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Doctoral thesis report

Mgr. Kirill Popov
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"Organocatalytic Reduction of Imines with Trichlorosilane"

Reviewer:
RNDr. Ivo Starý, CSc.
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Kirill Popov's PhD thesis is focused on the development of a synthetic methodology for the organocatalytic reduction of imines/enamines to the corresponding amines with emphasis on absolute control of stereochemistry when dealing with prochiral substrates. Based on the knowledge gained in this area, he then focused on the stereoselective synthesis of Ezetimibe and its novel fluorinated analogues. In my opinion, this is an excellent targeted synthetic study that not only extends modern organic synthetic methodologies but also applies them in the original preparation of the aforementioned therapeutically and commercially important drug. There is no doubt that this is a modern and useful synthetic study that has contributed to the development of the PhD candidate's professional synthetic skills in various areas of organic synthesis, stereoselective synthesis and catalysis. Kirill Popov had to master not only the demanding procedures of organic synthesis, some of which he had to fundamentally optimise, but also to demonstrate extensive literature knowledge and a mechanistic understanding of the chemical processes with which he was concerned. I can hardly forgive myself for remarking that I am impressed by the scope and quality of his experimental work, as well as by the very good handling and presentation of the extensive literature data.

Reductive amination of carbonyl compounds is one of the fundamental processes in organic synthesis and although this reaction has been given constant attention for many decades, not all its aspects have been satisfactorily investigated, especially its implementation in terms of tolerance to functional groups, structural variability of substrates, mild reaction conditions, catalytic design, atom economy, environmental friendliness, practical large-scale application and steric control. Kirill Popov contributed to the expansion of knowledge in several of these aspects. I appreciate that, based on this acquired knowledge, the PhD candidate paid attention to the updated preparation

of the original Ezetimibe and its novel fluorinated analogues. It is one of the best-selling drugs worldwide, used in the treatment of hypercholesterolemia associated with cardiovascular events. The introduction of the SF_5 group, whose effect on the biological activity of drugs has not yet been sufficiently investigated in contrast to the F and CF_3 substituents, is particularly worthy of appreciation. It is good that the dominant synthetic work is supplemented also by the results of preliminary biological tests.

The doctoral thesis collects an above-average amount of literature data (356 original papers are cited). The "Chapter 1. Reductive amination" section (28 pp) comprehensively describes a variety of approaches to this valuable synthetic transformation. The organocatalytic reduction of imines using $HSiCl_3$ is discussed in detail, including an asymmetric version and important mechanistic models obtained from calculations. Another theoretical part “Chapter III. Application of reductive amination” (34 pp) is mainly focused on the drug Ezetimibe, its mechanism of action, academic and industrial syntheses. This literature review is detailed, informative, well-structured and could serve as the basis for a useful review article.

The aims of the thesis are not formulated in a specific section, but are implicitly expressed in the sections "Chapter II: Results and discussion" (19 pp) and "Chapter IV: Results and discussion" (32 pp), each section related to the investigation of reductive amination of aldehydes/ketones and asymmetric synthesis of new Ezetimibe analogues. Here, the PhD candidate extensively optimised the reductive amination of aldehydes/ketones and explored a large matrix of these substrates, amines including amino acids, ammonia and hydrazines, as well as various reaction conditions relying on reduction by $HSiCl_3$ and the organocatalytic role of dimethylformamide or dimethylacetamide. Based on this, a modified general synthetic methodology for organocatalytic reductive amination was developed and the author openly mentioned its limitations. This section is clearly described and the conclusions are well documented with reliable results. The second experimental part organically follows the previous one, where the author described his contribution to the asymmetric synthesis of Ezetimibe and its new fluorinated derivatives. I appreciate that the author also mentioned less successful approaches to the synthesis of Ezetimibe, including model experiments. However, this most interesting part of his work deserves some criticism because there is no explicit conclusion. In addition, this part indicates that the author already placed less emphasis on the precision of the presentation of his results or he was running out of time to write his dissertation more carefully. In particular, the discussion on the asymmetric/diastereoselective CBS reduction of ketones **4.20a**-**d** should be better structured and the assignment of configuration to individual stereoisomers **4.21a**-**d** should be presented in more detail. Also, the use of the terms asymmetric or diastereoselective is not completely correct. For example, the author did not specify at all which stereoisomers, the ratio of which is given, are in Scheme 68 (p 108).

In the section "Chapter V: Experimental part" (55 pp), the author described the experiments performed in a standard way and also presents routine characterisation of the prepared compounds, which generally corresponds to the needs of a scientific

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publication. The experiments are described in a convincing manner and the reviewer has no doubts about their validity, accuracy, and originality.

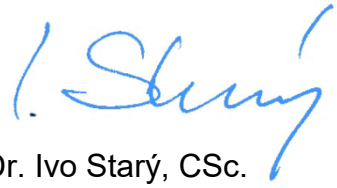
Kirill Popov presents a doctoral thesis that is a useful scientific work and documents his high ability to independently and successfully pursue modern academic research in the field of organic synthesis, stereoselective synthesis, catalysis and medicinal chemistry. He presents his results clearly with a critical evaluation. The work contains only a small number of errors. There is no information on whether important parts of the dissertation have already been published in peer-reviewed international journals or not.

Formal comments:
The thesis is written well in English. Although the work contains a small number of stylistic inaccuracies and formal errors, the discussion deserves only the following criticisms:
(a) Figure 9 (p 21): In the legend to the figure it would be appropriate to indicate what **C4** and **C5** are, it is not clear from the picture what **C1.C4a** and **C1.C4b** are (it is necessary to look at the original work).
(b) Scheme 23 (p 37): If *p*-toluidine is used, **2.2b** and not **2.2h** should be indicated.
(c) Scheme 37 (p 68): Should not the compound **3.21** have an *S* configuration?
(d) It does not say (at least I could not find it) who did the bioassays?

Questions for the defence:
(a) The developed methodology of organocatalytic reductive amination in two discrete but connected operations and with ambitions for application in large-scale preparation calls for the implementation of the flow reactor technique. However, it would be necessary to deal with the use of solid molecular sieves. Does the PhD candidate see any solution in this regard?
(b) With easily enolisable aldehydes/ketones, there is a dichotomy of enamine vs. imine formation. Can a PhD candidate provide a rationale and predict the outcome of such a reaction?
(c) How does the author see the possibility of reductive amination at peptides or even proteins, which could be relevant in terms of their labelling and functionalisation?

In conclusion, I find that the doctoral thesis of Kirill Popov "Organocatalytic Reduction of Imines with Trichlorosilane" meets the standard requirements for doctoral theses in the field of organic chemistry, and therefore I unequivocally recommend this scientific work for defence.

Prague, 3 June 2024



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