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Report on Thesis submitted by Franz Steppeler for the Degree of Doctor of Philosophy

Thesis title – *„Synthesis of chiral 2-azabicycloalkane derivatives and their application in asymmetric synthesis"*

In the light of current needs of various branches of chemical, pharmaceutical, food and cosmetic industry, an easy access to enantiomerically pure chiral compounds seems to be of primary importance. The use of products of natural origin is a naturally emerging solution to the problem of acquisition of chiral compound. Nature, although it seems to be an inexhaustible source of chiral product, usually provides compounds in one enantiomeric form, leaving the problem of acquiring the opposite enantiomer open.

Resolution of racemates through the formation of diastereoisomers belongs to the widespread and well-established methods, however, it is not without its drawbacks. In principle, classical kinetic resolution of racemates allows for the "recovery" of the desired, optically pure enantiomer with maximum 50% yield, which means that the remaining 50% of the substrate (the unwanted enantiomer) is useless. The more efficient processes requiring i.e., simultaneous kinetic resolution of the racemate associated with racemization of the unwanted enantiomer are restricted to specific substrates.

Catalytic asymmetric synthesis, which is the alternative to the exploration of natural resources and the separation of racemates, belongs to one of the most sophisticated areas of organic chemistry. On the one hand, this is related to the structure of the catalyst, often designed and made for a specific reaction, sometimes even for a specific substrate. On the other hand, the sophistication of asymmetric synthesis is associated with reactions that are of scientific interest, especially transformations which until recently have been considered difficult or even impossible to conduct.

Of the many molecules that are used in asymmetric synthesis as catalysts, some are referred to as privileged catalysts. This privilege originates from their versatility, which is understood, inter alia, as the ability to catalyze more than one reaction, their availability and potentiality to fine tuning for specific applications. The first above-mentioned property, in turn, can be associated with certain structural features of a given molecule, such as the presence of a quinuclidine nitrogen atom in alkaloids, a rigid vicinal diamine fragment in salen or axial chirality, as is the case of BINAP and BINOL's-based catalysts.

From an economic point of view, the "good" catalysts used in asymmetric synthesis should be highly active, readily available, and cost-effective. It is usually impossible to meet these requirements at the same time. Even the cursory analysis of the literature on the subject leads to the conclusion that the greatest expectations are associated with several trends, of which two seemed to be the most important ones.

The first of them (it can be called classic) is catalysis with metal complexes, where the metal can be used in its neutral or ionic form. The known modern catalysts are prone to catalyze reactions at very low concentration, with high turnover close to that reported for biocatalysts operating in living organisms. On the other hand, the high cost of metal compounds (especially of noble metals), often difficult and laborious preparation of the complexes as well as usually very strict requirements for reaction conditions can be considered as the main disadvantages of metal-based catalysis.

The second approach, commonly referred to as "organocatalysis" assumes the use of small chiral organic molecules as catalysts. The spectacular successes of several teams (i.e. Jorgensen, Barbas, MacMillan) give an impression that catalytic synthesis has gained a universal synthetic tool. The most important advantage of organocatalytic approach to catalysis relies on (rather postulated than generally accepted) overcoming inconveniences associated with metal catalysis and, above all, a lack of metal.

The doctoral thesis of Mr. Franz Steppeler, entitled "*Synthesis of chiral 2-azabicycloalkane derivatives and their application in asymmetric synthesis*" was devoted to the issues related to asymmetric synthesis. This work was carried out under the guidance of Prof. Elżbieta Wojaczyńska from the Wrocław University of Technology, and Prof. Marie-Christine Scherrmann from the University of Paris-Saclay. This particular dissertation can be treated as a continuation of an important thread of research on chiral heterocyclic compounds, carried out in the group of the Supervisor. Prof. Wojaczyńska is the co-author of publications presenting achievements of the PhD student to date. These works were published in 2020-2023 in international journals. In addition, the PhD student can take credit for several conference speeches, patents and has completed two several-week internships abroad.

What is worth emphasizing – the work has been written in the form of a traditional dissertation divided into a literature part, a discussion of the results with a short summary, an experimental part, a bibliography and an appendix in which additional information, including all NMR spectra, was collected. As a reviewer, I will add that the first two parts, each of a similar length, are contained in a total of 80 pages.

The aim of the work was defined as the stereoselective synthesis of new 2-azabicycloalkanes, their functionalization and their subsequent use as ligands and organocatalysts in asymmetric catalysis. In relation to the title of the work, a new element appeared, namely the use of such derivatives in the biological study.

