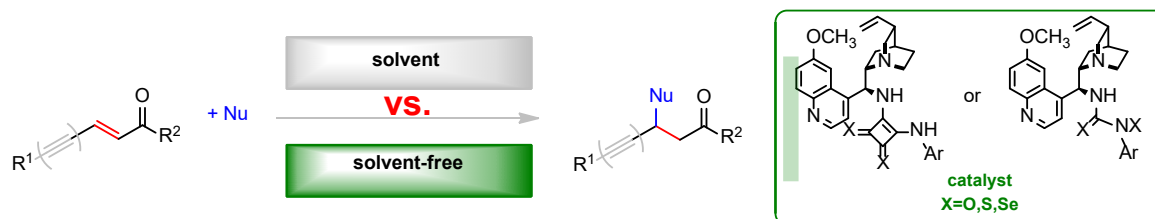


New methods of activation in catalysis mediated by hydrogen-bond donors

Presented dissertation entitled "New methods of activation in catalysis with the participation of hydrogen bonds" was carried out at the Department of Bioorganic Chemistry at the Faculty of Chemistry, Wrocław University of Technology under the supervision of prof. Rafał Kowalczyk. The research is focused on the reactivity of $\alpha,\beta(\gamma,\delta)$ -unsaturated carbonyl compounds (enynones, dienones, chalcones and benzoyl acrylates) with three types of nucleophiles: nitro compounds, 1,4-dithian-2,5-diol and dithiomalonates in reactions catalyzed by chiral bifunctional hydrogen bond donors. Moreover, studies were performed using several different synthesis techniques: solvent-free milling in a planetary ball mill that generates mechanical and thermal energy and thermal activation with standard convection and microwave radiation. Thus, the main goal of the presented dissertation was the development of a new highly effective methodology of synthesizing multifunctional building blocks for molecules with an extensive structure by combining several chemical tools.



This work was divided into two main parts: literature and research. The literature part is an introduction to the catalysis promoted by weak intermolecular interactions, to the sulfur analogues of malonic acid esters, and a brief overview of mechanochemical experiments, with particular emphasis on reactions catalyzed by hydrogen bonds. The second part is devoted to performed studies and is presented in the form of three subsections.

The first one concerns the reactivity studies of $\alpha,\beta(\gamma,\delta)$ -conjugated carbonyl compounds with nitro compounds and provides information on the preferred nucleophilic addition sites in the compound containing three potential reactive sites. It is worth mentioning that through the selective Michael addition of nitroalkanes to poorly reactive polyunsaturated carbonyl compounds, an additional, synthetically important, functional group is being introduced, but the molecule still has available a triple bond (in the case of enynones) or a double bond (in the case of dienones), which allows for further transformations towards cyclic compounds. This section also presents the preliminary results of studies performed in a planetary ball mill and

the optimization of the mechanochemical method for catalytic applications. An important element of that research was the use of modular chiral organocatalysts to promote chemical transformations via hydrogen bonds. Both the classical synthesis technique and the solvent-free strategy led to the products in a highly efficient and enantioselective manner.

The second subsection presents the synthesis pathway of chiral tetrahydrothiophene derivatives containing three adjacent stereocenters. The effectiveness of this chemical transformation depended on the temperature of the reaction and the perfect fit of the electrophile and the catalyst via tailored hydrogen bonds. The carefully designed chiral hydrogen bond donor/acceptor and the reaction conditions enabled the decomposition of the stable 1,4-dithian-2,5-diol into the reactive thioacetaldehyde and the sulfa-Michael/intramolecular aldol reactions cascade promoted by the squaramide derivatives leading to highly functionalised products, which are very valuable building blocks for molecules with biological activity. The target heterocycles were obtained with excellent yields and enantio- and diastereoselectivity.

A third area of research covers the reactivity of sulfur analogs of malonic acid esters as potentially more reactive acyl donors. Despite one example, oxoesters remained unreactive in tested reaction conditions. Five dithiomalonates have been synthesized, two of which are completely new compounds in the scientific literature. An important stage of the research in this part was the development of a highly selective method for the synthesis of Michael adducts starting from many structurally diversified substrates. Classical solution experiments led to formation of three different types of products. The developed new synthesis path under solvent-free conditions and Cinchona alkaloid based squaramides ensured exclusively the target adducts were obtained in a highly efficient and enantioselective manner, without decomposition of any of the reagents.

The interpretation of the results was based on analytical (HPLC, HRMS) and spectroscopic (1D and 2D NMR) techniques. The performed crystallographic measurements confirmed the absolute configuration of the obtained products and the computational methods rationalized the plausible reaction mechanism.

The research was carried out as part of the Sonata Bis project of the National Science Center entitled "Hydrogen bond donors in non-classical asymmetric catalysis", led by prof. Rafał Kowalczyk. All the results presented in this doctoral dissertation have been described in the form of four publications in international scientific journals, as well as presented at many national and international scientific conferences.