Università degli Studi di Cagliari

PHD DEGREE

Chemical Science and Technology

Cycle: XXXIII

DEVELOPMENT OF AN OXIDATION CATALYST DERIVED FROM RENEWABLE MATERIALS FOR APPLICATION TO BIOREFINERY

Scientific Disciplinary Sector(s)

CHIM06 / Organic Chemistry

PhD Student:	M.Sc. Andrea Beccu
Supervisor:	Prof. Stefano Enzo
Co-Supervisor:	Dr. Massimo Carraro

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Summary

Chapter One

Introduction

1) Introduction

Alcohol oxidation is a common conversion in both laboratory and industrial scale. Primary alcohols can be oxidized to aldehydes and carboxylic acids and secondary alcohols to ketones; due to the wide applications of these carbonylic compounds (e.g.: polymeric products, cosmetic, synthetic fibers, solvents, synthetic intermediates) this transformation have fundamental importance in organic chemistry synthesis.

During the years several oxidation protocols has been developed, which can be divided into stoichiometric and catalytic methods.

Unfortunately both methods have limitations as for the stoichiometric the heavy use of hazardous oxidizing agents (e.g.: Dess-Martin periodinane, SO_3/pyridine, CrO_3, etc.), formation of large amount of by-products and related issues in the large scale applications; for catalytic systems the limited availability and important toxicity of some transition metal based catalyst (e.g. Ru, Pd), low activity over some substrates (e.g.: sterically crowded alcohols with TEMPO) and the high cost of biciclyc nitroxyl radical catalyst (e.g.: ABNO, AZADO and their modifications), these catalytic systems need metal complexes as co-catalysts (e.g.: Cu) and primary oxidants with low atom economy and safety issues (e.g.: NaOCl, $NaClO_2$, $NaNO_3$, $Ca(OCl)_2$). Moreover, the biciclyc nitroxyl radicals, are synthetised using petroleum derivatives as starting materials, and in their synthesis many heavy metals and toxic solvents are used. Thus, the aim of this thesis is to synthesize a new biciclyc nitroxyl radical using glucose as renewable starting material and to develop a sustainable synthesis.

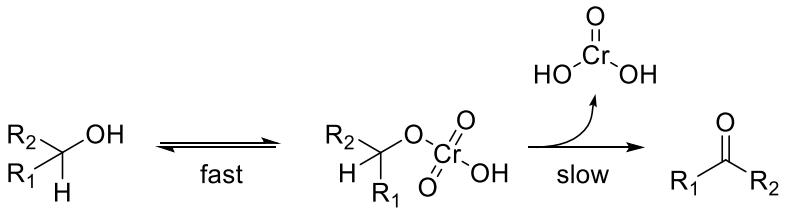
1.1 Non catalytic methods

There is a great number of compounds suitable for stoichiometric alcohols oxidation based on transition metals as Cr (Jones, Sarett and Collins, PDC, PPC), Mn (MnO2, KMnO4), Ru (RuO4, TPAP), activated dimethyl sulfoxide and hypervalent iodine compounds.

1.1.1 Chromium based oxidants

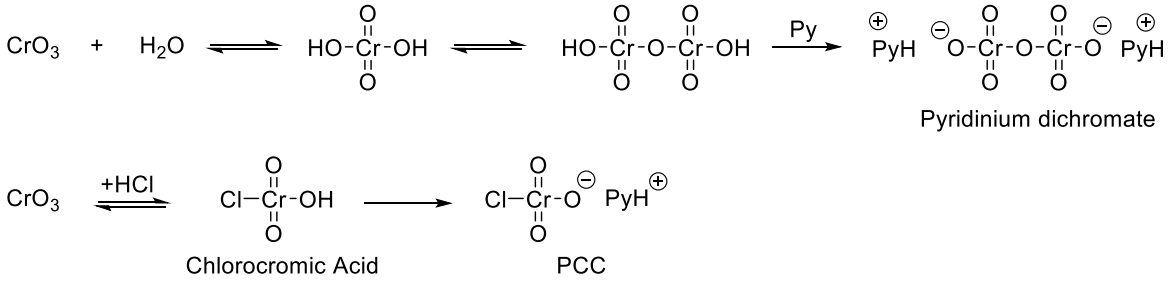
Chromium trioxide is a strong oxidant soluble in organic solvents like tert-butyl alcohol, pyridine or acetic anhydride, however its use isn't recommended because the resulting mixtures tends to explode. Mixing CrO_3 with pyridine lead to strong exothermical formation of CrO_3·Py complex that is soluble in organic solvents, a solution of this complex in pyridine is called Sarett Reagent[1], while CrO_3·Py solution in CH_2Cl_2 is called Collins Reagent[2]. Preparation of both Sarett and Collins reagent can be dangerous and they are highly hygroscopic, moreover CrO_3 derivates are very strong oxidant that can explode in presence of organic matter.

Safe use of CrO_3 is possible by preparing a solution with sulfuric acid and acetone, these properties lead to development of *Jones Oxidation*[3] method that became one of the most employed procedures for the oxidation of alcohols.



Scheme 1 Jones Oxidation

Pyridinium dichromate (PDC) and pyridinium chlorochromate (PCC), compared to others CrO_3 derivates, are safer to prepare (Scheme 2) and to store while Jones, Sarett and Collins are cheaper.



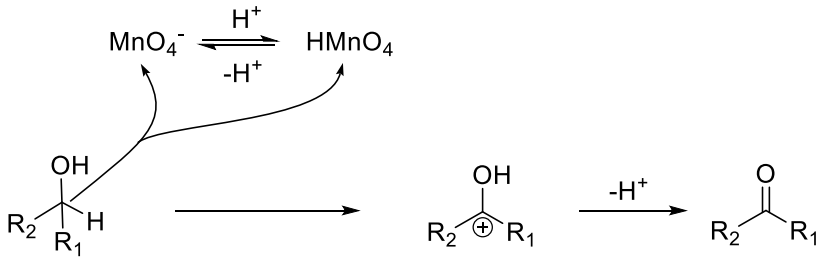
Scheme 2 PDC and PCC preparation

Main disadvantages of hygroscopic chromium systems used for oxidizing alcohol is that they lead to hydrated aldehydes that can be oxidized to carboxylic acid by the same chromium-based reagent[4]. Non hygroscopic oxidants as PCC needs anyway an anhydrous reaction environment to maintain their selectivity.

1.1.2 Manganese based oxidants

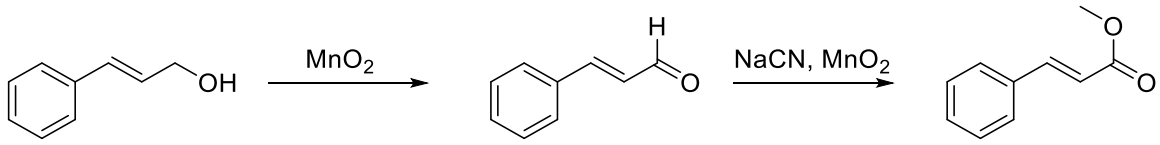
Potassium permanganate is a very strong oxidant used in many applications as industry (water purification)[5], pharmacology (skin diseases)[6], and chemical synthesis (oxidations)[7]. Despite his many applications, even in pharmacology, potassium permanganate it's known as toxic and non-environmentally friendly reagent. In fact, due the ease of its degradation, it's often necessary to use it in a large excess. Moreover, is toxic for the aquatic live with long lasting effects. Potassium permanganate has been largely used in alcohol oxidations during the last century and many protocol modifications have been developed as pH variation, solvent mixtures and use of co-oxidants. The reaction can be

catalysed both by acidic and basic conditions, but invariably aldehydes are further oxidized to carboxylic acids faster than they are formed.



Scheme 3 Oxidation mechanism in acidic conditions

Manganese dioxide is used in batteries[8], pigments and as precursor of $KMnO_4$. However, is even used as it is as oxidant for a,b-unsaturated and benzylic alcohols to give aldehydes that it is subsequently treated with sodium cyanide and an alcohol to give the corresponding ester.[9]



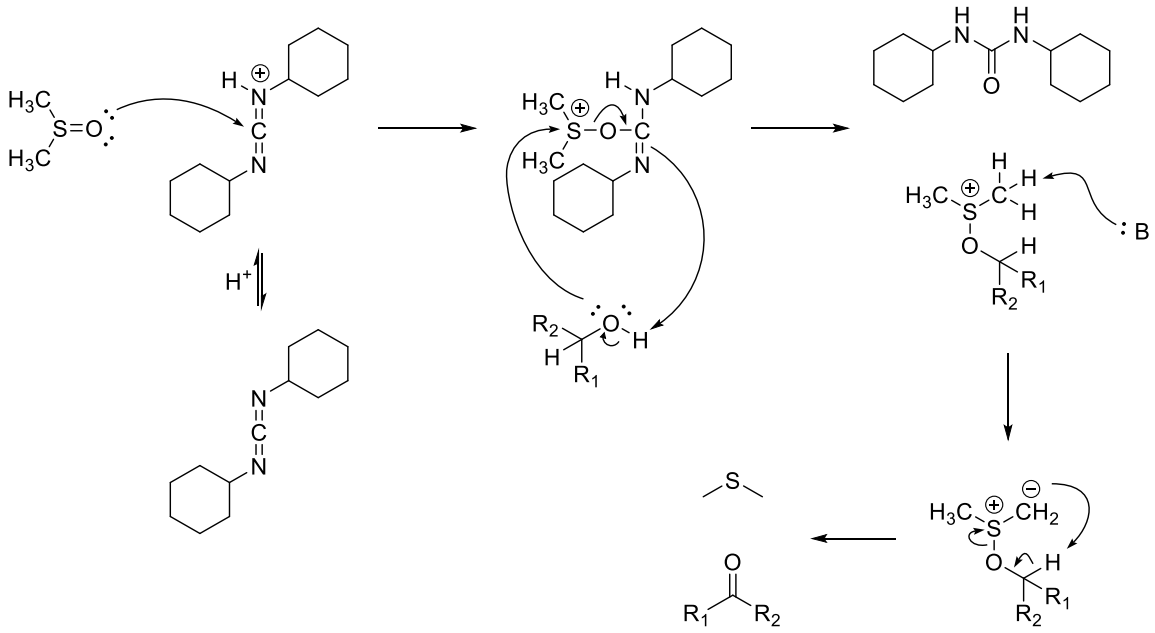
Scheme 4 Oxidation with MnO_2

However, this method uses a large excess of manganese and cyanide, highly toxic by itself and in contact with water or acid (generating hydrogen cyanide). For these reasons, MnO_2 is better used for selective oxidation of allylic and benzylic alcohols to just aldehyde or ketone stage.

1.1.3 Activated dimethyl sulfoxide methods

As reported in 1963 by Moffatt and Pfitzner[10] alcohols can be oxidized to aldehydes and ketones by a system with DMSO, dicylohexylcarbodiimide (DCC) and a mild acid, the mechanism of this oxidation suggested by Moffatt et al.[11] and Albright et al.[12] consists in the reaction between protonated DCC and DMSO that lead to "activated DMSO" complex with electrophilic S and a good leaving group, dicyclohexylurea (DCU). The nucleophilic oxygen from the alcohol can attack the "activated DMSO" with exit of DCU yielding a salt that loses a proton giving a sulfur ylide. An intramolecular reaction extract one proton from alcohol and yields dimethyl sulfide and the carbonylic compound.

The "activated DMSO" complex can suffer H^++DCU elimination before alcohol attack giving the high reactive ion $(H_2C{=}S{-}CH_3)^+$ that can react with the alcohol giving a methylthiomethyl ether as by-product. However, this side reaction demands a higher temperature than the one required for oxidation (room temperature or less).



Scheme 5 Moffat oxidation mechanism

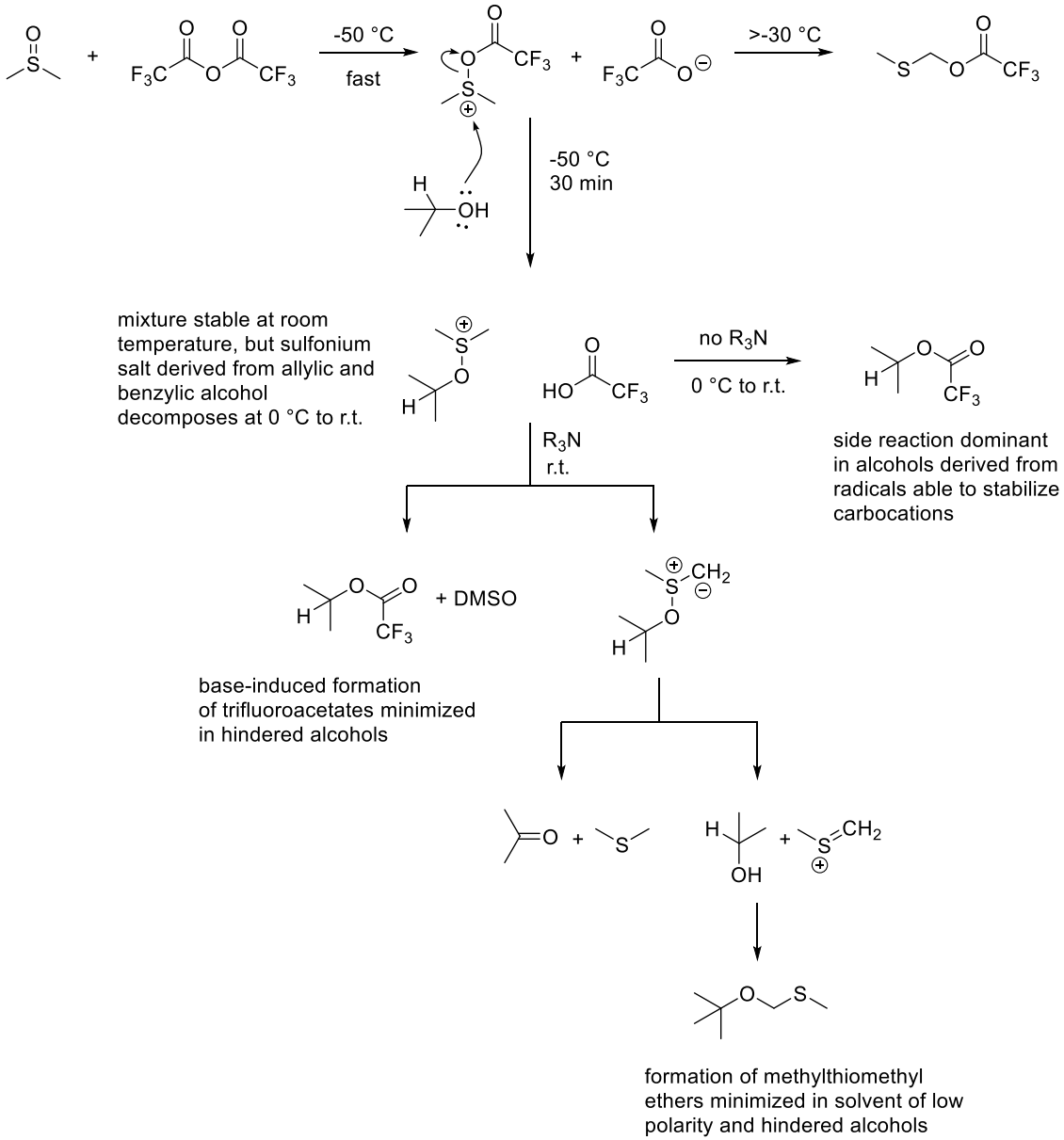
"Activated DMSO" methods work well on sensitive substrates and don't produce over oxidated species in primary alcohols oxidations. An issue of this method is the odor generated by the by-product dimethyl sulfide that stenches, possesses a low odor threshold and is very volatile. Another disadvantage of this method is the toxicity of reagents as DCC (or other dehydrating agents). Moreover, it is necessary to carefully choose the acid, in fact too strong acids (HCl, H_2SO_4, $HclO_4$) can prevent the formation of sulfur ylide intermediate while too weak acids (CH_3COOH) lead to slow and incomplete or no reaction at all. According to the Pfitzner–Moffatt method, developed using testosterone as a model substrate[11], the best reaction conditions are 0.5 eq of DCC, DMSO or a mixture DMSO-benzene as a solvent and pyridinium trifluoroacetate as the acid.

Various methods have been developed based on Pfitzner–Moffatt Method, including:

- Albright–Goldman[13] oxidized the model substrate yohimbine at room temperature simply replacing DCC with acetic anhydride (5 eq.) as DMSO activating agent. It's interesting to note that steric hindered alcohols give the best yield by slowing downside reactions. On the other hand, with simple substrates, this method gives large amounts of by-products, making this method not the first choice for regular alcohols oxidations, moreover the large excess of acetic anhydride implies a high waste production.

- Omura–Sharma–Swern[14]: Swern proved that the activate DMSO complex with trifluoroacetic anhydride is stable at low temperature and can be used as alcohols oxidant. In fact, while at room temperature the mixture of DMSO and TFAA react in an explosive

way, at low temperature and in the presence of CH_2Cl_2, the solution is stable and the "activated DMSO" trifluoroacetoxydimethylsulfonium trifluoroacetate is generated.



Scheme 6 Omura–Sharma–Swern oxidation

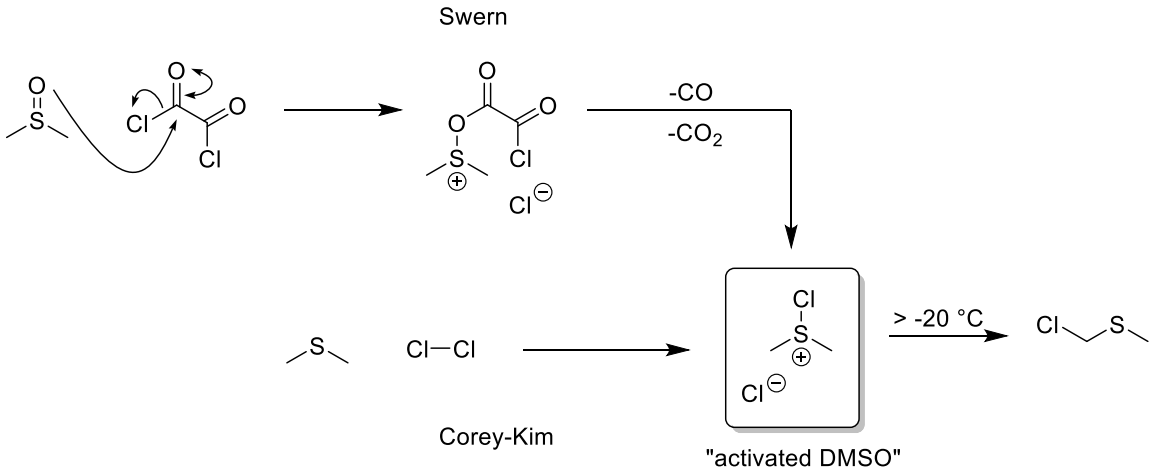
As the Albright–Goldman Method, this method tends to generate side products and this issue is suppressed for sterically hindered alcohols and low polar solvents.

- Swern Method[15–17]: this method has been, for many years, the default method for alcohols oxidation with "activated DMSO" because of his good yield with many substrates and the mild reaction conditions required. Oxalyl chloride reacts safely with DMSO at -60 °C giving chlorodimethylsulfonium chloride.

The first product decomposes with the elimination of CO and CO_2 giving the stable "activated DMSO", alcohol is added at ~-60 °C and react quickly with

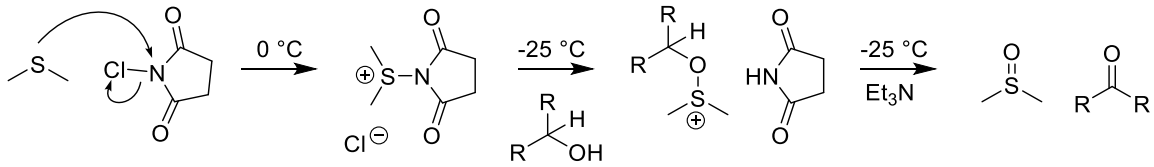
chlorodimethylsulfonium chloride giving the reaction intermediate that, after the addition of the base, yield the carbonylic compound and dimethyl sulfide.

- Corey–Kim[18–20] differs from all others “activated DMSO” methods by the preparation of the reagent, while in all others methods “activates DMSO” the starting product was DMSO, in this case is dimethyl sulfide.



Scheme 7 Swern and Corey-Kim “activated DMSO” preparation

Corey and Kim obtained the Swern “activated DMSO” by reacting dimethyl sulfide and chlorine, it is known that operating with gaseous chlorine is unsafe and unhandy so another “activated DMSO”-like species can be obtained replacing chlorine with N-chlorosuccinimide (NCS).



Scheme 8 Corey-Kim “activated DMSO” preparation

The Corey–Kim oxidation present the advantage that the oxidation can be carried out at relatively high temperature, but the method shares the same issues of all other methods.

Corey-Kim method in absence of base can be used for transformation of allylic and benzylic alcohols into halogenides, because in that case sulfoxonium intermediate is not stable and tend to undergo to a nucleophilic substitution by chloride (or bromide if NBS is used instead of NCS) anion[21].

1.1.4 Hypervalent Iodine Compounds

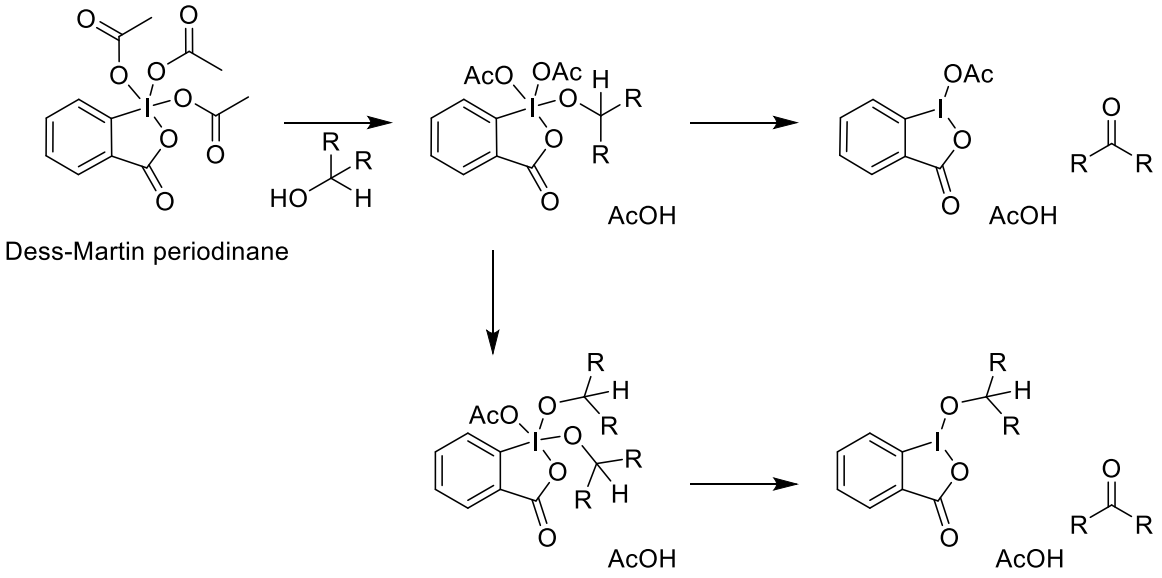
High valence state iodine owns strong oxidant behaviour, rarely used in organic synthesis for his poor stability and solubility in organic solvents until back in 1983 when Dess and

Martin proved that a new reagent based on 2-iodoxybenzoic acid can oxidize alcohols in mild conditions and with high yields and simple workup.

- Dess-Martin periodinane (DMP)[22]: it's prepared by treatment of iodobenzoic acid with potassium bromate or Oxone and acetylation of resulting o-iodoxybenzoic acid with acetic anhydride and acetic acid, the resulting compound (DMP), is quite stable and very soluble in organic solvents.

The DMP is efficient in the oxidation of alcohols in CH_2Cl_2 at room temperature and side reactions caused by acetic acid can be solved by adding a base. Mechanism of oxidation involves the initial replacement of an acetate by the alcohol molecule, then the intermediate evolves to yield the carbonyl compound, monoacetoxyiodinane and two acetic acid molecules. In case of excess of alcohols, the rate of oxidations increases, but a side reaction is activated and consists in the substitution of two acetates by the alcohols to give the carbonyl compound, alkoxyperiodinane and acetic acid.

Dess-Martin oxidations are normally carried out in CH_2Cl_2 but the method works in many organic solvents as $CHCl_3$, benzene, toluene, DMSO, DMF, THF, EtOAc under very mild conditions. The instability of hypervalent iodine compounds forming during DMP synthesis or as byproduct in alcohols oxidation, hampered the diffusion of this reagent.

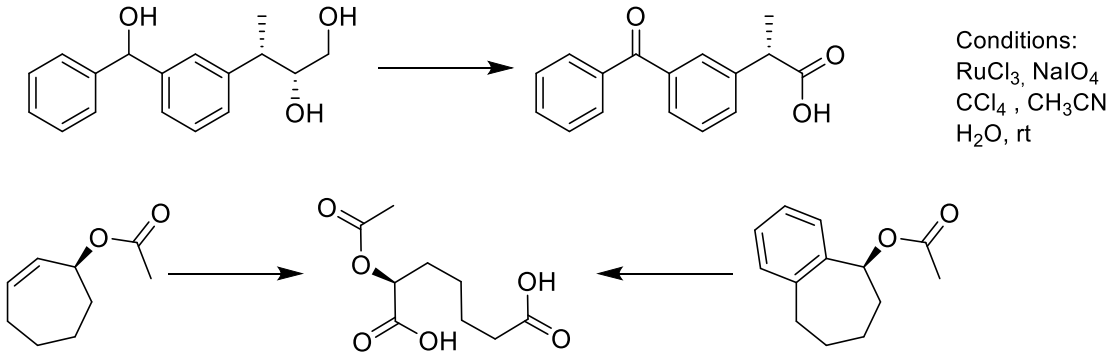


Scheme 9 Dess-Martin oxidation

1.1.5 Ruthenium-based oxidations

RuO_4 (similarly to OsO_4) is a strong oxidant useful in the dihydroxylation of alkenes, but is less expensive and toxic, however it reacts violently with common organic solvents and must be used with solvents refractory to ignitions as carbon tetrachloride. For these issues RuO_4 is not commonly used in alcohols oxidation but it can be useful for oxidation of very

hindered secondary alcohols that resist to other oxidants. RuO_4 can be, more conveniently generated in situ from a catalytic amount of RuO_2 or $RuCl_3$ with a stoichiometric amount of NaClO, $NaBrO_3$, CH_3COOOH, HIO_4, $NaIO_4$, $KMnO_4$, HIO_4, Cl_2, $Ce(SO_4)_2$ or $KHSO_5$; nevertheless selectivity can be an issue, because generated RuO_4 can oxidize a variety of functional groups, as shown in Scheme 10.



Scheme 10 oxidations with RuO_4 generated in situ

Perruthenate (RuO_4^-) and ruthenate (RuO_4^{2-}) ions, compared to RuO_4, own a lower oxidation state and are milder oxidants. They are able to oxidize alcohols, but both are unstable in water solution and requires to work under basic conditions. RuO_4^- ion can be used in organic solvents by coupling it with tetrapropyl ammonium. Griffith and Ley[23] showed that tetra-n-propylammoniumperruthenate (TPAP) is soluble and stable in organic solvents and is a good oxidant for alcohols. N-methylmorpholine N-oxide (NMNO) can regenerate reduced perruthenate, thus catalytic quantity of TPAP can oxidize alcohols to aldehydes and ketones under mild conditions in presence of NMNO.

1.2 Green chemistry

The environmental impact of the production and non-production[24] processes covers, as today, a main role into the international debate and it is a well-known argument even in the everyday life. On these years, the population around the world has reached a major consciousness about the huge consequences, in short and long time, that having bad behaviours in terms of energy consumption and waste production have on climate, plant and animal kingdoms, and even on humans' health. For instance, recycling and house trash separation is part of everyday life nowadays, while, just two decades ago, was not even strictly regulated. That new feeling is confirmed by the presence of eco-friendly products that are easy to find in every field (food, cosmetic, car, heating systems, energy production). Many classifications have been developed to recognize and sort all those products in terms of sustainability. However, in science, debate and concern about processes sustainability started long time ago, culminating, in chemistry, in the nineties with the twelve green chemistry principles described by Anastas and Warner[25], a guideline about the design of products and processes that minimize or eliminate the use and generation of hazardous substances.

- **Prevention**. It is better to prevent waste than to treat or clean up waste after it has been created.
- **Atom Economy**. Synthetic methods should be designed to maximize incorporation of all materials used in the process into the final product.
- **Less Hazardous Chemical Syntheses**. Wherever practicable, synthetic methods should be designed to use and generate substances that possess little or no toxicity to human health and the environment.
- **Designing Safer Chemicals**. Chemical products should be designed to preserve efficacy of function while reducing toxicity
- **Safer Solvents and Auxiliaries**. The use of auxiliary substances (e.g., solvents, separation agents, etc.) should be made unnecessary wherever possible and, innocuous when used.
- **Design for Energy Efficiency**. Energy requirements should be recognized for their environmental and economic impacts and should be minimized. Synthetic methods should be conducted at ambient temperature and pressure.
- **Use of Renewable Feedstocks**. A raw material or feedstock should be renewable rather than depleting whenever technically and economically practicable.
- **Reduce Derivatives**. Unnecessary derivatization (use of blocking groups, protection/deprotection, temporary modification of physical/chemical processes) should be minimized or avoided if possible, because such steps require additional reagents and can generate waste.
- **Catalysis**. Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.
- **Design for Degradation**. Chemical products should be designed so that at the end of their function they break down into innocuous degradation products and do not persist in the environment.
- **Real-time analysis for Pollution Prevention**. Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.
- **Inherently Safer Chemistry for Accident Prevention**. Substances and the form of a substance used in a chemical process should be chosen to minimize the potential for chemical accidents, including releases, explosions, and fires.

1.3 Green metrics

If the 12 principles are intended to found and guide the practice of sustainable chemistry, the green metrics are needed to measure the "greenness" of a process and give tools to compare different processes.

Traditionally the efficiency of a chemical process has been measured by yield, and this metric is still the most highlighted in the majorities of scientific papers, however, the yield considered alone does not give any information about sustainability of a process and it can even be misleading. In facts, the percentual yield can only give the percentual amount of reagent converted into product and it does not give any information about waste generated or amount of other reagents used. Moreover, the nature of reagents and by products (benign or not) is not evaluated.

In front of these considerations, it became evident that new parameters were needed to properly evaluate a chemical process and, during the years, many has been proposed.

Atom economy (AE). Was introduced by Trost in 1991[26,27] and is calculated by the ratio between the mass of desired product to the total mass of products (expressed as a percentage).

AE $\left(\frac{molecular\ mass\ of\ product}{\sum molecular\ mass\ of\ reagents} x100\right)$ is one of the most widely used metrics in green chemistry, a value of Atom Economy near to 100% means that most of the atoms of the reactant are incorporated in the product. Usually addition and rearrangement reaction, isomerization and catalytic reaction are the most common to reach a high Atom Economy value, while substitution reaction and elimination reaction, for their nature, usually give a low Atom Economy value. AE is not designed to take account of yield.

Carbon Economy (CE). Calculated as $\frac{moles\ of\ product * number\ of\ carbons\ in\ product}{\sum moles\ of\ reagent * numeber\ of\ carbons\ in\ reagent} x100$; this parameter is widely use in synthesis of pharmaceuticals as, building a carbon skeleton, is a key objective in drugs development. A high Carbon Economy value means that most of the reagent's carbon atoms are incorporates in the product and are not generating waste. CE, differently from AE, takes account of yield.

Reaction Mass Efficiency (RME). RME is a parameter proposed by Constable et al. in 2002[28], and is the percentage of the mass of the reactants that remain in the product. Is calculated as $\frac{mass\ product}{\sum mass\ of\ reagents} x100$. RME takes account of Yield and Atom Economy.

