Appel à projets communs interlabex

IDENTIFICATION DES EQUIPES PRESENTES DANS LE PROJET

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Axe prioritaire de recherche de CHARMMMAT : Axe A

DESCRIPTION SCIENTIFIQUE DU PROJET

Titre :

Direct use of oxime for the generation of iminyl radicals via electrocatalysis

Résumé :

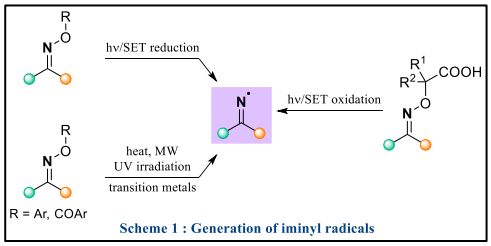
Nitrogen-centered radicals (NCRs) are versatile and highly reactive intermediates and have long been studied in organic chemistry. They can participate in diverse C–N and C–C bond formation reactions, leading to the synthesis of highly important polyfunctionalized nitrogenated chemicals. Among them, iminyl radicals are highly studied because of the wide applications they have found in various types of chemistry. Despite the number of syntheses currently available to access these radicals, it is still necessary to develop new access answering the new environmental and economic challenges of the 21st century. Thus, this project aims to develop an original access to these radicals directly from non-protected oximes by using a catalytic amount of a trivalent phosphine. An electrochemical $P^{III}/P^{V}=O$ catalytic redox cycle is planned to mediate the formation of the key nitrogen radical and avoid the concomitant generation of a stoichiometric amount of phosphine oxide waste, which is a major environmental drawback. The reactivity of key iminyl radicals will be exploited in diverse transformations.

Objectifs scientifiques du projet

The main objective of this project is to implement an economical and environmentally benign access to iminyl radical intermediates to exploit their high and versatile reactivity directly from non-protected oximes. In order to develop these new catalytic transformations, the planned method will involve electrochemistry to perform a new $P^{III}/P^{V}=O$ catalytic redox cycle where a trivalent phosphine will be first oxidized and will mediate the formation of the desired *N*-centered radical *via* a β-scission of a phosphoranyl radical. A concomitant formation of a stoichiometric amount of phosphine oxide is usually observed during such a PR_3-mediated deoxygenation process, which is today a problematic waste in academia or industry. We are planning to use electrochemistry to perform a 2 electrons cathodic reduction to reduce the strong P–O bond of the phosphine oxide and so, perform the formation of iminyl radical with a catalytic amount of trivalent phosphine.

Etat de l'art (présentation et analyse critique)

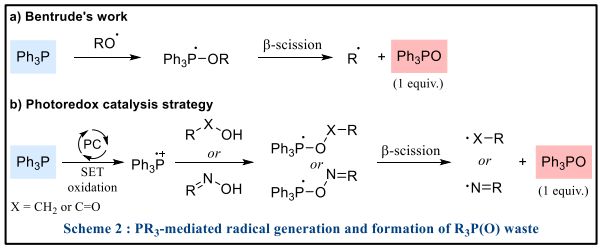
Nitrogen atom has a central role in organic chemistry and can find applications in different fields such as pharmaceutical, agrochemical science, materials and polymers.[1] As an example, in 2018, more than 80 % of the top 200 selling drugs had a nitrogen atom in their structure, which play an important role in the bioactivity.[2] This prime importance has stimulated continuous interest in the development of efficient and sustainable C–N bond formation reactions. Radical-based chemistry has always played a vital role in the construction of complex molecules of interest.[3] Nitrogen Center Radicals (NCRs), which remained for a long period of time hardly accessible took benefit from the dramatic advances in photoredox chemistry and have been established as versatile and important class of chemical intermediates attracting a recent interest in synthetic chemistry.[4] Given their high and versatile reactivity, **iminyl radicals** occupy an important place in the field of NCRs chemistry.[4] They are use as electrophilic species leading to the development of diverse radical-based transformations, such as radical cyclization, to generate valuable nitrogen heterocycles, radical addition for C–N bond formation, inert C–H bond activation *via* 1,3-hydrogen transfer or 1,5-hydrogen transfer. The strain release fragmentation into carbon-center radical for C–C bond formation leading to the synthesis of complex molecules is also a noteworthy transformation. Consequently, intense research and strong efforts are being made toward the generation of such intermediates. Usually, they have been obtained through N–O bond homolysis of O-acyl or O-aryl oxime derivatives under elevated temperatures, microwave, UV irradiation or photoredox reductive SET (*Scheme 1*).[5] More recently, seminal work from Leonori's team and Studer's group interestingly showed



