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Evaluation
of the PhD thesis of MSc (Eng.) Franz Steppeler, entitled “Synthesis of chiral 2-azabicycloalkane derivatives and their application in asymmetric synthesis”

The thesis of MSc. Franz Steppeler was submitted in 2023 to the Scientific Council of the Discipline of Chemical Sciences at the Wrocław University of Technology in the procedure for promotion to Doctor of Philosophy degree in the field of natural sciences. The thesis was prepared under the supervision of Prof. Dr. Elżbieta Wojaczyńska together with Prof. Dr. Marie-Christine Scherrmann (University Paris-Saclay) who served as co-supervisor.

The dissertation is located on total 176 pages and is divided into 5 general parts, namely Introduction (2 pages), Literature Survey (36 pages), and Results and Scientific Work (34). The final part of the thesis contains 347 of literature citations, and full set of experimental data (49 pages) followed by copies of MS and NMR spectra and selected HPLC chromatograms.

The Introduction part that opens the thesis provides good background for further discussion. The Author defined the main goal of his research as the development of new synthetic routes leading to 2-azabicycloalkanes and attempts to use them as possible ligands for organocatalysis and their characterization as biologically active compounds.

The next chapter is devoted to discussing the current state of knowledge about the stereoselective synthesis of complex aza-polycyclic systems using amino acids, among others, as chiral inductors or chiral building blocks. The text provides a large number of well-documented literature examples illustrating the efficiency and effectiveness of such synthetic strategies. Examples of such syntheses came from the prestigious research groups of Prof. Yamada, Enders (not Ender!), Evans, Oppolzer, and others. Another important element of the literature review is the discussion of the issue of organocatalysis, with particular emphasis on bifunctional catalysis, in which the source of stereochemical information was, among others, L-proline and its derivatives, as well as some *Cinchona* alkaloids. Some information about the biological activity of polycyclic derivatives containing elements derived from proline, tropane and quinuclidine is also included at the end of this chapter.

In my opinion, the text of the entire chapter discussed above has been written highly professionally. It contains many examples of the most important achievements in the field of catalysis and organocatalysis using azacyclic chiral derivatives, but not omitting their other important applications. Without major modifications it could be submitted as a good quality review article. The high scientific value of this literature survey proves the Candidate's good knowledge and orientation in his field of study. My assessment of this fragment of the dissertation is therefore very positive.

The results of the Candidate's own research are included in the next, very extensive part of the thesis. The leitmotif of Mr. Steppeler's studies was the development of new methods for the synthesis of bicyclic structures derived from 2-azabicyclo[2.2.1]heptanes and 2-azabicyclo[3.2.1]octanes, containing triazole or thiourea submotifs that may have an impact to various fields of organic chemistry serving as ligands in mono- and bifunctional organocatalysts, or being biologically active. It is worth noting that he compared the results of his research in the field of the synthesis of triazoles and thioureas already at the beginning of the chapter with the previous results of the parent research group. The goal of synthesis of a series of 1,2,3-triazoles was not easy to achieve. It required the development of procedures for obtaining the appropriate substrates, which were alkyne and azide derivatives. He dealt with these issues in an elegant way, skilfully modifying known procedures and synthetic approaches. Subsequent "click" reactions enabled the synthesis of a number of triazole derivatives, which were subjected to scrupulous physicochemical analysis, including X-ray diffraction and conformational analysis. In turn, a set of thiourea derivatives was obtained by two complementary procedures involving the formation of the appropriate isothiocyanates. Highly innovative results were then obtained as a result of fruitful cooperation with foreign groups specializing in the chemistry of calix[4]arenes (Alberto Marra (IBBM University of Montpellier) and Marie-Christine Scherrmann (ICCMO University Paris-Saclay)). As a result of this cooperation, a number of very interesting hybrid derivatives were obtained, which, containing both a chiral part and a macromolecular pocket, can be considered as effective organocatalysts, chemosensors or biological drug carriers. Again, the effective and controlled synthesis of these hybrid compounds was a significant experimental challenge, because calixarenes are molecules with complex dynamic stereochemistry, which requires appropriate decoration of the molecule in order to stabilize it in a suitable form. In addition, the presence of many reactive functional groups forces the use of highly selective methods of their functionalization. It was undoubtedly a very ambitious research task and it can be said responsibly that obtaining positive results required not only experimental proficiency, but above all a thorough knowledge of the chemistry and physicochemistry of this type of molecules. Although not all synthetic goals intended by the author have been achieved, the obtained and confirmed results can be considered highly interesting and prospective. The extensive knowledge of the chemical literature enabled the Author to note the fact that the chiral thiourea derivatives obtained earlier, containing an additional amino group, can act as bifunctional organocatalysts. Thus, these compounds along with thiourea-decorated calixarenes were tested as catalysts in two asymmetric Michael-type additions giving very good conversions of the substrates with moderate-to-excellent chirality transfer efficiency.

It should be mentioned also, that an interesting outcome concerning the synthesis of square-planar platinum complexes, which are cis-platinum analogues with potential use in cancer chemotherapy appeared as a result of the cooperation with pharmaceutical research group.

In general, the Author appreciates the value of collaborating with scientists in the field of bioorganic chemistry. During this cooperation, all triazoles and selected thioureas described in the dissertation were tested. Biological tests on antiproliferative, antiviral, antibacterial, antifungal and anthelmintic activity were performed on several microorganisms and cell lines, which significantly increases the value of the doctoral thesis, extending its scope beyond the field closely related to synthetic organic chemistry.

The entire text of the dissertation has been prepared, in my opinion, perfectly. It is written in the correct scientific language, and the professional and transparent chemical graphics makes it user-friendly. In terms of content, this work is an example of an ambitiously planned research task and its effective implementation. From a scientific point of view, I evaluate the work very positively. Its quality is also evidenced by the fact that some of the results have already been published in the form of two original publications and three patents or patent applications. Mr. Steppeler was also the co-author of two review papers and a number of conference presentations. Therefore, it is an achievement that places the author among the most promising young chemists.

In conclusion, I therefore state that Mr. Franz Steppeler's doctoral dissertation meets all statutory criteria for doctoral theses (*art. 187 ustawy z dnia 20 lipca 2018 r. Prawo o szkolnictwie wyższym i nauce (t.j. Dz. U. z 2023 r., poz. 742)*).

Therefore, I submit to the High Council of the Discipline of Chemical Sciences of the Wrocław University of Technology a request for acceptance the thesis and I support the application to confer on Mr. Franz Steppeler the PhD degree in Science, in the discipline of Chemical Sciences.

Finally, taking into account the high scientific value of the presented results, confirmed by publications and patent applications, and in particular the innovative work on hybrid macromolecular organocatalysts based on the calix[4]arene structure, I suggest honouring the dissertation.



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