Effective Mass Efficiency. Proposed by Hudlicky in 1996[29] this metric attempts to takes into account the nature of reagents and it's calculated by $\frac{mass\ product}{\sum mass\ of\ non\ benign\ materials} x100$, materials includes reagents, solvents and catalyst. However, the concept of "non benign", cannot be objectively and universally defined while environmental impact and/or toxicologic data are not available for all existent chemicals.

Environmental factor (E-Factor). Introduced by Sheldon in 1992[30] point the attention on the mass of waste produced per mass of product, is calculated by $\frac{Total\ waste\ (kg)}{Kg\ of\ product}$.

Mass Intensity (MI). Is calculated by $\frac{Total\ mass\ used}{mass\ of\ product}$ and takes into account solvents and any other reagents and catalysts used in the process, *Total mass used* includes materials used in the work-up as solvents for extraction/crystallization, anhydrification salts. MI was later re-named Process Mass Intensity (PMI)[31]. From MI, can be derived Mass Productivity by his reciprocal multiplied by 100. $MP = \frac{1}{MI} x100 = \frac{mass\ of\ product}{Total\ mass\ used} x100$.

These green metrics are needed and helpful into the attempt of evaluating the greenness of a process and comparing different processes, however, they suffer a lack of definitions and accordance in scientific community about *What it really is a waste? How and how much one can consider a solvent recyclable? How to take into accounts the energy/materials used for recover a solvent/catalyst?*

All those who have found themselves having to calculate green metrics asked themselves these questions, often not finding an unambiguous answer, and many green metrics attracted criticism for their not clearly and univocal application. For those reasons and for the background needed to understand and use them, green metrics struggles to become widely used and the yield still, almost exclusively, the parameter used to evaluate a reaction. However, looking in the field of green chemistry, even facing the criticism described above, green metrics are rising, and are helping to dig and investigate the nature of the chemical processes.

1.4 Notable examples

An interesting case is that of isobutylphenylpropionic acid, commonly known as ibuprofen. Ibuprofen is a nonsteroidal anti-inflammatory drug used for treating pain, fever, and inflammation.

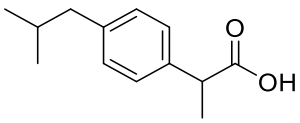
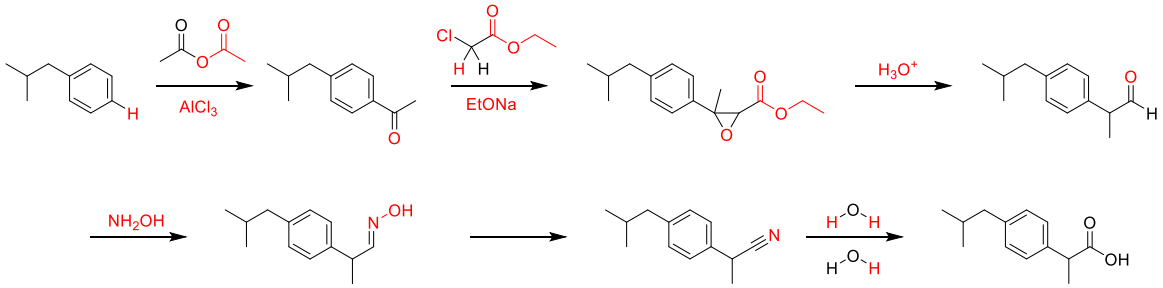


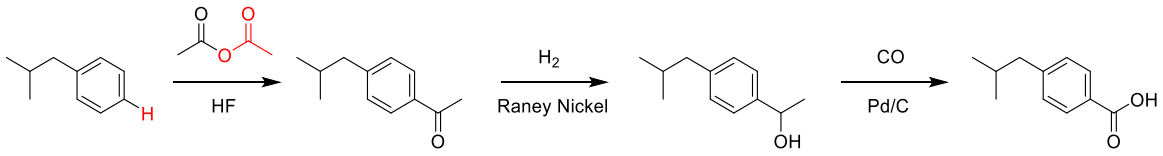
Figure 1 Ibuprofen

The synthesis for this drug has been patented in the ‘60s by Boots company, the process led to the desired product in 6 steps, but large amount of reactants are wasted and not incorporated into the final product. The result it’s a poor atom economy, in fact about 60% of used material are wasted, since the annual production of ibuprofen it’s around 13 kilotons, around 16 kilotons of waste are produced every year. Moreover, there isn’t a focus on catalysis and use of low environmental impact reagent and intermediates.



Scheme 11 Boots ibuprofen synthesis (wasted materials in red)

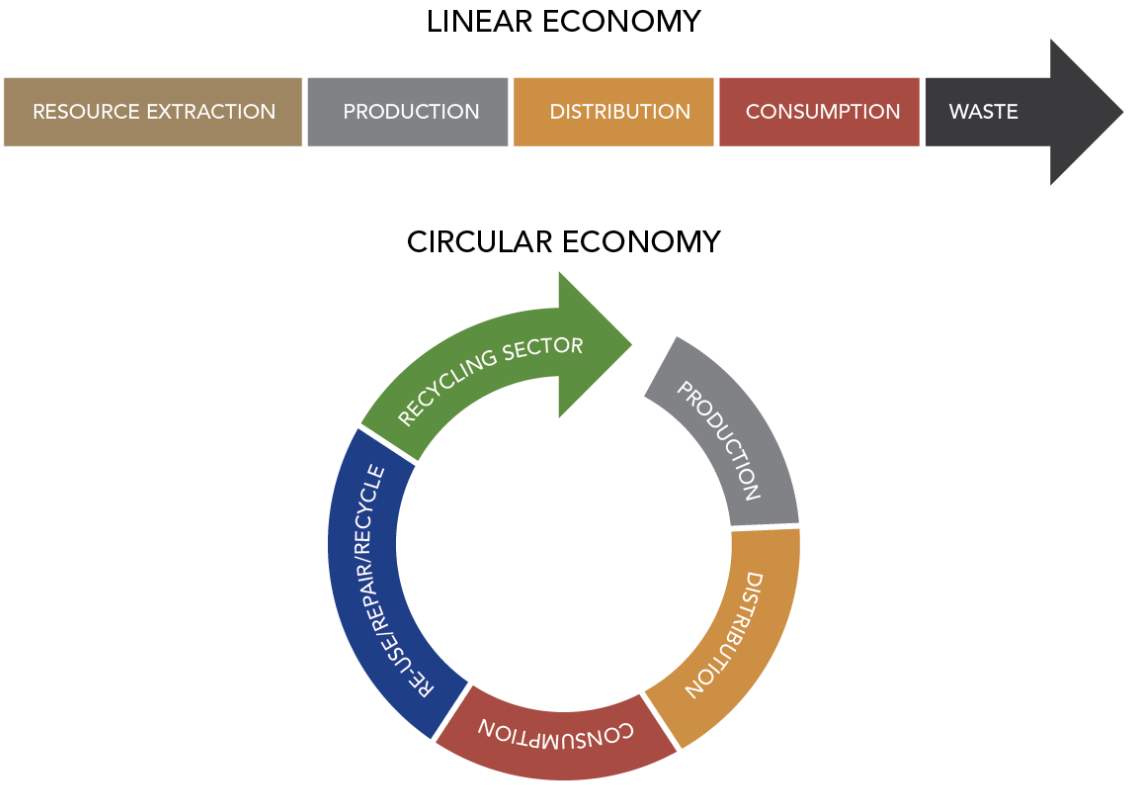
When the patent ran out, BHC company developed a new synthesis bringing the atom economy at 77% (90% if the acetic acid generated in step 1 is recovered and recycled). Moreover, the BHC synthesis is a 3-steps catalytic synthesis, differently than Boots synthesis that uses reagents in stoichiometric amounts.



Scheme 12 BHC ibuprofen synthesis (wasted materials in red)

1.5 Circular Economy and Biorefinery

Linear economy is a model where resources are extracted and transformed by the production chain into goods that are distributed for consumption and, at the end, wasted. Such a model relies on a hypothetical infinite source of raw materials and a system able to accept waste without limits. Nowadays, it is clear that such a system is not sustainable, because the supply of commodities as oil and minerals has limited production capabilities and the waste accumulation poses a serious pollution problem (e.g.: plastics in the land and water bodies, greenhouse gases in the atmosphere). Circular economy is a concept where the production is based on recycled or renewable materials that should stem from the end of the life of commercial goods.

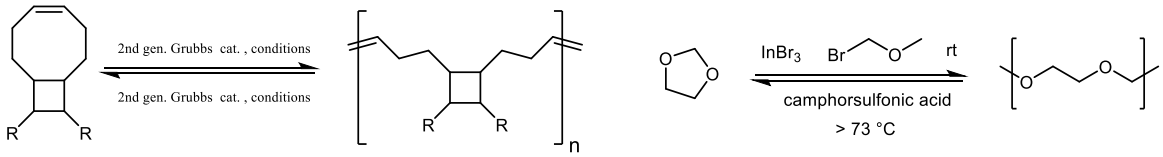


An approach of this kind is infused in the European Community directive 2008/98[32,33] which defines a waste hierarchy to better manage the problem:

1. Prevention (processes that generate products and not waste).
2. Preparing for re-use (giving a finished product a second life).
3. Recycling (e.g.: paper, plastics, glass, and metals)
4. Recovery (e.g.: composting and incinerating plants to partially recover organic matter and energy)
5. Disposal (e.g.: landfill)

Focusing on processes and materials that involve organic chemistry, it is important to point out that a complete revision of the life cycle needs to be implemented. Plastics, for instance, are typically derived from fossil fuels, a depleting source, and their recycle is not very effective. Recycling is done by re-melting and reforming used plastics into new items: this can cause the polymer to partially degrade and also requires the complicated and expensive task of sorting the waste by both color and chemical composition before being reprocessed. Failures in this process leads to materials with undesired properties and low commercial value. There are many ways to tackle the problem, design improvements in the packaging could make plastic recycle simpler and more effective and halve its cost[34]. Depolymerize[35] a polymer at the end of its use is a challenge pursued at the top notch of applied research[36,37]; recent results demonstrated that, by controlling conditions such as

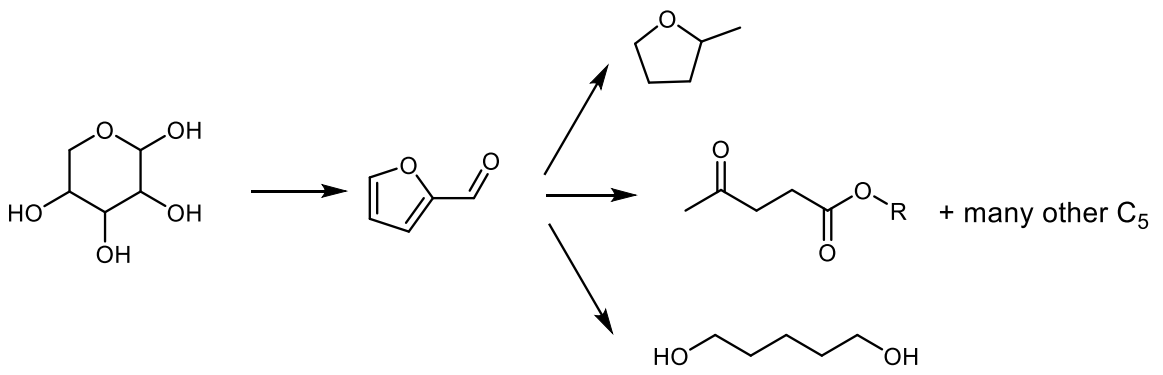
temperature and catalyst, it was possible to convert a monomer into a technological useful polymer and back to the parent monomer with excellent yields.



Scheme 13 Conversion of monomers

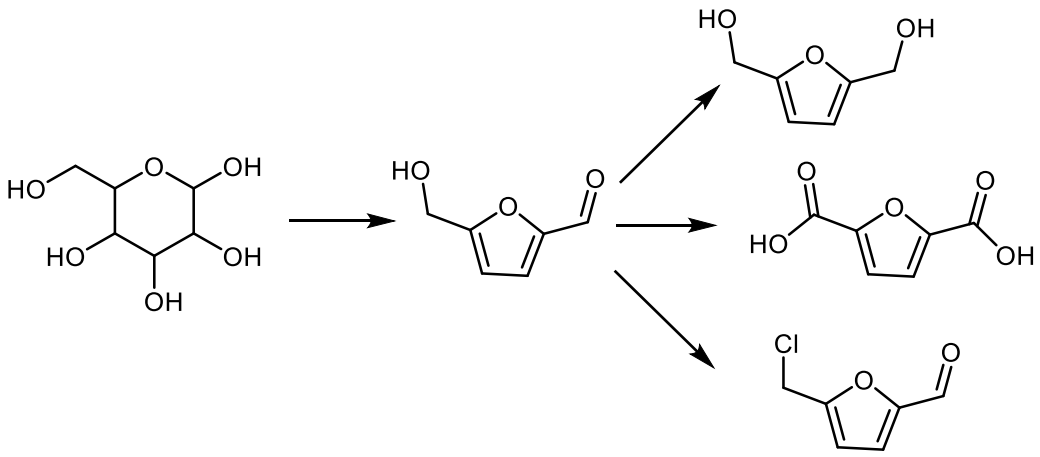
Another approach resorts to the synthesis of biodegradable plastics starting from renewable materials. Plant derived starch can be plasticized and formulated to obtain a thermoplastic material used for multiple applications, including shopping bags, single-use plates and cutlery that can be collected and sent to composting plant, generating compost and carbon dioxide that will be converted again to starch by plants. The development of starting materials and products from plants and other organisms is therefore a cornerstone of circular economy embodied in the biorefinery concept.

Considering that the humankind depends on agriculture and animal farming for nutrition, an integrated production of food, feed, chemicals, materials, fuels, energy, and goods must be judiciously planned and designed. Therefore, key strategies for sustainability of a biorefinery are, among others, marginal lands cultivation and use of residues and waste. Cellulose, hemicellulose and lignin are the main constituent of plants and in particular of residues from the processing of food and non-edible plants. The hydrolysis of cellulose and hemicellulose can be performed to obtain non-food grade carbohydrates, potential raw materials to build platform chemicals. Complex mixtures of sugars can be fermented to ethanol, a C2 platform. Pentoses can be dehydrated to furfural, a starting point to obtain ethers, alcohols, esters and other compounds with five carbon atoms (or multiples).



Scheme 14 Pentoses as starting material

Hexoses, like the widespread glucose and fructose, can be dehydrated to hydromethylfurfural, a C6 platform chemical that has been converted to by reduction, oxidation and other manipulations to give, for instance, bis-hydroxymethylfurfural, furandicarboxylic acid (a candidate to substitute terephtalic acid in PET), chloromethylfurfural (an intermediate in the synthesis of the drug ranitidine[38] an H2 histamine receptor antagonist used as antiacid)



Scheme 15 Hexoses as starting material

1.6 Photoredox catalysis

Photoredox catalysis is one of the more growing topics in organic chemistry in the last decade in both academic research and industrial applications.[39]

This high interest comes from the opportunity to reveal new reaction pathways, inaccessible under thermal control, from the impressive advantages in replacing common synthetic methods with new light guided, environmentally friends process in mild conditions, and from the convenient scale-up in flow reactors.

The activation of organic molecules using UV light is an old concept in chemistry, however, the high energy content in the UV radiation drive to poor selectivity and many side reactions, significantly reducing the compatible substrates. Most of these issues can be solved with the use of visible light, its low energy content allows to run reaction under mild conditions and leads to investigate novel photocatalysts and chemical transformations.

1.7 Environmental and economic considerations

In a historical moment where the concerning about energy and resources consumption becomes more and more prominent, science, and chemistry first, have looked on new

strategies and guidelines in order to reduce the environmental impact of the chemical processes, with the well knows twelve principles of green chemistry[25], nowadays photochemistry seems to be an excellent implementation of several principles.[40]

It is noticeable that light is free energy source, non-hazardous and its efficiency is extremely high compared to the classical thermal energy. Substrate activation proceeds through catalyst, these catalysts operate in mild conditions, while their activation is achieved by photons, high temperatures and pressures are not used. Photoredox catalysts can generate highly reactive species from low energy reagents without the use of complex activation groups. In these growing years for photochemistry, more photocatalysts have been proposed and characterized by scientific community, this allows the selection of a catalyst by the required reduction and oxidation potential for the activation of specific functional groups, this, in principle, avoids temporary modifications as introduction of protecting groups, and, in general, allows to choose simpler and less hazardous reagents.

Worth to mention some economics advantages in photochemistry, intuitively, the solar energy is the biggest and free source of photons, it can be collected, focused, and used in continuous flow microreactor.[41] While some expensive metal catalysts (Ir) are still used, cheaper metal (W, Cu, Fe, Ru) and metal free (e.g.: Acr^{+}-Mes[42], Eosin Y[43]) catalyst are raising in organic synthesis research.

In summary, a wise selection of energy sources, reagents and catalyst, can drive to a conspicuous advantage in terms of sustainability: conditions are in general mild, light is an efficient energy source and reaction are usually highly selective and shows good functionals groups tolerance, this leads to the chance to choose the best substrates in terms of similarity to desired products, low toxicity, low cost.

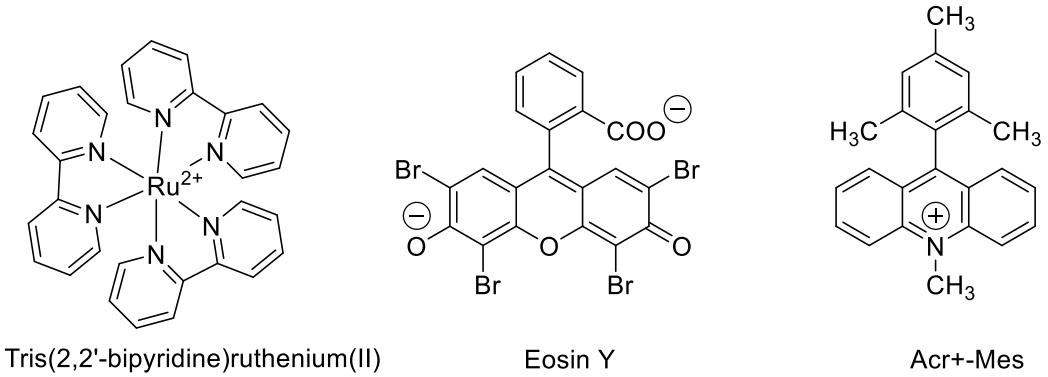
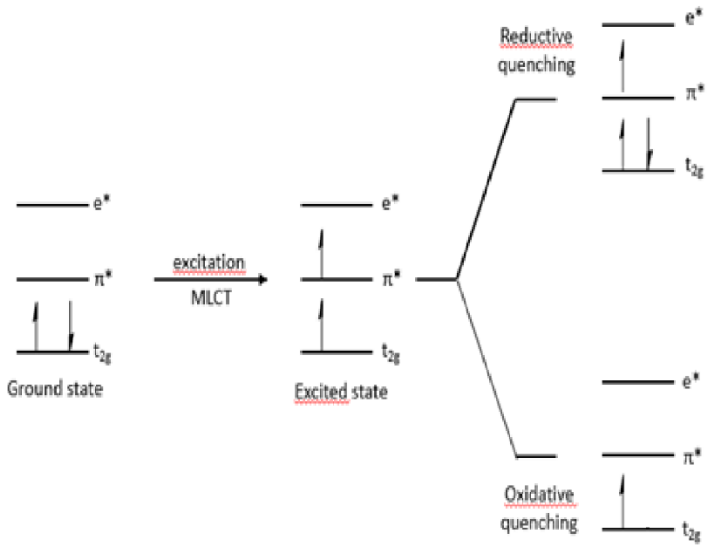


Figure 2 Photocatalysts

1.8 Mechanism overview

In general, photoredox catalysts activity, can be schematized in 3 phases: excitation, electron exchange and photocatalyst regeneration.



Scheme 16: Simplified molecular orbital scheme for $Ru(bpy)_3^{2+}$- example of excitation step

In phase 1, the photocatalyst (*PC*) absorbs energy from a light source with appropriate wavelength, the absorption drive to the excitation of an electron from a t_{2g} orbital to a π* orbital via Metal to Ligand Charge Transfer (MLCT) and *PC** is generated. In phase 2, *PC** interacts with substrate extracting or donating electrons, in the first case the reductive quench occurs, and PC radical anion is generated, in the second case oxidative quench occurs, and PC radical cation is generated. In phase 3, *PC* is regenerated by a *Quenching Agent (QA)*, it's convenient and elegant when the *QA* it's an intermediate in the wanted chemical transformation, in that case, *Product* generation and *PC* regeneration occur in the same step and *no waste* is produced.

Phases 2 and 3 can proceed with two mechanisms: Hydrogen Atom Transfer (*HAT*), where a Hydrogen Atom is transferred from *Substrate* to *PC** and then from *PC** to *QA*, and Single Electron Transfer (*SET*) where an electron is transferred from *Substrate* to *PC**, or from *PC** to *Substrate,* and then *vice versa*.

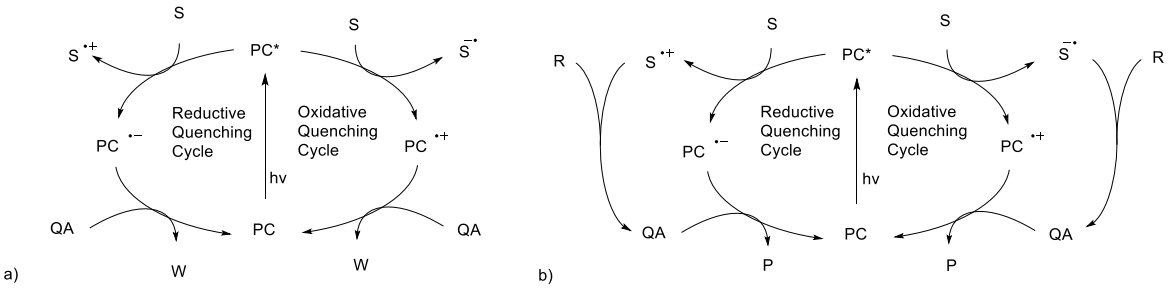
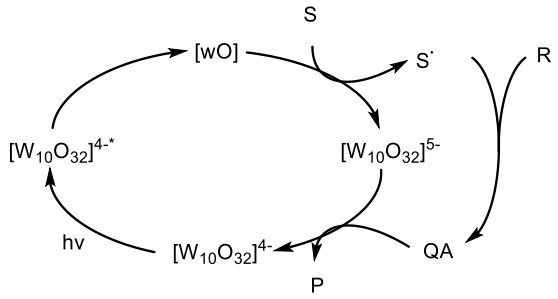


Figure 3 General Photoredox cycle (S: Substrate, QA: Quenching Agent, W: Waste, R: Reagent, P: Product)

TBADT chemistry

Tetrabutylammonium decatungstate (TBADT) belongs to polyoxometalate (POM) compounds group. POMs are a large family of compounds characterized by the presence of three or more oxoanions of transition metals (V, Nb, Ta, Mo, W) and p-block elements (B, Si, Ge, P, As, Sb, Te, I). Their general formula is $M_xO_y^{n-}$.[44] Due the large variety of POMs they found a wide range of applications in catalysis, natural science, and materials.[45] The decatungstate cluster, $[W_{10}O_{32}]^{4-}$, shows an absorption band centered at 324 nm, it can be related to an LMCT type electron transition from oxygen centers to tungsten atoms, this singlet specie, $[W_{10}O_{32}]^{4-*}$, have a lifetime in the order of picoseconds and it does not react directly with organic substrates. This singlet specie decays in a triplet specie wO that can interact with organic substrates with two mechanisms: HAT or SET, depending on the nature of the substrate. In both cases the monoelectronic oxidation of the substrate leads to the reduced photocatalyst in the protonated, $H^+[W_{10}O_{32}]^{5-}$, or non-protonated form $[W_{10}O_{32}]^{5-}$.[46]



Scheme 17 TBADT catalytic cycle

1.9 Examples in academic research

1.9.1 C-C bond formation

Diels-Alder reaction is a well-known method to synthesize new C-C bonds through the combination between a *diene* **1** (electron-rich) and a *dienophile* **2** (electron-poor), if the reactivity of these two components matches, two C-C bonds and a new cycle are formed. So, although the Diels-Alder reaction is powerful, his scope is limited by the *diene* and *dienophile* electron behaviour. *Yoon et al.*[47] shows the opportunity to carry, through photocatalysis, the Diels-Alder reaction using non-conventional reagents.

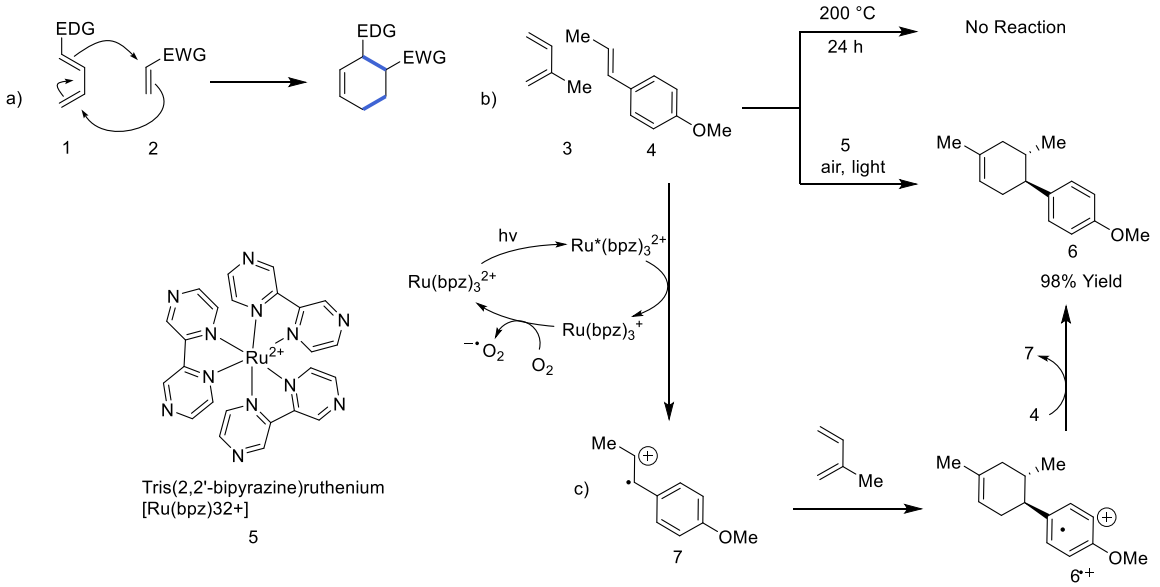


Figure 4: Photocatalyzed Diels-Alder reaction proposed mechanism

In absence of EWG and EDG groups in the diene **3** and dienophile **4**, product **6** will not be formed not even with high temperature and long reaction time, with the addition of $Ru(bpz)_3^{2+}$ (**5**) product is formed in high yield and short reaction time. In the proposed mechanism photocatalyst is irradiated by visible light and, after a MLCT transition, $Ru^*(bpz)_3^{2+}$ is formed. This excited specie, via SET, oxidize the diene (**4**) and the resulting radical cation (**7**) can easily afford the Diels-Alder reaction product ($\mathbf{6}^{\cdot+}$), this radical is quenched with another equivalent of (**4**) giving the product (**6**). Reduced catalyst $Ru(bpz)_3^{+}$ is oxidized by O_2 and the photocatalyst is generated again.

1.9.2 Alkenylation of alkanes and aldehydes

The alkenylation of C–H bonds is a useful transformation to build and derivatize natural products and pharmaceuticals.[48] The reaction is often carried in presence of transition metal catalysts or stoichiometric salt (Cu and Ag) as oxidation agents. Furthermore, these synthetic ways show selectivity issues with alkanes and aldehydes. Wu shows that this challenging transformation can be carried using TBADT coupled with Chloro(pyridine)cobaloxime(III).[49] This methodology shows high site selectivity and yields in complex pharmaceuticals compounds as bicyclic and hormones.

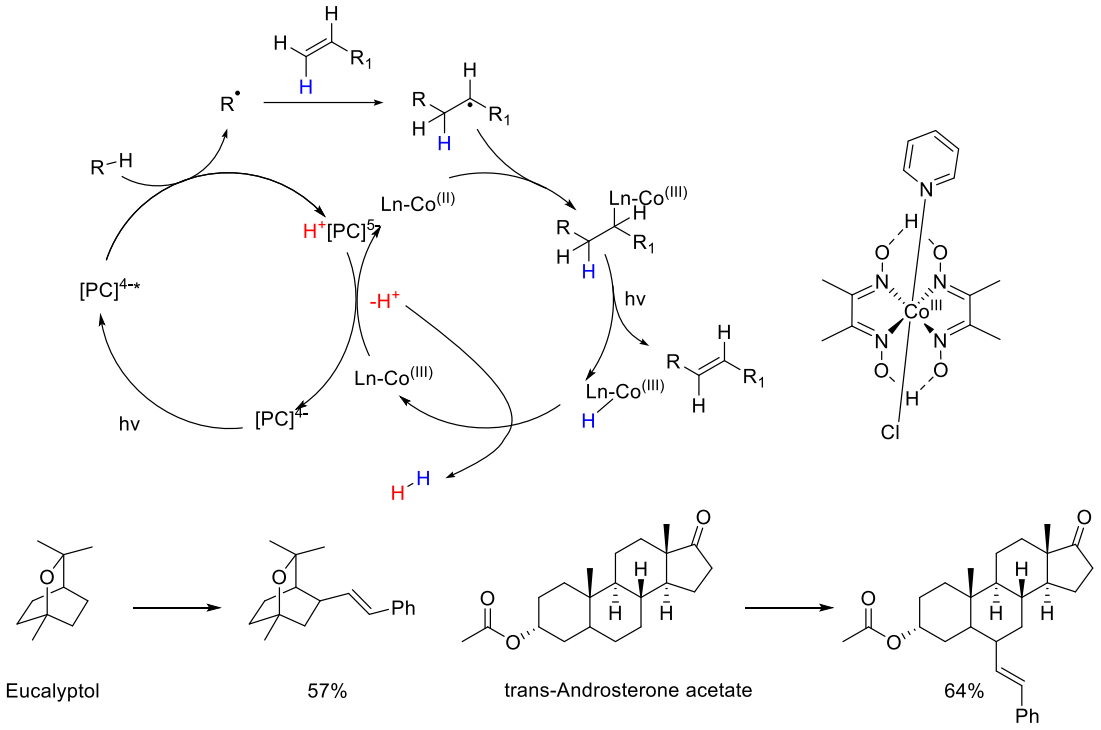


Figure 5: Proposed mechanism for the Alkanes alkenylation

1.10 Applications in the industry

1.10.1 Fluorination of inactivated C-H bonds

C–F bonds plays an important role in medicinal chemistry, while the substitution of and hydrogen atom with fluorine causes minor steric variances, it leads mayor modifications in terms of conformational changes and chemical properties as acidity and basicity and in terms of pharmacological activity. Nowadays the number of fluorine-containing drugs in the market has reached the 25%.[50] DiRocco and Britton[51] shows an easy and sustainable method for the big scale synthesis of the fluorinated drug Odanacatib using TBADT as photocatalyst.

Early, the key-intermediate γ-fluoroleucine was synthesized by multi-step process with yields between 20% and 70% using various substrates and fluorinating agents TBADT chemistry allows the direct fluorination of inactivated C-H bonds choosing convenient substrate and fluorinating agents, hitting 90% yield.

