EVALUATION REPORT

From Plamen Angelov Angelov, PhD, Associate professor at the University of Plovdiv "Paisii Hilendarski"

About submitted doctoral thesis in the field of higher education "Natural Sciences, Mathematics and Informatics", professional classification 4.2. "Chemical Sciences", doctoral programme "Organic Chemistry".

Thesis author: Irena Bocheva Zagranyarska

Thesis title: Stereoselective synthesis of functionalized chiral amino alcohols – configuration and application

Scientific advisors:
Assoc. prof. Kalina Kostova, PhD
Prof. Vladimir Dimitrov, DSc

1. General description of the submitted documents

I have been designated as a member of a scientific jury according to order № РД-09-180/03.07.2020 by the director of the Institute of Organic Chemistry with Centre of Phytochemistry (IOCCP), with the task of reviewing and evaluating the thesis described above, submitted for the scientific and educational degree 'doctor'. As such, I confirm that the author of the thesis, Mrs Irena Zagranyarska, has submitted the complete set of required documents in compliance with the IOCCP regulations and the Law for the Development of the Academic Staff in the Republic of Bulgaria. Two scientific papers in connection with the doctoral thesis have been published in peer-reviewed journals so far, and these are also included with the documents.

2. Brief biographical information about the doctoral candidate

Mrs Irena Zagranyarska graduated from the National High School of Mathematics and Natural Sciences "Academician Lyubomir Chakalov" in 2001. In 2005 she graduated from the Sofia University "St. Kliment Ohridski" with a bachelor's degree in chemistry. Later, in 2007, she was awarded a master's degree in chemistry from the same university. Since 2005 she has been working at the IOCCP as a chemist, promoted to assistant in 2008 – a position that she currently holds. During her employment at the IOCCP Mrs Zagranyarska took maternity leave for two years.

3. Relevance of the thesis aims and objectives to the field of research

The presented doctoral thesis is in the field of asymmetric organic synthesis. The main objective of the research is the synthesis of new chiral amino alcohols and investigation of their catalytic activity and chiral induction ability in model addition reactions between diethylzinc and aromatic aldehydes. Enantiose-

lective variants of such C-C forming reactions are potentially applicable to many syntheses of all kinds of useful compounds. Considering the variety of possible applications, the catalytic asymmetric methods for C-C bond formation are of great importance to the field of organic synthesis. Therefore, the development of new chiral ligands for asymmetric catalysis is immutably relevant to the advancement of the research field of this thesis.

4. Characteristics and evaluation of the thesis

The doctoral thesis is 151 pages long (including Title, Contents and List of abbreviations) and is divided into the following chapters:

- Introductions (3 pages)
- Aims and Objectives (1 page)
- Literature Review (42 pages)
- Results and Discussion (48 pages)
- Conclusions (1 page)
- Experimental (44 pages)
- References (6 pages)

The thesis starts with a brief and informative introduction which lays the ground for well formulated and substantiated list of aims and objectives. This is followed by a comprehensive and detailed review of the literature in the field, with a total of 203 references. The literature review is well done and includes not only the latest developments in the field, but also a brief introduction to the basics of the organozinc additions to carbonyls. Such a well-structured and meticulous literature review is indicative of thorough understanding of the chosen research problem – an impression that is further strengthened by the rest of the thesis and the own research work of the doctoral candidate. The research methodology is flawless, with application of all contemporary methods for organic structure analysis implemented on state-of-the-art equipment. The synthetic work is described in sufficient detail to be replicated and upgraded by other researchers in the field. The thesis includes 21 tables, 9 figures and 57 schemes.

The results of the own research work of the doctoral candidate, along with the corresponding discussion, are divided into two subchapters, depending on the type of studied chiral ligands – aminoalcohols with menthane skeleton or aminomethylnaphthols of the Betti base type.

The synthesis of the first group of ligands is accomplished through addition of organolithiums to (–)-menthone. (–)-Menthone is chosen as the source of chirality in these experiments because of its commercial availability, good reactivity and the previous experience of the Dimitrov group with this compound. The addition reactions of five organolithium reagents to (–)-menthone have been studied - thiophen-2-yllithium, 2-((dimethylamino)methyl)phenyllithium, 2-(dimethylamino)phenyllithium and TMS-substituted variants of the first two. All studied reactions are found to be highly diastereoselective, with equatorial attack of the nucleophile leading to products in which the OH-group is axially located. The obtained prod-

ucts are thoroughly characterized with NMR spectroscopy, mass spectroscopy, elemental analysis and specific optical rotation.

