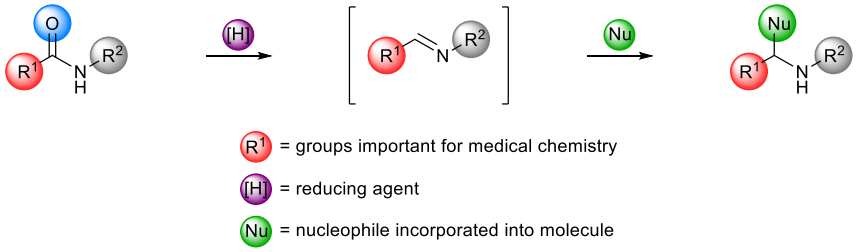
# The chemoselective synthesis of previously inaccessible imines and iminium ions from inert amides - their useful transformations and practical utility

The amide group is one of the most significant chemical moieties. It is present in all living organisms in great numbers, in the form of amide bonds in proteins – the building blocks of life. This structural motif has long been known to be chemically inert and difficult to modify. Despite its long-known importance and presence in a myriad of biologically relevant natural products and medicinally active compounds, only recently has it started to be appreciated as a viable starting point in synthetic organic chemistry. Over the last decade, a range of methods have appeared that take advantage of the unique reactivity of the amide bond to modify it selectively. One of the most interesting new methods of interacting with the amide bond is the reduction reaction. This methodology allows the transformation of the inert amide bonds into reactive functional groups such as imines or iminium salts, which are known to be susceptible to a wide range of synthetic methods, most of which involve the addition of nucleophiles – compounds rich in electrons. This transformation gives an amine group, which is present in a plethora of compounds invaluable in medicine and chemistry, making this kind of reaction highly desirable.

The presented project aims to develop a new and flexible route for the synthesis of structurally diverse imines or iminium cations *via* chemoselective partial reduction of the corresponding amides. The imine group is one of the most versatile functional groups, used in the synthesis of a wide array of biologically and chemically relevant compounds. However, they are known for their instability and difficulties in their generation. The classic approach, well known in literature, consists of a condensation between a carbonyl group and an appropriate amine. The availability of imines is thus limited by the possibility of obtaining the corresponding aldehydes – a task that is often daunting, as a number of aldehydes are either unstable or unknown at all. A prime example is the case of aldehydes containing a tetrazole moiety. For example, tetrazoleacetic aldehyde is not commercially available, even in the hemiacetal or acetal form. In contrast, the corresponding acids (and their esters or anhydrides) are readily available and, in the case of tetrazoleacetic acid esters, inexpensive. The tetrazole group is known for being a bioisostere for the carboxylic acid group, which makes it extremely interesting for medicinal chemistry and pharmaceutical industry. The developed strategy of imine synthesis is based on readily accessible amides and their chemoselective partial reduction to imines by complementary methods – zirconium-based Schwartz reagent or one of the iridium-based catalytic systems. This approach provides a manner of solving the described problem.

Moreover, the proposed project also addresses the issue of instability of some imines by generating these species *in situ* (in the reaction mixture, with no subsequent isolation) and transforming them in a one-pot nucleophilic addition reaction – with the reactant subjected to successive chemical reactions in a single reactor, allowing to avoid a lengthy separation and purification of intermediates, thus saving time and improving the product yield. This transformation leads to functionalized amines – compounds widespread in biologically active natural products and medicines. As a final step, the developed strategy will be applied for the synthesis of medicinally relevant compounds. The presented methodology allow to synthesis of selected bioisosteres as well as heterocyclic scaffold and can be applied to late-stage functionalization of drug compounds.




The author of this project strongly believes that the presented method of obtaining imines or iminium cations inaccessible by other classic synthetic pathways will significantly broaden the current state of the art in the synthesis and reactivity of amides, imines, and ultimately, amines. In contrast to the known, severely limited synthetic routes based on inaccessible or expensive aldehydes and amines, the developed strategy is simple and flexible. Therefore, this investigations will open up new possibilities for widely considered organic synthesis, medicinal chemistry, and pharmacology.