

Alkaloids are a very large and extremely diverse group of natural products. Many of them exhibit intriguing biological properties responsible for the therapeutic activity of several plants and other organisms known in the traditional medicine. Contemporary pharmacology uses isolated and well characterized alkaloids and their derivatives as important drugs. A striking example of very structurally complex alkaloids of crucial pharmacological importance are vincristine and vinblastine, strong anti-cancer agents isolated from *Catharanthus roseus*. The molecules of several alkaloids are quite complex, featuring one or more nitrogen atoms responsible for the basic character as well as extraordinary structural motifs, particularly several rings connected to form a cage-like structure. Such structure is usually rigid and is decorated with functional groups with well-defined spatial arrangement. In consequence, several alkaloids interact strongly and specifically with proteins, which makes them not only excellent drug candidates, but also good probes for studying protein-protein interactions which are responsible for the signal transduction in living organisms. Such studies are beginning to play a major role in the search and design of new therapeutic leads directed toward particular diseases.

Many biologically interesting alkaloids are scarcely available from natural sources. Chemical synthesis remains a crucial source of their supply, but, due to the structural complexity of alkaloid molecules their total syntheses usually involve a lot of synthetic steps and very low total yield of the final product. Moreover, synthetic strategies are often designed for specific targets and do not allow for ready modifications to obtain whole libraries of structurally diverse analogues of the natural compounds. Preparation of such the analogues directly from the parent (natural) alkaloids is also severely limited by the functional groups already present in their structure.

Extensive and systematic structure – biological activity studies of alkaloid-like structures require access to alkaloids and their analogues in appropriate quantities. This can be achieved by the development of new, flexible synthetic strategies that transform simple precursors of varied structure into complex, polycyclic nitrogen-containing scaffolds that contain reactive synthetic "handles" for further modifications. The project aims at the design and development of transformations of this kind, based upon palladium-catalyzed cascade reactions of nitrogen containing precursors – nitrones.

The so called cascade (or domino) reactions are processes in which several new chemical bonds are formed consecutively, in a single synthetic step. Obviously, high efficiency of such transformations reduces the number of reagents, protecting groups, solvents, catalysts, as well as resources required to reach the desired synthetic target and therefore allows for performing chemical synthesis in a much more economical and environmentally friendly way. In particular, palladium-catalyzed cascade reactions have been developed very actively in the recent years. The use of nitrones in such processes has become possible with our discovery of addition of alkylpalladium species to the nitron double carbon-nitrogen bond, with the formation of a new carbon-carbon bond. The designed cascade processes will close at least two new rings and place the nitron nitrogen atom in the appropriate position of the formed polycyclic skeleton, corresponding to the structure of a natural alkaloid. Moreover, the reactive nitron functionality will be still present in the product, allowing for further increase of molecular complexity and diversity, for example attaching handles for bioconjugation. Last but not least, palladium-catalyzed reactions can be performed in the presence of chiral palladium-binding ligands, which enables the preparation of the target products as single enantiomers, that is as only one of the two molecular forms that are mirror images of each other. This feature is crucial for the further studies of interactions with biomolecules.