd (double doublet), q (quartet), dt (double triplet), ddd (doublet of doublet of doublet), m (multiplet).
- ✓ NMR Fourier transform, integration and pick picking were done with Bruker TopSpin software or with MestRenova software.
- ✓ Infrared spectra were recorded on Shimadzu FTIR-8400S spectrometer and the absorption bands are reported in reciprocal centimeters (cm-1).
- ✓ Mass spectra were recorded using an orbitrap Q Exactive Thermo Fisher spectrometer.
- ✓ The electrolysis were performed using a DC Power Supply DF1730SB3A 50Hz, 220V/1.5A.
- ✓ The UPLC-MS analyzes were performed on a Waters UPLC-MS device. Samples were prepared in acetonitrile and spectra were recorded at 210 nm. Hereunder are listed the characteristics of the acidic gradient method
    - Eluent A: Water/acetonitrile (99/1) + 0.01 % formic acid
    - Eluent B: Acetonitrile + 0.01 % formic acid
    - Column: XSelect CSHC18 1.7 µm 50*2.1 mm
    - Column oven: 50 °C
    - Detector: PDA

[244] *Purification of Laboratory Chemicals*, 5 th ed.; Armarego, W.L.F; Chai, C.L.L.; Eds.; Butterworth Heinemann, 2003.

| Time (min) | % A | % B | Flow (ml/min) |
|---|---|---|---|
| 0 | 100 | 0 | 0.8 |
| 0.2 | 100 | 0 | 0.8 |
| 3.4 | 10 | 90 | 0.8 |
| 3.9 | 10 | 90 | 0.8 |
| 4 | 100 | 0 | 0.8 |
| 10 | 100 | 0 | 0.05 |

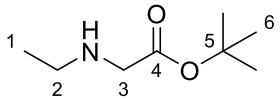
## 10.2 Experimental protocols and analyses

*Synthesis of tert-butyl ethylglycinate*




**3.12** **3.13** **3.14**

$K_2CO_3$ (10.17 g, 73.58 mmol, 2 eq.) was added to a solution of ethylamine hydrochloride (3.00g, 36.79 mmol, 1 eq.) in 37 ml of acetonitrile. The reaction mixture was allowed to stir for 30 minutes. Then tert-butyl bromoacetate (5.40 ml, 36.79 mmol, 1 eq.) was added dropwise to the reaction medium at 0°C. The solution is allowed to stir overnight. The reaction was quenched with 10 ml of water and extracted three times with 10 ml of diethyl ether. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (DCM, DCM/MEOH 99/1).

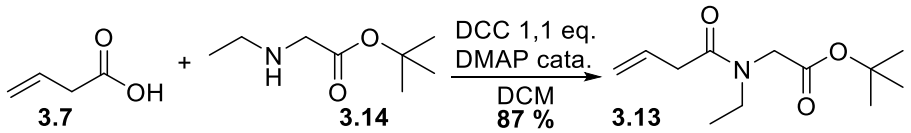



**$^1$H NMR (300 MHz, $CDCl_3$) : δ** 3.43 (s, 2H, $C_3$**HH**), 2.75 (q, J = 7.2 Hz, 2H, $C_2$**HH**), 1.46 (s, 9H, $C_6$**HHH**), 1.09 (t, J = 7.2 Hz, 1H, $C_1$**HHH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 171.63 (s, $C_4$), 81.57 (s, $C_5$), 51.72 (s, $C_3$), 43.62 (s, $C_2$), 28.59 (s, $C_6$), 15.28 (s, $C_1$).

**IR (film, cm$^{-1}$):** 1731, 1452, 1387, 1292, 1236, 1103, 967, 915, 758.

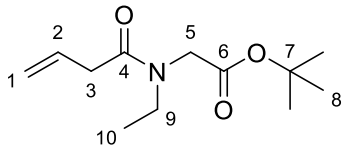
*Synthesis of tert-butyl N-(but-3-enoyl)-N-ethylglycinate*




**3.7** **3.14** **3.13**

A solution of vinylacetic acid (1.45 ml, 17.07 mmol, 1.0 eq.) in 34.00 ml of DCM, DCC (3.87 g, 18.78 mmol, 1.1 eq.) and a catalytic amount of DMAP were added dropwise to a solution of tert-butylethylglycinate (2.00 g, 17.07 mmol, 1.0 eq.) in 34.00 ml of DCM at 0°C. The reaction was allowed to stir overnight. The solution

was filtered, quenched with 20.00 ml of an aqueous solution of $NaHCO_3$ and extracted three times with 20.00 ml of DCM. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (DCM/MeOH 99/1).




**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 5.90 (m, 1H, $C_2$**H**), 5.20 – 4.98 (m, 2H, $C_1$**HH**), 3.89 (s, 1.4H, $C_5$**HH**), 3.85 (s, 0.6H, $C_5$**HH**), 3.32 (q, J = 7.2 Hz, 2H, $C_9$**HH**), 3.13 (dt, J = 6.4, 1.5 Hz, 1.4H, $C_3$**HH**), 2.99 (dt, J = 6.5, 1.5 Hz, 0.6H, $C_3$**HH**), 1.41 (s, 2H, $C_8$**HHH**), 1.39 (s, 7H, $C_8$**HHH**), 1.12 (t, J = 7.2 Hz, 1.7H, $C_{10}$**HHH**), 1.02 (t, J = 7.2 Hz, 1.3H, $C_{10}$**HHH**).

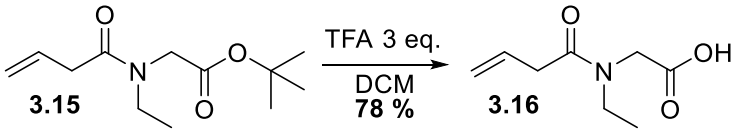
**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 170.95 (s, $C_6$), 168.55 (s, $C_4$), 131.53 (s, $C_2$), 117.79 (s, $C_1$), 82.61 (s, $C_7$), 81.61 (s, $C_7$), 50.36 (s, $C_5$), 47.69 (s, $C_5$), 43.66 (s, $C_9$), 42.27 (s, $C_9$), 38.80 (s, $C_3$), 38.16 (s, $C_3$), 28.06 (s, $C_8$), 28.03 (s, $C_8$), 13.87 (s, $C_{10}$), 12.61 (s, $C_{10}$).

**IR (film, cm$^{-1}$):** 1741, 1650, 1454, 1367, 1290, 1226, 1153, 987, 914, 854, 748.

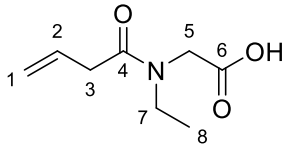
**HRMS**, m/z: calculated $[C_{12}H_{22}O_3N]^+$ : 228.15942, found: 228.15947.

**MS/MS** (p ESI): m/z (%): 104.07065, (100); 154.08577, (2); 172.09625, (58); 228.15870, (2) $[M-H]^+$.

*Synthesis of N-(but-3-enoyl)-N-ethylglycine*




*Tert*-butyl ester **3.15** (1.5 g, 6.60 mmol, 1 eq.) was diluted in 13.2 ml of DCM (0.5 mol/l), and the solution temperature was cooled to 0°C. Trifluoroacetic acid (1.52 ml, 19.8 mmol, 3 eq.) was subsequently added dropwise to this mixture. The mixture was then allowed to stir for one hour. After completion of the reaction, the solution was extracted two times with 10 ml of water, and the aqueous phases were combined and extracted two times with AcOEt. The aqueous phase was then acidified with an aqueous solution of HCl 37% to a pH value of 1. Finally, the acid product was extracted from the aqueous phase using two times 10 ml of AcOEt.



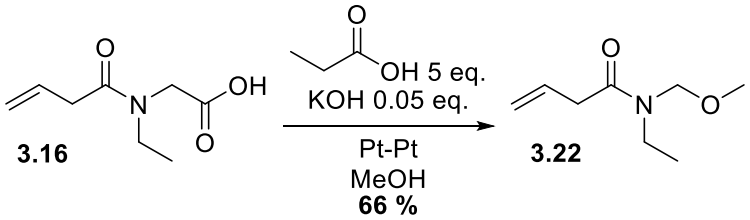

**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 5.98 – 5.78 (m, 1H, $C_2$**H**), 5.29 – 5.09 (m, 2H, $C_1$**HH**), 4.13 (s, 1.85H, $C_5$**HH**), 3.99 (s, 0.15H, $C_5$**HH**), 3.48 (q, J = 7.2 Hz, 2H, $C_7$**HH**), 3.28 (dt, J = 6.3, 1.5 Hz, 1.7H, $C_3$**HH**), 3.19 – 3.09 (m, 0.3H, $C_3$**HH**), 1.29 –

1.21 (m, 2.5H, $C_8$**HHH**), 1.15 (t, J = 7.2 Hz, 2.5H, $C_8$**HHH**), 1.05 (t, J = 7.2 Hz, 0.5H, $C_8$**HHH**).

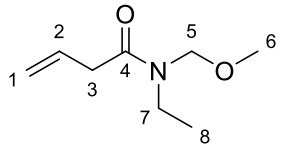
**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 172.79 (s, $C_6$), 172.21 (s, $C_4$), 131.18 (s, $C_2$), 130.88 (s, $C_2$), 118.24 (s, $C_1$), 118.04 (s, $C_1$), 49.09 (s, $C_5$), 47.56 (s, $C_5$), 44.18 (s, $C_7$), 42.35 (s, $C_7$), 38.77 (s, $C_3$), 37.99 (s, $C_3$), 13.78 (s, $C_8$), 12.46 (s, $C_8$).

**IR (film, cm$^{-1}$):** 1737, 1764, 1434, 1365, 1217, 912, 748.

*Synthesis of N-ethyl-N-(methoxymethyl)but-3-enamide*




In an undivided cell with platinum electrodes (4 cm²), potassium hydroxide (0.075 mmol, 0.05 eq.) and the propionic acid (7.500 mmol, 5.00 eq.) were dissolved in MeOH. Then, carboxylic acid (1.500 mmol, 1.00 eq., 66 mM in methanol) was added to the mixture. The intensity of the current was fixed at 100 mA and the mixture was electrolyzed until completion of the reaction, as shown by TLC. The solution was treated with an aqueous solution of $NaHCO_3$ and extracted three times $Et_2O$. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica gel chromatography.




**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 6.03 - 5.97 (m, 1H, $C_2$**H**), 5.25 – 5.06 (m, 2H, $C_1$**HH**), 4.82 (s, 0.86H, $C_5$**HH**), 4.64 (s, 1.14H, $C_5$**HH**), 3.54 – 3.35 (m, 2H, $C_7$**HH**), 3.31 (s, 1.75H, $C_6$**HHH**), 3.28 (s, 1.25H, $C_6$**HHH**), 3.21 (dt, J = 11.7, 4.0 Hz, 2H, $C_3$**HH**), 1.28 – 1.08 (m, 3H, $C_8$**HHH**).

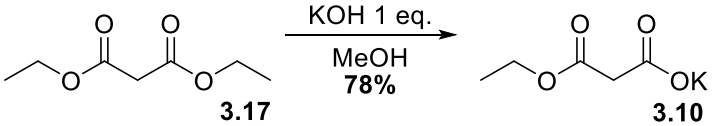
**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 171.59 (s, $C_4$), 131.68 (s, $C_2$), 131.53 (s, $C_2$), 117.94 (s, $C_1$), 117.70 (s, $C_1$), 79.85 (s, $C_5$), 75.61 (s, $C_5$), 55.97 (s, $C_6$), 55.26 (s, $C_6$), 41.39 (s, $C_7$), 40.92 (s, $C_7$), 38.48 (s, $C_3$), 14.42 (s, $C_8$), 13.50 (s, $C_8$).

**IR (film, cm$^{-1}$):** 1747, 1652, 1546, 1456, 1392, 1261, 1155, 1080, 995, 914, 794.

**HRMS**, m/z: calculated $[C_8H_{16}O_2N]^+$ : 158.11756, found: 158.11762.

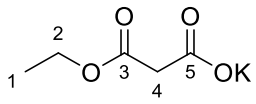
**MS/MS** (p ESI): m/z (%): 58.06570, (100); 69.03391, (3); 96.96265, (4); 126.09090, (19); 158.11684, (6) $[M-H]^+$.

*Synthesis of potassium 3-ethoxy-3-oxopropanoate*




**3.17** **3.10**

A solution of potassium hydroxide (2.24 g, 40 mmol, 1 eq.) in 8 ml of MeOH was added dropwise to a solution of diethyl malonate (6.40 g, 40 mmol, 1 eq.) in 8 ml of MeOH at 0°C. The mixture was allowed to stir 15 minutes. The solution was filtered and the solid formed was washed three times with 5 ml of cold methanol, yielding 5.30 g of a white powder (78 %).

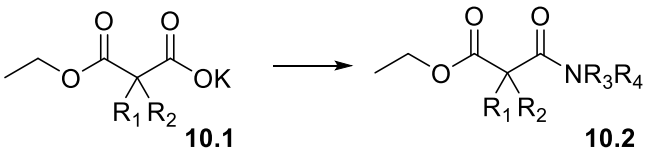



**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 4.08 (q, J = 7.24 Hz, 2H, $C_2$**HH**), 3.19 (s, 2H, $C_4$**HH**), 1.16 (t, J = 7.23 Hz, 3H, $C_1$**HHH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 174.1 (s, $C_5$), 171.4 (s, $C_3$), 60.0 (s, $C_2$), 44.5, (s, $C_4$), 13.2 (s, $C_1$).

**IR (film, $cm^{-1}$):** 1739, 1595, 1380, 1310, 1230, 1188, 1045, 915.

*General Procedure for preparing amide from the corresponding secondary amine using DCC coupling agent*

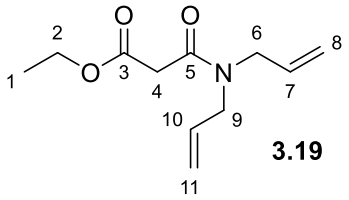



**10.1** **10.2**

A solution of secondary allylic amine (20.0 mmol, 1.00 eq., 0.25 M in DCM) was cooled down to 0°C and potassium 3-ethoxy-3-oxopropanoate (20 mmol, 1.00 eq.), DCC (22.0 mmol, 1.10 eq.), DMAP (0.2 mmol, 0.01 eq.), and HCl (20.0 mmol, 1.00 eq.) were added to the solution. The reaction was allowed to stir overnight. The solution was filtered, quenched with an aqueous solution of $NaHCO_3$ (same volume as DCM) and extracted three times with DCM. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica gel chromatography.

*Synthesis of ethyl 3-(diallylamino)-3-oxopropanoate*

This molecule was synthetized according to the general procedure for preparing amide from the corresponding secondary amine using DCC coupling agent (see p. 203).




**3.19**

**Yield:** 84 % - colourless-oil.

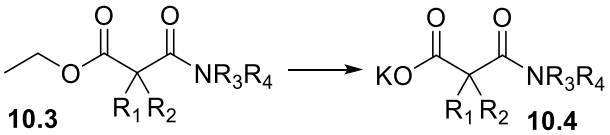
**Purification:** chromatography on silica gel. Eluent: DCM/MeOH 0.99/0.01.

**$^{1}$H NMR (300 MHz, $CDCl_3$)** : **δ** 5.89 – 5.63 (m, 2H, $C_7$**H**, $C_{10}$**H**), 5.27 – 5.09 (m, 4H, $C_8$**HH**, $C_{11}$**HH**), 4.19 (q, J = 7.13 Hz, 2H, $C_2$**HH**), 4.00 (d, J = 5.82 Hz, 2H, $C_6$**HH** or $C_9$**HH**), 3.87 (dt, J = 4.72, 1.72 Hz, 2H, $C_6$**HH** or $C_9$**HH**), 3.42 (s, 2H, $C_4$**HH**), 1.27 (t, J = 7.14 Hz, 3H, $C_1$**HHH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 167.6 (s, $C_3$), 166.1 (s, $C_5$), 132.5 (s, $C_7$ or $C_{10}$), 132.3 (s, $C_7$ or $C_{10}$), 117.4 (s, $C_8$ or $C_{11}$), 117.0 (s, $C_8$ or $C_{11}$), 61.4 (s, $C_2$), 49.7 (s, $C_6$ or $C_9$), 47.9 (s, $C_6$ or $C_9$), 41.1 (s, $C_4$), 14.0 (s, $C_1$).

**IR (film, cm$^{-1}$):** 1732, 1651, 1641, 1466, 1444, 1416, 1367, 1319, 1261, 1213, 1188, 1157, 1035, 993, 925, 969.

*General Procedure for preparing the potassium salt from the corresponding ester*

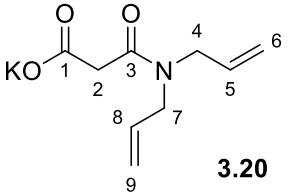



**10.3** **10.4**

A solution of KOH (30 mmol, 1 eq.) in MeOH (0.2 M) was added dropwise to a solution of ester (30 mmol, 1 eq.) in MeOH (0.2 M), at 0°C. Then the reaction mixture was allowed to stir overnight. Finally the solvent was evaporated under reduce pressure and the crude product was purified by silica gel chromatography.

*Synthesis of potassium 3-(diallylamino)-3-oxopropanoate*

This molecule was synthetized according to the general procedure for preparing potassium salt from the corresponding ester (see p. 204).




**3.20**

**Yield:** 93 % - colourless-oil.

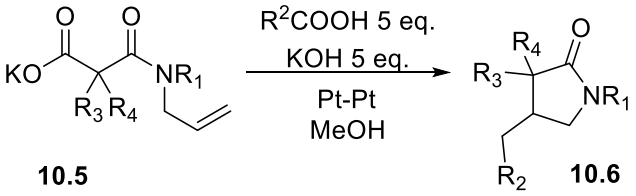
**Purification:** chromatography on silica gel. Eluent: DCM/MeOH 0.9/0.1.

**$^{1}$H NMR (300 MHz, DMSO) : δ** 5.99 – 5.62 (m, 2H, $C_5$**H**, $C_8$**H**), 5.36 – 5.02 (m, 4H, $C_6$**HH**, $C_9$**HH**), 3.96 (d, J = 5.21 Hz, 2H, $C_4$**HH** or $C_7$**HH**), 3.85 (d, J = 5.22 Hz, 2H, $C_4$**HH** or $C_7$**HH**), 3.07 (s, 2H, $C_2$**HH**).

**$^{13}$C NMR (75 MHz, DMSO) : δ** 169.3 (s, $C_1$ or $C_3$), 169.2 (s, $C_1$ or $C_3$), 134.5 (s, $C_5$ or $C_8$), 133.7 (s, $C_5$ or $C_8$), 116.2 (s, $C_6$ or $C_9$), 115.9 (s, $C_6$ or $C_9$), 49.6 (s, $C_4$ or $C_7$), 48.5 (s, $C_4$ or $C_7$), 46.5 (s, $C_2$).

**IR (film, cm-1):** 1748, 1643, 1350, 1216, 1049, 1024, 1003, 931, 823, 760, 658, 652.

*General procedure for the electrocyclization of functionalized 2-pyrrolidinones*

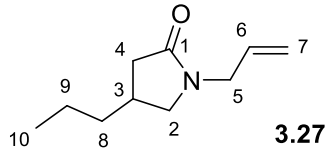



**10.5** **10.6**

In an undivided cell with platinum electrodes (4 cm²), potassium hydroxide (7.5 mmol, 5 eq.), and a co-acid (7.5 mmol, 5 eq.) were dissolved in MeOH. Then, potassium salt (1.5 mmol, 1 eq., 66 mM in methanol) was added to the mixture. The intensity of the current was fixed at 100 mA and the mixture was electrolyzed until completion of the reaction, as shown by TLC (240 min). The solution was treated with an aqueous solution of $NaHCO_3$ and extracted three times $Et_2O$. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica gel chromatography.

*Synthesis of 1-allyl-4-propylpyrrolidin-2-one*

This molecule was synthetized according to the general procedure for the electrocyclization of functionalized 2-pyrrolidinones (see p. 205).




**3.27**

**Yield:** 71 % - colourless-oil.

**Purification:** chromatography on silica gel. Eluent: AcOEt/EP 0.2/0.8.

**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 5.87 – 5.60 (m, 1H, $C_6$**H**), 5.33 – 5.04 (m, 2H, $C_7$**HH**), 4.03 – 3.75 (m, 2H, $C_5$**HH**), 3.54 – 3.29 (m, 1H, $C_2$**H**H), 3.06 – 2.84 (m, 1H, $C_2$H**H**), 2.61 – 2.44 (m, 1H, $C_4$**H**H), 2.44 – 2.26 (m, 1H, $C_3$**H**), 2.07 (dd, J =

16.45, 7.74 Hz, 1H, $C_4H\mathbf{H}$), 1.48 – 1.25 (m, 4H, $C_8\mathbf{HH}$, $C_9\mathbf{HH}$), 0.91 (t, J = 7.17 Hz, 3H, $C_{10}\mathbf{HHH}$).

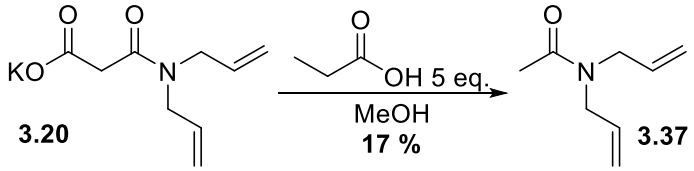
**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 175.0 (s, $C_1$), 132.1 (s, $C_6$), 118.0 (s, $C_7$), 52.7 (s, $C_2$), 45.2 (s, $C_5$), 37.5 (s, $C_4$), 31.4 (s, $C_3$), 20.5 (s, $C_8$), 13.9 (s, $C_9$), 13.9 (s, $C_{10}$).

**IR (film, cm$^{-1}$):** 1746, 1735, 1724, 1695, 1686, 1681, 1648, 1639, 1631, 1627, 1447, 1418, 1280, 1266, 1258, 1202, 1196, 1148, 915.

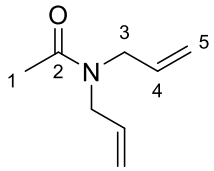
**HRMS**, m/z: calculated $[C_{10}H_{18}ON]^+$ : 168.13829, found : 168.13835.

**MS/MS** (p ESI): m/z (%): 83.08609, (8); 111.08067, (8); 140.14327, (10); 168.13818, (100) $[M-H]^+$.

*Synthesis of N,N-diallylacetamide*




Propionic acid (0.1667 g, 2.25 mmol, 5 eq.) was added dropwise to a solution of the potassium salt (0.1000 g, 0.45 mmol, 1 eq.) in 10 ml of methanol at room temperature. The reaction was then allowed to stir for four hours and the degradation of the potassium salt in an acidic medium was monitored by TLC. Then the solution was quenched with 10 ml of an aqueous solution of $NaHCO_3$ and extracted three times with 10 ml of DCM. The combined organic layers were dried over $MgSO_4$ and were concentrated under reduced pressure. Finally the crude product was purified by silica gel chromatography (DCM/MeOH 99/1).



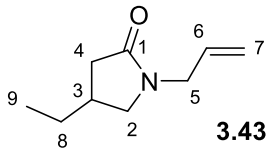

**$^1$H NMR (300 MHz, $CDCl_3$) : δ** 5.91 – 5.64 (m, 2H, $C_4\mathbf{H}$), 5.34 – 5.05 (m, 4H, $C_5\mathbf{HH}$), 4.07 – 4.00 (m, 4H, $C_3\mathbf{HH}$), 2.13 (s, 3H, $C_1\mathbf{HHH}$).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 170.15 (s, $C_2$), 132.62 (s, $C_4$), 117.27 (s, $C_5$), 48.16 (s, $C_3$), 27.72 (s, $C_1$).

**IR (film, cm$^{-1}$):** 1715, 1602, 1463, 1417, 1190, 1076, 924, 840.

*Synthesis of 1-allyl-4-ethylpyrrolidin-2-one*

This molecule was synthetized according to the general procedure for the electrocyclization of functionalized 2-pyrrolidinones (see p. 205).




**3.43**

**Yield:** 61 % - colourless-oil.

**Purification:** chromatography on silica gel. Eluent: AcOEt/EP 0.2/0.8.

**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 5.72 (m, 1H, $C_6$**H**), 5.28 – 5.07 (m, 2H, $C_7$**HH**), 3.96 – 3.78 (m, 2H, $C_5$**HH**), 3.43 (dd, J = 9.72, 7.95 Hz, 1H, $C_2$**H**H), 2.97 (dd, J = 9.72, 6.53 Hz, 1H, $C_2$H**H**), 2.54 (dd, J = 16.43, 8.52 Hz, 1H, $C_4$**H**H), 2.34 – 2.16 (m, 1H, $C_3$**H**), 2.09 (dd, J = 16.42, 7.61 Hz, 1H, $C_4$H**H**), 1.47 (dq, J = 7.43, 13.50 Hz, 2H, $C_8$**HH**), 0.93 (t, J = 7.32 Hz, 3H, $C_9$**HHH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 174.2 (s, $C_1$), 132.5 (s, $C_6$), 117.7 (s, $C_7$), 52.3 (s, $C_2$), 45.1 (s, $C_5$), 37.4 (s, $C_4$), 33.2 (s, $C_3$), 27.6 (s, $C_8$), 11.7 (s, $C_9$).

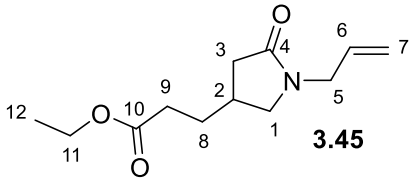
**IR (film, cm$^{-1}$):** 1754, 1688, 1683, 1652, 1464, 1439, 1268, 1207, 935, 914.

**HRMS**, m/z: calculated $[C_9H_{16}ON]^+$ : 154.12264, found : 154.12268.

**MS/MS** (p ESI): m/z (%): 72.08144, (1); 81.07046, (1); 94.06558, (1); 97.06518, (27); 99.08079, (1); 112.07592, (1); 124.11217, (1); 126.12775, (15); 131.71102, (6); 136.11201, (1); 152.10681, (1); 154.12248, (100) $[M-H]^+$.

*Synthesis of ethyl 3-(1-allyl-5-oxopyrrolidin-3-yl)propanoate*

This molecule was synthetized according to the general procedure for the electrocyclization of functionalized 2-pyrrolidinones (see p. 205).




**3.45**

**Yield:** 70 %

**Purification:** chromatography on silica gel. Eluent: AcOEt/EP 0.2/0.8.

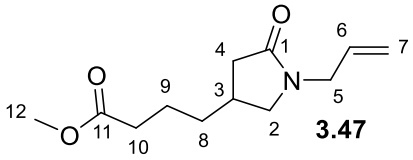
**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 5.82 – 5.60 (m, 1H, $C_6$**H**), 5.27 – 5.07 (m, 2H, $C_7$**HH**), 4.13 (q, J = 7.1 Hz, 2H, $C_{11}$**HH**), 3.94 – 3.77 (m, 2H, $C_5$**HH**), 3.45 (dd, J = 9.7, 8.0 Hz, 1H, $C_1$**H**H), 2.99 (dd, J = 9.7, 6.7 Hz, 1H, $C_1$H**H**), 2.56 (dd, J = 16.4, 8.6 Hz, 1H, $C_3$**H**H), 2.49 – 2.23 (m, 3H, $C_2$**H**, $C_9$**HH**), 2.19 – 2.02 (m, 1H, $C_3$H**H**), 1.84 – 1.71 (m, 2H, $C_8$**HH**), 1.25 (t, J = 7.8 Hz, 3H, $C_{12}$**HHH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 173.74 (s, $C_4$), 172.89 (s, $C_{10}$), 132.33 (s, $C_6$), 118.07 (s, $C_7$), 60.59 (s, $C_{11}$), 52.20 (s, $C_1$), 45.15 (s, $C_5$), 37.36 (s, $C_3$), 32.21 (s, $C_8$), 31.21 (s, $C_9$), 29.69 (s, $C_2$), 14.21 (s, $C_{12}$).

**IR (film, cm$^{-1}$):** 1724, 1648, 1643, 1622, 1467, 1459, 1278, 1200, 945, 916.

*Synthesis of methyl 4-(1-allyl-5-oxopyrrolidin-3-yl)butanoate*

This molecule was synthetized according to the general procedure for the electrocyclization of functionalized 2-pyrrolidinones (see p. 205).




**3.47**

**Yield:** 65 %

**Purification:** chromatography on silica gel. Eluent: AcOEt/EP 0.2/0.8.

**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 5.73 – 5.68 (m, 1H, $C_6$**H**), 5.28 – 5.05 (m, 2H, $C_7$**HH**), 3.96 – 3.77 (m, 2H, $C_5$**HH**), 3.67 (s, 3H, $C_{12}$**HHH**), 3.44 (dd, J = 9.74, 8.03 Hz, 1H, $C_2$**H**H), 2.97 (dd, J = 9.74, 6.76 Hz, 1H, $C_2$H**H**), 2.66 – 2.46 (m, 1H, $C_4$**H**H), 2.36 – 2.32 (m, 3H, $C_3$**H**, $C_{10}$**HH**), 2.20 – 2.00 (m, 1H, $C_4$H**H**), 1.71 – 1.55 (m, 2H, $C_9$**HH**), 1.55 – 1.37 (m, 2H, $C_8$**HH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 173.9 (s, $C_{11}$), 173.6 (s, $C_1$), 132.3 (s, $C_6$), 117.9 (s, $C_7$), 52.3 (s, $C_2$), 51.5 (s, $C_{12}$), 45.0 (s, $C_5$), 37.5 (s, $C_4$), 34.1 (s, $C_{10}$), 33.7 (s, $C_9$), 31.4 (s, $C_3$), 22.7 (s, $C_8$).

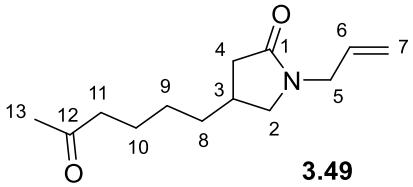
**IR (film, cm$^{-1}$):** 1732, 1678, 1643, 1491, 1436, 1419, 1338, 1261, 1196, 1173, 1097, 993, 933, 914, 748.

**HRMS**, m/z: calculated $[C_{12}H_{20}O_3N]^+$ : 226.14377, found : 226.14375.

**MS/MS** (p ESI): m/z (%): 166.12252, (7); 176.10688, (5); 194.11740, (83); 226.14345, (100) $[M-H]^+$.

*Synthesis of 1-allyl-4-(5-oxohexyl)pyrrolidin-2-one*

This molecule was synthetized according to the general procedure for the electrocyclization of functionalized 2-pyrrolidinones (see p. 205).




**3.49**

**Yield:** 60 % - colourless-oil.

**Purification:** chromatography on silica gel. Eluent: AcOEt/EP 0.2/0.8.

**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 5.80 – 5.61 (m, 1H, $C_6$**H**), 5.24 – 5.09 (m, 2H, $C_7$**HH**), 3.93 – 3.78 (m, 2H, $C_5$**HH**), 3.48 – 3.42 (m, 1H, $C_2$**H**H), 2.94 (dd, J = 9.71,

6.73 Hz, 1H, $C_2H\mathbf{H}$), 2.51 (dt, J = 15.15, 7.63 Hz, 1H, $C_4\mathbf{H}H$), 2.43 (t, J = 7.32 Hz, 2H, $C_{11}\mathbf{HH}$), 2.28 (ddd, J = 21.34, 14.44, 6.83 Hz, 1H, $C_3\mathbf{H}$), 2.12 (s, 3H, $C_{13}\mathbf{HHH}$), 2.11 – 1.99 (m, 1H, $C_4H\mathbf{H}$), 1.57 (dt, J = 14.84, 7.31 Hz, 2H, $C_{10}\mathbf{HH}$), 1.49 – 1.36 (m, 2H, $C_9\mathbf{HH}$), 1.36 – 1.15 (m, 2H, $C_8\mathbf{HH}$).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 208.8 (s, $C_{12}$), 174.1 (s, $C_1$), 132.4 (s, $C_6$), 117.8 (s, $C_7$), 52.5 (s, $C_2$), 45.1 (s, $C_5$), 43.4 (s, $C_{11}$), 37.6 (s, $C_4$), 34.6 (s, $C_3$), 31.5 (s, $C_8$), 29.9 (s, $C_{13}$), 26.9 (s, $C_9$), 23.5 (s, $C_{10}$).

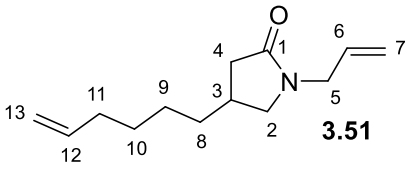
**IR (film, cm$^{-1}$):** 2914, 2852, 1708, 1645, 1442, 1417, 1359, 1269, 919, 729.

**HRMS**, m/z: calculated $[C_{13}H_{22}O_2N]^+$ : 224.16451, found : 224.16449.

**MS/MS** (p ESI): m/z (%): 81.07042, (19); 93.07029, (8); 107.08578, (9); 121.10125, (7); 131.08547, (5); 149.09595, (4); 184.13305, (6); 196.16941, (15); 206.15374, (7); 224.16417, (100) $[M\text{-}H]^+$.

*Synthesis of 1-allyl-4-(hex-5-en-1-yl)pyrrolidin-2-one*

This molecule was synthetized according to the general procedure for the electrocyclization of functionalized 2-pyrrolidinones (see p. 205).




**3.51**

**Yield:** 45 %

**Purification:** chromatography on silica gel. Eluent: AcOEt/EP 0.2/0.8.

**$^1$H NMR (300 MHz, $CDCl_3$) : δ** 5.93 – 5.60 (m, 2H, $C_6\mathbf{H}$, $C_{12}\mathbf{H}$), 5.34 – 4.77 (m, 4H, $C_7\mathbf{HH}$, $C_{13}\mathbf{HH}$), 3.92 – 3.83 (m, 2H, $C_5\mathbf{HH}$), 3.43 (dd, J = 9.7, 8.0 Hz, 1H, $C_2\mathbf{H}H$), 2.96 (dd, J = 9.7, 6.7 Hz, 1H, $C_2H\mathbf{H}$), 2.54 (dd, J = 16.5, 8.6 Hz, 1H, $C_4\mathbf{H}H$), 2.31 (dd, J = 15.1, 7.7 Hz, 1H, $C_3\mathbf{H}$), 2.15 – 1.95 (m, 1H, $C_4H\mathbf{H}$), 1.84 – 1.27 (m, 8H, $C_8\mathbf{HH}$, $C_9\mathbf{HH}$, $C_{10}\mathbf{HH}$, $C_{11}\mathbf{HH}$).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 172.21 (s, $C_1$), 132.84 (s, $C_6$ or $C_{12}$), 132.51 (s, $C_6$ or $C_{12}$), 117.09 (s, $C_7$ or $C_{13}$), 116.68 (s, $C_7$ or $C_{13}$), 52.66 (s, $C_5$), 45.14 (s, $C_2$), 37.83 (s, $C_4$), 31.70 (s, $C_3$), 29.77 (s, $C_8$, $C_9$, $C_{10}$ or $C_{11}$), 28.76 (s, $C_8$, $C_9$, $C_{10}$ or $C_{11}$), 28.20 (s, $C_8$, $C_9$, $C_{10}$ or $C_{11}$), 26.91 (s, $C_8$, $C_9$, $C_{10}$ or $C_{11}$).

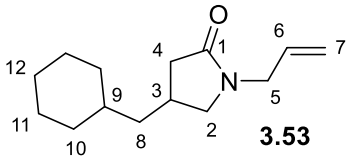
**IR (film, cm$^{-1}$):** 2926, 2853, 1679, 1641, 1488, 1440, 1415, 1331, 1261, 1176, 993, 914, 800.

**HRMS**, m/z: calculated $[C_{13}H_{22}ON]^+$ : 208.16959, found : 208.16964.

**MS/MS** (p ESI): m/z (%): 85.05952, (55); 180.10193, (19); 208.16964, (100) $[M\text{-}H]^+$; 234.00439, (16); 277.19095, (61); 299.17293, (38); 309.14608, (20); 385.10972, (14).

*Synthesis of 1-allyl-4-(cyclohexylmethyl)pyrrolidin-2-one*

This molecule was synthetized according to the general procedure for the electrocyclization of functionalized 2-pyrrolidinones (see p. 205).




**3.53**

**Yield:** 36 % - colourless-oil.

**Purification:** chromatography on silica gel. Eluent: AcOEt/EP 0.2/0.8.

**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 5.88 – 5.61 (m, 1H, $C_6$**H**), 5.27 – 5.21 (m, 2H, $C_7$**HH**), 3.94 – 3.67 (m, 2H, $C_5$**HH**), 3.47 – 3.27 (m, 1H, $C_2$**H**H), 3.08 – 2.84 (m, 2H, $C_2$H**H**), 2.83 – 2.54 (m, 1H, $C_4$**H**H), 2.52 – 2.20 (m, 1H, $C_3$**H**), 2.14 – 1.96 (m, 1H, $C_4$H**H**), 1.80 – 1.38 (m, 11H, $C_9$**H**, $C_{10}$**HH**, $C_{11}$**HH**, $C_{12}$**HH**), 0.96 – 0.77 (m, 2H, $C_8$**HH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 171.37 (s, $C_1$), 132.55 (s, $C_6$), 117.96 (s, $C_7$), 54.29 (s, $C_5$), 47.52 (s, $C_2$), 35.74 (s, $C_4$), 32.85 (s, $C_3$), 29.84 (s, $C_8$), 29.16 (s, $C_9$), 26.87 (s, $C_{10}$), 26.27 (s, $C_{11}$), 25.45 (s, $C_{12}$).

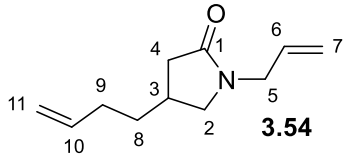
**IR (film, $cm^{-1}$):** 1756, 1725, 1721, 1695, 1648, 1638, 1631, 1449, 1428, 1270, 1258, 1202, 1198, 1158, 955.

**HRMS**, m/z: calculated $[C_{14}H_{24}ON]^+$ : 222.18524, found : 222.18593.

**MS/MS** (p ESI): m/z (%): 81.07008, (4); 95.08552, (4); 98.09633, (26); 222.18390, (100) $[M-H]^+$.

*Synthesis of 1-allyl-4-(but-3-en-1-yl)pyrrolidin-2-one*

This molecule was synthetized according to the general procedure for the electrocyclization of functionalized 2-pyrrolidinones (see p. 205).




**3.54**

**Yield:** 3 % - colourless-oil.

**Purification:** chromatography on silica gel. Eluent: AcOEt/EP 0.2/0.8.

**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 5.94 – 5.63 (m, 2H, $C_6$**H**, $C_{10}$**H**), 5.46 – 4.65 (m, 4H, $C_7$**HH**, $C_{11}$**HH**), 3.93 – 3.81 (m, 2H, $C_5$**HH**), 3.54 – 3.36 (m, 1H, $C_2$**H**H), 3.08 – 2.95 (m, 1H, $C_2$H**H**), 2.61 – 2.50 (m, 1H, $C_4$**H**H), 2.47 – 2.19 (m, 1H, $C_3$**H**), 2.20 – 1.99 (m, 1H, $C_4$H**H**), 1.25 (s, 2H, $C_9$**HH**), 0.95 – 0.80 (m, 2H, $C_8$**HH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) :** 172.46 (s, $C_1$), 139.01 (s, $C_{10}$), 132.21 (s, $C_6$), 117.35 (s, $C_7$), 115.36 (s, $C_{11}$), 56.23 (s, $C_5$), 52.32 (s, $C_2$), 39.84 (s, $C_4$), 36.45 (s, $C_8$), 32.83 (s, $C_9$), 28.59 (s, $C_3$).

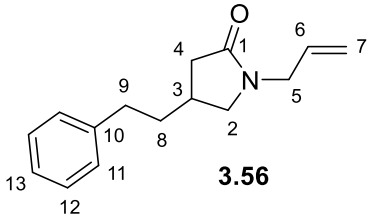
**IR (film, $cm^{-1}$):** 2974, 2892, 1769, 1645, 1632, 1469, 1428, 1382, 1266, 959, 767.

**HRMS**, m/z: calculated $[C_{11}H_{18}ON]^+$ : 180.13829, found: 180.13831.

**MS/MS** (p ESI): m/z (%): 72.08146, (3); 81.07049, (26); 84.04495, (4); 93.07036, (4); 95.08598, (21); 100.03970, (10); 123.08056, (5); 138.05489, (5); 152.14327, (6); 162.12761, (3); 180.13803, (100) $[M-H]^+$.

*Synthesis of 1-allyl-4-phenethylpyrrolidin-2-one*

This molecule was synthetized according to the general procedure for the electrocyclization of functionalized 2-pyrrolidinones (see p. 205).




**3.56**

**Yield:** 4 % - colourless-oil.

**Purification:** chromatography on silica gel. Eluent: AcOEt/EP 0.2/0.8.

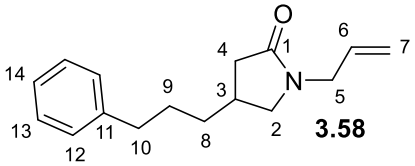
**$^1$H NMR (300 MHz, $CDCl_3$) : δ** 7.57 – 6.71 (m, 5H, Ph**H**), 5.88 – 5.54 (m, 1H, $C_6$**H**), 5.40 – 4.75 (m, 2H, $C_7$**HH**), ), 4.14 – 3.79 (m, 2H, $C_5$**HH**), 3.46 – 2.94 (m, 2H, $C_2$**HH**), 2.91 – 1.86 (m, 5H, $C_4$**HH**, $C_3$**H**, $C_9$**HH**), 1.24 – 1.02 (m, 2H, $C_8$**HH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 172.1 (s, $C_1$), 142.3 (s, $C_{10}$), 128.4 (s, $C_{12}$), 128.0 (s, $C_{11}$), 125.8 (s, $C_{13}$), 131.7 (s, $C_6$), 117.6 (s, $C_{7)}$, 56.4 (s, $C_2$), 35.2 (s, $C_9$), 40.1 (s, $C_8$), 39.6 (s, $C_4$), 26.2 (s, $C_3$).

**IR (film, $cm^{-1}$):** 2957, 1804, 1743, 1666, 1662, 1643, 1484, 1451, 1439, 1427, 1267, 1247, 993, 924.

*Synthesis of 1-allyl-4-(3-phenylpropyl)pyrrolidin-2-one*

This molecule was synthetized according to the general procedure for the electrocyclization of functionalized 2-pyrrolidinones (see p. 205).




**3.58**

**Yield:** 30 % - colourless-oil.

**Purification:** chromatography on silica gel. Eluent: AcOEt/EP 0.2/0.8.

**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 7.66 – 6.73 (m, 5H, Ph**H**), 5.88 – 5.59 (m, 1H, $C_6$**H**), 5.35 – 5.01 (m, 2H, $C_7$**HH**), 4.35 – 3.79 (m, 2H, $C_5$**HH**), 3.49 – 3.35 (m, 1H, $C_2$**H**H), 3.03 – 2.82 (m, 1H, $C_2$H**H**), 2.66 – 2.62 (m, 2H, $C_{10}$**HH**), 2.54 (dd, J = 16.5, 8.7 Hz, 1H, $C_4$**H**H), 2.43 – 2.24 (m, 1H, $C_3$**H**), 2.21 – 1.99 (m, 1H, $C_4$H**H**), 1.78 – 0.77 (m, 4H, $C_8$**HH,** $C_9$**HH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 174.27 (s, $C_1$), 141.99 (s, $C_{11}$), 132.45 (s, $C_6$), 128.37 (s, $C_{13}$), 128.33 (s, $C_{12}$), 125.89 (s, $C_{14}$), 118.04 (s, $C_7$), 52.92 (s, $C_5$), 45.14 (s, $C_2$), 37.86 (s, $C_{10}$), 34.30 (s, $C_3$), 31.70 (s, $C_8$), 29.28 (s, $C_9$).

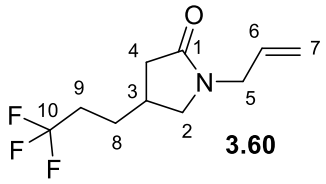
**IR (film, cm$^{-1}$):** 2937, 2864, 1800, 1733, 1664, 1652, 1643, 1494, 1452, 1438, 1417, 1267, 1247, 1182, 993, 914.

**HRMS**, m/z: calculated $[C_{16}H_{22}ON]^+$ : 244.16959, found : 244.16964.

**MS/MS** (p ESI): m/z (%): 91.05421, (22); 98.09628, (58); 117.06940, (5); 129.06918, (12); 143.08466, (6); 147.07948, (24); 169.10011, (6); 216.17333, (6); 244.16792, (100) $[M-H]^+$.

*Synthesis of 1-allyl-4-(3,3,3-trifluoropropyl)pyrrolidin-2-one*

This molecule was synthetized according to the general procedure for the electrocyclization of functionalized 2-pyrrolidinones (see p. 205).




**3.60**

**Yield:** 68 %

**Purification:** chromatography on silica gel. Eluent: AcOEt/EP 0.2/0.8.

**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 5.82 – 5.62 (m, 1H, $C_6$**H**), 5.31 – 5.10 (m, 2H, $C_7$**HH**), 3.96 – 3.82 (m, 2H, $C_5$**HH**), 3.56 – 3.42 (m, 1H, $C_2$**H**H), 3.01 (dd, J = 9.8, 6.6 Hz, 1H, $C_2$H**H**), 2.66 – 2.54 (m, 1H, $C_4$**H**H), 2.50 – 2.30 (m, 1H, $C_3$**H**), 2.23 – 1.98 (m, 3H, $C_4$H**H**, $C_9$**HH**), 1.82 – 1.63 (m, 2H, $C_8$**HH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 173.78 (s, $C_1$), 132.09 (s, $C_6$), 128.61 (s, $C_{10}$), 118.25 (s, $C_7$), 52.02 (s, $C_2$), 45.13 (s, $C_5$), 37.21 (s, $C_4$), 31.85 (q, $C_9$), 30.73 (s, $C_3$), 26.80 (s, $C_8$).

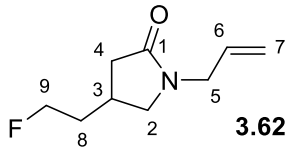
**IR (film, cm$^{-1}$):** 2959, 1686, 1647, 1443, 1304, 1257, 1150, 1056, 1043, 935.

**HRMS**, m/z: calculated$[C_{10}H_{15}ONF_3]^+$ : 222.11003, found: 222.10992.

**MS/MS** (p ESI): m/z (%): 97.04487, (3); 117.05081, (5), 165.05151, (27); 194.11431, (12); 222.10902, (100) $[M-H]^+$.

*Synthesis of 1-allyl-4-(2-fluoroethyl)pyrrolidin-2-one*

This molecule was synthetized according to the general procedure for the electrocyclization of functionalized 2-pyrrolidinones (see p. 205).




**3.62**

**Yield:** 34 % - colourless-oil.

**Purification:** chromatography on silica gel. Eluent: AcOEt/EP 0.2/0.8.

**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 5.87 – 5.58 (m, 1H, $C_6$**H**), 5.32 – 5.07 (m, 2H, $C_7$**HH**), 4.67 – 4.51 (m, 1H, $C_9$**H**HF), 4.50 – 4.33 (m, 1H, $C_9$H**H**F), 3.99 – 3.77 (m, 2H, $C_5$**HH**), 3.56 – 3.44 (m, 1H, $C_2$**H**H), 3.05 (dd, J = 9.83, 6.85 Hz, 1H, $C_2$H**H**), 2.72 – 2.41 (m, 2H, $C_4$**H**H, $C_3$**H**), 2.28 – 2.02 (m, 1H, $C_4$H**H**), 1.83 (ddt, J = 24.36, 12.23, 7.34 Hz, 2H, $C_8$**HH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) :** 173.6 (s, $C_1$), 132.3 (s, $C_6$), 118.0 (s, $C_7$), 82.5 (d, J = 165.8 Hz, $C_9$), 52.2 (s, $C_2$), 45.1 (s, $C_5$), 37.5 (s, $C_4$), 35.2 (d, J = 19.6 Hz, $C_8$), 28.8 (d, J = 3.7 Hz, $C_3$).

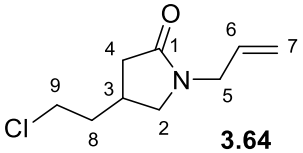
**IR (film, cm$^{-1}$):** 1722, 1688, 1662, 1653, 1646, 1441, 1435, 1429, 1419, 1363, 1275, 1230, 1218, 1197, 1092, 1075, 1069, 1042, 1037, 989, 913, 743.

**HRMS**, m/z: calculated $[C_9H_{15}ONF]^+$ : 172.11322, found: 172.11321.

**MS/MS** (p ESI): m/z (%): 58.06592, (5); 67.05493, (12); 69.07056, (2); 87.06095, (2); 95.04954, (14); 109.10143, (2); 115.05555, (39); 144.11815, (16); 172.11299, (100) $[M-H]^+$.

*Synthesis of 1-allyl-4-(2-chloroethyl)pyrrolidin-2-one*

This molecule was synthetized according to the general procedure for the electrocyclization of functionalized 2-pyrrolidinones (see p. 205).




**3.64**

**Yield:** 27 %

**Purification:** chromatography on silica gel. Eluent: AcOEt/EP 0.2/0.8.

**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 5.95 – 5.53 (m, 1H, $C_6$**H**), 5.38 – 4.99 (m, 2H, $C_7$**HH**), 4.28 – 3.12 (m, 6H, $C_2$**HH**, $C_5$**HH**, $C_9$**HH**), 2.94 – 2.72 (m, 1H, $C_4$**H**H), 2.71 – 2.50 (m, 1H, $C_3$**H**), 2.42 – 2.17 (m, 1H, $C_4$H**H**), 1.74 – 1.62 (m, 2H, $C_8$**HH**).

