Palladium-catalyzed tandem 5-exo-dig cyclizations of acetylenic carbonyl compounds followed by coupling with (pseudo)halide (hetero)aryl compounds

M.Sc. Aleksandra Błocka

Supervisor: dr hab. Wojciech Chaładaj

In modern synthetic chemistry, complexes of transition metals, palladium in particular, enable multidirectional functionalization of simple organic structures. An additional advantage of such a synthetic concept is the possibility of implementing these transformations in one pot conditions, which allows to avoid the often-tedious stage of isolation and purification of intermediate compounds.

In this dissertation, I described the results of three research projects in which I used palladium phosphine complexes as effective catalytic systems in the carbocyclization/coupling reaction with aryl halides. Using the mild activation conditions of third-generation Buchwald-type palladacyclic precatalysts, I first obtained a number of cyclic products in the *5-exo-dig* cyclization for activated, terminal acetylene derivatives of malonates, diketones and cyanoesters. An additional advantage is the applicability of this method also for organophosphorus compounds and compatibility with aryl chlorides.

The next step was an attempt to apply an analogous methodology for more demanding substrates, such as internal alkynes. In this case, it was also possible to obtain a wide group of cyclic compounds, and the range of applicability of this approach was investigated on the example of many different aryl bromides. In addition, this method turned out to be compatible with alkyne substrates and with respect to the degree of crowding both at the nucleophilic center and on the side of the triple bond. The vast majority of the obtained structures were characterized by complete diastereoselectivity of the *E* double bond (except for a few cases of cyclization with electron-poor bromides).

The last project carried out as part of my doctoral thesis was the development of conditions for the cyclization/coupling reaction of non-activated compounds, which has not been described in the literature so far. I managed to find optimal conditions for the preparation of five-membered carbocyclic compounds using aryl triflates as coupling partners. In order to increase the nucleophilicity of monocarbonyl substrates, I used the transformation of ketones into appropriate enamines, which enabled effective cyclization and subsequent coupling. The possibility of using enamines as a crude product turned out to be a significant facilitation, which further increases the usefulness of this methodology.

The final step in each project was to perform control experiments to propose the most likely mechanistic pathway. In addition, DFT calculations were performed to provide additional information on the mechanisms of the described reactions.