1. SUMMARY

1.1 Summary description of the project objectives

On the one hand, it is now assumed that in the near future the starting materials in chemistry have to come from renewable feedstock and not only from petroleum cracking. On the other hand, the stability of the chemical bonds in saturated hydrocarbons makes them generally unreactive, and a large variety of hydrocarbons constitute a large low-cost feedstock misused, which is treated as fuel or waste. Fortunately, the recent invention of processes in which carbon–hydrogen (C–H) bonds in hydrocarbons can be activated is allowing chemists to exploit organic compounds in previously unimaginable ways. Following the principle of Green Chemistry the first issue described could be solved "C–H activating" natural renewable molecules (simple molecules obtained easily from, for example, oil from plants) and employ them as starting materials for fine chemistry.

The global objective of this project is to learn the last top advances in catalytic C–H activation and apply them to the transformation of natural renewable molecules. The specific aims of the research project are:

1) Devising C–H activation-initiated tandem reactions with Rhodium catalysts and explore its application to organic synthesis. Outgoing Phase.

2) Transfer the developed methodology to the transformation of some natural renewable products – in particular Oleic Acid – into valuable molecules like drugs or drug-precursors. Outgoing and Returning Phases.

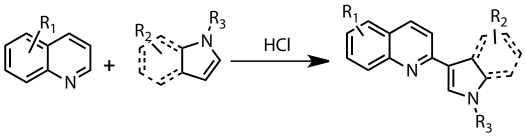
3) Initiate the development of new catalysts for C–H activation-initiated tandem reactions based on group 10 metals. Outgoing Phase.

1.2 Description of the work performed since the beginning of the project, and main results achieved

The technical achievements can be separated in three sets of results articulated around the development of *Cross Dehydrogenative Couplings* where two C–H bonds are directly coupled to form a new C–C bond: 1) A simple **coupling between Indole and Quinoline** was developed. 2) Focusing on C–H in carbon carbon double bond, a common motif in natural products, we developed and studied an **oxidative olefination of aryl oximes**, setting a base toward the design of a tandem reaction initiated by C–H activation with a Rhodium catalyst. 3) Pursuing our interest in the latter reaction we carried a **Mechanistic Study** to understand the key elementary steps of the oxidative olefination in order to develop the reaction on rational basis.

- **Simple Coupling of Quinoline with Indoles or Pyrroles.**

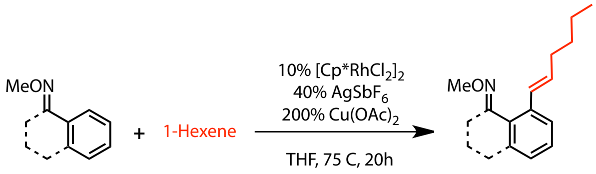
While evaluating the potential of Rh(I) catalysts in our project, we discovered a really facile coupling of indole with quinoline.[1]



We optimized this reaction that now proceeds in good yield without **neither solvent nor catalyst** only in presence of HCl giving the possibility to easily couple a large scope of quinolines to different indoles and pyrroles.

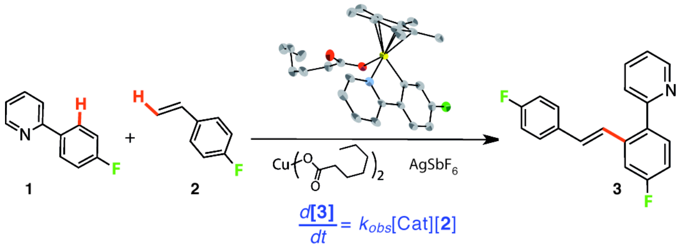
- **Oxidative Olefination of Aryl Oximes with Unactivated Alkenes Catalyzed by Rh(III).**

In the last few years several versatile Rhodium (III) systems that are able to catalyze the coupling of aromatic substrates with different substrates alkynes, alkenes or even imines or aldehydes appeared in the literature.[2] In the Bergman' and Ellman's groups who jointly developed several methods for C–H functionalization with Rhodium (I) catalysts,[3] we discovered such a Rh(III) system that oxidatively couples aryl oximes with unactivated alkenes. This is a dramatic expansion on the previous limitations of this type of oxidative chemistry which had only proceeded with activated alkenes such as acrylates or styrenes, and is of particular interest in the frame of our global project. Our work focused first on the improvement of this new methodology and the study of the scope in alkene and aryl oximes.[4] **It is now possible to couple aryls to simple terminal alkenes that can derive form fatty acids**.



Mechanistic Study of the Oxidative Olefination of Aryl with Alkenes Catalyzed by Rh(III).

A further step is to study the mechanism of the reaction in order to improve it. We did so and proposed a catalytic cycle for the oxidative coupling of styrene to phenylpyridine catalyzed by Rh(III) based on a comprehensive mechanistic study. We showed that an unexpected Carboxylate Rhodacycle and a styrene adduct Rhodacycle were the resting states, that only concentration in catalyst and styrene were rate determining and we concluded that the migratory insertion of styrene into the Rh–C bond is the slow step in this transformation.[5] This showed that **C–H activation is not a barrier anymore** in this transformation but it is the intermediate reactivity towards alkene that is the hurdle.



1.3 final results and their potential impact and use

Although the project deviated form its planned path, the tandem reactivity was not explored thus far, these discoveries are anticipated to produce and impact in both academia and industrial settings. The three developed projects contribute to the **progress of *Cross Dehydrogenative Couplings*** (CDC) methodologies[6] that are considered as the pinnacle for the construction of Carbon backbones present in most of the molecules of interest in pharmacy, materials, electronics, etc. The development and the understanding of the mechanism of these simple CDC methodologies to couple aryl to alkenes or heterocycles together represent a great improvement in terms of substrate versatility, waste production, atom economy and efficiency complying with the requirements of **Green Chemistry**.

References

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