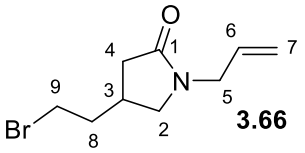
**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 172.78 (s, $C_1$), 132.05 (s, $C_6$), 118.35 (s, $C_7$), 50.07 (s, $C_5$), 47.04 (s, $C_9$), 45.19 (s, $C_2$), 35.32 (s, $C_4$), 33.56 (s, $C_3$), 29.73 (s, $C_8$).

**IR (film, $cm^{-1}$):** 1643, 1440, 1425, 1265, 1094, 1076, 922, 731, 690.

**HRMS**, m/z: calculated $[C9H15ON^{35}Cl]^+$ : 188.08367, found: 188.08371.

*Synthesis of 1-allyl-4-(2-bromoethyl)pyrrolidin-2-one*

This molecule was synthetized according to the general procedure for the electrocyclization of functionalized 2-pyrrolidinones (see p. 205).




**3.66**

**Yield:** 14 % - colourless-oil.

**Purification:** chromatography on silica gel. Eluent: AcOEt/EP 0.2/0.8.

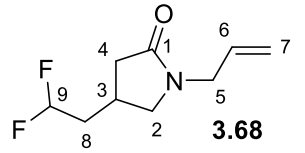
**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 5.85 – 5.80 (m, 1H, $C_5$**H**), 5.16 – 5.20 (m, 2H, $C_7$**HH**), 3.87 – 3.84 (m, 2H, $C_5$**HH**), 3.50 – 3.45 (m, 1H, $C_2$**H**H), 3.30 – 3.26 (m, 2H, $C_9$**HH**), 3.02 – 2.98 (m, 1H, $C_2$H**H**), 2.64 – 2.60 (m, 1H, $C_4$**H**H), 2.33 – 2.29 (m, 1H, $C_3$**H**), 2.05 – 1.99 (m, 1H, $C_4$H**H**), 1.75 – 1.70 (m, 2H, $C_8$**HH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) :** 173.46 (s, $C_1$), 132.34 (s, $C_6$), 117.24 (s, $C_7$), 54.28 (s, $C_5$), 47.45 (s, $C_2$), 38.21 (s, $C_8$), 36.21 (s, $C_4$), 32.23 (s, $C_3$), 30.56 (s, $C_9$).

**IR (film, $cm^{-1}$):** 2904, 2842, 1709, 1645, 1462, 1418, 1360, 1256, 919, 739, 455.

*Synthesis of 1-allyl-4-(2,2-difluoroethyl)pyrrolidin-2-one*

This molecule was synthetized according to the general procedure for the electrocyclization of functionalized 2-pyrrolidinones (see p. 205).




**3.68**

**Yield:** 36 % - colourless-oil.

**Purification:** chromatography on silica gel. Eluent: AcOEt/EP 0.2/0.8.

**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 6.22 – 5.82 (m, 1H, $C_9$FF**H**), 5.83 – 5.63 (m, 1H, $C_6$**H**), 5.49 – 5.01 (m, 2H, $C_7$**HH**), 4.03 – 3.77 (m, 2H, $C_5$**HH**), 3.43 – 3.39 (m, 1H, $C_2$**H**H), 3.03 – 2.73 (m, 1H, $C_2$H**H**), 2.69 – 2.52 (m, 1H, $C_4$**H**H), 2.51 – 2.30 (m, 1H, $C_3$**H**), 2.26 – 2.09 (m, 1H, $C_4$H**H**), 1.99 – 1.72 (m, 2H, $C_8$**HH**).

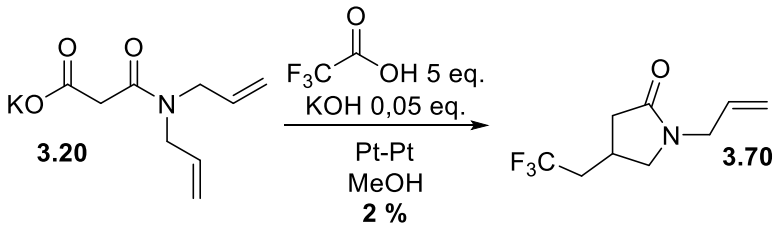
**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 174.48 (s, $C_1$), 132.33 (s, $C_6$), 118.24 (s, $C_7$), 117.92 (t, $C_9$), 58.85 (s, $C_8$), 52.50 (s, $C_5$), 45.10 (s, $C_2$), 40.93 (s, $C_4$), 29.68 (s, $C_3$).

**IR (film, $cm^{-1}$):** 2930, 1747, 1683, 1652, 1436, 1417, 1259, 1120, 1047.

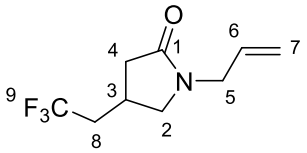
**HRMS**, m/z: calculated $[C_9H_{14}ONF_2]^+$ : 190.10350, found : 190.10374.

**MS/MS** (p ESI): m/z (%): 85.04517, (8); 133.04563, (21); 148.09273, (8); 162.10833, (11); 190.10314, (100) $[M-H]^+$.

*Synthesis of 1-allyl-4-(2,2,2-trifluoroethyl)pyrrolidin-2-one*




Potassium hydroxide (0.084 g, 1.50 mmol, 0.66 eq.) was added to a solution of potassium 3-(diallylamino)-3-oxopropanoate (0.500 g, 2.26 mmol, 1.00 eq.) in 10 ml of MeOH. The intensity of the current was fixed at 100 mA, and the mixture was electrolyzed until completion of the reaction, while a solution of TFA (0.120 ml, 1.50 mmol, 0.66 eq.) in MeOH 3.500 ml was added, over three and a half hours. The solution was treated with an aqueous solution of NaHCO3 (20.000 ml) and extracted three times with 20.000 ml of $Et_2O$. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Finally, the crude product was purified by silica gel chromatography (AcOEt/EP 8/2).

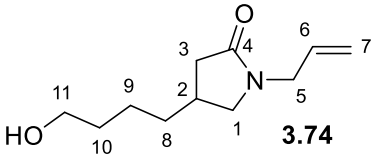



**HRMS**, m/z: calculated $[C_9H_{13}ONF_3]^+$ : 208.09438, found : 208.09472.

**MS/MS** (p ESI): m/z (%): 103.03501, (5); 151.03537, (18); 166.08251, (63); 180.09800, (10); 208.09270, (100) $[M-H]^+$.

*Synthesis of 1-allyl-4-(4-hydroxybutyl)pyrrolidin-2-one*

This molecule was synthetized according to the general procedure for the electrocyclization of functionalized 2-pyrrolidinones (see p. 205).




**Yield:** 6 % - colourless-oil.

**Purification:** chromatography on silica gel. Eluent: AcOEt/EP 0.2/0.8.

**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 5.87 – 5.80 (m, 1H, $C_6$**H**), 5.20 – 5.17 (m, 2H, $C_7$**HH**), 3.88 – 3.85 (m, 2H, $C_5$**HH**), 3.64 – 3.61 (m, 2H, $C_{11}$**HH**), 2.99 – 2.96 (m, 1H, $C_1$**H**H), 2.70 – 2.67 (m, 1H, $C_1$H**H**), 2.60 – 2.56 (m, 1H, $C_3$**H**H), 2.30 – 2.27 (m, 1H, $C_3$H**H**), 1.89 – 1.85 (m, 1H, $C_2$**H**), 1.43 – 1.28 (m, 4H, $C_{10}$**HH**, $C_{11}$**HH**), 1.15 – 1.20 (m, 2H, $C_8$**HH**).

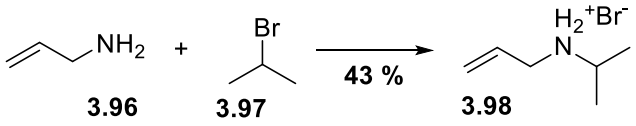
**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 173.2 (s, $C_1$), 131.4 (s, $C_6$), 117.2 (s, $C_7$), 62.6 (s, $C_{11}$), 54.3 (s, $C_2$), 43.5 (s, $C_5$), 39.7 (s, $C_4$), 36.5 (s, $C_8$), 32.7 (s, $C_{10}$), 26.5 (s, $C_2$), 20.4 (s, $C_9$).

**IR (film, cm$^{-1}$):** 1718, 1644, 1462, 1427, 1350, 1259, 929, 720.

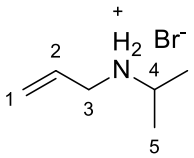
**HRMS**, m/z: calculated $[C_{11}H_{20}O_2N]^+$ : 198.14886, found: 198.14894.

**MS/MS** (p ESI): m/z (%): 98.09694, (42); 124.07592, (10); 140.10706, (6); 180.13833, (58); 198.14899, (100) $[M-H]^+$.

*Synthesis of N-isopropylprop-2-en-1-aminium*




2-bromopropane (4.69 ml, 50 mmol, 1.0 eq.) was added to allylamine (4.50 ml, 60 mmol, 1.2 eq.). The solution was allowed to stir overnight at 60°C. After total consumption of the starting material, the solution was concentrated under reduced pressure. The solid obtained was washed two times with 10 ml of cold ether and dried under vacuum.

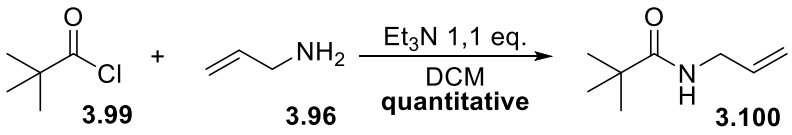



**$^{1}$H NMR (300 MHz, DMSO) : δ** 8.26 (s (br), 2H, N**HH**), 6.13 – 5.77 (m, 1H, $C_2$**H**), 5.65 – 5.19 (m, 2H, $C_1$**HH**), 3.65 – 3.61 (m, 1H, $C_3$**H**H), 3.50 (dt, J = 6.0, 1.4 Hz, 1H, $C_3$H**H**), 3.35 – 3.28 (m, 1H, $C_4$**H**), 1.26 (d, J = 6.5 Hz, 6H, $C_5$**HHH**).

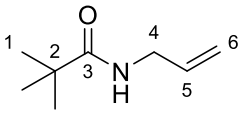
**$^{13}$C NMR (75 MHz, DMSO) : δ** 129.84 (s, $C_2$), 120.31 (s, $C_1$), 49.34 (s, $C_4$), 46.51 (s, $C_3$), 19.09 (s, $C_5$).

**IR (film, cm$^{-1}$):** 1662, 1365, 1228, 1217, 1001, 823, 759.

*Synthesis of N-allylpivalamide*



Pivaloyl chloride (6.56 ml, 53.3 mmol, 1.00 eq.) was added dropwise to a solution of allylamine (4.00 ml, 53.3 mmol, 1.00 eq.) and triethylamine (7.50 ml, 54.0 mmol, 1.01 eq.) in 50.00 ml of DCM at 0°C. The reaction was allowed to stir overnight while the temperature warm up to room temperature. The solution was quenched with 40.00 ml of water and extracted two times with 30.00 ml of DCM. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was used without further purification.

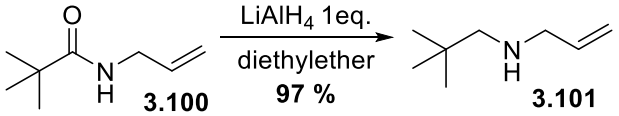



**$^1$H NMR (300 MHz, $CDCl_3$) : δ** 5.94 – 5.63 (m, 1H, $C_5$**H**), 5.32 – 4.99 (m, 2H, $C_6$**HH**), 3.85 (ddt, J = 5.6, 4.1, 1.5 Hz, 2H, $C_4$**HH**), 1.20 (s, 5.14H, $C_1$**HHH**), 1.19 (s, 3.86H, $C_1$**HHH**).

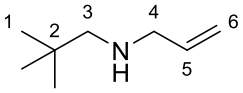
**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 178.21 (s, $C_3$), 134.54 (s, $C_5$), 116.00 (s, $C_6$), 41.86 (s, $C_4$), 38.69 (s, $C_2$), 27.60 (s, $C_1$).

**IR (film, cm$^{-1}$):** 3326, 2953, 1636, 1537, 1481, 1458, 1419, 1398, 1365, 1296, 1257, 1207, 985, 912.

*Synthesis of N-neopentylprop-2-en-1-amine*




Lithium aluminum hydride (2.00 g, 55 mmol, 1.04 eq.) was added to a solution of N-neopentylprop-2-en-1-amine (6.74 g, 53 mmol, 1.00 eq.) in 265 ml of diethyl ether, at – 10°C. Then, the reaction was allowed to stir overnight. Finally, the solution was quenched with 2 ml of water, 4 ml of an aqueous solution of NaOH 10% and 6 ml of water, and the medium was allowed to stir 30 min. After the solution was filtered through a pad of celite, and the mixture was washed with an aqueous solution of $NaHCO_3$ and extracted two times with diethyl ether. The combined organic layers were dried over $MgSO_4$ and were concentrated under reduced pressure. The final amine was used without further purification.

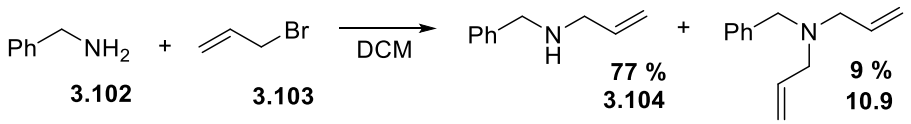



**$^1$H NMR (300 MHz, $CDCl_3$) : δ** 6.00 – 5.77 (m, 1H, $C_5$**H**), 5.72 (s (br), 1H, N**H**), 5.29 – 4.97 (m, 2H, $C_6$**HH**), 3.34 – 3.15 (m, 2H, $C_4$**HH**), 2.35 (s, 2H, $C_3$**HH**), 1.13 (s, 9H, $C_1$**HHH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 137.32 (s, $C_5$), 115.46 (s, $C_6$), 61.78 (s, $C_4$), 53.29 (s, $C_3$), 31.33 (s, $C_2$), 27.78 (s, $C_1$).

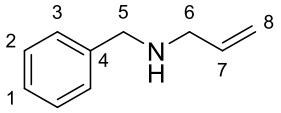
**IR (film, cm$^{-1}$):** 1648, 1203, 910.

*Synthesis of N-benzylprop-2-en-1-amine*




**3.102** **3.103** **77 %** **3.104** **9 %** **10.9**

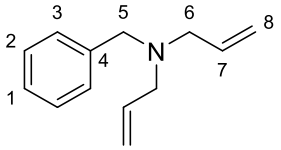
A solution of allyl bromide (0.94 ml, 10 mmol, 1.0 eq.) in 15 ml of DCM was added dropwise to a solution of benzyl amine (2.73 ml, 25 mmol, 2.5 eq.) at 0°C. Then reaction mixture was allowed to stir overnight. The solution was quenched with 10 ml of an aqueous solution of $NaHCO_3$ and extracted three times with 10 ml of DCM. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (DCM, DCM/MeOH 99/1).




**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 7.44 – 7.23 (m, 5H, Ph**H**), 6.10 – 5.79 (m, 1H, $C_7$**H**), 5.35 – 5.08 (m, 2H, $C_8$**HH**), 3.83 (s, 2H, $C_5$**HH**), 3.31 (dt, J = 6.0, 1.4 Hz, 2H, $C_6$**HH**), 2.46 – 2.17 (s (br), 1H, N**H**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 139.65 (s, $C_4$), 136.24 (s, $C_7$), 128.45 (s, $C_2$), 128.32 (s, $C_3$), 127.11 (s, $C_1$), 116.51 (s, $C_8$), 53.02 (s, $C_5$), 51.53 (s, $C_6$).

**IR (film, cm$^{-1}$):** 1643, 1494, 1452, 1417, 1255, 1107, 1072, 1027, 993, 736.



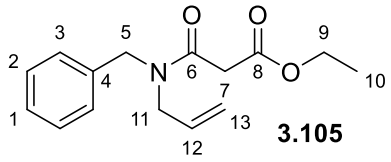

**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 7.44 – 7.23 (m, 5H, Ph**H**), 6.10 – 5.79 (m, 2H, $C_7$**H**), 5.35 – 5.08 (m, 4H, $C_8$**HH**), 3.60 (s, 2H, $C_5$**HH**), 3.10 (dt, J = 6.3, 1.2 Hz, 4H, $C_6$**HH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 135.87 (s, $C_7$), 128.90 (s, $C_3$), 128.16 (s, $C_2$), 126.87 (s, $C_4$), 126.80 (s, $C_1$), 117.39 (s, $C_8$), 57.53 (s, $C_5$), 56.41 (s, $C_6$).

**IR (film, cm$^{-1}$):** 1653, 1478, 1448, 1265, 1167, 1082, 1011, 998, 766.

*Synthesis of ethyl 3-(allyl(benzyl)amino)-3-oxopropanoate*

This molecule was synthetized according to the general procedure for preparing amide from the corresponding secondary amine using DCC coupling agent (see p. 203).




**3.105**

**Yield:** 78 % - colourless-oil.

**Purification:** chromatography on silica gel. Eluent: AcOEt/EP 0.1/0.9.

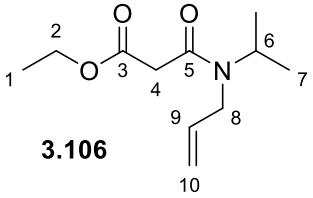
**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 7.49 – 7.11 (m, 5H, Ph**H**), 5.76 (dddd, J = 15.32, 12.74, 10.81, 5.43 Hz, 1H, $C_{12}$**H**), 5.40 – 5.02 (m, 2H, $C_{13}$**HH**), 4.63 (s, 1.23H, $C_5$**HH**), 4.51 (s, 0.77H, $C_5$**HH**), 4.25 (q, J = 7.12 Hz, 2H, $C_9$**HH**), 4.03 (d, J = 5.81 Hz, 0.77H, $C_{11}$**HH**), 3.83 (dd, J = 3.22, 1.7 Hz, 1.23H, $C_{11}$**HH**), 3.51 (s, 1.23H, $C_7$**HH**), 3.49 (s, 0.77H, $C_7$**HH**), 1.33 – 1.28 (t, J = 7.13 Hz, 3H, $C_{13}$**HHH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 167.7 (s, $C_8$), 166.5 (s, $C_6$), 136.1 (s, $C_4$), 132.2 (s, $C_{12}$), 132.1 (s, $C_{12}$), 129.0 (s, $C_2$), 128.6 (s, $C_2$), 128.0 (s, $C_3$), 127.4 (s, $C_3$), 126.3 (s, $C_1$), 117.9 (s, $C_{13}$), 117.3 (s, $C_{13}$), 61.5 (s, $C_9$), 50.9 (s, $C_5$), 49.8 (s, $C_5$), 48.4 (s, $C_{11}$), 48.1 (s, $C_{11}$), 41.1 (s, $C_7$), 14.1 (s, $C_{10}$), 14.0 (s, $C_{10}$).

**IR (film, $cm^{-1}$):** 1731, 1647, 1446, 1415, 1319, 1305, 1259, 1159, 700.

*Synthesis of ethyl 3-(allyl(isopropyl)amino)-3-oxopropanoate*

This molecule was synthetized according to the general procedure for preparing amide from the corresponding secondary amine using DCC coupling agent (see p. 203).




**3.106**

**Yield:** 77 % - colourless-oil.

**Purification:** chromatography on silica gel. Eluent: AcOEt/EP 0.5/0.5.

**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 5.96 – 5.65 (m, 1H, $C_9$**H**), 5.37 – 4.98 (m, 2H, $C_{10}$**HH**), 4.80 (hept, J = 6.81 Hz, 1H, $C_6$**H**), 4.19 (q, J = 7.12, 2H, $C_2$**HH**), 3.91 – 3.74 (m, 2H, $C_8$**HH**), 3.48 (s, 2H, $C_4$**HH**), 1.31 – 1.22 (m, 3H, $C_1$**HHH**), 1.21 (d, J = 6.7 Hz, 2.3H, $C_7$**HHH**), 1.13 (d, J = 6.8 Hz, 3.7H, $C_7$**HHH**).

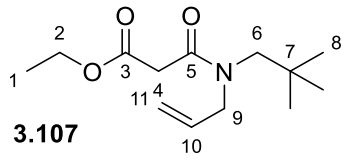
**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 167.9 (s, $C_3$), 166.4 (s, $C_5$), 134.7 (s, $C_9$), 116.6 (s, $C_{10}$), 115.8 (s, $C_{10}$), 61.3 (s, $C_2$), 61.2 (s, $C_2$), 49.6 (s, $C_6$), 45.4 (s, $C_8$), 45.0 (s, $C_6$), 41.7 (s, $C_4$), 21.2 (s, $C_7$), 20.0 (s, $C_7$), 14.0 (s, $C_1$).

**IR (film, $cm^{-1}$):** 1732, 1651, 1632, 1470, 1410, 1367, 1310, 1246, 1157, 1130, 1095, 1034, 991, 925, 735.

**HRMS**, m/z: calculated $[C_{11}H_{20}O_3N]^+$ : 214.14377, found : 214.14377.

*Synthesis of ethyl 3-(allyl(neopentyl)amino)-3-oxopropanoate*

This molecule was synthetized according to the general procedure for preparing amide from the corresponding secondary amine using DCC coupling agent (see p. 203).




**3.107**

**Yield:** 80 % - colourless-oil.

**Purification:** chromatography on silica gel. Eluent: AcOEt/EP 0.2/0.8.

**$^1$H NMR (300 MHz, $CDCl_3$) : δ** 5.85 – 5.67 (m, 1H, $C_{10}$**H**), 5.26 – 5.04 (m, 2H, $C_{11}$**HH**), 4.19 (q, J = 7.13 Hz, 2H, $C_2$**HH**), 4.07 (m, 0,4H, $C_9$**HH**), 3.97 (m, 1,6H, $C_9$**HH**), 3.49 (s, 0.4H, $C_4$**HH**), 3.41 (s, 1.6H, $C_4$**HH**), 3.20 (s, 1.6H, $C_6$**HH**), 3.10 (s, 0.4H, $C_6$**HH**), 1.27 (t, J = 7.14 Hz, 3H, $C_1$**HHH**), 0.97 (s, 1.8H, $C_8$**HHH**), 0.94 (s, 7.2H, $C_8$**HHH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 167.8 (s, $C_3$), 167.3 (s, $C_5$), 132.6 (s, $C_{10}$), 116.4 (s, $C_{11}$), 61.3 (s, $C_2$), 56.9 (s, $C_9$), 52.6 (s, $C_6$), 41.6 (s, $C_4$), 34.3 (s, $C_7$), 28.3 (s, $C_8$), 14.1 (s, $C_1$).

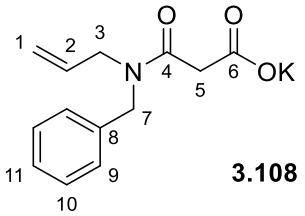
**IR (film, cm$^{-1}$):** 2951, 1738, 1651, 1477, 1419, 1365, 1323, 1250, 1203, 1155, 1034, 959, 922.

**HRMS**, m/z: calculated $[C_{13}H_{24}O_3N]^+$ : 242.17507, found : 242.17503.

**MS/MS** (p ESI): m/z (%): 102.12818, (2); 242.17503, (100) $[M-H]^+$ ; 264.15673, (19); 280.13078, (8); 381.73246, (9); 393.71577, (38); 505.32483, (30).

*Synthesis of potassium 3-(allyl(benzyl)amino)-3-oxopropanoate*

This molecule was synthetized according to the general procedure for preparing potassium salt from the corresponding ester (see p. 204).




**3.108**

**Yield:** 90 % - colourless-oil.

**Purification:** chromatography on silica gel. Eluent: DCM/MeOH 0.9/0.1.

**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 7.51 – 6.90 (m, 5H, Ph**H**), 5.89 – 5.50 (m, 1H, $C_2$**H**), 5.06 (dd, J = 33.01, 23.02 Hz, 2H, $C_1$**HH**), 4.49 (s, 2H, $C_7$**HH**), 3.90 – 3.66 (m, 2H, $C_3$**HH**), 3.43 (s, 0.88H, $C_5$**HH**), 3.29 (s, 1.12H, $C_5$**HH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 173.2 (s, $C_6$), 173.1 (s, $C_6$), 171.7 (s, $C_4$), 171.7 (s, $C_4$), 137.4 (s, $C_8$), 136.7 (s, $C_8$), 133.0 (s, $C_2$), 132.9 (s, $C_2$), 128.6 (s, $C_{10}$), 128.5 (s, $C_{10}$), 127.7 (s, $C_9$), 127.3 (s, $C_9$), 127.1 (s, $C_{11}$), 126.7 (s, $C_{11}$), 117.3 (s, $C_1$), 117.0 (s, $C_1$), 50.4 (s, $C_7$), 50.1 (s, $C_7$), 48.0 (s, $C_3$), 47.7 (s, $C_3$), 44.9 (s, $C_5$), 44.9 (s, $C_5$).

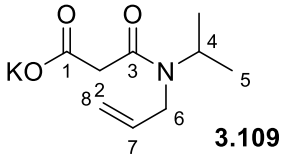
**IR (film, $cm^{-1}$):** 1739, 1649, 1440, 1365, 1217, 1155, 912, 746.

**HRMS**, m/z: calculated $[C_{13}H_{14}O_3N]^-$: 232.09682, found: 232.09686.

**MS/MS** (p ESI): m/z (%): 58.02813, (61); 72.04376, (11); 83.04850, (32); 91.05360, (24); 105.06927, (6); 117.03289, (13); 131.03599, (31); 147.06735, (100); 188.10683, (69); 232.08658, (2) $[M]^-$.

## *Synthesis of potassium 3-(allyl(isopropyl)amino)-3-oxopropanoate*

This molecule was synthetized according to the general procedure for preparing potassium salt from the corresponding ester (see p. 204).




**3.109**

**Yield:** 88 % - colourless-oil.

**Purification:** chromatography on silica gel. Eluent: DCM/MeOH 0.9/0.1.

**$^{1}$H NMR (300 MHz, DMSO) : δ** 5.99 – 5.67 (m, 1H, $C_7$**H**), 5.29 – 4.95 (m, 2H, $C_8$**HH**), 4.63 – 4.57 (m, 0.5H, $C_4$**H**), 4.20 – 4.00 (m, 0.5H, $C_4$**H**), 3.98 – 3.86 (d, 1H, $C_6$**H**H), 3.82 (d, J = 5.22 Hz, 1H, $C_6$H**H**), 3.21 (s, 2H, $C_2$**HH**), 1.16 (d, J = 6.73 Hz, 2.45H, $C_5$**HHH**), 1.08 (d, J = 6.83 Hz, 3.55H, $C_5$**HHH**).

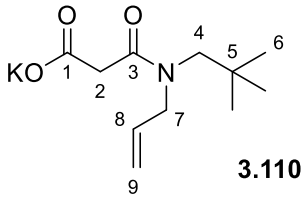
**$^{13}$C NMR (75 MHz, DMSO) : δ** 170.1 (s, $C_1$), 169.1 (s, $C_3$), 137.6 (s, $C_7$), 137.0 (s, $C_7$), 115.3 (s, $C_8$), 115.1 (s, $C_8$), 49.0 (s, $C_6$), 48.9 (s, $C_6$), 45.1 (s, $C_2$), 44.4 (s, $C_4$), 21.4 (s, $C_5$), 20.4 (s, $C_5$).

**IR (film, $cm^{-1}$):** 1632, 1301, 1049, 1022, 989, 914, 881, 823, 762, 652.

**HRMS**, m/z: calculated $[C_9H_{14}O_3N]^-$ : 184.09682, found : 184.09682.

## *Synthesis of potassium 3-(allyl(neopentyl)amino)-3-oxopropanoate*

This molecule was synthetized according to the general procedure for preparing potassium salt from the corresponding ester (see p. 204).




**3.110**

**Yield:** 86 % - colourless-oil.

**Purification:** chromatography on silica gel. Eluent: DCM/MeOH 0.9/0.1.

**$^{1}$H NMR (300 MHz, DMSO) : δ** 5.77 (m, 1H, $C_8$**H**), 5.30 – 4.88 (m, 2H, $C_9$**HH**), 3.97 (m, 2H, $C_7$**HH**), 3.28 – 2.96 (m, 4H, $C_2$**HH**, $C_4$**HH**), 0.90 (s, 9H, $C_6$**HHH**).

**$^{13}$C NMR (75 MHz, DMSO) : δ** 171.0 (s, $C_1$ or $C_3$), 170.3 (s, $C_1$ or $C_3$), 135.0 (s, $C_8$), 134.2 (s, $C_8$), 116.5 (s, $C_9$), 116.0 (s, $C_9$), 55.8 (s, $C_7$), 52.6 (s, $C_4$), 44.3 (s, $C_2$), 34.4 (s, $C_5$), 33.8 (s, $C_5$), 28.8 (s, $C_6$), 28.6 (s, $C_6$).

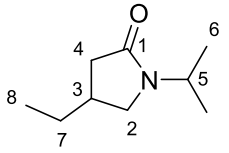
**IR (film, cm$^{-1}$):** 1640, 1303, 1034, 978, 865, 763, 642.

**HRMS**, m/z: calculated $[C_{11}H_{18}O_3N]^-$: 212.12812, found: 212.12875.

**MS/MS** (p ESI): m/z (%): 110.09464, (3); 114.08947, (69); 126.12572, (100); 14.10487, (5); 168.13603, (16); 17.11862, (5); 212.12577, (2) $[M]^-$.

*Synthesis of 4-ethyl-1-isopropylpyrrolidin-2-one*

This molecule was synthetized according to the general procedure for the electrocyclization of functionalized 2-pyrrolidinones (see p. 205).




**3.113**

**Yield:** 50 %

**Purification:** chromatography on silica gel. Eluent: AcOEt/EP 0.2/0.8.

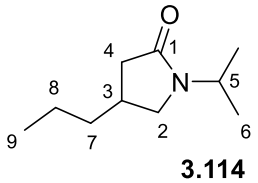
**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 4.18 (hept, J = 13.7 Hz, 1H, $C_5$**H**), 3.63 – 3.02 (m, 2H, $C_2$**HH**), 2.52 – 2.25 (m, 1H, $C_4$**H**H), 2.24 – 2.08 (m, 1H, $C_3$**H**), 2.08 – 1.97 (m, 1H, $C_4$H**H**), 1.45 – 1.37 (m, 2H, $C_7$**HH**), 1.26 – 1.18 (m, 6H, $C_6$**HHH**), 0.98 (t, J = 7.8 Hz, 3H, $C_8$**HHH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 174.76 (s, $C_1$), 52.41 (s, $C_2$), 43.56 (s, $C_5$), 35.79 (s, $C_4$), 32.17 (s, $C_3$), 26.67 (s, $C_7$), 20.07 (s, $C_6$), 19.79 (s, $C_6$), 11.32 (s, $C_8$).

**IR (film, cm$^{-1}$):** 1769, 1689, 1461, 1442, 1419, 1271, 1263, 1190, 1078.

*Synthesis of 1-isopropyl-4-propylpyrrolidin-2-one*

This molecule was synthetized according to the general procedure for the electrocyclization of functionalized 2-pyrrolidinones (see p. 205).




**3.114**

**Yield:** 64 % - colourless-oil.

**Purification:** chromatography on silica gel. Eluent: AcOEt/EP 0.2/0.8.

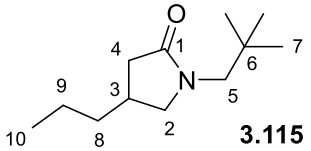
**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 4.44 – 4.26 (m, 1H, $C_5$**H**), 3.41 (dd, J = 9.41, 7.77 Hz, 1H, $C_2$**H**H), 2.90 (dd, J = 9.52, 6.61 Hz, 1H, $C_2$H**H**), 2.49 (dd, J = 16.31, 8.54 Hz, 1H, $C_4$**H**H), 2.37 – 2.16 (m, 1H, $C_3$**H**), 2.04 (dd, J = 16.32, 7.72 Hz, 1H, $C_4$H**H**), 1.44 – 1.24 (m, 4H, $C_7$**HH,** $C_8$**HH**), 1.12 (d, J = 2.37 Hz, 3H, $C_6$**HHH**), 1.10 (d, J = 2.70 Hz, 3H, $C_6$**HHH**), 0.93 (q, J = 7.22 Hz, 3H, $C_9$**HHH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 173.6 (s, $C_1$), 47.4 (s, $C_2$), 42.1 (s, $C_5$), 38.3 (s, $C_4$), 31.6 (s, $C_3$), 20.7 (s, $C_7$) 20.6 (s, $C_8$), 19.8 (s, $C_6$), 19.6 (s, $C_6$), 14.0 (s, $C_9$).

**IR (film, $cm^{-1}$):** 1677, 1643, 1425, 1367, 1284, 1238, 1198, 1169, 1128, 1076, 1062, 914, 743.

*Synthesis of 1-neopentyl-4-propylpyrrolidin-2-one*

This molecule was synthetized according to the general procedure for the electrocyclization of functionalized 2-pyrrolidinones (see p. 205).




**3.115**

**Yield:** 65 % - colourless-oil.

**Purification:** chromatography on silica gel. Eluent: AcOEt/EP 0.2/0.8.

**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 3.59 – 3.50 (m, 1H, $C_4$**H**H), 3.16 – 3.06 (m, 1H, $C_4$H**H**), 3.04 (s, 2H, $C_5$**HH**), 2.60 – 2.42 (m, 1H, $C_2$**H**H), 2.41 – 2.20 (m, 1H, $C_3$**H**), 2.15 – 1.98 (m, 1H, $C_2$H**H**), 1.51 – 1.21 (m, 4H, $C_8$**HH**, $C_9$**HH**), 1.04 – 0.81 (m, 12H, $C_7$**HHH**, $C_{10}$**HHH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 175.48 (s, $C_1$), 55.03 (s, $C_5$), 37.54 (s, $C_2$), 36.74 (s, $C_4$), 33.67 (s, $C_6$), 32.02 (s, $C_3$), 28.30 (s, $C_7$), 20.62 (s, $C_8$), 14.04 (s, $C_9$), 14.02 (s, $C_{10}$).

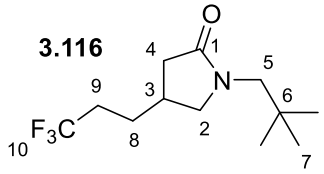
**IR (film, $cm^{-1}$):** 2957, 1747, 1693, 1671, 1990, 1475, 1464, 1435, 1421, 1396, 1365, 1327, 1284, 1242, 1213, 1155, 1072, 1029, 905, 887.

**HRMS**, m/z: calculated $[C_{12}H_{24}ON]^+$ : 198.18524, found : 198.18521.

**MS/MS** (p ESI): m/z (%): 128.10662, (36); 198.18453, (100) $[M-H]^+$.

*Synthesis of 1-neopentyl-4-(3,3,3-trifluoropropyl)pyrrolidin-2-one*

This molecule was synthetized according to the general procedure for the electrocyclization of functionalized 2-pyrrolidinones (see p. 205).




**Yield:** 69 % - colourless-oil.

**Purification:** chromatography on silica gel. Eluent: AcOEt/EP 0.2/0.8.

**$^1$H NMR (300 MHz, $CDCl_3$) : δ** 3.86 – 3.52 (m, 1H, $C_2$**H**H), 3.56 – 3.33 (m, 1H, $C_2$H**H**), 3.26 (s, 2H, $C_5$**HH**), 2.82 – 2.57 (m, 1H, $C_4$**H**H), 2.29 – 2.10 (m, 1H, $C_4$H**H**), 1.89 – 1.70 (m, 1H, $C_3$**H**), 1.58 – 1.61 (m, 2H, $C_9$**HH**), 1.33 – 1.07 (m, 2H, $C_8$**HH**), 0.92 (s, 9H, $C_7$**HHH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 173.42 (s, $C_1$), 132.53 (s, $C_{10}$), 55.06 (s, $C_5$), 45.78 (s, $C_2$), 37.28 (s, $C_4$), 33.75 (s, $C_6$), 33.63 (s, $C_3$), 31.23 (s, $C_9$), 28.21 (s, $C_7$), 26.53 (s, $C_8$).

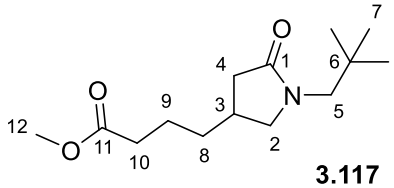
**IR (film, cm$^{-1}$):** 1677, 1477, 1450, 1396, 1365, 1255, 1137, 1107, 910, 733.

**HRMS**, m/z: calculated $[C_{12}H_{21}ON^{23}NF_3]^+$ : 252.15698, found: 252.15631.

**MS/MS** (p ESI): m/z (%): 72.08945, (5); 128.14324, (8); 182.07834, (62); 252.15620, (100) $[M-H]^+$.

*Synthesis of methyl 4-(1-neopentyl-5-oxopyrrolidin-3-yl)butanoate*

This molecule was synthetized according to the general procedure for the electrocyclization of functionalized 2-pyrrolidinones (see p. 205).




**Yield:** 60 % - colourless-oil.

**Purification:** chromatography on silica gel. Eluent: AcOEt/EP 0.4/0.6.

**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 3.67 (s, 3H, $C_{12}$**HHH**), 3.59 – 3.51 (m, 1H, $C_2$**H**H), 3.16 – 3.08 (m, 1H, $C_2$H**H**), 3.01 (s, 2H, $C_5$**HH**), 2.56 – 2.45 (m, 1H, $C_4$**H**H), 2.39 – 2.20 (m, 3H, $C_3$**H**, $C_{10}$**HH**), 2.11 – 2.00 (m, 1H, $C_4$H**H**), 1.70 – 1.54 (m, 2H, $C_9$**HH**), 1.52 – 1.39 (m, 2H, $C_8$**HH**), 0.92 (s, 9H, $C_7$**HHH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 175.2 (s, $C_1$), 173.7 (s, $C_{11}$), 56.2 (s, $C_5$), 55.0 (s, $C_2$), 51.6 (s, $C_{12}$), 37.4 (s, $C_4$), 33.9 (s, $C_8$), 33.8 (s, $C_{10}$), 33.6 (s, $C_6$), 32.0 (s, $C_3$), 28.3 (s, $C_7$), 22.8 (s, $C_9$).

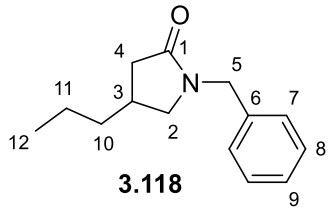
**IR (film, $cm^{-1}$):** 1737, 1730, 1492, 1477, 1436, 1396, 1247, 1197, 1172, 908, 891, 730.

**HRMS**, m/z: calculated $[C_{14}H_{26}O_3N]^+$ : 256.19072, found: 256.19061.

**MS/MS** (p ESI): m/z (%): 154.08605, (5); 186.11222, (4); 224.16412, (20); 256.19011, (100) $[M-H]^+$.

*Synthesis of 1-benzyl-4-propylpyrrolidin-2-one*

This molecule was synthetized according to the general procedure for the electrocyclization of functionalized 2-pyrrolidinones (see p. 205).




**3.118**

**Yield:** 59 % - colourless-oil.

**Purification:** chromatography on silica gel. Eluent: DCM/MeOH 0.99/0.01.

**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 7.38 – 7.20 (m, 5H, Ph**H**), 4.43 (s, 2H, $C_5$**HH**), 3.33 (dd, J = 9.63, 8.02 Hz, 1H, $C_2$H**H**), 2.87 (dd, J = 9.64, 6.72 Hz, 1H, $C_2$**H**H), 2.57 (dd, J = 16.44, 8.58 Hz, 1H, $C_4$H**H**), 2.30 (dt, J = 15.44, 7.76 Hz, 1H, $C_3$**H**), 2.18 – 2.06 (m, 1H, $C_4$**H**H), 1.46 – 1.19 (m, 4H, $C_{10}$**HH**, $C_{11}$**HH**), 0.88 (t, J = 7.15 Hz, 3H, $C_{12}$**HHH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 174.5 (s), 136.5 (s, $C_6$), 128.6 (s, $C_8$), 128.1 (s, $C_7$), 127.5 (s, $C_9$), 52.4 (s, $C_2$), 46.5 (s, $C_5$), 37.7 (s, $C_4$), 36.8 (s, $C_{10}$), 31.4 (s, $C_3$), 20.5 (s, $C_{11}$), 13.9 (s, $C_{12}$).

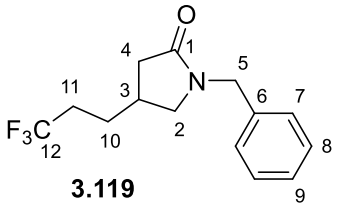
**IR (film, $cm^{-1}$):** 1743, 1681, 1491, 1440, 1425, 1361, 1286, 1263, 1244, 1203, 914, 744, 702.

**HRMS**, m/z: calculated $[C_{14}H_{20}ON]^+$ : 218.15394, found: 218.15404.

**MS/MS** (p ESI): m/z (%): 91.05451, (53); 131.08523, (4); 140.10658, (13); 218.15324, (100) $[M-H]^+$.

*Synthesis of 1-benzyl-4-(3,3,3-trifluoropropyl)pyrrolidin-2-one*

This molecule was synthetized according to the general procedure for the electrocyclization of functionalized 2-pyrrolidinones (see p. 205).




**3.119**

**Yield:** 43 % - colourless-oil.

**Purification:** chromatography on silica gel. Eluent: EP/AcOEt 0.7/0.3.

**$^{1}$H NMR (300 MHz, $CDCl_3$) δ** 7.50 – 7.12 (m, 5H, Ph**H**), 4.46 (s, 2H, $C_5$**HH**), 3.39 (dt, J = 17.8, 8.9 Hz, 1H, $C_2$**H**H), 2.91 (dd, J = 9.7, 6.6 Hz, 1H, $C_2$H**H**), 2.65 (dd, J = 16.5, 8.6 Hz, 1H, $C_4$**H**H), 2.37 (dt, J = 29.3, 10.8 Hz, 1H, $C_3$**H**), 2.26 – 1.95 (m, 3H, $C_4$H**H**, $C_{11}$**HH**), 1.76 – 1.63 (m, 2H, $C_{10}$**HH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 173.56 (s, $C_1$), 135.35 (q, $C_{12}$), 126.52 (s, $C_6$), 128.77 (s, $C_8$), 128.13 (s, $C_7$), 127.73 (s, $C_9$), 51.80 (s, $C_2$), 46.54 (s, $C_5$), 37.50 (s, $C_{11}$), 37.23 (s, $C_4$), 30.72 (s, $C_3$), 26.52 (s, $C_{10}$).

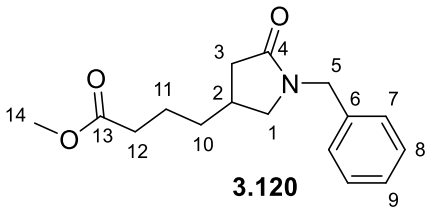
**IR (film, $cm^{-1}$):** 1739, 1681, 1456, 1438, 1363, 1257, 1217, 1137, 1097, 742, 702.

**HRMS**, m/z: calculated $[C_{14}H_{17}ONF_3]^+$ : 272.12568, found: 272.12556.

**MS/MS** (p ESI): m/z (%): 91.05449, (19); 194.07815, (17); 272.12429, (100) $[M-H]^+$.

*Synthesis of methyl 4-(1-benzyl-5-oxopyrrolidin-3-yl)butanoate*

This molecule was synthetized according to the general procedure for the electrocyclization of functionalized 2-pyrrolidinones (see p. 205).




**3.120**

**Yield:** 56 % - colourless-oil.

**Purification:** chromatography on silica gel. Eluent: EP/AcOEt 0.7/0.3.

**$^{1}$H NMR (300 MHz, $CDCl_3$) δ** 7.39 – 7.19 (m, 5H, Ph**H**), 4.44 (s, 2H, $C_5$**HH**), 3.65 (s, 3H, $C_{14}$**HHH**), 3.35 (dd, J = 6.74, 2.92 Hz, 1H, $C_1$**H**H), 2.82 (dd, J = 9.66, 6.03 Hz, 1H, $C_1$H**H**), 2.61 (dd, J = 16.52, 8.53 Hz, 1H, $C_3$**H**H), 2.49 – 2.18 (m, 3H, $C_2$**H**,

$C_{12}$**HH**), 2.08 (dd, J = 16.55, 6.83 Hz, 1H, $C_3$H**H**), 1.43 – 1.00 (m, 4H, $C_{10}$**HH**, $C_{11}$**HH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 173.7, (s, $C_4$), 173.1, (s, $C_{13}$), 128.6 (s, $C_8$), 128.1 (s, $C_7$), 127.5 (s, $C_9$), 53.9 (s, $C_1$), 51.3, (s, $C_{14}$) 46.4 (s, $C_5$), 39.4 (s, $C_3$), 33.2 (s, $C_{12}$), 30.6 (s, $C_2$), 26.3 (s, $C_{10}$), 19.7 (s, $C_{11}$).

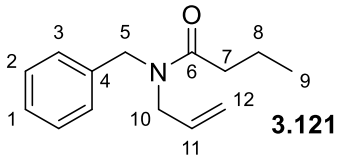
**IR (film, cm$^{-1}$):** 1672, 1494, 1438, 1267, 1176, 914, 744, 702.

**HRMS**, m/z: calculated $[C_{16}H_{22}O_3N]^+$ : 276.15942, found: 276.15929.

**MS/MS** (p ESI): m/z (%): 91.5457, (39); 117.06986, (27); 145.06446, (12); 177.09060, (77); 202.12214, (16); 244.13251, (27); 276.15840, (100) [M-H*]+*.

*Synthesis of N-allyl-N-benzylbutyramide*

This molecule was synthetized according to the general procedure for the electrocyclization of functionalized 2-pyrrolidinones (see p. 205).




**3.121**

**Yield:** 14 % - colourless-oil.

**Purification:** chromatography on silica gel. Eluent: DCM/MeOH 0.99/0.01.

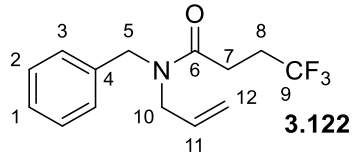
**$^1$H NMR (300 MHz, $CDCl_3$) : δ** 7.42 – 7.10 (m, 5H, Ph**H**), 5.88 – 5.64 (m, 1H, $C_{11}$**H**), 5.28 – 4.99 (m, 2H, $C_{12}$**HH**), 4.60 (s, 1.2H, $C_5$**HH**), 4.51 (s, 0.8H, $C_5$**HH**), 4.01 (d, J = 5.94 Hz, 0.8H, $C_{10}$**HH**), 3.83 (dd, J = 7.93, 6.14 Hz, 1.2H, $C_{10}$**HH**), 2.40 – 2.29 (m, 2H, $C_7$**HH**), 1.74 – 1.69 (m, 2H, $C_8$**HH**), 0.97 – 0.93 (m, 3H, $C_9$**HHH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 173.5 (s, $C_6$), 137.7 (s, $C_4$), 137.0 (s, $C_4$), 133.1 (s, $C_{11}$), 132.7 (s, $C_{11}$), 128.8 (s, $C_3$), 128.5 (s, $C_3$), 128.1 (s, $C_3$), 127.5 (s, $C_3$), 127.2 (s, $C_1$), 126.2 (s, $C_1$), 117.3 (s, $C_{12}$), 116.7 (s, $C_{12}$), 50.0 (s, $C_5$), 49.0 (s, $C_5$), 48.0 (s, $C_{10}$), 47.8 (s, $C_{10}$), 35.1 (s, $C_7$), 34.9 (s, $C_7$), 18.8 (s, $C_8$), 13.9 (s, $C_9$).

**IR (film, cm$^{-1}$):** 1733, 1641, 1494, 1452, 1361, 1213, 921, 734, 700.

*Synthesis of N-allyl-N-benzyl-4,4,4-trifluorobutanamide*

This molecule was synthetized according to the general procedure for the electrocyclization of functionalized 2-pyrrolidinones (see p. 205).




**3.122**

**Yield:** 12 % - colourless-oil.

**Purification:** chromatography on silica gel. Eluent: EP/AcOEt 0.7/0.3.

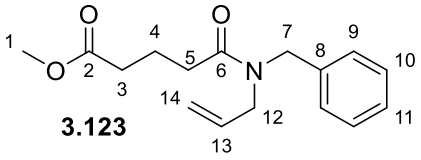
**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 7.40 – 6.96 (m, 5H, Ph**H**), 5.85 – 5.56 (m, 1H, $C_{11}$**H**), 5.23 – 4.87 (m, 2H, $C_{12}$**HH**), 4.52 (s, 2H, $C_5$**HH**), 3.83 (dt, J = 10.6, 6.8 Hz, 2H, $C_{10}$**HH**), 2.71 – 2.39 (m, 2H, $C_7$**HH**), 2.19 – 1.84 (m, 2H, $C_8$**HH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 170.19 (s, $C_6$), 170.07 (s, $C_6$), 137.22 (s, $C_4$), 137.14 (s, $C_4$), 132.65 (s, $C_{11}$), 132.09 (s, $C_{11}$), 129.07 (s, $C_4$), 128.66 (s, $C_4$), 128.21 (s, $C_3$), 127.55 (s, $C_1$), 126.21 (q, $C_9$), 126.11 (q, $C_9$), 117.90 (s, $C_{12}$), 117.05 (s, $C_{12}$), 50.01 (s, $C_5$), 49.02 (s, $C_5$), 48.73 (s, $C_{10}$), 48.43 (s, $C_{10}$), 29.93 (s, $C_8$), 29.70 (s, $C_8$), 25.82 (s, $C_7$).

**IR (film, $cm^{-1}$):** 1739, 1720, 1645, 1637, 1440, 1377, 1365, 1255, 1226, 1217, 1135, 1105, 979, 923, 740, 700.

*Synthesis of methyl 5-(allyl(benzyl)amino)-5-oxopentanoate*

This molecule was synthetized according to the general procedure for the electrocyclization of functionalized 2-pyrrolidinones (see p. 205).




**3.123**

**Yield:** 11 % - colourless-oil.

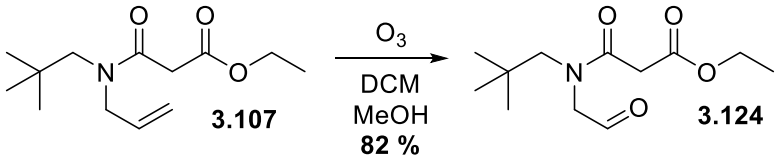
**Purification:** chromatography on silica gel. Eluent: EP/AcOEt 0.7/0.3.