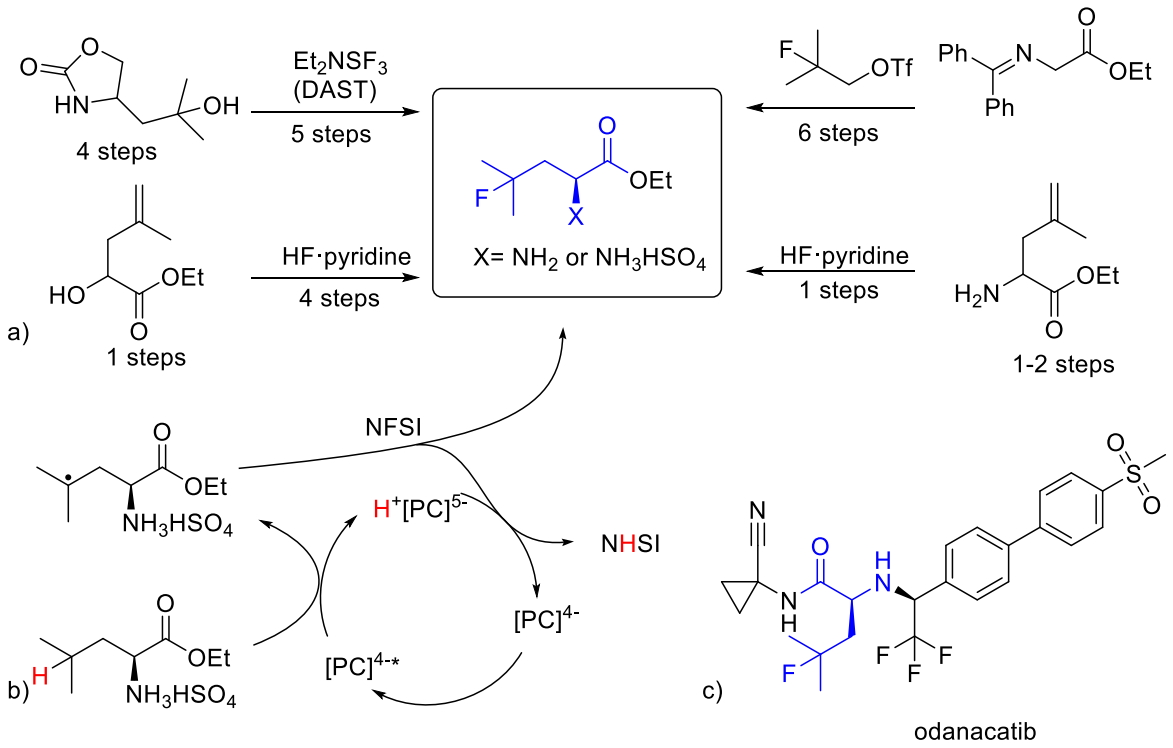


Figure 6: γ-fluoroleucine synthesis proposed mechanism

1.10.2 Indoline dehydrogenation

Elbasvir is a highly potent and effective drug for the treatment of hepatitis C. During the synthetic route for the Elbasvir, the oxidation of chiral hemiaminal ether to indole, shows issues due the epimerization of the hemiaminal stereocenter. It has been found that $KMnO_4$ was the oxidant capable of carry out this transformation, unfortunately, it brings to undesired by-products and cannot be used in a large-scale production due its poor environmental sustainability. Knowles et all. showed a photooxidation path that leads to indoline dehydrogenation using an Iridium complex as photocatalyst. Authors claims that this is one of the first demonstrations of photoredox catalysis in the production of a pharmaceutical intermediate, and using a flow reactor, 100 g of indoline substrate could be processed in a few hours.[52]

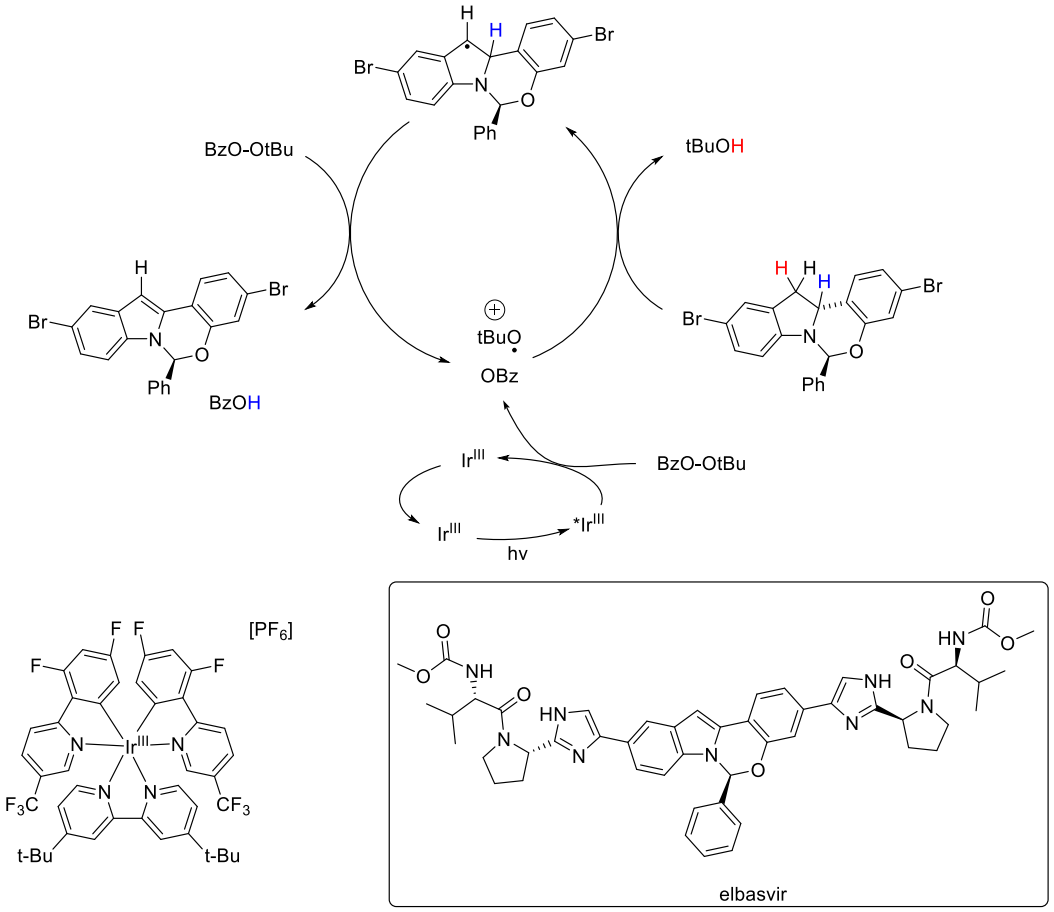


Figure 7: Indoline dehydrogenation proposed mechanism

1.11 Conclusion

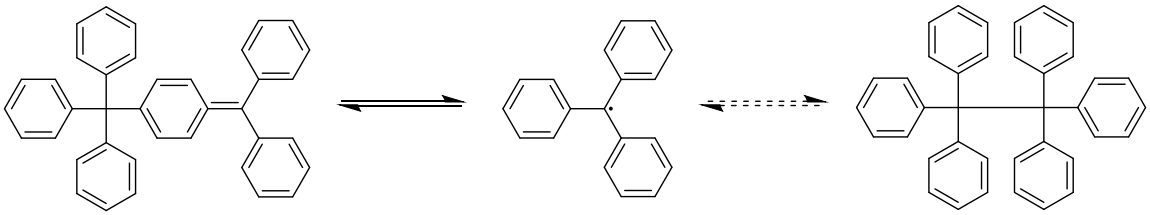
Historically, the use of photochemistry has been avoided due its issues in scalability and selectivity.[53] In the last decades photochemistry raised thanks to the discovery of many new photocatalysts able to work under visible light and mild conditions. Photocatalysis is not just an alternative method to achieve known reactions, it allows to achieve brand-new chemical transformations inaccessible by classic methodologies in chemistry. Worth to mention the environmental aspect of photochemistry, the development of new photocatalysts, methods and reactors, will allows the use of solar radiation as energy source. However, photochemistry cannot completely replace classic synthetic methodologies in chemistry, but it can effectively complement the classic methods to develop convenient and greener synthetic pathways to both complex pharmaceuticals compounds and high value platform chemicals.

1.12 Catalytic methods

As already pointed out, stoichiometric oxidants can be quite hazardous, expensive and generate large amounts of byproducts. The use of cheap and stable "electron acceptor" such as dioxygen, hydrogen peroxide, hypochlorite or peroxysulfate has the added benefit of generating "light" by-products as water, chlorides or sulfates. The more stable oxidants, like O_2, nevertheless require a proper activation by an opportune catalyst. There are plenty of catalysts to oxidize alcohols, most of them based on transition metal; here the discussion will be focused on nitroxyl radicals.

1.12.1 Organic Radicals

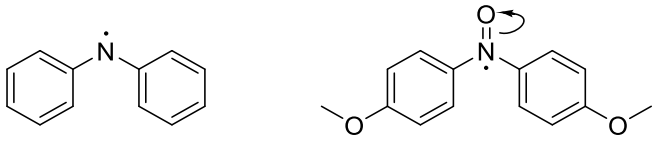
The first example of organic radical has been discovered by Moses Gomberg in 1900[54]. He already synthesized tetraphenylmethane and trying to synthesize hexaphenylethane with triphenylmethyl chloride and zinc he found that his product was not inert as expected but reacted with oxygen to give triphenylmethyl peroxide and with halogens to give the triphenylmethyl halides. Thus, he postulated the formation of the triphenylmethyl radical. Due to its stability and ease of preparation this radical has been important in the development of EPR spectroscopy.



Scheme 18 Synthesis by Moses Gomberg

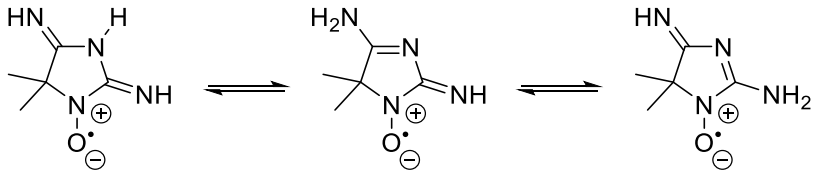
The stability of this radical is explained by the delocalization of the unpaired electron over the three phenyl rings (described with several limiting resonance structures) and its steric hindrance. It was suggested that in solution triphenylmethyl radical could be in equilibrium with his dimer; because of the steric hindrance around the central carbon, this dimer is not hexaphenylethane but it possesses a quinoid structure.

Similar stabilized non-ionic nitrogen radicals have been developed by Wieland in 1911 from tetraphenylhydrazine that dissociates in diphenylamino radicals and bis-(p-methoxyphenyl)nitroxide these are the first examples of stable organic nitrogen radicals.



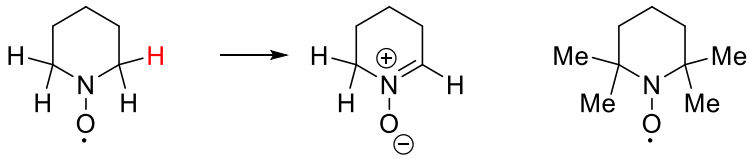
Scheme 19 Radicals developed by Wieland

The first heterocyclic radical compound called porphyrexide was synthesized by Piloty and Graf Schwerin in 1901[55]. This stable radical is a strong oxidizer and shows 3 tautomeric structures where the formation of a conjugated diene or triene system is possible.



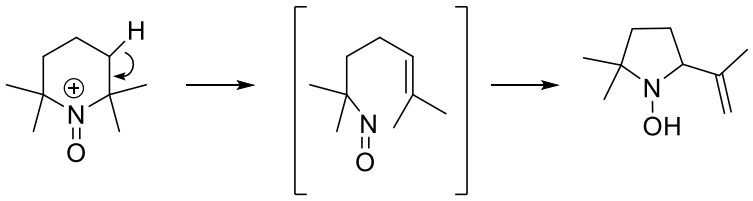
Scheme 20 Porphyrexide synthesized by Piloty

Another class of stable organic radicals is represented by non-conjugated nitroxyl compounds, their existence in solution was postulated by Rogers et al.,[56] they showed the stability of nitroxyl radicals with no a-hydrogen atoms. For example piperidine-1-oxyl is unstable, because it can evolve to nitrone by elimination of one a-hydrogen atom, while the alkylated compound (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) is stable due the absence of a-hydrogen atoms.



Scheme 21 α-hydrogen elimination in piperidine-1-oxyl radical

While in first sight a nitroxyl radical can be considered stable with the absence of a-hydrogens, that isn't the only path of decomposition, in fact TEMPO can also suffer the b-elimination of a proton giving the N-hydroxy pyrrolidine.



Scheme 22 β-hydrogen elimination in TEMPO radical

To avoid elimination to nitrone an alternative is to use bicyclic compounds with nitrogen between two bridgehead carbons that, for the Bredt's rule, cannot give a C-N double bond. Compounds of this category are AZADO, ABNO and the likes.

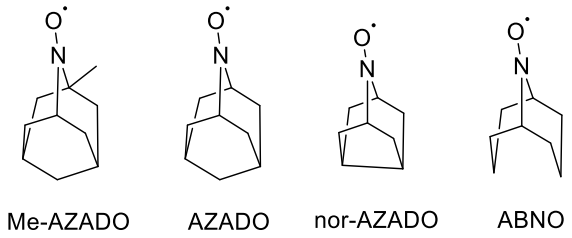
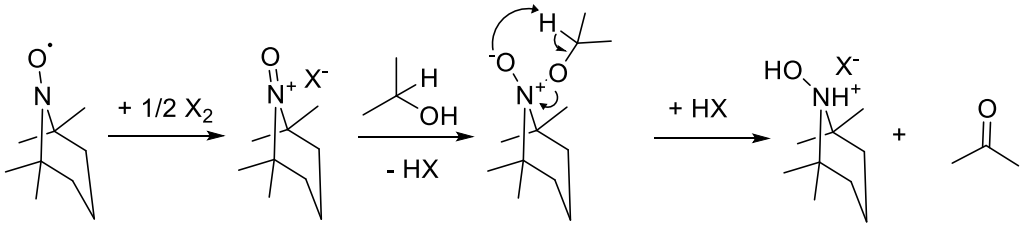


Figure 8 Bicyclic nitroxyl radicals

Nitroxyl radicals don't possess a conjugate system and the unpaired electron must be delocalized just on nitrogen and oxygen atom, giving a two-center three-electron N-O bond; radicals of this class can dissolve in both polar and non-polar solvents and can take part in non-radical reactions. Starting with TEMPO, Stable Nitroxyl Radicals have been used for alcohols oxidation since '60s[57], and, during the last 60 years, their development have been continued by theorization of several structures and structural modification that should increase their oxidant activity. TEMPO and derivatives have been investigated very deeply by studying effects of structural modifications and co-catalysts, various reaction conditions, rate of oxidation on many substrates and reaction mechanism. These studies revealed that the active species isn't the TEMPO radical itself but the oxoammonium cation produced by one electron oxidation. Golubev et al. hypothesized that the oxoammonium cation can react with an alcohol giving a nitrogen tetracoordinate intermediate that by hydrogen extraction evolves to hydroxylammine and the carbonylic compound.



Scheme 23 Oxidation mechanism

After the work of Golubev many methods to generate oxoammonium cation, that is an unstable compound, and to build catalytic cycles have been developed.

AZADO (2-Azaadamantane-N-oxyl) was synthesized in 1975 by Dupeyre and Rassat[58] interested in studying physical properties of nitroxyl radicals. Compared to TEMPO, AZADO own a less hindered nitrogen that gives it greater activity as oxidant.

ABNO (9-Azabicyclo[3.3.1]nonane N-oxyl) synthesized by Dupeyre in 1966[59] compared to AZADO own a similar oxidant activity and requires a shorter and easier synthesis.

During time, it become evident, that modification of the carbon skeleton, increase the catalytic activity of the nitroxyl radicals, especially with the work of Iwabuchi et al.[60–62] that introduced and tested many modification to nitroxyl radicals and catalytic systems.

In particular they investigated the presence of electron withdrawing groups in the azaadamantane skeleton in positions 1, 5 and 7.

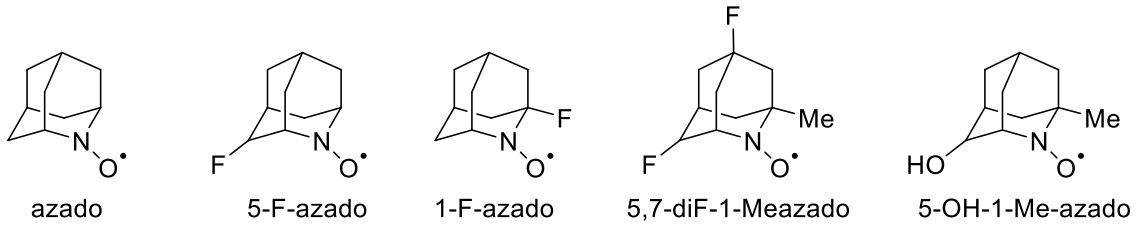


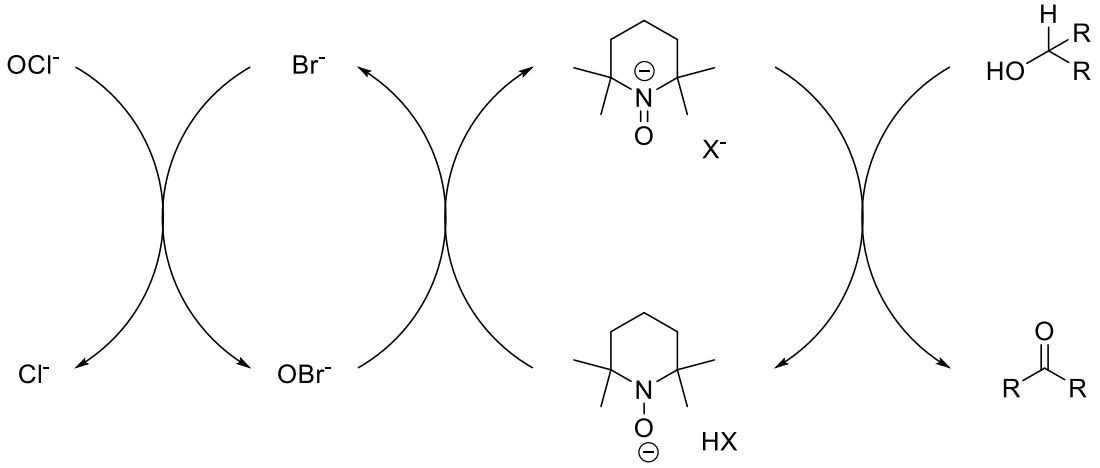
Figure 9 Some structures investigated by Iwabuchi et al.

The collected results show that the presence of electron withdrawing groups significantly increase the catalytic activity, especially when the EWD group is located in position 5. The suggested explanation is that the oxoammonium cation become more electron poor compared with the one generated by azado, this charge distribution helps the interaction between the alcohol and the catalytic center of the nitroxyl radical where three notable electronegative atoms must approach to starts the alcohol oxidation. Even if there are many mechanisms proposed and many catalytic systems known, in each of them an interaction between the N-O from the catalyst and oxygen, or, at least, a hydrogen atom near the oxygen from the alcohol is needed, and generally described as the slow step.

1.12.2 SNR – NaClO

Anelli–Montanari catalytic conditions[63]: carried out at 0 °C generation of oxoammonium salt is achieved in presence of KBr, NaClO and $NaHCO_3$. OBr^-, being a stronger oxidant compared to ClO^-, produces an accelerating effect in the oxidation of TEMPO to oxoammonium increasing the rate of alcohol oxodation.

$NaHCO_3$ was added to get the pH to optimal value balancing the acidity of bleach.



Scheme 24 Anelli–Montanari catalytic conditions

This method is effective but shows the limitation of use of NaClO that, in the reaction condition, generate HOCl and lead to formation of chlorinated by-products, moreover it is not compatible with other chemicals as ammonia. A wide range of stoichiometric oxidants can be used instead bleach, including metal complexes and O_2.

1.12.3 SNR – Metal complexes

- Copper complexes

The first study by Semmelhack in 1984[64] shows the oxidant activity of TEMPO combined with CuCl and O_2 in DMF at 25 °C. This catalytic system can oxidize benzylic and allylic alcohols but isn't effective for aliphatic alcohols.

Since this work, many systems have been studied including the one by Sheldon[65] that used a Cu(II) complex with 2,2'-bipyridine in CH_3CN/H_2O and t-BuOK as base. This system uses oxygen from air and oxidizes activated alcohols at 25 °C in 2-5 hours. The system proved ineffective with secondary alcohols and sluggish with primary alkyl alcohols. For safety reasons on large scale a mixture of <10% O_2 in N_2 was used.

Sheldon's system was later improved by Koskinen[66] that, with kinetic studies, found that better results can be obtained using organic bases as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and N-methylimidazole (NMI) in CH_3CN as solvent. This system can oxidize secondary alcohol although not reaching high values of conversion.

Hoover and Stahl[67] found that Cu(I) used with NMI is more effectives than Cu(II), this brings the issue of over oxidation to carboxylic acid or to others by-product, moreover diols and hindered alcohol show poor yields with both Cu(I) and Cu(II) complexes and also Ru(II) complex.

- Iron complexes

In Fe/TEMPO systems Iron(III) salts are normally employed, best performance for oxidations are observed in weakly coordinating solvents. Unlike Cu/TEMPO systems a base isn't needed and oxidation of secondary alcohols is possible. Iron ion in Fe/TEMPO system don't require the use of ligans, thus compared to Cu/TEMPO the system is less hindered.

$FeCl_3$–TEMPO–$NaNO_2$ system, proposed by Wang et al. in 2005[68] with the purpose of develop a noble metals free and cheap system, show an efficient oxidation of primary and secondary alcohols under ambient atmosphere and at room temperature in DCM. In 2011 Ma et al. improved this method[69] by replacing $FeCl_3$ with $Fe(NO_3)_3 \cdot 9H_2O$ and NaCl as additive. System by Ma et al. show a better oxidation efficiency on very hindered substrates.

1.12.4 Low environmental impact systems

Using a metal free catalytic system shows environmental and economic advantages. From the chemical point of view using a system with fewer component and less hindered makes easier to study and improve reaction conditions and gives a more accessible active site for the reaction. In the absence of metals and complexing agent the system requests less reagents and produce less waste, thus is more environmental and economical friendly.

In early works metals free systems has been developed (using bleach: Anelli–Montanari), however these methods uses halides, acids, bases and other reactants, new generation methods aims to reach best yields with systems as simple as possible.

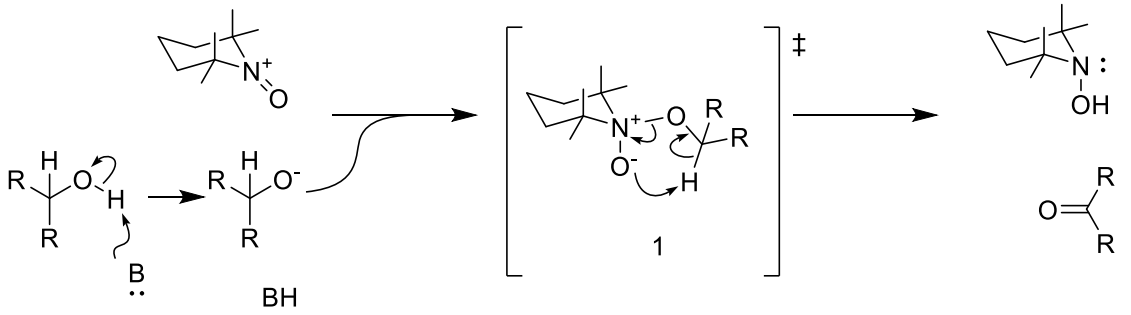
1.13 Reaction mechanism

There are many oxidation mechanisms proposed in the literature, starting from the case where deprotonated alcohol oxygen coordinates with SNR's nitrogen, continuing with concerted interaction alcohol oxygen-SNR's nitrogen and alcohol a hydrogen-SNR's oxygen and radical pathways as well. Proposed reaction mechanism depends as well from the nature of co-catalyst and reaction conditions. However, to date, there is no single widely accepted mechanism for this reaction.

1.13.1 Mechanism proposal 1

Bailey et al.[70] in 2007 proposed a mechanism in basic and acidic conditions, his computational work is based on Semmelhack et al.[71] 1986 experimental work. Both suggests that the oxidation of an alcohol in basic conditions starts with a formation of a *pre-oxidation intermediate* (1). That intermediate consists in the attack of alkoxide to oxoammonium salt nitrogen. At lower pH and with steric hindered/secondary alcohol the formation of that intermediate is less favored, in agreement with the observation that primary alcohol in basic conditions have higher oxidation rates.

The oxidation step consists in a hydrogen cation abstraction by SNR oxygen and consequent rearrangement of alkoxide to aldehyde or ketone.

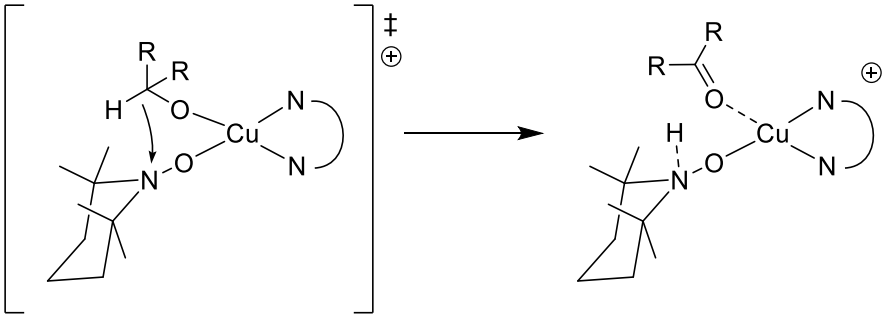


Scheme 25 Mechanism proposed by Bailey et al.

In acidic condition the suggested *pre-oxidation intermediate* cannot be formed, then, the mechanism, has to be significantly different. The proposed path involves a hydride transfer from alcohol to oxoammonium salt, calculated $DG^{‡}$ show lower rates for secondary alcohols. This computational result is in agreement with the experimental observation that, in acidic conditions secondary alcohols are oxidates fastest than primary. In other words, isopropyl alcohol is oxidized to acetone fastest than methanol to formaldehyde, that behavior, according to the authors, depends on the higher stability of secondary radicals compared to primary radicals and confirms the radical pathway in acidic conditions.

1.13.2 Mechanism proposal 2

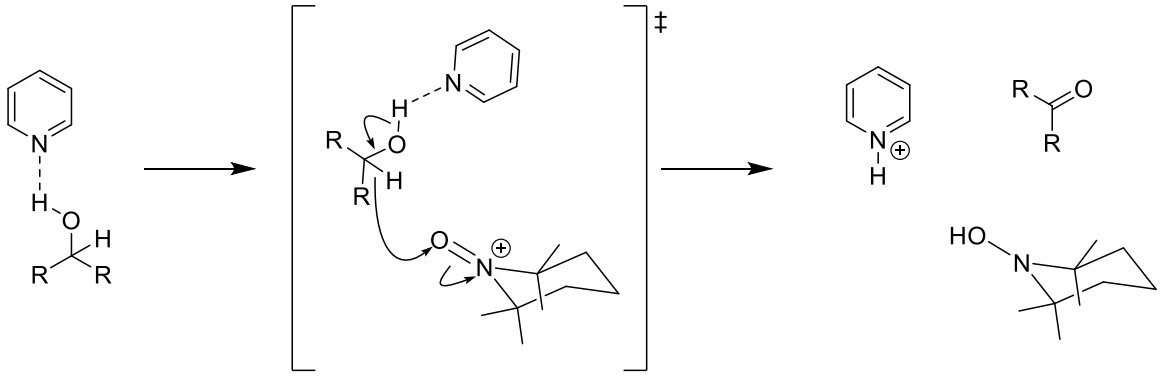
Another computational study is the one proposed by Belanzoni et al. in 2011[72], in this work the authors try to unravel the oxidation mechanism in presence of $Cu(bipy)^{2+}$ as co-catalyst. They investigated two possible mechanisms: the N-pathway and the O-pathway. In both cases, first, the alkoxide and the catalyst coordinates with the Cu atom, that results in as oxidation to $TEMPO^{+}$ and the generation of an empty electrophilic p* orbital. In the N-pathway the acceptor of H- ion is the TEMPO nitrogen, while in the O-pathways the acceptor of H- ion is the TEMPO oxygen. The computational study shows that the N-pathway is sensibly favourite because of exothermic DE in the hydride abstraction step, while the O-pathways is not favourable by the energetic point of view.



Scheme 26 Mechanism proposed by Belanzoni et al.

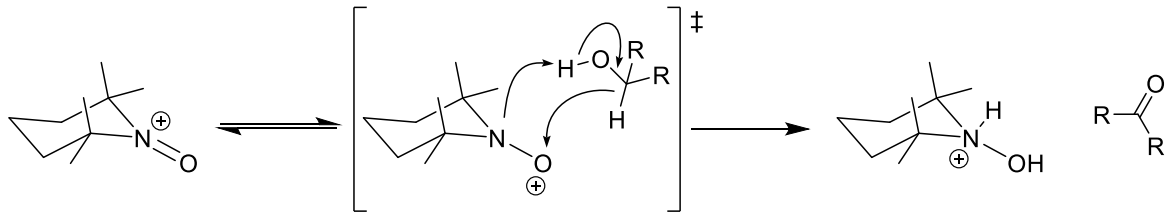
1.13.3 Mechanism proposal 3

Bobbitt et al. in 2014[73] with both experimental and computational work studied the alcohols oxidation in presence of pyridines. Bobbitt highlined that the oxoammonium nitrogen atom it's too hindered to coordinate any other atom from another compound, so he suggested a pathway where that atom is not directly involved in bonding alcohol/alkoxide (as is in mechanism 1) and does not act as hydride acceptor (as is in mechanism 2). In fact, in the proposed mechanism, the hydride acceptor is the oxoammonium's oxygen atom and subsequently the oxoammonium evolve in hydroxylamine.



Scheme 27 Base assisted mechanism proposed by Bobbitt et al.

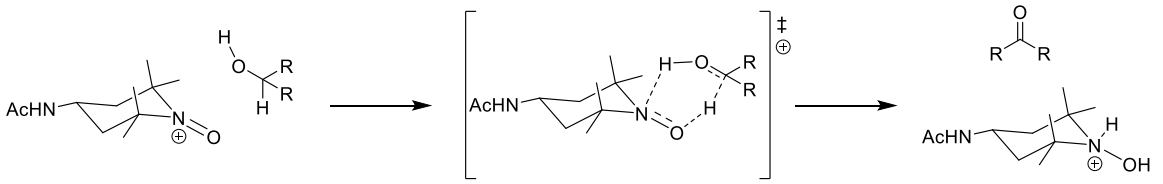
This mechanism differs from the case of the oxidation without bases. In neutral condition the hydride transfer continues to occur to the oxygen, while the hydrogen cation transfer occur to the nitrogen. This mechanism seems to make sense because of the less hindered state of nitrogen and the six-atom transition state.



Scheme 28 Non-base assisted mechanism proposed by Bobbitt et al.

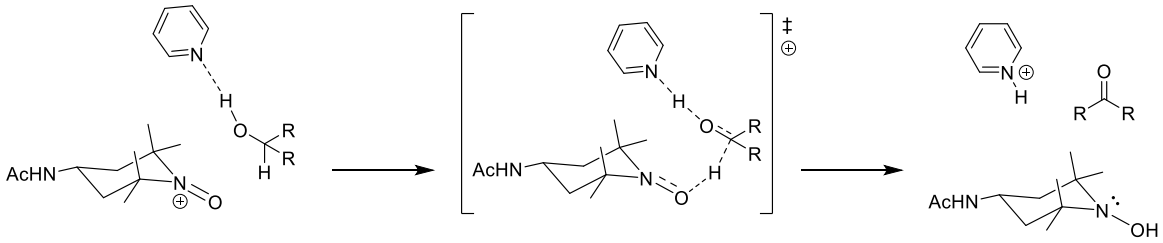
1.13.4 Mechanism proposal 4

Another both experimental and computational works is the one from Hamlin et al.[74] The authors looks for a unified mechanism for oxoammonium salt based oxidations. In the case of non-base assisted oxidation, they propose a mechanism where, in the transition state, first, there is a hydride transfer from alcohol to oxygen, followed by a proton transfer to nitrogen.



Scheme 29 Non-base assisted mechanism proposed by Hamlin et al.

In the case of base assisted oxidation, they propose a mechanism where there is a hydrogen-bonding complex between the alcohol and the base, followed by the hydride transfer to oxygen as happen in the non-base assisted mechanism.