In the literature part, the PhD student describes some nitrogen-containing heterocyclic compounds, including their synthesis as well as applications in asymmetric synthesis. Since this issue is very broad, the PhD student rightly limited himself to discussing mainly 2-azabicycloalkanes. The applications of the above-mentioned compounds as chiral auxiliary, ligands of metals of main and transition groups and organocatalysts have been described. Finally, the PhD student describes the biological activity of selected 2-azabicycloalkane derivatives. This fragment of the dissertation shows the PhD student's good knowledge of the subject of the thesis. The most important information has been given. However, it is a pity that, apart from Figure 12, at least a few (stereochemical) models showing the role and influence of fragments of appropriate catalysts on the degree of asymmetric induction were missing.

The description of the Author's own research began with the presentation of detailed research goals in the context of previous work carried out in the group of prof. Wojaczyńska. In this work, the PhD student focused on triazole and thiourea derivatives of 2-azabicycloalkanes, specifically 2-azabicycloheptane and 2-azabicyclooctane. Both compounds can be conveniently prepared by an aza-Diels-Alder reaction and ring expansion sequence, if necessary. The introduction of an azide or alkyne group allows for the subsequent synthesis of triazole derivatives via a "click" reaction. In turn, modification of the skeleton of the appropriate 2-azabicycloalkane by introducing an amino or isothiocyano group allows for the synthesis of thiourea derivatives, differing mainly in the length of the chain connecting the aromatic fragment with the nitrogen atom. A question that is important in the context of potential catalytic applications arises: did the author carry out in-depth structural studies of the obtained compounds? In contrast to ureas, conformations of thiourea derivatives are characterized by greater lability, and, among others, the bulkiness of the substituent determines whether it will be a *Z,Z* or *Z,E* conformation system.

The modification of the calix[4]arene skeleton with four fragments of 2-azabicyclooctane is a certain novelty. Unfortunately, the analysis of the structure of this very interesting compound has been treated somewhat superficially. In Figure 30, the author shows the ^1H NMR spectrum of the compound, measured at room temperature. Unfortunately, it has been shown "as is", with no correlation with the structure. Moreover, the author mentions that temperature-dependent NMR spectra have been measured, but he does not show them. I hope that during the defense this topic will be treated a bit more in-depth approach.

The obtained compounds were initially investigated as palladium ligands. Here, a trimeric C_3-symmetrical triazole derivative allowing to obtain an isolated complex with $PdCl_2$ turned out to be the only effective ligand. Unfortunately, the exact structure of the complex remained unknown at the time of writing the dissertation.

Catalytic activity tests were carried out for one type of reaction – the Michael-type addition of an enol to an α,β-unsaturated compound. The only difference between the reactions is the carbonyl compound used – either malonate or cyclohexanone. The degree of asymmetric induction, measured by an enantiomeric excess, was very diverse and ranged from 0 to 96%, albeit with a very low degree of substrate conversion. In fact, it can be said that none of the tested catalysts met the expectations (for these particular reactions) – either the enantiomeric excesses were unsatisfactory or the conversions were low. The question arises – why were these reactions chosen and why only these? I do not quite understand why the Author refuses to develop a method of isolation and purification of the reaction products. Does it make sense to develop asymmetric reactions whose products cannot be isolated? It is difficult to accurately estimate enantiomeric excesses if the peaks are on the slopes or are barely visible above the baseline. It is also worth comparing the results obtained by the Author with the literature data (if available). There is no stereochemical model of the reaction(s), linking the structure of the catalyst with the observed absolute configuration of the product. The author's commentary on the conducted research is only half a page - it is not much, considering the purpose of the work contained in the title of the dissertation.

The last part of own research concerns the biological activity of the tested derivatives. These studies were conducted in cooperation with various centers, and the important role of the PhD student was to provide material for research. In my opinion, this part of the research could have been completely omitted. Instead, I would expect more emphasis on catalytic research. Long tables with brief comments to the data contained do not allow to form an opinion whether, and to what extent, the obtained derivatives are better than the existing ones and what their mechanism of action is.

The last part of the paper contains detailed descriptions of experimental procedures and product characteristics. This passage proves a very good mastery of the craft. The PhD Student seems to feel confident in the laboratory. The Author is focused on creating new chemical entities, and slightly less on analyzing the results in detail. Considering the lack of good synthesis chemists, the former is a very desirable feature.

In summary, it is my opinion that the thesis submitted by Franz Steppeler, entitled: „*Synthesis of chiral 2-azabicycloalkane derivatives and their application in asymmetric synthesis*", fulfils the requirements of a PhD dissertation in chemical sciences provided for in the relevant legal acts. Therefore, I recommended the candidate to be admitted to the next stages of the PhD conferment procedure.

Marcin Kwit