The second group of ligands, for brevity named “aminomethylnaphthols”, is prepared by three-component Betti condensation of steroidal 2-naphthol, aromatic aldehydes and chiral amines. Desoxyisoequilenine is chosen as the naphthol component because of the combination of steric bulk and chirality that it offers. This steroidal naphthol is prepared by the doctoral candidate from commercially available steroid estrone by dehydrogenation and subsequent Kishner-Wolff reduction. In the role of the amine component is used either (S)-(–)-1-phenylethylamine or (*S*)-(–)-1-(2-naphthyl)ethylamine, and the aldehyde component is provided by one of four aromatic aldehydes (1-naphthaldehyde, 2-naphthadehyde, 2-methoxybenzaldehyde or 2-pyridinecarbaldehyde). Thus, the Betti condensation is performed with six different combinations of the three components. In one of the combinations the condensation is completely diastereoselective, leading to a single product, while the other five variants lead to diastereomeric mixtures in approximately 8:2 ratios (determined by ^{1}H-NMR). Full preparative separation of the diastereoisomers has not always been possible, but in all cases the major diastereoisomer has been successfully isolated by column chromatography. Next, the aminomethylnaphthols are transformed into their corresponding 1,3-dihydrooxazine derivatives by cyclocondensation reactions with formaldehyde. In this way the determination of the relative stereochemistry of the newly formed stereogenic center by NMR is greatly facilitated due to the introduced conformational constraint, combined with a diastereotopic CH_2 group giving well separated ^{1}H-NMR signals. The relative stereochemical configuration here is easily translated into absolute, thanks to the neighboring stereogenic center of the amine component with known configuration. The stereochemical assignments are confirmed by single-crystal X-ray diffraction for two of the aminomethylnaphthols and one 1,3-dihydrooxazine derivative. Additional advantage of this derivatization is the easier preparative chromatographic separation of the diastereomeric 1,3-dihydrooxazines, compared to that of the corresponding aminomethylnaphthols.

Along with the synthesis of the chiral ligands, each subchapter includes investigations of their catalytic activity in a model addition reaction of diethylzinc to aromatic aldehydes. The catalytic potential of the aminoalcohols with menthane skeleton is investigated in reactions of diethylzinc with three aromatic aldehydes, and the activity of the aminomethylnaphthols is assessed in reactions of diethylzinc with a series of seven aromatic aldehydes. The reactions are tried under various conditions and detailed data is presented in tables. Both ligand types show good catalytic activity (applied in 3 mol %) but the aminomethylnaphthols stand out with much better chiral induction in more of the studied reactions. In some cases, the asymmetric induction of these ligands leads to enantiomeric excesses of more than 90% (98% in the best instance).

Overall, both the amount and the quality of the experimental work are impressive. All synthetic and chromatographic procedures are properly described in the corresponding chapter of the thesis, with full spectral characteristics of the synthesized compounds. The compounds are characterized with NMR and mass-spectra, melting points, elemental analysis and specific optical rotation. Single-crystal X-ray diffraction data is included for three of the compounds. The enantiomeric excesses are determined by chiral phase GC or HPLC and the chromatographic conditions are given in detail for each compound.

5. Publications in connection with the thesis and personal contribution of the doctoral candidate

Results from this doctoral thesis have been published in two separate peer-reviewed papers in recognized journals with impact factor:

5.1. I. Zagranyarska, K. Kostova, A. Chimov, V. Dimitrov, Diastereoselective addition of functionalized organolithium compounds to (–)-menthone – synthesis of chiral ligands for enantioselective addition of diethylzinc to aldehydes, *Bulg. Chem. Commun.,* **2017**, *49 (Special Edition B)*, 10-17. (IF 0.242, Scimago Q4)

5.2. I. Zagranyarska, K. Kostova, A. Chimov, Y. Zagranyarski, R. Nikolova, B. Shivachev, V. Dimitrov, Estrone derived 2-naphthol analogue in the diastereoselective one-pot Betti-condensation, *Molecular Diversity* (DOI: https://doi.org/10.1007/s11030-019-09998-5). (IF 2.013, Scimago Q3)

These papers fully correspond to the results presented in the thesis and the doctoral candidate is the first co-author in both of them, which is a good indication of her own involvement and contribution. So far one citation of the first paper has been noticed in the literature.

The doctoral candidate presented results from her work at 14 scientific forums.

6. Remarks and recommendations

I have no major remarks or recommendations.

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, Irena Bocheva Zagranyarska, 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 doctoral degree** to Irena Bocheva Zagranyarska.

31.08. 2020 .....

Assoc. Prof. Plamen Angelov, PhD