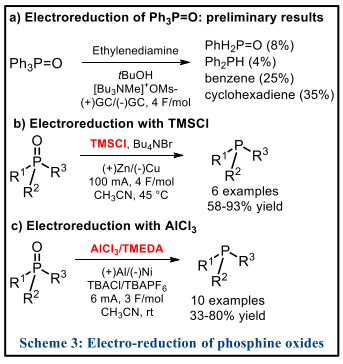
Scheme 1 : Generation of iminyl radicals

that iminyl radicals could be obtained by a photoredox decarboxylation of α-imino-oxy acids as an oxime derivative (*Scheme 1*).[6] Although these methods are today highly used to generate the desired iminyl radical, they involved somewhat harsh conditions (elevated temperature, MW or UV irradiation), expensive transition metals, which could hampered the development of large-scale processes. Therefore, the search for cost-effective and efficient methods to generate these type of radicals remains highly interesting and required.

In the 1970s, Bentrude showed that C–O bonds could be directly activated through the *in situ* generation of a tetravalent phosphoranyl radical.[7] This latter was involved in a β-scission leading to the formation the desired carbon-centered radical (*Scheme 2a)*. Very recently, this strategy was applied to deoxygenation of carboxylic acids, oximes and alcohols.[8] However, these works were based on the strong P–O affinity between an oxygen anion and the PPh_3 radical cation, which was obtained through a photoredox mediated oxidative SET (*Scheme 2b)*. While these methods offer interesting new avenues to generate acyl, carbon and iminyl radicals, they suffer from several disadvantages. Beside the use of a rare earth transition metal (Ir), the formation of a stoichiometric amount of triphenyl phosphine oxide ($O{=}PPh_3$) is a major environmental drawback since it lowers the atom economy of the reaction and complicates the purification process. Due to the economic and environmental challenges of our century, it is now highly desirable to develop phosphine-catalyzed processes.[9] *In such a context, this project aims at developing an efficient, economic and environmentally benign access to versatile and important iminyl radicals from an unprotected oxime and a catalytic amount of a trivalent phosphine by using electrochemistry.*



Scheme 2 : PR_3-mediated radical generation and formation of $R_3P(O)$ waste

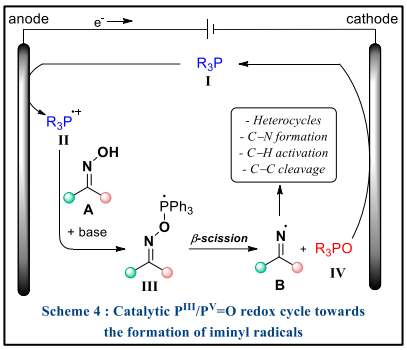


Scheme 3: Electro-reduction of phosphine oxides

Concerning the state of the art in electroreduction of phosphine oxide, initial work was quite disappointing since the homolytic cleavage of the P–C bond occurred preferentially to the P–O bond (*Scheme 3a*).[10a,b] In 2011, Tanaka described the electro-reduction of triarylphosphine oxides in good yields (*Scheme 3b*).[10c] The addition of trimethylsilyl chloride (TMSCl) proved to be fundamental to successfully isolate the corresponding trivalent phosphine, without cleavage of the P–C bond. The use of triaryl borate was also exemplified.[10d] Another strategy developed by Yanilkin was based on the use of soluble aluminum anodes and a solution of aluminum trichloride as a Lewis acid (*Scheme 3c*).[10e,f] If now these methods of electro-reduction of phosphine oxides are more robust, in the context of this project we will have to re-optimize the experimental conditions, in particular to use a relatively low constant current in order to not degrade the other substrates and/or products present in the reaction mixture. Thanks to this collaboration, particular attention will be paid to the design and synthesis of cyclic phosphines, in order to decrease the reduction potential of the P–O bond. Moreover, it must be emphasized that in the literature, no phosphine-catalyzed processes *via in situ* electro-reduction of phosphine oxide has been described.