Scheme 30 Base assisted mechanism proposed by Hamlin et al.

These mechanisms are in agreement with those proposed by Bobbitt previously showed (mechanism 3).

Chapter Two

Objective

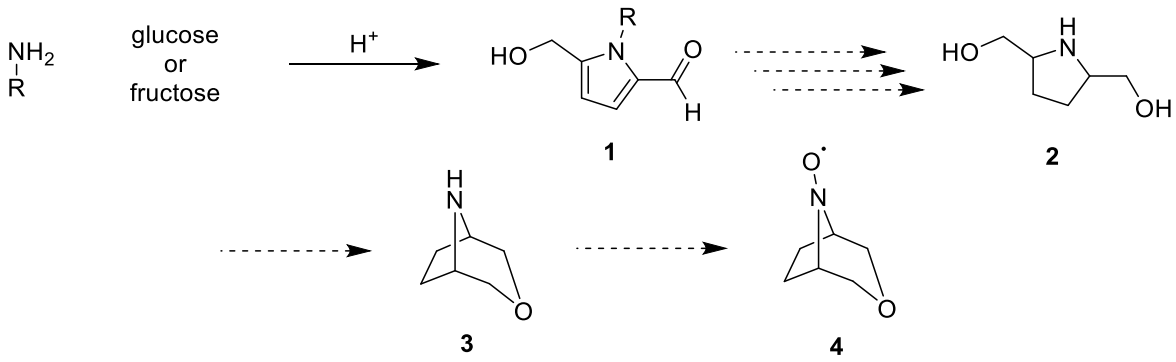
2) Objective

In the framework of green chemistry and circular economy, the objective of this thesis is to develop the synthesis of a new catalyst for alcohol oxidation starting from a renewable material. The chosen starting material was glucose, from which, through a multi-step synthesis, it should be possible to synthesise the new catalyst. It is worth to mention that not only the starting material was chosen focusing on low toxicity and renewable nature, but the whole synthetic process was designed looking for a low environmental impact. The introduction by a photoactivated reaction of fluorine in the compound at different stages of the synthesis should be an added source of variability searched to obtain variation in the electron density of the final catalyst.

During my PhD, I've collaborated with the company Matrìca S.p.a., as a part of my work I developed a procedure to separate and recycle two metal catalysts from a biorefinery aqueous waste solution. The procedure has been developed with primary attention to avoid generation of waste and to avoid the use of solvents and reagents, with both environmental and economic reasons.

2.1 Planned synthesis

Starting materials are glucose (or fructose), an acid catalyst and a primary amine, substances obtainable from renewable sources and with low toxicity. The first step, giving compound **1** is known in literature[75,76]. The first step leads to a N protected pyrrole, this substrate, if reduced give a pyrrolidine. With a following cyclization and oxidation, a new bicyclic stable nitroxyl radical is obtained. Worth to mention that the carbon skeleton of this radical is completely derivate from glucose.



Scheme 31 Planned synthesis

Chapter Three

Results and discussion

3) Results and discussion

3.1 Synthesis

This chapter aims to give a discursive view of the synthetic process pointing on considerations on sustainability, recycling and toxicity of the used materials, for procedure, data and spectra please refer to the experimental chapter.

Toxicity and biodegradability data discussed were obtained from products safety data sheets.

3.1.1 Solvents used in the synthesis

The solvents used in the synthesis are listed in table 1 and their greenness expressed by scores described in CHEM21 solvent selection guides[77].

Solvent	Worst H3xx	Safety score	Health score	Environmental score
Water	None	1	1	1
MeOH	H301	4	7	5
EtOH	H319	4	3	3
i-PrOH	H319	4	3	3
Acetone	H319	5	3	5
THF	H351	6	7	5
Ethyl acetate	H319	5	3	3
Hexane	H361	8	7	7
DCM	H351	1	7	7
$CHCl_3$	H351	2	7	5
Acetonitrile	H319	4	3	3
DMSO	None	1	1	5
Acetic acid	H314	3	7	3
TEA	H314	6	7	3
CPME	H302	7	2	5

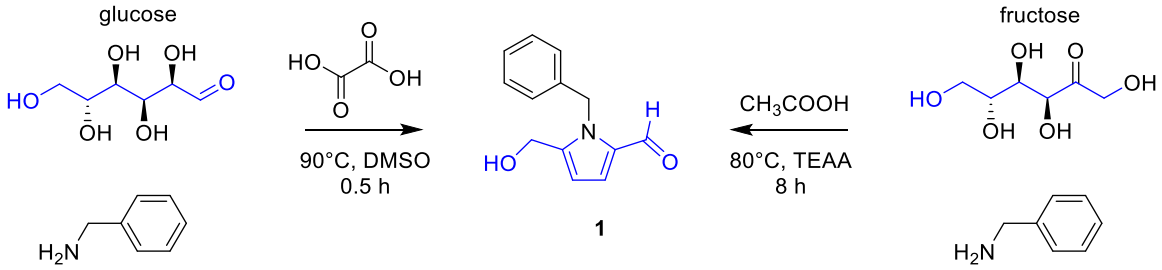
Table 1 CHEM21 selection guide

3.2 Step 1 – Synthesis of 1-benzyl-5-(hydroxymethyl)-1H-pyrrole-2-carbaldehyde

The first step of this synthesis, proposed by Adhikary et al.[75] is a condensation reaction of glucose with benzyl amine in presence of oxalic acid in DMSO to give 1-benzyl-5-(hydroxymethyl)-1H-pyrrole-2-carbaldehyde.

An alternative method was proposed by Cao et al. and it starts using fructose in triethylammonium acetate (TEAA), an ionic liquid prepared by mixing acetic acid and

triethylamine, with this procedure the needed acid catalyst is represented by an excess of acetic acid in the ionic liquid. In both literature procedures the work-up is carried out by neutralization, extraction with ethyl acetate and the purification by column chromatography.



Scheme 32 Synthesis of 1-benzyl-5-(hydroxymethyl)-1H-pyrrole-2-carbaldehyde

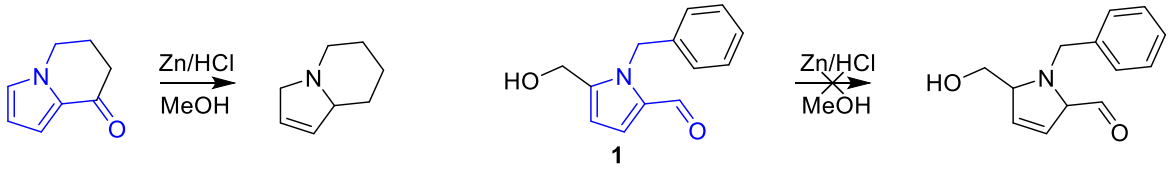
At first look it is easy to note that the main starting materials, glucose and fructose are renewable materials with no toxicity or any environmental hazard. Same consideration except for renewability, can be done for oxalic acid, in fact this solid acid it's quickly biodegraded in the soil and it's harmful only in case of ingestion. Benzylamine, as oxalic acid, it's quickly biodegraded in the soil and it's harmful if ingested or inhaled. The work-up of the first reaction presents several critical issues such as the difficulty in eliminating the DMSO during the extractions, the formation of insoluble solid and emulsions that make difficult to separate the phases and to obtain a pure product even after chromatographic separation. The substitution of DMSO with water or the deep eutectic solvent (DES) choline chloride: $ZnCl_2$ 1:2 gave no pyrrole. The extraction from TEAA does not present the typical criticalities of DMSO in the extraction phase, but the product obtained is not pure even after chromatography. A real improvement could be introduced by removing 90% of DMSO by distillation under vacuum, with the obvious reduction of the amount of ethyl acetate used but also with an improvement in the purity of the product obtained by chromatography. The solvents used in the work up have been recycled up to 5 times without any loss of yield. The main new concept introduced in this step is in the purification, while in literature it's carried out by column chromatography, with large use of silica and solvents, it was found that the product can be isolated by sublimation straight after the extraction, washing and solvent evaporation.

Summing up, the first step of the synthesis does not involve any hazardous reagent, solvents used during the work up can be recycled and the purification is carried out by sublimation. By-products of this reaction are water and harmless humic acids.

3.3 Attempts to reduce 1-benzyl-5-(hydroxymethyl)-1H-pyrrole-2-carbaldehyde

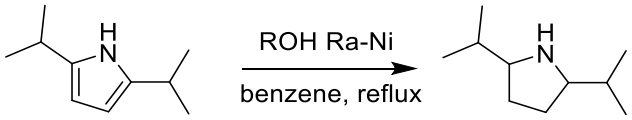
No literature procedure was known to reduce the 1-benzyl-5-(hydroxymethyl)-1H-pyrrole-2-carbaldehyde obtained from step 1, but in the attempt to reduce the substrate many procedures for similar substrates have been tested. In most of the cases resulting in substrate degradation in complex mixtures and no reduced product not even in traces.

- Gourlay et al.[78] showed how to partially reduce the 6,7-dihydroindolizin-8(5H)-one to 3,5,6,7,8,8a-hexahydroindolizine with zinc/HCl in methanol. The substrate can be seen as a carbonyl pyrrole N-substituted. Unfortunately, this procedure isn't effective with the substrate and lead to its degradation.



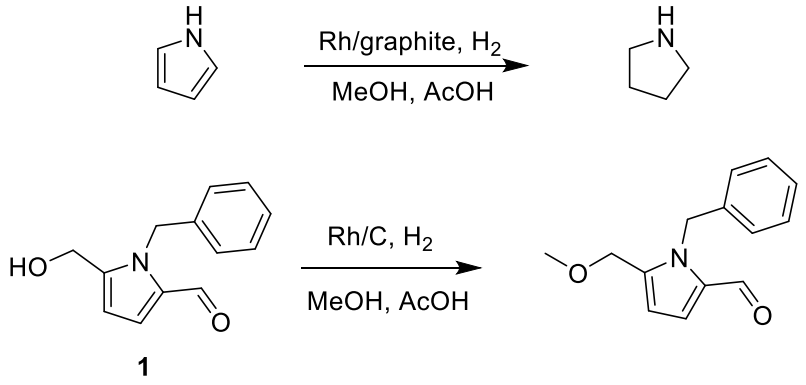
Scheme 33 Gourlay reduction of pyrroles

- Botta et al.[79] showed how 2,5-diisoproylpyrrole was partially reduced with Raney-Nickel in benzene at reflux. Benzene, for his well-known health and environmental complications, have been replaced with toluene. However, as in previous case, only substrate degradation was observed.



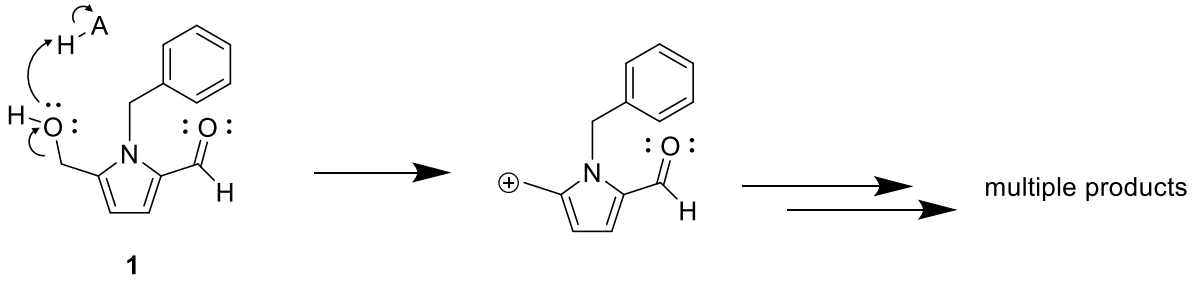
Scheme 34 Botta reductions of pyrroles

- Based on Savoia et al.[80] work, some reduction with hydrogen at low and high pressure and rhodium catalyst was attempted. At low pressure (3–5 atm) conversion of hydroxymethyl function to ether has been observed, at high pressure (100 atm), substrate degraded.



Scheme 35 Savoia reductions of pyrroles and by-product ether formation

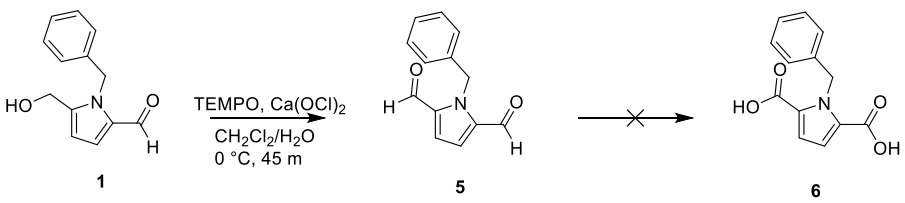
The troubles in the reduction of this substrate can be approached by, at least, 2 points of view: first, pyrrole is well known as an electron rich heterocycle, this makes it more difficult to reduce (add electrons), compared to others aromatic compounds. Second, the hydroxymethyl group, are highly reactive under acidic conditions and can lead to degradation of substrate starting with formation of a stabilized carbocation.



Scheme 36 Degradation pathway for compound 1

These considerations led to the plan to oxidize the alcoholic function to make the substrate less electron rich and less prone to the formation of a carbocation.

3.4 Oxidation of 1-benzyl-5-(hydroxymethyl)-1H-pyrrole-2-carbaldehyde



Scheme 37 Oxidation of 1-benzyl-5-(hydroxymethyl)-1H-pyrrole-2-carbaldehyde

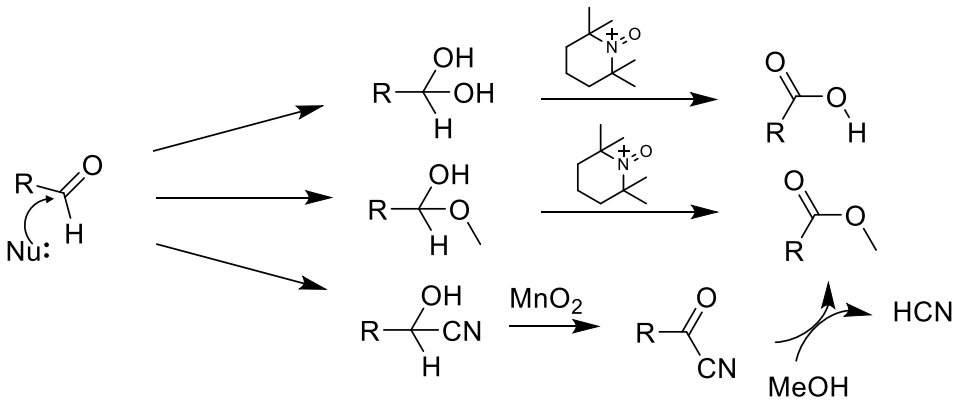
No literature procedure was known to oxidize the 1-benzyl-5-(hydroxymethyl)-1H-pyrrole-2-carbaldehyde obtained from step 1. The method published from Lin et al.[81] was

used first. The method is based on the Anelli Oxidation, using $Ca(OCl)_2$ as the stoichiometric oxidant. One expected product for this oxidation was 1-benzyl-1H-pyrrole-2,5-dicarboxylic acid, in fact, working with an excess of hypochlorite in presence of water it is well known that alcohols oxidations with TEMPO tends to evolve to carboxylic acids and does not stop at aldehydes intermediates. However, in our case, the oxidation gives selectively the 1-benzyl-1H-pyrrole-2,5-dicarbaldehyde. Work-up consists in a simply extraction with CH_2Cl_2 followed by sublimation.

Calcium hypochlorite used as co-catalyst is a "*solid bleach*", that can be handled safely at room temperature without decomposition. TEMPO has been used in catalytic amount and it can be dangerous only if heated around the decomposition temperature. Salts used were KBr, tetrabutyl ammonium bromide, $NaHCO_3$, none of them have any critical issues on the safety point of view. Therefore, all used reagents can be considered as a low environmental impact materials. Beyond the water, the other used solvent is CH_2Cl_2, a volatile compound with known issue because of its toxicity to human and environment, nevertheless, its lack of flammability provides a good margin of safety in presence of oxidizing compounds.

Attempts to oxidize 1-benzyl-5-(hydroxymethyl)-1H-pyrrole-2-carbaldehyde and 1-benzyl-1H-pyrrole-2,5-dicarbaldehyde directly to ester or carboxylic acid were also made with: Anelli oxidation with OXONE as co-catalyst[82], OXONE[83], Urea-H_2O_2[84], Corey-Ganem ($NaCN/MnO_2$) [85] but they failed.

Because all the methods attempted passes by the addition of a nucleophile (water, methanol, cyanide) through an intermediate (gem-diol, hemiacetal, cyanohydrin) that is easily oxidized, the reason of our results could reside in the limited electrophilicity of pyrrolecarbaldehyde.



Scheme 38 Aldehyde oxidations

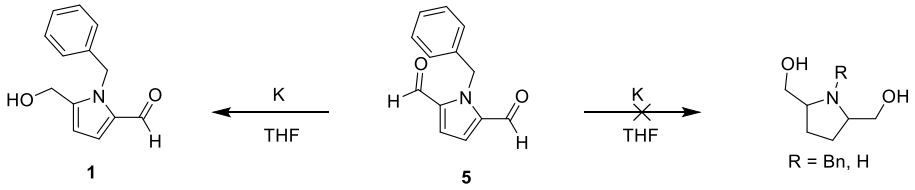
However, the method using TEMPO-$Ca(OCl)_2$ ensure a quickly catalytic reaction with mild conditions, the product is formed selectively with good yield, the work-up is simple and

the sublimated product is pure. For those reason, 1-benzyl-1H-pyrrole-2,5-dicarbaldehyde, was adopted as new intermediate for the synthesis.

3.5 Attempts to reduce 1-benzyl-1H-pyrrole-2,5-dicarbaldehyde

Methods reported in paragraph 2.2 has been use in the attempt to reduce 1-benzyl-1H-pyrrole-2,5-dicarbaldehyde (**5**). In this case the degradation of the substrate hasn't been observed, this can be a confirmation that the previously observed degradations, as supposed, were caused by the hydroxymethyl group. However, the formation of desired product wasn't observed.

Reduction with metallic potassium was tried, in this case it was observed the reduction of one of the carbonyls and not the reduction of the heterocycle or the cleavage of benzyl group. This results it was somehow predicted, in fact, it is known that aldehyde group is less stable to reduction compared to heterocycle π bonds; if we consider the conjugation of the carbonyl to the aryl ring, a full reduction will imply the transfer of eight electrons (ten if the benzyl was removed).



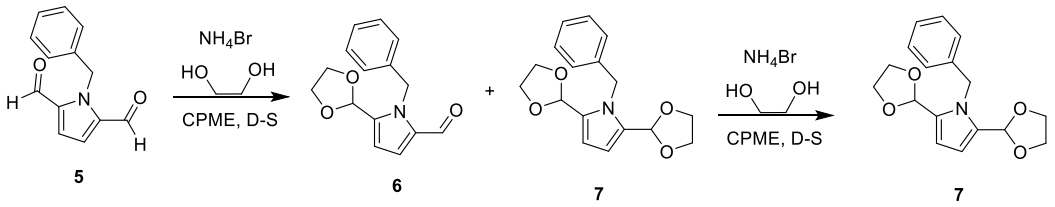
Scheme 39 Reduction of 1-benzyl-1H-pyrrole-2,5-dicarbaldehyde with K

After this observation, it was decided to protect the aldehyde groups.

3.6 Aldehydes group protection in 1-benzyl-1H-pyrrole-2,5-dicarbaldehyde

For the protection of the aldehyde groups, the cyclic acetal group was chosen. This protecting group is resistant to reductive conditions and it is easily cleaved with mild acids. Furthermore, the reaction is carried out in a low environmental impact solvent such as cyclopentyl methyl ether, the catalyst is a mild acid salt as ammonium salt[86,87], and the by-product is water. The protecting block is the ethanediol that is easily degraded if exposed to air and does not have any critical issues on the safety point of view. The reaction was performed with NH_4Br and NH_4HSO_4 for extended reaction times and various excess of glycol, but the reaction invariably gave a 1:1 mixture of monoacetal **6** and diacetal **7** demonstrating once more the scarce electrophilicity of compound **5**. The complete conversion to **7**, with an isolated yield of 90% was obtained only by working-up the

reaction mixture and submitting the crude mixture to a second acetalization. Work-up for this step it's a simple filtration to remove the catalyst followed by washing with a mild alkaline aqueous solution and filtration over a thin silica or celite pad.

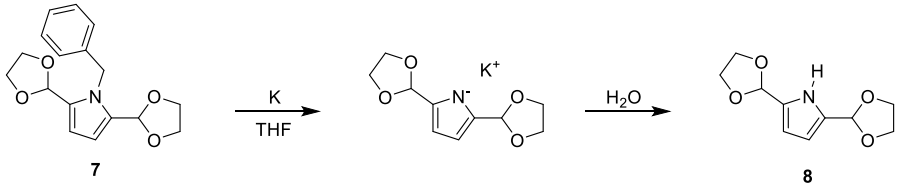


Scheme 40 Aldehydes group protection

3.7 Deprotection of compound 7

- Benzyl group cleavage from 1-benzyl-2,5-di(1,3-dioxolan-2-yl)-1H-pyrrole

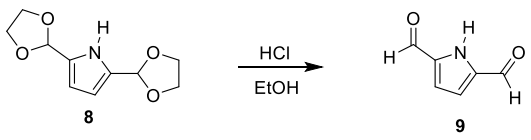
Reduction with metallic potassium have been tried, in this case it was observed the cleavage of the benzyl group giving 2,5-di(1,3-dioxolan-2-yl)-1H-pyrrole. After the cleavage of the benzyl group, a negative charge appears on the pyrrole, in this condition, reducing the substrate (we have to see it as "*adding more electrons*"), becomes too hard. Then, quenching the reaction with water, gives the N unprotected pyrrole. The product is isolated by filtration over a thin silica or celite pad.



Scheme 41 Benzyl group cleavage

- Acetals Cleavage from 2,5-di(1,3-dioxolan-2-yl)-1H-pyrrole

Acetals are easily deprotected by stirring the dioxolane in a mixture of ethanol and diluted HCl for two hours. 1H-pyrrole-2,5-dicarbaldehyde is isolated by washing with an alkaline aqueous solution to remove ethanediol and acid traces. As stated before, the ethanediol isn't a harmful compound, however, it can be recovered and recycled by distillation or extraction. Ethanol is a benign solvent from the environmental point of view, and it can be recovered and reused as well.



Scheme 42 Acetals Cleavage

3.8 Modification of 1H-pyrrole-2,5-dicarbaldehyde

In order to keep the substrate electron poor all over the reduction, aldehydes have been converted to carboxylic acid and then to methyl esters. Later, the free nitrogen has been protected with a tert-butyl carboxylate group. A good result of these three reactions is that all the products can be used into the next step straight after the work-up without any purification.

- Oxidation to 1H-pyrrole-2,5-dicarboxylic acid

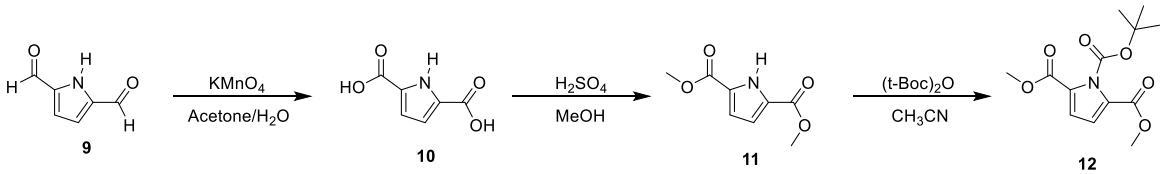
For the first oxidation, the method by Barker et al.[88] has been followed. The solvent in this oxidation is a mixture of acetone and water, oxidant is potassium permanganate. The reaction mixture is quenched with a solution of sodium sulphite in water, giving the much less hazardous manganese dioxide and the harmless sodium sulphate. Some slight modification to the original procedure were the recovery of acetone from the reaction mixture and substitution of chloroform with ethyl acetate for extraction, reducing the overall impact of the synthesis.

- Esterification to dimethyl 1H-pyrrole-2,5-dicarboxylate

Crude 1H-pyrrole-2,5-dicarboxylic acid has been oxidized to the methyl ester using the well-known Fischer esterification[89]. The reaction mixture is washed with an alkaline aqueous solution to remove acid traces and extracted with ethyl acetate.

- Protection of nitrogen

The protection of nitrogen with tert-butoxy carbonyl group was carried out according to Fu et al.[90] to give crude 1-(tert-butyl) 2,5-dimethyl 1H-pyrrole-1,2,5-tricarboxylate. The solvent is acetonitrile and the base is 4-(dimethylamino)pyridine. Unfortunately, DMAP it is not recommended from an environmental point of view; however, it is used in catalytic amount. An alternative suggested in literature[91] was triethylamine, but in this case it didn't work. Work-up consists in a simple aqueous work-up with an alkaline solution to remove tert-butyl alcohol.

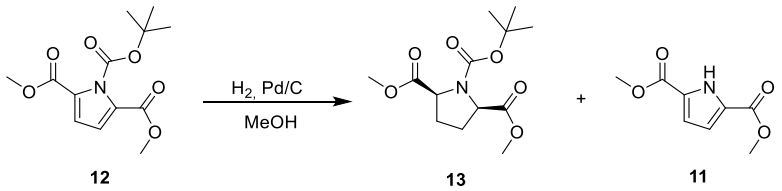


Scheme 43 Modification of 1H-pyrrole-2,5-dicarbaldehyde

3.9 Reduction steps for the 1-(tert-butyl) 2,5-dimethyl 1H-pyrrole-1,2,5-tricarboxylate

- Reduction to 1-(tert-butyl) 2,5-dimethyl (2S,5R)-pyrrolidine-1,2,5-tricarboxylate

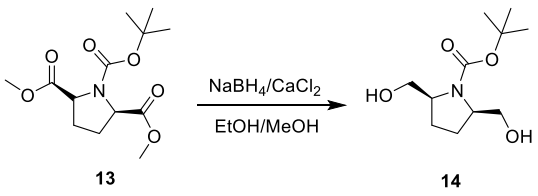
The crude product obtained in the previous step is placed in a high-pressure reactor with methanol as solvent and palladium on carbon as catalyst. The reactor is loaded with 50 atm of hydrogen, heated to 50 °C and leaved under stirring for 5 days. Later the catalyst has been filtered out under inert gas and the solvent evaporated to give 1-(tert-butyl) 2,5-dimethyl (2S,5R)-pyrrolidine-1,2,5-tricarboxylate **13** and a small amount of pyrrole diester **11**. Products have been separated by crystallisation in methanol. The pyrrolidine insoluble in cold methanol is used in the next step, while the unprotected pyrrole can be recycled as substrate in a new synthesis cycle. Catalyst and solvent can be recycled as well. It was observed that the reaction was ineffective at room temperature.



Scheme 44 Heterocycle reduction

- Reduction to tert-butyl (2S,5R)-2,5-bis(hydroxymethyl)pyrrolidine-1-carboxylate

Ester functions were reduced to alcohols using the procedure by Walker and Rogier[92] with sodium borohydride in a solvent mixture of ethanol and methanol in presence of $CaCl_2$. Reaction is quenched with water and extracted with ethyl acetate. Pure product has been obtained by purification by flash chromatography. The procedure was preferred to the traditional $LiAlH_4$ reduction of esters, employed by Chênevert et al[93], because Lewis acid activated borohydride is much easier to handle and quench, gives better atom economy and it can be used in environmental friendly protic solvents methanol and ethanol.

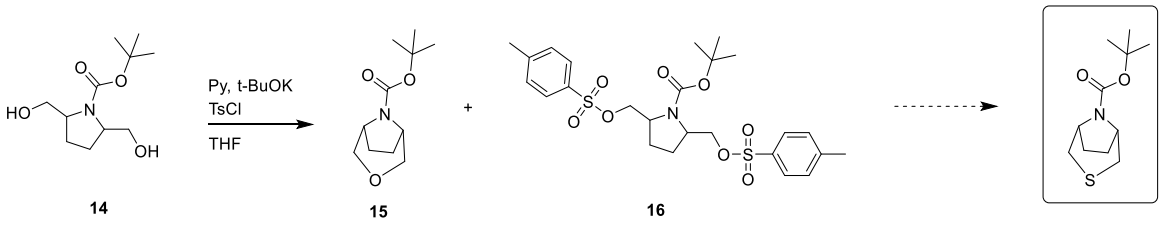


Scheme 45 Esters reduction

3.10 Cyclization of tert-butyl 2,5-bis(hydroxymethyl)pyrrolidine-1-carboxylate

tert-butyl (2S,5R)-2,5-bis(hydroxymethyl)pyrrolidine-1-carboxylate has been cyclized following the procedure recently patented by Wang et al.[94] Reaction has been carried out

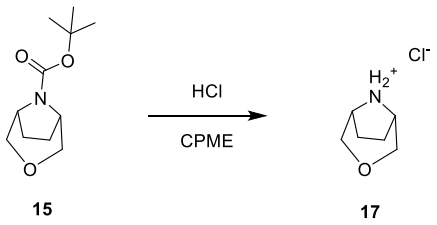
in THF in presence of pyridine, potassium tert butoxide and p-toluene sulfonyl chloride. A mixture of the cyclized product tert-butyl 3-oxa-8-azabicyclo[3.2.1]octane-8-carboxylate **15** and tert-butyl 2,5-bis((tosyloxy)methyl)pyrrolidine-1-carboxylate **16** was obtained in 1:4 ratio. The result is quite different from the 94% yield of compound **15** claimed by the cited patent, but compound **16** gives the opportunity to access to another potential substrate: the tert-butyl 3-thia-8-azabicyclo[3.2.1]octane-8-carboxylate by treatment with sulfur salt Na_2S. By-product of these reaction are water and p-toluenesulfonic acid. Interestingly data about degradability of the acid were not available on material safety data sheet but analogue compounds (chloride and sodium salt[95]) are readily biodegradable.



Scheme 46 Cyclization

3.11 Deprotection of oxaazabicyclooctane

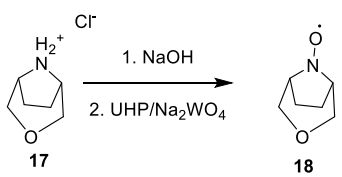
Cleavage of tert butoxy carbonyl protecting group has been carried out by mixing under stirring at -10 °C compound **15** in CPME in presence of HCl. Product has been recrystallized in methanol. By-product of the cleavage are CO_2 and tert butoxy alcohol, both can be considered harmless



Scheme 47 t-Boc cleavage

3.12 Generation of nitroxyl radical

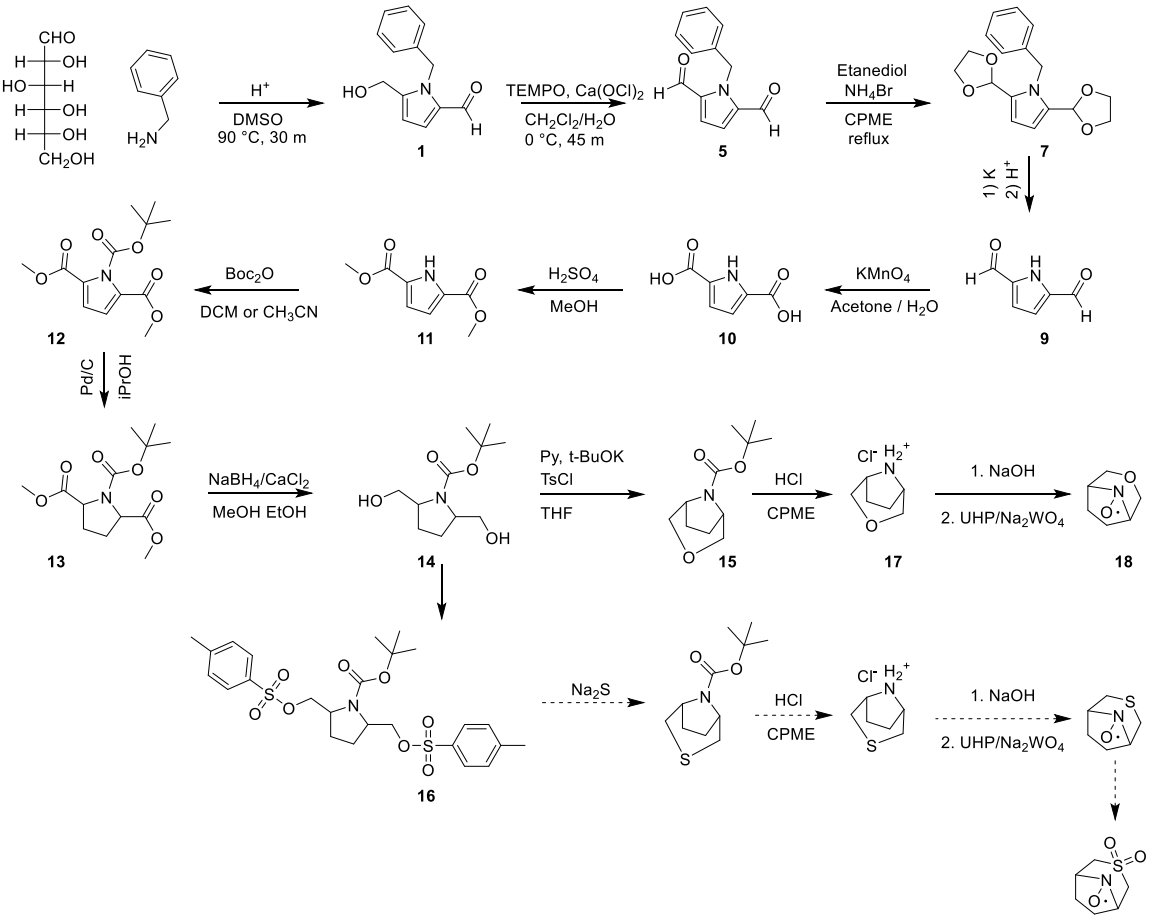
Compound 17 has been treated first, with an aqueous basic solution to liberate the free base and then oxidized with the complex urea-hydrogen peroxide and sodium tungstate to give the desired nitroxyl radical.