**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 7.45 – 7.06 (m, 5H, Ph**H**), 5.91 – 5.59 (m, 1H, $C_{13}$**H**), 5.14 (dddd, J = 16.92, 16.04, 12.63, 1.45 Hz, 2H, $C_{14}$**HH**), 4.58 (s, 1.2H, $C_7$**HH**), 4.50 (s, 0.8H, $C_7$**HH**), 4.00 (d, J = 6.02 Hz, 0.8H, $C_{12}$**HH**), 3.89 – 3.77 (m, 1.2H, $C_{12}$**HH**), 3.66 (s, 1.9H, $C_1$**HHH**), 3.63 (s, 1.1H, $C_1$**HHH**), 2.53 – 2.30 (m, 4H, $C_3$**HH**, $C_5$**HH**), 2.09 – 1.88 (m, 2H, $C_4$**HH**).

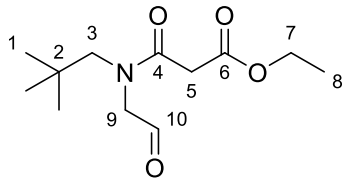
**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 173.7 (s, $C_2$), 173.7 (s, $C_2$), 172.4 (s, $C_6$), 172.3 (s, $C_6$), 137.5 (s, $C_8$), 136.7 (s, $C_8$), 133.0 (s, $C_{13}$), 132.5 (s, $C_{13}$), 128.9 (s, $C_{10}$), 128.5 (s, $C_{10}$), 128.1 (s, $C_9$), 127.5 (s, $C_9$), 127.3 (s, $C_{11}$), 126.2 (s, $C_{11}$), 117.4 (s, $C_{14}$), 116.7 (s, $C_{14}$), 51.5 (s, $C_1$), 49.9 (s, $C_7$), 49.0 (s, $C_7$), 48.2 (s, $C_{12}$), 48.0 (s, $C_{12}$), 33.2 (s, $C_5$), 32.0 (s, $C_3$), 31.8 (s, $C_3$), 20.5 (s, $C_4$).

**IR (film, $cm^{-1}$):** 1731, 1724, 1631, 1494, 1434, 1417, 1361, 1201, 1174, 1153, 1027, 993, 921, 736, 700.

*Synthesis of ethyl 3-(neopentyl(2-oxoethyl)amino)-3-oxopropanoate*




The olefin (0.2973 g, 1.23 mmol, 1 eq.) was introduced in a two necked flask filled with 26 ml of DCM and 26 ml of MeOH. An ozone flux was bubbled through the mixture at – 78°C until the solution turned blue. Excess of ozone was removed using oxygen flux. The solution wad stirred for twelve hours at room temperature. Finally, the reaction mixture was washed with 30 ml of water and the aqueous layer was extracted two times with 30 ml of DCM. The combined organic layers were dried over $MgSO_4$ and were concentrated under reduced pressure. The product was used without further purification.




**$^1$H NMR (300 MHz, $CDCl_3$) : δ** 9.67 (s, 0,2H, $C_{10}$**H**), 9.52 (s, 0,8H, $C_{10}$**H**), 4.27 – 4.16 (m, 2H, $C_7$**HH**), 4.05 (s, 2H, $C_9$**HH**), 3.49 (s, 2H, $C_5$**HH**), 3.22 (s, 2H, $C_3$**HH**), 1.37 – 1.20 (m, 3H, $C_8$**HHH**), 1.09 – 0.85 (m, 9H, $C_1$**HHH**).

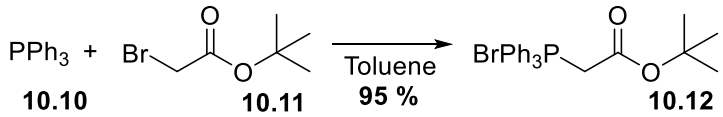
**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 197.44 (s, $C_{10}$), 168.31 (s, $C_6$), 167.22 (s, $C_7$), 61.65 (s, $C_9$), 61.45 (s, $C_7$), 59.17 (s, $C_3$), 40.67 (s, $C_5$), 34.03 (s, $C_2$), 28.10 (s, $C_1$), 14.08 (s, $C_8$).

**IR (film, cm$^{-1}$):** 2951, 1730, 1650, 1633, 1479, 1465, 1444, 1396, 1367, 1323, 1249, 1159, 1032.

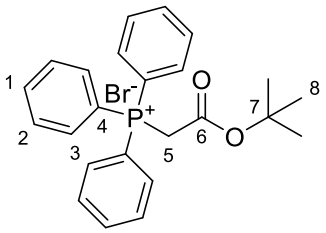
**HRMS**, m/z: calculated $[C_{12}H_{22}O_4N]^+$ : 244.15433, found: 244.15428.

**MS/MS** (p ESI): m/z (%): 86.02359, (27); 130.12177, (100); 138.09039, (11); 156.10070, (57); 174.07479, (13); 198.11094, (21); 244.15234, (37) $[M-H]^+$.

*Synthesis of tert-butyl 2-(bromotriphenyl-phosphaneyl)acetate*




Bromo tertbutylacetate (5 ml, 33.86 mmol, 1 eq.) was added dropwise to a solution of triphenylphosphine (8,88 g, 33.86 mmol, 1 eq) in 30 ml of toluene. Then, the mixture was hallowed to stir for one hour. Finally, the white solid formed was filtered, washed with a small volume of cold $Et_2O$ and dried under vacuum.

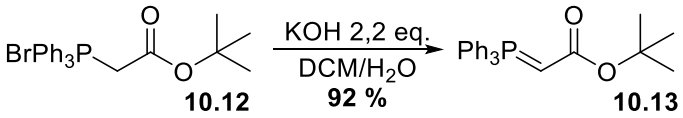



**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 8.02 – 7.56 (m, 15H, Ph**H**), 5.46 (d, J = 14.0 Hz, 2H, $C_5$**HH**), 1.22 (s, 9H, $C_8$**HHH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 163.07 (s, $C_6$), 135.04 (s, $C_1$), 134.22 (s, $C_3$), 134.08 (s, $C_3$), 130.29 (s, $C_2$), 130.08 (s, $C_2$), 118.74 (s, $C_4$), 84.72 (s, $C_7$), 34.47 (s, $C_5$), 27.61 (s, $C_8$).

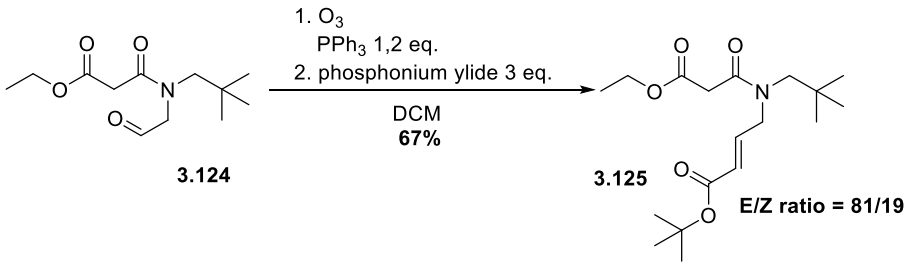
**IR (film, cm$^{-1}$):** 1720, 1437, 1394, 1371, 1282, 1261, 1137, 1110, 997, 912, 808.

*Synthesis of tert-butyl 2-(triphenyl-phosphaneylidene)acetate*



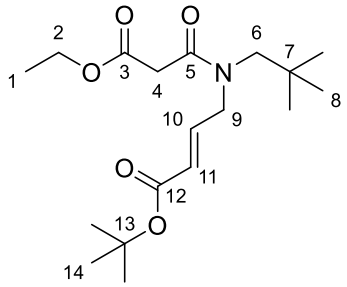

A solution of phosphonium salt (6.1742 g, 13.50 mmol, 1.0 eq.) in 35 ml of DCM and a solution of KOH (1.6663 g, 56.11 mmol, 2.2 eq.) in 24 ml of water were introduced in a separating funnel. The mixture was shaken vigorously. Then, the aqueous layer was washed with 35 ml of water. The combined organic layers were dried over $MgSO_4$ and were concentrated under reduced pressure. The crude product was dissolved in diethyl ether and was hallowed to stir for one hour. Finally the white crystals obtain were washed two times with 10 ml of cold diethyl ether.

*Synthesis of tert-butyl (E)-4-(3-ethoxy-N-neopentyl-3-oxopropanamido)but-2-enoate*




The olefin (1.0000 g, 4.15 mmol, 1.0 eq.) was introduced in a two necked flask filled with 35 ml of DCM. An ozone flux was bubbled through the mixture at – 78°C until the solution turned blue. Excess of ozone was removed using oxygen flux and triphenylphosphine was added (1.3000 g, 4.95 mmol, 1.2 eq.). The solution was stirred for 12 hours, at room temperature. Then, the phosphonium ylide (4.6866 g, 12.45 mmol, 3.0 eq.) was introduced in one portion and the solution was stirred at room temperature for twelve hours. The solution was quenched with water (35 ml)

and the aqueous layer was extracted three times with 30 ml of DCM. The combined organic layers were dried over $MgSO_4$ and were concentrated under reduced pressure. The crude product was purified by silica gel chromatography (MeOH/DCM 99/1).



**$^1$H NMR (300 MHz, $CDCl_3$) : δ** 6.75 – 6.59 (m, 0.8H, $C_{10}$**H**), 6.11 – 5.94 (m, 0.2H, $C_{10}$**H**), 5.91 – 5.65 (m, 1H, $C_{11}$**H**), 4.37 – 4.00 (m, 4H, $C_2$**HH,** $C_9$**HH**), 3.62 – 3.31 (m, 2H, $C_4$**HH**), 3.32 – 3.05 (m, 2H, $C_6$**HH**), 1.56 – 1.35 (m, 9H, $C_{14}$**HHH**), 1.38 – 1.19 (t, J = 7.20 Hz, 3H, $C_1$**HHH**), 0.98 (s, 9H, $C_8$**HHH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 167.58 (s, $C_{12}$), 167.18 (s, $C_3$), 164.84 (s, $C_5$), 141.19 (s, $C_{10}$), 140.95 (s, $C_{10}$), 124.07 (s, $C_{11}$), 123.84 (s, $C_{11}$), 81.08 (s), 80.51 (s, $C_{13}$), 61.55 (s, $C_2$), 59.19 (s, $C_2$), 57.18 (s, $C_9$), 51.16 (s, $C_6$), 41.64 (s, $C_4$), 41.23 (s, $C_4$), 34.54 (s, $C_7$), 34.18 (s, $C_7$), 28.46 (s, $C_8$), 28.37 (s, $C_8$), 28.07 (s, $C_{14}$), 14.13 (s, $C_1$).

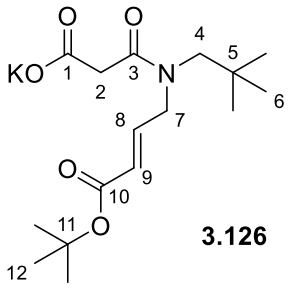
**IR (film, cm$^{-1}$):** 2954, 1739, 1712, 1647, 1477, 1463, 1446, 1421, 1396, 1369, 1319, 1301, 1280.

**HRMS**, m/z: calculated $[C_{18}H_{32}O_5N]^+$ : 342.22750, found : 342.22761.

**MS/MS** (p ESI): m/z (%): 84.04421, (1); 154.12112, (66); 240.12060, (8); 286.16212, (100); 342.22415, (4) $[M-H]^+$.

### *Synthesis of potassium (E)-3-((4-(tert-butoxy)-4-oxobut-2-en-1-yl)(neopentyl)amino)-3-oxopropanoate*

This molecule was synthetized according to the general procedure for preparing the potassium salt from the corresponding ester (see p. 204).



**3.126**

**Yield:** 54 % - white powder.

**Purification:** chromatography on silica gel. Eluent: DCM/MeOH 9/1.

**$^{1}$H NMR (300 MHz, DMSO) : δ** 6.56 - 6.32 (m, 1H, $C_8$**H**), 5.82 – 5.73 (m, 1H, $C_9$**H**), 4.36 – 4.28 (m, 2H, $C_7$**HH**), 3.63 (s, 2H, $C_2$**HH**), 3.21 – 3.10 (m, 2H, $C_4$**HH**), 1.39 (s, 9H, $C_{12}$**HHH**), 0.86 (s, 9H, $C_6$**HHH**).

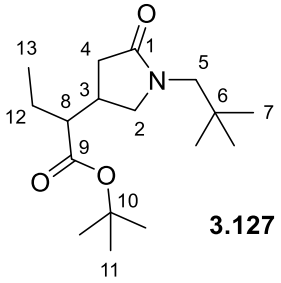
**$^{13}$C NMR (75 MHz, DMSO) : δ** 174.08 (s, $C_1$), 172.70 (s, $C_{10}$), 171.54 (s, $C_3$), 121.11 (s, $C_9$), 114.43 (s, $C_8$), 80.30 (s, $C_{11}$), 57.51 (s, $C_4$), 51.75 (s, $C_7$), 37.97 (s, $C_2$), 33.87 (s, $C_5$), 28.58 (s, $C_{12}$), 28.19 (s, $C_6$).

**IR (film, cm$^{-1}$):** 2964, 1742, 1724, 1657, 1473, 1444, 1386, 1360, 1320, 1280.

**MS/MS** (p ESI): m/z(%): 107.04137, (8); 123.01515, (80); 253.08378, (29); 299.12584, (89); 310.10538, (61); 341.13658, (37); 352.15233, (100) $[M-H]^+$; 390.10833, (46).

*Synthesis of tert-butyl 2-(1-neopentyl-5-oxopyrrolidin-3-yl)butanoate*

This molecule was synthetized according to the general procedure for preparing the electrocyclization of functionalized 2-pyrrolidinones (see p. 205).




**3.127**

**Yield:** 65 % - colourless-oil.

**Purification:** chromatography on silica gel. Eluent: EP/AcOEt 0.8/0.2.

**$^{1}$H NMR (300 MHz, $CDCl_3$): δ** 3.59 – 3.21 (m, 1H, $C_2$H**H**), 3.19 – 2.84 (m, 3H, $C_2$**H**H, $C_5$**HH**), 2.82 – 1.96 (m, 4H, $C_3$**H**, $C_4$**HH**, $C_8$**H**), 1.82 – 1.53 (m, 2H, $C_{12}$**HH**), 1.44 (s, 9H, $C_{11}$**HHH**), 1.04 – 0.95 (m, 3H, $C_{13}$**HHH**), 0.89 (s, 9H, $C_7$**HHH**).

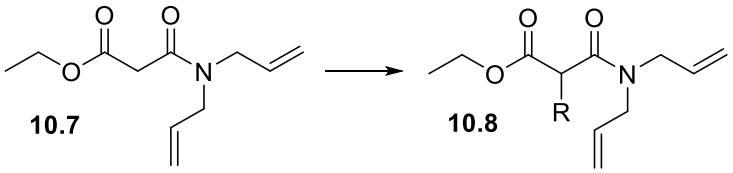
**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 176.30 (s, $C_1$), 171.05 (s, $C_9$), 55.05 (s, $C_5$), 36.60 (s, $C_2$), 35.90 (s, $C_4$), 33.52 (s, $C_6$), 32.63 (s, $C_3$), 28.31 (s, $C_{11}$), 28.09 (s, $C_7$), 22.78 (s, $C_8$), 12.17 (s, $C_{12}$), 10.93 (s, $C_{13}$).

**IR (film, cm$^{-1}$):** 2944, 1728, 1657, 1476, 1449, 1431, 1386, 1360, 1309, 1280.

**HRMS**, m/z: calculated $[C_{17}H_{32}O_3N]^+$ : 298.23767, found: 298.23769.

**MS/MS** (p ESI): m/z (%): 242.17359, (100); 298.23608, (5) $[M-H]^+$.

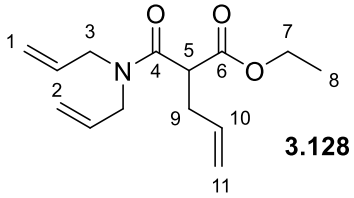
*General Procedure for preparing functionalized malonates from the corresponding malonate*




NaH 60% (15 mmol, 1 eq.) was added to a solution of the ester (15 mmol, 1 eq., 1.25 M) in THF, at 0°C. The mixture was allowed to stir for 30 minutes, at room temperature. Allyl bromide (15 mmol, 1 eq.) was then added dropwise. The mixture was allowed to stir for two hours, at room temperature, until completion of the reaction; as shown by TLC. The solution was quenched with water and extracted three times with diethyl ether. Finally the combined organic layer was extracted with brine, dried over MgSO4 and concentrated under reduced pressure. The crude product was purified by silica gel chromatography.

*Synthesis of ethyl 2-(diallylcarbamoyl)pent-4-enoate*

This molecule was synthetized according to the general procedure for preparing functionalized malonates from the corresponding malonate (see p. 233).




**Yield:** 99 % - colourless-oil.

**Purification:** chromatography on silica gel. Eluent: EP/AcOEt 0.8/0.2.

**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 5.86 – 5.64 (m, 3H, $C_2$**H**, $C_{10}$**H**), 5.31 – 4.99 (m, 6H, $C_1$**HH**, $C_{11}$**HH**), 4.25 – 4.01 (m, 4H, $C_7$**HH**, $C_3$**HH**), 3.93 – 3.76 (m, 2H, $C_3$**HH**), 3.65 – 3.54 (m, 1H, $C_5$**H**), 2.74 – 2.62 (m, 2H, $C_9$**HH**), 1.24 (t, J = 7.16 Hz, 3H, $C_8$**HHH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 169.4 (s, $C_4$), 168.2 (s, $C_6$), 134.8 (s, $C_{10}$), 132.7 (s, $C_2$), 132.6 (s, $C_2$), 117.3 (s, $C_{11}$), 117.1 (s, $C_1$), 117.0 (s, $C_1$), 61.4 (s, $C_7$), 49.2 (s, $C_3$), 48.8 (s, $C_3$), 48.2 (s, $C_5$), 33.5 (s, $C_9$), 14.1 (s, $C_8$).

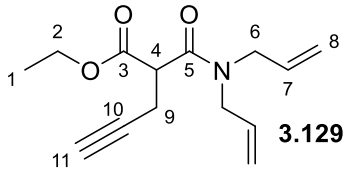
**IR (film, $cm^{-1}$):** 1741, 1639, 1465, 1444, 1415, 1367, 1330, 1265, 1236, 1116, 1029, 995, 916.

**HRMS**, m/z: calculated $[C_{14}H_{22}O_3N]^+$ : 252.15942, found: 252.15938.

**MS/MS** (p ESI): m/z (%): 124.07593, (3); 206.11768, (4); 238.14349, (6); 252.15938, (100) $[M-H]^+$.

*Synthesis of ethyl 2-(diallylcarbamoyl)pent-4-ynoate*

This molecule was synthetized according to the general procedure for preparing functionalized malonates from the corresponding malonate (see p. 233).




**3.129**

**Yield:** 95 % - colourless-oil.

**Purification:** chromatography on silica gel. Eluent: EP/AcOEt 0.8/0.2.

**$^1$H NMR (300 MHz, $CDCl_3$) : δ** 5.94 – 5.63 (m, 2H, $C_7$**H**), 5.37 – 5.03 (m, 4H, $C_8$**HH**), 4.29 – 3.83 (m, 6H, $C_2$**HH**, $C_6$**HH**), 3.79 (t, J = 7.54 Hz, 1H, $C_4$**H**), 2.84 (dd, J = 7.43, 2.69 Hz, 2H, $C_9$**HH**), 1.98 (t, J = 2.71 Hz, 1H, $C_{11}$**H**), 1.26 (t, J = 7.12 Hz, 3H, $C_1$**HHH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 168.3 (s, $C_5$), 167.4 (s, $C_3$), 132.5 (s, $C_7$), 132.4 (s, $C_7$), 117.2 (s, $C_8$), 117.1 (s, $C_8$), 81.0 (s, $C_{10}$), 70.0 (s, $C_{11}$), 61.7 (s, $C_2$), 49.4 (s, $C_4$), 48.3 (s, $C_6$), 47.8 (s, $C_6$), 18.9 (s, $C_9$), 14.0 (s, $C_1$).

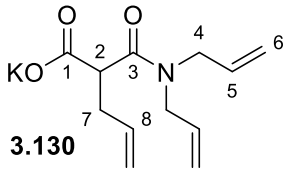
**IR (film, $cm^{-1}$):** 1739, 1731, 1645, 1469, 1444, 1415, 1330, 1265, 1238, 1176, 1010, 923.

**HRMS**, m/z: calculated $[C_{14}H_{20}O_3N]^+$ : 250.14377, found: 250.14365.

**MS/MS** (p ESI): m/z (%): 81.07007, (6); 98.09633, (16); 124.07518, (59); 204.10082, (27); 222.11123, (36); 250.14218, (100) $[M-H]^+$.

*Synthesis of potassium 2-(diallylcarbamoyl)pent-4-enoate*

This molecule was synthetized according to the general procedure for preparing the potassium salt from the corresponding ester (see p. 204).




**3.130**

**Yield:** 73 % - white solid.

**Purification:** filtration and diethyl ether wash.

**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 5.88 – 5.61 (m, 3H, $C_5$**H**, $C_8$**H**), 5.34 – 4.88 (m, 6H, $C_6$**HH**, $C_9$**HH**), 4.33 – 3.76 (m, 4H, $C_4$**HH**), 3.61 (t, J = 7.42 Hz, 1H, $C_2$**H**), 2.77 – 2.58 (m, 2H, $C_7$**HH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 169.9 (s, $C_1$), 168.2 (s, $C_3$), 134.7 (s, $C_8$), 132.7 (s, $C_5$), 132.6 (s, $C_5$), 117.4 (s, $C_6$), 117.3 (s, $C_6$), 117.0 (s, $C_8$), 52.4 (s, $C_2$), 49.3 (s, $C_4$), 48.7 (s, $C_4$), 33.5 (s, $C_7$).

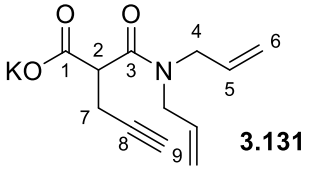
**IR (film, $cm^{-1}$):** 1739, 1633, 1469, 1415, 1238, 1190, 995, 914.

**HRMS**, m/z: calculated $[C_{12}H_{17}O_3N^{39}K]^+$: 262.08400, found: 262.08385.

**MS/MS** (p ESI): m/z (%): 81.07034, (6); 94.92990, (9); 104.10479, (100); 122.11511, (20); 145.04926, (4); 202.10692, (7); 230.13578, (16); 261.12847, (13) [M].

*Synthesis of potassium 2-(diallylcarbamoyl)pent-4-ynoate*

This molecule was synthetized according to the general procedure for preparing the potassium salt from the corresponding ester (see p. 204).




**3.131**

**Yield:** 69 % - white solid.

**Purification:** filtration and diethyl ether wash.

**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 5.95 – 5.62 (m, 2H, $C_5$**H**), 5.35 – 4.99 (m, 4H, $C_6$**HH**), 4.36 – 3.80 (m, 4H, $C_4$**HH**), 3.72 (t, J = 7.43 Hz, 1H, $C_2$**H**), 2.85 – 2.57 (m, 2H, $C_7$**HH**), 1.99 (s, 1H, $C_9$**H**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 173.4 (s, $C_1$), 170.9 (s, $C_3$), 132.9 (s, $C_5$), 132.8 (s, $C_5$), 117.1 (s, $C_6$), 116.9 (s, $C_6$), 82.3 (s, $C_8$), 69.7 (s, $C_9$), 49.8 (s, $C_2$), 49.6 (s, $C_2$), 48.3 (s, $C_4$), 19.9 (s, $C_7$).

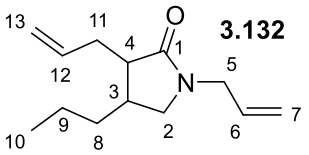
**IR (film, cm-1):** 1770, 1739, 1371, 1236, 1217, 1207, 1056.

**HRMS**, m/z: calculated $[C_{12}H_{15}O_3N^{39}K]^+$ : 260.06835, found: 260.06819.

**MS/MS** (p ESI): m/z (%): 136.05220, (6); 148.06026, (18); 228.12042, (3); 260.06792, (100) $[M-H]^+$.

*Synthesis of 1,3-diallyl-4-propylpyrrolidin-2-one*

This molecule was synthetized according to the general procedure for preparing the electrocyclization of functionalized 2-pyrrolidinones (see p. 205).




**3.132**

**Yield:** 66 % - colorless-oil.

**Purification:** chromatography on silica gel. Eluent: EP/AcOEt 0.8/0.2.

**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 5.90 – 5.60 (m, 2H, $C_6$**H**, $C_{12}$**H**), 5.28 – 4.94 (m, 4H, $C_7$**HH**, $C_{13}$**HH**), 4.00 – 3.72 (m, 2H, $C_5$**HH**), 3.43 – 3.30 (m, 1H, $C_2$**H**H), 2.87 (dd, J = 9.72, 6.84 Hz, 1H, $C_2$H**H**), 2.55 – 2.28 (m, 2H, $C_4$**H**, $C_{11}$**H**H), 2.19 (td, J = 7.22, 4.84 Hz, 1H, $C_{11}$H**H**), 2.13 – 1.97 (m, 1H, $C_3$**H**), 1.65 – 1.15 (m, 4H, $C_8$**HH**, $C_9$**HH**), 0.98 – 0.81 (m, 3H, $C_{10}$**HHH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 175.4 (s, $C_1$), 135.5 (s, $C_{12}$), 132.5 (s, $C_6$), 117.7 (s, $C_7$), 117.1 (s, $C_{13}$), 51.0 (s, $C_2$), 47.8 (s, $C_4$), 45.2 (s, $C_5$), 36.5 (s, $C_8$), 36.2 (s, $C_3$), 34.6 (s, $C_{11}$), 20.3 (s, $C_9$), 14.1 (s, $C_{10}$).

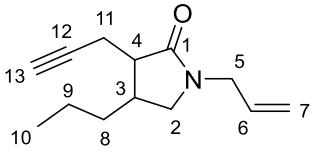
**IR (film, $cm^{-1}$):** 1679, 1643, 1490, 1415, 1292, 1261, 1191, 993, 914.

**HRMS**, m/z: calculated $[C_{13}H_{22}ON]^+$ : 208.16959, found: 208.16966.

**MS/MS** (p ESI): m/z (%): 83.08588, (72); 180.17408, (26); 208.16892, (100) $[M-H]^+$.

*Synthesis of 1-allyl-3-(prop-2-yn-1-yl)-4-propylpyrrolidin-2-one*

This molecule was synthetized according to the general procedure for preparing the electrocyclization of functionalized 2-pyrrolidinones (see p. 205).




**3.133**

**Yield:** 64 % - colourless-oil.

**Purification:** chromatography on silica gel. Eluent: EP/AcOEt 0.7/0.3.

**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 5.84 – 5.58 (m, 1H, $C_6$**H**), 5.26 – 5.09 (m, 2H, $C_7$**HH**), 4.02 – 3.77 (m, 2H, $C_5$**HH**), 3.50 – 3.35 (m, 1H, $C_2$**H**H), 2.98 – 2.86 (m, 1H, $C_2$H**H**), 2.63 – 2.54 (m, 2H, $C_{11}$**HH**), 2.41 – 2.18 (m, 2H, $C_4$**H**), 2.00 – 1.91 (m, 1H, $C_{13}$**H**), 1.81 – 1.57 (m, 1H, $C_3$**H**), 1.49 – 1.25 (m, 4H, $C_8$**HH**, $C_9$**HH**), 1.01 – 0.88 (m, 3H, $C_{10}$**HHH**).

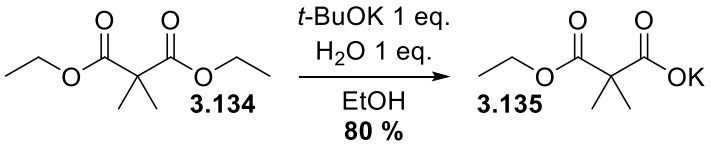
**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 174.1 (s, $C_1$), 132.3 (s, $C_6$), 117.7 (s, $C_7$), 81.3 (s, $C_{12}$), 70.0 (s, $C_{13}$), 51.0 (s, $C_2$), 46.9 (s, $C_4$), 45.3 (s, $C_5$), 36.6 (s, $C_3$), 36.3 (s, $C_8$), 20.4 (s, $C_9$), 19.6 (s, $C_{11}$), 14.1 (s, $C_{10}$).

**IR (film, cm$^{-1}$):** 1674, 1490, 1444, 1417, 1294, 1261, 1186, 993, 925, 734.

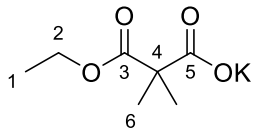
**HRMS**, m/z: calculated $[C_{13}H_{20}ON]^+$ : 206.15394, found: 206.15402.

**MS/MS** (p ESI): m/z (%): 67.05484, (12); 81.07032, (15); 164.10667, (5); 178.15862, (2); 206.15349, (100) $[M-H]^+$.

*Synthesis of potassium 3-ethoxy-2,2-dimethyl-3-oxopropanoate*




A solution of KOH (30 mmol, 1 eq.) in MeOH (0.2 M) was added dropwise to a solution of ester (30 mmol, 1 eq.) in MeOH (0.2 M), at 0°C. Then the reaction mixture was allowed to stir overnight. Subsequently, the solvent was evaporated under reduce pressure and the crude product was dried under vacuum. Finally, the solid obtained was washed three times with 15 ml of diethyl ether and then dried under vacuum.

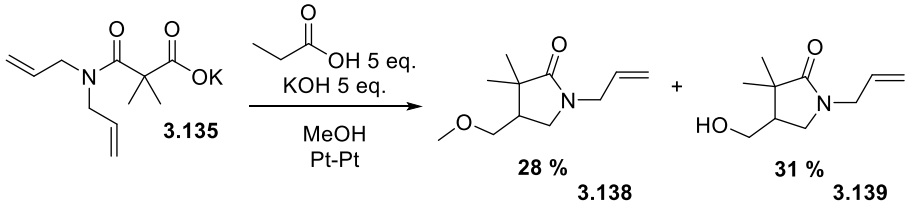



**$^1$H NMR (300 MHz, DMSO) : δ** 3.92 (q, J = 7.1 Hz, 2H, $C_2$**HH**), 1.18 – 1.04 (m, 9H, $C_1$**HHH**, $C_6$**HHH**).

**$^{13}$C NMR (75 MHz, DMSO) : δ** 176.63 (s, $C_5$), 174.02 (s, $C_3$), 59.16 (s, $C_2$), 51.54 (s, $C_4$), 24.59 (s, $C_6$), 14.63 (s, $C_1$).

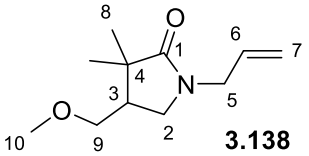
**IR (film, cm$^{-1}$):** 1740, 1596, 1383, 1312, 1231, 1189, 1046, 916.

*Synthesis of 1-allyl-4-(hydroxymethyl)-3,3-dimethylpyrrolidin-2-one and 1-allyl-4-(methoxymethyl)-3,3-dimethylpyrrolidin-2-one*




This molecule was synthetized according to the general procedure for preparing the electrocyclization of functionalized 2-pyrrolidinones (see p. 205).

*Data for 1-allyl-4-(methoxymethyl)-3,3-dimethylpyrrolidin-2-one*




**3.138**

**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 5.82 – 5.62 (m, 1H, $C_6$**H**), 5.24 – 5.07 (m, 2H, $C_7$**HH**), 3.89 (dd, J = 10.7, 9.5 Hz, 2H, $C_5$**HH**), 3.54 - 3.48 (m, 1H, $C_9$**H**H), 3.40 – 3.29 (m, 5H, $C_2$**H**H, $C_9$H**H**, $C_{10}$**HHH**), 3.02 (dd, J = 9.9, 8.0 Hz, 1H, $C_2$H**H**), 2.38 – 2.19 (m, 1H, $C_3$**H**), 1.20 (s, 3H, $C_8$**HHH**), 0.98 (s, 3H, $C_8$**HHH**).

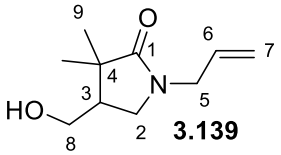
**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 178.95 (s, $C_1$), 132.47 (s, $C_6$), 117.87 (s, $C_7$), 71.96 (s, $C_9$), 59.05 (s, $C_{10}$), 47.33 (s, $C_2$), 45.27 (s, $C_5$), 43.17 (s, $C_3$), 42.49 (s, $C_4$), 24.91 (s, $C_8$), 18.77 (s, $C_8$).

**IR (film, cm$^{-1}$):** 3288, 2923, 2853, 1668, 1449, 1377, 1125, 1092, 949, 846.

**HRMS**, m/z: calculated $[C_{11}H_{20}O_2N]^+$ : 198.14886, found : 198.14892.

**MS/MS** (p ESI): m/z (%): 83.08716, (6); 138.12942, (13); 166.12471, (7); 198.15133, (100) $[M-H]^+$.

*Data for 1-allyl-4-(hydroxymethyl)-3,3-dimethylpyrrolidin-2-one*




**3.139**

**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 5.82 – 5.60 (m, 1H, $C_6$**H**), 5.28 – 5.09 (m, 2H, $C_7$**HH**), 3.94 – 3.83 (m, 2H, $C_5$**HH**), 3.70 – 3.63 (m, 1H, $C_8$**H**H), 3.55 – 3.34 (m, 2H, $C_2$**H**H, $C_8$H**H**), 3.11 – 2.98 (m, 1H, $C_2$H**H**), 2.50 – 2.31 (m, 1H, $C_3$**H**), 1.23 (s, 3H, $C_9$**HHH**), 1.01 (s, 3H, $C_9$**HHH**).

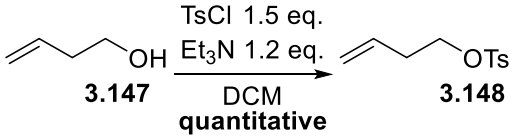
**13C NMR (75 MHz, CDCl3) δ** 178.23 (s, $C_1$), 132.20 (s, $C_6$), 118.24 (s, $C_7$), 47.93 (s, $C_2$), 45.94 (s, $C_3$), 45.30 (s, $C_5$), 43.63 (s, $C_8$), 43.40 (s, $C_4$), 24.53 (s, $C_9$), 18.53 (s, $C_9$).

**IR (film, cm$^{-1}$):** 3285, 2924, 2853, 1671, 1449, 1377, 1123, 1099, 930, 726.

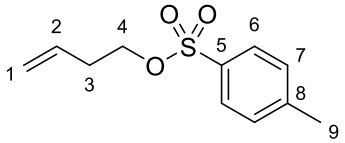
**HRMS**, m/z: calculated $[C_{10}H_{18}O_2N]^+$ : 184.13321, found: 184.13334.

**MS/MS** (p ESI): m/z (%): 83.08725, (8); 138.12956, (10); 184.13563, (100) $[M-H]^+$.

*Synthesis of but-3-en-1-yl 4-methylbenzenesulfonate*




Triethylamine (1.67 ml, 12.0 mmol, 1.2 eq.) and a solution of *para*-toluenesulfonyl chloride (2.0018 g, 10.5 mmol, 1.5 eq.) in 10.00 ml of DCM were added dropwise to a solution of buten-1-ol (0.86 ml, 10.0 mmol, 1.0 eq.) in 10.00 ml of DCM at 0°C. The reaction was allowed to stir for one hour at 0°C, and then for three hours at room temperature. The solution was quenched with 15.00 ml of water and extracted three times with 10.00 ml of DCM. The combined organic layers were dried over $MgSO_4$ and were concentrated under reduced pressure. Finally, the crude product was purified by silica gel chromatography.

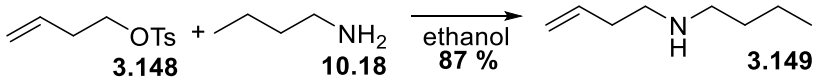


**$^1$H NMR (300 MHz, $CDCl_3$) δ** 7.77 – 7.68 (m, 2H, $C_6$**H**), 7.32 – 7.23 (m, 2H, $C_7$**H**), 5.69 – 5.50 (m, 1H, $C_2$**H**), 5.08 – 4.93 (m, 2H, $C_1$**HH**), 3.99 (t, J = 6.7 Hz, 2H, $C_4$**HH**), 2.38 (s, 3H, $C_9$**HHH**), 2.37 – 2.28 (m, 2H, $C_3$**HH**).

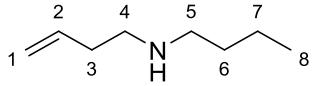
**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 144.75 (s, $C_5$), 133.09 (s, $C_8$), 132.40 (s, $C_2$), 129.82 (s, $C_7$), 127.92 (s, $C_6$), 118.23 (s, $C_1$), 69.41 (s, $C_4$), 33.15 (s, $C_3$), 21.66 (s, $C_9$).

**IR (film, cm$^{-1}$):** 1598, 1355, 1188, 1176, 1097, 958, 904, 813, 773.

*Synthesis of N-butylbut-3-en-1-amine*




N-butylamine (2.73 g, 37.30 mmol, 5 eq.) was added dropwise to a solution of but-3-en-1-yl 4-methylbenzenesulfonate (1.69 g, 7.46 mmol, 1 eq.) in 8 ml of ethanol. The reaction was allowed to stir 22 hours at 75°C. The solution was quenched with 5 ml of potassium hydroxide solution 1 M and 5 ml of water and extracted three times with 5 ml of DCM. The combined organic layers were dried over $MgSO_4$ and were concentrated under reduced pressure. Finally, the crude product was purified by silica gel chromatography (AcOEt/$Et_3N$, EP 1/1/8).



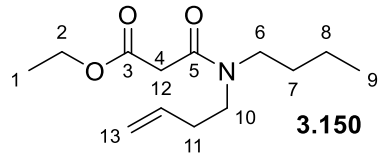
**$^1$H NMR (300 MHz, $CDCl_3$) : δ** 5.89 – 5.66 (m, 1H, $C_2$**H**), 5.18 – 4.93 (m, 2H, $C_1$**HH**), 2.67 (t, J = 6.9 Hz, 2H, $C_4$**HH**), 2.63 – 2.58 (m, 2H, $C_5$**HH**), 2.28 – 2.20 (m, 2H, $C_3$**HH**), 1.51 – 1.28 (m, 4H, $C_6$**HH**, $C_7$**HH**), 0.91 (t, J = 10.2Hz, 3H, $C_8$**HHH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 136.41 (s, $C_2$), 116.31 (s, $C_1$), 49.52 (s, $C_4$), 48.83 (s, $C_5$), 34.19 (s, $C_3$), 32.09 (s, $C_6$), 20.49 (s, $C_7$), 13.96 (s, $C_8$).

**IR (film, cm$^{-1}$):** 1641, 1456, 1326, 1159, 1055, 1034, 1010, 912, 732.

*Synthesis of ethyl 3-(but-3-en-1-yl(butyl)amino)-3-oxopropanoate*

This molecule was synthetized according to the general procedure for preparing amide from the corresponding secondary amine using DCC coupling agent (see p. 203).




**3.150**

**Yield:** 66 % - colourless-oil.

**Purification:** chromatography on silica gel. Eluent: AcOEt/EP 0.1/0.9.

**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 5.94 – 5.58 (m, 1H, $C_{12}$**H**), 5.21 – 4.95 (m, 2H, $C_{13}$**HH**), 4.20 (q, J = 7.12 Hz, 2H, $C_2$**HH**), 3.45 (s, 0.8H, $C_4$**HH**), 3.43 (s, 1.2H, $C_4$**HH**), 3.41 – 3.14 (m, 4H, $C_6$**HH**, $C_{10}$**HH**), 2.32 (m, 2H, $C_{11}$**HH**), 1.64 – 1.18 (m, 7H, $C_1$**HHH**, $C_7$**HH**, $C_8$**HH**), 0.93 (m, 3H, $C_9$**HHH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 167.8 (s, $C_3$), 165.6 (s, $C_5$), 135.3 (s, $C_{12}$), 133.9 (s, $C_{12}$), 117.8 (s, $C_{13}$), 116.6 (s, C13), 61.4 (s, $C_2$), 48.6 (s, $C_{10}$), 47.8 (s, $C_6$), 41.4 (s, $C_4$), 41.2 (s, $C_4$), 31.9 (s, $C_{11}$), 29.5 (s, $C_7$), 20.1 (s, $C_8$), 20.0 (s, $C_8$), 14.1 (s, $C_1$), 13.8 (s, $C_9$), 13.8 (s, $C_9$).

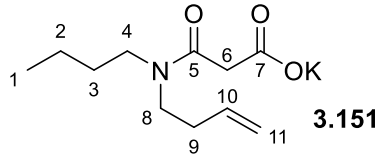
**IR (film, cm$^{-1}$):** 1731, 1643, 1545, 1446, 1367, 1319, 1031, 916, 730.

**HRMS**, m/z: calculated $[C_{13}H_{24}O_3N]^+$: 242.17507, found : 242.17518.

**MS/MS** (p ESI): m/z (%): 86.09678, (95); 112.07570, (15); 154.12218, (100); 188.12756, (5); 196.13268, (18); 200.12754, (12); 214.14314, (4); 242.17421, (86) $[M-H]^+$.

*Synthesis of potassium 3-(but-3-en-1-yl(butyl)amino)-3-oxopropanoate*

This molecule was synthetized according to the general procedure for preparing potassium salt from the corresponding ester (see p. 204).




**3.151**

**Yield:** 93 % - colourless-oil.

**Purification:** chromatography on silica gel. Eluent: DCM/MeOH 0.9/0.1.

**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 5.83 – 5.61 (m, 1H, $C_{10}$**H**), 5.15 – 4.90 (m, 2H, $C_{11}$**HH**), 3.71 (s, 2H, $C_6$**HH**), 3.43 – 3.19 (m, 4H, $C_4$**HH**, $C_8$**HH**), 2.37 – 2.10 (m, 2H, $C_9$**HH**), 1.60 – 1.35 (m, 2H, $C_3$**HH**), 1.35 – 1.16 (m, 2H, $C_2$**HH**), 0.93 (q, J = 7.2 Hz, 3H, $C_1$**HHH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 169.7 (s, $C_7$), 169.4 (s, $C_5$), 134.7 (s, $C_{10}$), 133.4 (s, $C_{10}$), 118.3 (s, $C_{11}$), 117.0 (s, $C_{11}$), 48.3 (s, $C_8$), 47.5 (s, $C_8$), 46.3 (s, $C_4$), 46.1 (s, $C_4$), 37.4 (s, $C_6$), 32.8 (s, $C_9$), 31.8 (s, $C_9$), 30.7 (s, $C_3$), 29.4 (s, $C_3$), 20.1 (s, $C_2$), 20.0 (s, $C_2$), 13.7 (s, $C_1$), 13.7 (s, $C_1$).

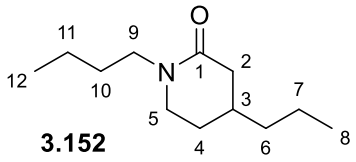
**IR (film, $cm^{-1}$):** 1731, 1649, 1465, 1315, 1257, 1159, 748.

**HRMS**, m/z: calculated $[C_{11}H_{18}O_3N]^-$ : 212.12812, found: 212.12791.

**MS/MS** (p ESI): m/z (%): 89.02257, (82); 114.09058, (100); 137.03376, (16); 168.13772, (17); 212.12791, (63) $[M]^-$.

*Synthesis of 1-butyl-4-propylpiperidin-2-one*

This molecule was synthetized according to the general procedure for the electrocyclization of functionalized 2-pyrrolidinones (see p. 205).




**3.152**

**Yield:** 70 % - colourless-oil.

**Purification:** chromatography on silica gel. Eluent: EP/AcOEt 0.9/0.1.

**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 3.75 (m, 1H, $C_5$**H**H), 3.47 – 3.40 (m, 2H, $C_9$**HH**), 3.28 (m, 1H, $C_5$H**H**), 2.78 – 2.40 (m, 1H, $C_2$**H**H), 2.41 – 2.15 (m, 1H, $C_2$H**H**), 1.77 – 1.46 (m, 5H, $C_3$**H**, $C_4$**HH**, $C_{10}$**HH**), 1.47 – 1.05 (m, 6H, $C_6$**HH**, $C_7$**HH**, $C_{11}$**HH**), 1.06 – 0.70 (m, 6H, $C_8$**HHH**, $C_{12}$**HHH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 169.6 (s, $C_1$), 47.0 (s, $C_5$), 46.8 (s, $C_9$), 38.6 (s, $C_2$), 37.8 (s, $C_6$), 32.6 (s, $C_3$), 29.1 (s broad, $C_4$, $C_{10}$), 20.1 (s, $C_{11}$), 19.6 (s, $C_7$), 14.1 (s, $C_8$), 13.9 (s, $C_{12}$).

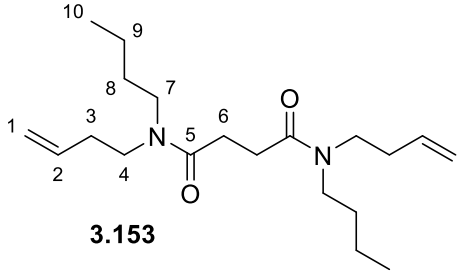
**IR (film, $cm^{-1}$):** 1630, 1496, 1458, 1342, 1307, 1253, 1095, 916, 732.

**HRMS**, m/z: calculated $[C_{12}H_{24}ON]^+$ : 198.18518, found: 198.18524.

**MS/MS** (p ESI): m/z (%): 102.12811, (24); 128.14347, (41); 170.15389, (5); 198.18517, (100) $[M-H]^+$.

*Synthesis of N1,N4-di(but-3-en-1-yl)-N1,N4-dibutylsuccinamide*

This molecule was synthetized according to the general procedure for the electrocyclization of functionalized 2-pyrrolidinones (see p. 205).



**3.153**

**Yield:** 13 % - colourless-oil.

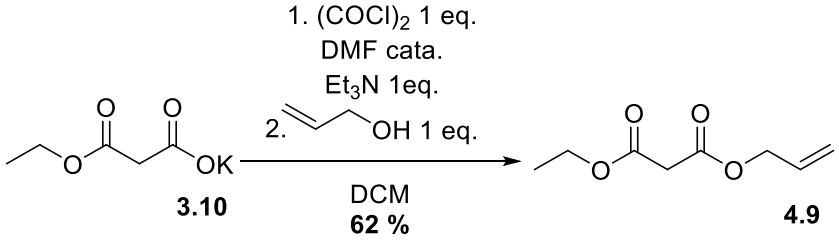
**Purification:** chromatography on silica gel. Eluent: EP/AcOEt 0.9/0.1.

**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 5.85 – 5.75 (m, 2H, $C_2$**H**), 5.18 – 4.96 (m, 4H, $C_1$**HH**), 3.43 – 3.19 (m, 8H, $C_4$**HH**, $C_7$**HH**), 2.58 – 2.53 (m, 2H, $C_6$**HH**), 2.50 – 2.46 (m, 2H, $C_6$**HH**), 2.23 – 2.19 (m, 4H, $C_3$**HH**), 1.54 – 1.49 (m, 4H, $C_8$**HH**), 1.32 – 1.27 (m, 4H, $C_9$**HH**), 0.92 (t, J = 7.15 Hz, 6H, $C_{10}$**HHH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 167.38 (s, $C_5$), 135.94 (s, $C_2$), 116.37 (s, $C_1$), 50.47 (s, $C_4$), 49.73 (s, $C_7$), 31.14 (s, $C_3$), 30.66 (s, $C_6$), 30.21 (s, $C_8$), 20.74 (s, $C_9$), 13.41 (s, $C_{10}$).

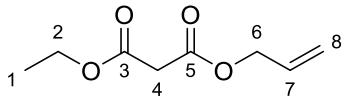
**IR (film, cm$^{-1}$):** 2984, 2872, 1754, 1674, 1652, 1470, 1418, 1392, 1236, 969, 777.

*Synthesis of allyl ethyl malonate*




**3.10** **4.9**

Oxalyl chloride (2.18 ml, 25.85 mmol, 1.1 eq.) was added dropwise to a solution of ethyl potassium malonate (4.00 g, 23.50 mmol, 1.0 eq.) in 50 ml of DCM, at 0°C. Then a catalytic amount of DFM was added and the mixture was allowed to stir one hour at 0°C and two hours, at room temperature. After total conversion into the corresponding acyl chloride, allyl alcohol (2.39 ml, 35.25 mmol, 1.5 eq.), and triethylamine (3.27 ml, 23.50 mmol, 1.0 eq.) were added dropwise at 0°C. The solution was then quenched with 50 ml of water and the aqueous layer was extracted three times with 30 ml of DCM. The combined organic layers were dried over $MgSO_4$ and were concentrated under reduced pressure. Finally the white solid formed was filtered, washed with a small volume of cold $Et_2O$, and dried under vacuum.

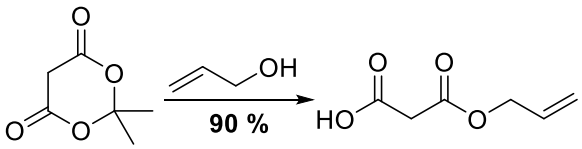


**$^{1}$H NMR (300 MHz, $CDCl_3$): δ** 5.93 – 5.89 (m, 1H, $C_7$**H**), 5.47 – 5.15 (m, 2H, $C_8$**HH**), 4.65 (dt, J = 5.7, 1.4 Hz, 2H, $C_6$**HH**), 4.21 (q, J = 7.1 Hz, 2H, $C_2$**HHH**), 3.40 (s, 2H, $C_4$**HH**), 1.28 (t, J = 7.1 Hz, 3H, $C_1$**HHH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$): δ** 166.41 (s, $C_3$), 166.23 (s, $C_5$), 131.47 (s, $C_7$), 118.68 (s, $C_8$), 65.98 (s, $C_6$), 61.54 (s, $C_2$), 41.53 (s, $C_4$), 14.02 (s, $C_1$).