Description scientifique du projet, méthodes et résultats attendus dans le contexte du LabEx

Electrochemistry is one of the privileged methods used in redox catalysis and has witnessed a renaissance in organic synthesis. This methodology is recognized as being environmentally friendly and inexpensive.[11] Indeed, the main reagent are electrons, which can serve as a green and cheap alternative to the use of expensive and/or toxic stoichiometric chemical oxidants or reductants and the wastes are usually hydrogen. The objective of our project is to use electrochemistry to set up a $P^{III}/P^{V}{=}O$ catalytic redox cycle allowing the generation of the desired iminyl radical and its reaction yielding to the discovery of the synthesis of various class of interesting products (*Scheme 4*). We hypothesized that an anodic oxidation of a trivalent phosphine (**I**) could induce the formation of a phosphine radical cation (**II**), which would react in a presence of an inorganic base with the oxime (**A**). The key iminyl radical could be obtain via a β-scission of (**III**) with a concomitant formation of a phosphine oxide (**IV**). The radical (**B**) could then be involved in the designed reaction with a radical acceptor while a cathodic reduction of (**IV**) would allow a regeneration of the initially introduced trivalent phosphine (**I**) to close the redox catalytic cycle. Thus, a catalytic amount of a phosphine and an unsubstituted oxime would allow us to exploit the wide diversity of the iminyl radical chemistry. *In order to successfully carry out this project, the expertise of Dr A. Voituriez in the phosphorous chemistry area[12] and the knowledge of Dr T. Castanheiro in the redox chemistry and nitrogen radicals area[13] will be use. The two partners have already worked together on a Labex Charm3at project involving also Dr. Mohamed Mellah (ICMMO, UPSay) as a partner. This project already involved redox electrocatalysis, but in a totally different framework, namely the development of an electrocatylic (and asymmetric) Wittig reaction.*

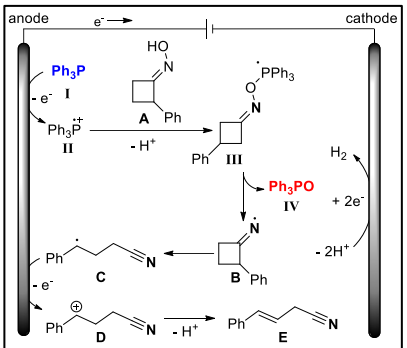


Scheme 4 : Catalytic $P^{III}/P^{V}{=}O$ redox cycle towards the formation of iminyl radicals

This project is divided in three distinct scientific tasks:

(1) Study of the formation of iminyl radicals and their reactivity in electrochemistry with a stoichiometric amount of trivalent phosphine