Scheme 48 Generation of nitroxyl radical

3.13 Synthetic process overview

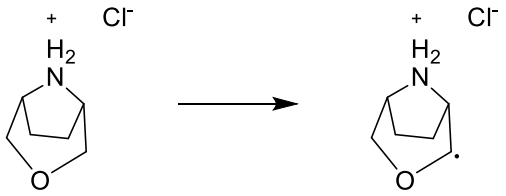
The synthetic process developed was far more complicated from the initial design, however, the target radical has been synthesized. Twelve steps were needed to reach the target molecule starting from glucose, and in all of them we focused on using harmless materials, obtain harmless by-product, and use recyclable and benign solvent, in most of the cases the objective have been fully achieved. One of the most interesting points, is that many of the steps do not need a purification to go on to the next step, because a deep optimization was performed on every step to avoid messy reaction mixture to isolate crystalline solid products as intermediate. This objective has been difficult to achieve because of the presence of many different functional groups during the synthesis and, also, because when the intermediate becomes symmetric, all reaction had to be optimized to go to completion on both side of the substrate.



Scheme 49 overall synthetic pathway

3.14 Structure modification

Using TBADT chemistry it is possible to activate C-H bond to functionalize carbon skeleton generating new C-C, C-N and C-F bonds.[46] TBADT was applied with different intermediates, to introduce a fluorine directly to the pyrrole ring, but the compounds tested gave no reation. THF is known to undergoes fluorination on carbon 2, using TBADT as photocatalyst and N-fluorobenzenesulfonimide as fluorinating agent. For these reasons we tested such functionalization on 3-oxa-8-azabicyclo[3.2.1]octan-8-ium chloride obtained toward the end of the present work. Our substrate seems to be suitable to undergo C-H activation with TBADT in literature conditions. Functionalization experiments will be performed in the future.



Scheme 50 Activation of C-H bond

3.15 Preliminary oxidation tests

The obtained radical was tested in the oxidation of two model substrates, and the results compared with TEMPO. The chosen substrates were menthol and benzyl alcohol. Menthol have been chosen because of its steric hindrance. The second model substrate is the benzyl alcohol, it was chosen to test the oxidation over a benzylic substrate. Chosen conditions for both radicals and alcohols are based on those used in the second step of the synthesis developed by Lin et al.[81], using 1% mol/mol of catalyst instead of 2% mol/mol and 45 minutes reaction time. In both cases the synthetised radical gave better results than TEMPO. In the case of menthol, the conversion is 16% versus 2% with TEMPO. In the case of benzyl alcohol, the conversion is 21% versus 12% with TEMPO. With menthol, considering the steric hindrance of TEMPO, a better conversion could be obtained, with the less hindered benzyl alcohol a greater catalytic activity of the new synthesized radicals was confirmed.

These results are to be considered as an index about the success of the synthesis of the new catalyst starting from renewable materials. However, it is necessary, in the future, to develop and optimize a catalytic system with optimize reaction conditions for the new catalyst.

3.16 Separating and recycling metal catalysts

As a part of the PhD with industrial characterization, I've collaborated with the company Matrìca S.p.a. The company, based in Porto Torres, Sardinia, Italy, focuses in the production of a range of bioproducts for many sectors (Bioplastics, Polymers, Biolubricants, Greases, Electronic Industry, Phytosanitary, Detergents, Pharmaceutical, Cosmetics and Feed), starting from vegetable oils.

The process can't be described in details for confidentiality reasons; however, this chapter is dedicated to the work done for Matrìca.

The company aims to obtain bioproducts by a process with low environmental impact, the vegetable oils are transformed in azelaic acid, pelargonic acid, light fatty acid blends C5-C9, vegetable heavy tails with high boiling temperature and glycerol, later, the acids are transformed into esters used for cosmetic formulations, biolubricants and extender oils.

As discussed in precedent chapters, avoid the production of waste and recycling is one of the key points of green chemistry. In fact, looking at the starting materials and products, a biorefinery perfectly fits in green chemistry principles, but we must not lose sight on by-products and recycling of catalysts used in chemical processes. In this case, at the end of the process that gives esters from vegetable oil, an aqueous solution with two metal catalysts (from now on called "A" and "B") used in the process and organic by products, partially emulsified (esters, fatty acids), is generated.

The work has been focused on the set up of a procedure to separate and recover the metal catalysts for their recycling.

3.16.1 Developing a concept for selectively extracting each catalyst

Even if many procedure (extract/precipitate with proper solvents, adjust the pH), can be developed for testing purpose, aiming to reach the objective in a fast way for a synthetic chemist, I started placing boundaries on what can be done, and what can't be done, from the environmental sustainability and industrial point of view.

The procedure should've planned to avoid:

- Addition of large amount of solvents
- Addition of unsafe and polluting materials
- Addition of materials that leads to waste generation
- Energy consuming procedure
- Time consuming procedure

The procedure should've planned to pursuit:

- Scalability
- Recycling of used materials
- Use of common labware materials
- Use of cheap and easily available materials

Therefore, consideration about metal catalysts have been done. The metal "A", is present in the aqueous solution in form of oxoanion, while the metal "B" is in form of cation. Furthermore, the radius of the two metal is noticeably different even when considered both in cationic form. These differences suggest the use of adsorbent materials, selective for ionic radius, easily exchanged, and reusable.

Clays are cheap and common materials, well known for their cations exchange behaviours[96]. There are many forms of clays, in general they are hydrous aluminium phyllosilicates, but the structure can be arranged in many different geometries and compositions. Roughly, aluminosilicate forms polymeric lamellae with a neat negative charge balanced by sodium and calcium cation occupying the space between the anionic layers. Sodium and calcium can be exchanged by different cations depending from concentration and charge to size ratio.

3.16.2 Planning the procedure

As for the synthesis chapter, this chapter aims to give a discursive view of the procedure for selectively isolating and recovering metal catalysts from and aqueous solution focusing on considerations on sustainability, procedure, data and spectra can be found in the experimental chapter.

3.16.3 Selectively extracting metal cation "A" from the solution

Three clays have been chosen for the ion exchange test, all three comes from a mine near the biorefinery site, later these clays have been analysed by X-Ray spectroscopy to determine their nature, furthermore, a couple of vermiculites from packaging and a commercial Montmorillonite K10 have been tested. The choice of materials coming from nearby the plant is an added value, because the cost for transportation should be considered in the life cycle assessment of a process.

For the preliminary tests, an aqueous standard solution of metal "A" (5 mL) was prepared and stirred at room temperature with the adsorbent material (1 g). Solid have been filtered and the aqueous solution have been analysed to determine the concentration of metal "A". With this standard solution one of the packaging vermiculites and two of the clays

tested gave the best result with more than 50% of cations adsorbed (1300/2100 ppm). The test have been reproduced in a range of pH from 2 to 5,3, adsorbent activity seems to be not linearly dependent on pH, however, best results came from the most acid pH. This result fit with a planned test using the biorefinery catalytic aqueous waste solution, in fact that solution comes at acidic pH (between 2 and 3) depending on the presence of the two metal catalysts. Moreover, neutral and alkaline pH are not accessible because in those conditions the metal catalyst will precipitate.

Furthermore, some tests have been conducted to determine the influence of treatment time, the standard solution were stirred with the adsorbent material from 10 minutes to 2 days, showing that the plateau is quickly reached in the first 30 minutes of stirring.

Once it was shown that the metal cation “A” can be adsorbed by the clays from a standard solution, adsorption tests on the biorefinery waste solution have been started. Results have been coherent with what seen on the standard solution, except for the vermiculite that gave worse results. For these reasons the best of the tested clays has been chosen as preferred adsorbent material.

3.16.4 Extracting metal cations “A” from the clay

The aim of the project it is to recover the catalysts to permit their reuse, therefore, the metal cation “A”, should be easily back-extracted from the clay. Sodium salts solutions have been chosen for this task. The clay, loaded with metal “A”, have been stirred with a Na^+ rich solution (e.g., brine), in this case too, the ion exchange is completed quickly and near 100% of metal “A” in the clay have been extracted in the brine solution.

Now, the metal cation in the brine solution can be easily isolated by precipitation operating on pH or extracted with a proper complexing agent. All these materials can be recycled, e.g., brine can be neutralised and reused or organic solvent used for extraction can be recycled as well. However, in batch, the amount of cations adsorbed by 1 gram of bentonite from 5 mL of biorefinery waste solution is still fixed around 50%, while, in order to recover both metal catalysts, its needed to completely adsorb cations “A” from the solution, consequently, the metal catalyst “B” will be isolated in the filtered solution and easily recoverable. To raise the quantity of cation “A” adsorbed from the bentonite, we switched to a flow system, where the catalytic waste solution it is allowed to flow through 1 g of bentonite, it was observed that this amount of bentonite it’s enough to adsorb 100% of the metal cation from 9 mL of the solution.

3.16.5 Extracting metal catalyst "B" from the solution

After the metal cation "A" have been completely extracted from the solution, only the metal catalyst "B" and organic by products are still present in the solution. When this composition is reached the metal catalyst "B" can be easily precipitated operating on pH. Precipitate can be filtered and the resulting solution is a metal free waste, containing just by-products derived from vegetable oils.

3.16.6 Recycle of clay

Catalysts were isolated and recovered, but, the entire process, will be sustainable only if clay can be reused at the end of the cycle, for this reason, after the treatment with the Na^+ rich solution, the clay have been dried and reused in the first step of extracting metal cations "A" from the clay. It was observed that the clay can be reused for the entire procedure at least 5 times without losing activity.

Summing up, the procedure is working for selectively extracting and recovering the metal catalyst "A", while the metal catalyst "B" is easily recovered when it remains the only metal in the waste solution. Used clay is reactivated during the process itself and can be reused without losing adsorbent activity. The entire process it is quick and virtually no waste will be produced, while the eventual final waste, if the clay after a high number of cycles should lose his adsorbent activity, will be a phyllosilicate not contaminated with transition metals. After the treatment, the biorefinery catalytic aqueous waste solution will contain only vegetable oils by products.

Chapter Four

Conclusions

4) Conclusions

4.1 Radical synthesis

We synthesized the target bicyclic radical starting from a renewable material, that is, to the best of our knowledge, a unique case in the synthesis of a compound belonging to the family stable nitroxyl radicals. Moreover, the synthesized radical, proved suitable for C-H photochemical bond activation, providing an easy way for further functionalization. One of the intermediates of the proposed synthesis, could be a starting material for the synthesis of two more radicals, widening the family of accessible bicyclic radicals from this synthesis.

The synthesized radical, as it is, proved to be active for its use as catalyst for alcohol oxidation in mild conditions, giving good results in two model substrates.

4.2 Separating and recycling metal catalysts

During the work with the company Matrìca S.p.A., a method for separating and recycling metal catalysts from an aqueous waste solution was developed. The developed method, organic solvent free, ensures recovering of each metal catalyst present in the waste solution and their reuse, through a fast and clean process using a cheap clay that is simply mixed with the aqueous solution. Moreover, the used clay, can be used many times without losing its activity. Therefore, the developed method, allows to separate and recover metals from an aqueous solution with a virtually zero waste process.

Chapter Five

Experimental

5) Experimental

5.1 Synthesis of 1-benzyl-5-(hydroxymethyl)-1H-pyrrole-2-carbaldehyde

D-Glucose (9 g, 1 eq), Benzylamine (1 eq) and Citric acid (1 eq) were put in a round bottom flask with 30 mL of DMSO at 90 °C and the solution was stirred for 30 minutes. At the end of this time, the mixture was diluted with 300 mL of deionized water and extracted with 3x300 mL of ethyl acetate. The organic phase was evaporated and the resulting viscous oil was sublimated at 100-110 °C and 0.004 mbar, giving the pure product as white solid. Yield 40%. ^{1}H NMR (400 MHz, Chloroform- d) δ 9.56 (s, 1H), 7.33 – 7.18 (m, 3H), 7.03 – 6.97 (m, 2H), 6.95 (d, J = 4.0 Hz, 1H), 6.31 (d, J = 4.0 Hz, 1H), 5.76 (s, 2H), 4.56 (s, 2H). ^{13}C NMR (101 MHz, CDCl3) δ 179.89, 142.27, 137.88, 132.80, 128.84, 127.49, 124.52, 110.85, 56.65, 48.62.

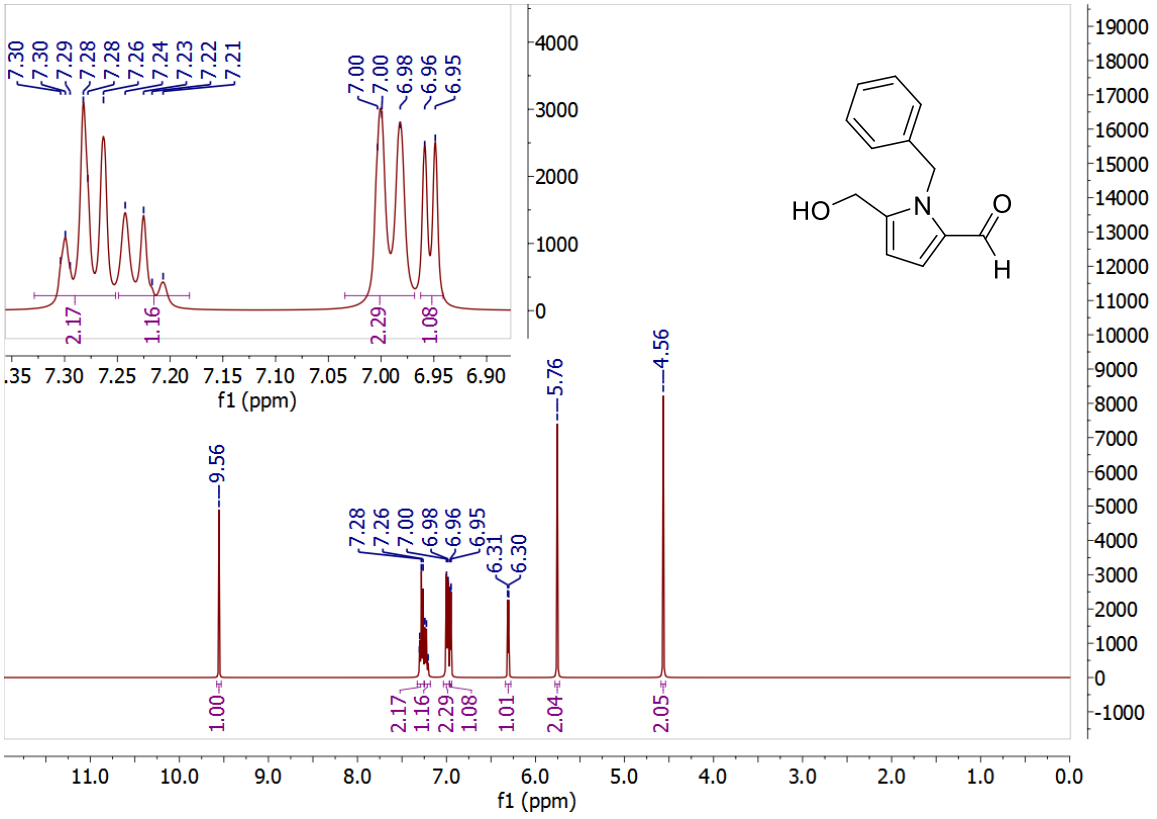


Figure 10 ^{1}H NMR Spectra of 1-benzyl-5-(hydroxymethyl)-1H-pyrrole-2-carbaldehyde

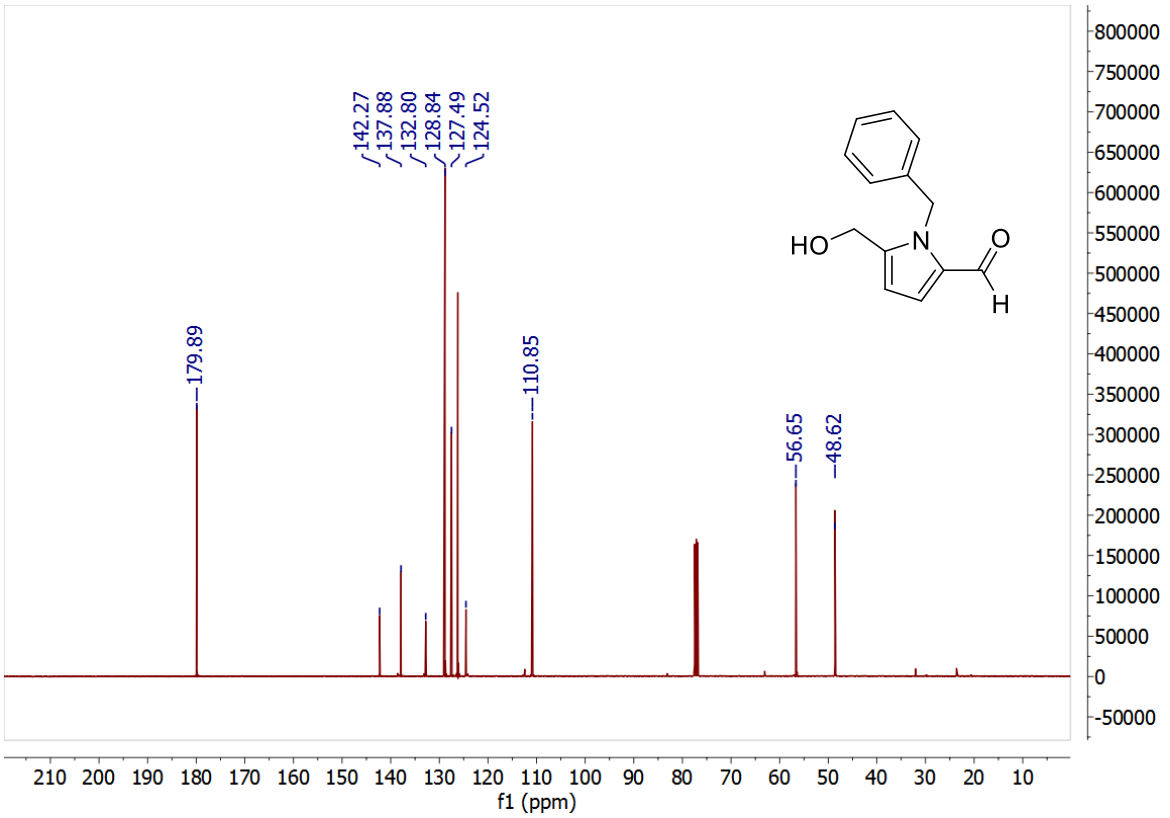


Figure 11 ^{13}C NMR spectra of 1-benzyl-5-(hydroxymethyl)-1H-pyrrole-2-carbaldehyde

5.2 Synthesis of of 1-benzyl-1H-pyrrole-2,5-dicarbaldehyde

1-benzyl-5-(hydroxymethyl)-1H-pyrrole-2-carbaldehyde (0.8 g, 1 eq), TEMPO (5% w/w), KBr (0.2 eq), TBAB (0.02 eq) were put in a round bottom flask with 45 mL of DCM and 45 mL of a saturated aqueous $NaHCO_3$ solution at 0 °C and the mixture was stirred for 45 minutes. $Ca(OCl)_2$ (3 eq) was added.in small portions. At the end of this time, the mixture was extracted with 3x50 mL of DCM. The organic phase was evaporated and the resulting viscous oil was sublimated at 90-100 °C and 0.004 mbar, giving the pure product as white solid. Yield 68%.^{1}H NMR (400 MHz, DMSO-d6) δ 9.87 (s, 2H), 7.36 – 7.25 (m, 2H), 7.23 (d, J = 3.9 Hz, 3H), 7.00 (d, J = 7.1 Hz, 2H), 5.98 (s, 2H). ^{13}C NMR (101 MHz, DMSO) δ 183.33, 138.02, 135.68, 128.55, 127.25, 126.05, 121.89, 48.42.

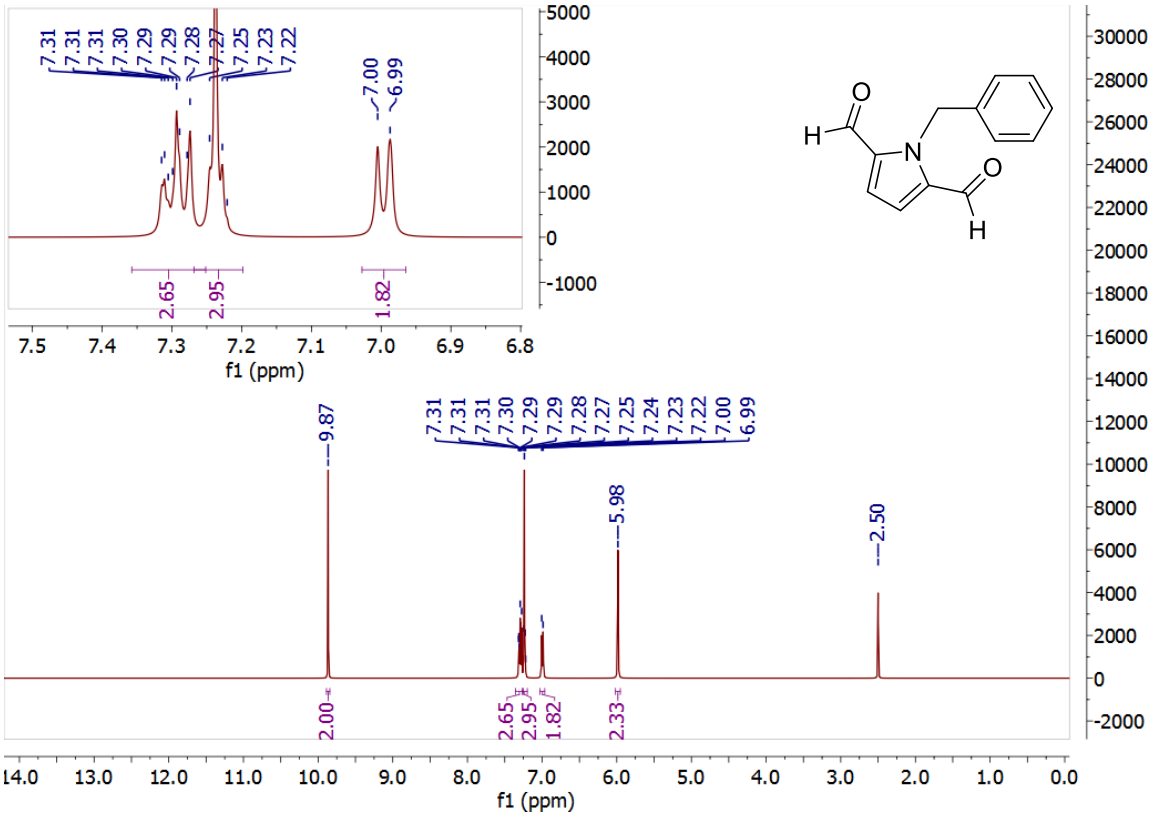


Figure 12 ^{1}H NMR Spectra of 1-benzyl-1H-pyrrole-2,5-dicarbaldehyde

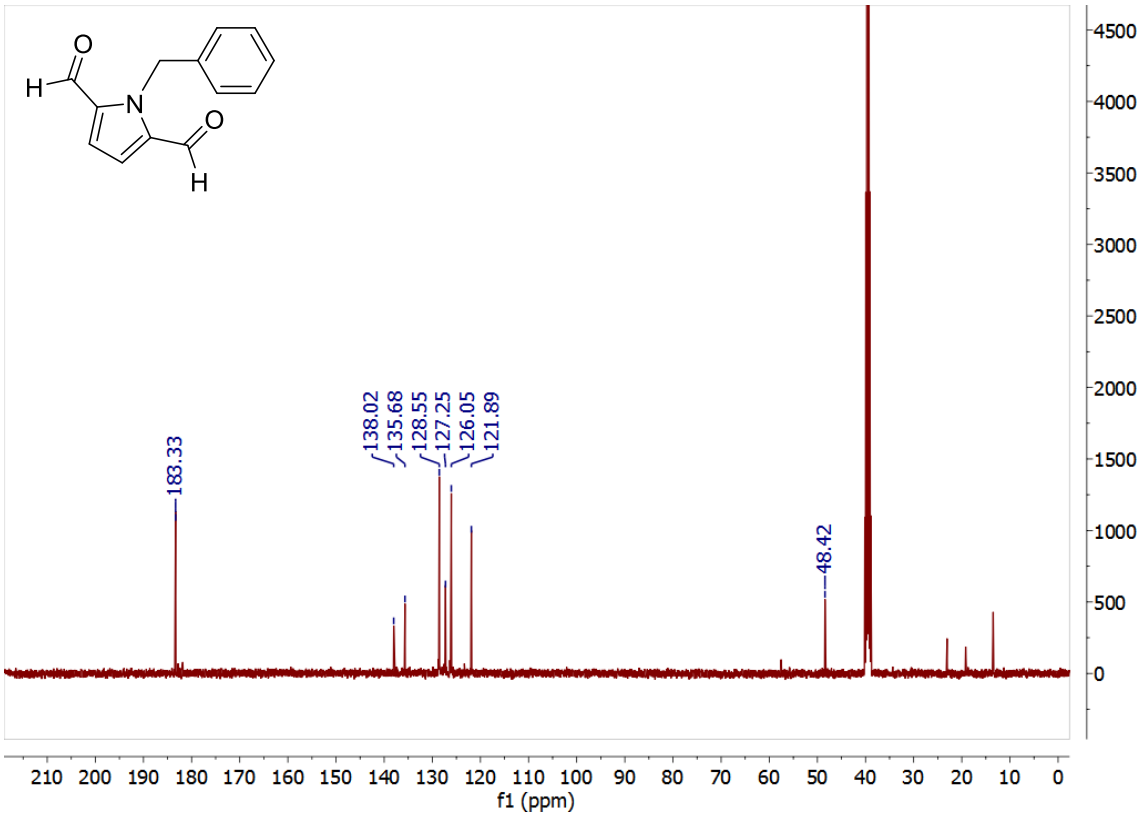


Figure 13 ^{13}C NMR Spectra of 1-benzyl-1H-pyrrole-2,5-dicarbaldehyde

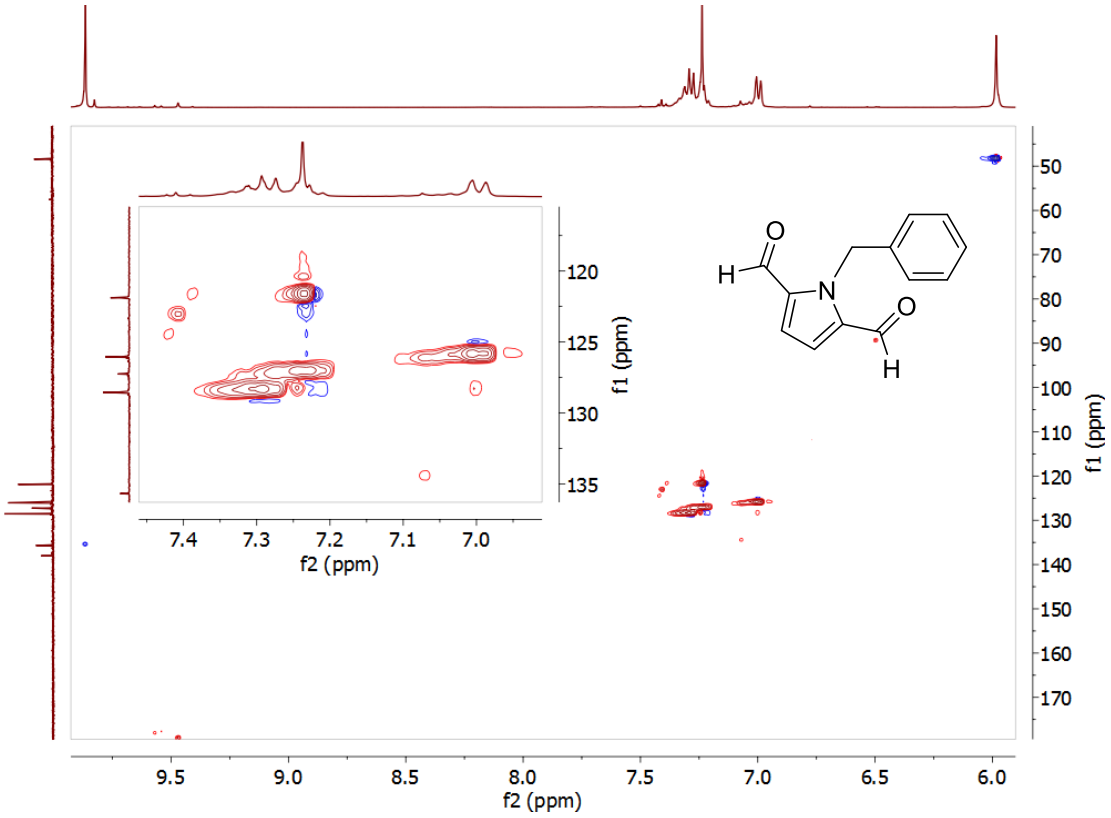


Figure 14 HSQC Spectra of 1-benzyl-1H-pyrrole-2,5-dicarbaldehyde

5.3 Synthesis of 1-benzyl-2,5-di(1,3-dioxolan-2-yl)-1H-pyrrole

1-benzyl-1H-pyrrole-2,5-dicarbaldehyde (0.1 g, 1 eq), NH_4Br (10% mol) and ethanediol (60 µL, 2.5 eq) were put in a round bottom flask with 2 mL of CPME at reflux overnight with a Dean-Stark apparatus to remove water. The mixture was filtrated to remove the catalyst, diluted with a saturated solution of $NaHCO_3$ and extracted with 3x50 mL of ethyl acetate. The organic phase was evaporated, and the resulting viscous oil was put in a round bottom flask with 2 mL of CPME, NH_4Br (10% mol) and ethanediol (60 µL, 2.5 eq) kept at reflux for additional 12 hours with a Dean-Stark apparatus. The aqueous work-up was repeated and the resulting oil filtrated over a thin silica or celite pad, giving the pure product as white solid. Yield 90%.^{1}H NMR (400 MHz, Chloroform-d) δ 7.32 – 7.17 (m, 3H), 7.04 – 6.97 (m, 2H), 6.28 (s, 2H), 5.74 (s, 2H), 5.37 (s, 2H), 4.03 – 3.84 (m, 8H). ^{13}C NMR (101 MHz, CDCl3) δ 138.67, 131.17, 128.61, 127.11, 126.14, 108.47, 98.93, 64.85, 48.49.