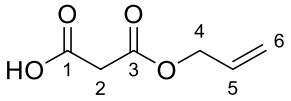
**IR (film, $cm^{-1}$):** 3000, 1731, 1651, 1448, 1413, 1369, 1328, 1303, 1269, 1184, 1145, 1097, 1031, 991, 933, 914, 844.

*Synthesis of 3-(allyloxy)-3-oxopropanoic acid*




**4.11** **4.12**

Meldrum's acid, 2,2-dimethyl-1,3-dioxane-4,6-dione, (4.00 g, 27.74 mmol, 1 eq.) was dissolved in allyl alcohol (20 ml). Then the solution was heated up to 97°C and was allowed to stir overnight. After total consumption of the starting material, the solution was cooled down and was diluted with 50 ml of DCM. The solution was extracted with 50 ml of a saturated aqueous solution of $NaHCO_3$. The pH of the aqueous solution was lowered to 1 with a 1 M solution of aqueous HCl. Then the aqueous solution was extracted three times with 50 ml of $Et_2O$. The combined organics layers were dried over $MgSO_4$ and were concentrated under reduced pressure at ambient temperature. Finally, the crude oil was used without further purifications.

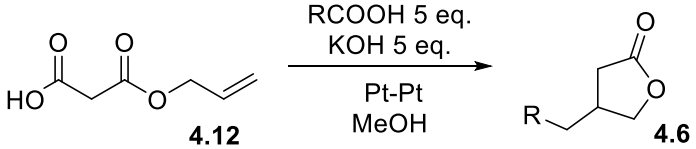



**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 6.06 – 5.77 (m, 1H, $C_5$**HH**), 5.45 – 5.07 (m, 2H, $C_6$**HH**), 4.65 (dt, J = 5.8, 1.3 Hz, 2H, $C_4$**HH**), 3.42 (s, 2H, $C_2$**HH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 170.51 (s, $C_1$), 166.52 (s, $C_3$), 131.20 (s, $C_5$), 119.02 (s, $C_6$), 66.33 (s, $C_4$), 40.86 (s, $C_2$).

**IR (film, $cm^{-1}$):** 2947, 1714, 1699, 1633, 1411, 1369, 1319, 1145, 1095, 991, 929, 881, 856, 840.

*General Procedure for the electrosynthesis of substituted γ-lactones*

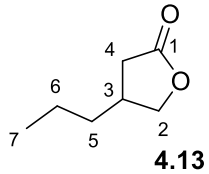



**4.12** **4.6**

In an undivided cell with platinum electrodes (4 $cm^2$), potassium hydroxide (7.5 mmol, 5 eq.) and the co-acid (7.5 mmol, 5 eq.) were dissolved in MeOH. Then, carboxylic acid (1.5 mmol, 1 eq., 66 mM in methanol) was added to the mixture. The intensity of the current was fixed at 100 mA and the mixture was electrolyzed until completion of the reaction, as shown by TLC. The solution was treated with an aqueous solution of $NaHCO_3$ and extracted three times $Et_2O$. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica gel chromatography.

*Synthesis of 4-propyldihydrofuran-2(3H)-one*

This molecule was synthetized according to the general procedure for the electrosynthesis of substituted γ-lactones (see p. 243).




**4.13**

**Yield:** traces - colourless-oil.

**Purification:** chromatography on silica gel. Eluent: AcOEt/EP 0.1/0.9.

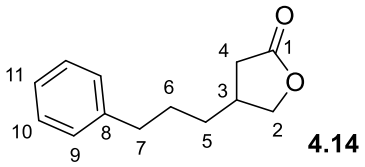
**$^1$H NMR (300 MHz, $CDCl_3$) : δ** 4.21 (d, J = 17.1 Hz, 1H, $C_2$**H**H), 4.00 (d, J = 12.4 Hz, 1H, $C_2$H**H**), 2.32 - 2.26 (m, 2H, $C_4$**H**H), 2.19 – 2.17 (m, 2H, $C_4$H**H**), 2.08 – 1.97 (m, 1H, $C_3$**H**), 1.45 – 1.31 (m, 1H, $C_5$**HH**), 1.33 – 1.21 (m, 1H, $C_6$**HH**), 0.89 (t, J = 7.2 Hz, 3H, $C_7$**HHH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 176.34 (s, $C_1$), 75.49 (s, $C_2$), 39.04 (s, $C_5$), 37.82 (s, $C_4$), 27.93 (s, $C_3$), 19.89 (s, $C_6$), 14.36 (s, $C_7$).

**IR (film, $cm^{-1}$):** 2917, 1765, 1734, 1461, 1378, 1180, 1040, 993, 930, 867, 678.

*Synthesis of 4-(3-phenylpropyl)dihydrofuran-2(3H)-one*

This molecule was synthetized according to the general procedure for the electrosynthesis of substituted γ-lactones (see p. 243).




**4.14**

**Yield:** 4 % - colourless-oil.

**Purification:** chromatography on silica gel. Eluent: AcOEt/EP 0.3/0.7.

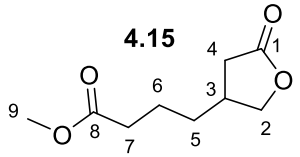
**$^1$H NMR (300 MHz, $CDCl_3$) : δ** 7.29 – 7.20 (m, 5H, Ph**H**), 4.35 - 4.29 (m, 1H, $C_2$**H**H), 3.84 – 3.71 (m, 1H, $C_2$H**H**), 2.97 – 2.93 (m, 1H, $C_4$**H**H), 2.74 – 2.55 (m, 1H, $C_4$H**H**), 2.33 (s, 1H, $C_3$**H**), 2.15 – 1.77 (m, 6H, $C_5$**HH**, $C_6$**HH**, $C_7$**HH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 176.18 (s, $C_1$), 142.46 (s, $C_8$), 128.51 (s, $C_{10}$), 128.13 (s, $C_9$), 125.93 (s, $C_{11}$), 75.72 (s, $C_2$), 37.89 (s, $C_4$), 36.39 (s, $C_5$), 36.02 (s, $C_7$), 28.23 (s, $C_3$), 26.15 (s, $C_6$).

**IR (film, cm$^{-1}$):** 2930, 1765, 1734, 1629, 1451, 1423, 1182, 1045, 963, 698.

*Synthesis of methyl 4-(5-oxotetrahydrofuran-3-yl)butanoate*

This molecule was synthetized according to the general procedure for the electrosynthesis of substituted γ-lactones (see p. 243).




**Yield:** traces - colourless-oil.

**Purification:** chromatography on silica gel. Eluent: AcOEt/EP 0.1/0.9.

**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 4.39 – 4.36 (m, 1H, $C_2$**H**H), 4.14 – 4.09 (m, 1H, $C_2$H**H**), 3.61 (s, 3H, $C_9$**HHH**), 2.39 – 2.36 (m, 1H, $C_4$**H**H), 2.30 – 2.26 (m, 2H, $C_7$**HH**), 2.14 – 2.11 (m, 1H, $C_4$H**H**), 2.04 – 1.99 (m, 1H, $C_3$**H**), 1.68 – 1.64 (m, 2H, $C_6$**HH**), 1.21 – 1.18 (m, 2H, $C_5$**HH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 176.12 (s, $C_1$), 173.09 (s, $C_8$), 75.05 (s, $C_2$), 51.95 (s, $C_9$), 37.82 (s, $C_4$), 36.29 (s, $C_5$), 33.92 (s, $C_7$), 27.93 (s, $C_3$), 22.21 (s, $C_6$).

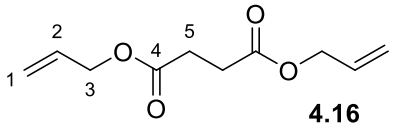
**IR (film, cm$^{-1}$):** 2927, 1755, 1724, 1451, 1379, 1182, 1042, 990, 868, 679.

**HRMS**, m/z: calculated $[C_9H_{15}O_4]^+$ : 187.09649, found: 187.09659.

**MS/MS** (p ESI): m/z (%): 85.06540, (6); 102.12812, (25); 109.06516, (10); 127.07553, (15); 145.08595, (56); 152.10699, (20); 173.08093, (22); 187.09656, (62) $[M-H]^+$.

*Synthesis of diallyl succinate*

This molecule was synthetized according to the general procedure for the electrosynthesis of substituted γ-lactones (see p. 243).




**Yield:** 15 % - colourless-oil.

**Purification:** chromatography on silica gel. Eluent: AcOEt/EP 0.1/0.9.

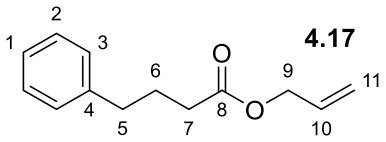
**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 6.15 – 6.03 (m, 2H, $C_2$**H**), 5.35 – 5.29 (m, 4H, $C_1$**HH**), 4.65 – 4.58 (m, 4H, $C_3$**HH**), 2.73 (s, 4H, $C_5$**HH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 173.10 (s, $C_4$), 132.18 (s, $C_2$), 118.21 (s, $C_1$), 65.73 (s, $C_3$), 29.56 (s, $C_5$).

**IR (film, cm$^{-1}$):** 2927, 1755, 1744, 1639, 1451, 1181, 1043, 983, 877, 698.

*Synthesis of allyl 4-phenylbutanoate*

This molecule was synthetized according to the general procedure for the electrosynthesis of substituted γ-lactones (see p. 243).




**Yield:** 47 % - colourless-oil.

**Purification:** chromatography on silica gel. Eluent: AcOEt/EP 0.3/0.7.

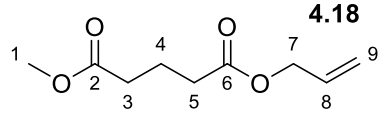
**$^{1}$H NMR (300 MHz, $CDCl_3$) :** 7.27 – 7.13 (m, 5H, Ph**H**), 6.08 – 6.03 (m, 1H, $C_{10}$**H**), 5.33 – 5.30 (m, 2H, $C_{11}$**HH**), 4.69 (m, 2H, $C_9$**HH**), 2.63 (t, J = 7.5 Hz, 2H, $C_5$**HH**), 2.32 (t, J = 7.4 Hz, 2H, $C_7$**HH**), 1.84 – 1.80 (m, 2H, $C_6$**HH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) :** 173.15 (s, $C_8$), 142.00 (s, $C_4$), 132.16 (s, $C_{10}$), 128.86 (s, $C_2$), 128.12 (s, $C_3$), 126.03 (s, $C_1$), 118.23 (s, $C_{11}$), 65.93 (s, $C_9$), 35.12 (s, $C_5$), 33.64 (s, $C_7$), 26.42 (s, $C_6$).

**IR (film, cm$^{-1}$):** 2932, 1764, 1744, 1639, 1461, 1413, 1162, 1025, 943, 696.

*Synthesis of allyl methyl glutarate*

This molecule was synthetized according to the general procedure for the electrosynthesis of substituted γ-lactones (see p. 243).




**Yield:** 30 % - colourless-oil.

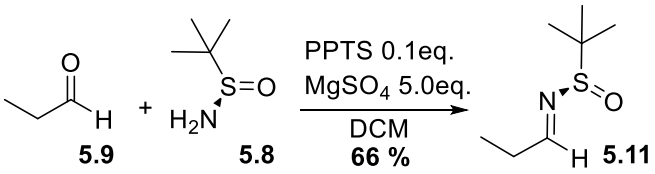
**Purification:** chromatography on silica gel. Eluent: AcOEt/EP 0.1/0.9.

**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 6.05 – 6.01 (m, 1H, $C_8$**H**), 5.32 – 5.29 (m, 2H, $C_9$**HH**), 4.69 – 4.66 (m, 2H, $C_7$**HH**), 3.61 (s, 3H, $C_1$**HHH**), 2.42 – 2.34 (m, 4H, $C_3$**HH**, $C_5$**HH**), 2.26 – 2.22 (m, 2H, $C_4$**HH**).

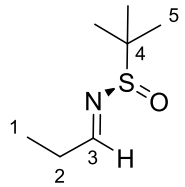
**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 173.15 (s, $C_2$), 173.11 (s, $C_6$), 132.11 (s, $C_8$), 118.22 (s, $C_9$), 65.93 (s, $C_7$), 51.94 (s, $C_1$), 33.42 (s, $C_5$), 33.05 (s, $C_3$), 20.01 (s, $C_4$).

**IR (film, cm$^{-1}$):** 2930, 1754, 1754, 1679, 1630, 1464, 1423, 1026, 953, 698.

*Synthesis of (R,E)-2-methyl-N-propylidenepropane-2-sulfinamide*




PPTS (0.2073 g, 0.825 mmol, 0.1 eq.) and $MgSO_4$ (4.9653 g, 41.250 mmol, 5.1 eq.) were added to a solution of R-*tert*-butanesulfinamide (1.0000 g, 8.250 mmol, 1.0 eq.) in 11 ml. Then propionaldehyde (0.9583 g, 16.500 mmol, 2.0 eq.) was added dropwise and the mixture was allowed to stir overnight. After total consumption of the starting material, the solution was filtered through a celite pad and concentrated under reduced pressure. Finally, the crude product was purified by silica gel chromatography (EP/AcOEt 9/1).

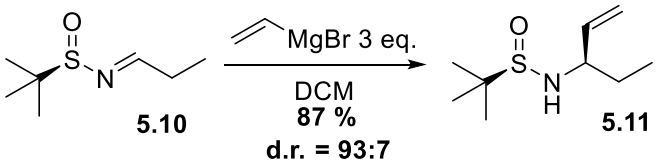


**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 8.10 (t, J = 4.3 Hz, 1H, $C_3$**H**), 2.54 (qd, J = 7.4, 4.2 Hz, 2H, $C_2$**HH**), 1.23 – 1.13 (m, 12H, $C_1$**HHH**, $C_5$**HHH**).

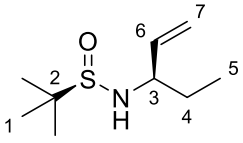
**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 170.28 (s, $C_3$), 56.46 (s, $C_4$), 29.52 (s, $C_2$), 22.28 (s, $C_5$), 9.59 (s, $C_1$).

**IR (film, cm$^{-1}$):** 1747, 1623, 1458, 1392, 1361, 1309, 1211, 1132, 1078, 1041, 912.

*Synthesis of (R)-2-methyl-N-((R)-pent-1-en-3-yl)propane-2-sulfinamide*




Vinyl Grignard 1 M in THF (11.21 ml, 11.21 mmol, 3 eq.) was added dropwise to a solution of sulfinimine (0.6027 g, 3.73 mmol, 1 eq.) in 19.00 ml of DCM, at -78°C. The reaction was allowed to stir eight hours at -78°C and overnight at room temperature. The solution was quenched with 10 ml of brine, 10.00 ml of water, and 10.00 ml of an aqueous solution saturated in $NH_4Cl$. The solution was then extracted two times with 20.00 ml of DCM. The combined organic layers were dried over $MgSO_4$, filtered through a celite pad, and were concentrated under reduced pressure. Finally the crude product was purified by silica gel chromatography (DCM/MeOH 99/1).

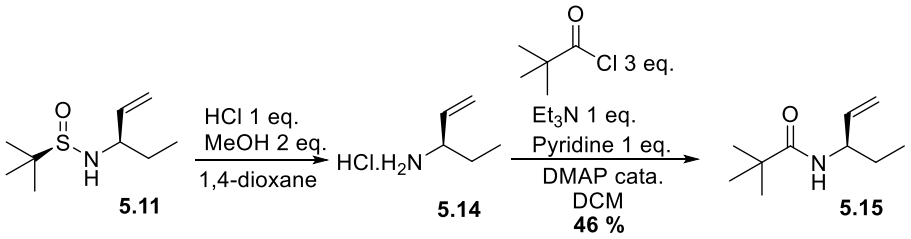


**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 5.91 – 5.54 (m, 1H, $C_6$**H**), 5.23 (dddd, J = 12.3, 11.5, 7.6, 2.3 Hz, 2H, $C_7$**HH**), 3.81 – 3.59 (m, 1H, $C_3$**H**), 3.10 (s (br), 1H, N**H**), 1.78 – 1.45 (m, 2H, $C_4$**HH**), 1.20 (s, 9H, $C_1$**HHH**), 0.99 – 0.88 (m, 3H, $C_5$**HHH**).

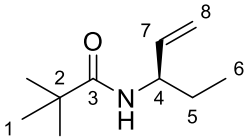
**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 139.58 (s, $C_6$), 138.79 (s, $C_6$), 117.22 (s, $C_7$), 116.64 (s, $C_7$), 59.97 (s, $C_3$), 59.62 (s, $C_3$), 55.73 (s, $C_2$), 55.40 (s, $C_2$), 29.38 (s, $C_4$), 28.11 (s, $C_4$), 22.60 (s, $C_1$), 9.94 (s, $C_5$), 9.91 (s, $C_5$).

**IR (film, $cm^{-1}$):** 3255, 2952, 1643, 1456, 1363, 1176, 1124, 989, 918.

*Synthesis of (R)-N-(pent-1-en-3-yl)pivalamide*




1.32 ml of a HCl 4 M solution in 1,4-dioxane and MeOH (0.42 ml, 10.56 mmol, 2 eq.) were added dropwise to a solution of sulfinamine (1.000g, 5.28 mmol, 1 eq.) in 7.2 ml of 1,4-dioxane at 0°C. The reaction was allowed to stir two hours, at room temperature, until completion of the reaction as shown by TLC. Then triethylamine (0.74 ml, 5.28 mmol, 1 eq.), DMAP (0.0318 g, 0.26 mmol, 0.05 eq.), pyridine (0.43 ml, 5.28 mml, 1 eq.), and pivaloyl chloride (1.905 g, 15.84 mmol, 3 eq.) were added dropwise to the solution at 0°C. The reaction was allowed to stir overnight. The solution was quenched with 10.00 ml of a saturated aqueous solution of $NaHCO_3$ and extracted two times with 10.00 ml of DCM. The combined organic layers were dried over $MgSO_4$ and were concentrated under reduced pressure. Finally, the crude product was purified by silica gel chromatography (EP/AcOEt 9/1).




**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 5.77 (ddd, J = 17.2, 10.4, 5.4 Hz, 1H, $C_7$**H**), 5.46 (s, 1H, N**H**), 5.20 – 5.02 (m, 2H, $C_8$**HH**), 4.50 – 4.30 (m, 1H, $C_4$**H**), 1.77 – 1.33 (m, 2H, $C_5$**HH**), 1.22 (s, 9H, $C_1$**HHH**), 0.91 (t, J = 7.4 Hz, 3H, $C_6$**HHH**).

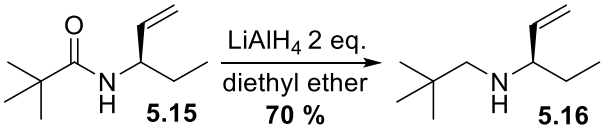
**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 180.08 (s, $C_3$), 138.66 (s, $C_7$), 114.64 (s, $C_8$), 52.25 (s, $C_4$), 38.63 (s, $C_2$), 27.92 (s, $C_5$), 27.81 (s, $C_1$), 10.22 (s, $C_6$).

**IR (film, $cm^{-1}$):** 3353, 2960, 1774, 1631, 1531, 1458, 1383, 989, 912, 798.

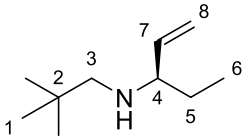
**HRMS**, m/z: calculated $[C_{10}H_{20}ON]^+$ : 170.15393, found : 170.15394.

**MS/MS** (p ESI): m/z (%): 84.08115, (5); 86.09676, (9); 91.22393, (4); 102.09143, (84); 106.81034, (7); 170.15344, (100) $[M-H]^+$.

*Synthesis of (R)-N-neopentylpent-1-en-3-amine*




$LiAlH_4$ (0.500 g, 13.04 mmol, 1.9 eq.) was added by portions to a solution of (R)-N-(pent-1-en-3-yl)pivalamide (1.155 g, 6.83 mmol, 1.0 eq.) in 21.0 ml of diethyl ether at -10°C. The reaction mixture was allowed to stir overnight. The solution was quenched with 0.5 ml of water, 1.0 ml of a 10% KOH aqueous solution, and 2.0 ml of water. The solution was filtrated through a celite pad and the organic layer was extracted with 10.0 ml of a saturated aqueous solution of $NaHCO_3$. Finally, the aqueous layers were extracted with 20.0 ml of DCM and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure at room temperature. The product was used without further purification.



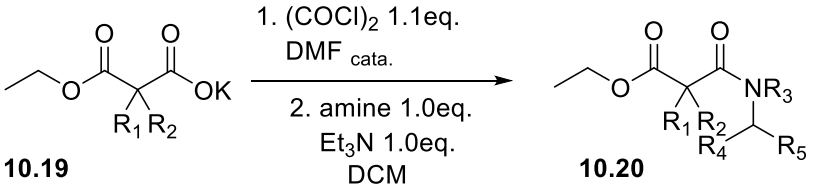

**$^1$H NMR (300 MHz, $CDCl_3$) : δ** 5.71 – 5.50 (m, 1H, $C_7$**H**), 5.14 – 5.04 (m, 2H, $C_8$**HH**), 2.83 (dt, J = 13.2, 6.5 Hz, 1H, $C_4$**H**), 2.38 (d, J = 11.4 Hz, 1H, $C_3$**H**H), 2.22 (d, J = 11.4 Hz, 1H, $C_3$H**H**), 1.55 – 1.42 (m, 2H, $C_5$**HH**), 0.91 (s, 9H, $C_1$**HHH**), 0.87 (t, J = 4.5 Hz, 3H, $C_6$**HHH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 133.34 (s, $C_7$), 117.92 (s, $C_8$), 64.41 (s, $C_4$), 59.34 (s, $C_3$), 31.33 (s, $C_2$), 27.83 (s, $C_1$), 27.71 (s, $C_5$), 10.44 (s, $C_6$).

**HRMS**, m/z: calculated $[C_{10}H_{22}N]^+$ : 156.174698, found: 156.17470.

**MS/MS** (p ESI): m/z (%): 67.05487, (4); 69.07049, (97); 71.08610, (16); 86.09683, (54); 88.11243, (69); 156.17439, (100) $[M-H]^+$.

*General procedure for preparing amide from the corresponding secondary amine using oxalyl chloride*

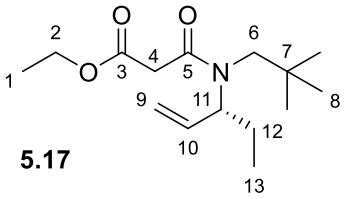



Oxalyl chloride (0.34 ml, 4.4 mmol, 1.1 eq.) and a drop of DMF were added dropwise to a solution of ethyl potassium malonate (0.75 g, 4.4 mmol, 1.1 eq.) in 10 ml of DCM at 0°C. A bubbler system was used, and the reaction was allowed to stir one hour at 0°C, and then one hour at room temperature. After total conversion into the corresponding acyl chloride, the secondary amine (4.0 mmol, 1.0 eq.), and triethylamine (0.56 ml, 4.0 mmol, 1.0 eq.) were added dropwise to the reaction

mixture at 0°C. Then the reaction was allowed to stir overnight. Finally, the solution was quenched with 10 ml of water and extracted with two times with 10 ml of DCM. The combined organic layers were dried over $MgSO_4$ and were concentrated under reduced pressure. The crude product was purified by silica gel chromatography.

*Synthesis of ethyl (R)-3-(neopentyl(pent-1-en-3-yl)amino)-3-oxopropanoate*

This molecule was synthetized according to the general procedure for preparing amide from the corresponding secondary allylic amine using oxalyl chloride (see p. 249).




**5.17**

**Yield:** 62 % - oil.

**Purification:** chromatography on silica gel. Eluent: EP/AcOEt 0.8/0.2.

**$^1$H NMR (300 MHz, $CDCl_3$) : δ** 6.37 – 5.60 (m, 1H, $C_{10}$**H**), 5.26 – 4.89 (m, 2H, $C_9$**HH**), 4.15 – 4.10 (m, 2H, $C_2$**HH**), 3.57 – 3.31 (m, 2H, $C_4$**HH**), 3.31 – 2.89 (m, 2H, $C_6$**HH**), 2.20 – 1.30 (m, 3H, $C_{11}$**H**, $C_{12}$**HH**), 1.30 – 1.12 (m, 5H, $C_1$**HHH,** $C_{13}$**HHH** or $C_8$**HHH**), 1.02 – 0.71 (m, 10H, $C_8$**HHH,** $C_{13}$**HHH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 167.92 (s, $C_3$), 167.10 (s, $C_5$), 137.67 (s, $C_{10}$), 136.96 (s, $C_{10}$), 116.34 (s, $C_9$), 116.23 (s, $C_9$), 64.41 (s, $C_{11}$), 62.19 (s, $C_2$), 61.33 (s, $C_6$), 61.23 (s, $C_6$), 42.92 (s, $C_4$), 33.81 (s, $C_7$), 33.63 (s, $C_7$), 28.68 (s, $C_8$), 28.38 (s, $C_8$), 26.81 (s, $C_{12}$), 25.48 (s, $C_{12}$), 14.12 (s, $C_1$), 11.68 (s, $C_{13}$).

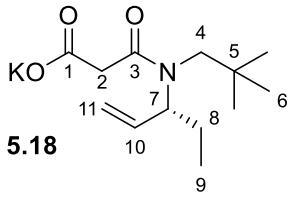
**IR (film, cm$^{-1}$):** 2952, 1733, 1635, 1519, 1463, 1417, 1301, 1097, 919.

**HRMS**, m/z: calculated $[C_{15}H_{28}O_3N]^+$ : 270.20637, found: 270.20623.

**MS/MS** (p ESI): m/z (%): 74.09698, (100); 86.09684, (88); 104.03443, (7); 132.06534, (4); 172.09645, (4); 200.12770, (5); 270.20564, (2) $[M-H]^+$.

*Synthesis of potassium (R)-3-(neopentyl(pent-1-en-3-yl)amino)-3-oxopropanoate*

This molecule was synthetized according the general procedure for preparing potassium salt from the corresponding ester (see p. 204).




**5.18**

**Yield:** 87 % - white powder.

**Purification:** chromatography on silica gel. Eluent: DCM/isopropanol 0.9/0.1.

**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 6.37 – 5.76 (m, 1H, $C_{10}$**HH**), 5.32 – 4.82 (m, 2H, $C_{11}$**HH**), 3.53 – 2.83 (m, 4H, $C_2$**HH**, $C_4$**HH**), 2.16 – 1.51 (m, 3H, $C_7$**H**, $C_8$**HH**), 1.01 – 0.82 (m, 9H, $C_6$**HHH**), 0.84 – 0.79 (m, 3H, $C_9$**HHH**).

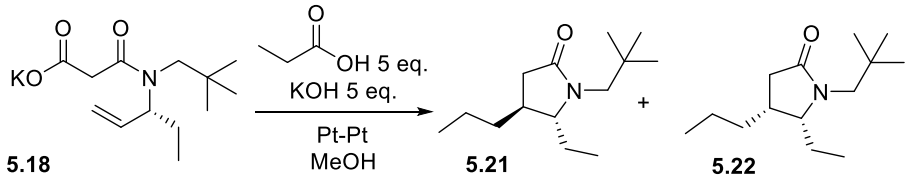
**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 172.63 (s, $C_1$), 172.58 (s, $C_1$), 171.83 (s, $C_3$), 171.06 (s, $C_3$), 137.56 (s, $C_{10}$), 137.25 (s, $C_{10}$), 116.47 (s, $C_{11}$), 116.10 (s, $C_{11}$), 64.48 (s, $C_7$), 64.24 (s, $C_7$), 61.87 (s, $C_4$), 44.62 (s, $C_2$), 44.54 (s, $C_2$), 33.63 (s, $C_5$), 33.51 (s, $C_5$), 28.77 (s, $C_6$), 28.41 (s, $C_6$), 25.56 (s, $C_8$), 25.36 (s, $C_8$), 11.82 (s, $C_9$).

**IR (film, cm$^{-1}$):** 2952, 1739, 1600, 1479, 1419, 1365, 1201, 999, 912, 742.

**HRMS**, m/z: calculated $[C_{13}H_{22}O_3N]^-$ : 240.15942, found: 240.16055.

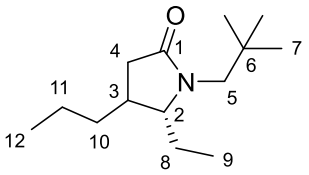
**MS/MS** (p ESI): m/z (%): 168.13843, (8); 180.13861, (20); 183.00211, (84); 199.17004, (100); 198.14919, (5); 240.07329, (16) $[M]^-$.

*Synthesis of (5R)-1-allyl-5-ethyl-4-propylpyrrolidin-2-one*




**5.18** **5.21** **5.22**

In an undivided cell with platinum electrodes (4 cm²), potassium hydroxide (0.1850 g, 3.30 mmol, 5 eq.) and propionic acid (0.2445 g, 3.30 mmol, 5 eq.) were dissolved in 10 ml of MeOH. Then, the potassium salt (0.1844 g, 0.66 mmol, 1 eq.) was added to the mixture. The intensity of the current was fixed at 100 mA and the mixture was electrolyzed until completion of the reaction, as shown by TLC. The solution was treated with an aqueous solution of $NaHCO_3$ (10 ml) and extracted three times with 10 ml of diethyl ether. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (AcOEt/EP 2/8). Finally, the diastereomeric ratio was determined by chiral HPLC.




**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 3.34 (s, 2H, $C_5$**HH**), 3.30 – 2.95 (m, 1H, $C_2$**H**), 2.64 – 1.94 (m, 3H, $C_3$**H**, $C_4$**HH**), 1.79 – 1.46 (m, 2H, $C_8$**HH**), 1.39 – 1.14 (m, 4H, $C_{10}$**HH**, $C_{11}$**HH**), 1.06 – 0.78 (m, 15H, $C_7$**HHH**, $C_9$**HHH**, $C_{12}$**HHH**).

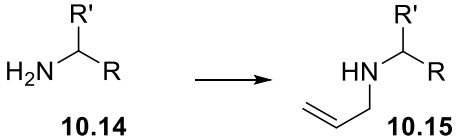
**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 172.35 (s, $C_1$), 75.35 (s, $C_2$), 59.18 (s, $C_5$), 35.46 (s, $C_4$), 31.01 (s, $C_6$), 30.63 (s, $C_3$), 29.85 (s, $C_{10}$), 29.85 (s, $C_{11}$), 28.66 (s, $C_7$),19.88 (s, $C_8$), 14.07 (s, $C_{12}$), 10.45 (s, $C_9$).

**IR (film, $cm^{-1}$):** 1747, 1693, 1671, 1990, 1475, 1464, 1421, 1396, 1327, 1284, 1242, 1213, 1155, 905, 887.

**HRMS**, m/z: calculated $[C_{14}H_{28}ON]^+$ : 226.21554, found: 226.21544.

**MS/MS** (p ESI): m/z (%): 102.12820, (12); 118.12295, (7); 156.17482, (15); 186.14901, (22); 214.18030, (16); 226.21544, (5) $[M-H]^+$.

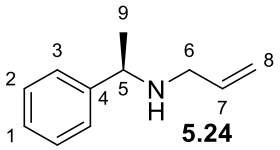
*General Procedure for preparing the secondary allyl amine from the corresponding primary amine*




A solution of the primary amine (25 mmol, 1 eq., 0.1 M) in THF was cooled down to – 78°C and nBuLi (25 mmol, 1 eq., 1.6 M in hexane) was added in 30 minutes. Then allyl bromide was added dropwise and the temperature was allowed to warm up to the room temperature. The mixture was stirred overnight. Finally, the solution was quenched with a saturated aqueous solution of $NH_4Cl$ and was extracted three times with ethyl acetate. The combined organic layers were extracted with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The product did not need purification.

*Synthesis of (R)-N-(1-phenylethyl)prop-2-en-1-amine*

This molecule was prepared according to the general procedure for preparing the secondary allyl amine from the corresponding primary amine (see p. 252).




**Yield:** 89 % - colourless-oil.

**Purification:** purification not necessary.

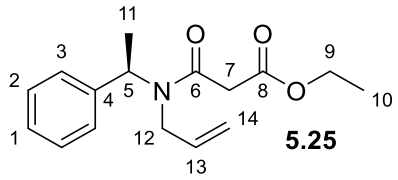
**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 7.35 – 7.09 (m, 5H, Ph**H**), 5.94 – 5.69 (m, 1H, $C_7$**H**), 5.18 – 4.95 (m, 2H, $C_8$**HH**), 3.77 (q, J = 6.63 Hz, 1H, $C_5$**H**), 3.08 – 3.02 (m, 2H, $C_6$**HH**), 2.08 (s, 1H, N**H**), 1.34 (d, J = 6.62 Hz, 3H, $C_9$**HHH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 144.8 (s, $C_4$), 136.3 (s, $C_7$), 128.5 (s, $C_2$), 127.0 (s, $C_3$), 126.7 (s, $C_1$), 116.2 (s, $C_8$), 57.5 (s, $C_5$), 50.0 (s, $C_6$), 23.9 (s, $C_9$).

**IR (film, $cm^{-1}$):** 1641, 1602, 1492, 1450, 1120, 995, 916, 761.

*Synthesis of ethyl (R)-3-(allyl(1-phenylethyl)amino)-3-oxopropanoate*

This molecule was synthetized according to the general procedure for preparing amide from the corresponding secondary amine using DCC as a coupling agent (see p. 203).




**Yield:** 76 % - colourless-oil.

**Purification:** chromatography on silica gel. Eluent: EP/AcOEt 0.7/0.3.

**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 7.43 – 7.05 (m, 5H, Ph**H**), 6.03 (q, J = 7.13 Hz, 1H, $C_5$**H**), 5.81 – 5.42 (m, 1H, $C_{13}$**H**), 5.15 – 4.90 (m, 2H, $C_{14}$**HH**), 4.33 – 3.98 (m, 2H, $C_9$**HH**), 3.76 – 3.26 (m, 4H, $C_7$**HH**, $C_{12}$**HH**), 1.53 (d, J = 7.12 Hz, 3H, $C_{11}$**HHH**), 1.20 (t, J = 7.23 Hz, 3H, $C_{10}$**HHH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) δ** 167.8 (s, $C_8$), 167.0 (s, $C_6$), 140.3 (s, $C_4$), 140.0 (s, $C_4$), 134.6 (s, $C_{13}$), 134.2 (s, $C_{13}$), 128.7 (s, $C_2$), 128.4 (s, $C_2$), 127.7 (s, $C_3$), 127.5 (s, $C_3$), 127.4 (s, $C_1$), 126.6 (s, $C_1$), 116.8 (s, $C_{14}$), 116.2 (s, $C_{14}$), 61.5 (s, $C_9$), 61.4 (s, $C_9$), 56.4 (s, $C_5$), 51.3 (s, $C_5$), 46.3 (s, $C_{12}$), 45.6 (s, $C_{12}$), 41.8 (s, $C_7$), 41.7 (s, $C_7$), 18.7 (s, $C_{11}$), 16.5 (s, $C_{11}$), 14.1 (s, $C_{10}$).

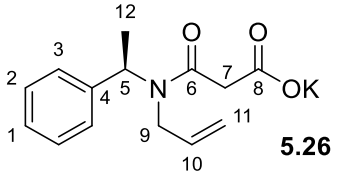
**IR (film, $cm^{-1}$):** 1737, 1650, 1425, 1367, 1326, 1155, 1029, 955, 923, 756, 740.

**HRMS**, m/z: calculated $[C_{16}H_{22}O_3N]^+$ : 276.15942, found: 276.15939.

**MS/MS** (p ESI): m/z (%): 105.06965, (50); 126.05438, (5); 144.06472, (15); 172.09577, (100); 276.15766, (1) $[M-H]^+$.

*Synthesis of potassium (R)-3-(allyl(1-phenylethyl)amino)-3-oxopropanoate*

This molecule was synthetized according to the general procedure for preparing the potassium salt from the corresponding ester (see p. 204).




**5.26**

**Yield:** 72 % - white solid.

**Purification:** filtration and diethyl ether wash.

**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 7.39 – 7.11 (m, 5H, Ph**H**), 5.92 (q, J = 6.82 Hz, 0,63H, $C_5$**H**), 5.76 – 5.44 (m, 1H, $C_{10}$**H**), 5.27 (m, 0.37H, $C_5$**H**), 5.12 – 4.81 (m, 2H, $C_{11}$**HH**), 4.01 – 3.18 (m, 4H, $C_7$**HH**, $C_9$**HH**), 1.53 (d, J = 6.32 Hz, 1.05H, $C_{12}$**HHH**), 1.40 (d, J = 7.02 Hz, 1.95H, $C_{12}$**HHH**).

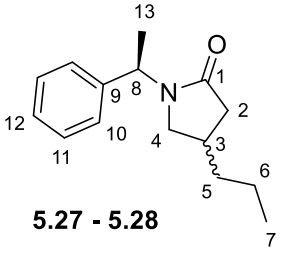
**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 173.4 (s, $C_8$), 173.4 (s, $C_8$), 171.9 (s, $C_6$), 171.1 (s, $C_6$), 141.0 (s, $C_4$), 140.6 (s, $C_4$), 135.4 (s, $C_{10}$), 135.2 (s, $C_{10}$), 128.4 (s, $C_8$), 128.3 (s, $C_8$), 127.5 (s, $C_3$), 127.3 (s, $C_3$), 127.1 (s, $C_1$), 116.3 (s, $C_{11}$), 115.7 (s, $C_{11}$), 56.2 (s, $C_5$), 51.1 (s, $C_5$), 46.5 (s, $C_9$), 45.3 (s, $C_7$), 45.0 (s, $C_7$), 18.2 (s, $C_{12}$), 16.7 (s, $C_{12}$).

**IR (film, $cm^{-1}$):** 1749, 1573, 1450, 1363, 1323, 1207, 1176, 918, 786, 698.

**HRMS**, m/z: calculated $[C_{14}H_{16}O_3N]^-$ : 246.11247, found: 246.11252.

*Synthesis of 1-((R)-1-phenylethyl)-4-propylpyrrolidin-2-one*

This molecule was synthetized according to the general procedure for preparing the electrocyclization of functionalized 2-pyrrolidinones (see p. 205).




**5.27 - 5.28**

**Yield:** 61 % - d.r. = 96:4 - colourless-oil.

**Purification:** chromatography on silica gel. Eluent: AcOEt/EP 0.3/0.7.

**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 7.43 – 7.10 (m, 5H, Ph**H**), 5.56 – 5.31 (m, 1H, $C_8$**H**), 3.04 (dd, J = 9.52, 7.83 Hz, 1H, $C_4$**H**H), 2.88 (dd, J = 9.52, 7.04 Hz, 1H, $C_4$H**H**), 2.59 – 2.43 (m, 1H, $C_2$**H**H), 2.22 – 2.02 (m, 3H, $C_2$H**H**, $C_3$**H**), 1.46 (d, J = 7.04, 3H, $C_{13}$**HHH**), 1.42 – 1.15 (m, 4H, $C_5$**HH**, $C_6$**HH**), 0.89 (t, J = 7.51 Hz, 3H, $C_7$**HHH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 174.0 (s, $C_1$), 140.3 (s, $C_9$), 128.4 (s, $C_{11}$), 127.3 (s, $C_{10}$), 126.9 (s, $C_{12}$), 48.7 (s, $C_8$), 48.1 (s, $C_4$), 38.1 (s, $C_2$), 36.8 (s, $C_5$), 31.6 (s, $C_3$), 20.6 (s, $C_6$), 16.1 (s, $C_{13}$), 14.0 (s, $C_7$).

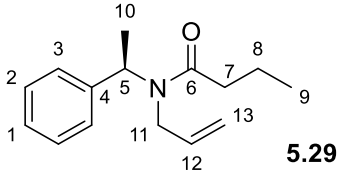
**IR (film, $cm^{-1}$):** 1668, 1494, 1450, 1421, 1377, 1284, 1267, 1230, 1027, 916, 784, 742, 700.

**HRMS**, m/z: calculated $[C_{15}H_{22}ON]^+$ : 232.16959, found: 232.16953.

**MS/MS** (p ESI): m/z (%): 105.06999, (42); 128.10678, (100); 232.16889, (41) $[M-H]^+$.

*Synthesis of (R)-N-allyl-N-(1-phenylethyl)butyramide*

This molecule was synthetized according to the general procedure for preparing the electrocyclization of functionalized 2-pyrrolidinones (see p. 205).




**5.29**

**Yield:** 12 % - colourless-oil.

**Purification:** chromatography on silica gel. Eluent: AcOEt/EP 0.3/0.7.

**$^1$H NMR (300 MHz, $CDCl_3$) : δ** 7.44 – 7.12 (m, 5H, Ph**H**), 6.09 (q, J = 7.13 Hz, 0.71H, $C_5$**H**), 5.85 – 5.41 (m, 1H, $C_{12}$**H**), 5.13 (q, J = 6.91 Hz, 0.29H, $C_5$**H**), 5.08 – 4.86 (m, 2H, $C_{13}$**HH**), 3.79 – 3.28 (m, 2H, $C_{11}$**HH**), 2.40 (t, J = 7.53 Hz, 0.58H, $C_7$**HH**), 2.31 – 2.18 (t, 1.42H, $C_7$**HH**), 1.78 – 1.62 (m, 2H, $C_8$**HH**), 1.58 (d, J = 6.94 Hz, 0.92H, $C_{10}$**HHH**), 1.46 (t, J = 8.25 Hz, 2.08H, $C_{10}$**HHH**), 0.92 (t, J = 7.49 Hz, 3H, $C_9$**HHH**).

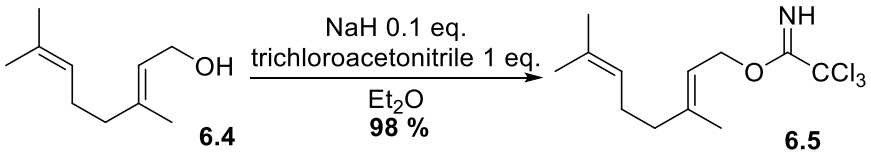
**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 173.8 (s, $C_6$), 141.1 (s, $C_4$), 140.8 (s, $C_4$), 135.3 (s, $C_{12}$), 135.2 (s, $C_{12}$), 128.6 (s, $C_2$), 128.3 (s, $C_2$), 127.5 (s, $C_3$), 127.2 (s, $C_3$), 126.6 (s, $C_1$), 116.1 (s, $C_{13}$), 115.8 (s, $C_{13}$), 55.3 (s, $C_5$), 50.8 (s, $C_5$), 45.9 (s, $C_{11}$), 45.5 (s, $C_{11}$), 35.6 (s, $C_7$), 18.8 (s, $C_8$), 16.7 (s, $C_{10}$), 13.9 (s, $C_9$).

**IR (film, $cm^{-1}$):** 1737, 1716, 1643, 1635, 1494, 1450, 1409, 1375, 1228, 1205, 1180, 1093, 1027, 983, 914, 784, 742.

**HRMS**, m/z: calculated $[C_{15}H_{22}ON]^+$ : 232.1701, found: 232.1710.

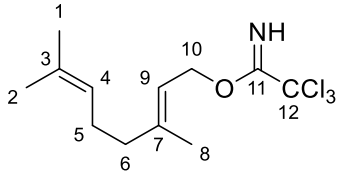
**MS/MS** (p ESI): m/z (%): 105.0713, (12); 128.1084, (43); 232.1710, (100) $[M-H]^+$; 233.1745, (14).

*Synthesis of (E)-3,7-dimethylocta-2,6-dien-1-yl 2,2,2-trichloroacetimidate*[245]




**6.4** **6.5**

NaH (0.410 g, 10.3 mmol, 0.1 eq.) was diluted in 60 ml of diethyl ether. A solution of geraniol (15.400 g, 99.3 mmol, 1.0 eq.) in 15 ml of diethyl ether was added over 5 minutes. The solution was then cooled to between -10 and 0°C in an ice bath. Trichloroacetonitrile (14.400 g, 99.6 mmol, 1.0 eq.) was added dropwise to the stirred solution, while the reaction temperature was maintained below 0°C. The reaction mixture was allowed to warm to room temperature. Consecutively diethyl ether was removed with a rotary evaporator. 150 ml of pentane was added, the mixture was shaken vigorously for one minute and the solution was filtered. Finally, the combined organic layers were concentrated under reduced pressure.

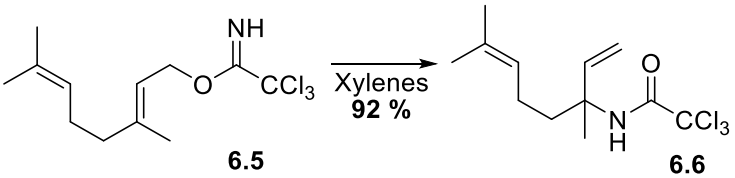



**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 8.20 (s (br), 1H, N**H**), 5.53 – 5.41 (m, 1H, $C_9$**H**), 5.09 (tdd, J = 5.4, 2.7, 1.3 Hz, 1H, $C_4$**H**), 4.81 (d, J = 6.9 Hz, 2H, $C_{10}$**HH**), 2.19 – 2.01 (m, 4H, $C_5$**HH**, $C_6$**HH**), 1.74 (s, 3H, $C_1$**HHH** or $C_2$**HHH**), 1.68 (s, 3H, $C_1$**HHH** or $C_2$**HHH**), 1.60 (s, 3H, $C_8$**HHH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 162.84 (s, $C_{11}$), 143.18 (s, $C_7$), 131.85 (s, $C_3$), 123.69 (s, $C_4$), 117.69 (s, $C_9$), 91.64 (s, $C_{12}$) 66.30 (s, $C_{10}$), 39.52 (s, $C_6$), 26.24 (s, $C_5$), 25.68 (s, $C_1$ or $C_2$), 17.70 (s, $C_1$ or $C_2$), 16.64 (s, $C_8$).

**IR (film, cm$^{-1}$):** 3373, 2974, 1693, 1616, 1450, 1379, 1239, 1108, 830, 751, 678, 620.

*Synthesis of 2,2,2-trichloro-N-(3,7-dimethylocta-1,6-dien-3-yl)acetamide*

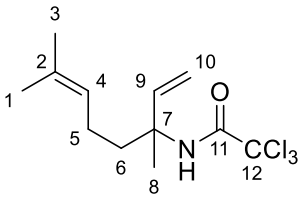



**6.5** **6.6**

Imidate **6.5** (26.87 g, 90 mmol, 1 eq.) was diluted in 300 ml of xylene. The solution was refluxed for eight hours. After cooling to room temperature, the solution was filtered through a short column packed with silica gel and toluene. The column was

[245] Clizbe, L.A.; Overman, L.E. *Org. Synth.* **1978**, 58, 4.

eluted with an additional 250 ml of toluene. Finally, the organic layer was concentered under reduced pressure.

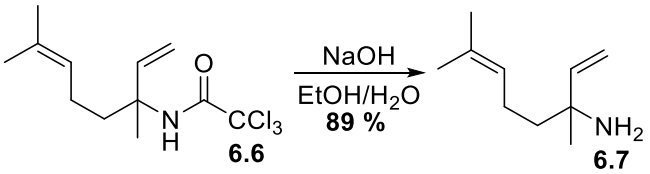



**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 6.59 (s (br), 1H, N**H**), 5.84 (dd, J = 17.4, 10.8 Hz, 1H, $C_9$**H**), 5.19 – 4.98 (m, 3H, $C_4$**H**, $C_{10}$**HH**), 2.02 – 1.64 (m, 4H, $C_5$**HH**, $C_6$**HH**), 1.61 (s, 3H, $C_1$**HHH** or $C_3$**HHH**), 1.52 (s, 3H, $C_1$**HHH** or $C_3$**HHH**), 1.45 (s, 3H, $C_8$**HHH**).

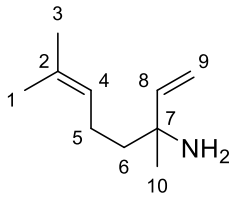
**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 160.16 (s, $C_{11}$), 141.16 (s, $C_9$), 132.93 (s, $C_2$), 123.33 (s, $C_4$), 113.43 (s, $C_{10}$), 93.31 (s, $C_{12}$), 58.84 (s, $C_7$), 39.09 (s, $C_6$), 25.79 (s, $C_8$), 23.99 (s, $C_1$ or $C_3$), 22.59 (s, $C_5$), 17.72 (s, $C_1$ or $C_3$).

**IR (film, cm$^{-1}$):** 3423, 2978, 2935, 1709, 1508, 1451, 1412, 1375, 1249, 1121, 1076, 991, 920, 819, 676.

*Synthesis of 3,7-dimethylocta-1,6-dien-3-amine*




Octadiene **6.6** (9 g, 30 mmol, 1 eq.) was diluted in 160 ml of methanol and 150 ml of an aqueous solution of sodium hydroxide (6 N). The solution was stirred, at room temperature, for 40 hours. Diethyl ether 300 ml was added, the organic layer was separated, and the aqueous layer was concentrated under reduced pressure, affording a white semi solid residue, which was extracted four times with 50 ml of boiling hexane. The extract was finally concentrated with a rotary evaporator.

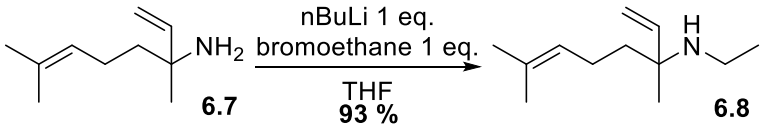



**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 5.89 (dd, J = 17.4, 10.7 Hz, 1H, $C_8$**H**), 5.18 – 4.95 (m, 3H, $C_4$**H**, $C_9$**HH**), 2.04 – 1.86 (m, 2H, $C_5$**HH**), 1.65 (s, 3H, $C_1$**HHH** or $C_3$**HHH**), 1.59 (s, 3H, $C_1$**HHH** or $C_3$**HHH**), 1.52 – 1.37 (m, 2H, $C_6$**HH**), 1.16 (s, 3H, $C_{10}$**HHH**).