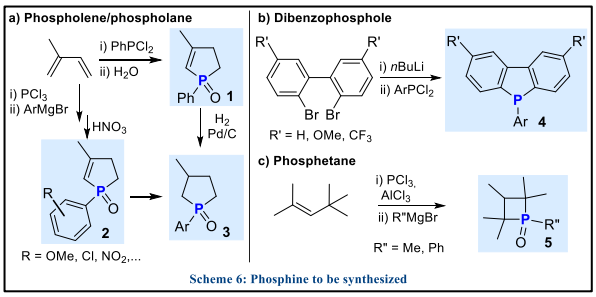
To determine if the phosphine-mediated formation of iminyl radical would be applicable in electrochemistry, the first objective is to develop an electrochemical synthesis of interesting allylic cyano molecules by using an equivalent amount of triphenylphosphine (Ph_3P) and a cyclic non-protected oxime (**A**) (*Scheme 5*). In 1994, Ohmori synthesized some alkane derivatives *via* the phosphine-mediated reduction of alcohols by the use of PPh_3, which was oxidized at the anode. An equivalent amount of $O{=}PPh_3$ was concomitantly obtained.[14] Although this work gives us a good starting point, the stoichiometric strategy of generation of iminyl radical, which has not been developed, is still very important to consider the further development of the targeted catalytic $P^{III}/P^{V}{=}O$ redox cycle. The allylic nitrile derivatives that we are planning to synthesize are interesting molecules because the nitrile function could be easily modified and is commonly found in both materials and APIs. A first selective anodic oxidation of Ph_3P ($E_{1/2}$ = + 0.98 V vs SCE)[15] should generate the Ph_3P radical cation. This latter would react with the oxime (**A**) leading to the key iminyl radical (**B**) *via* a β-scission of the phosphoranyl radical (**III**). It has to be pointed that the starting oxime should not be impacted by an anodic oxidation as the calculated $Ep/_2$ for the oxime functional groups is in between + 1.5 V and + 2.2 V vs SCE.[16] Once (**B**) would be generated, a very well-known C–C bond cleavage[4d] will yield to a new carbon-centered radical (**C**), which would be oxidized at the anode giving the carbocation (**D**). A loss of a proton could then give the desired alkene derivative (**E**). Alternatively, depending of the solvent used in this transformation, a nucleophilic addition of the solvent such as acetonitrile could lead to the distal aminated cyano-alkyl product. Uses of DMF or DMSO should avoid this last process.



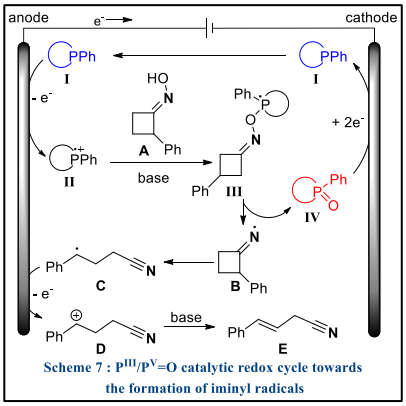
Scheme 5 : Generation of iminyl radical with a stoichiometric amount of phosphine in electrochemistry

(2) Development of the catalytic $P^{III}/P^{V}{=}O$ redox cycle to generate the iminyl radicals

Once an electrochemical process allowing the trivalent phosphine-mediated iminyl radical formation with a stoichiometric amount of R_3P will be established, we will focus our study towards the development of the catalytic version of this transformation. Inspired by previous work,[10] we initially plan to reproduce the electro-reductive conditions of $O{=}PPh_3$ in our reactions. To facilitate the reduction of the P–O bond, we attend to use cyclic phosphines, as it is well established that cyclic phosphines are much more easily reducible than acyclic congeners.[17] Thus, the synthesis of cyclic phosphines is needed. Here is the importance of our collaboration where the expertise of Dr A. Voituriez would allow to choose the optimal phosphine catalyst. Particular attention will be paid to the effects of the substituents of the phosphorus atom and the cyclic backbone. Indeed, 3- methyl-1-phenyl-2-phospholene 1- oxide (**1**) could be easily synthesized by Partner 2 from isoprene and dichlorophenylphosphine (*Scheme 6a*). The synthesis of other P-aryl substituted phospholenes (**2**), phospholane (**3**), substituted dibenzophosphole (**4**) and phosphetanes (**5**) are also easily achievable (*Scheme 6b,c*). The electrochemical reduction of these cyclic trivalent phosphine oxides will be then evaluated to get the mildest and simplest electrochemical reductive conditions by an optimization of the reaction conditions (current, charge, electrodes, solvent and electrolyte). All these investigations will be done thanks to the electrochemical platform present in the team of Partner 1 and the conditions will be applied to the designed electrochemical method (see section (1)) (*Scheme 7*). A one electron transfer would allow the formation of the radical cation (**II**). The desired reaction would occur to give the desired product (**E**) *via* the same mechanism of section 1 (*Scheme 7*). During the reaction, a catalytic amount of a cyclic phosphine oxide (**IV**) would be generated. The electrochemical reductive conditions should allow to reduce the phosphine oxide, through a 2 electrons reduction, to recover the cyclic phosphine (**I**) without any impact on the synthesized products. It has to be noted that the electronic balance is well respected in this mechanism.