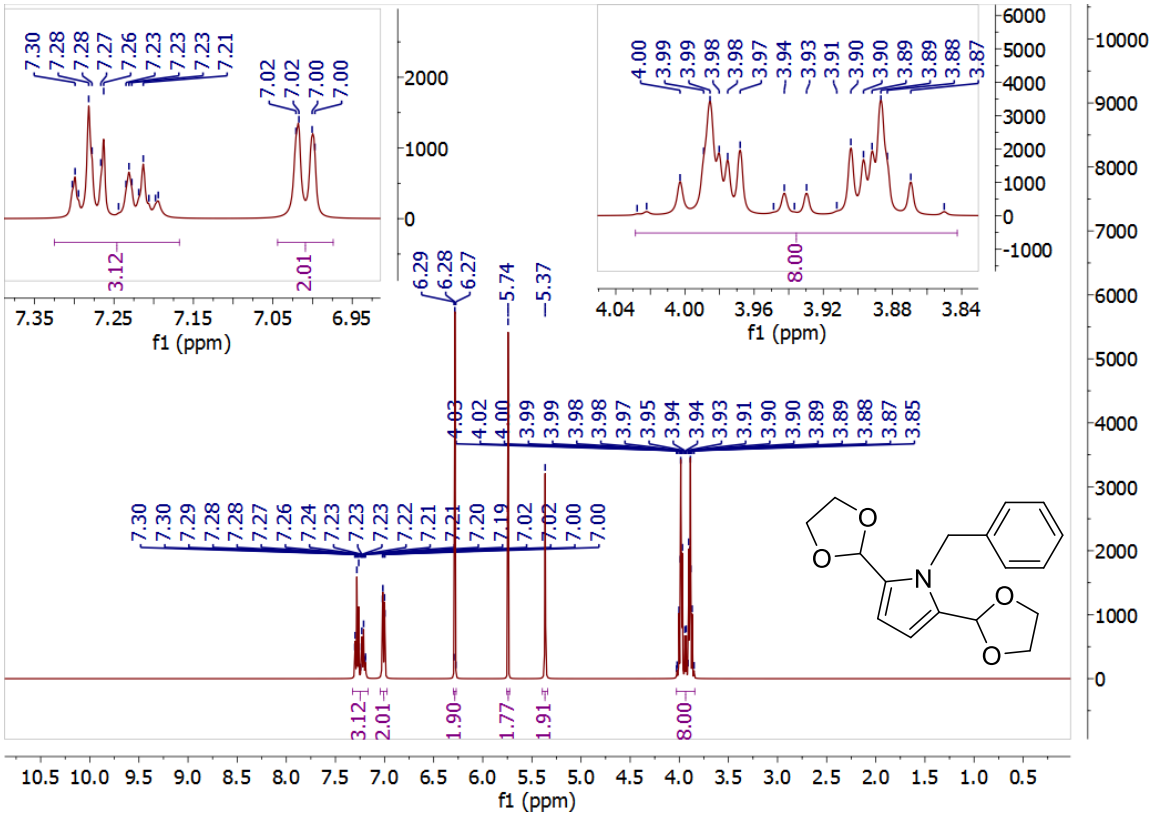


Figure 15 ^{1}H NMR Spectra of 1-benzyl-2,5-di(1,3-dioxolan-2-yl)-1H-pyrrole

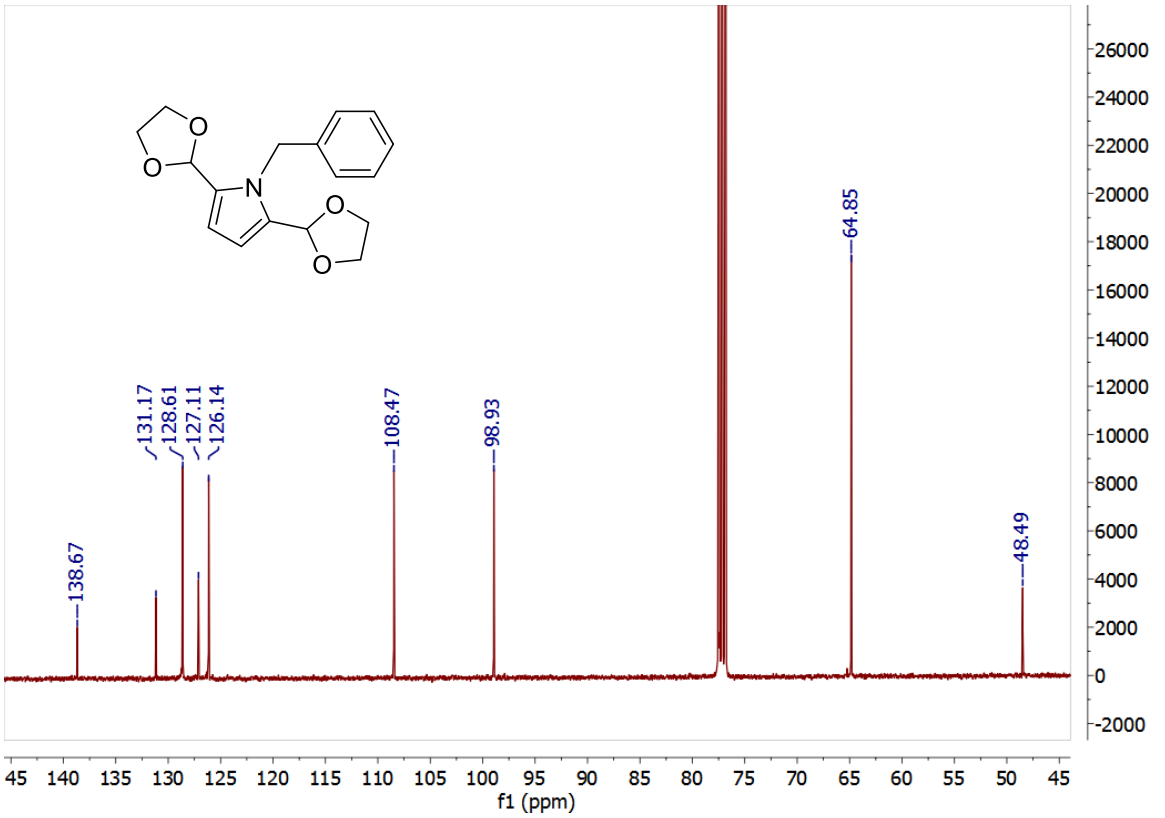


Figure 16 ^{13}C NMR Spectra of 1-benzyl-2,5-di(1,3-dioxolan-2-yl)-1H-pyrrole

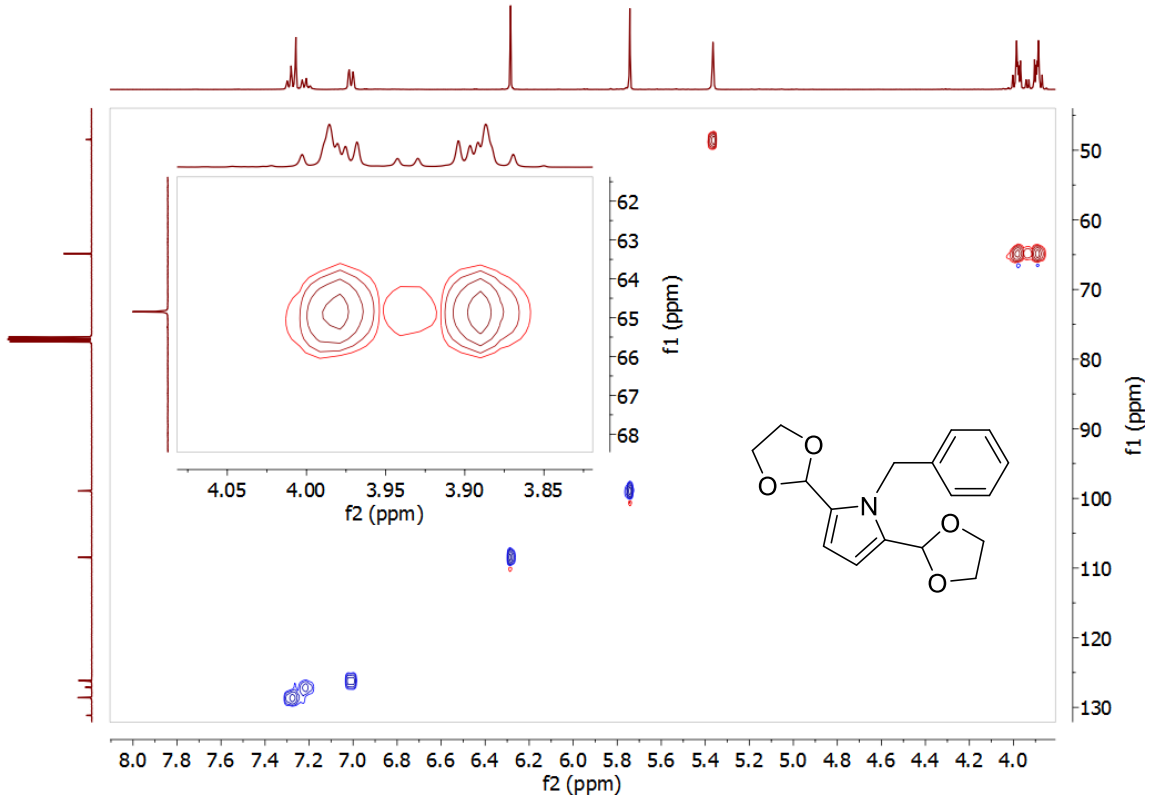


Figure 17 HSQC Spectra of 1-benzyl-2,5-di(1,3-dioxolan-2-yl)-1H-pyrrole

5.4 Synthesis of 1H-pyrrole-2,5-dicarbaldehyde

Metallic Sodium (8 eq) was placed under argon in a two-necked round bottom flask, anhydrous THF (5 mL) was added and the mixture was stirred at reflux until the sodium was completely dissolved, then 1-benzyl-2,5-di(1,3-dioxolan-2-yl)-1H-pyrrole (0.1 g, 1 eq) was added at 0 °C and the mixture was stirred for 4 hours. The reaction was quenched with water and the organic phase was separated and evaporated. Then, the crude product was placed in a round bottom flask with 5 mL of ethanol and an HCl 1 M solution (10 eq), the mixture was stirred for 5 hours. At the end of this time, the mixture was diluted with 10 mL of deionized water and extracted with 3x10 mL of ethyl acetate. The organic phase was evaporated and the pure product was isolated by filtration over a thin silica or celite pad. Yield 90%. ^{1}H NMR (400 MHz, DMSO-d6) δ 13.16 (s, 1H), 9.76 (s, 2H), 7.06 (d, J = 2.2 Hz, 2H).

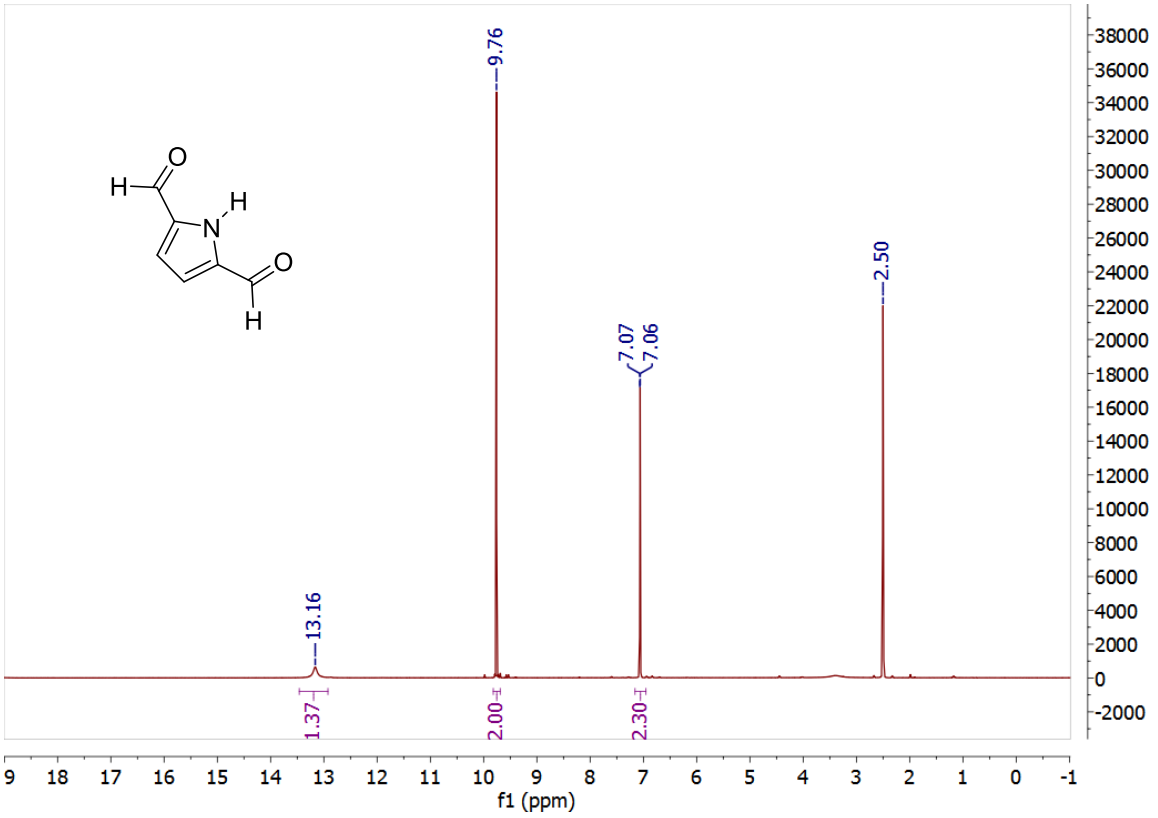


Figure 18 ^{1}H NMR Spectra of 1H-pyrrole-2,5-dicarbaldehyde

5.5 Synthesis of 1H-pyrrole-2,5-dicarboxylic acid

1H-pyrrole-2,5-dicarbaldehyde (0.5 g, 1 eq) was placed in a round bottom flask with 100 mL of acetone and 80 mL of deionized water. $KMnO_4$ (6 eq) was dissolved in 130 mL of acetone and added dropwise at 30 °C during 3 hours. After 4 hours the reaction was quenched using a mixture of HCl 34% (15 mL), H2O (130 mL) and saturate aqueous NaHSO3 (36 mL). Acetone was evaporated and the aqueous phase was extracted with 3x200 mL of ethyl acetate. The organic phase was evaporated and the resulting white solid was used in the next step without further purification. Yield 88%. ^{1}H NMR (400 MHz, DMSO-d6) δ 12.77 (s, 1H), 12.14 (s, 2H), 6.74 (s, 2H).

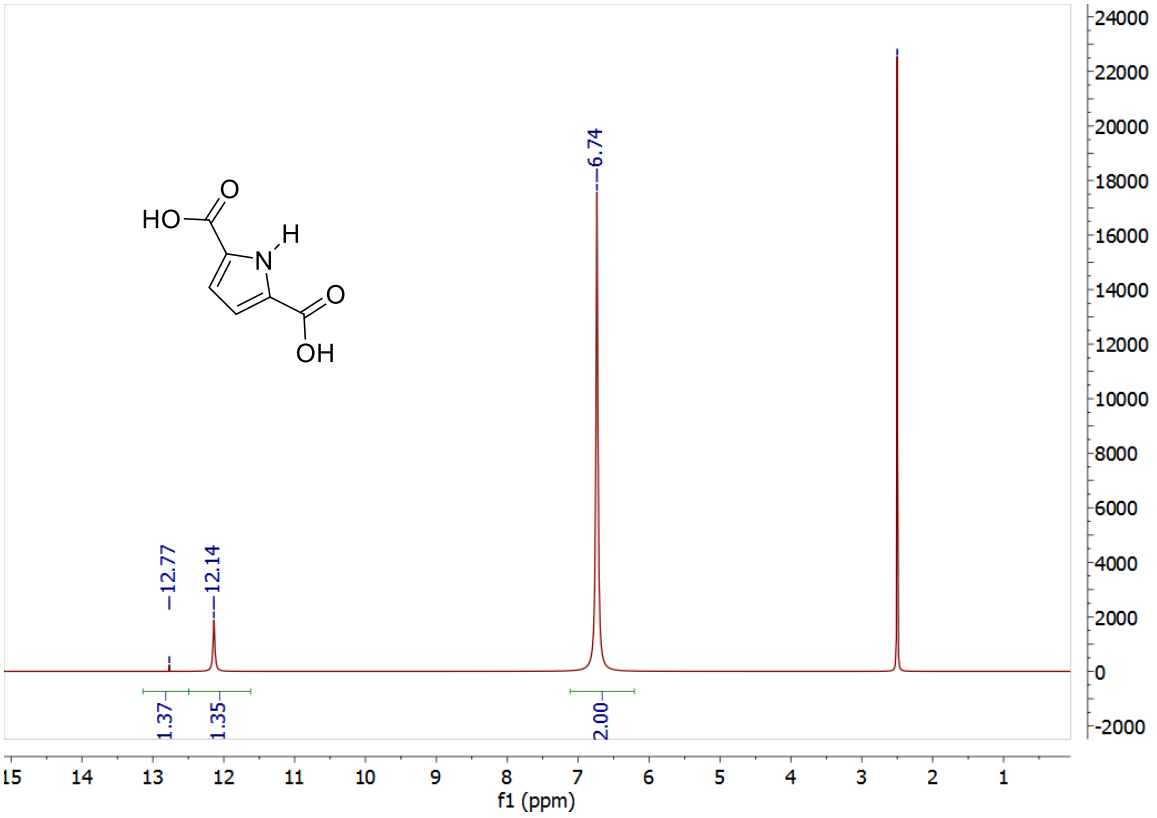


Figure 19 ^{1}H NMR Spectra of 1H-pyrrole-2,5-dicarboxylic acid

5.6 Synthesis of dimethyl 1H-pyrrole-2,5-dicarboxylate

1H-pyrrole-2,5-dicarboxylic acid (1.9 g, 1 eq) was placed in a round bottom flask with 70 mL of methanol, H2SO4 (12 eq) was added and the mixture was stirred overnight at reflux. A saturated solution of aqueous NaHCO3 was added until the acid was quenched, methanol was evaporated and the aqueous phase was extracted with ethyl acetate. The organic phase was evaporated and the resulting solid was used in the next step without further purification. Yield 90%. ^{1}H NMR (400 MHz, Chloroform-d) δ 9.74 (s, 1H), 6.87 (d, J = 2.6 Hz, 2H), 3.89 (s, 6H).

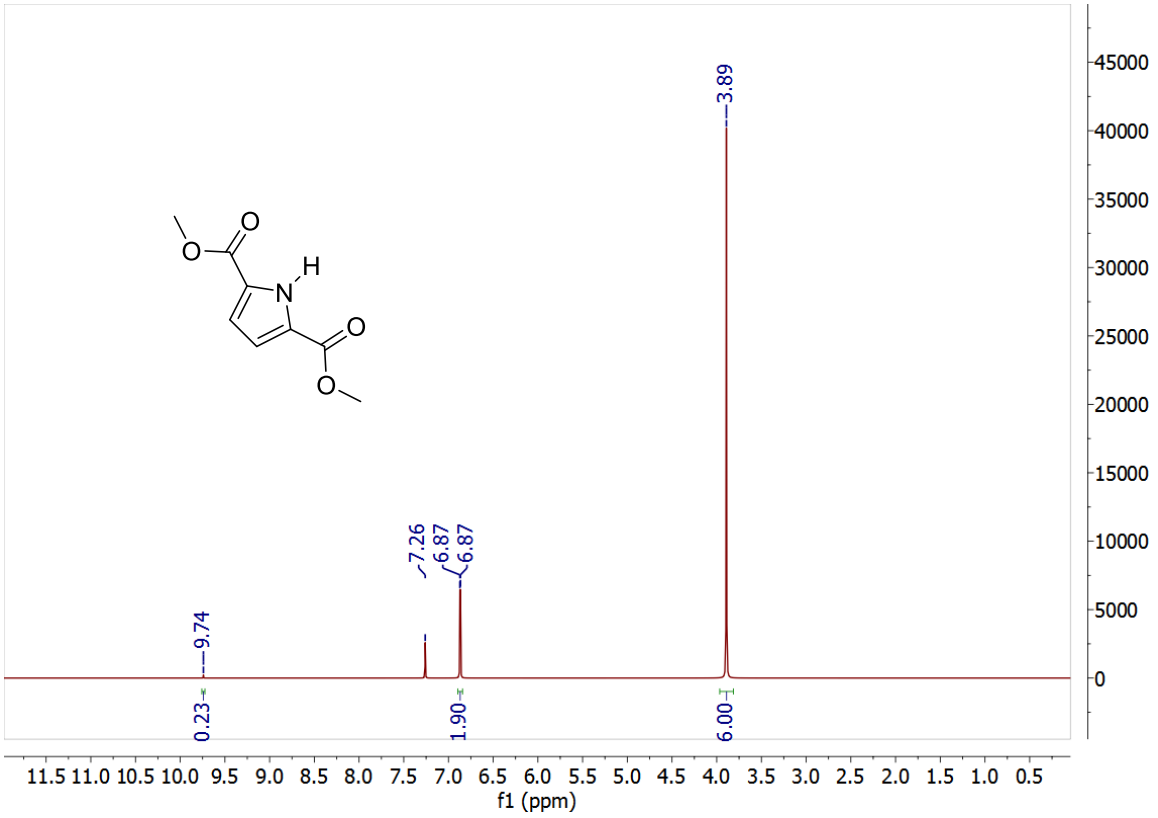


Figure 20 ^{1}H NMR Spectra of dimethyl 1H-pyrrole-2,5-dicarboxylate

5.7 Synthesis of 1-(tert-butyl) 2,5-dimethyl 1H-pyrrole-1,2,5-tricarboxylate

Dimethyl 1H-pyrrole-2,5-dicarboxylate (1.87 g, 1 eq), di-tert-butyl dicarbonate (1.10 eq) and DMAP (0.05 eq) were put in a round bottom flask with 20 mL of acetonitrile at room temperature, the mixture was stirred for 3 hours. At the end of this time, a 1 M solution of Na_2CO_3 (20 mL) was added the mixture was extracted with 3x50 mL of ethylacetate. The organic phase was evaporated and the resulting solid was filtrated over a thin silica or celite pad, giving the pure product as white solid. Yield 90%. ^{1}H NMR (400 MHz, Chloroform-d) δ 6.83 (s, 2H), 3.86 (s, 6H), 1.66 (s, 9H).

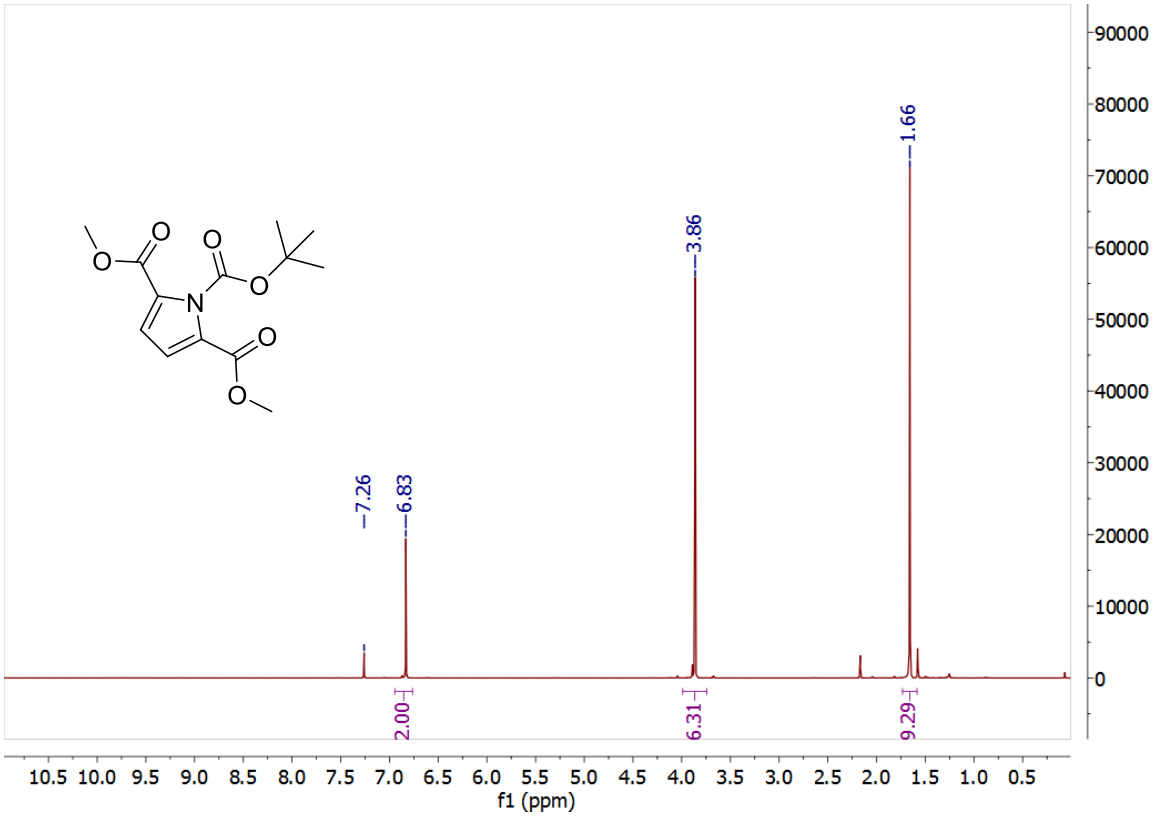


Figure 21 ^{1}H NMR Spectra of 1-(tert-butyl) 2,5-dimethyl 1H-pyrrole-1,2,5-tricarboxylate

5.8 Synthesis of 1-(tert-butyl) 2,5-dimethyl pyrrolidine-1,2,5-tricarboxylate

1-(tert-butyl) 2,5-dimethyl 1H-pyrrole-1,2,5-tricarboxylate was dissolved in hot isopropyl alcohol and put in a high-pressure reactor with Pd/C catalyst (5% w/w). The mixture was stirred for 5 days at 50 °C and 50 atm of hydrogen. At the end of this time, the reactor was cooled, vented and purged with argon, the mixture decanted and the supernatant solution evaporated to give the crude product as a white solid. The product was purified by column chromatography Yield: 85%. ^{1}H NMR (400 MHz, Chloroform-d) δ 4.35 (ddd, J = 50.7, 7.2, 3.7 Hz, 2H), 3.75 (s, 6H), 2.16 (ddd, J = 21.2, 15.1, 8.2 Hz, 4H), 1.42 (s, 9H). ^{13}C NMR (101 MHz, CDCl3) δ 172.61, 172.34, 153.64, 80.95, 77.16, 60.19, 59.68, 52.35, 52.18, 29.69, 28.91, 28.36.

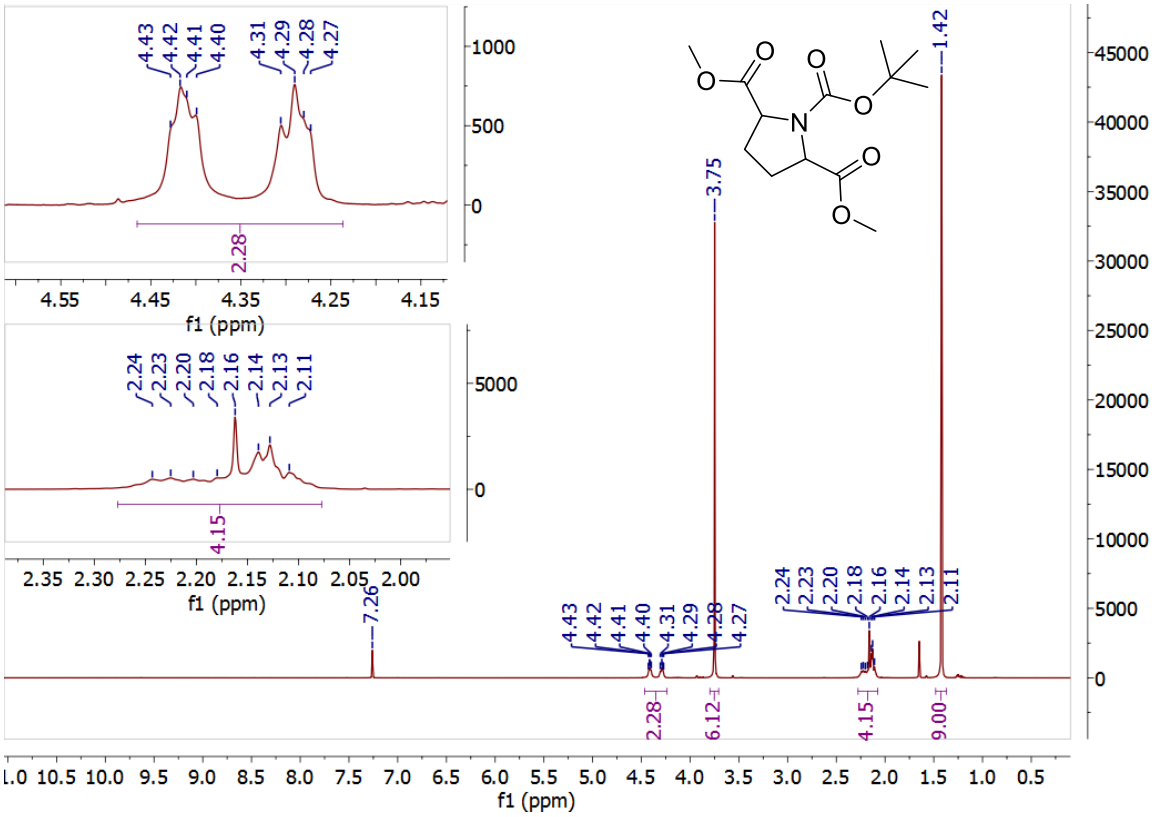


Figure 22: ^{1}H NMR Spectra of 1-(tert-butyl) 2,5-dimethyl pyrrolidine-1,2,5-tricarboxylate

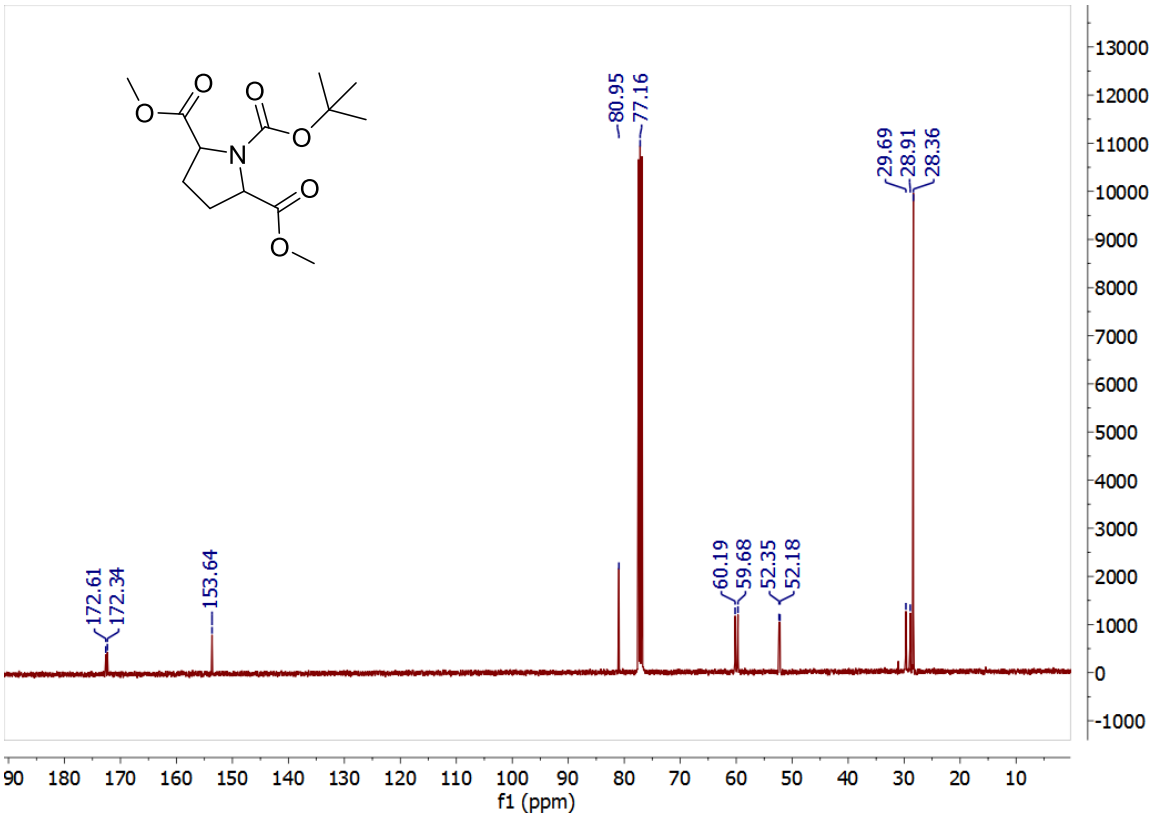


Figure 23 ^{1}H NMR Spectra of 1-(tert-butyl) 2,5-dimethyl pyrrolidine-1,2,5-tricarboxylate

5.9 Synthesis of tert-butyl 2,5-bis(hydroxymethyl)pyrrolidine-1-carboxylate

1-(tert-butyl) 2,5-dimethyl pyrrolidine-1,2,5-tricarboxylate (0.7 g, 1 eq) and $CaCl_2$ (3 eq) were put in a round bottom flask with 25 mL of ethanol and 3 mL of methanol at room temperature, the mixture was stirred for 3 hours. $NaBH_4$ (6 eq) was added in small portions during 2 hours, at the end of this time methanol was added (3 mL), after 15 minutes deionized water (25 mL) was added. The mixture was then concentrated in vacuo and extracted with ethyl acetate 3x50 mL. The organic phase was evaporated and the resulting solid was filtrated over a thin silica or celite pad, giving the pure product as white solid. Yield 85%. ^{1}H NMR (400 MHz, Chloroform-d) δ 4.53 (br, 1H), 4.05 – 3.67 (m, 5H), 3.49 (m, 2H), 2.32 – 1.71 (m, 5H), 3.29 (br, 1H) 1.44 (s, 9H).