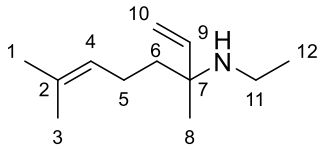
**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 147.12 (s, $C_8$), 131.47 (s, $C_2$), 124.38 (s, $C_4$), 110.70 (s, $C_9$), 53.88 (s, $C_7$), 43.03 (s, $C_6$), 28.31 (s, $C_{10}$), 25.68 (s, $C_1$ or $C_3$), 22.98 (s, $C_1$ or $C_3$), 17.63 (s, $C_5$).

**IR (film, $cm^{-1}$):** 2958, 2924, 2852, 1675, 1336, 831, 745, 680.

*Synthesis of N-ethyl-3,7-dimethylocta-1,6-dien-3-amine*




Linalylamine (1.89 g, 12.33 mmol, 1 eq.) was diluted in 16 ml of THF (0.78 mol/l) and this solution was cooled to a temperature of – 78°C. *N*-butyllithium 1.6 mol/l in hexane was then added dropwise and the solution was subsequently stirred, 30 min, at – 78°C. Bromoethane was added dropwise to the solution and the mixture was allowed to stir overnight. After completion of the reaction, the reaction was quenched with 10 ml of an aqueous solution saturated in $NH_4Cl$. The aqueous phase was extracted two times with 10 ml of AcOEt. Finally, the organic layers were combined, dried over $Na_2SO_4$ and concentrated under reduced pressure. The crude product was purified via silica gel chromatography (EP/AcOEt/$Et_3N$ 8/1/1).




**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 6.07 – 5.57 (m, 1H, $C_9$**H**), 5.51 – 4.95 (m, 3H, $C_4$**H**, $C_{10}$**HH**), 2.22 – 1.78 (m, 4H, $C_5$**HH**, $C_{11}$**HH**), 1.68 (s, 3H, $C_1$**HHH** or $C_3$**HHH**), 1.60 (s, 3H, $C_1$**HHH** or $C_3$**HHH**), 1.47 (s, 3H, $C_8$**HHH**), 1.34 – 1.24 (m, 2H, $C_6$**HH**), 0.91 (t, J = 7.2 Hz, 3H, $C_{12}$**HHH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 138.11 (s, $C_9$), 132.97 (s, $C_2$), 122.47 (s, $C_4$), 114.13 (s, $C_{10}$), 62.62 (s, $C_7$), 41.39 (s, $C_6$), 39.13 (s, $C_{11}$), 28.45 (s, $C_8$), 25.64 (s, $C_1$ or $C_3$), 22.82 (s, $C_5$), 17.66 (s, $C_1$ or $C_3$), 14.23 (s, $C_{12}$).

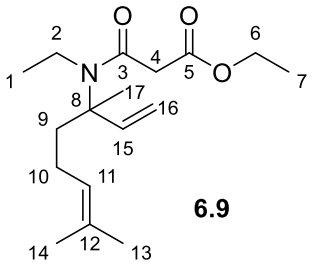
**IR (film, $cm^{-1}$):** 3314, 2966, 2927, 2852, 1667, 1514, 1453, 1376, 919.

**HRMS**, m/z: calculated $[C_{12}H_{24}N]^+$ : 182.19040, found: 182.19033.

**MS/MS** (p ESI): m/z (%): 81.07038, (100); 95.08586, (15); 137.13231, (13); 182.19011, (2) $[M-H]^+$.

*Synthesis of ethyl 3-((3,7-dimethylocta-1,6-dien-3-yl)(ethyl)amino)-3-oxopropanoate*

This molecule was synthetized according to the general procedure for preparing amide from the corresponding secondary amine using DCC as coupling agent (see p. 203).



**6.9**

**Yield:** 66 % - colourless oil.

**Purification:** chromatography on silica gel. Eluent: EP/AcOEt 9/1.

**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 6.03 (ddd, J = 65.1, 17.7, 10.7 Hz, 1H, $C_{15}$**H**), 5.18 – 4.99 (m, 3H, $C_{11}$**H**, $C_{16}$**HH**), 4.19 (q, J = 7.20 Hz, 2H, $C_6$**HH**), 3.43 (s, 2H, $C_4$**HH**), 3.30 (q, J = 7.05 Hz, 2H, $C_2$**HH**), 2.23 – 1.82 (m, 4H, $C_9$**HH**, $C_{10}$**HH**), 1.66 (s, 3H, $C_{13}$**HHH** or $C_{14}$**HHH**), 1.58 (s, 3H, $C_{13}$**HHH** or $C_{14}$**HHH**), 1.50 (s, 3H, $C_{17}$**HHH**), 1.28 (t, J = 7.20 Hz, 3H, $C_7$**HHH**), 1.18 (t, J = 7.1 Hz, 3H, $C_1$**HHH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 168.09 (s, $C_5$), 164.81 (s, $C_3$), 143.60 (s, $C_{15}$), 131.53 (s, $C_{12}$), 124.09 (s, $C_{11}$), 112.31 (s, $C_{16}$), 63.63 (s, $C_8$), 61.25 (s, $C_6$), 43.62 (s, $C_4$), 40.97 (s, $C_2$), 38.34 (s, $C_9$), 25.66 (s, $C_{13}$ or $C_{14}$), 22.98 (s, $C_{10}$), 22.96 (s, $C_{17}$), 17.61 (s, $C_{13}$ or $C_{14}$), 16.75 (s, $C_1$), 14.10 (s, $C_7$).

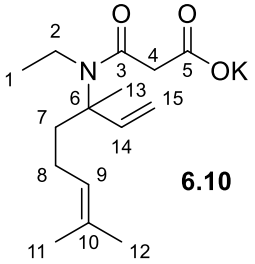
**IR (film, cm$^{-1}$):** 3210, 2905, 2853, 1668, 1632, 1524, 1454, 1326, 939.

**HRMS**, m/z: calculated$[C_{17}H_{30}O_3N]^+$ : 296.22202, found: 296.22187.

**MS/MS** (p ESI): m/z (%): 81.07049, (21); 132.06555, (18); 160.09679, (100); 172.09672, (14); 296.222187, (20) $[M-H]^+$.

### *Synthesis of potassium 3-((3,7-dimethylocta-1,6-dien-3-yl)(ethyl)amino)-3-oxopropanoate*

This molecule was synthetized according the general procedure for preparing potassium salt from the corresponding ester (see p. 199).



**6.10**

**Yield:** 77 % - white solid.

**Purification:** filtration and wash with cold diethyl ether.

**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 6.25 – 5.86 (m, 1H, $C_{14}$**H**), 5.20 – 4.80 (m, 3H, $C_9$**H**, $C_{15}$**HH**), 3.44 – 3.11 (m, 4H, $C_2$**HH**, $C_4$**HH**), 2.12 – 1.72 (m, 4H, $C_7$**HH**, $C_8$**HH**), 1.63 (s, 1.05H, $C_{11}$**HHH** or $C_{12}$**HHH**), 1.61 (s, 1.95H, $C_{11}$**HHH** or $C_{12}$**HHH**), 1.55 (s, 1.05H, $C_{11}$**HHH** or $C_{12}$**HHH**), 1.53 (s, 1.95H, $C_{11}$**HHH** or $C_{12}$**HHH**), 1.46 (s, 1.05H, $C_{13}$**HHH**), 1.39 (s, 1.95H, $C_{13}$**HHH**), 1.16 (t, J = 7.5 Hz, 3H, $C_1$**HHH**).

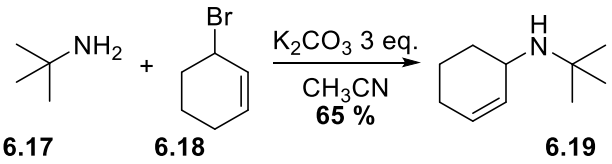
**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 172.68 (s, $C_5$), 170.56 (s, $C_3$), 144.03 (s, $C_{14}$), 131.43 (s, $C_{10}$), 124.19 (s, $C_9$), 111.90 (s, $C_{15}$), 63.39 (s, $C_6$), 45.12 (s, $C_2$), 43.41 (s, $C_2$), 40.77 (s, $C_4$), 33.94 (s, $C_7$), 25.66 (s, $C_{11}$ or $C_{12}$), 23.24 (s, $C_{13}$), 23.03 (s, $C_8$), 17.66 (s, $C_{11}$ or $C_{12}$), 16.82 (s, $C_1$).

**IR (film, cm$^{-1}$):** 2915, 2823, 1665, 1630, 1503, 1411, 1316, 863.

**HRMS**, m/z: calculated $[C_{15}H_{25}O_3N^{39}K]^+$ : 306.14660, found: 306.14666.

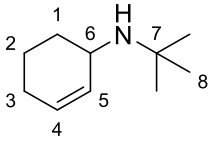
**MS/MS** (p ESI): m/z (%): 170.02148, (100); 306.14666, (78) $[M-H]^+$.

*Synthesis of N-(tert-butyl)cyclohex-2-en-1-amine*




**6.17** **6.18** **6.19**

*Tert*-butylamine (2.088 g, 28.5 mmol, 1 eq.) was diluted in 36.53 ml of THF (0.78 mol/l) and this solution was cooled down to a temperature of – 78°C. *N*-butyllithium 1.6 mol/l in hexane was then added dropwise and the solution was allowed to stir, for 30 min, at – 78°C. 3-bromocyclohexene (4.580 g, 28.5 mmol, 1 eq.) was then added dropwise and this mixture was stirred overnight. After completion of the reaction, the reaction was quenched with 30 ml of an aqueous solution of $NH_4Cl$. The aqueous layer was subsequently extracted two times with 20 ml of AcOEt. The organic layers were combined, dried over $Na_2SO_4$ and concentered under reduced pressure. Finally, the crude product was purified via silica gel chromatography (EP/AcOEt/$Et_3N$ 2/1/0.15).



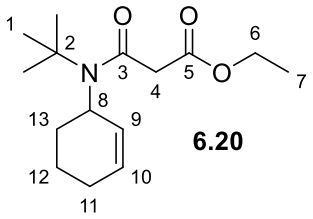

**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 5.73 – 5.53 (m, 2H, $C_4$**H**, $C_5$**H**), 3.20 (td, J = 4.5, 2.2 Hz, 1H, $C_6$**H**), 2.01 – 1.88 (m, 2H, $C_3$**HH**), 1.85 – 1.64 (m, 2H, $C_1$**H**H, $C_2$**H**H), 1.63 – 1.35 (m, 2H, $C_1$H**H**, $C_2$H**H**), 1.10 (s, 9H, $C_8$**HHH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 132.64 (s, $C_4$), 127.75 (s, $C_5$), 51.18 (s, $C_7$), 47.05 (s, $C_6$), 33.04 (s, $C_1$), 29.86 (s, $C_8$), 24.87 (s, $C_3$), 20.51 (s, $C_2$).

**IR (film, cm$^{-1}$):** 2805, 1643, 1626, 1504, 1361, 1202, 1117, 1007.

*Synthesis of ethyl 3-(tert-butyl(cyclohex-2-en-1-yl)amino)-3-oxopropanoate*

This molecule was synthetized according to the general procedure for preparing amide from the corresponding secondary amine using DCC ass coupling agent (see p. 203).




**6.20**

**Yield:** 66 % - colourless oil.

**Purification:** chromatography on silica gel. Eluent: EP/AcOEt 9/1.

**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 5.64 (dd, J = 25.5, 15.4 Hz, 2H, $C_9$**H**, $C_{10}$**H**), 4.39 – 4.26 (m, 1H, $C_8$**H**), 4.11 (q, J = 7.05 Hz, 2H, $C_6$**HH**), 3.55 – 3.44 (m, 2H, $C_4$**HH**), 2.07 – 1.55 (m, 6H, $C_{11}$**HH**, $C_{12}$**HH**, $C_{13}$**HH**), 1.46 (s, 9H, $C_1$**HHH**), 1.26 (t, J = 7.05 Hz, 2H, $C_6$**HH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 168.85 (s, $C_5$), 165.36 (s, $C_3$), 131.91 (s, $C_{10}$), 128.33 (s, $C_9$), 60.96 (s, $C_6$), 59.10 (s, $C_2$), 52.75 (s, $C_8$), 44.94 (s, $C_4$), 31.20 (s, $C_{13}$), 29.35 (s, $C_1$), 24.02 (s, $C_{11}$), 22.69 (s, $C_{12}$), 14.11 (s, $C_7$).

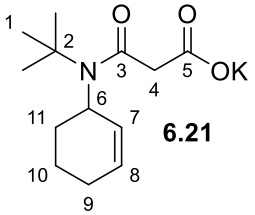
**IR (film, $cm^{-1}$):** 2924, 2848, 1732, 1584, 1457, 1360, 1292, 1238, 1147, 1037, 726, 671.

**HRMS**, m/z: calculated $[C_{15}H_{26}O_3N]^+$ : 268.19072, found: 268.19049.

**MS/MS** (p ESI): m/z (%): 81.07048, (16); 132.06552, (100); 188.12804, (13); 212.12802, (11); 268.19042, (3) $[M-H]^+$.

*Synthesis of potassium 3-(tert-butyl(cyclohex-2-en-1-yl)amino)-3-oxopropanoate*

This molecule was synthetized according to the general procedure for preparing potassium salt from the corresponding ester (see p. 204).




**6.21**

**Yield:** 84 % - white solid.

**Purificatio:** filtration and wash with cold diethyl ether.

**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 6.00 – 5.45 (m, 2H, $C_7$**HH**, $C_8$**HH**), 4.23 – 4.20 (m, 1H, $C_6$**H**), 3.76 – 3.10 (m, 2H, $C_4$**HH**), 2.18 – 1.49 (m, 6H, $C_9$**HH**, $C_{10}$**HH**, $C_{11}$**HH**), 1.43 (s, 3.51H, $C_1$**HHH**), 1.36 (s, 5.49H, $C_1$**HHH**).

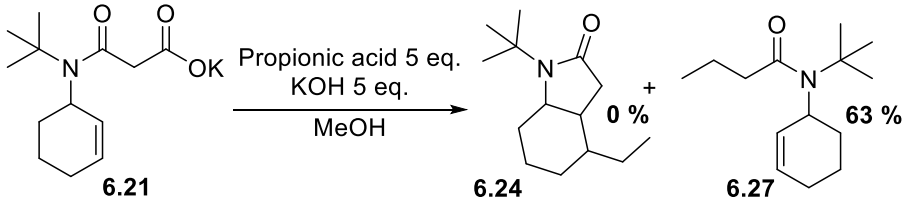
**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 169.15 (s, $C_5$), 168.28 (s, $C_3$), 132.84 (s, $C_8$), 131.81 (s, $C_8$), 128.44 (s, $C_7$), 127.67 (s, $C_7$), 59.29 (s, $C_2$), 52.15 (s, $C_6$), 44.76 (s, $C_4$), 33.11 (s), 31.29 (s), 29.90 (s, $C_1$), 29.37 (s, $C_1$), 24.01 (s, $C_{11}$), 22.87 (s, $C_9$), 20.52 (s, $C_{10}$).

**IR (film, cm$^{-1}$):** 2904, 2837, 1733, 1650, 1564, 1361, 1282, 1146, 1007, 823.

**HRMS**, m/z: calculated $[C_{13}H_{21}O_3N^{39}K]^+$ : 278.11530, found: 278.11517.

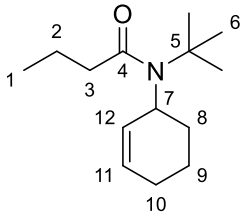
**MS/MS** (p ESI): m/z (%): 94.93016, (13); 150.95592, (7); 194.94577, (9); 278.11516, (100) $[M-H]^+$.

*Synthesis of 1-(tert-butyl)-4-ethyloctahydro-2H-indol-2-one*




**6.21** **6.24** **6.27**

These molecules were synthetized according to the procedure for the electrocyclization of functionalized 2-pyrrolidinones (see p. 203).
**Purification:** chromatography on silica gel. Eluent: EP/AcOEt 9/1.




**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 5.81 – 5.57 (m, 2H, $C_{11}$**H**, $C_{12}$**H**), 4.34 – 3.29 (m, 1H, $C_7$**H**), 2.20 – 1.57 (m, 10H, $C_2$**HH**, $C_3$**HH**, $C_8$**HH**, $C_9$**HH**, $C_{10}$**HH**), 1.47 (s, 9H, $C_6$**HHH**), 0.95 (t, J = 7.5 Hz, 3H, $C_1$**HHH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 170.88 (s, $C_4$), 131.81 (s, $C_{11}$), 128.34 (s, $C_{12}$), 59.17 (s, $C_5$), 52.14 (s, $C_7$), 31.15 (s, $C_3$), 29.95 (s, $C_8$), 29.36 (s, $C_6$), 28.96 (s, $C_{10}$), 24.00 (s, $C_9$), 22.69 (s, $C_2$), 12.40 (s, $C_1$).

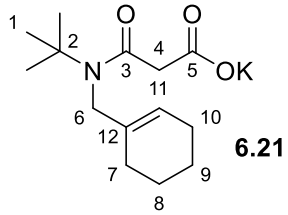
**IR (film, cm$^{-1}$):** 1738, 1650, 1395, 1335, 1256, 1184, 1034, 942, 723.

**HRMS**, m/z: calculated $[C_{14}H_{26}ON]^+$ : 224.20089, found: 224.20078.

**MS/MS** (p ESI): m/z (%): 81.07049, (1); 93.07032, (3); 126.12780, (12); 136.07526, (5); 168.13786, (100); 224.20052, (63) $[M-H]^+$.

*Synthesis of potassium 3-(tert-butyl(cyclohex-1-en-1-ylmethyl)amino)-3-oxopropanoate*

This molecule was synthetized according to the general procedure for preparing potassium salt from the corresponding ester (see p. 204).




**6.21**

**Yield:** 83 % - white solid.

**Purification:** filtration and wash with cold diethyl ether.

**$^1$H NMR (300 MHz, $CDCl_3$) δ :** 5.54 – 5.48 (m, 1H, $C_{11}$**HH**), 3.80 – 3.61 (m, 2H, $C_6$**HH**), 3.42 – 3.24 (m, 2H, $C_4$**HH**), 2.17 – 1.47 (m, 8H, $C_7$**HH**, $C_8$**HH**, $C_9$**HH**, $C_{10}$**HH**), 1.48 – 1.37 (m, 9H, $C_1$**HHH**).

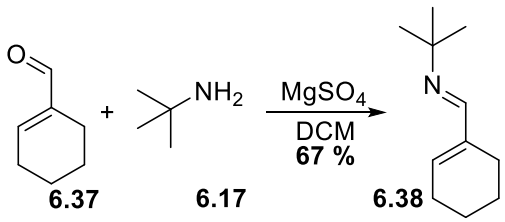
**$^{13}$C NMR (75 MHz, $CDCl_3$) δ :** 171.44 (s, $C_5$), 169.22 (s, $C_3$), 133.11 (s, $C_{12}$), 121.81 (s, $C_{11}$), 59.18 (s, $C_2$), 50.16 (s, $C_6$), 33.87 (s, $C_4$), 28.17 (s, $C_1$), 26.39 (s, $C_7$), 24.96 (s, $C_{10}$), 24.70 (s, $C_9$), 22.29 (s, $C_8$).

**IR (film, cm$^{-1}$):** 3388, 2925, 1598, 1437, 1357, 1198, 910, 643.

**HRMS**, m/z: calculated $[C_{14}H_{23}O_3N^{39}K]^+$ : 292.13095, found: 292.13102.

**MS/MS** (p ESI): m/z (%): 206.13071, (8); 292.13120, (100) $[M-H]^+$.

*Synthesis of (E)-N-tert-butyl-1-(cyclohex-1-en-1-yl)methanimine*[246]

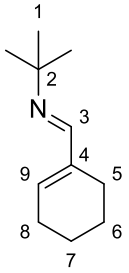



**6.37** **6.17** **6.38**

1-cyclohexene-1-carboxalehyde (3.10 ml, 27.23 mmol, 1.00 eq.), *tert*-butylamine (3.14 ml, 29.95 mmol, 1.10 eq.), and $MgSO_4$ (2.042 g, 40 mmol, 1.47 eq.) were dissolved in 28 ml of DCM. The solution was then stirred under reflux overnight.

[246] De Kimpe, N.; Stanoeva, E.; Verhe, R.; Schamp, N. *Synthesis* **1988**, 8, 587.

After completion of the reaction, the solution was filtered and the concentered under reduced pressure. The final product was used without further purification.

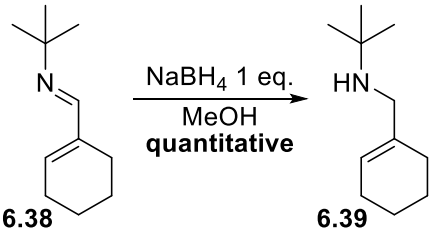



**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 7.81 (s, 1H, $C_3$**H**), 6.23 – 6.04 (m, 1H, $C_9$**H**), 2.44 – 2.12 (m, 4H, $C_5$**HH**, $C_8$**HH**), 1.78 – 1.51 (m, 4H, $C_6$**HH**, $C_7$**HH**), 1.19 (s, 9H, $C_1$**HHH**).

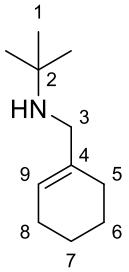
**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 158.57 (s, $C_3$), 138.64 (s, $C_9$), 137.47 (s, $C_4$), 56.40 (s, $C_2$), 29.83 (s, $C_1$), 26.07 (s, $C_8$), 23.78 (s, $C_5$), 22.59 (s, $C_7$), 22.09 (s, $C_6$).

**IR (film, $cm^{-1}$):** 2981, 2890, 1662, 1385, 1242, 1139, 1071, 957, 749.

*Synthesis of N-(cyclohex-1-en-1-ylmethyl)-2-methylpropan-2-amine*




The conjugated imine (2.707 g, 16.38 mmol, 1 eq.) was diluted in methanol 23 ml, and this solution was cooled to a temperature of 0°C. $NaBH_4$ (0.619 g, 16.38 mmol, 1 eq.) was subsequently added portionwise over 15 min. The solution was then stirred at room temperature until completion of the reaction, as shown by TLC. 20 ml of water was then slowly added. The aqueous layer was extracted two times with 15 ml of DCM. The organic layers were combined, dried over $MgSO_4$ and concentered under reduced pressure. Finally, the crude product was purified by silica gel chromatography (DCM/MeOH 99/1).



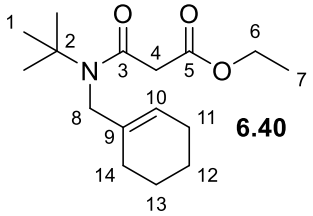

**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 5.60 – 5.54 (m, 1H, $C_9$**H**), 3.22 – 3.00 (m, 2H, $C_3$**HH**), 2.21 – 1.95 (m, 4H, $C_5$**HH**, $C_8$**HH**), 1.74 – 1.50 (m, 4H, $C_6$**HH**, $C_7$**HH**), 1.17 – 1.06 (m, 9H, $C_1$**HHH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 136.99 (s, $C_4$), 121.51 (s, $C_9$), 50.16 (s, $C_2$), 49.07 (s, $C_3$), 29.09 (s, $C_1$), 27.40 (s, $C_5$), 25.09 (s, $C_8$), 22.84 (s, $C_7$), 22.56 (s, $C_6$).

**IR (film, cm$^{-1}$):** 1650, 1638, 1578, 1393, 1256, 1104, 1024, 982.

*Synthesis of ethyl 3-(tert-butyl(cyclohex-1-en-1-ylmethyl)amino)-3-oxopropanoate*

This molecule was synthetized according to the general procedure for preparing amide from the corresponding secondary amine using DCC coupling agent (see p. 203).




**6.40**

**Yield:** 63 % - colourless oil.

**Purification:** chromatography on silica gel. Eluent: EP/AcOEt 9.5/0.5.

**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 5.65 – 5.54 (m, 1H, $C_{10}$**H**), 4.19 (q, J = 7.1 Hz, 2H, $C_6$**HH**), 3.69 (s, 2H, $C_8$**HH**), 3.34 (s, 2H, $C_4$**HH**), 2.03 – 1.98 (m, 2H, $C_{11}$**HH**), 1.86 – 1.82 (m, 2H, $C_{14}$**HH**), 1.71 – 1.51 (m, 4H, $C_{12}$**HH**, $C_{13}$**HH**), 1.43 (s, 9H, $C_1$**HHH**), 1.27 (t, J = 7.2 Hz, 3H, $C_7$**HHH**).

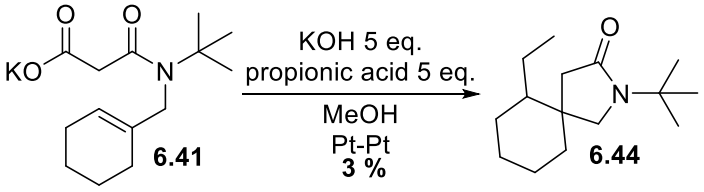
**$^{13}$C NMR (75 MHz, $CDCl_3$) δ** 168.50 (s, $C_5$), 167.51 (s, $C_3$), 134.29 (s, $C_9$), 121.73 (s, $C_{10}$), 61.15 (s, $C_6$), 57.78 (s, $C_2$), 50.75 (s, $C_8$), 43.72 (s, $C_4$), 28.34 (s, $C_1$), 26.45 (s, $C_{14}$), 24.80 (s, $C_{11}$), 22.51 (s, $C_{12}$ or $C_{13}$), 22.49 (s, $C_{12}$ or $C_{13}$), 14.13 (s, $C_7$).

**IR (film, cm$^{-1}$):** 2928, 1737, 1650, 1395, 1365, 1309, 1257, 1194, 1152, 1034, 952, 924, 849, 713, 645.

**HRMS**, m/z: calculated $[C_{16}H_{28}O_3N]^+$ : 282.20637, found: 282.20640.

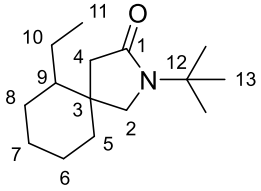
**MS/MS** (p ESI): m/z (%): 95.08610, (34); 115.03933, (4); 132.06571, (100); 188.12829, (4); 226.14388, (56); 282.20644, (8) $[M-H]^+$.

*Synthesis of 2-(tert-butyl)-6-ethyl-2-azaspiro[4.5]decan-3-one*




**6.41** **6.44**

This molecule was synthetized according to the general procedure for the electrocyclization of functionalized 2-pyrrolidinones (see p. 205).
**Purification:** chromatography on silica gel. Eluent: EP/AcOEt 9/1.

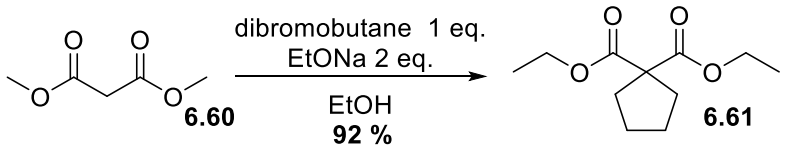



**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 3.36 – 3.02 (m, 2H, $C_2$**HH**), 2.46 – 2.16 (m, 2H, $C_4$**HH**), 2.11 – 1.49 (m, 11H, $C_5$**HH**, $C_6$**HH**, $C_7$**HH**, $C_8$**HH**, $C_9$**H**, $C_{10}$**HH**), 1.45 (s, 5H, $C_{13}$**HHH**), 1.40 (s, 4H, $C_{13}$**HHH**), 1.03 (t, J = 6.9 Hz, 3H, $C_{11}$**HHH**).

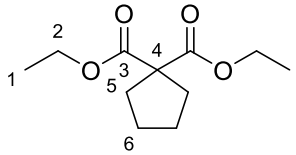
**IR (film, cm$^{-1}$):** 3345, 2973, 2926, 1653, 1379, 1160, 1128, 950, 816.

**HRMS**, m/z: calculated $[C_{15}H_{28}ON]^+$ : 238.21654, found: 238.21635.

*Synthesis of diethyl cyclopentane-1,1-dicarboxylate*




A solution of dimethyl malonate (9.40 ml, 82.2 mmol, 1.00 eq.) in 40 ml of ethanol was added dropwise to a solution of EtONa (11.1873 g, 164.4 mmol, 2.00 eq.) in 106 ml of ethanol. Consecutively, 1,4-dibromobutane (10.32 ml, 86.4 mmol, 1.05 eq.) was added dropwise. The solution was then stirred two hours at reflux. After completion of the reaction, the solution was cooled to room temperature and 40 ml of water was added. Ethanol was evaporated under reduced pressure and the aqueous layer was extracted two times with 30 ml of AcOEt. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Finally, the crude product was purified via silica gel chromatography (EP/AcOEt 9/1).



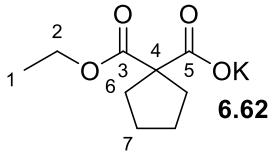

**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 4.16 (q, J = 4.16 Hz, 2H, $C_2$**HH**), 2.20 – 2.16 (m, 2H, $C_5$**HH**), 1.73 – 1.60 (m, 2H, $C_6$**HH**), 1.22 (t, J = 6.6 Hz, 3H, $C_1$**HHH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 172.70 (s, $C_3$), 61.19 (s, $C_2$), 60.32 (s, $C_4$), 34.47 (s, $C_5$), 25.45 (s, $C_6$), 14.04 (s, $C_1$).

**IR (film, cm$^{-1}$):** 2980, 2875, 1728, 1447, 1364, 1258, 1174, 1156, 1097, 1078, 1027, 862.

*Synthesis of potassium 1-(ethoxycarbonyl)cyclopentane-1-carboxylate*

This molecule was synthetized according to the general procedure for preparing potassium salt from the corresponding ester (see p. 204).




**6.62**

**Yield:** 74 % - white solid

**Purification:** filtration and wash with cold diethyl ether

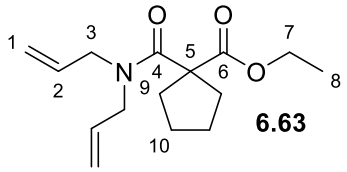
**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 4.18 (q, J = 7.1 Hz, 2H, $C_2$**HH**), 2.20 – 2.16 (m, 4H, $C_6$**HH**), 1.70 – 1.66 (m, 4H, $C_7$**HH**), 1.24 (t, J = 7.1 Hz, 3H, $C_1$**HHH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 168.46 (s, $C_5$), 167.41 (s, $C_3$), 61.24 (s, $C_2$), 52.67 (s, $C_4$), 34.54 (s, $C_6$), 25.45 (s, $C_7$), 14.10 (s, $C_1$).

**IR (film, cm$^{-1}$):** 3362, 2955, 1715, 1573, 1438, 1369, 1266, 1166, 1019.

*Synthesis of ethyl 1-(diallylcarbamoyl)cyclopentane-1-carboxylate*

This molecule was synthetized according to the general procedure for preparing amide from the corresponding secondary amine using DCC (see p. 203).




**6.63**

**Yield:** 18 % - colourless oil.

**Purification:** chromatography on silica gel. Eluent: EP/AcOEt 9/1.

**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 5.83 – 5.47 (m, 2H, $C_2$**H**), 5.16 (dt, J = 25.3, 13.1 Hz, 4H, $C_1$**HH**), 4.13 (q, J = 7.2 Hz, 2H, $C_7$**HH**), 3.85 – 3.81 (m, 4H, $C_9$**HH**), 2.38 – 2.03 (m, 4H, $C_{10}$**HH**), 1.25 (t, J = 7.2 Hz, 3H, $C_8$**HHH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 175.06 (s, $C_6$), 171.09 (s, $C_4$), 132.59 (s, $C_2$), 118.14 (s, $C_1$), 116.85 (s, $C_1$), 61.21 (s, $C_7$), 59.40 (s, $C_5$), 48.84 (s, $C_3$), 47.35 (s, $C_3$), 35.82 (s, $C_9$), 26.02 (s, $C_{10}$), 14.10 (s, $C_8$).

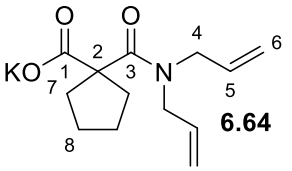
**IR (film, cm$^{-1}$):** 2925, 2852, 1732, 1679, 1651, 1435, 1407, 1371, 1251, 1164, 925, 760.

**HRMS**, m/z: calculated $[C_{15}H_{24}O_3N]^+$ : 266.17507, found: 266.17497.

**MS/MS** (p ESI): m/z (%): 67.05595, (33); 95.05102, (21); 124.07765, (36); 141.09302, (100); 187.09917, (26); 220.13636, (65); 266.17871, (23) $[M-H]^+$.

*Synthesis of potassium 1-(diallylcarbamoyl)cyclopentane-1-carboxylate*

This molecule was synthetized according to the general procedure for preparing potassium salt from the corresponding ester (see p. 204).




**6.64**

**Yield:** 69 % - white solid.

**Purification:** filtration and wash with diethyl ether.

**$^1$H NMR (300 MHz, DMSO) : δ** 5.71 – 5.68 (m, 2H, $C_5$**H**), 5.09 – 5.06 (m, 4H, $C_6$**HH**), 3.80 – 3.76 (m, 4H, $C_4$**HH**), 2.01 – 1.83 (m, 4H, $C_7$**HH**), 1.60 – 1.28 (m, 4H, $C_8$**HH**).

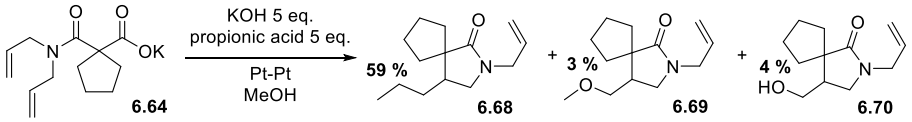
**$^{13}$C NMR (75 MHz, DMSO) : δ** 175.95 (s, $C_1$), 175.45 (s, $C_3$), 136.01 (s, $C_5$), 134.41 (s, $C_5$), 117.40 (s, $C_6$), 116.08 (s, $C_6$), 62.24 (s, $C_2$), 46.09 (s, $C_4$), 35.96 (s, $C_7$), 26.34 (s, $C_8$).

**IR (film, cm$^{-1}$):** 2250, 2124, 1053, 1025, 1006, 820, 757, 622.

**HRMS**, m/z: calculated $[C_{13}H_{19}O_3N^{39}K]^+$ : 276.09965, found: 276.09955.

**MS/MS** (p ESI): m/z (%): 96.92793, (4); 232.03178, (9); 276.09862, (100) $[M-H]^+$.

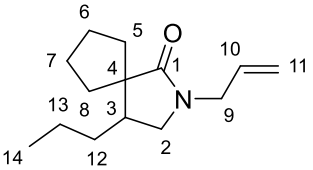
*Synthesis of 2-(prop-2-yn-1-yl)-4-propyl-2-azaspiro[4.4]nonan-1-one*




**6.64** **6.68** **6.69** **6.70**

These molecules were synthetized according to the general procedure for the electrocyclization of functionalized 2-pyrrolidinones (see page 205).

**Purification:** chromatography on silica gel. Eluent: EP/AcOEt 8/2.




**$^1$H NMR (300 MHz, $CDCl_3$) : δ** 5.73 – 5.68 (m, 1H, $C_{10}$**H**), 5.19 – 5.08 (m, 2H, $C_{11}$**HH**), 4.01 – 3.83 (m, 2H, $C_9$**HH**), 3.28 (dd, J = 9.9, 7.2 Hz, 1H, $C_2$**H**H), 2.86 (dd,

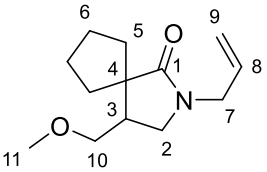
J = 9.5, 8.2 Hz, 1H, $C_2H$**H**), 2.11 – 1.19 (m, 13H, $C_3$**H**, $C_5$**HH**, $C_6$**HH**, $C_7$**HH**, $C_8$**HH**, $C_{12}$**HH**, $C_{13}$**HH**), 0.92 (t, J = 7.5 Hz, 3H, $C_{14}$**HH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 180.35 (s, $C_1$), 132.85 (s, $C_{10}$), 117.51 (s, $C_{11}$), 53.91 (s, $C_4$), 49.87 (s, $C_2$), 45.31 (s, $C_9$), 43.16 (s, $C_3$), 35.61 (s, $C_{12}$), 30.75 (s, $C_5$, $C_8$), 30.19 (s, $C_5$, $C_8$), 26.25 (s, $C_6$, $C_7$), 25.85 (s, $C_6$, $C_7$), 20.92 (s, $C_{13}$), 14.34 (s, $C_{14}$).

**IR (film, cm$^{-1}$):** 2926, 2855, 1689, 1415, 1271, 924.

**HRMS**, m/z: calculated $[C_{14}H_{24}ON]^+$ : 222.18524, found: 222.18521.

**MS/MS** (p ESI): m/z (%): 192.13830, (72); 222.18522, (100) $[M\text{-}H]^+$.



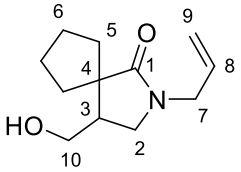

**$^1$H NMR (300 MHz, $CDCl_3$) : δ** 5.84 – 5.62 (m, 1H, $C_8$**H**), 5.24 – 5.10 (m, 2H, $C_9$**HH**), 3.90 – 3.85 (m, 2H, $C_7$**HH**), 3.81 – 3.67 (m, 1H, $C_{10}$**H**H), 3.51 – 3.21 (m, 5H, $C_2$**H**H, $C_{10}$H**H**, $C_{11}$**HHH**), 3.10 (dd, J = 9.9, 5.5 Hz, 1H, $C_2$H**H**), 2.35 – 2.24 (m, 1H, $C_3$**H**), 2.00 – 1.51 (m, 8H, $C_5$**HH**, $C_6$**HH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 181.35 (s, $C_1$), 132.60 (s, $C_8$), 117.69 (s, $C_9$), 72.19 (s, $C_{10}$), 59.01 (s, $C_{11}$), 53.33 (s, $C_4$), 47.76 (s, $C_2$), 45.54 (s, $C_7$), 42.48 (s, $C_3$), 36.70 (s, $C_5$), 29.93 (s, $C_5$), 25.75 (s, $C_6$), 25.10 (s, $C_6$).

**IR (film, cm$^{-1}$):** 2921, 2852, 1740, 1651, 1435, 1190, 1096, 929, 674.

**HRMS**, m/z: calculated $[C_{13}H_{22}O_2N]^+$ : 224.16451, found: 224.16462.

**MS/MS** (p ESI): m/z (%): 70.06573, (15); 109.10128, (10); 135.11660, (8); 164.14307, (21); 196.16925, (11); 224.16392, (100) $[M\text{-}H]^+$.

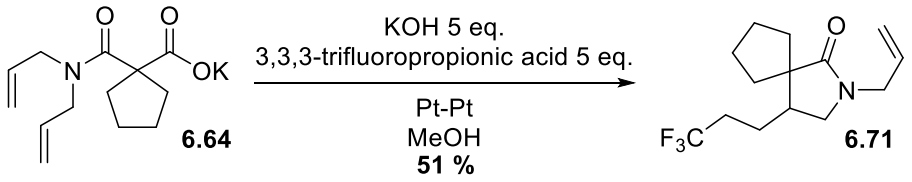



**$^1$H NMR (300 MHz, $CDCl_3$) : δ** 5.96 – 5.58 (m, 1H, $C_8$**H**), 5.27 – 5.04 (m, 2H, $C_9$**HH**), 3.97 – 3.82 (m, 2H, $C_7$**HH**), 3.74 – 3.25 (m, 3H, $C_{10}$**HH**, $C_2$**H**H), 2.97 – 2.84 (m, 1H, $C_2$H**H**), 2.62 – 2.43 (m, 1H, $C_3$**H**), 2.13 – 1.46 (m, 8H, $C_5$**HH**, $C_6$**HH**).

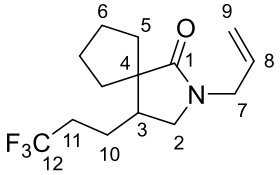
**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 179.03 (s, $C_1$), 132.06 (s, $C_8$), 118.42 (s, $C_9$), 65.68 (s, $C_{10}$), 51.25 (s, $C_4$), 49.09 (s, $C_2$), 45.64 (s, $C_7$), 37.47 (s, $C_3$), 34.12 (s, $C_5$), 33.17 (s, $C_5$), 25.61 (s, $C_6$), 24.94 (s, $C_6$).

**IR (film, cm$^{-1}$):** 3344, 2925, 2854, 1729, 1644, 1553, 1449, 1271, 1125, 927.

*Synthesis of 2-allyl-4-(3,3,3-trifluoropropyl)-2-azaspiro[4.4]nonan-1-one*




This molecule was synthetized according to the general procedure for the electrocyclization of functionalized 2-pyrrolidinones (see p. 205).
**Purification:** chromatography on silica gel. Eluent: EP/AcOEt 7/3.



**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 5.80 – 5.60 (m, 1H, $C_8$**H**), 5.25 – 5.10 (m, 2H, $C_9$**HH**), 3.99 – 3.83 (m, 2H, $C_7$**HH**), 3.39 – 3.26 (m, 1H, $C_2$**H**H), 2.89 (dd, J = 9.6, 7.8 Hz, 1H, $C_2$H**H**), 2.33 – 1.37 (m, 13H, $C_3$**H**, $C_5$**HH**, $C_6$**HH**, $C_{10}$**HH**, $C_{11}$**HH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 179.76 (s, $C_1$), 132.42 (s, $C_8$), 125.15 (s, $C_{12}$), 118.07 (s, $C_9$), 53.87 (s, $C_4$), 49.26 (s, $C_2$), 45.36 (s, $C_7$), 42.23 (s, $C_3$), 35.67 (s, $C_{11}$), 32.59 (s, $C_5$), 31.94 (s, $C_5$), 30.13 (s, $C_{10}$), 26.15 (s, $C_6$), 25.70 (s, $C_6$).

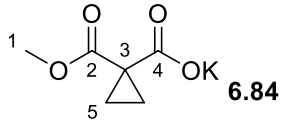
**IR (film, cm$^{-1}$):** 3332, 2925, 2854, 1747, 1683, 1442, 1417, 1257, 1147, 927.

**HRMS**, m/z: calculated $[C_{14}H_{21}ONF_3]^+$ : 276.15698, found: 276.15686.

**MS/MS** (p ESI): m/z (%): 70.06570, (7); 191.10374, (28); 248.16134, (39); 276.15595, (100) $[M-H]^+$.

*Synthesis of potassium 1-(methoxycarbonyl)cyclopropane-1-carboxylate*

This molecule was synthetized according to the general procedure for preparing potassium salt from the corresponding ester (see p. 204).




**Yield:** 80 % - white solid.

**Purification:** filtration and wash with cold diethyl ether.

**$^{1}$H NMR (300 MHz, DMSO) : δ** 3.51 (s, 3H, $C_1$**HHH**), 0.92 – 0.88 (m, 2H, $C_5$**HH**), 0.78 – 0.67 (m, 2H, $C_5$**HH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 178.69 (s, $C_4$), 175.94 (s, $C_2$), 56.28 (s, $C_1$), 36.01 (s, $C_3$), 17.45 (s, $C_5$).

**IR (film, cm$^{-1}$):** 2958, 1727, 1707, 1586, 1486, 1406, 1383, 1322, 1190, 1126, 1036, 969, 874, 814, 754, 704, 515.

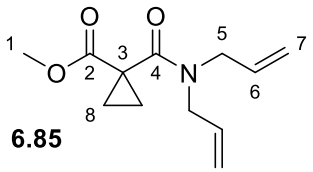
**HRMS**, m/z: calculated $[C_6H_8O_4{}^{39}K]^+$ : 183.00542, found: 183.00546.

**HRMS**, m/z: calculated $[C_6H_7O_4]^-$ : 143.03389, found: 143.03380.

**MS/MS** (p ESI): m/z (%): 71.04843, (65); 81.03277, (31); 85.02761, (100); 99.04330, (49); 143.10596, (38) $[M]^-$.

*Synthesis of methyl 1-(diallylcarbamoyl)cyclopropane-1-carboxylate*

This molecule was synthetized according to the general procedure for preparing amide from the corresponding secondary amine using oxalyl chloride (see p. 249).




**6.85**

**Yield:** 99 % - colourless oil.

**Purification:** chromatography on silica gel. Eluent: EP/AcOEt 9/1.

**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 5.83 – 5.62 (m, 2H, $C_6$**H**), 5.28 – 5.10 (m, 4H, $C_7$**HH**), 4.04 – 3.94 (m, 4H, $C_5$**HH**), 3.71 (s, 3H, $C_1$**HHH**), 1.51 – 1.44 (m, 2H, $C_8$**HH**), 1.38 – 1.31 (m, 2H, $C_8$**HH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 171.99 (s, $C_4$), 167.88 (s, $C_2$), 132.70 (s, $C_6$), 132.34 (s, $C_6$), 118.18 (s, $C_7$), 117.03 (s, $C_7$), 52.53 (s, $C_1$), 49.65 (s, $C_5$), 46.83 (s, $C_5$), 28.87 (s, $C_3$), 16.15 (s, $C_8$).

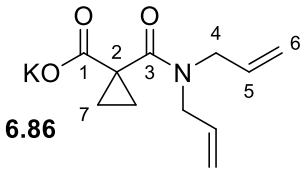
**IR (film, cm$^{-1}$):** 3079, 2958, 1726, 1640, 1455, 1435, 1413, 1308, 1217, 1193, 1155, 1127, 994, 924, 756.

**HRMS**, m/z: calculated $[C_{12}H_{18}O_3N]^+$ : 224.12812, found: 224.12816.

**MS/MS** (p ESI): m/z (%): 59.05018, (5); 95.01356, (19); 127.03949, (100); 145.04999, (27); 224.12880, (7) $[M-H]^+$.

*Synthesis of potassium 1-(diallylcarbamoyl)cyclopropane-1-carboxylate*

This molecule was synthetized according to the general procedure for preparing potassium salt from the corresponding ester (see p. 204).




**6.86**

**Yield:** 78 % - white solid.

**Purification:** filtration and wash with diethyl ether.

**$^{1}$H NMR (300 MHz, DMSO) : δ** 5.98 – 5.52 (m, 2H, $C_5$**H**), 5.38 – 4.97 (m, 4H, $C_6$**HH**), 4.03 – 3.69 (m, 4H, $C_4$**HH**), 0.94 – 0.79 (m, 2H, $C_7$**HH**), 0.64 – 0.60 (m, 2H, $C_7$**HH**).

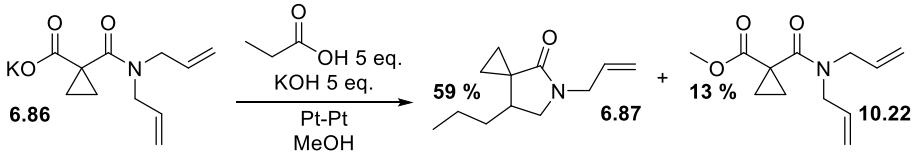
**$^{13}$C NMR (75 MHz, DMSO) : δ** 172.61 (s, $C_1$), 171.80 (s, $C_3$), 135.86 (s, $C_5$), 134.08 (s, $C_5$), 117.21 (s, $C_6$), 116.33 (s, $C_6$), 49.97 (s, $C_4$), 45.72 (s, $C_4$), 31.50 (s, $C_2$), 12.64 (s, $C_7$).

**IR (film, cm$^{-1}$):** 3075, 2980, 2916, 1620, 1585, 1461, 1409, 1373, 1308, 1190, 1132, 913, 772.

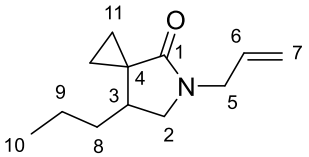
**HRMS**, m/z: calculated $[C_{11}H_{15}O_3N^{39}K]^+$ : 248.06835, found: 248.06830.

**MS/MS** (p ESI): m/z (%): 216.12053, (5); 248.06805, (100) $[M-H]^+$.

*Synthesis of 5-allyl-7-propyl-5-azaspiro[2.4]heptan-4-one*




These molecules were synthetized according to the general procedure for the electrocyclization of functionalized 2-pyrrolidinones (see p. 205).
**Purification:** chromatography on silica gel. Eluent: EP/AcOEt 8/2.



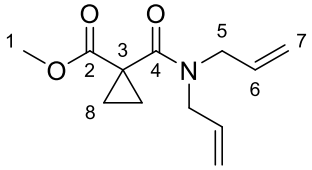

**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 5.85 – 5.65 (m, 1H, $C_6$**H**), 5.29 – 5.09 (m, 2H, $C_7$**HH**), 4.01 – 3.85 (m, 2H, $C_5$**HH**), 3.52 (dd, J = 13.3, 6.6 Hz, 1H, $C_2$**H**H), 3.02 (dd, J = 9.5, 6.6 Hz, 1H, $C_2$H**H**), 2.36 – 2.14 (m, 1H, $C_3$**H**), 1.63 – 1.04 (m, 7H, $C_8$**HH**, $C_9$**HH**, $C_{11}$**H**H, $C_{11}$H**H**, $C_{11}$H**H**), 0.89 (t, J = 6.9 Hz, 3H, $C_{10}$**HHH**), 0.64 – 0.54 (m, 1H, $C_{11}$**H**H).

**13C NMR (75 MHz, CDCl3) : δ** 176.48 (s, $C_1$), 132.34 (s, $C_6$), 117.03 (s, $C_7$), 50.67 (s, $C_2$), 45.71 (s, $C_5$), 35.60 (s, $C_3$), 34.01 (s, $C_8$), 28.86 (s, $C_4$), 20.03 (s, $C_9$), 16.15 (s, $C_{11}$), 14.23 (s, $C_{10}$), 11.74 (s, $C_{11}$), 9.45 (s, $C_{11}$).

