EVALUATION REPORT

from Plamen Angelov Angelov, PhD – associate professor at the Paisii Hilendarski Univerisy of Plovdiv, member of the scientific jury appointed with administrative act РД-09-20/21.01.2021

regarding The quality of doctoral thesis in the field of higher education "Natural Sciences, Mathematics and Informatics", professional classification 4.2. "Chemical Sciences", scientific specialty "Organic Chemistry"

Author: Martin Antoniev Ravutsov

Title: SULFONAMIDE-DIRECTED *ORTHO*-METALATION AS A TOOL FOR REGIO- AND STEREOSELECTIVE SYNTHESIS OF MULTIFUNCTIONAL AROMATIC COMPOUNDS

Supervisor: prof. Vladimir Dimitrov, Institute of Organic Chemistry, BAS, Sofia

1. Topicality of the thesis

The presented doctoral thesis is in the field of organic chemistry, and more specifically – asymmetric organic synthesis and catalysis. The research is aimed at the development of new chiral ligands with possible application in the asymmetric catalysis and the discovery of new antimycobacterial compounds. Considering the general importance of asymmetric catalytic methods in organic synthesis and the current need for new and more effective antitubercular drugs, this research is topical and of significant interest.

2. Characteristics and scientific contributions of the thesis

The doctoral thesis is 144 pages long and contains three main parts – Literature Review, Results and Discussion, and Experimental Section. These are accompanied by Introduction, Conclusions and References. A total of 165 literature sources have been cited in the thesis. The Literature Review is detailed and is built around the mechanistic aspects of the directed *ortho*-lithiation reaction, with special attention to regio- and stereoselective lithiations of naphthalenes and ferrocenes. The author's own research results are presented in detail and are discussed at length. Two leading research directions are clearly defined and presented in separate subsections:

1. Directed *ortho*-lithiation of chiral 1- and 2-naphthylsulfonamides and its application in the synthesis of new chiral ligands

For the purposes of this research, initially a set of tertiary alpha- and beta-naphthylsulfonamides has been prepared. This is done in a two-step process, by reactions of the corresponding naphthylsulfonyl chlorides with chiral amines and subsequent N-ethylation of the obtained secondary sulfonamides. Then the directing properties of the sulfonamide groups have been studied in a number of experiments with lithia-

tion reactions and subsequent trapping of the organolithium intermediates with electrophilic reagents. Some of the products obtained in these experiments have further been tested as chiral *P,O*-ligands in a model *Pd*-catalysed asymmetric allylic substitution. Excellent yields have been achieved in this model study, although with low enantioselectivity.

2. Synthesis of 1,2-disubstituted planar-chiral ferrocene derivatives and antimycobacterial assay of the obtained products.

By analogy with the previous task, here the author has synthesized a set of ferrocenylsulfonamides by reactions of ferrocenylsulfonyl chloride with chiral amines, however with more efforts directed at the optimization of the reaction conditions. The obtained chiral ferrocenylsulfonamides have then been used to investigate their lithiation reactions. The lithiated intermediates have been successfully trapped with various electrophiles – benzophenone, acetone, (–)-menthone, (–)- and (+)-fenchone, formaldehyde, iodine and N,N-dimethylcarbamoyl chloride. Diastereoisomeric mixtures of 1,2-disubstituted planar-chiral ferrocene derivatives have been obtained in these experiments and the factors affecting the diastereoselectivity have been carefully studied. The NMR measurements related to the structure and configuration of the ferrocene derivatives are presented in detail and discussed at length. Some of the newly synthesized compounds have been assayed for antitubercular activity and eleven of them are found to be more active than the reference compound ethambutol dihydrochloride.

The Experimental Section of the thesis contains detailed descriptions of all synthetic procedures, chromatographic separations and physical properties of the compounds. All new compounds are properly characterized with NMR and MS data. The structure and configuration of four planar-chiral ferrocene derivatives is confirmed by single crystal X-ray diffraction.

3. Dissemination of the results

Results from this thesis have been published in two peer-reviewed articles and a third manuscript has recently been accepted for publication in the reputable journal *Organometallics*:

1. Ravutsov, M., Petkova, Z., Dimitrov, V. Directed ortho-lithiation as a tool for synthesis of chiral 1,2-disubstituted arylsulfonamides. *Monatshefte für Chemie*, *149*, 12, Springer-Verlag GmbH Austria, **2018**, ISSN:1434-4475, DOI:10.1007/s00706-018-2296-6, 2207-2229. ISI IF:1.285 Q3 (Web of Science)

2. Simeonov, S., Ravutsov, M., Mihovilovic, M. Biorefinery via Achmatowicz Rearrangement: Synthesis of Pentane-1,2,5-triol from Furfuryl Alcohol. *ChemSusChem*, *12*, 12, WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim, **2019**, DOI:10.1002/cssc.201900601, 2748-2754. JCR-IF: 7.804 Q1 (Web of Science).

3. Journal: *Organometallics*, Manuscript ID: om-2020-00712z.R2, Title: "1,2-Disubstituted Planar Chiral Ferrocene Derivatives from Sulfonamide Directed ortho-Lithiation: Synthesis, Absolute Configuration

and Chiroptical Properties", Authors: Ravutsov, Martin; Dobrikov, Georgi; Dangalov, Miroslav; Nikolova, Rositsa ; Dimitrov, Vladimir; Mazzeo, Giuseppe; Longhi, Giovanna; Abbate, Sergio; Paoloni, Lorenzo; Fusè, Marco; Barone, Vincenzo; Manuscript Status: Accepted

The results have also been presented at twelve scientific conferences, with one award.

CONCLUSION

This doctoral thesis contains original research results which contribute to the development of the scientific field and satisfy the requirements for quality and novelty imposed by the Law for the Development of the Academic Staff in the Republic of Bulgaria. The thesis clearly shows that its author, Martin Antoniev Ravutsov, has sufficient theoretical knowledge and professional skill in the field of Organic Chemistry. The author demonstrates abilities for independent research. In view of the above, I kindly recommend the scientific jury **to grant the PhD degree** to Martin Antoniev Ravutsov.

12.02. 2021 .....

Assoc. Prof. Plamen Angelov, PhD