Assessment of Ph.D. Thesis of MSc. Olga Bakhanovich titled

Synthesis of *N*-(per)fluoroalkyl azoles by rhodium(II)-catalyzed transannulation of *N*-(per)fluoroalkyl-1,2,3-triazoles

The Thesis is aimed in the synthesis of *N*-(per)fluoroalkylated pyrroles and indoles using pioneering approach employing as the key intermediates *N*-(per)fluoroalkylated triazoles, developed as a new class of fluorinated building blocks in the laboratory of supervisor Dr. Beier. The Thesis is thus a continuation of a larger project devoted to the applications of fluorotriazoles.

In the first Introduction part, various previous variants of the synthesis of fluoroalkylated azoles are listed and this part thus serves to the reader as a nice introduction to the studied problematics. Regarding the key role of the rhodium catalyst shown, I am missing some introductory part dealing with the activity and mechanism of action of such catalysts, especially in connection with the esp ligand employed, and general information about rhodium carbenes and their reactivity. Introduction only includes tentative mechanism designed originally for sulfonylated triazoles and employed in the supervisor's group for the synthesis of fluoroimidazoles and pyrroles. Also, I would also like to comment on author's statement that for alternative syntheses of azoles, toxic gases are used. Ref. 11 uses for the synthesis of trifluoromethylated indoles tetrabutylammonium dihydrogen trifluoride reagent, which is stable commercially available reagent and even enables the work in standard common glass aparatuses.

Second part declares two main targets of the project, i.e. synthesis of *N*-(per)fluoroalkylated pyrroles employing reactions of *N*-(per)fluoroalkylated triazoles with alkynes, and synthesis of *N*-(per)fluoroalkylated indoles based on the corresponding cyclohexenylated triazoles. As a part of these two main targets spread over three objectives investigated in the Thesis, starting triazoles had to be synthesized and some additional reactions of the selected representatives of both classes of fluorinated azoles.

Results and Discussion part describes in detail the results of authors' work and is separated into two main parts corresponding to the declared aims. First, author synthesized starting perfluorinated azides and employed them for the synthesis of key intermediary triazoles following procedures previously developed in the supervisor's group. Unfortunately, there is no detailed information about the synthesis of the triazoles **41** neither in the Result and Discussion section nor in the Experimental. I have thus feeling that they were prepared during parallel research by another members of the group? If so, they should be cited, if not, at least their synthesis and structures mentioned in general part of Experimental. There structures **41a** to **41i** are briefly mentioned and from the Result and Discussion part structures of triazoles **41a-d** can be guessed, but remaining structures are unclear. In general, in Experimental part structures and numbering of azides is completely omitted (e.g. in the synthesis of indoles **49**). Similarly, there is no information about starting azides employed in the synthesis of triazoles **47c** and **47d**, which were probably synthesized by another member of the group (Ziabko?).

The key reaction of the first part of fluorotriazoles with acetylenes proved to be non-regioselective and most of the products **43** were isolated as mixtures. Here I was missing more detailed information about identification of individual products and their signals by 2D NMR methods.

The most original part of the Thesis is related to the synthesis of new fluorinated indoles, where a library of fluorotriazoles substituted with various cyclohexenyl groups was obtained and employed in the key cyclization reaction. This is the most successful part of the Thesis, all products leading to hexahydroindoles are correctly characterized. Selected examples were then

successfully aromatized to the target indoles. Synthesis of triazoles **47c** and **47d** is not included in Scheme **38**.

Finally, some standard transformation were accomplished with fluorinated indoles **49**.

Chapter 4 summarizes the results obtained, I am missing here any potential connection with practical applications of the compounds obtained apart of general statement „valuable substructures in medicinal chemistry“, it would be nice to present in more detail how these structures could be „valuable“.

Experimental part is written well and most structures are correctly characterized. However, I am missing assigment of individual signals in ^{13}C NMR spectra for primed and non-primed pyrroles **42**. With the exception of **42a**, where the structures were separated, no details are given about this. Also, correct description of coupling constants *J* should include the interacting nuclei and number of bonds over which the coupling occurs, e.g. $^{4}J_{H\text{-}F}$ etc.

The Thesis is written in very good English with minimum of factual errors and contains minimum typos. Comments and questions are listed below:

Comments:

Esp is not quite common ligand and depicting the structures of the rhodium catalysts used would be desirable.

It is sad that author was not able to disclose unknown structure of compound **51**, is it really so difficult having to disposal many advanced 2D NMR techniques?

On page 35, Scheme 25 is correctly Scheme 28.

Table headings should be placed at the top of the tables, not below them.

Questions:

Author states that in the synthesis of pyrroles, *ortho*-substituted arylacetylenes gave no isolable products. Did she consider the use of *meta*-substituted arylacetylenes to improve regioselectivity?

Oxidation of the propyl chain in **48k** to acrolein unit is extremely surprising. Did author found similar transformation in the literature? If not, it surely deserves more attention.

For compound **42**', long range H-F coupling over 4 and 5 bonds was observed (probably?), but this is not the case for **42** (described as singlet). Has author some explanation for this?

Scheme **32** does not show, how the bonds are transferred from Rh and the mechanism significantly differs from Scheme **41**. Are the mechanism simply ad hoc created or has author some indication for the given mechanism. Computational study could probably bring more clear view on the mechanism.

Compound **46'** is shown in square brackets. Were attempts made to isolate it?

To evaluate the Thesis as a whole, it is well written, easily readable and brings new valuable results in the synthesis of scarcely described fluorinated azoles. The results of author's work are published in two papers with high impact factors directly connected to the Thesis, student being the first author. All targets postulated in the Aims of the Thesis were achieved and I hence **recommend** her Ph.D. Thesis as the basis for defending her **Ph.D.** title.

In Prague, 14. 3. 2024 Prof. Ing. Jaroslav Kvíčala, CSc.