Scheme 6: Phosphine to be synthesized

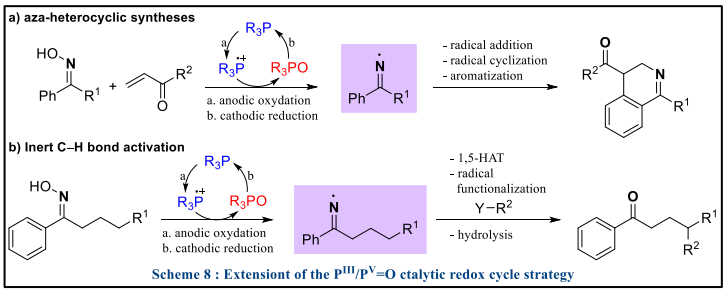


Scheme 7 : $P^{III}/P^{V}{=}O$ catalytic redox cycle towards the formation of iminyl radicals

(3) Applications of the catalytic process to new reactions involving an iminyl radical

As a perspective of this work, we are planning to apply this new redox phosphine-catalyzed iminyl radical generation in new synthetic transformations involving this key radical. As an example, we are already targeting the

synthesis of nitrogen heterocycles,[18] which are important chemicals in medicinal chemistry and highly represented in natural products (*Scheme 8a*). Indeed, more than 67% of the chemical used in the pharmaceutical or agrochemical areas contain at least one aza-heterocycle in their structure. Moreover, non-cyclic alkyl oxime could also be introduced in such a process. This would allow a distal functionalization of tertiary, secondary and primary C(sp^3) centers, a hot topic today in organic synthesis, through a 1,5-hydrogen atom transfer and a radical acceptor (*Scheme 8b*).[19]



Scheme 8 : Extensiont of the P^{III}/P^{V}=O etalytic redox cycle strategy

Programme de travail

To achieve the main objective, this project will be divided in four tasks:

- Task 1 will be dedicated to the implementation of the phosphine-mediated deoxygenation in an electrochemical process. This will allow us to see if such reaction strategy is compatible with electrochemistry.
- Slightly out of step with the start of the postdoc contract, the synthesis of cyclic phosphine and the study of their electrochemical reduction will be carried out in order to find the best and mildest electrochemical reductive conditions.
- Task 3 correspond to the development of the electrochemical P^{III}/P^{V}=O catalytic redox cycle by combining the conditions found in Task 1 and in Task 2 on the reaction described above.
- **Finally depending on the resulting time of the postdoc contract**, task 4 will be dedicated to exploit this new access to iminyl radical and applied it to the synthesis of various interesting polyfunctionalized molecules.

Apport de la collaboration et résultats escomptés

The first expected result of this project is the new generation of iminyl radical and his reaction in a C–C bond cleavage process by using a stoichiometric amount of phosphine and electricity as oxidant source. Then, we are expecting to get mild redox conditions to reduce selectively cyclic trivalent phosphine oxide, which will then be applied in order to reach the main objective of this project: **the development of P^{III}/P^{V}=O catalytic redox cycle to generate iminyl radicals** and exploit their reactivity. Depending on the time schedule we are also expecting to apply this catalytic redox cycle to the synthesis of nitrogen heterocycles such as pyrrolidines and piperidines and towards activation of inert C–H bond *via* hydrogen atom transfer. Thus, this project needs various expertise and knowledge. First of all, competencies on the development of new synthetic methodologies is needed and brought by the two partners. While Dr T. Castanheiro will bring to the project his skills on redox chemistry and nitrogen centered radical (NCRs) transfer, the expertise of Dr A. Voituriez in the area of phosphorous chemistry and phosphine catalyzed/mediated reactions is highly needed.

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