**IR (film, $cm^{-1}$):** 2957, 2926, 2855, 1694, 1491, 1438, 1416, 1299, 1228, 923, 744.

**HRMS**, m/z: calculated $[C_{12}H_{20}ON]^+$ : 194.15394, found: 194.15401.

**MS/MS** (p ESI): m/z (%): 109.10136, (3); 124.11206, (4); 152.10679, (6); 166.15880, (6); 194.15375, (100) $[M-H]^+$.




**$^1$H NMR (300 MHz, $CDCl_3$) : δ** 5.83 – 5.62 (m, 2H, $C_6$**H**), 5.28 – 5.10 (m, 4H, $C_7$**HH**), 4.04 – 3.94 (m, 4H, $C_5$**HH**), 3.71 (s, 3H, $C_1$**HHH**), 1.51 – 1.44 (m, 2H, $C_8$**HH**), 1.38 – 1.31 (m, 2H, $C_8$**HH**).

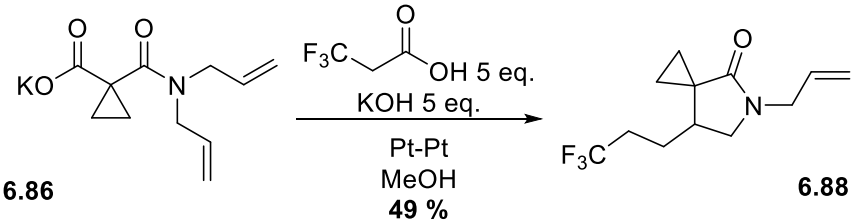
**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 171.99 (s, $C_4$), 167.88 (s, $C_2$), 132.70 (s, $C_6$), 132.34 (s, $C_6$), 118.18 (s, $C_7$), 117.03 (s, $C_7$), 52.53 (s, $C_1$), 49.65 (s, $C_5$), 46.83 (s, $C_5$), 28.87 (s, $C_3$), 16.15 (s, $C_8$).

**IR (film, $cm^{-1}$):** 3079, 2958, 1726, 1640, 1455, 1435, 1413, 1308, 1217, 1193, 1155, 1127, 994, 924, 756.

**HRMS**, m/z: calculated $[C_{12}H_{18}O_3N]^+$ : 224.12812, found: 224.12816.

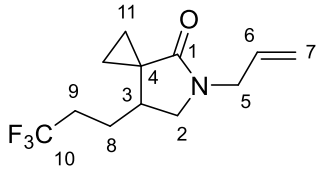
**MS/MS** (p ESI): m/z (%): 59.05018, (5); 95.01356, (19); 127.03949, (100); 145.04999, (27); 224.12880, (7) $[M-H]^+$.

*Synthesis of 5-allyl-7-(3,3,3-trifluoropropyl)-5-azaspiro[2.4]heptan-4-one*




**6.86** **6.88**

This molecule was synthetized according to the general procedure for the electrocyclization of functionalized 2-pyrrolidinones (see p. 205).
**Purification:** chromatography on silica gel. Eluent: EP/AcOEt 7/3.



**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 5.83 – 5.65 (m, 1H, $C_6$**H**), 5.33 – 5.07 (m, 2H, $C_7$**HH**), 4.05 – 3.84 (m, 2H, $C_5$**HH**), 3.56 (dd, J = 9.6, 8.2 Hz, 1H, $C_2$**H**H), 3.01 (dd, J = 16.1, 8.0 Hz, 1H, $C_2$H**H**), 2.38 – 2.26 (m, 1H, $C_3$**H**), 2.23 – 1.86 (m, 2H, $C_9$**HH**), 1.59 – 1.39 (m, 2H, $C_8$**HH**), 1.17 (ddd, J = 10.2, 6.6, 3.8 Hz, 1H, $C_{11}$**H**H), 1.06 – 0.97 (m, 1H, $C_{11}$H**H**), 0.91 – 0.79 (m, 1H, $C_{11}$H**H**), 0.72 – 0.60 (m, 1H, $C_{11}$**H**H).

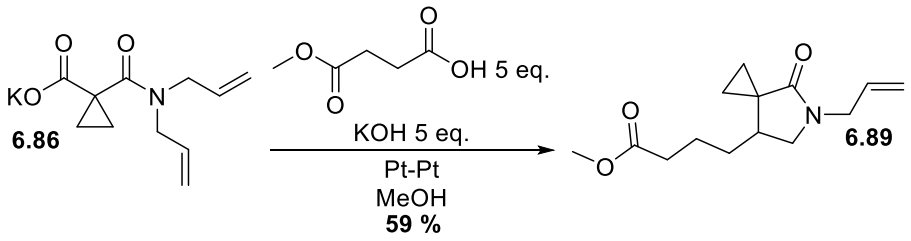
**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 175.93 (s, $C_1$), 132.42 (s, $C_6$), 127.11 (s, $C_{10}$) 118.33 (s, $C_7$), 49.79 (s, $C_2$), 45.76 (s, $C_5$), 34.83 (s, $C_3$), 31.27 (s, $C_9$), 30.88 (s, $C_4$), 24.40 (s, $C_8$), 12.61 (s, $C_{11}$), 9.29 (s, $C_{11}$).

**IR (film, cm$^{-1}$):** 2931, 1692, 1443, 1306, 1258, 1141, 1041, 927.

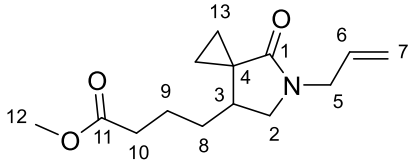
**HRMS**, m/z: calculated $[C_{12}H_{15}ONF_3]^+$ : 246.11003, found: 246.10999.

**MS/MS** (p ESI): m/z (%): 101.02375, (10); 113.02117, (9); 149.05728, (5); 190.08376, (6); 218.11508, (10); 246.10994, (100) $[M\text{-}H]^+$.

*Synthesis of methyl 4-(5-allyl-4-oxo-5-azaspiro[2.4]heptan-7-yl)butanoate*




This molecule was synthetized according to the general procedure for the electrocyclization of functionalized 2-pyrrolidinones (see p. 205).
**Purification:** chromatography on silica gel. Eluent: EP/AcOEt 7/3.



**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 5.82 – 5.65 (m, 1H, $C_6$**H**), 5.25 – 5.13 (m, 2H, $C_7$**HH**), 3.93 – 2.89 (m, 2H, $C_5$**HH**), 3.67 (s, 3H, $C_{12}$**HHH**), 3.52 (dd, J = 13.7, 6.8 Hz, 1H, $C_2$**H**H), 3.03 (dd, J = 9.6, 6.3 Hz, 1H, $C_2$H**H**), 2.37 – 2.19 (m, 3H, $C_3$**H**, $C_{10}$**HH**), 1.75 – 1.41 (m, 2H, $C_9$**HH**), 1.33 – 1.19 (m, 2H, $C_8$**HH**), 1.14 (ddd, J = 13.8, 6.0, 3.9 Hz, 1H, $C_{13}$**H**H), 0.90 – 0.86 (m, 2H, $C_{13}$H**H**), 0.59 (ddd, J = 9.4, 7.0, 3.9 Hz, 1H, $C_{13}$**H**H).

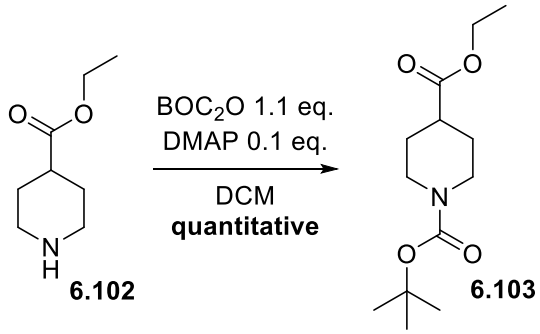
**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 176.23 (s, $C_1$), 173.68 (s, $C_{11}$), 132.69 (s, $C_6$), 117.95 (s, $C_7$), 51.61 (s, $C_{12}$), 50.41 (s, $C_2$), 45.73 (s, $C_5$), 35.70 (s, $C_3$), 33.94 (s, $C_{10}$), 31.39 (s, $C_8$), 27.23 (s, $C_4$), 22.16 (s, $C_9$), 12.02 (s, $C_{13}$), 9.46 (s, $C_{13}$).

**IR (film, cm$^{-1}$):** 2924, 2854, 1735, 1687, 1492, 1436, 1417, 1302, 1160, 929, 744.

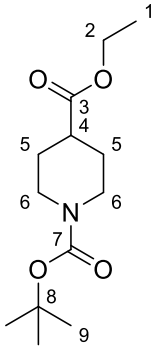
**HRMS**, m/z: calculated $[C_{14}H_{22}O_3N]^+$ : 252.15942, found: 252.15925.

**MS/MS** (p ESI): m/z (%): 202.12189, (6); 220.13234, (63); 252.15829, (100) $[M-H]^+$.

*Synthesis of 1-(tert-butyl) 4-ethyl piperidine-1,4-dicarboxylate*




Ethyl isonipeconate (5.000 g, 31.80 mmol, 1.00 eq.) was dissolved in 200 ml of methanol (0.15 mol/l). $Boc_2O$ (7.634 g, 34.98 mmol, 1.10 eq.) and DMAP (0.194 g, 1.59 mmol, 0.05 eq.) were added. The mixture was then stirred overnight. After completion of the reaction, 50 ml of an aqueous solution saturated in $NaHCO_3$ was added. The aqueous layer was extracted two times with 30 ml of DCM. Finally, the organic layers were combined, dried over $Na_2SO_4$ and concentrated under reduced pressure. The final product was used without further purifications.



**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 4.15 (q, J = 7.1 Hz, 2H, $C_2$**HH**), 4.10 – 3.92 (m, 2H, $C_6$**HH**), 2.86 – 2.82 (m, 2H, $C_6$**HH**), 2.46 – 2.42 (m, 1H, $C_4$**H**), 1.90 – 1.86 (m, 2H, $C_5$**HH**), 1.71 – 1.54 (m, 2H, $C_5$**HH**), 1.46 (s, 9H, $C_9$**HHH**), 1.26 (t, J = 7.1 Hz, 3H, $C_1$**HHH**).

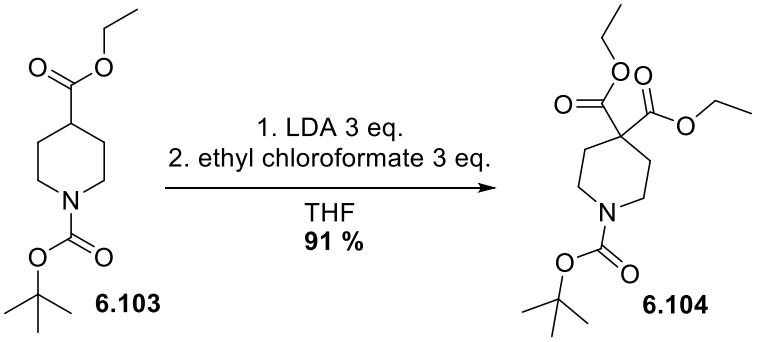
**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 174.59 (s, $C_3$), 154.70 (s, $C_7$), 79.54 (s, $C_8$), 60.48 (s, $C_2$), 43.03 (s, $C_6$), 41.15 (s, $C_4$), 28.42 (s, $C_9$), 27.97 (s, $C_5$), 14.20 (s, $C_1$).

**IR (film, cm$^{-1}$):** 2976, 2860, 1731, 1690, 1449, 1419, 1312, 1156, 1040, 868, 768.

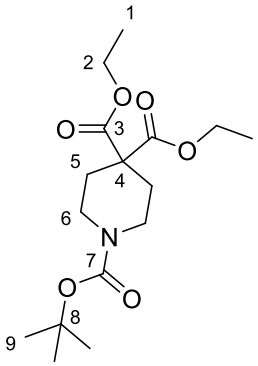
**HRMS**, m/z: calculated $[C_{13}H_{24}O_4N]^+$ : 258.16998, found: 258.16996.

**MS/MS** (p ESI): m/z (%): 84.08143, (13); 112.07607, (22); 128.07079, (28); 156.10204, (76); 184.09692, (100); 202.10749, (43); 258.27909, (5) $[M-H]^+$.

*Synthesis of 1-(tert-butyl) 4,4-diethyl piperidine-1,4,4-tricarboxylate*




The substrate **6.103** (8.183 g, 31.8 mmol, 1 eq.) was dissolved in 83 ml of THF and this solution was cooled down to a temperature of – 78°C. LDA (11.83 ml, 95.4 mmol, 3 eq.) was then added dropwise over 30 min, at – 78°C. The solution was subsequently stirred 30 min, at – 78°C. Ethyl chloroformate (9.12 ml, 95.4 mmol, 3 eq.) was subsequently added dropwise and the solution was stirred overnight. After completion of the reaction 40 ml of an aqueous solution saturated in $NH_4Cl$ was added. The aqueous layer was extracted with 30 ml of AcOEt. Finally, the crude product was purified via silica gel chromatography (EP/AcOEt 9/1).




**$^1$H NMR (300 MHz, $CDCl_3$) : δ** 4.20 (q, J = 7.1 Hz, 4H, $C_2$**HH**), 3.47 – 3.39 (m, 4H, $C_6$**HH**), 2.08 – 2.00 (m, 4H, $C_5$**HH**), 1.44 (s, 9H, $C_9$**HHH**), 1.25 (t, J = 7.1 Hz, 3H, $C_1$**HHH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 170.81 (s, $C_3$), 154.65 (s, $C_7$), 79.67 (s, $C_8$), 61.54 (s, $C_2$), 53.21 (s, $C_4$), 40.79 (s, $C_6$), 30.46 (s, $C_5$), 28.40 (s, $C_9$), 14.04 (s, $C_1$).

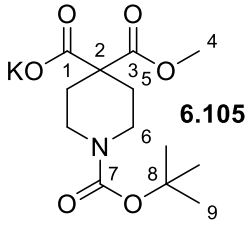
**IR (film, cm$^{-1}$):** 2978, 2937, 1730, 1693, 1421, 1365, 1307, 1245, 1130, 1067, 1022, 957, 864, 768.

**HRMS**, m/z: calculated $[C_{16}H_{28}O_6N]^+$ : 330.19111, found: 330.19120.

**MS/MS** (p ESI): m/z (%): 110.06044, (22); 156.10205, (17); 184.09695, (100); 230.13879, (54) $[M-H]^+$; 331.20913, (3).

*Synthesis of potassium 1-(tert-butoxycarbonyl)-4-(methoxycarbonyl)piperidine-4-carboxylate*

This molecule was synthetized according to the general procedure for preparing potassium salt from the corresponding ester (see page 204).




**Yield:** 72 % - white solid.

**Purification:** filtration and wash with cold diethyl ether.

**$^1$H NMR (300 MHz, DMSO) : δ** 3.68 (s, 1.48H, $C_4$**HHH**), 3.56 – 3.43 (m, 3.09H, $C_4$**HHH**, $C_6$**HH**), 3.40 – 3.27 (m, 2.43H, $C_6$**HH**), 1.98 – 1.85 (m, 1.13H, $C_5$**HH**), 1.81 – 1.72 (m, 2.87H, $C_5$**HH**), 1.38 (s, 2.66H, $C_9$**HHH**), 1.37 (s, 6.34H, $C_9$**HHH**).

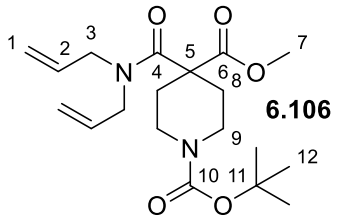
**$^{13}$C NMR (75 MHz, DMSO) : δ** 174.81 (s, $C_1$), 171.19 (s, $C_3$), 171.11 (s, $C_3$), 154.66 (s, $C_7$), 78.67 (s, $C_8$), 55.46 (s, $C_6$), 51.36 (s, $C_4$), 40.72 (s, $C_2$), 28.57 (s, $C_5$), 28.49 (s, $C_9$).

**IR (film, cm$^{-1}$):** 2980, 2859, 1688, 1596, 1423, 1364, 1167, 1135, 1068, 948, 769.

**MS/MS** (p ESI): m/z (%): 96.92825, (9); 208.11576, (9); 239.10837, (12); 284.05306, (27) $[M-H]^+$; 340.11580, (100).

*Synthesis of 1-(tert-butyl) 4-methyl 4-(diallylcarbamoyl)piperidine-1,4-dicarboxylate*

This molecule was synthetized according to the general procedure for preparing amide from the corresponding secondary amine using oxalyl chloride (see p. 249).



**Yield:** 60 % - colourless oil.

**Purification:** chromatography on silica gel. Eluent: EP/AcOEt 9/1.

**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 5.73 – 5.46 (m, 2H, $C_2$**H**), 5.22 – 4.96 (m, 4H, $C_1$**HH**), 3.93 – 3.68 (m, 4H, $C_3$**HH**), 3.66 (s, 3H, $C_7$**HHH**), 3.60 – 3.28 (m, 4H, $C_9$**HH**), 2.10 – 1.83 (m, 4H, $C_8$**HH**), 1.38 (s, 9H, $C_{12}$**HHH**).

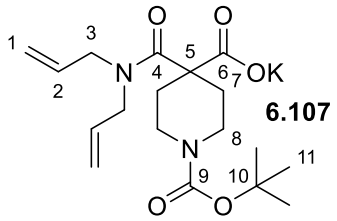
**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 173.71 (s, $C_6$), 169.54 (s, $C_4$), 154.67 (s, $C_{10}$), 132.39 (s, $C_2$), 117.37 (s, $C_1$), 79.58 (s, $C_{11}$), 52.61 (s, $C_3$), 51.75 (s, $C_7$), 48.53 (s, $C_9$), 48.02 (s, $C_9$), 39.88 (s, $C_5$),31.83 (s, $C_8$), 31.44 (s, $C_8$), 28.42 (s, $C_{12}$).

**IR (film, $cm^{-1}$):** 2976, 2926, 1731, 1693, 1647, 1407, 1249, 1171, 1146, 1070, 984, 925.

**HRMS**, m/z: calculated $[C_{19}H_{30}O_5N_2{}^{23}Na]^+$ : 389.20469, found: 389.20515.

*Synthesis of potassium 1-(tert-butoxycarbonyl)-4-(diallylcarbamoyl)piperidine-4-carboxylate*

This molecule was synthetized according to the general procedure for preparing potassium salt from the corresponding ester (see p. 204).




**6.107**

**Yield:** 55 % - white solid.

**Purification:** filtration and wash with cold diethyl ether.

**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 5.73 – 5.49 (m, 2H, $C_2$**H**), 5.27 – 4.90 (m, 4H, $C_1$**HH**), 3.90 – 3.68 (m, 4H, $C_3$**HH**), 3.59 – 3.42 (m, 2H, $C_8$**HH**), 3.27 – 3.10 (m, 2H, $C_8$**HH**), 2.02 – 1.70 (m, 4H, $C_7$**HH**), 1.33 (s, 9H, $C_{11}$**HHH**).

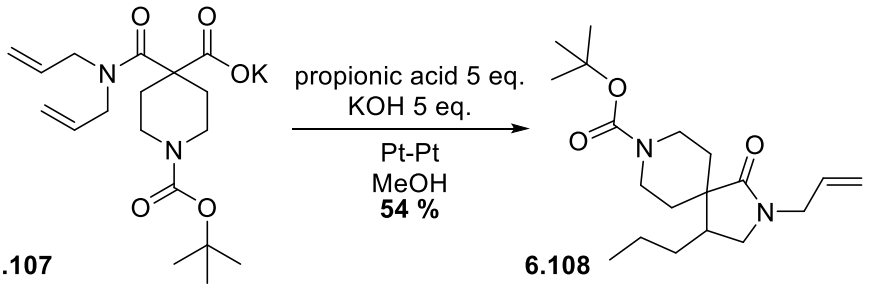
**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 177.06 (s, $C_6$), 172.34 (s, $C_4$), 154.71 (s, $C_9$), 132.70 (s, $C_2$), 118.20 (s, $C_1$), 116.85 (s, $C_1$), 79.47 (s, $C_{10}$), 52.96 (s, $C_5$), 49.36 (s, $C_3$), 47.72 (s, $C_3$), 40.98 (s, $C_8$), 40.13 (s, $C_8$), 31.94 (s, $C_7$), 28.36 (s, $C_{11}$).

**IR (film, $cm^{-1}$):** 3415, 2977, 2936, 1687, 1644, 1415, 1366, 1283, 1249, 1173, 1149, 926.

**HRMS**, m/z: calculated $[C18H28O5N_2{}^{39}K]^+$ : 391.16298, found: 391.16355.

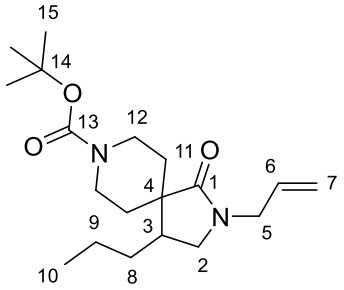
**MS/MS** (p ESI): m/z (%): 96.92869, (11); 212.97291, (16); 290.15691, (100); 390.30036, (21) [M].

*Synthesis of tert-butyl 2-allyl-1-oxo-4-propyl-2,8-diazaspiro[4.5]decane-8-carboxylate*




**6.107** **6.108**

This molecule was synthetized according to the general procedure for the electrocyclization of functionalized 2-pyrrolidinones (see p. 205).
**Purification:** chromatography on silica gel. Eluent: EP/AcOEt 7/3.



**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 5.80 – 5.61 (m, 1H, $C_6$**H**), 5.21 – 5.10 (m, 2H, $C_7$**HH**), 4.05 – 3.36 (m, 6H, $C_5$**HH**, $C_{12}$**HH**), 3.36 – 3.25 (m, 1H, $C_2$**H**H), 2.96 – 2.89 (m, 1H, $C_2$H**H**), 2.02 – 1.85 (m, 1H, $C_3$**H**), 1.66 – 1.10 (m, 17H, $C_8$**HH**, $C_9$**HH**, $C_{11}$**HH**, $C_{15}$**HHH**), 0.91 (t, J = 6.9 Hz, 3H, $C_{10}$**HHH**).

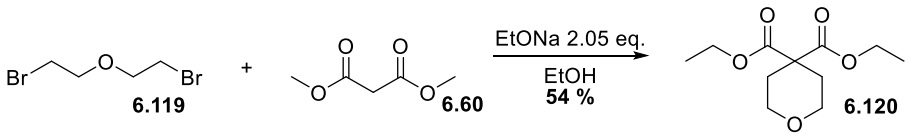
**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 177.97 (s, $C_1$), 154.98 (s, $C_{13}$), 132.49 (s, $C_6$), 117.88 (s, $C_7$), 79.26 (s, $C_{14}$), 48.84 (s, $C_2$), 45.05 (s, $C_5$), 43.90 (s, $C_3$), 40.10 (s, $C_{12}$), 30.32 (s, $C_{11}$), 28.47 (s, $C_{15}$), 28.32 (s, $C_8$), 20.92 (s, $C_9$), 14.23 (s, $C_{10}$).

**IR (film, cm$^{-1}$):** 2965, 2927, 2867, 1683, 1416, 1365, 1244, 1175, 1153, 1085, 1002, 926, 867, 769, 544.

**HRMS**, m/z: calculated $[C_{19}H_{33}O_3N_2]^+$ : 337.24857, found: 337.24841.

**MS/MS** (p ESI): m/z (%): 220.17028, (5); 263.17602, (100); 337.21330, (5) $[M-H]^+$.

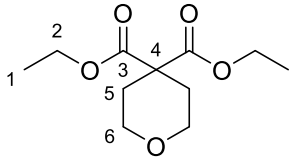
*Synthesis of diethyl tetrahydro-4H-pyran-4,4-dicarboxylate*




**6.119** **6.60** **6.120**

A solution of sodium ethoxide in ethanol 20% w/w (24.1 ml, 61.5 mmol, 2.05 eq.)

was diluted in 29.0 ml of ethanol. Dimethyl malonate was subsequently added dropwise to this solution and the mixture was stirred 20 min. Bis(2-bromoethyl)-ether (4.15 ml, 33 mmol, 1.1 eq.) was added dropwise to this solution and this mixture was then stirred overnight at reflux. After completion of the reaction, 40 ml of water was added, and the pH of the solution was adjusted to a pH of 3. The solution was then extracted, three times, with 30 ml of ethyl acetate. The organic layers were combined, dried over $MgSO_4$ and concentrated under reduced pressure. Finally, the crude product was purified by silica gel chromatography (EP/AcOEt 30/1).



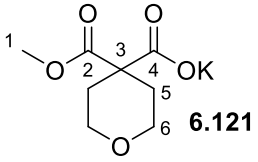

**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 4.22 (q, J = 7.2 Hz, 4H, $C_2$**HH**), 3.70 (t, J = 5.4 Hz, 4H, $C_6$**HH**), 2.12 (t, J = 5.4 Hz, 4H, $C_5$**HH**), 1.27 (t, J = 7.2 Hz, 6H, $C_1$**HHH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 170.14 (s, $C_3$), 63.98 (s, $C_6$), 60.75 (s, $C_2$), 51.53 (s, $C_4$), 30.20 (s, $C_5$), 13.25 (s, $C_1$).

**IR (film, cm$^{-1}$):** 3458, 2969, 2848, 1728, 1590, 1445, 1367, 1301, 1239, 1131, 1104, 1137, 1073, 1030, 964, 862, 548.

### *Synthesis of potassium 4-(methoxycarbonyl)tetrahydro-2H-pyran-4-carboxylate*

This molecule was synthetized according to the general procedure for preparing potassium salt from the corresponding ester (see p. 204).




**6.121**

**Yield:** 75 % - white solid.

**Purification:** filtration and wash with cold diethyl ether.

**$^{1}$H NMR (300 MHz, DMSO) : δ** 3.69 (s, 0.80H, $C_1$**HHH**), 3.67 – 3.53 (m, 2.11H, $C_6$**HH**), 3.52 (s, 2.20H, $C_1$**HHH**), 3.39 – 3.22 (m, 1.89H, $C_6$**HH**), 2.02 – 1.73 (m, 4H, $C_5$**HH**).

**$^{13}$C NMR (75 MHz, DMSO) : δ** 174.92 (s, $C_4$), 171.75 (s, $C_2$), 171.15 (s, $C_2$), 65.62 (s, $C_6$), 64.23 (s, $C_6$), 54.59 (s, $C_3$), 53.22 (s, $C_1$), 51.37 (s, $C_1$), 32.75 (s, $C_5$), 31.23 (s, $C_5$).

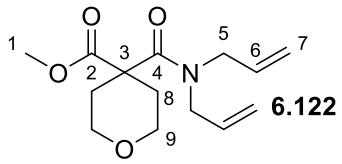
**IR (film, cm$^{-1}$):** 3496, 2958, 2848, 1712, 1599, 1446, 1365, 1307, 1220, 1194, 1101, 1071, 1026, 957, 837, 698, 542.

**HRMS**, m/z: calculated $[C_8H_{11}O_5]^-$ : 187.06010, found: 187.05977.

**MS/MS** (p ESI): m/z (%): 113.05909, (15); 143.06978, (100); 187.05998, (3) $[M]^-$.

*Synthesis of methyl 4-(diallylcarbamoyl)tetrahydro-2H-pyran-4-carboxylate*

This molecule was synthetized according to the general procedure for preparing amide from the corresponding secondary amine using oxalyl chloride (see p. 249).




**6.122**

**Yield:** 64 % - colourless oil.

**Purification:** chromatography on silica gel. Eluent: EP/AcOEt 9/1.

**$^1$H NMR (300 MHz, $CDCl_3$) : δ** 5.88 – 5.49 (m, 2H, $C_6$**H**), 5.35 – 4.99 (m, 4H, $C_7$**HH**), 3.88 – 3.66 (m, 7H, $C_1$**HHH**, $C_9$**HH**), 2.29 – 1.94 (m, 4H, $C_8$**HH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 173.69 (s, $C_2$), 169.53 (s, $C_4$), 132.44 (s, $C_6$), 117.02 (s, $C_7$), 64.34 (s, $C_9$), 64.22 (s, $C_9$), 52.59 (s, $C_1$), 51.06 (s, $C_3$), 32.28 (s, $C_8$), 30.78 (s, $C_8$).

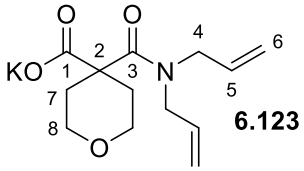
**IR (film, $cm^{-1}$):** 2955, 2848, 1786, 1730, 1639, 1434, 1407, 1301, 1247, 1196, 1107, 992, 930, 840, 545.

**HRMS**, m/z: calculated $[C_{14}H_{22}O_4N]^+$ : 268.15433, found: 268.15418.

**MS/MS** (p ESI): m/z (%): 113.05962, (100); 124.07543, (27); 143.06980, (8); 178.12206, (6); 236.12720, (10); 268.15322, (5) $[M-H]^+$.

*Synthesis of potassium 4-(diallylcarbamoyl)tetrahydro-2H-pyran-4-carboxylate*

This molecule was synthetized according to the general procedure for preparing potassium salt from the corresponding ester (see p. 204).




**6.123**

**Yield:** 56 % - white solid.

**Purification:** filtration and wash with diethyl ether.

**$^{1}$H NMR (300 MHz, DMSO) : δ** 5.86 – 5.54 (m, 2H, $C_5$**H**), 5.30 – 4.94 (m, 4H, $C_6$**HH**), 4.05 – 3.29 (m, 8H, $C_4$**HH**, $C_8$**HH**), 2.10 – 1.57 (m, 4H, $C_7$**HH**).

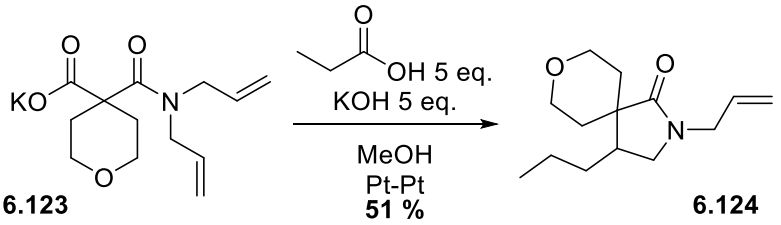
**$^{13}$C NMR (75 MHz, DMSO) : δ** 174.58 (s, $C_1$), 173.99 (s, $C_3$), 133.55 (s, $C_5$), 116.21 (s, $C_6$), 65.09 (s, $C_8$), 63.80 (s, $C_8$), 53.11 (s, $C_2$), 52.96 (s, $C_4$), 50.75 (s, $C_4$), 33.92 (s, $C_7$), 32.39 (s, $C_7$).

**IR (film, cm$^{-1}$):** 2959, 2845, 1592, 1577, 1407, 1362, 1320, 1227, 1199, 1102, 1019, 920, 838, 788, 538.

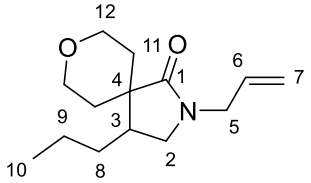
**HRMS**, m/z: calculated $[C_{13}H_{18}O_4N]^-$ : 252.12303, found: 252.12342.

**MS/MS** (p ESI): m/z (%): 96.08011, (64); 167.09365, (25); 208.13304, (100); 252.12332, (2) $[M]^-$.

*Synthesis of 2-allyl-4-propyl-8-oxa-2-azaspiro[4.5]decan-1-one*




This molecule was synthetized according to the general procedure for the electrocyclization of functionalized 2-pyrrolidinones (see p. 205).
**Purification:** chromatography on silica gel. Eluent: EP/AcOEt 7/3.




**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 5.82 – 5.59 (m, 1H, $C_6$**H**), 5.26 – 5.06 (m, 2H, $C_7$**HH**), 4.35 – 4.25 (m, 1H, $C_{12}$**H**H), 4.06 – 3.91 (m, 1H, $C_{12}$**H**H), 3.87 (d, J = 6.1 Hz, 2H, $C_5$**HH**), 3.80 – 3.62 (m, 2H, $C_{12}$**HH**), 3.41 – 3.22 (m, 1H, $C_2$**H**H), 2.99 – 2.90 (m, 1H, $C_2$H**H**), 2.06 – 1.88 (m, 1H, $C_3$**H**), 1.76 – 1.51 (m, 4H, $C_{11}$**HH**), 1.49 – 1.32 (m, 2H, $C_9$**HH**), 1.31 – 1.15 (m, 2H, $C_8$**HH**), 0.94 (t, J = 6.8 Hz, 3H, $C_{10}$**HHH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 178.14 (s, $C_1$), 132.55 (s, $C_6$), 117.88 (s, $C_7$), 64.13 (s, $C_{12}$), 63.70 (s, $C_{12}$), 48.72 (s, $C_2$), 45.09 (s, $C_5$), 43.24 (s, $C_4$), 42.84 (s, $C_3$), 32.77 (s, $C_8$), 30.34 (s, $C_{11}$), 28.12 (s, $C_{11}$), 20.90 (s, $C_9$), 14.24 (s, $C_{10}$).

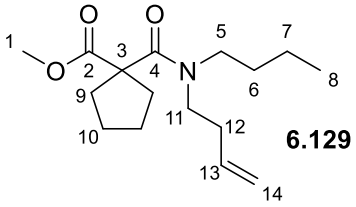
**IR (film, cm$^{-1}$):** 2954, 2871, 1682, 1438, 1245, 1102, 1014, 927.

**HRMS**, m/z: calculated $[C_{14}H_{24}O_2N]^+$ : 238.18016, found: 238.18016.

**MS/MS** (p ESI): m/z (%):81.07020, (9); 95.08566, (7); 220.16877, (11); 238.17911, (100) $[M-H]^+$.

*Synthesis of methyl 1-(but-3-en-1-yl(butyl)carbamoyl)cyclopentane-1-carboxylate*

This molecule was synthetized according to the general procedure for preparing amide from the corresponding secondary amine using oxalyl chloride (see p. 249).




**6.129**

**Yield:** 59 % - colourless oil.

**Purification:** chromatography on silica gel. Eluent: EP/AcOEt 9/1.

**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 5.85 – 5.60 (m, 1H, $C_{13}$**H**), 5.19 – 4.93 (m, 2H, $C_{14}$**HH**), 3.73 (s, 1.15H, $C_1$**HHH**), 3.70 (s, 0.70H, $C_1$**HHH**), 3.69 (s, 1.15H, $C_1$**HHH**), 3.43 – 3.00 (m, 4H, $C_5$**HH**, $C_{11}$**HH**), 2.37 – 2.05 (m, 6H, $C_9$**HH**, $C_{12}$**HH**), 1.81 – 1.18 (m, 8H, $C_6$**HH**, $C_7$**HH**, $C_{10}$**HH**), 0.93 (t, J = 7.2 Hz, 3H, $C_8$**HHH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 175.32 (s, $C_2$), 171.02 (s, $C_4$), 135.65 (s, $C_{13}$), 134.27 (s, $C_{13}$), 117.38 (s, $C_{14}$), 116.42 (s, $C_{14}$), 61.08 (s, $C_3$), 59.48 (s, $C_3$), 52.82 (s, $C_1$), 52.34 (s, $C_1$), 47.01 (s, $C_{11}$), 46.24 (s, $C_{11}$), 45.23 (s, $C_5$), 44.83 (s, $C_5$), 35.83 (s, $C_9$), 35.79 (s, $C_9$), 34.27 (s, $C_9$), 34.11 (s, $C_9$), 32.45 (s, $C_{12}$), 31.51 (s, $C_{12}$), 30.14 (s, $C_6$), 28.96 (s, $C_6$), 26.04 (s, $C_{10}$), 25.52 (s, $C_{10}$), 20.22 (s, $C_7$), 20.16 (s, $C_7$), 13.89 (s, $C_8$).

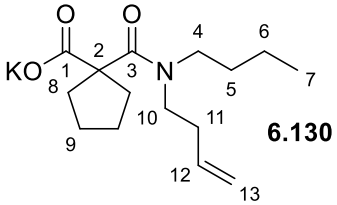
**IR (film, $cm^{-1}$):** 2950, 2851, 1735, 1682, 1632, 1458, 1205, 1107, 1024, 987.

**HRMS**, m/z: calculated $[C_{16}H_{28}O_3N]^+$ : 282.20637, found: 282.20626.

**MS/MS** (p ESI): m/z (%): 86.09670, (34); 95.04933, (26); 127.07503, (100); 154.12205, (44); 250.17918, (19); 282.20522, (6) $[M-H]^+$.

*Synthesis of potassium 1-(but-3-en-1-yl(butyl)carbamoyl)cyclopentane-1-carboxylate*

This molecule was synthetized according to the general procedure for preparing potassium salt from the corresponding ester (see p. 204).




**6.130**

Yield: 62 % - white solid.

Purification: filtration and wash with diethyl ether.

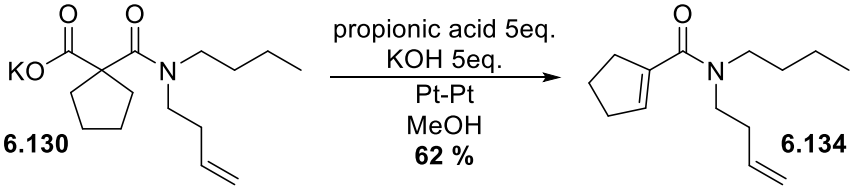
**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 5.87 – 5.79 (m, 1H, $C_{12}$**H**), 5.20 – 4.97 (m, 2H, $C_{13}$**HH**), 3.58 – 3.09 (m, 4H, $C_4$**HH**, $C_{10}$**HH**), 2.65 – 2.55 (m, 2H, $C_8$**HH**), 2.55 – 2.39 (m, 2H, $C_8$**HH**), 2.39 – 2.23 (m, 2H, $C_{11}$**HH**), 1.99 – 1.82 (m, 4H, $C_9$**HH**), 1.61 – 1.45 (m, 2H, $C_5$**HH**), 1.44 – 1.14 (m, 2H, $C_6$**HH**), 0.90 (t, *J* = 7.5 Hz, 3H, $C_7$**HHH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 180.99 (s, $C_1$), 169.98 (s, $C_3$), 135.18 (s, $C_{12}$), 116.96 (s, $C_{13}$), 58.73 (s, $C_2$), 47.84 (s, $C_{10}$), 45.66 (s, $C_4$), 39.78 (s, $C_8$), 39.20 (s, $C_8$), 32.84 (s, $C_{11}$), 30.12 (s, $C_5$), 26.14 (s, $C_9$), 25.39 (s, $C_9$), 22.93 (s, $C_6$), 13.83 (s, $C_7$).

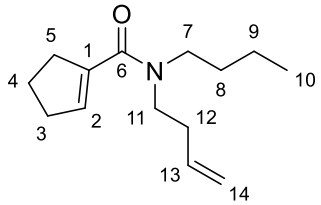
**IR (film, cm$^{-1}$):** 2953, 2841, 17365, 1684, 1632, 1428, 1105, 1014, 997.

**HRMS, m/z:** calculated $[C_{15}H_{25}O_3N^{39}K]^+$ : 306.14660, found: 306.14661.

*Synthesis of N-(but-3-en-1-yl)-N-butylcyclopent-1-ene-1-carboxamide*




This molecule was synthetized according to the general procedure for the electrocyclization of functionalized 2-pyrrolidinones (see p. 205).
**Purification:** chromatography on silica gel. Eluent: EP/AcOEt 8/2.

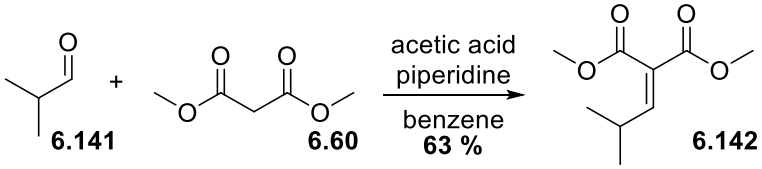



**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 5.92 – 5.60 (m, 2H, $C_2$**H**, $C_{13}$**H**), 5.15 – 4.97 (m, 2H, $C_{14}$**HH**), 3.57 – 3.17 (m, 4H, $C_7$**HH**, $C_{11}$**HH**), 2.65 – 2.55 (m, 2H, $C_5$**HH**), 2.56 – 2.41 (m, 2H, $C_3$**HH**), 2.39 – 2.23 (m, 2H, $C_8$**HH**), 2.05 – 1.84 (m, 2H, $C_3$**HH**), 1.61 – 1.44 (m, 2H, $C_{12}$**HH**), 1.38 – 1.20 (m, 2H, $C_9$**HH**), 0.90 (t, J = 7.2 Hz, 3H, $C_{10}$**HHH**).

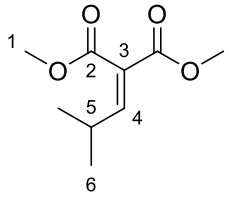
**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 169.98 (s, $C_6$), 139.18 (s, $C_2$), 136.02 (s, $C_1$), 130.96 (s, $C_{13}$), 117.11 (s, $C_{14}$), 48.68 (s, $C_{11}$), 44.34 (s, $C_7$), 34.78 (s, $C_5$), 33.20 (s, $C_3$), 31.95 (s, $C_8$), 31.65 (s, $C_{12}$), 22.93 (s, $C_4$), 20.21 (s, $C_9$), 13.83 (s, $C_{10}$).

**IR (film, cm$^{-1}$):** 2852, 1682, 1635, 1428, 1200, 1103, 1014, 907.

*Synthesis of dimethyl 2-(2-methylpropylidene)malonate*




Isobutyraldehyde (2.5238 g, 35 mmol, 1 eq.), dimethyl malonate (4.6238 g, 35 mmol, 1 eq.), 0.1 ml of acetic acid and 0.2 ml of piperidine were diluted in 15 ml of benzene. The mixture was stirred overnight, at reflux, with azeotropic removal of water. The benzene was removed under reduced pressure. Finally, the crude product was purified via silica gel chromatography (EP/AcOEt 9/1).

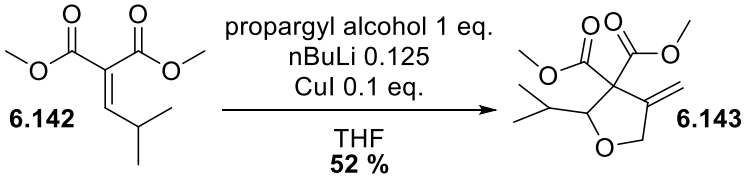



**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 6.82 (d, J = 10.6 Hz, 1H, $C_4$**H**), 3.82 (s, 3H, $C_1$**HHH**), 3.77 (s, 3H, $C_1$**HHH**), 2.77 – 2.58 (m, 1H, $C_5$**H**), 1.07 (d, J = 6.6 Hz, 6H, $C_6$**HHH**).

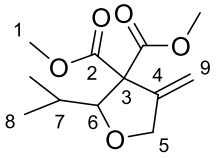
**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 166.04 (s, $C_2$), 164.55 (s, $C_2$), 155.89 (s, $C_4$), 125.76 (s, $C_3$), 52.34 (s, $C_1$), 52.26 (s, $C_1$), 29.53 (s, $C_5$), 21.80 (s, $C_6$).

**IR (film, cm$^{-1}$):** 2959, 1724, 1645, 1436, 1366, 1325, 1251, 1220, 1148, 1057, 997, 929, 834, 764, 723.

*Synthesis of dimethyl 2-isopropyl-4-methylenedihydrofuran-3,3(2H)-dicarboxylate*




Propargyl alcohol (2.160 ml, 37.10 mmol, 1.000 eq.) was diluted in 75 ml of THF (0.5 mol/l) and the mixture was cooled to a temperature of -78 °C. *N*-Butyl lithium 2.5 N in hexanes (1.856 ml, 4.64 mmol, 0.125 eq.) was then added dropwise. The mixture was subsequently stirred at room temperature 20 minutes. This solution was consecutively added dropwise to a solution of the Michael acceptor **6.142** (3.455 g, 18.550 mmol, 0.500 eq.) in 37.1 ml of THF (0.5 mol/l). Afterwards, CuI was added (0.710 g, 3.71 mmol, 0.100 eq.) to the solution. The mixture was stirred three hours; the solution was filtered over a silica pad and concentered. The crude product was purified via silica gel chromatography (EP/AcOEt 9/1).

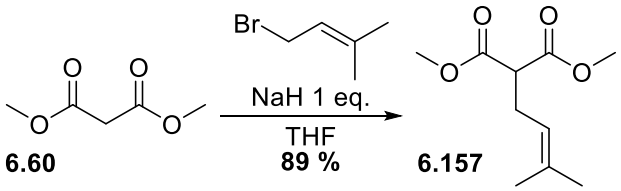



**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 5.32 – 5.26 (m, 1H, $C_9$**H**H), 5.16 – 5.11 (m, 1H, $C_9$H**H**), 4.62 – 4.53 (m, 1H, $C_5$**H**H), 4.38 – 4.30 (m, 1H, $C_5$H**H**), 4.14 (d, J = 7.8 Hz, 1H, $C_6$**H**), 3.80 (s, 3H, $C_1$**HHH**), 3.75 (s, 3H, $C_1$**HHH**), 1.81 – 1.64 (m, 1H, $C_7$**H**), 1.03 (d, J = 6.5 Hz, 3H, $C_8$**HHH**), 0.97 (d, J = 6.7 Hz, 3H, $C_8$**HHH**).

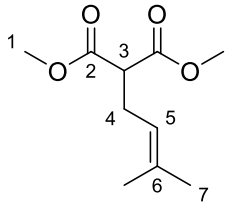
**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 168.90 (s, $C_2$), 168.71 (s, $C_2$), 147.49 (s, $C_4$), 108.13 (s, $C_9$), 90.12 (s, $C_6$), 70.61 (s, $C_5$), 66.09 (s, $C_3$), 52.80 (s, $C_1$), 52.58 (s, $C_1$), 30.62 (s, $C_7$), 19.92 (s, $C_8$), 19.57 (s, $C_8$).

**IR (film, $cm^{-1}$):** 2955, 1730, 1435, 1336, 1262, 1226, 1154, 1123, 1090, 1054, 955, 908, 779, 620, 507.

*Synthesis of dimethyl 2-(3-methylbut-2-en-1-yl)malonate*




Dimethyl malonate (6.5162 g, 34.62 mmol, 1 eq.) was dissolved in 28 ml of THF (1.25mol/l). The mixture was then cooled to a temperature of 0°C. Additionally, NaH 60% (1.3848 g, 34.62 mmol, 1 eq.) was added to le solution, and the mixture was stirred, at room temperature, for 30 minutes. Consecutively, 3,3-dimethylallyl bromide (5.1600 g, 34.62 mmol, 1 eq.) was added dropwise, and the mixture was stirred, for two hours, until completion of the reaction. The reaction was quenched by careful addition of water and the solution was extracted two times with 20 ml of diethyl ether. Finally, the organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Finally, the crude product was purified via silica gel chromatography (AcOEt/EP 0.5/10.0).

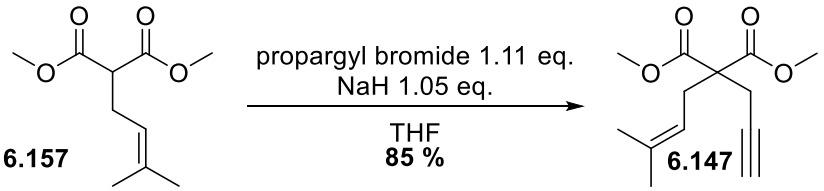



**$^{1}$H NMR (300 MHz, $CDCl_3$) :** δ 5.10 – 4.99 (m, 1H, $C_5$**H**), 3.73 (s, 6H, $C_1$**HHH**), 3.36 (t, J = 7.7 Hz, 1H, $C_3$**H**), 2.67 – 2.54 (m, 2H, $C_4$**HH**), 1.68 (s, 3H, $C_7$**HHH**), 1.63 (s, 3H, $C_7$**HHH**).

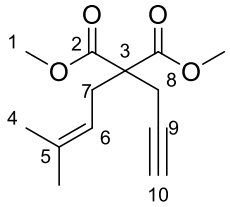
**$^{13}$C NMR (75 MHz, $CDCl_3$) δ** 169.61 (s, $C_2$), 135.13 (s, $C_6$), 119.44 (s, $C_5$), 52.45 (s, $C_1$), 51.92 (s, $C_3$), 27.63 (s, $C_4$), 25.76 (s, $C_7$), 17.72 (s, $C_7$).

**IR (film, $cm^{-1}$):** 2958, 2924, 2852, 1737, 1437, 1340, 1275, 1245, 1207, 1152, 1041.

*Synthesis of dimethyl 2-(3-methylbut-2-en-1-yl)-2-(prop-2-yn-1-yl)malonate*




NaH (1.2384 g, 30.96 mmol, 1.05 eq.) was dissolved in 82 ml of THF (0.36 mol/l). The mixture was then cooled to a temperature of 0°C. Dimethyl 2-(3-methylbut-2-en-1-yl)malonate (5.9050 g, 29.49 mmol, 1 eq.) was subsequently added dropwise to the reaction mixture. After addition, the ice bath was removed, and the solution was stirred, for one hour, until hydrogen was totally released. Subsequently, the solution was cooled to a temperature of 0°C. Propargyl bromide (3.65 ml, 32.73 mmol, 1.11 eq.) was then added dropwise to the solution. The solution was stirred for 30 minutes and the ice bath was then removed. Finally, the mixture was stirred overnight, and the reaction was quenched via a slow addition of water. The solution was consecutively concentrated under reduced pressure and extracted three times with 20 ml of diethyl ether. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified via silica gel chromatography (EP/AcOEt 9/1).

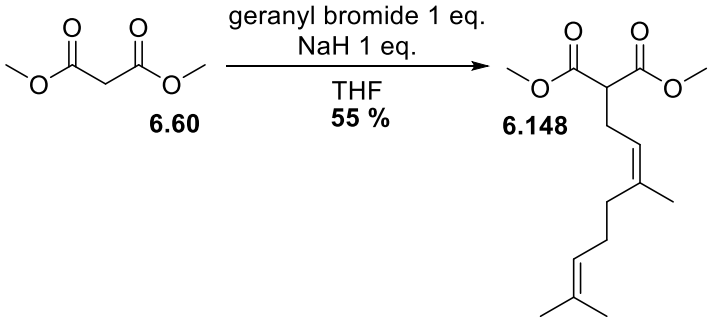



**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 4.95 – 4.84 (m, 1H, $C_6$**H**), 3.73 (s, 6H, $C_1$**HHH**), 2.82 – 2.73 (m, 4H, $C_7$**HH**, $C_8$**HH**), 2.00 (t, J = 2.7 Hz, 1H, $C_{10}$**H**), 1.70 (s, 3H, $C_4$**HHH**), 1.65 (s, 3H, $C_4$**HHH**).