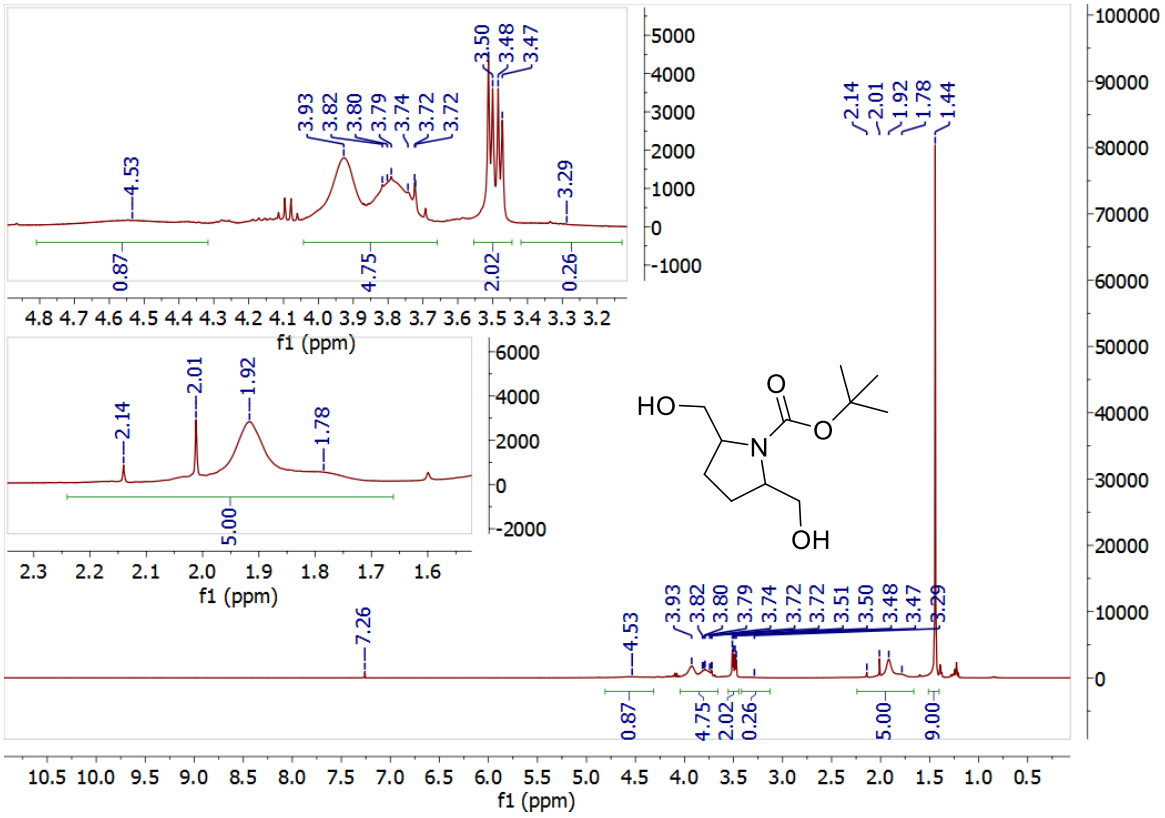


Figure 24 ^{1}H NMR Spectra of tert-butyl 2,5-bis(hydroxymethyl)pyrrolidine-1-carboxylate

5.10 Synthesis of 3-oxa-8-azabicyclo[3.2.1]octan-8-ium chloride

Tert-butyl 2,5-bis(hydroxymethyl)pyrrolidine-1-carboxylate (0.6 g, 1 eq) and pyridine (1.20 eq) were put in a round bottom flask with 7 mL of THF under argon at -10 °C. A solution of potassium tert-butoxide (3 eq) in THF (2 mL) was added dropwise at room temperature and the mixture are stirred until the reagent was disappeared. Then, a solution of p-toluenesulfonyl chloride (1.13 eq) in THF (2 mL) was added dropwise at -10 °C. After 30 minutes the reaction was quenched with a saturated aqueous $NaHCO_3$ and extracted with ethyl acetate. The organic phase was evaporated and the product was isolated by crystallization from heptane. Yield: 20%. ^{1}H NMR (400 MHz, Chloroform-d) δ 9.99 (s, 2H), 4.23 (d, J = 12.4 Hz, 2H), 4.01 – 3.89 (m, 2H), 3.65 (dd, J = 12.8, 2.0 Hz, 2H), 2.33 – 2.18 (m, 2H), 2.21 – 2.10 (m, 2H).

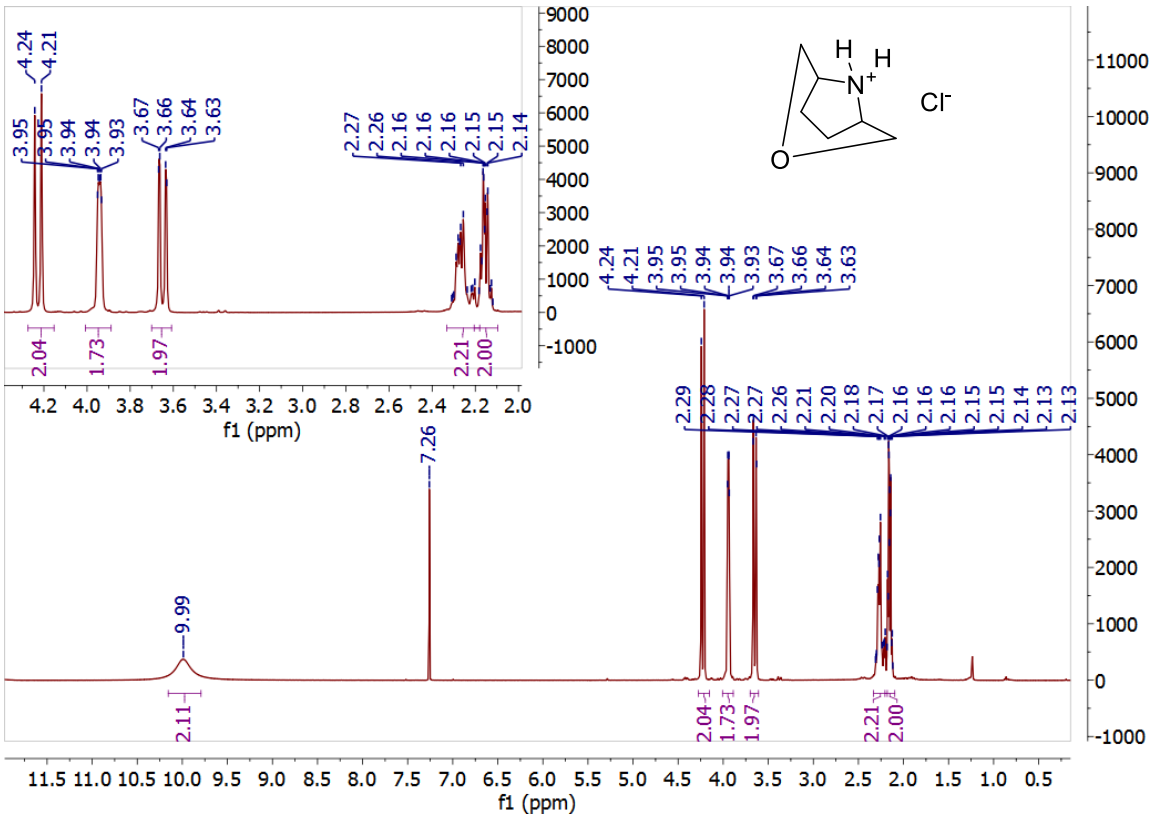


Figure 25 ^{1}H NMR Spectra of 3-oxa-8-azabicyclo[3.2.1]octan-8-ium chloride

5.11 Synthesis of tert-butyl 2,5-bis((tosyloxy)methyl)pyrrolidine-1-carboxylate

Tert-butyl 2,5-bis(hydroxymethyl)pyrrolidine-1-carboxylate (0.6 g, 1 eq) and pyridine (1.20 eq) were put in a round bottom flask with 7 mL of THF under argon at -10 °C. A solution of potassium tert-butoxide (3 eq) in THF (2 mL) was added dropwise at room temperature and the mixture are stirred until the reagent was disappeared. Then, a solution of p-toluenesulfonyl chloride (3 eq) in THF (2 mL) was added dropwise at -10 °C. The mixture was stirred overnight at room temperature, quenched with a saturated aqueous $NaHCO_3$ and extracted with ethyl acetate. The organic phase was evaporated and the product was isolated by crystallization from heptane. Yield: 80%. ^{1}H NMR (400 MHz, Chloroform-d) δ 9.99 (s, 2H), 4.23 (d, J = 12.4 Hz, 2H), 4.01 – 3.89 (m, 2H), 3.65 (dd, J = 12.8, 2.0 Hz, 2H), 2.33 – 2.18 (m, 2H), 2.21 – 2.10 (m, 2H). ^{13}C NMR (101 MHz, CDCl3) δ 154.11, 145.05, 132.94, 130.10, 128.07, 80.88, 77.16, 69.72, 56.89, 28.59, 28.35, 21.78.

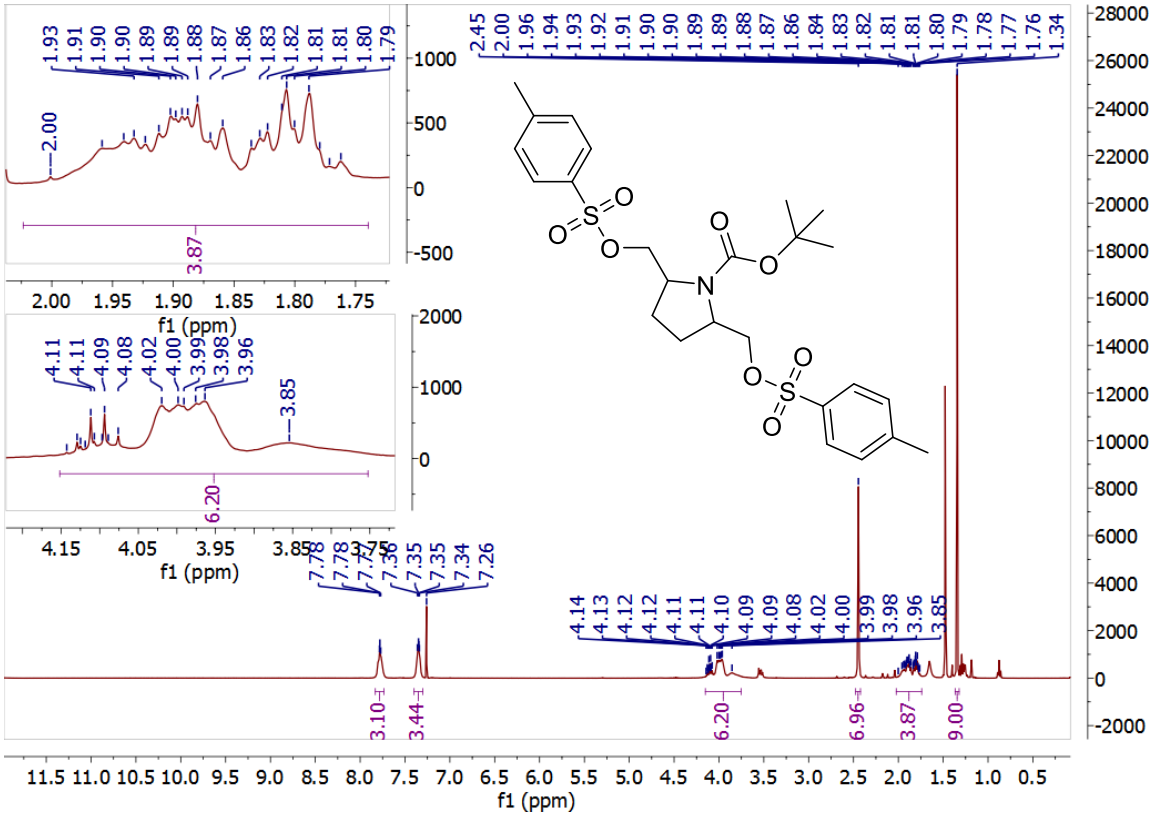


Figure 26 ^{1}H NMR Spectra of tert-butyl 2,5-bis((tosyloxy)methyl)pyrrolidine-1-carboxylate

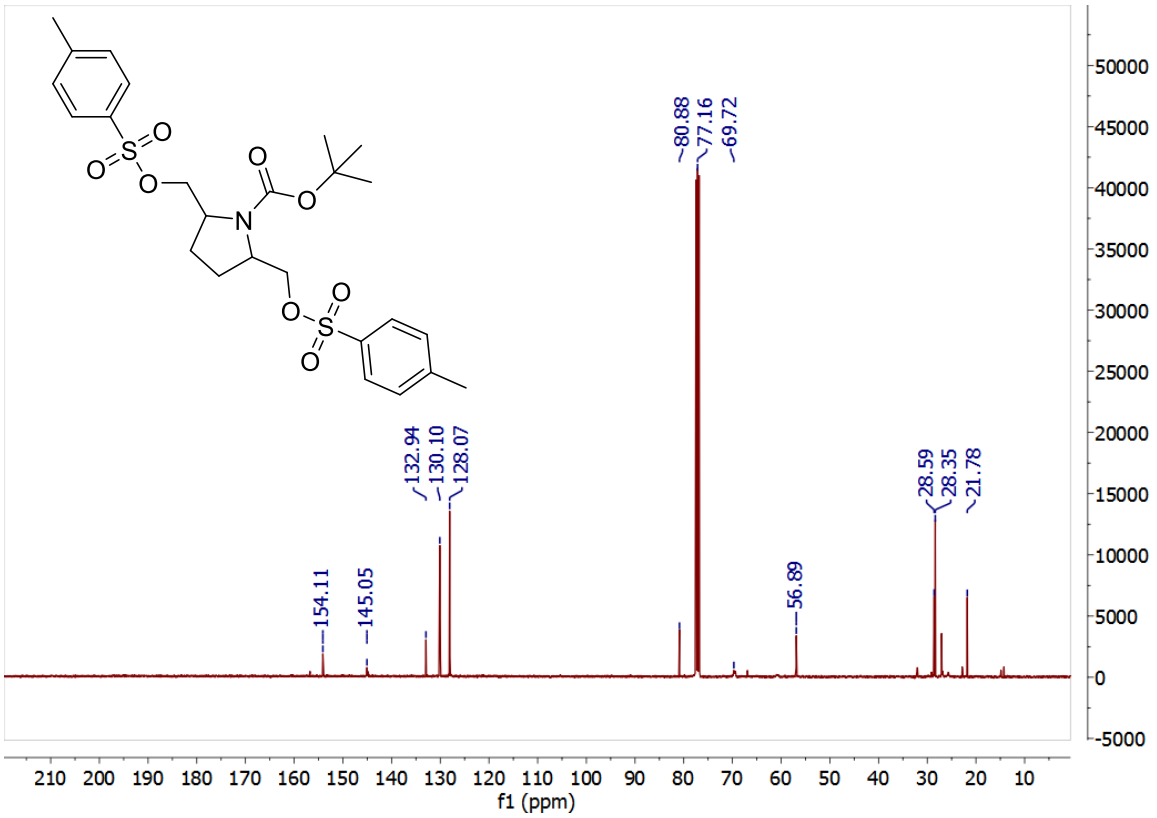


Figure 27 ^{1}H NMR Spectra of tert-butyl 2,5-bis((tosyloxy)methyl)pyrrolidine-1-carboxylate

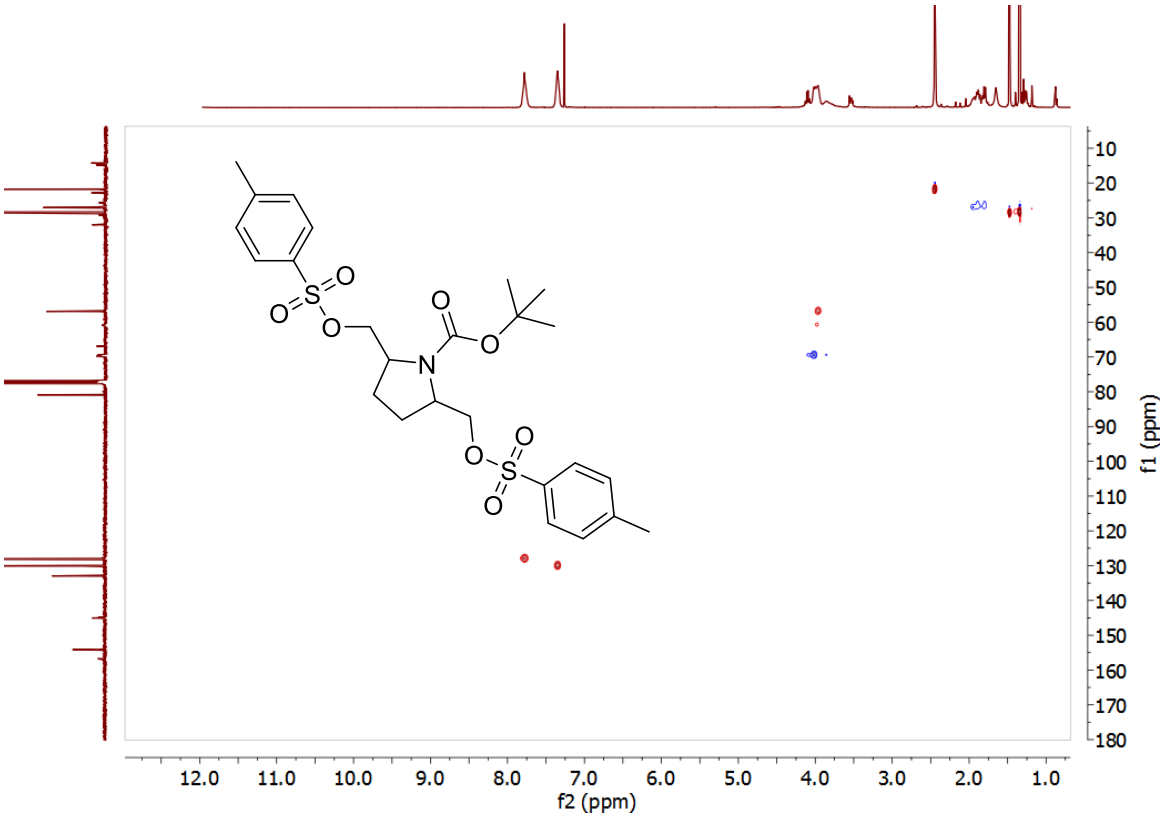


Figure 28: HSQC spectra of tert-butyl 2,5-bis((tosyloxy)methyl)pyrrolidine-1-carboxylate

5.12 Synthesis of 3-oxa-8-azabicyclo[3.2.1]octane-N-oxyl radical

3-oxa-8-azabicyclo[3.2.1]octan-8-ium chloride (1 g, 1 eq) was placed in a round bottom flask with H_2O (3 mL) and NaOH 1 M (1.2 eq) was added dropwise at 0 °C. The solution was left stirring at room temperature for 30 minutes. At the end of this time the mixture was extracted with 3x10 mL of DCM. The organic phase was evaporated and the resulting white solid was used in the next step. (Yield: 81%).

The white solid (0.7 g, 1 eq) was placed in a round bottom flask with acetonitrile (3 mL) and methanol (3 mL) and Na_2WO_4 $2H_2O$ (0.25 eq), the solution was stirred at 0 °C for 30 minutes. At the end of this time urea-hydrogen peroxide (3 eq) was added in small portions during 1 hours, then the reaction was stirred for 1.5 hours at 0 °C and for 24 hours at room temperature. At the end of this time the mixture was concentrated, deionized H_2O was added and the solution was extracted with $CHCl_3$ (3x10 mL). The organic phase was evaporated and the resulting red solid was stored in the fridge. (Yield: 90%) In order to collect an NMR spectra of the product and confirm its formation, a oxidation it is performed to the radical.

5.14 Synthesis of 3-oxa-8-azabicyclo[3.2.1]octan-8-ol

3-oxa-8-azabicyclo[3.2.1]octane-N-oxyl radical is placed in a round bottom flask with sodium ascorbate (2 eq) in water (5 mL) and the solution was stirred for 30 minutes. At the endo of this time the mixture was extracted with diethyl ether (3x5 mL). The organic phase was evaporated and the resulting white solid was analysed by ^{1}H NMR. 1H NMR (400 MHz, Chloroform-d) δ 3.66 (d, J = 11.1 Hz, 2H), 3.58 (dd, J = 11.5, 2.3 Hz, 2H), 3.43 (dq, J = 5.1, 2.2, 1.7 Hz, 2H), 2.16 – 2.07 (m, 2H), 1.89 – 1.82 (m, 2H).

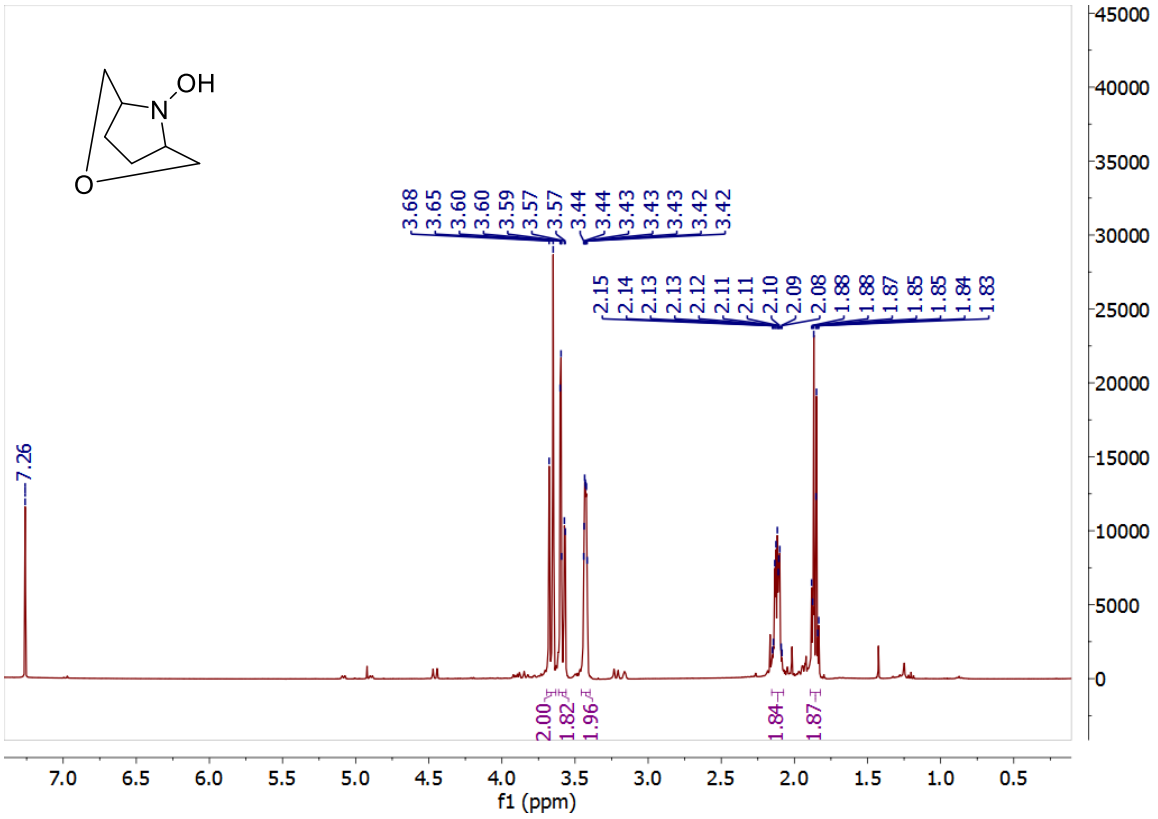


Figure 29 ^{1}H NMR Spectra of 3-oxa-8-azabicyclo[3.2.1]octan-8-ol

5.15 Synthesis of TBADT[97]

Sodium tungstate dihydrate (5.0 g) and tetrabutyl ammonium bromide (2.4 g) were placed in two round bottom flask and dissolved in water (150 mL) at 90 °C, the two solutions were stirred and concentrated HCl is added dropwise to both solution until the pH of both solutions were 2. The two solutions were mixed and stirred for 30 minutes at 90 °C. At the end of this time the solution was cooled at room temperature and filtered under vacuum, the white solid was washed with water and dried in oven at 130 °C for 3 hours. The white solid was dissolved in DCM and stirred for 2 hours at room temperature. At the end of this time the solution was filtered under vacuum, giving TBADT as white solid.

5.16 Functionalization of 3-oxa-8-azabicyclo[3.2.1]octan-8-ium chloride

Substrate (amine or THF, 0.25 mmol, 1 eq) is placed in a vial with acetonitrile (2.5 mL) and TBADT (2% w/w). The vial is placed in front of a white light source and left stirring for 24 hours at room temperature. At the end of this time the solution in both vials turned intense blue, attesting the formation of a radical.

5.17 Oxidation of model alcohols

Alcohol (0.2 mmol, 1 eq), catalyst (1% mol/mol), KBr (0.2 eq) and TBAB (0.02 eq) were put in a round bottom flask with 3 mL of DCM and 3 mL of a saturated aqueous $NaHCO_3$ solution at 0 °C and the mixture was stirred for 45 minutes. $Ca(OCl)_2$ (1.5 eq) was added in small portions. At the end of this time, the mixture was extracted with 3x3 mL of DCM. The organic phase was evaporated and the resulting viscous oil was characterized by ^1H NMR spectroscopy. The conversion of menthol was evaluated by integration of td at 3.37 ppm (1H alcohol) and the ddd at 2.32 ppm (1H ketone).

The conversion of benzyl alcohol was evaluated by integration of s at 4.59 ppm (2H alcohol) and the s at 9.91 ppm (1H aldehyde).

