DOCTORAL THESIS REVIEW

THESIS NAME: Organocatalytic Reduction of Imines with Trichlorosilane
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The doctoral thesis by Kirill Popov aims to test, unify, and develop a universal procedure for the simple reduction of imines using trichlorosilane. Another goal is to utilize a developed methodology for a novel preparation of Ezetimibe analogues to broaden the pool of these important inhibitors of cholesterol absorption.

The thesis is divided into five parts describing the above-mentioned problems separately. Chapter 1 offers a mini−review of various reductive aminations described in the literature. Based on that review author built up the second chapter which is dedicated to the results of particular reductive aminations of various aromatic aldehydes, enolizable substrates, branched substrates, amino acids derived imines, ammonia-derived imines, reductive hydrazinations, *N*-oxide reductions, and attempts to introduce "green chemistry conditions".

The third chapter follows with another mini−review of Ezetimibe analogues and various biological consequences regarding cholesterol absorption including Ezetimibe synthesis and the role of fluorine atom in drug design. Closely related chapter four describes a retrosynthetic analysis of Ezetimibe together with the list of published total syntheses of Ezetimibe analogues, followed by practical results. Various attempts to develop a new total synthesis of fluorinated Ezetimibe analogues were performed resulting in a particularly successful route towards a final compound. Final compounds were subjected to preliminary biological experiments showing promising metabolic stability but poor cell permeability which needs to be optimized further to meet the criteria for the drug. Chapter five contains the experimental part followed by the list of references.

Overall, the doctoral thesis by Kirill Popov is relatively well written and the author uses solid English. However, a few mistakes including typing and formatting errors can be found in the text e.g., various sizes of figures and schemes – scheme 15, figure 8, figure 9 which was directly copied from the original article, or the typing error in the citation 252. I understand that some specific figures are hard to reproduce but the author should have taken more time and redrawn the chemical reactions at least. Another problem to mention was the difficult

orientation in the text, especially during the first round of reading. The reader must often list between the pages to keep track of the text (some paragraphs describe the later figures or schemes). On the other hand, the author proved good synthetic skills and strategic planning, particularly in the total synthesis of Ezetimibe analogues, which includes the preparation of starting materials and catalysts. I appreciate the multiple attempts and changes in the synthetic strategy, which were performed during the Ph.D. study. This overall deserves deep knowledge of organic chemistry.

To conclude, I would like to say that the doctoral thesis by Kirill Popov represents a solid piece of work which might be useful for other researchers in the field. This doctoral thesis fulfils standard criteria for this type of work and, thus, I **recommend this thesis for defence** and other procedures leading to the Ph.D. title. Regarding the defence procedure, I have following questions to ask.

Questions:

1) Page 34; The author mentioned that P=O bond stayed intact during the given conditions of reductive amination. In my opinion, it could be expected because the reduction of the P=O bond in phosphine oxides is not easy. Are there any other methods, which could be used for the successful reduction of phosphine oxides to corresponding phosphines?

2) Page 37; What is the reaction mechanism for the formation of compound **2.7** from compound **2.1** in scheme 23?

3) Page 43; How would you explain the unsuccessful reduction of carvone and camphor to their corresponding alcohols (steric limitations)?

4) Page 44; What is the meaning of “self-immolative catalyst” during the reduction of quinoline *N*-oxide **2.17**?

5) Page 58; In scheme 28 author mentioned “chiral chromatography”. Did you mean HPLC chromatography on the chiral stationary phase? Page 59; “chiral centre” maybe stereogenic centre?

6) Page 92; What could have happened in the reaction of compound **4.11b** after the addition of *t*BuMgCl?

7) Page 97; What can happen with the SF_5 group when treated by unreacted BuLi during the preparation of “home-made” LDA?

Ing. Ondřej Baszczyński, PhD. 30. 05. 2024 in Prague