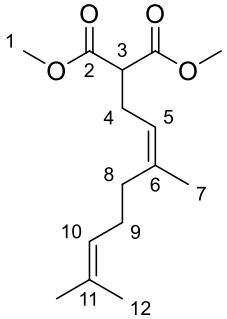
**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 170.48 (s, $C_2$), 136.95 (s, $C_5$), 116.93 (s, $C_6$), 79.27 (s, $C_9$), 71.16 (s, $C_{10}$), 57.15 (s, $C_3$), 52.69 (s, $C_1$), 30.77 (s, $C_7$), 26.05 (s, $C_4$), 22.51 (s, $C_8$), 17.92 (s, $C_4$).

**IR (film, $cm^{-1}$):** 3344, 2971, 2933, 1648, 1466, 1379, 1305, 1160, 1128, 950, 816, 628.

*Synthesis of dimethyl (Z)-2-(3,7-dimethylocta-2,6-dien-1-yl)malonate*




Dimethyl malonate (0.9468 g, 5.04 mmol, 1 eq.) was dissolved in 5 ml of THF (1.25 mol/l). The mixture was then placed at a temperature of 0°C, and NaH (0.2016 g, 5.04 mmol, 1 eq.) was subsequently added. The solution was stirred 30 minutes at room temperature. Consecutively, geranyl bromide (1.0940 g, 5.04 mmol, 1 eq.) was introduced dropwise. The mixture was then stirred, two hours, at room temperature, and the course of the reaction was followed via TLC. After completion of the reaction, 5 ml of water was slowly added to the solution and the organic layer was washed with 5 ml of brine. Subsequently, the combined organic layer was dried over $MgSO_4$, concentrated under reduced pressure. Finally, the crude product was purified via silica gel chromatography (EP/AcOEt 9.5/0.5).



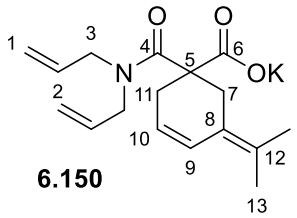

**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 5.12 – 5.00 (m, 2H, $C_5$**H**, $C_{10}$**H**), 3.73 (s, 6H, $C_1$**HHH**), 3.38 (t, J = 7.7 Hz, 1H, $C_3$**H**), 2.69 – 2.55 (m, 2H, $C_4$**HH**), 2.09 – 1.88 (m, 4H, $C_8$**HH**, $C_9$**HH**), 1.72 – 1.53 (m, 9H, $C_7$**HHH**, $C_{12}$**HHH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 169.61 (s, $C_2$), 138.73 (s, $C_6$), 131.52 (s, $C_{11}$), 123.96 (s, $C_{10}$), 119.39 (s, $C_5$), 52.43 (s, $C_1$), 51.92 (s, $C_3$), 39.67 (s, $C_8$), 27.56 (s, $C_4$), 26.53 (s, $C_9$), 25.66 (s, $C_{12}$), 17.68 (s, $C_7$), 16.02 (s, $C_{12}$).

**IR (film, $cm^{-1}$):** 2961, 2924, 2852, 1737, 1438, 1382, 1340, 1238, 1152.

### *Synthesis of potassium 1-(diallylcarbamoyl)-5-(propan-2-ylidene)cyclohex-3-ene-1-carboxylate*

This molecule was synthetized according to the general procedure for preparing potassium salt from the corresponding ester (see p. 204).




**6.150**

**Yield:** 98 % - white solid.

**Purification:** filtration and wash with cold diethyl ether.

**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 5.87 – 5.56 (m, 4H, $C_1$**HH**), 5.28 – 4.99 (m, 4H, $C_2$**H**, $C_9$**H**, $C_{10}$**H**), 3.90 (m, 4H, $C_3$**HH**), 2.48 (m, 4H, $C_7$**HH**, $C_{11}$**HH**), 1.82 (s, 3H, $C_{13}$**HHH**), 1.78 (s, 3H, $C_{13}$**HHH**).

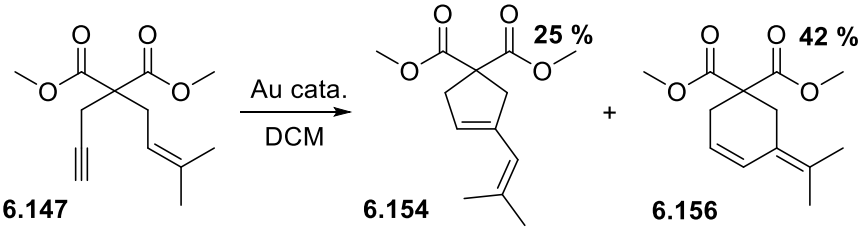
**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 177.27 (s, $C_6$), 171.00 (s, $C_4$), 145.35 (s, $C_{12}$), 137.52 (s, $C_8$), 132.47 (s, $C_2$), 126.45 (s, $C_{10}$), 120.95 (s, $C_9$), 118.40 (s, $C_1$), 117.09 (s, $C_1$), 66.01 (s, $C_5$), 49.08 (s, $C_3$), 47.43 (s, $C_3$), 34.95 (s, $C_7$), 33.11 (s, $C_7$), 29.70 (s, $C_{11}$), 27.43 (s, $C_{13}$), 19.91 (s, $C_{13}$).

**IR (film, cm$^{-1}$):** 2933, 1735, 1676, 1632, 1444, 1305, 1223, 1151, 1022, 881.

**HRMS**, m/z: calculated $[C_{17}H_{23}O_3N^{39}K]^+$ : 328.13095, found : 328.13092.

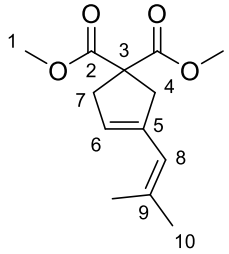
**MS/MS** (p ESI): m/z (%): 81.07048, (8); 104.10495, (10); 119.08569, (16); 124.07581, (31); 148.07316, (25); 187.07284, (19); 203.09930, (22); 310.09555, (41); 327.17615, (100) [M].

*Synthesis of dimethyl 3-(2-methylprop-1-en-1-yl)cyclopent-3-ene-1,1-dicarboxylate*




**6.147** **6.154** **6.156**

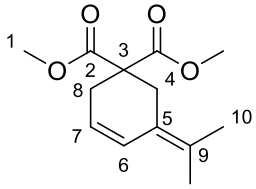
The enyne **6.147** (0.2383 g, 1.00 mmol, 1.00 eq.) was dissolved into 10 ml of DCM (0.1 mol/l). Subsequently, [bis(trifluoromethanesulfonyl)imidate]($PPh_3$)Gold (I) (2:1) toluene adduct (0.0080 g, 0.005 mmol, 0.005 eq.) was added to the solution. The solution was then stirred for four hours. After completion of the reaction, the solution was filtered over celite and concentrated under reduced pressure. Finally, the crude product was purified via silica gel chromatography (EP/AcOEt 10.0/0.5).



**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 5.81 – 5.27 (m, 2H, $C_6$**H**, $C_8$**H**), 3.74 (s, 6H, $C_1$**HHH**), 3.27 – 2.98 (m, 4H, $C_4$**HH**, $C_7$**HH**), 1.87 – 1.69 (m, 6H, $C_{10}$**HHH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 172.64 (s, $C_2$), 138.73 (s, $C_5$), 135.67 (s, $C_9$), 124.43 (s, $C_6$), 120.62 (s, $C_8$), 59.32 (s, $C_3$), 52.84 (s, $C_1$), 52.63 (s, $C_1$), 43.25 (s, $C_7$), 40.27 (s, $C_4$), 27.28 (s, $C_{10}$), 19.84 (s, $C_{10}$).

**IR (film, $cm^{-1}$):** 2954, 1734, 1434, 1251, 1198, 1164, 1074, 967, 864, 791.

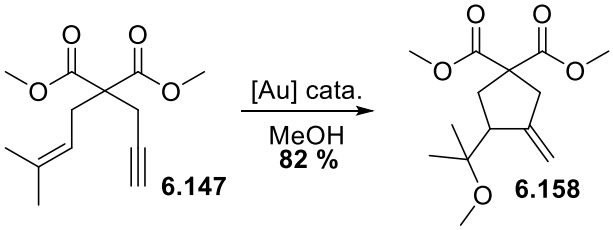


**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 5.70 (s, 1H, $C_7$**H**), 5.49 (s, 1H, $C_6$**H**), 3.62 (s, 6H, $C_1$**HHH**), 2.60 – 2.51 (m, 2H, $C_8$**HH** or $C_4$**HH**), 2.42 – 2.32 (m, 2H, $C_8$**HH** or $C_4$**HH**), 1.74 (s, 3H, $C_{10}$**HHH**), 1.70 (s, 3H, $C_{10}$**HHH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 172.01 (s, $C_2$), 146.13 (s, $C_5$), 138.06 (s, $C_9$), 124.82 (s, $C_7$), 120.66 (s, $C_6$), 65.93 (s, $C_3$), 52.67 (s, $C_1$), 34.74 (s, $C_4$), 32.12 (s, $C_8$), 27.42 (s, $C_{10}$), 19.90 (s, $C_{10}$).

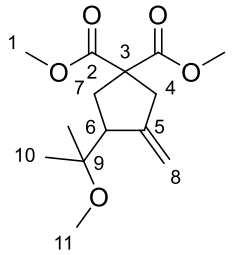
**IR (film, $cm^{-1}$):** 2954, 1733, 1434, 1249, 1161, 1062, 861.

*Synthesis of dimethyl 3-(2-methoxypropan-2-yl)-4-methylenecyclopentane-1,1-dicarboxylate*




The enyne **6.147** (0.2383 g, 1.00 mmol, 1.00 eq.) was dissolved into 10 ml of methanol (0.1 mol/l). Subsequently, [bis(trifluoromethanesulfonyl)imidate](PPh$_3$)Gold (I) (2:1) toluene adduct (0.0471 g, 0.03 mmol, 0.03 eq.) was added to the solution. The solution was then stirred for four hours. After completion of the reaction, the solution was filtered over celite and

concentrated under reduced pressure. Finally, the crude product was purified via silica gel chromatography (EP/AcOEt 9/1).



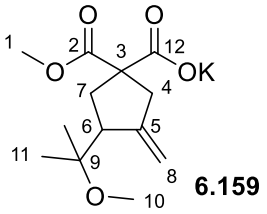

**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 5.06 – 5.02 (m, 1H, $C_8$**H**H), 4.99 – 4.96 (m, 1H, $C_8$H**H**), 3.73 (s, 3H, $C_1$**HHH**), 3.72 (s, 3H, $C_1$**HHH**), 3.19 (s, 3H, $C_{11}$**HHH**), 2.92 – 2.79 (m, 3H, $C_4$**HH**, $C_6$**H**), 2.57 – 2.53 (m, 1H, $C_7$**H**H), 2.03 – 1.99 (m, 1H, $C_7$H**H**), 1.18 (s, 3H, $C_{10}$**HHH**), 1.12 (s, 3H, $C_{10}$**HHH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 172.03 (s, $C_2$), 171.93 (s, $C_2$), 148.17 (s, $C_5$), 110.54 (s, $C_8$), 76.76 (s, $C_9$), 58.57 (s, $C_3$), 52.74 (s, $C_1$), 52.70 (s, $C_1$), 49.08 (s, $C_{11}$), 49.03 (s, $C_6$), 43.38 (s, $C_4$), 36.00 (s, $C_7$), 22.64 (s, $C_{10}$), 22.21 (s, $C_{10}$).

**IR (film, $cm^{-1}$):** 2925, 2853, 1733, 1434, 1380, 1364, 1271, 1232, 1203, 1167, 1077, 893.

### *Synthesis of potassium 1-(methoxycarbonyl)-3-(2-methoxypropan-2-yl)-4-methylenecyclopentane-1-carboxylate*

This molecule was synthetized according to the general procedure for preparing potassium salt from the corresponding ester (see p. 204).




**6.159**

**Yield:** 67 % - white solid.

**Purification:** filtration and wash with cold diethyl ether.

**$^{1}$H NMR (300 MHz, DMSO) : δ** 4.88 – 4.72 (m, 2H, $C_8$**HH**), 3.47 (s, 3H, $C_1$**HHH**), 3.07 (s, 3H, $C_{10}$**HHH**), 2.93 – 2.55 (m, 3H, $C_6$**H**, $C_4$**HH**), 2.27 (dd, J = 12.7, 8.3 Hz, 1H, $C_7$**H**H), 1.72 (dd, J = 12.8, 10.5 Hz, 1H, $C_7$H**H**), 1.11 – 0.94 (m, 6H, $C_{11}$**HHH**).

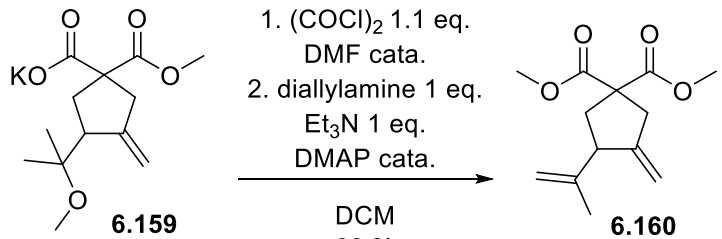
**$^{13}$C NMR (75 MHz, DMSO) : δ** 175.81 (s, $C_{12}$), 172.23 (s, $C_2$), 152.40 (s, $C_5$), 107.88 (s, $C_8$), 77.07 (s, $C_9$), 62.04 (s, $C_3$), 53.11 (s, $C_6$), 51.39 (s, $C_1$), 48.70 (s, $C_{10}$), 44.82 (s, $C_4$), 37.14 (s, $C_7$), 23.29 (s, $C_{11}$), 22.00 (s, $C_{11}$).

**IR (film, $cm^{-1}$):** 2974, 2826, 1716, 1653, 1591, 1439, 1363, 1306, 1235, 1201, 1166, 1078, 1052, 1884, 780, 710, 689, 642.

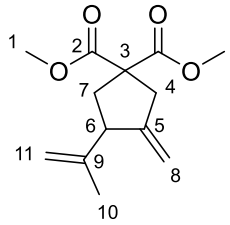
**HRMS**, m/z: calculated $[C_{13}H_{20}O_5{}^{39}K]^+$ : 295.09423, found: 295.09430.

**MS/MS** (p ESI): m/z (%): 119.08538, (6); 147.08051, (100); 179.10708, (6); 211.13375, (9); 232.94410, (16); 262.95508, (24); 295.26468, (59) $[M-H]^+$.

*Synthesis of dimethyl 3-methylene-4-(prop-1-en-2-yl)cyclopentane-1,1-dicarboxylate*




The potassium salt **6.159** (4.492 g, 15.26 mmol, 1 eq.) was dissolved in 40 ml of DCM (0.4 mol/l). The solution was then cooled to a temperature of 0°C. A bubbler system was installed in order to monitor the evolution of CO and $CO_2$. Subsequently, oxalyl chloride (2.1311 g, 16.79 mmol, 1.1 eq.) was added dropwise to the solution, and a drop of DFM was added. The solution was stirred, at room temperature, until completion of the acyl chloride formation. The solution was then cooled to a temperature of 0°C and a solution of diallylamine (1.4827 g, 15.25 mmol, 1 eq.) in 40 ml of DCM (0.4 mol/l) was added dropwise to the reaction mixture. Additionally, triethylamine (1.5441 g, 15.26 mmol, 1 eq.) was added dropwise, and a catalytic amount of DMAP was introduced. The mixture was stirred overnight. After completion of the reaction, 50 ml of $NaHCO_3$ saturated aqueous solution was added and the aqueous layer was then extracted two times with 20 ml of DCM. The organic layers were combined, dried over $MgSO_4$, concentrated under reduced pressure. The crude product was finally purified via silica gel chromatography (EP/AcOEt 9/1).



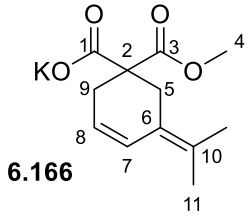

**$^1$H NMR (300 MHz, $CDCl_3$) : δ** 5.06 – 4.76 (m, 4H, $C_8$**HH**, $C_{11}$**HH**), 3.75 (s, 3H, $C_1$**HHH**), 3.73 (s, 3H, $C_1$**HHH**), 3.34 – 3.20 (m, 1H, $C_6$**H**), 3.07 (dd, J = 16.8, 1.2 Hz, 1H, $C_4$**H**H), 2.92 (ddd, J = 16.8, 5.2, 2.6 Hz, 1H, $C_4$H**H**), 2.52 (ddd, J = 13.0, 7.8, 1.5 Hz, 1H, $C_7$**H**H), 2.12 (dd, J = 13.0, 11.3 Hz, 1H, $C_7$H**H**), 1.66 – 1.63 (m, 3H, $C_{10}$**HHH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 172.09 (s, $C_2$), 171.99 (s, $C_2$), 149.21 (s, $C_5$), 144.67 (s, $C_9$), 113.45 (s, $C_{11}$), 108.10 (s, $C_8$), 58.69 (s, $C_3$), 52.84 (s, $C_1$), 52.77 (s, $C_1$), 51.05 (s, $C_6$), 40.87 (s, $C_4$), 38.60 (s, $C_7$), 18.13 (s, $C_{10}$).

**IR (film, cm$^{-1}$):** 3076, 2954, 1732, 1645, 1434, 1267, 1250, 1199, 1159, 1079, 891.

*Synthesis of potassium 1-(methoxycarbonyl)-5-(propan-2-ylidene)cyclohex-3-ene-1-carboxylate*

This molecule was synthetized according to the general procedure for preparing potassium salt from the corresponding ester (see p. 204).




**6.166**

**Yield:** 68 % - white solid.

**Purification:** filtration and wash with cold diethyl ether.

**$^{1}$H NMR (300 MHz, DMSO) : δ** 5.83 – 5.72 (m, 1H, $C_8$**H**), 5.58 – 5.45 (m, 1H, $C_7$**H**), 3.60 (s, 3H, $C_4$**HHH**), 2.59 – 2.41 (m, 2H, $C_5$**HH** or $C_9$**HH**), 2.19 – 1.92 (m, 2H, $C_5$**HH** or $C_9$**HH**), 1.83 – 1.70 (m, 6H, $C_{11}$**HHH**).

**$^{13}$C NMR (75 MHz, DMSO) : δ** 174.96 (s, $C_1$), 174.47 (s, $C_3$), 144.04 (s, $C_6$), 143.98 (s, $C_6$), 135.96 (s, $C_{10}$), 135.91 (s, $C_{10}$), 126.25 (s, $C_8$), 126.15 (s, $C_8$), 121.60 (s, $C_7$), 121.58 (s, $C_7$), 64.03 (s, $C_2$), 60.47 (s, $C_9$), 52.03 (s, $C_4$), 34.92 (s, $C_9$), 20.00 (s, $C_{11}$), 14.58 (s, $C_{11}$).

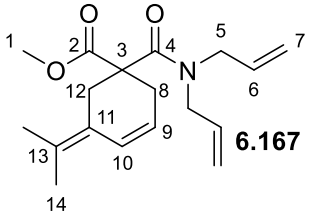
**IR (film, cm$^{-1}$):** 2943, 1743, 1464, 1345, 1239, 1171, 1082, 881.

**HRMS**, m/z: calculated $[C_{12}H_{16}O_4{}^{39}K]^+$ : 263.06802, found: 263.06811.

**MS/MS** (p ESI): m/z (%): 85.05943, (6); 148.98799, (100); 164.98289, (22); 201.08850, (14); 219.09906, (14); 230.01757, (30); 263.08872, (13) $[M\text{-}H]^+$.

*Synthesis of methyl 1-(diallylcarbamoyl)-5-(propan-2-ylidene)cyclohex-3-ene-1-carboxylate*

This molecule was synthetized according the general procedure for preparing amide from the corresponding secondary amine using oxalyl chloride (see p. 249).




**6.167**

**Yield:** 22 % - colourless oil.

**Purification:** chromatography on silica gel. Eluent: EP/AcOEt 9/1.

**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 5.85 – 5.52 (m, 4H, $C_6$**H**, $C_9$**H**, $C_{10}$**H**), 5.30 – 4.98 (m, 4H, $C_7$**HH**), 4.06 – 3.74 (m, 4H, $C_5$**HH**), 3.68 (s, 3H, $C_1$**HHH**), 2.80 – 2.29 (m, 4H, $C_8$**HH**, $C_{12}$**HH**), 1.82 (s, 3H, $C_{14}$**HHH**), 1.78 (s, 3H, $C_{14}$**HHH**).

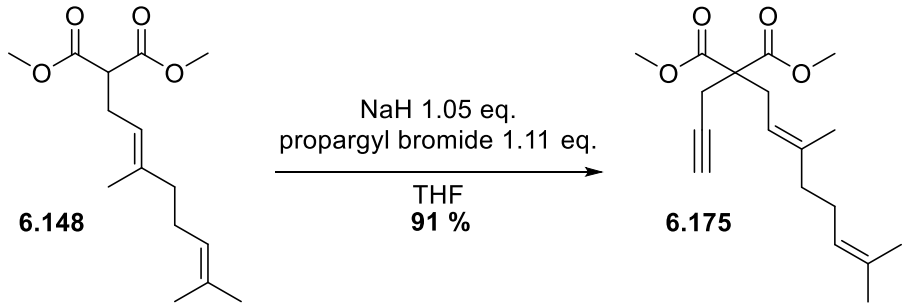
**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 172.96 (s, $C_2$), 170.61 (s, $C_4$), 144.94 (s, $C_{13}$), 137.53 (s, $C_{11}$), 132.56 (s, $C_6$), 132.46 (s, $C_6$), 126.37 (s, $C_9$), 120.85 (s, $C_{10}$), 118.10 (s, $C_7$), 116.91 (s, $C_7$), 65.92 (s, $C_3$), 52.56 (s, $C_1$), 48.66 (s, $C_5$), 47.28 (s, $C_5$), 34.96 (s, $C_{12}$), 32.81 (s, $C_8$), 27.37 (s, $C_{14}$), 19.90 (s, $C_{14}$).

**IR (film, cm$^{-1}$):** 2923, 1733, 1678, 1633, 1454, 1365, 1233, 1111, 1002, 891.

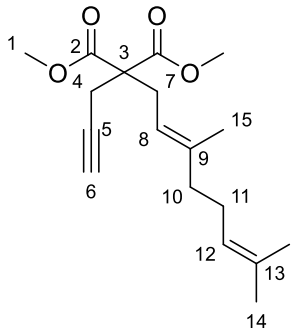
**HRMS**, m/z: calculated $[C_{18}H_{26}O_3N]^+$ : 304.19072, found: 304.19064.

**MS/MS** (p ESI): m/z (%): 119.08563, (25); 124.07569, (34); 147.08024, (29); 179.10643, (100); 244.16922, (43); 304.19045, (5) $[M-H]^+$.

*Synthesis of dimethyl (E)-2-(3,7-dimethylocta-2,6-dien-1-yl)-2-(prop-2-yn-1-yl)malonate*




NaH 60% (0.1050 g, 2.625 mmol, 1.05 eq.) was diluted in 7 ml of THF (0.36 mol/l).The mixture was then placed at a temperature of 0°C and the monosubstituted malonate **6.148** (0.6720 g, 2.500 mmol, 1.00 eq.) was added dropwise. Subsequently the ice bath was removed and the mixture was stirred for one hour. Afterwards, the solution was cooled to a temperature of 0°C and propargyl bromide (0.4342 g, 2.92 mmol, 1.11 eq.) was introduced dropwise. The solution was stirred 20 minutes at 0°C and at room temperature overnight. Finally, the solution was slowly quenched with 5 ml of water, concentrated and extracted with 15 ml of diethyl ether. The organic layer was washed with 10 ml of water and 10 ml of brine. The combiner organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. Finally, the crude product was purified via silica gel chromatography (EP/AcOEt 9/1).

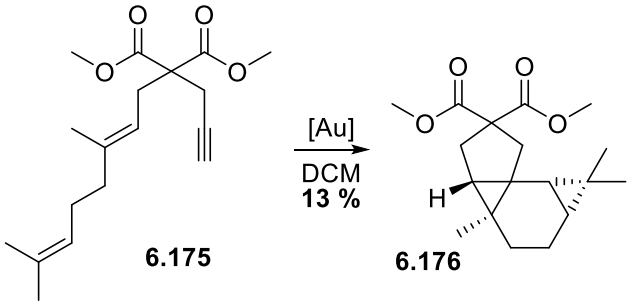



**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 5.10 – 4.85 (m, 2H, $C_8$**H**, $C_{12}$**H**), 3.73 (s, 6H, $C_1$**HHH**), 2.84 – 2.74 (m, 4H, $C_4$**HH**, $C_7$**HH**), 2.14 – 1.92 (m, 5H, $C_6$**H**, $C_{10}$**HH**, $C_{11}$**HH**), 1.72 – 1.53 (m, 9H, $C_{14}$**HHH**, $C_{15}$**HHH**).

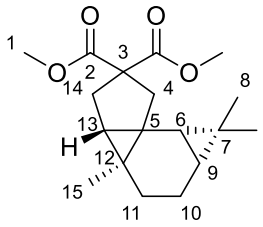
**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 170.47 (s, $C_2$), 140.49 (s, $C_9$), 131.61 (s, $C_{13}$), 123.95 (s, $C_{12}$), 117.00 (s, $C_8$), 79.33 (s, $C_5$), 71.15 (s, $C_6$), 57.17 (s, $C_3$), 52.70 (s, $C_1$), 39.96 (s, $C_{10}$), 30.64 (s, $C_7$), 26.46 (s, $C_{11}$), 25.68 (s, $C_{14}$), 22.42 (s, $C_4$), 17.70 (s, $C_{14}$), 16.16 (s, $C_{15}$).

**IR (film, cm$^{-1}$):** 3292, 2954, 2924, 1737, 1437, 1291, 1222, 1202, 1056, 648.

*Synthesis of dimethyl (1aS,3aS,3bS,6bR)-1,1,3a-trimethyloctahydrocyclopenta[2,3]cyclopropa[1,2-a]cyclopropa[c]benzene-5,5(6H)-dicarboxylate*




The enyne **6.175** (0.3060 g, 1.00 mmol, 1.00 eq.) was dissolved into 10 ml of DCM (0.1 mol/l). Subsequently, [bis(trifluoromethanesulfonyl)imidate](PPh$_3$)Gold (I) (2:1) toluene adduct (0.0314 g, 0.02 mmol, 0.02 eq.) was dissolved in 20 ml of DCM and the enyne solution was added dropwise to that mixture. The solution was then stirred for four hours. After completion of the reaction, the solution was filtered over celite and concentrated under reduced pressure. Finally, the crude product was purified via silica gel chromatography (EP/AcOEt 9.5/0.5).



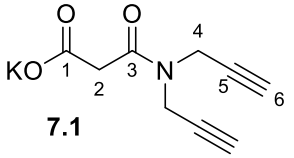
**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 3.76 (s, 3H, $C_1$**HHH**), 3.75 – 3.69 (m, 14H), 3.68 (s, 3H, $C_1$**HHH**), 2.55 (ddd, *J* = 14.6, 7.2, 1.8 Hz, 1H, $C_{14}$**H**H), 2.41 (dd, *J* = 14.6, 1.8 Hz, 1H, $C_4$**H**H), 2.23 – 2.12 (m, 1H, $C_{14}$H**H**), 2.02 – 1.93 (m, 1H, $C_4$H**H**), 1.76 – 1.46 (m, 4H, $C_{10}$**HH**, $C_{11}$**HH**), 1.15 – 1.04 (m, 1H, $C_{13}$**H**), 1.01 (s, 3H, $C_{15}$**HHH**), 0.92 (s, 3H, $C_8$**HHH**), 0.89 (s, 3H, $C_8$**HHH**), 0.86 – 0.80 (m, 2H, $C_6$**H**, $C_9$**H**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 173.75 (s, $C_2$), 171.64 (s, $C_2$), 68.13 (s, $C_3$), 52.74 (s, $C_1$), 52.41 (s, $C_1$), 40.10 (s, $C_4$), 38.19 (s, $C_{13}$), 34.89 (s, $C_{11}$), 34.27 (s, $C_{14}$), 33.03 (s, $C_5$), 28.93 (s, $C_8$), 28.20 (s, $C_8$), 24.98 (s, $C_9$), 23.93 (s, $C_{15}$), 20.22 (s, $C_7$), 17.54 (s, $C_6$), 16.56 (s, $C_{10}$), 14.36 (s, $C_{12}$).

**IR (film, $cm^{-1}$):** 3359, 2922, 2854, 1736, 1659, 1633, 1470, 1436, 1255, 1201, 1178, 1075.

### *Synthesis of potassium 3-(di(prop-2-yn-1-yl)amino)-3-oxopropanoate*

This molecule was synthetized according to the general procedure for preparing potassium salt from the corresponding ester (see p. 204).



**7.1**

**Yield:** 87 % - white powder.

**Purification:** filtration and diethyl ether wash.

**$^{1}$H NMR (300 MHz, DMSO) : δ** 4.40 (d, J = 2.0 Hz, 2H, $C_4$**HH**), 4.11 (d, J = 2.1 Hz, 2H, $C_4$**HH**), 3.25 (s, 1H, $C_6$**H**), 3.13 (s, 1H, $C_6$**H**), 2.99 (s, 2H, $C_2$**HH**).

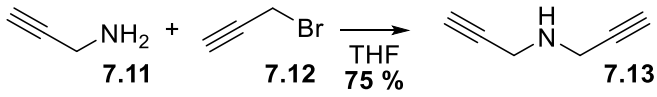
**$^{13}$C NMR (75 MHz, DMSO) : δ** 169.35 (s, $C_1$), 167.03 (s, $C_3$), 74.67 (s, $C_5$), 74.08 (s, $C_6$), 36.61 (s, $C_4$), 33.43 (s, $C_2$).

**IR (film, $cm^{-1}$):** 3280, 2125, 1741, 1650, 1438, 1413, 1332, 1257, 1211, 1163, 1014, 956, 690.

**HRMS**, m/z: calculated $[C_9H_8O_3N]^-$ : 178.04987, found: 178.04986.

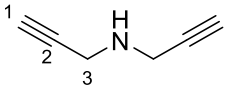
**MS/MS** (p ESI): m/z (%): 66.03331, (32); 78.03332, (5); 90.03336, (5); 92.04902, (16); 94.02824, (32); 108.04393, (100); 178.0356, (5) $[M]^-$.

*Synthesis of di(prop-2-yn-1-yl)amine*




**7.11** **7.12** **7.13**

Propargyl amine (9.00 ml, 140 mmol, 3 eq.,) was diluted in 83 ml of THF (1.7 mol/l), and the solution was cooled to a temperature of 0°C. Afterwards, propargyl bromide 80 wt. % in toluene (5.22 ml, 46.66 mmol, 1 eq.) was added dropwise to the solution and the mixture was allowed to stir, at room temperature, overnight. After completion of the reaction, the solution was diluted with 30 ml of DCM and extracted two times with 50 ml of water. The aqueous layer was then extracted with 30 ml of DCM and the organic layers were combined, dried over $MgSO_4$ and concentrated under reduced pressure. The final product was finally used without further purifications.



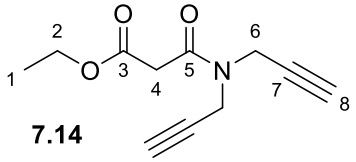

**$^1$H NMR (300 MHz, $CDCl_3$) : δ** 3.53 (d, J = 2.4 Hz, 2H, $C_3$**HH**), 2.23 (t, J = 2.4 Hz, 1H, $C_1$**H**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 81.09 (s, $C_2$), 71.83 (s, $C_1$), 36.83 (s, $C_3$).

**IR (film, cm$^{-1}$):** 3330, 3282, 3216, 2969, 2115, 1640, 1414, 1362, 1319, 1265, 1153, 1096, 949, 855.

*Synthesis of ethyl 3-(di(prop-2-yn-1-yl)amino)-3-oxopropanoate*

This molecule was synthetized according to the general procedure for preparing amide from the corresponding secondary amine using oxalyl chloride (see p. 249).




**7.14**

**Yield:** 71 % - colourless-oil.

**Purification:** chromatography on silica gel. Eluent: DCM 100 – DCM/MeOH 99/1.

**$^1$H NMR (300 MHz, $CDCl_3$) δ** 4.36 (d, J = 7.6 Hz, 2H, $C_6$**H**H), 4.29 – 4.14 (m, 4H, $C_2$**HH**, $C_6$H**H**), 3.54 (s, 2H, $C_4$**HH**), 2.39 – 2.29 (m, 1H, $C_8$**H**), 2.30 – 2.21 (m, 1H, $C_8$**H**), 1.27 – 1.24 (m, 3H, $C_1$**HHH**).

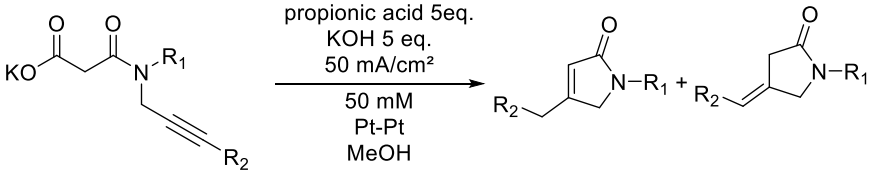
**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 166.94 (s, $C_3$), 165.47 (s, $C_5$), 73.50 (s, $C_7$), 72.73 (s, $C_8$), 61.71 (s, $C_2$), 36.81 (s, $C_6$), 34.29 (s, $C_4$), 14.08 (s, $C_1$).

**IR (film, cm$^{-1}$):** 3272, 3226, 2989, 2722, 2125, 1650, 1643, 1546, 1415, 1361, 1319, 1263, 1265, 1153, 1114, 1095, 929, 854, 808.

**HRMS**, m/z: calculated $[C_{11}H_{14}O_3N]^+$ : 208.09682, found: 208.09683.

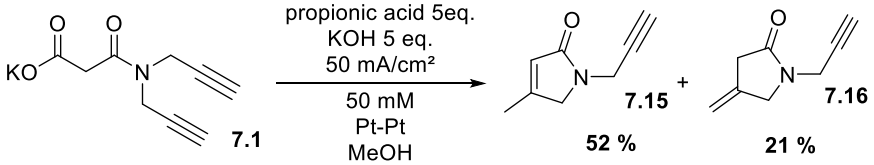
**MS/MS** (p ESI): m/z (%): 77.03920, (32); 79.01842, (13); 90.03433, (6); 92.04999, (27); 94.06552, (100); 96.04473, (11); 105.04501, (11); 120.04450, (13); 134.05997, (7); 208.11178, (5) $[M-H]^+$.

*General procedure for the electrosynthesis of pyrrolones and β,γ-unsaturated 2-pyrrolidinones*

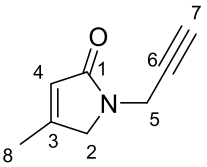



In an undivided cell with platinum electrodes (4 cm²), potassium hydroxide (3.75 mmol, 5 eq.), and propionic acid (3.75 mmol, 5eq.) were dissolved in 15 ml of MeOH. Then, the propargylic potassium salt (0.75 mmol, 1 eq.) was added to the mixture. The intensity of the current density was fixed at 50 mA/cm$^2$ and the mixture was electrolyzed until completion of the reaction, as shown by TLC. The solution was treated with an aqueous solution of $NaHCO_3$ (10 ml) and extracted three times with 10 ml of $Et_2O$. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica gel chromatography.

*Synthesis of 4-methyl-1-(prop-2-yn-1-yl)-1,5-dihydro-2H-pyrrol-2-one and 4-methylene-1-(prop-2-yn-1-yl)pyrrolidin-2-one*




These molecules were synthetized according to the general procedure for the electrosynthesis of pyrrolones and β,γ-unsaturated 2-pyrrolidinones (see p. 298).
**Purification:** chromatography on silica gel. – Eluent: AcOEt/EP 4/6.



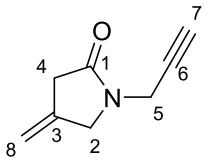
**$^1$H NMR (300 MHz, $CDCl_3$) : δ** 5.83 (dd, J = 3.0, 1.5 Hz, 1H, $C_4$**H**), 4.21 (t, J = 6.1 Hz, 2H, $C_5$**HH**), 3.94 (s, 2H, $C_2$**HH**), 2.23 (t, J = 2.5 Hz, 1H, $C_7$**H**), 2.07 (d, J = 1.4 Hz, 3H, $C_8$**HHH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) δ** 171.51 (s, $C_1$), 155.91 (s, $C_3$), 122.39 (s, $C_4$), 78.44 (s, $C_6$), 72.17 (s, $C_7$), 54.73 (s, $C_2$), 31.23 (s, $C_5$), 15.41 (s, $C_8$).

**IR (film, cm$^{-1}$):** 3276, 2925, 2125, 1668, 1647, 1456, 1436, 1406, 1350, 1147, 941.

**HRMS**, m/z: calculated $[C_8H_{10}ON]^+$ : 136.07569, found: 136.07575.

**MS/MS** (p ESI): m/z (%): 67.05493, (15); 81.07043, (8); 91.05469, (7); 93.05773, (13); 108.08102, (100); 110.06019, (8); 136.07557, (72) $[M-H]^+$.




**$^1$H NMR (300 MHz, $CDCl_3$) : δ** 4.39 – 4.32 (m, 2H, $C_5$**HH**), 3.92 (ddt, J = 9.0, 7.1, 6.3 Hz, 2H, $C_8$**HH**), 3.75 (s, 2H, $C_2$**HH**), 3.35 (s, 2H, $C_4$**HH**), 2.38 – 2.21 (m, 1H, $C_7$**H**).

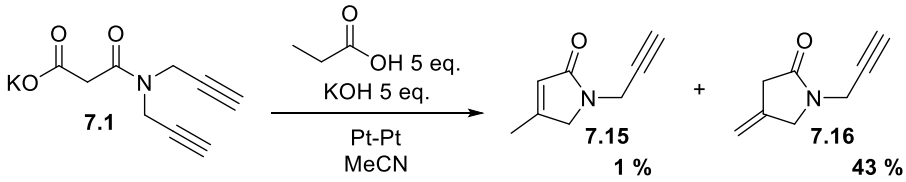
**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 168.02 (s, $C_1$), 166.32 (s, $C_3$), 77.57 (s, $C_6$), 73.24 (s, $C_7$), 70.73 (s, $C_8$), 59.22 (s, $C_4$), 52.75 (s, $C_2$), 36.46 (s, $C_5$), 34.44 (s, $C_5$).

**IR (film, cm$^{-1}$):** 1670, 1631, 1454, 1406, 1328, 1228, 1147, 941, 840, 688.

**HRMS**, m/z: calculated $[C_8H_{10}ON]^+$ : 136.07569, found: 136.07569.

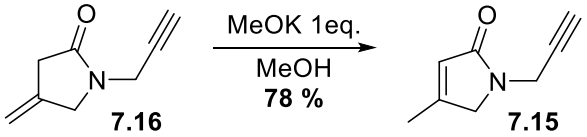
**MS/MS** (p ESI): m/z (%): 54.03460, (7); 67.05487, (14); 80.04998, (9); 91.05460, (12); 93.05765, (14); 108.08095, (100); 136.07547, (85) $[M-H]^+$.

*Synthesis of 4-methyl-1-(prop-2-yn-1-yl)-1,5-dihydro-2H-pyrrol-2-one and 4-methylene-1-(prop-2-yn-1-yl)pyrrolidin-2-one*



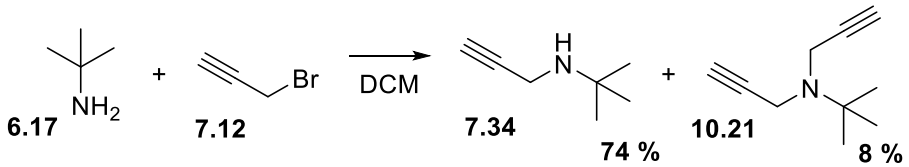

In an undivided cell with platinum electrodes (4 cm²), potassium hydroxide (0,2104 g, 3.75 mmol, 5 eq.), and propionic acid (0.2778g, 3.75 mmol, 5eq.) were dissolved in 15 ml of MeOH. Then, the potassium salt **7.1** (0,1629 g, 0.75 mmol, 1 eq.) was added to the mixture. The intensity of the current density was fixed at 50 mA/cm$^2$ and the mixture was electrolyzed, until completion of the reaction, as shown by TLC. The solution was treated with an aqueous solution of $NaHCO_3$ (10 ml), and extracted three times with 10 ml of $Et_2O$. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (AcOEt/EP 4/6).

*Synthesis of 4-methyl-1-(prop-2-yn-1-yl)-1,5-dihydro-2H-pyrrol-2-one*

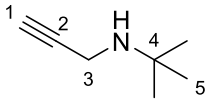



4-methylene-1-(prop-2-yn-1-yl)pyrrolidin-2-one (0.6758 g, 5 mmol, 1 eq.) was dissolved into 5 ml of methanol. The solution was cooled to 0°C. Subsequently, potassium hydroxide (0.3506 g, 5 mmol, 1 eq.) in 5 ml of methanol was added dropwise to this solution. The solution was treated with water (5 ml) and extracted three times with 5 ml of $Et_2O$. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (AcOEt/EP 4/6).

*Synthesis of N-(tert-butyl)prop-2-yn-1-amine*



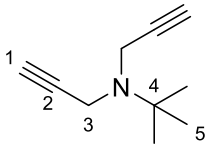

*Tert*-butyl amine (1 .5 ml, 20 mmol, 4.9 eq.) was diluted in 7 ml of DCM. Subsequently, propargyl bromide (0.46 ml, 4.1 mmol, 1 eq.) was added dropwise to the solution and the mixture was allowed to stir, overnight, at room temperature. After completion of the reaction, the mixture was diluted with 20 ml of DCM and extracted two times with 15 ml of water. The combined organic layers were then dried over $MgSO_4$ and concentrated under reduced pressure. The final product was used without further purification.



**$^1$H NMR (300 MHz, $CDCl_3$) : δ** 3.40 (d, J = 2.5 Hz, 2H, $C_3$**HH**), 2.23 – 2.18 (m, 1H, $C_1$**H**), 1.10 (s, 9H, $C_5$**HHH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 83.51 (s, $C_2$), 70.66 (s, $C_1$), 50.85 (s, $C_4$), 32.02 (s, $C_3$), 28.87 (s, $C_5$).

**IR (film, cm$^{-1}$):** 3210, 2954, 2260, 1664, 1600, 1435, 934, 827.



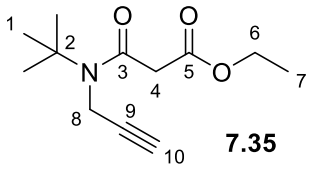
**$^1$H NMR (300 MHz, $CDCl_3$) : δ** 3.66 (d, J = 2.3 Hz, 4H, $C_3$**HH**), 2.23 – 2.18 (m, 2H, $C_1$**H**), 1.20 (s, 9H, $C_5$**HHH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 77.24 (s, $C_2$), 72.29 (s, $C_1$), 36.40 (s, $C_3$), 27.45 (s, $C_5$).

**IR (film, cm$^{-1}$):** 3283, 2934, 2230, 1566, 1521, 1462, 924, 719.

*Synthesis of ethyl 3-(tert-butyl(prop-2-yn-1-yl)amino)-3-oxopropanoate*

This molecule was synthetized according to the general procedure for preparing amide from the corresponding secondary amine using DCC coupling agent (see p. 203).




**7.35**

**Yield:** 77 % - colourless oil.

**Purification:** chromatography on silica gel. Eluent: EP/AcOEt 0.9/0.1.

**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 4.21 (q, J = 7.2Hz, 2H, $C_6$**HH**), 4.04 (d, J = 2.5Hz, 2H, $C_8$**HH**), 3.55 (s, 2H, $C_4$**HH**), 2.33 (t, J = 2.4 Hz, 1H, $C_{10}$**H**), 1.50 (s, 9H, $C_1$**HHH**), 1.30 (t, J = 6.6 Hz, 3H, $C_7$**HHH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 167.92 (s, $C_5$), 166.79 (s, $C_3$), 80.13 (s, $C_9$), 72.55 (s, $C_{10}$), 61.39 (s, $C_6$), 58.47 (s, $C_2$), 44.17 (s, $C_4$), 35.24 (s, $C_8$), 28.56 (s, $C_1$), 14.09 (s, $C_7$).

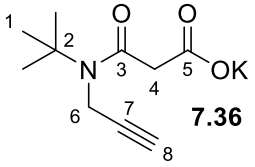
**IR (film, $cm^{-1}$):** 2250, 2111, 1762, 1733, 1314, 1252, 1173, 883, 752.

**HRMS**, m/z: calculated $[C_{12}H_{20}O_3N]^+$ : 226.14377, found: 226.14372.

**MS/MS** (p ESI): m/z (%): 124.03954, (5); 142.04995, (42); 170.08122, (100); 229.19618, (1) $[M-H]^+$.

*Synthesis of potassium 3-(tert-butyl(prop-2-yn-1-yl)amino)-3-oxopropanoate*

This molecule was synthetized according to the general procedure for preparing potassium salt from the corresponding ester (see p. 204).




**7.36**

**Yield:** 81 % - white powder.

**Purification:** filtration and wash with cold diethyl ether.

**$^{1}$H NMR (300 MHz, $CDCl_3$) δ :** 4.08 (d, J = 2.4 Hz, 2H, $C_6$**HH**), 3.48 (s, 2H, $C_4$**HH**), 2.36 (t, J = 2.4 Hz, 1H, $C_8$**H**), 1.49 (s, 9H, $C_1$**HHH**).

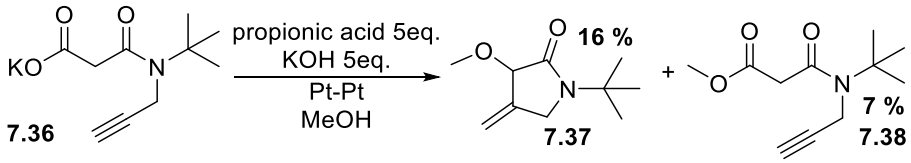
**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 170.88 (s, $C_5$), 169.08 (s, $C_3$), 78.88 (s, $C_7$), 73.45 (s, $C_8$), 59.70 (s, $C_2$), 38.99 (s, $C_4$), 34.74 (s, $C_6$), 28.50 (s, $C_1$).

**IR (film, cm$^{-1}$):** 2235, 2137, 1742, 1633, 1345, 1267, 1168, 883, 742.

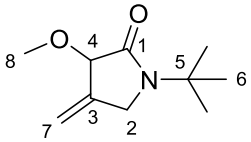
**HRMS**, m/z: calculated $[C_{10}H_{15}O_3N^{39}K]^+$ : 236.06835, found: 236.06828.

**MS/MS** (p ESI): m/z (%): 100.07627, (21); 123.05565, (19); 143.1181, (11); 179.98121, (94); 190.05011, (11); 204.12088, (12); 218.12088, (12); 235.21706, (100); 236.06835, (86) $[M-H]^+$.

*Synthesis of 1-(tert-butyl)-3-methoxy-4-methylenepyrrolidin-2-one*




These molecules were synthetized according to the general procedure for the electrosynthesis of pyrrolones and β,γ-unsaturated 2-pyrrolidinones (see p. 298).
**Purification:** chromatography on silica gel. Eluent: DCM/MeOH 99/1.



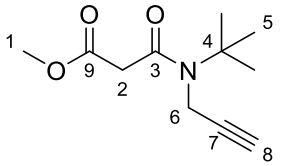

**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 5.26 (s, 1H, $C_4$**H**), 5.24 – 5.16 (m, 2H, $C_7$**HH**), 3.22 – 3.19 (m, 0.5H, $C_2$**H**H), 3.17 (s, 3H, $C_8$**HHH**), 3.15 – 3.11 (m, 0.5H, $C_2$**H**H), 2.96 – 2.85 (m, 1H, $C_2$H**H**), 1.46 (s, 9H, $C_6$**HHH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 173.60 (s, $C_1$), 137.67 (s, $C_3$), 111.82 (s, $C_7$), 91.17 (s, $C_4$), 54.48 (s, $C_5$), 50.50 (s, $C_8$), 37.40 (s, $C_2$), 27.94 (s, $C_6$).

**IR (film, cm$^{-1}$):** 3312, 2966, 2926, 1700, 1673, 1457, 1384, 1363, 1264, 1223, 1160, 1068, 909, 844, 636.

**HRMS**, m/z: calculated $[C_{10}H_{18}O_2N]^+$ : 184.13321, found: 184.13331.

**MS/MS** (p ESI): m/z (%): 96.04488, (31); 128.07073, (100); 184.13327, (5) $[M-H]^+$.



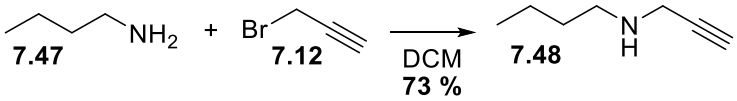

**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 4.03 (d, J = 2.4 Hz, 2H, $C_6$**HH**), 3.76 (s, 3H, $C_1$**HHH**), 3.57 (s, 2H, $C_2$**HH**), 2.32 (t, J = 2.4 Hz, 1H, $C_8$**H**), 1.49 (s, 9H, $C_5$**HHH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 168.79 (s, $C_9$), 166.79 (s, $C_3$), 81.13 (s, $C_7$), 77.63 (s, $C_8$), 58.47 (s, $C_4$), 52.75 (s, $C_1$), 44.06 (s, $C_2$), 35.48 (s, $C_6$), 28.59 (s, $C_5$).

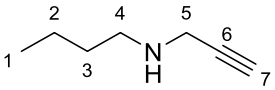
**IR (film, $cm^{-1}$):** 2224, 2127, 1751, 1638, 1328, 1287, 1100, 888, 749.