	Catalyst and Conversion	
Alcohol	TEMPO	Radical **18**
Menthol	2%	16%
Benzyl alcohol	12%	21%

Table 2 Oxidations on model substrates

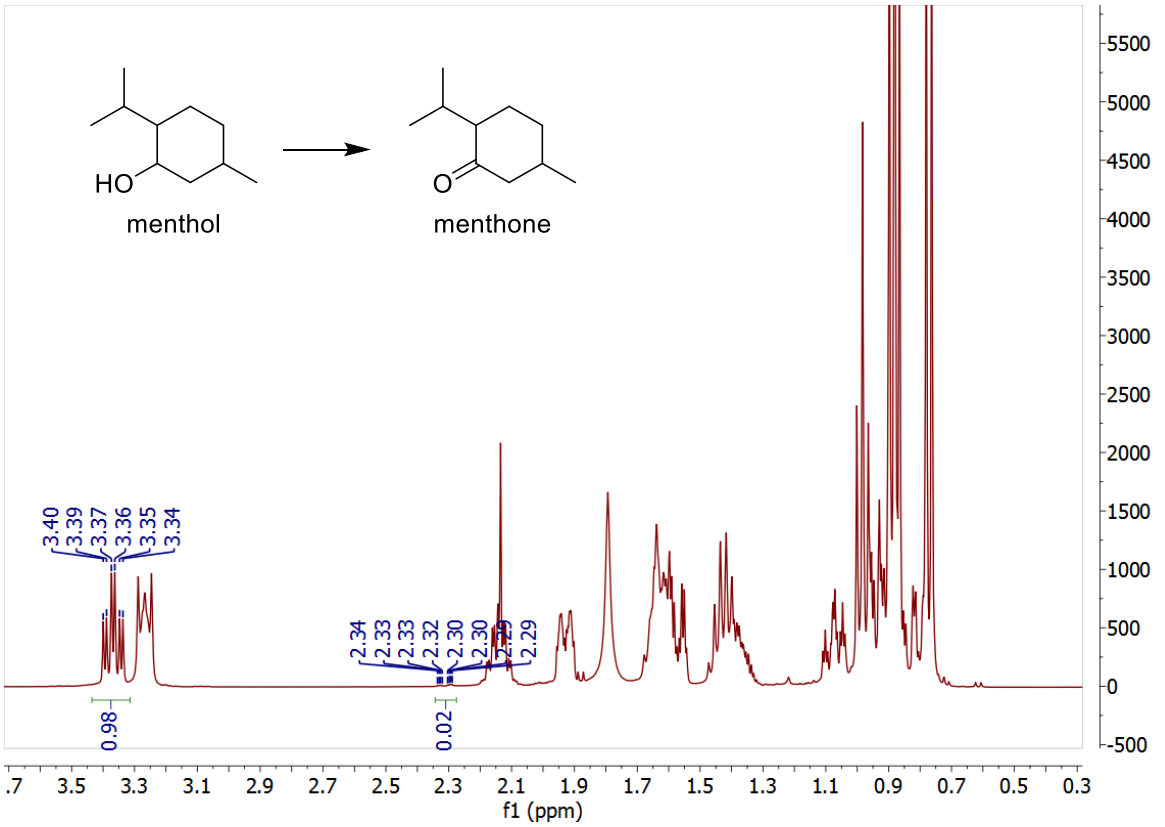


Figure 30 ^{1}H NMR Spectra of crude oxidation product – Menthol with TEMPO

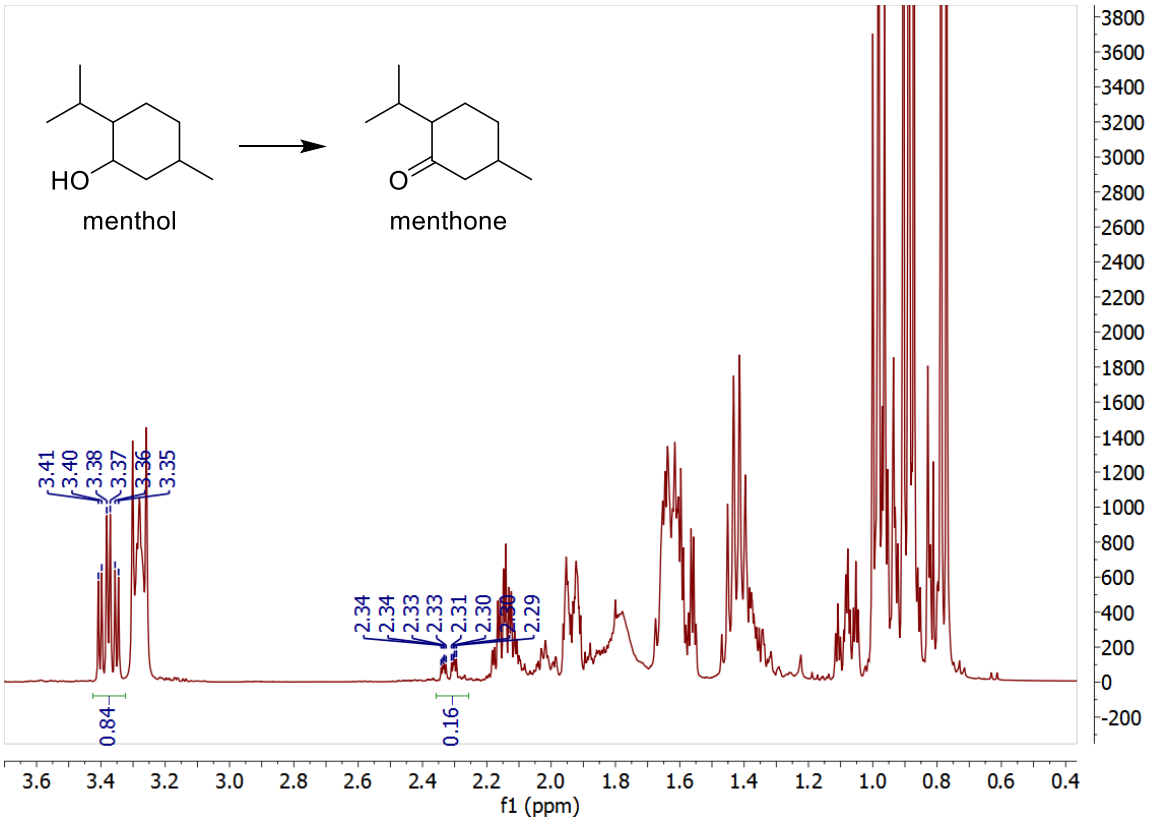


Figure 31 ^{1}H NMR Spectra of crude oxidation product – Menthol with new synthesized radical

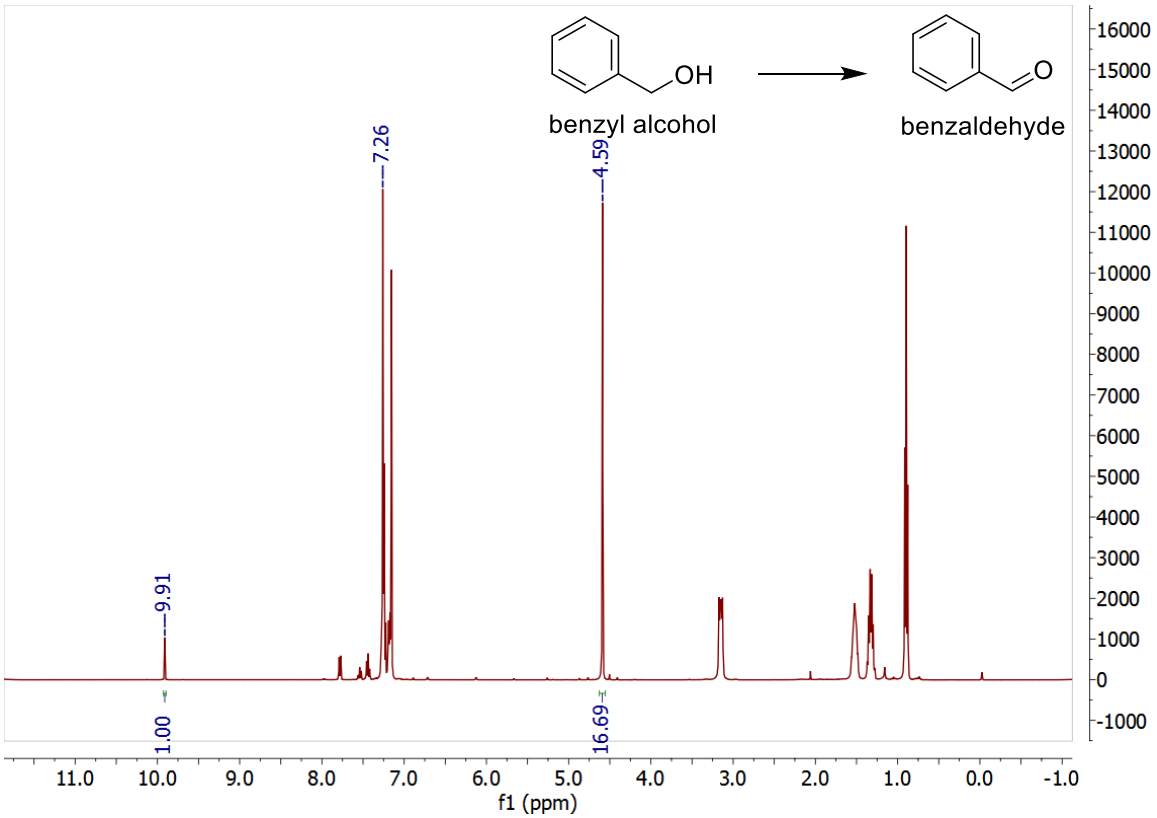


Figure 32 ^{1}H NMR Spectra of crude oxidation product – benzyl alcohol with TEMPO

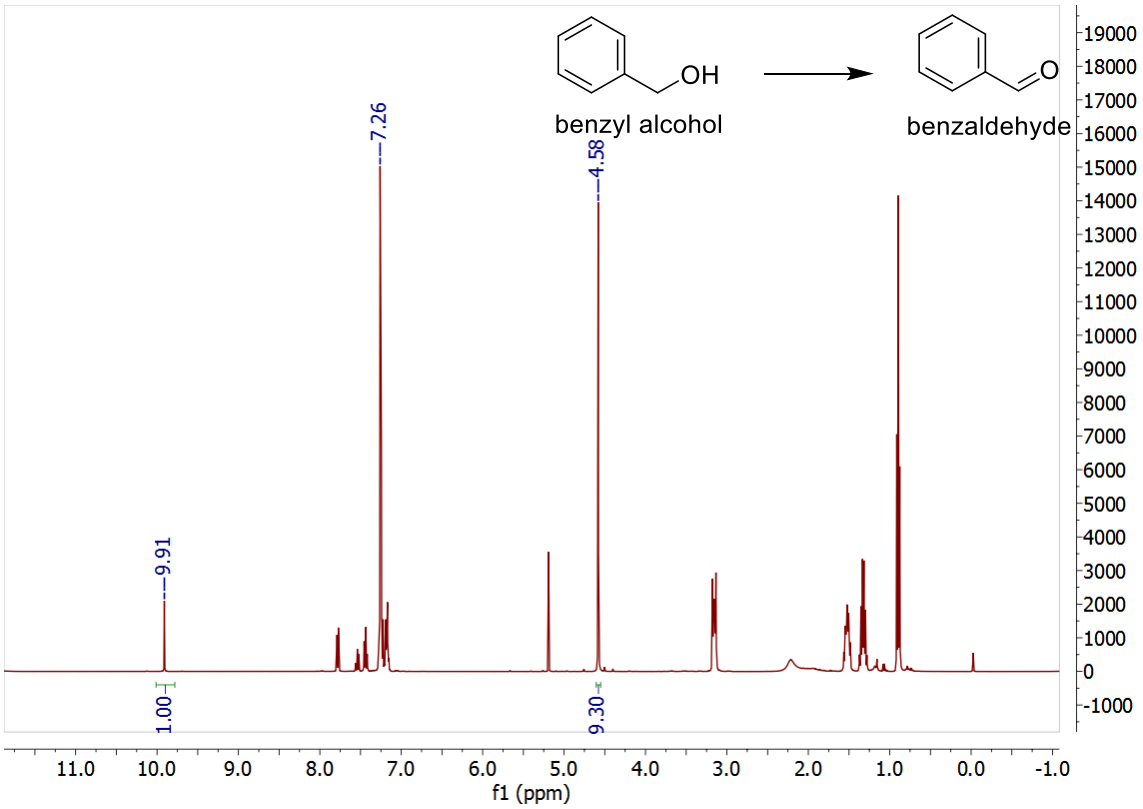


Figure 33 ^{1}H NMR Spectra of crude oxidation product – benzyl alcohol with new synthesized radical

5.18 Adsorbing metal “A” from an aqueous solution

An aqueous waste solution, partially an emulsion, containing two metal catalysts (called “A” and “B”) and organic by-products have been provided by the company Matrìca S.p.a.

General procedure: 5 ml of a solution containing metals is placed in a flask with adsorbent material and stirred at room temperature, after the stirring time the mixture have been filtered under vacuum and the aqueous solution have been characterized by Uv-vis spectroscopy to quantify the amount of metal adsorbed.

5.18.1 Testing a model metal “A” solution

A solution of metal “A” in water is prepared and characterized by Uv-vis spectroscopy. Identified the characteristic peak of metal “A”, a calibration curve is plotted.

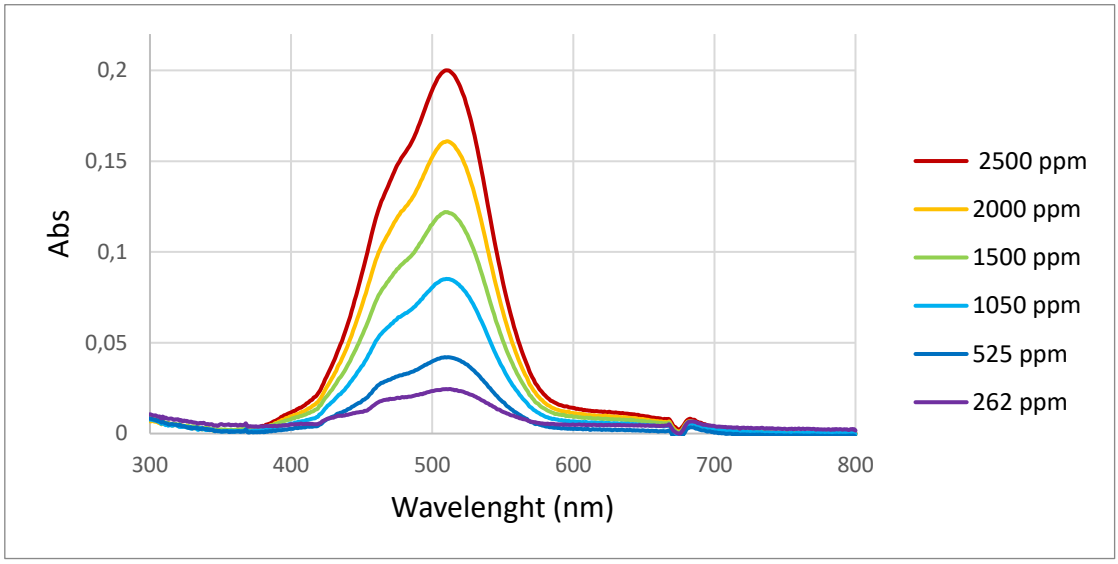


Figure 34: Standard solutions Uv-vis spectra

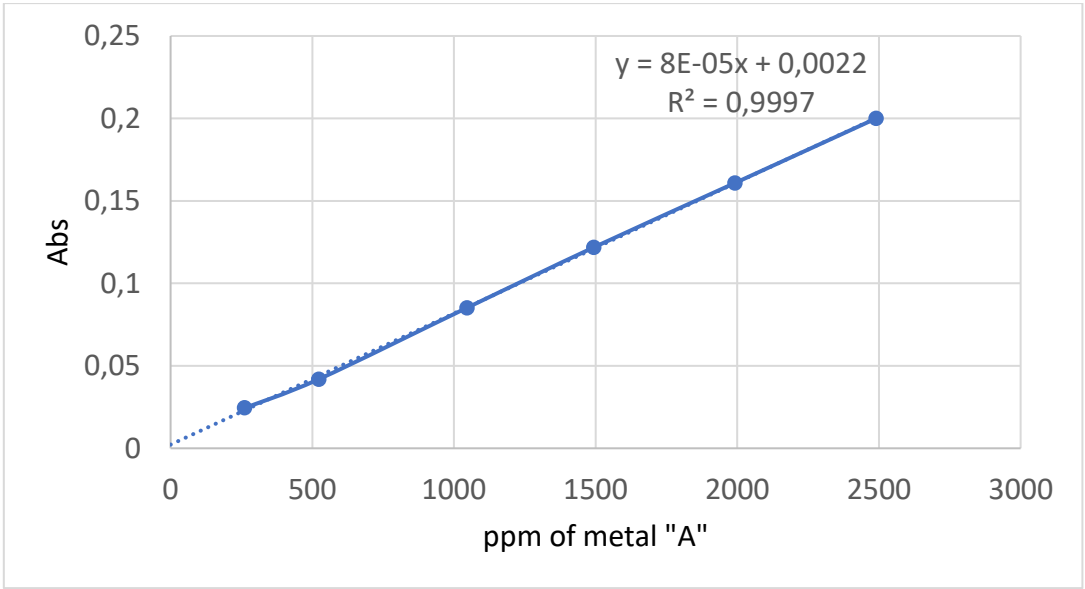


Figure 35: Calibration Curve for an aqueous solution of metal "A"

Adsorbent materials used have been: Montmorillonite K10, packaging vermiculite and three bentonites (C, D and N).

Adsorbent material	**Stirring time** *% of metal adsorbed*				
	0.5 h	**1 h**	**3 h**	**6 h**	**48 h**
Vermiculite	*63%*	*62%*			
Montmorillonite K10	*5%*				
Bentonite C	*52%*	*51%*	*57%*	*56%*	
Bentonite D			*24%*	*43%*	*45%*
Bentonite N			*39%*	*43%*	

Table 3: Experiments on a 5 mL/1 g scale

With these results, we proof that, in a model solution, the metal "A" can be successfully adsorbed by bentonites and vermiculite in relatively short time, therefore we proceed with the experiment with the Matrìca solution.

5.18.2 Adsorbing metal "A" from Matrìca solution

First, the Matrìca solution have been characterized by Uv-vis spectroscopy (Figure 3). Into the spectrum it is easy identified the metal peak (~500 nm), and a broad band (< 450 nm) that can be attributed to organic materials (by-products) presents in the Matrìca solution. As a proof for that, the aqueous solution is extracted with dichloromethane, and the resulting oil has been characterized with Uv-vis spectroscopy (Figure 4)

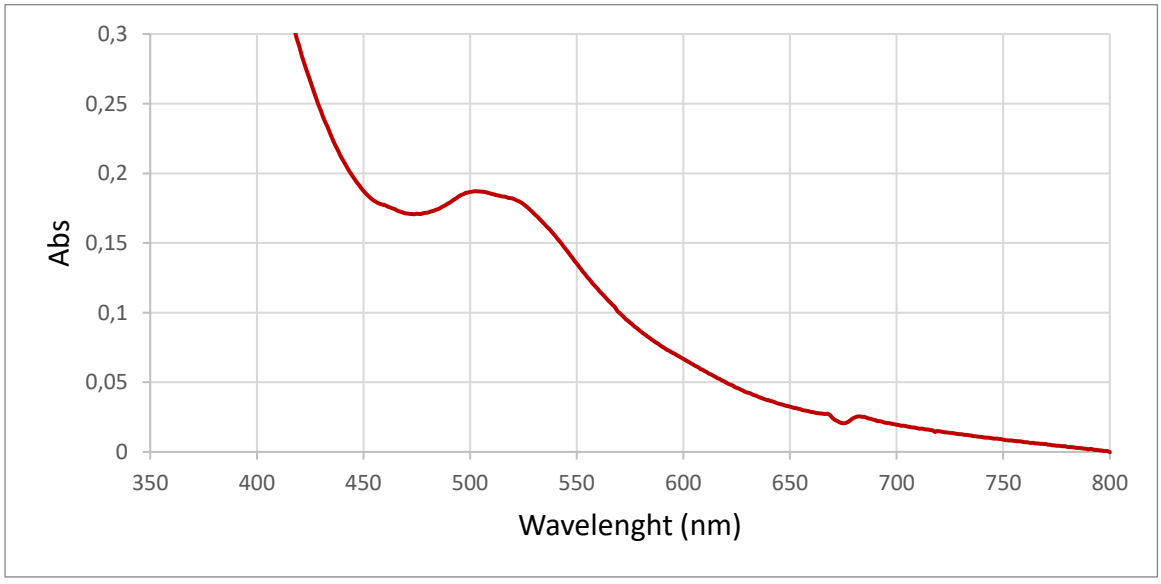


Figure 36: Uv-vis spectra of the starting aqueous solution

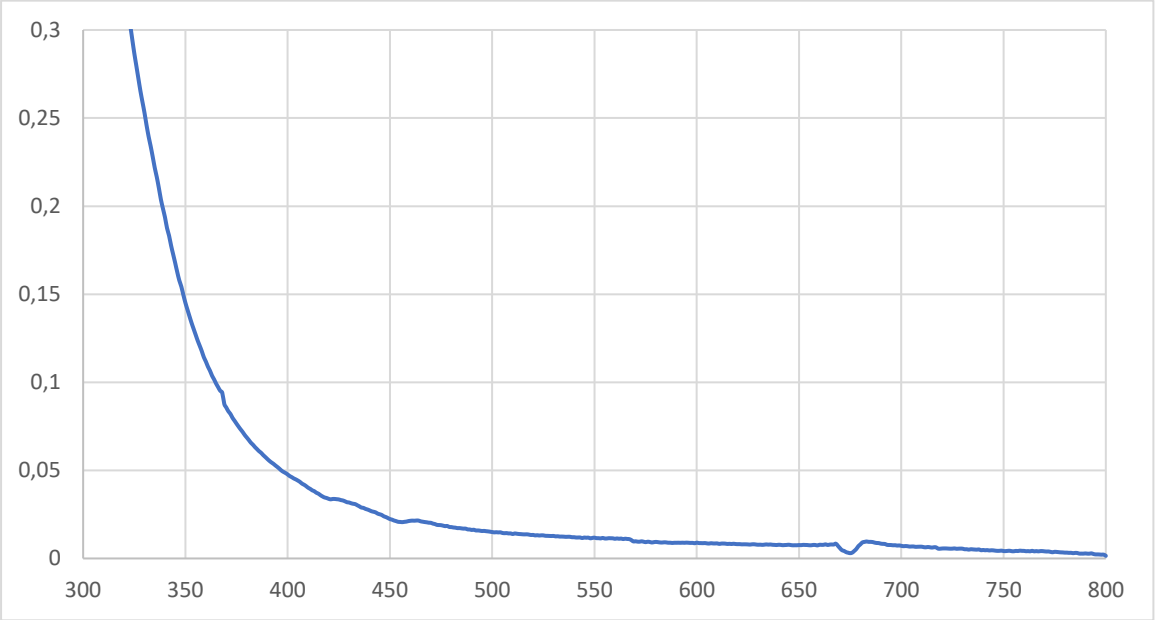


Figure 37: Uv-vis spectra of the extracted oil

The solution is treated with the described procedure using the adsorbent materials that gave good results with the model solution.

Adsorbent material	**Stirring time 0.5 h** *% of metal adsorbed*
Vermiculite	*55%*
Bentonite C	*49%*
Bentonite D	*58%*
Bentonite N	*58%*

Table 4: Experiments on a 5 mL/1 g scale

Experiment with Bentonites D and N have been repeated in a medium scale in order to pick the best adsorbent material between the tested ones.

Adsorbent material	**Stirring time 0.5 h** *% of metal adsorbed*
Bentonite D	*53%*
Bentonite N	*42%*

Table 5: Experiments on a 100 mL/20 g scale

5.19 Extracting metal cations “A” from the adsorbent material

General procedure: The dried adsorbent material is placed in a flask with a Na^+ containing solution (e.g.: brine) and stirred for 30 minutes at room temperature, after the stirring time the mixture have been filtered under vacuum and the aqueous solution have been characterized by Uv-vis spectroscopy to quantify the amount of metal extracted.

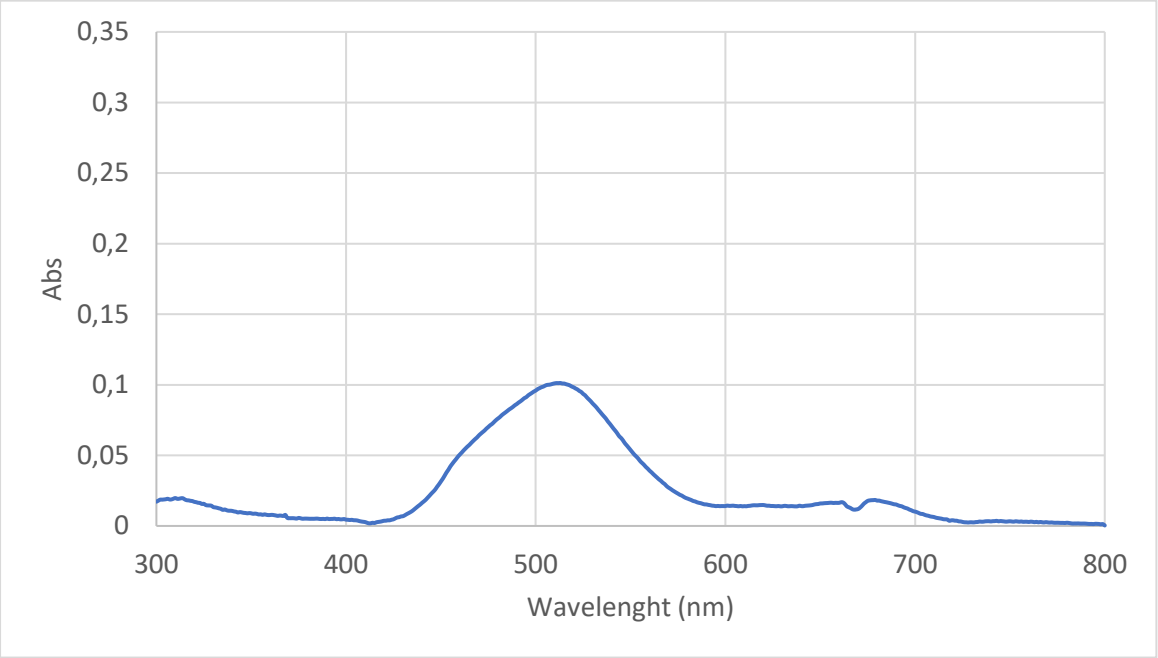


Figure 38 Uv-vis spectra of brine solution containing metal "A" after treatment of bentonite

Into the spectra it is easy to identify the peak from the metal and, moreover, the absent of the peak from organic by-products. Therefore, the metal "A", is successfully isolated from the starting aqueous solution.

A solution of metal "A" in brine is prepared and characterized by Uv-vis spectroscopy. Identified the characteristic peak of metal "A", a calibration curve is plotted.

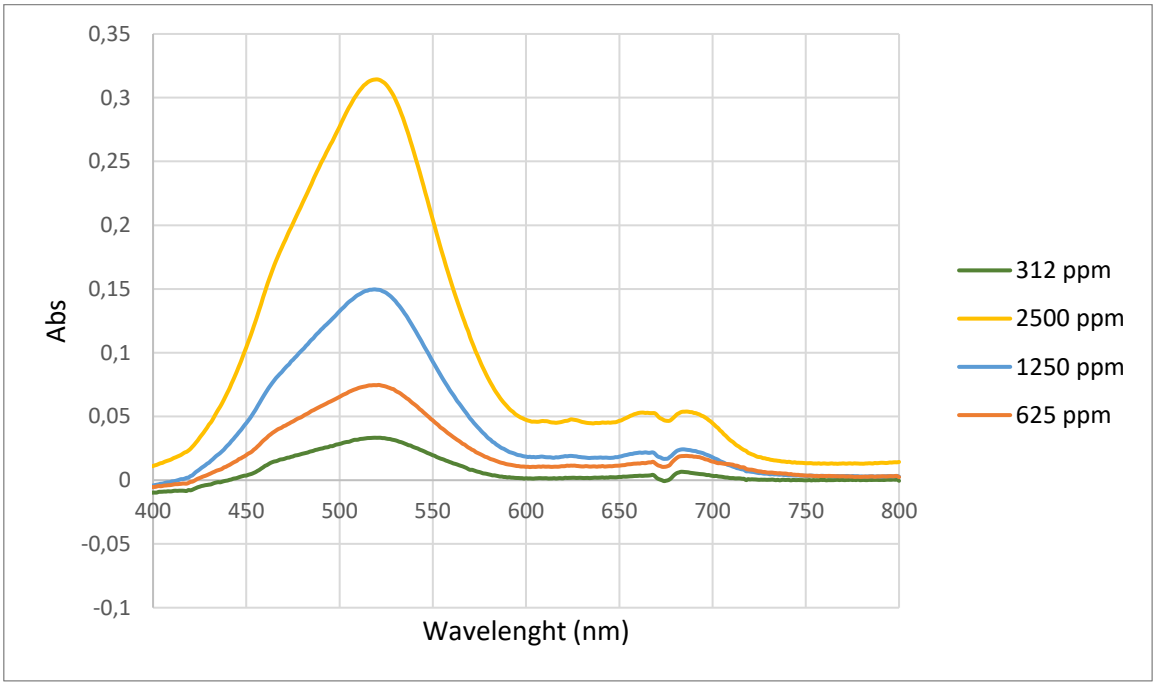


Figure 39: Standard solutions in brine Uv-vis spectra

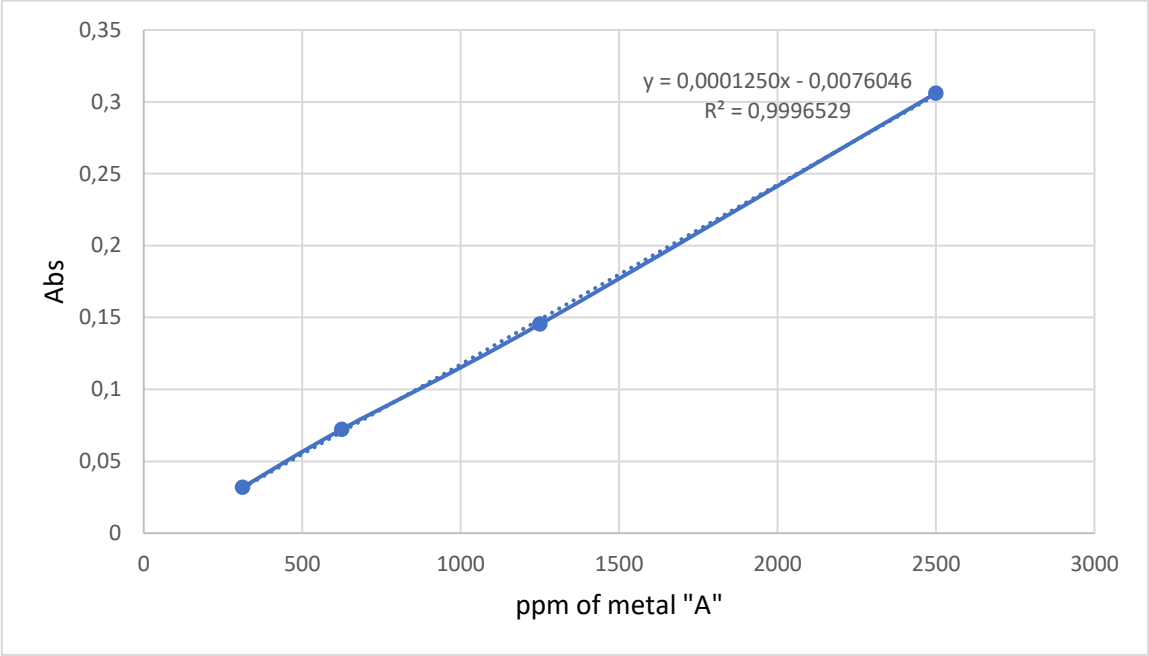


Figure 40: Calibration Curve for a brine solution of metal "A"

Two Na^+ cations solutions have been tested for the extraction of the metal "A" from the chosen bentonite D. The brine solution gave the best

Extracting solution		**Stirring time** *% of metal adsorbed*
	2 h	**3 h**
Brine	*91%*	*88%*
Sodium acetate	*69%*	*69%*

Table 6: Experiments on a 5 mL/1 g scale

5.20 Recycling the adsorbent material

Aiming to develop an efficient procedure on sustainability point of view, the adsorbent material should be reused in subsequent cycle of adsorbing and extracting without losing its activity.

Cycle #	**Adsorbing from the solution (%)**	**Extracting from the adsorbing material (%)**
1	44%	91%
2	*39%*	*96%*
3	*59%*	*95%*

Table 7: Experiments on a 5 mL/1 g scale

5.21 Determination of Bentonite structure

Bentonite have been analysed by X-Ray spectroscopy to determine its structure and composition. The collected data (black dots) it is perfectly stackable with the literature spectra of smectite (red line). The smectites are a mixture of clays materials (mainly montmorillonite, kaolinite and palygorskite). These clays have to ability of expand its interlayer distance to receive cations with a proper ionic ray, and, when dried, to shrink

again. Determination of the structure of the working bentonite, isn't intended just for an analytical purpose, in fact, the knowledge of its structure, it is a starting point to seek for others adsorbing materials.

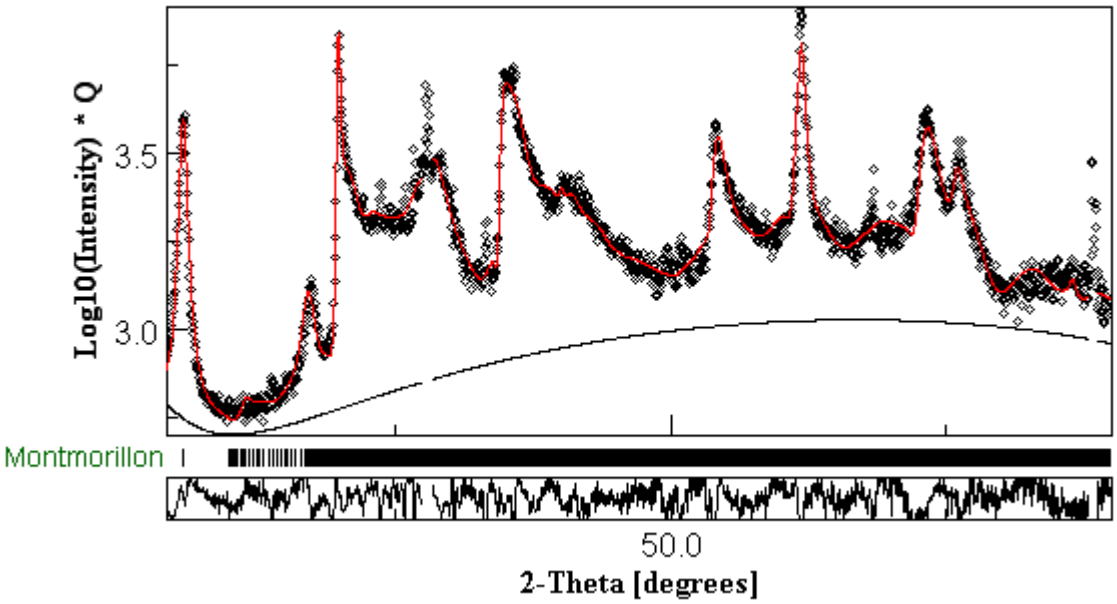


Figure 41 X-Ray spectra of bentonite

Chapter Six

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