**HRMS**, m/z: calculated $[C_{11}H_{18}O_3N]^+$ : 212.12835, found: 212.12826.

*Synthesis of N-(prop-2-yn-1-yl)butan-1-amine*[247]




*N*-butylamine (3.656 g, 50 mmol, 5 eq.) was dissolved in 10.6 ml of DCM and the solution was cooled to a temperature of 0°C. Propargyl bromine 80 % wt. in toluene (1.12 ml, 10 mmol, 1 eq.) was subsequently added dropwise to the reaction mixture. The solution was then allowed to stir until completion of the reaction, as shown by TLC. The solution was then diluted with 5 ml of DCM and extracted three times with 15 ml of water. Finally, the organic layers were combined, dried over $MgSO_4$ and concentrated under reduced pressure. The final product was used without further purifications.



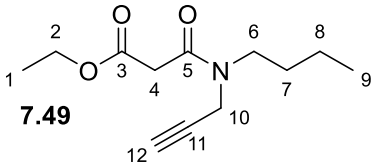

**$^1$H NMR (300 MHz, $CDCl_3$) : δ** 3.45 – 3.42 (m, 2H, $C_5$**HH**), 2.68 (t, J = 7.1 Hz, 2H, $C_4$**HH**), 2.20 (t, J = 2.4 Hz, 1H, $C_7$**H**), 1.55 – 1.27 (m, 4H, $C_2$**HH**, $C_3$**HH**), 0.92 (t, J = 7.2 Hz, 3H, $C_1$**HHH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 82.39 (s, $C_6$), 71.08 (s, $C_7$), 48.40 (s, $C_4$), 38.20 (s, $C_5$), 31.96 (s, $C_3$), 20.41 (s, $C_2$), 13.97 (s, $C_1$).

**IR (film, $cm^{-1}$):** 2954, 2922, 2852, 1661, 1463, 1377.

*Synthesis of ethyl 3-(butyl(prop-2-yn-1-yl)amino)-3-oxopropanoate*

This molecule was synthetized according to the general procedure for preparing amide from the corresponding secondary amine using DCC as coupling agent (see p. 203).




**Yiel:** 47 % - colourless oil.

**Purification:** chromatography on silica gel. Eluent: EP/AcOEt 9/1.

[247] Masse, G.; Strutz, G. *Synthesis* **1988**, 11, 907.

**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 4.32 – 3.97 (m, 4H, $C_2$**HH**, $C_{10}$**HH**), 3.60 – 3.32 (m, 4H, $C_4$**HH**, $C_6$**HH**), 2.27 – 2.24 (m, 1H, $C_{12}$**H**), 1.94 – 1.32 (m, 2H, $C_7$**HH**), 1.33 – 1.21 (m, 5H, $C_1$**HHH**, $C_8$**HH**), 1.01 – 0.85 (m, 3H, $C_9$**HHH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 167.56 (s, $C_3$), 167.39 (s, $C_3$), 165.78 (s, $C_5$), 165.65 (s, $C_5$), 78.65 (s, $C_{11}$), 78.28 (s, $C_{11}$), 72.90 (s, $C_{12}$), 71.85 (s, $C_{12}$), 61.97 (s, $C_2$), 61.53 (s, $C_2$), 47.67 (s, $C_6$), 46.39 (s, $C_6$), 41.57 (s, $C_4$), 41.15 (s, $C_4$), 38.01 (s, $C_{10}$), 34.34 (s, $C_{10}$), 29.41 (s, $C_7$), 19.97 (s, $C_8$), 14.10 (s, $C_1$), 13.83 (s, $C_9$), 13.75 (s, $C_9$).

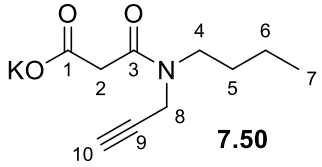
**IR (film, cm$^{-1}$):** 3266, 2926, 2854, 1738, 1651, 1446, 1368, 1318, 1157, 1037, 918, 731.

**HRMS**, m/z: calculated $[C_{12}H_{20}O_3N]^+$ : 226.14377, found: 226.14377.

**MS/MS** (p ESI): m/z (%): 82.03044, (13); 112.11383, (27); 138.09311, (100); 180.10420, (26); 226.14665, (28) $[M\text{-}H]^+$.

*Synthesis of potassium 3-(butyl(prop-2-yn-1-yl)amino)-3-oxopropanoate*

This molecule was synthetized according to the general procedure for preparing potassium salt from the corresponding ester (see p. 204).




**7.50**

**Yield:** 81 % - white powder.

**Purification:** filtration and wash with cold diethyl ether.

**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 4.19 – 4.06 (m, 2H, $C_8$**HH**), 3.45 – 3.23 (m, 4H, $C_2$**HH**, $C_4$**HH**), 2.38 – 2.32 (m, 1H, $C_{10}$**H**), 1.66 – 1.48 (m, 2H, $C_5$**HH**), 1.39 – 1.24 (m, 2H, $C_6$**HH**), 0.99 – 0.86 (m, 3H, $C_7$**HHH**).

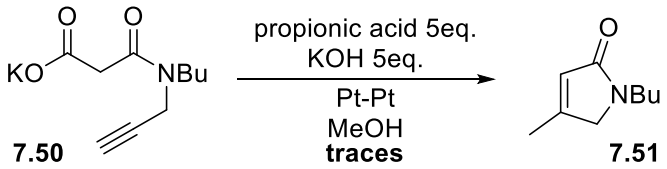
**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 169.34 (s, $C_1$), 163.17 (s, $C_3$), 79.49 (s, $C_9$), 72.00 (s, $C_{10}$), 48.21 (s, $C_4$), 42.20 (s ,$C_2$), 34.93 (s, $C_8$), 30.56 (s, $C_5$), 29.59 (s, $C_5$), 20.10 (s, $C_6$), 19.95 (s, $C_6$), 13.85 (s, $C_7$), 13.82 (s, $C_7$).

**IR (film, cm$^{-1}$):** 3283, 2924, 2853, 1630, 1461, 1370, 655.

**HRMS**, m/z: calculated $[C_{10}H_{15}O_3N^{39}K]^+$ : 236.06835, found: 236.06868.

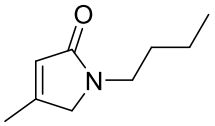
**MS/MS** (p ESI): m/z (%): 94.93146, (40); 192.02148, (18); 235.11664, (100); 236.06868, (66) $[M\text{-}H]^+$.

*Synthesis of 1-butyl-4-methylenepyrrolidin-2-one and 1-butyl-4-methyl-1,5-dihydro-2H-pyrrol-2-one*




**7.50** **7.51**

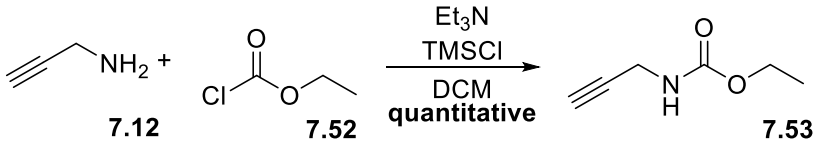
This molecule was synthetized according to the general procedure for the electrocyclization of pyrrolones and β,γ-unsaturated 2-pyrrolidinones (see p. 298).
**Purification:** chromatography on silica gel. Eluent: AcOEt/EP 4/6.




**HRMS**, m/z: calculated $[C_9H_{16}ON]^+$ : 154.12264, found: 154.12265.

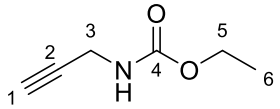
**MS/MS** (p ESI): m/z (%): 98.06185, (46); 154.12472, (100) $[M-H]^+$.

*Synthesis of ethyl prop-2-yn-1-ylcarbamate*




**7.12** **7.52** **7.53**

Propargyl amine (3.4 g, 63 mmol, 1 eq.) was dissolved into 137.1 ml of DCM (0.45 M), and the temperature mixture was cooled to 0°C. Consecutively, ethyl chloroformate (6.8 g, 63 mmol, 1 eq.) and triethylamine (7.4 g, 73 mmol, 1.2 eq.) were added dropwise to the reaction mixture. The solution was then stirred for one hour. After completion of the reaction, the solution was treated with 100 ml of HCl 1N and extracted two times with 50 ml of DCM. The combined organic layers were washed with 100 ml of brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified via silica gel chromatography (EP/AcOEt 9/1).

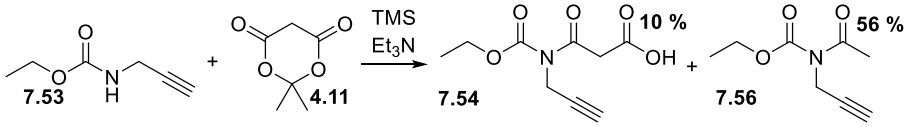



**$^1$H NMR (300 MHz, $CDCl_3$) : δ** 5.36 (s, 1H, N**H**), 4.05 (q, J = 7.1 Hz, 2H, $C_5$**HH**), 3.91 – 3.83 (m, 2H, $C_3$**HH**), 2.18 (t, J = 2.5 Hz, 1H, $C_1$**H**), 1.15 (t, J = 7.1 Hz, 3H, $C_6$**HHH**).

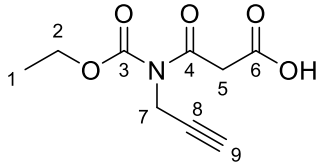
**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 156.22 (s, $C_4$), 79.90 (s, $C_2$), 71.36 (s, $C_1$), 61.21 (s, $C_5$), 30.65 (s, $C_3$), 14.53 (s, $C_6$).

**IR (film, cm$^{-1}$):** 3296, 2983, 1690, 1519, 1242, 1042, 633.

*Synthesis of 3-((ethoxycarbonyl)(prop-2-yn-1-yl)amino)-3-oxopropanoic acid*




Ethyl prop-2-yn-1-ylcarbamate (2.5 g, 20 mmol, 1.0 eq.) and triethylamine (2.8 g, 28 mmol, 1.4 eq.) were dissolved into 23.4 ml of DCM. Subsequently, TMSCl (3.3 g, 30 mmol, 1.5 eq.) was added dropwise to the solution. The reacting mixture was heated under reflux for 20 minutes, and then cooled to ambient temperature. Consecutively, Meldrum's acid (2.9 g, 20 mmol, 1.0 eq.) dissolved in 18.8ml of DCM was added to the solution. The mixture was stirred for one hour, at ambient temperature. After completion of the reaction, the solution was treated with 100 ml of an aqueous solution saturated in $KHCO_3$. The aqueous layer was then extracted three times with 20 ml of *n*-hexane. The combined aqueous layers were treated with a solution of HCl 37 %, until the pH was acidic. Finally, the aqueous layer was extracted three times with 20 ml of DCM. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The product was finally used without further purification.

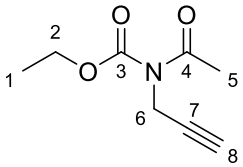


**$^1$H NMR (300 MHz, $CDCl_3$) : δ** 4.07 (q, J = 7.1 Hz, 2H, $C_2$**HH**), 3.92 – 3.87 (m, 2H, $C_7$**HH**), 3.63 (s, 2H, $C_5$**HH**), 2.19 (t, J = 2.7 Hz, 1H, $C_9$**H**), 1.20 (t, J = 7.1 Hz, 3H, $C_1$**HHH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 171.51 (s, $C_6$), 163.11 (s, $C_4$), 156.22 (s, $C_3$), 79.95 (s, $C_8$), 71.30 (s, $C_9$), 61.16 (s, $C_2$), 36.19 (s, $C_5$), 30.60 (s, $C_7$), 14.51 (s, $C_1$).

**IR (film, cm$^{-1}$):** 2246, 2140, 1741, 1724, 1680, 1436, 1202, 1002, 933.
**HRMS**, m/z: calculated $[C_9H_{12}O_5N]^+$ : 214.07100, found: 214.07093.

**MS/MS** (p ESI): m/z (%): 100.03934, (100); 128.07026, (49); 133.04909, (35); 214.01776, (36) $[M-H]^+$.



**$^1$H NMR (300 MHz, $CDCl_3$) : δ** 4.07 (q, J = 7.1 Hz, 2H, $C_2$**HH**), 3.92 – 3.88 (m, 2H, $C_6$**HH**), 2.19 (t, J = 2.7 Hz, 1H, $C_8$**H**), 1.72 (s, 3H, $C_5$**HHH**), 1.20 (t, J = 7.1 Hz, 3H, $C_1$**HHH**).

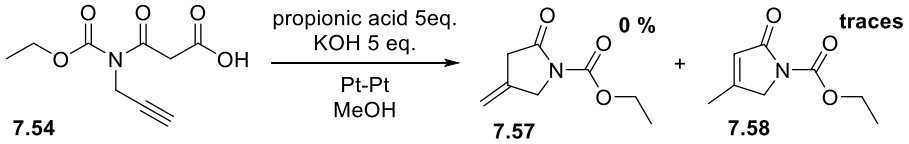
**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 163.11 (s, $C_4$), 156.22 (s, $C_3$), 79.95 (s, $C_7$), 71.30 (s, $C_8$), 61.16 (s, $C_2$), 30.60 (s, $C_6$), 27.47 (s, $C_5$), 14.51 (s, $C_1$).

**IR (film, cm$^{-1}$):** 2226, 1731, 1714, 1639, 1536, 1102, 1062, 983.

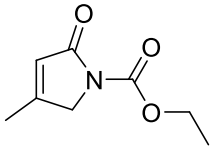
**HRMS**, m/z: calculated $[C_8H_{12}O_3N]^+$ : 170.08117, found: 170.08115.

**MS/MS** (p ESI): m/z (%): 98.06016, (24); 100.03937, (71); 153.01763, (66); 170.02811, (100) $[M-H]^+$.

*Synthesis of ethyl 4-methylene-2-oxopyrrolidine-1-carboxylate and ethyl 4-methyl-2-oxo-2,5-dihydro-1H-pyrrole-1-carboxylate*



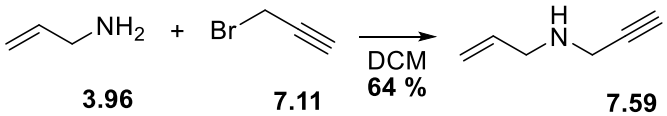

These molecules were synthetized according to the general procedure for the electrosynthesis of pyrrolones and β,γ-unsaturated 2-pyrrolidinones (see p. 298).
**Purification:** chromatography on silica gel. Eluent: AcOEt/EP 4/6.



**HRMS, m/z:** calculated $[C_8H_{12}O_3N]^+$ : 170.08117, found : 170.08111.

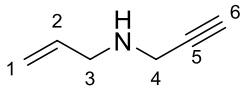
**MS/MS (p ESI): m/z (%):** 98.06024, (5) ; 124.03911, (11) ; 142.04949, (100) ; 170.08067, (7) $[M-H]^+$.

*Synthesis of N-(prop-2-yn-1-yl)prop-2-en-1-amine*[248]




Allylamine (11.26 ml, 150 mmol, 5 eq.) was dissolved in 53 ml of DCM, and the solution was cooled to a temperature of 0°C. Propargyl bromide 80 Wt. % in toluene (3.35 ml, 30 mmol, 1 eq.) was then added dropwise to the solution, and the solution was allowed to stir overnight, at room temperature. After completion of the reaction, the mixture was diluted with 30 ml of DCM, and extracted two times with 30 ml of water. The aqueous layer was subsequently extracted with 30 ml of DCM. Consecutively, the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Finally, the desired product was used without further purification.

[248] Yanwu, L.; Tobin, M. *Journal of the American Chemical Society* **1998**, 8, 1757.



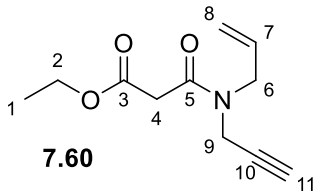

**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 6.06 – 5.73 (m, 1H, $C_2$**H**), 5.36 – 4.99 (m, 2H, $C_1$**HH**), 3.50 – 3.41 (m, 2H, $C_3$**HH**), 3.41 – 3.30 (m, 2H, $C_4$**HH**), 2.26 – 2.18 (m, 1H, $C_6$**H**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 135.95 (s, $C_2$), 116.65 (s, $C_1$), 82.03 (s, $C_5$), 71.38 (s, $C_6$), 50.88 (s, $C_4$), 41.66 (s, $C_3$).

**IR (film, $cm^{-1}$):** 2921, 2851, 1666, 1602, 1462, 927, 720.

*Synthesis of N-allyl-3-oxo-N-(prop-2-yn-1-yl)hexanamide*

This molecule was synthetized according to the general procedure for preparing amide from the corresponding secondary amine using DCC coupling agent (see p. 203).




**7.60**

**Yield:** 42 % - colourless oil.

**Purification:** chromatography on silica gel. Eluent: EP/AcOEt 9/1.

**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 5.80 – 5.76 (m, 1H, $C_7$**H**), 5.35 – 5.10 (m, 2H, $C_8$**HH**), 4.32 – 3.96 (m, 6H, $C_2$**HH**, $C_6$**HH**, $C_9$**HH**), 3.57 (s, 0.7H, $C_4$**HH**), 3.44 (s, 1.3H, $C_4$**HH**), 2.30 (t, J = 2.5 Hz, 0.4H, $C_{11}$**H**), 2.21 (t, J = 2.5 Hz, 0.6H, $C_{11}$**H**), 1.35 – 1.19 (m, 3H, $C_3$**HHH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 167.43 (s, $C_3$), 167.28 (s, $C_3$), 165.95 (s, $C_5$), 165.77 (s, $C_5$), 132.10 (s, $C_7$), 131.89 (s, $C_7$), 118.24 (s, $C_8$), 117.88 (s, $C_8$), 78.44 (s, $C_{10}$), 77.95 (s, $C_{10}$), 73.00 (s, $C_{11}$), 72.05 (s, $C_{11}$), 61.63 (s, $C_2$), 61.56 (s, $C_2$), 49.81 (s, $C_6$), 48.06 (s, $C_6$), 41.44 (s, $C_4$), 41.14 (s, $C_4$), 37.02 (s, $C_9$), 34.40 (s, $C_9$), 14.10 (s, $C_1$).

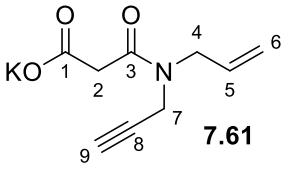
**IR (film, $cm^{-1}$):** 3269, 2922, 2852, 1737, 1650, 1444, 1369, 1321, 1159, 1127, 1096, 1027, 948, 846, 675.

**HRMS**, m/z: calculated $[C_{11}H_{16}O_3N]^+$ : 210.11247, found: 210.11253.

**MS/MS** (p ESI): m/z (%): 96.08247, (27); 122.06179, (100); 164.07263, (26); 210.11514, (17) $[M-H]^+$.

*Synthesis of potassium 3-(allyl(prop-2-yn-1-yl)amino)-3-oxopropanoate*

This molecule was synthetized according to the general procedure for preparing potassium salt from the corresponding ester (see p. 204).




**7.61**

**Yield:** 80 % - white powder.

**Purification:** filtration and wash with cold diethyl ether.

**$^{1}$H NMR (300 MHz, DMSO) : δ** 5.98 – 5.58 (m, 1H, $C_5$**H**), 5.33 – 5.00 (m, 2H, $C_6$**HH**), 4.29 – 3.81 (m, 4H, $C_4$**HH**, $C_7$**HH**), 3.67 – 3.32 (m, 2H, $C_2$**HH**), 3.28 – 3.07 (m, 1H, $C_9$**H**).

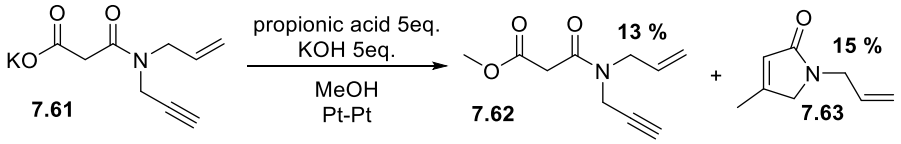
**$^{13}$C NMR (75 MHz, DMSO) : δ** 170.04 (s, $C_1$), 169.96 (s, $C_1$), 168.58 (s, $C_3$), 168.56 (s, $C_3$), 134.75 (s, $C_5$), 133.87 (s, $C_5$), 117.00 (s, $C_6$), 116.84 (s, $C_6$), 80.95 (s, $C_8$), 80.84 (s, $C_8$), 74.75 (s, $C_9$), 74.05 (s, $C_9$), 50.22 (s, $C_4$), 47.39 (s, $C_4$), 47.19 (s, $C_2$), 46.93 (s, $C_2$), 37.26 (s, $C_7$), 33.69 (s, $C_7$).

**IR (film, cm$^{-1}$):** 3272, 2924, 2852, 1745, 1598, 1431, 1369, 1260, 1200, 1168, 927, 836.

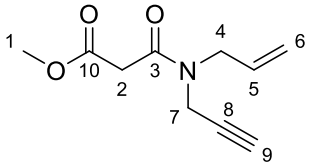
**HRMS**, m/z: calculated $[C_9H_{11}O_3N^{39}K]^+$ : 220.03705, found: 220.03703.

**MS/MS** (p ESI): m/z (%): 94.06688, (65); 119.03573, (18); 136.07753, (21); 140.98635, (15); 155.00217, (26); 178.01846, (100); 197.00060, (16); 220.03998, (36) $[M-H]^+$.

*Synthesis of N-allyl-2-methoxy-N-(prop-2-yn-1-yl)acetamide*




These molecules were synthetized according to the procedure for the electrosynthesis of pyrrolones and β,γ-unsaturated 2-pyrrolidinones (see p. 252).
**Purification:** chromatography on silica gel. Eluent: AcOEt/EP 4/6.

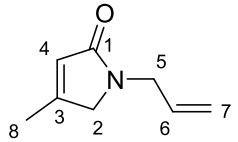



**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 5.80 – 5.76 (m, 1H, $C_5$**H**), 5.31 – 5.16 (m, 2H, $C_6$**HH**), 4.27 – 3.98 (m, 4H, $C_4$**HH**, $C_7$**HH**), 3.75 (s, 1.14H, $C_1$**HHH**), 3.74 (s, 1.86H, $C_1$**HHH**), 3.58 (s, 0.72H, $C_2$**HH**), 3.46 (s, 1.18H, $C_2$**HH**), 2.31 (t, J = 2.5 Hz, 0.38H, $C_9$**H**), 2.21 (t, J = 2.5 Hz, 0.62H, $C_9$**H**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 167.82 (s, $C_{10}$), 167.71 (s, $C_{10}$), 165.79 (s, $C_3$), 165.62 (s, $C_3$), 132.08 (s, $C_5$), 131.83 (s, $C_5$), 118.34 (s, $C_6$), 117.85 (s, $C_6$), 78.38 (s, $C_8$), 77.89 (s, $C_8$), 73.04 (s, $C_9$), 72.14 (s, $C_9$), 52.53 (s, $C_1$), 49.82 (s, $C_4$), 48.15 (s, $C_4$), 41.21 (s, $C_2$), 40.91 (s, $C_2$), 37.04 (s, $C_7$), 34.48 (s, $C_7$).

**IR (film, $cm^{-1}$):** 3266, 2922, 2852, 1739, 1651, 1434, 1416, 1242, 1189, 1119, 1095, 1050, 993, 970, 928, 674.

**HRMS**, m/z: calculated $[C_8H_{12}ON]^+$ : 196.09685, found: 196.09697.




**$^1$H NMR (300 MHz, $CDCl_3$) : δ** 5.87 – 5.80 (m, 2H, $C_4$**H**, $C_6$**H**), 5.19 – 5.16 (m, 2H, $C_7$**HH**), 3.95 (s, 2H, $C_2$**HH**), 3.92 – 3.87 (m, 2H, $C_5$**HH**), 2.08 – 2.06 (m, 3H, $C_8$**HHH**).

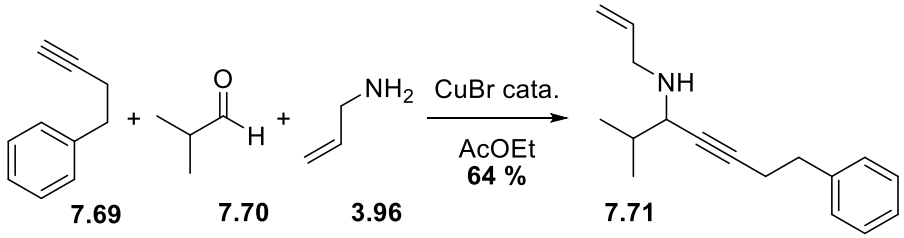
**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 173.47 (s, $C_1$), 155.82 (s, $C_3$), 131.72 (s, $C_6$), 122.48 (s, $C_4$), 117.39 (s, $C_7$), 54.27 (s, $C_2$), 49.67 (s, $C_5$), 15.72 (s, $C_8$).

**IR (film, $cm^{-1}$):** 2934, 2214, 1680, 1653, 1434, 1348, 1122, 943.

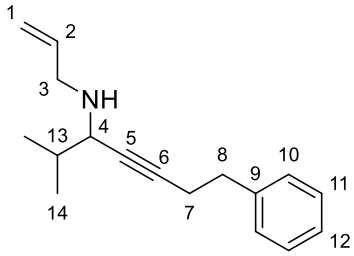
**HRMS**, m/z: calculated $[C_8H_{12}ON]^+$ : 138.09134, found : 138.09134.

**MS/MS** (p ESI): m/z (%): 83.05089, (26); 96.08256, (34); 110.09826, (48); 138.09321, (100) $[M-H]^+$.

*Synthesis of N-allyl-2-methyl-7-phenylhept-4-yn-3-amine*




Copper (I) bromide (0.83 g, 5.76 mmol, 0.6 eq.), allylamine (0.72 ml, 9.60 mmol, 1.0 eq.), isobutyraldehyde (1.14 ml, 12.48 mmol, 1.3 eq.) and 4-phenyl-1-butyne (2.70 ml, 19.20 mmol, 2 eq.) were dissolved into 19.20 ml of AcOEt. The solution was allowed to stir, at reflux, overnight. After completion of the reaction, the mixture was filtered over a celite pad and the celite pad was washed with 5 ml of diethyl ether. The combined organic layers were then dried over $MgSO_4$ and concentrated under reduced pressure. Finally, the crude product was purified via silica gel chromatography (EP/AcOEt 9/1).




**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 7.32 – 7.07 (m, 5H, Ph**H**), 5.91 – 5.71 (m, 1H, $C_2$**H**), 5.06 (dddd, J = 25.1, 10.2, 3.2, 1.5 Hz, 2H, $C_1$**HH**), 3.43 – 3.23 (m, 1H, $C_4$**H**), 3.18 – 3.01 (m, 2H, $C_3$**HH**), 2.75 (t, J = 7.2 Hz, 2H, $C_8$**HH**), 2.54 – 2.38 (m, 2H, $C_7$**HH**), 1.82 – 1.60 (m, 1H, $C_{13}$**H**), 0.86 (d, J = 6.7 Hz, 6H, $C_{14}$**HHH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 140.79 (s, $C_9$), 136.69 (s, $C_2$), 128.48 (s, $C_{11}$), 128.30 (s, $C_{10}$), 126.19 (s, $C_{12}$), 116.08 (s, $C_1$), 83.77 (s, $C_6$), 80.37 (s, $C_5$), 55.80 (s, $C_4$), 50.31 (s, $C_3$), 35.41 (s, $C_8$), 32.70 (s, $C_{13}$), 20.87 (s, $C_7$), 19.78 (s, $C_{14}$), 17.57 (s, $C_{14}$).

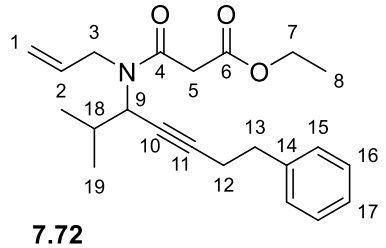
**IR (film, $cm^{-1}$):** 2805, 2004, 1647, 1587, 1368, 1326, 1234, 1122, 1064, 959, 847, 689.

**HRMS**, m/z: calculated $[C_{17}H_{24}N]^+$ : 242.19033, found: 242.19019.

**MS/MS** (p ESI): m/z (%): 58.06649, (74); 69.07125, (43); 91.05558, (18); 129.07116, (87); 143.08683, (100); 157.10261, (28); 185.13414, (26); 242.19235, (56).

*Synthesis of ethyl 3-(allyl(2-methyl-7-phenylhept-4-yn-3-yl)amino)-3-oxopropanoate*

This molecule was synthetized according to the general procedure for preparing amide from the corresponding secondary amine using DCC as coupling agent (see p. 203).




**7.72**

**Yield:** 70 % - colourless oil.

**Purification:** chromatography on silica gel. Eluent: EP.

**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 7.39 – 7.08 (m, 5H, Ph**H**), 5.92 – 5.65 (m, 1H, $C_2$**H**), 5.24 – 4.99 (m, 2H, $C_1$**HH**), 4.34 – 3.96 (m, 3H, $C_9$**H**, $C_7$**HH**), 3.96 – 3.83 (m, 2H, $C_3$**HH**), 3.60 – 3.27 (m, 2H, $C_5$**HH**), 2.80 (t, J = 7.4 Hz, 2H, $C_{13}$**HH**), 2.52 –

2.46 (m, 2H, $C_{12}$**HH**), 1.93 – 1.71 (m, 1H, $C_{18}$**H**), 1.31 – 1.22 (m, 3H, $C_8$**HHH**), 1.03 – 0.80 (m, 6H, $C_{19}$**HHH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 167.78 (s, $C_6$), 166.63 (s, $C_4$), 140.53 (s, $C_{14}$), 134.83 (s, $C_2$), 128.45 (s, $C_{16}$), 128.36 (s, $C_{15}$), 126.29 (s, $C_{17}$), 116.93 (s, $C_1$), 85.05 (s, $C_{11}$), 77.67 (s, $C_{10}$), 61.36 (s, $C_7$), 53.21 (s, $C_9$), 47.98 (s, $C_3$), 41.85 (s, $C_5$), 34.92 (s, $C_{13}$), 32.33 (s, $C_{18}$), 20.70 (s, $C_{12}$), 19.12 (s, $C_{19}$), 14.11 (s, $C_8$).

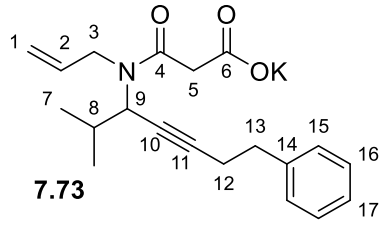
**IR (film, cm$^{-1}$):** 2962, 2929, 1738, 1650, 1454, 1409, 1368, 1316, 1260, 1182, 1158, 1034, 949, 747, 699.

**HRMS**, m/z: calculated $[C_{22}H_{30}O_3N]^+$ : 356.22202, found: 356.22203.

**MS/MS** (p ESI): m/z (%): 144.06704, (10); 1722.09859, (100); 356.22549, (14) $[M-H]^+$.

*Synthesis of potassium 3-(allyl(2-methyl-7-phenylhept-4-yn-3-yl)amino)-3-oxopropanoate*

This molecule was synthetized according to the general procedure for preparing potassium salt from the corresponding ester (see page 204).




**7.73**

**Yield:** 67 % - white powder.

**Purification:** filtration and wash with cold diethyl ether.

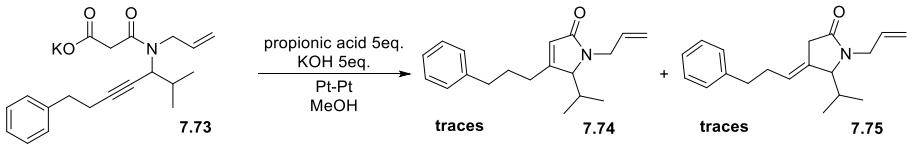
**$^1$H NMR (300 MHz, $CDCl_3$) : δ** 7.39 – 7.14 (m, 5H, Ph**H**), 5.86 – 5.82 (m, 1H, $C_2$**H**), 5.27 – 4.94 (m, 2H, $C_1$**HH**), 4.34 – 3.60 (m, 3H, $C_3$**HH**, $C_9$**H**), 3.42 – 3.19 (m, 2H, $C_5$**HH**), 2.80 (t, J = 7.4 Hz, 15H, $C_{13}$**HH**), 2.62 – 2.36 (m, 2H, $C_{12}$**HH**), 1.97 – 1.76 (m, 1H, $C_8$**H**), 1.05 – 0.77 (m, 6H, $C_7$**HHH**).

**13C NMR (75 MHz, CDCl3) : δ** 172.86 (s, $C_6$), 171.51 (s, $C_4$), 140.65 (s, $C_{14}$), 135.48 (s, $C_2$), 128.41 (s, $C_{16}$), 128.33 (s, $C_{15}$), 126.22 (s, $C_{17}$), 116.46 (s, $C_1$), 84.59 (s, $C_{11}$), 78.43 (s, $C_{10}$), 52.55 (s, $C_9$), 47.86 (s, $C_3$), 45.45 (s, $C_5$), 35.03 (s, $C_{13}$), 32.33 (s, $C_8$), 20.77 (s, $C_{12}$), 19.40 (s, $C_7$), 19.29 (s, $C_7$).

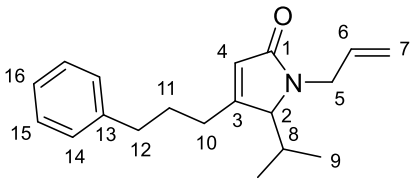
**IR (film, cm$^{-1}$):** 2942, 1758, 1632, 1554, 1469, 1328, 1232, 1102, 979.

**HRMS**, m/z: calculated $[C_{20}H_{24}O_3N]^-$ : 326.17507, found: 326.17656.

*Synthesis of 1-allyl-5-isopropyl-4-(3-phenylpropyl)-1,5-dihydro-2H-pyrrol-2-one*

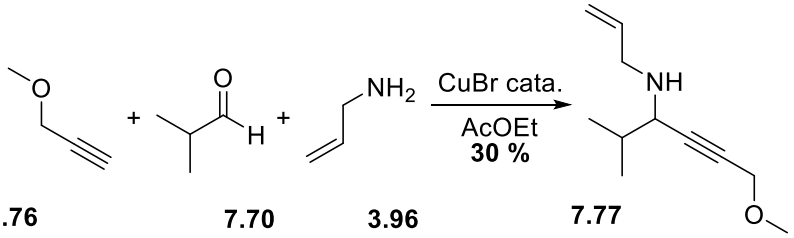



These molecules were synthetized according to the general procedure for the electrosynthesis of pyrrolones and β,γ-unsaturated 2-pyrrolidinones (see p. 298).

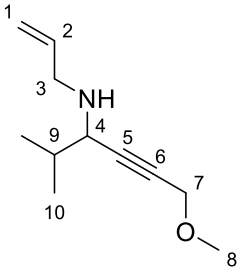


**HRMS**, m/z: calculated $[C_{19}H_{24}ON]^+$ : 282.18524, found: 282.18839.

*Synthesis of N-allyl-6-methoxy-2-methylhex-4-yn-3-amine*




Copper (I) bromide (1.033 g, 7.2 mmol, 0.6 eq.), allylamine (0.90 ml, 12 mmol, 1 eq.), isobutyraldehyde (1.42 ml, 15.6 mmol, 1.3 eq.) and methyl propargyl ether (2.02 ml, 24 mmol, 2 eq.) were dissolved in 24 ml of ethyl acetate. The solution was allowed to stir at reflux, until completion of the reaction, as shown by TLC. Subsequently, the mixture was filtered over a celite pad and the pad was washed with 10 ml of diethyl ether. The combined organic layers were dried over $MgSO_4$ and concentered under reduced pressure. Finally, the crude product was purified via silica gel chromatography (EP/AcOEt 9/1).



**$^1$H NMR (300 MHz, $CDCl_3$) : δ** 6.03 – 5.80 (m, 1H, $C_2$**H**), 5.31 – 5.00 (m, 2H, $C_1$**HH**), 4.15 (d, J = 1.7 Hz, 2H, $C_7$**H**), 3.53 – 3.48 (m, 1H, $C_4$**H**), 3.39 (s, 3H, $C_8$**HHH**), 3.33 – 3.18 (m, 2H, $C_3$**HH**), 1.94 – 1.77 (m, 1H, $C_9$**H**), 1.07 – 0.91 (m, 6H, $C_{10}$**HHH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 136.45 (s, $C_2$), 116.30 (s, $C_1$), 86.35 (s, $C_5$), 79.97 (s, $C_6$), 60.05 (s, $C_7$), 57.43 (s, $C_8$), 55.76 (s, $C_4$), 50.38 (s, $C_3$), 32.59 (s, $C_9$), 19.76 (s, $C_{10}$), 17.69 (s, $C_{10}$).

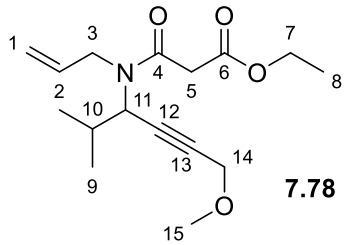
**IR (film, $cm^{-1}$):** 2227, 1458, 1282, 1149, 1086, 947, 926.

**HRMS**, m/z: calculated $[C_{11}H_{20}ON]^+$ : 182.15394, found: 182.15401.

**MS/MS** (p ESI): m/z (%): 91.05583, (66); 93.07146, (93); 95.08701, (100); 110.07416, (38); 125.09766, (19); 182.15601, (44) $[M-H]^+$.

*Synthesis of ethyl 3-(allyl(6-methoxy-2-methylhex-4-yn-3-yl)amino)-3-oxopropanoate*

This molecule was synthetized according to the general procedure for preparing amide from the corresponding secondary amine using DCC coupling agent (see p. 203).




**7.78**

**Yield:** 62 % - colourless oil.

**Purification:** chromatography on silica gel. Eluent: EP/AcOEt 9/1.

**$^1$H NMR (300 MHz, $CDCl_3$) : δ** 6.01 – 5.77 (m, 1H, $C_2$**H**), 5.29 – 5.07 (m, 3H, $C_1$**HH**, $C_{11}$**H**), 4.20 (q, J = 7.2 Hz, 2H, $C_7$**HH**), 4.10 (d, J = 1.9 Hz, 2H, $C_{14}$**HH**), 4.05 – 3.98 (m, 2H, $C_3$**HH**), 3.56 – 3.36 (m, 2H, $C_5$**HH**), 3.35 (s, 3H, $C_{15}$**HHH**), 2.07 – 1.88 (m, 1H, $C_{10}$**HH**), 1.28 (t, J = 7.2 Hz, 3H, $C_8$**HHH**), 1.06 (d, J = 6.7 Hz, 3H, $C_9$**HHH**), 0.93 (d, J = 6.7 Hz, 3H, $C_9$**HHH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 167.66 (s, $C_6$), 166.73 (s, $C_4$), 134.51 (s, $C_2$), 117.25 (s, $C_1$), 83.48 (s, $C_{12}$), 81.26 (s, $C_{13}$), 61.42 (s, $C_{14}$), 59.89 (s, $C_7$), 57.58 (s, $C_{15}$), 53.06 (s, $C_{11}$), 48.12 (s, $C_3$), 41.78 (s, $C_5$), 32.21 (s, $C_{10}$), 19.26 (s, $C_9$), 19.09 (s, $C_9$), 14.10 (s, $C_8$).

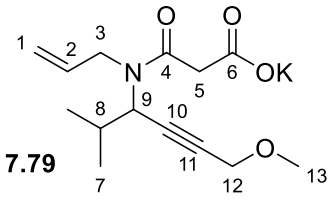
**IR (film, $cm^{-1}$):** 2969, 2927, 1740, 1651, 1408, 1262, 1157, 1096, 950, 906.

**HRMS**, m/z: calculated $[C_{16}H_{26}O_4N]^+$ : 296.18563, found: 296.18907.

**MS/MS** (p ESI): m/z (%): 144.067724, (14); 172.09881, (100); 264.16229, (35); 296.18892, (10) $[M-H]^+$.

*Synthesis of potassium 3-(allyl(6-methoxy-2-methylhex-4-yn-3-yl)amino)-3-oxopropanoate*

This molecule was synthetized according to the general procedure for preparing potassium salt from the corresponding ester (see p. 204).




**Yield:** 68 % - white solid.

**Purification:** filtration and wash with cold diethyl ether.

**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 6.24 – 5.74 (m, 1.43H, $C_2$**H**, $C_9$**H**), 5.33 – 4.99 (m, 2.57H, $C_1$**HH**, $C_9$**H**), 4.22 – 3.76 (m, 4H, $C_3$**HH**, $C_{12}$**HH**), 3.50 – 3.15 (m, 5H, $C_5$**HH**, $C_{13}$**HHH**), 1.96 – 1.88 (m, 1H, $C_8$**H**), 1.12 – 0.78 (m, 6H, $C_7$**HHH**).

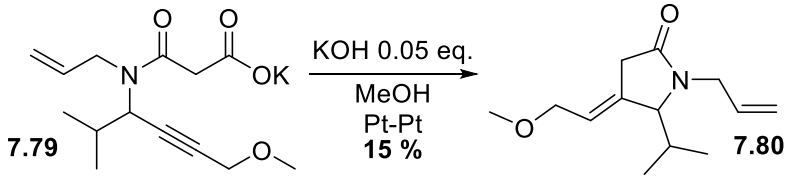
**$^{13}$C NMR (75 MHz, $CDCl_3$):** **δ** 172.74 (s, $C_6$), 171.20 (s, $C_4$), 134.90 (s, $C_2$), 116.90 (s, $C_1$), 84.10 (s, $C_{10}$), 80.88 (s, $C_{11}$), 59.92 (s, $C_{12}$), 57.59 (s, $C_{13}$), 52.71 (s, $C_9$), 48.00 (s, $C_3$), 44.71 (s, $C_5$), 31.99 (s, $C_8$), 19.50 (s, $C_7$), 19.25 (s, $C_7$).

**IR (film, cm$^{-1}$):** 3400, 2958, 2927, 1599, 1463, 1411, 1360, 1188, 1097, 907, 603.

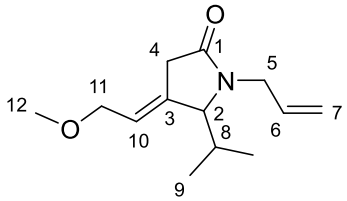
**HRMS**, m/z: calculated $[C_{14}H_{21}O_4N^{39}K]^+$ : 306.11022, found: 306.11017.

**MS/MS** (p ESI): m/z (%): 125.10913, (5); 306.29465, (100) $[M-H]^+$.

*Synthesis of (E)-1-allyl-5-isopropyl-4-(2-methoxyethylidene)pyrrolidin-2-one*




This molecule was synthetized according to the procedure for the electrosynthesis of pyrrolones and β,γ-unsaturated 2-pyrrolidinones (see p. 252).



**$^{1}$H NMR (300 MHz, $CDCl_3$) : δ** 5.80 – 5.65 (m, 1H, $C_6$**H**), 5.59 – 5.50 (m, 1H, $C_{10}$**H**), 5.28 – 5.12 (m, 2H, $C_7$**HH**), 4.14 – 4.08 (m, 1H, $C_2$**H**), 4.05 – 3.89 (m, 2H, $C_{11}$**HH**), 3.52 – 3.42 (m, 2H, $C_5$**HH**), 3.34 (s, 3H, $C_{12}$**HHH**), 3.09 – 2.97 (m, 2H, $C_4$**HH**), 2.15 – 2.04 (m, 1H, $C_8$**H**), 1.00 (d, J = 7.0 Hz, 3H, $C_9$**HHH**), 0.75 (d, J = 6.9 Hz, 3H, $C_9$**HHH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) : δ** 169.78 (s, $C_1$), 133.65 (s, $C_3$), 132.22 (s, $C_6$), 122.13 (s, $C_{10}$), 117.97 (s, $C_7$), 69.49 (s, $C_{11}$), 67.21 (s, $C_2$), 58.21 (s, $C_{12}$), 42.75 (s, $C_5$), 35.71 (s, $C_4$), 29.78 (s, $C_8$), 18.49 (s, $C_9$).

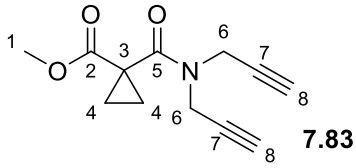
**IR (film, $cm^{-1}$):** 2924, 2853, 1676, 1460, 1257, 1097, 957.

**HRMS**, m/z: calculated $[C_{13}H_{22}O_2N]^+$ : 224.16451, found: 224.16453.

**MS/MS** (p ESI): m/z (%):93.07164, (4); 140.07243, (8); 224.16453, (100) $[M-H]^+$.

*Synthesis of methyl 1-(di(prop-2-yn-1-yl)carbamoyl)cyclopropane-1-carboxylate*

This molecule was synthetized according to the general procedure for preparing amide from the corresponding secondary amine using oxalyl chloride (see p. 249).




**7.83**

**Yield:** 86 % - colourless oil.

**Purification:** chromatography on silica gel. Eluent: EP/AcOEt 9/1.

**$^1$H NMR (300 MHz, $CDCl_3$) δ** 4.33 – 4.20 (m, 4H, $C_6$**HH**), 3.66 (s, 3H, $C_1$**HHH**), 2.36 – 2.17 (m, 2H, $C_8$**H**), 1.47 – 1.28 (m, 4H, $C_4$**HH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) δ** 171.4 (s, $C_2$), 167.3 (s, $C_5$), 79.9 (s, $C_7$), 74.7 (s, $C_8$), 54.4(s, $C_1$), 41.9 (s, $C_6$), 28.6 (s, $C_3$), 16.5 (s, $C_4$).

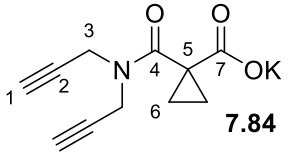
**IR (film, $cm^{-1}$)** 3288, 1724, 1651, 1434, 1416, 1309, 1213, 1152, 1079, 1036, 954, 928, 891, 859, 825, 755, 729, 646, 535, 481.

**HRMS, m/z:** calculated $[C_{12}H_{14}O_3N]^+$ : 220.09682, found: 220.09683.

**MS/MS (p ESI):** m/z (%): 95.01289, (11) ; 121.02818, (6); 127.03860, (100); 145.04895, (26); 188.06984, (9); 220.09596, (6) $[M-H]^+$.

*Synthesis of potassium 1-(di(prop-2-yn-1-yl)carbamoyl)cyclopropane-1-carboxylate*

This molecule was synthetized according to the general procedure for preparing potassium salt from the corresponding ester (see p. 204).




**7.84**

**Yield:** 68 % - white solid.

**Purification:** filtration and wash with diethyl ether.

**$^1$H NMR (300 MHz, DMSO) : δ** 4.35 – 4.08 (m, 4H, $C_3$**HH**), 3.28 – 3.11 (m, 2H, $C_1$**H**), 1.49 – 0.63 (m, 4H, $C_6$**HH**).

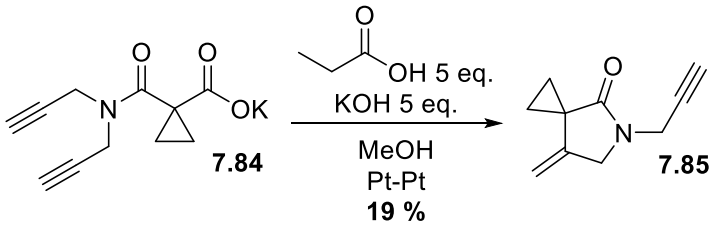
**$^{13}$C NMR (75 MHz, DMSO) : δ** 171.5 (s, $C_7$), 171.2 (s, $C_4$), 79.4 (s, $C_2$), 75.3 (s, $C_1$), 36.2 (s, $C_3$), 32.8 (s, $C_5$), 12.2 (s, $C_6$).

**IR (film, cm$^{-1}$)** 3254, 1730, 1644, 1581, 1454, 1407, 1373, 1311, 1188, 1036, 957, 765, 668, 636, 592, 546, 481.

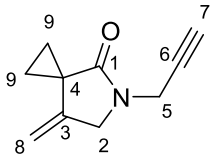
**HRMS, m/z:** calculated $[C_{11}H_{11}O_3NK]^+$ : 244.03705, found: 244,03705.

**MS/MS (p ESI): m/z (%):** 96.92826, (100) ; 243.28753, (5) [M].

*Synthesis of 7-methylene-5-(prop-2-yn-1-yl)-5-azaspiro[2.4]heptan-4-one*




This molecule was synthetized according to the general procedure for the electrocyclization of functionalized 2-pyrrolidinones (see p. 298).
**Purification:** chromatography on silica gel. Eluent: EP/AcOEt 6/4.




**$^1$H NMR (300 MHz, $CDCl_3$) δ** 4.84 – 4.81 (m, 1H, $C_8$**H**), 4.60 (t, *J* = 2.4 Hz, 1H, $C_8$**H**), 4.25 - 4.21 (m, 4H, $C_2$**HH**, $C_5$**HH**), 2.25 (t, *J* = 5.3, 2.7 Hz, 1H, $C_7$**H**), 1.52 - 1.47 (m, 2H, $C_9$**HH**), 1.05 - 1.00 (m, 2H, $C_9$**HH**).

**$^{13}$C NMR (75 MHz, $CDCl_3$) δ** 174.6 (s, $C_1$) 143.8 (s, $C_3$), 100.9 (s, $C_8$), 77.4 (s, $C_7$), 72.6 (s, $C_6$), 50.4 (s, $C_2$), 32.1 (s, $C_5$), 19.7 (s, $C_9$).

**IR (film, cm$^{-1}$)** 3294, 2923, 1698, 1665, 1481, 1436, 1344, 1270, 1231, 1177, 1040, 958, 876, 736, 638.

**HRMS, m/z:** calculated $[C_{10}H_{12}ON]^+$ : 162.09141, found: 162.09134.

**MS/MS (p ESI): m/z (%):** 81.07059, (23) ; 91.05488, (11) ; 94.06573, (17) ; 96.04497, (6) ; 107.04961, (15) ; 132.08102, (10) ; 134.09662, (69) ; 136.07585, (9) ; 162.09148, (100) $[M]^+$.