R E V I E W

By Assoc. Prof. Dr. Irena Lyubomirova Philipova,
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Subject: PhD thesis for the award of the educational and scientific degree "doctor", field of higher education 4. Natural sciences, Mathematics and Informatics, professional field 4.2. Chemical Sciences, Scientific Specialty "Organic Chemistry".

Author: Irena Bocheva Zagranyarska

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

Scientific Advisors: Assoc. Prof. Dr. Kalina Kostova and Prof. DSc. Vladimir Dimitrov

General description of the presented materials

According to order № RD-180/03.07.2020 of the Director of IOCCP-BAS, I have been approved as a member of the academic board for awarding the educational and academic degree "Doctor" of assistant Irena Bocheva Zagranyarska, PhD student in independent training at IOCCP-BAS, in professional field 4.2. Chemical Sciences, Scientific Specialty "Organic Chemistry". The title of the thesis is: "Stereoselective synthesis of functionalized chiral amino alcohols – configuration and application." At the first meeting of the academic board I was chosen as a reviewer of the PhD thesis.

The submitted set of documents and materials meets the requirements of the Law on the Development of Academic Staff in the Republic of Bulgaria and the Regulations on the terms and conditions for awarding scientific and academic degrees in IOCCP-BAS and includes the following documents: application form; autobiography; a copy of the diploma for completed master's degree; protocols from successfully passed exams according to an individual training plan; PhD thesis; abstract in Bulgarian and English; list and copies of scientific publications on the topic of the thesis; list of noticed citations; list of participations in scientific events; list of participations in projects. The documents are well organized.

1. Brief biographical data about the PhD student

Irena Zagranyarska graduated at Sofia University "St. Kliment Ohridski", Faculty of Chemistry in 2007 with a master's degree in Organic Chemistry. During the period 2005-2008 she worked as a chemist-specialist in the laboratory "Organic Synthesis and Stereochemistry", and since 2008 she has been appointed as an assistant in the same laboratory. Irena Zagranyarska is a co-author of 2 scientific publications, in which she is the first author. She has participated in 16 research projects funded by the Bulgarian National Science Fund, the SCOPES program of the Swiss Research Support Fund, the 7th FP of the EU, the Horizon 2020 program of the EC, as well as those funded by pharmaceutical companies.

2. Relevance of the topic and expediency of the set goals and objectives

The development of effective stereoselective methods for the formation of stereogenic carbon atoms using chiral reagents and catalysts is an extremely relevant field of organic chemistry. Enantioselective nucleophilic addition to carbonyl compounds catalyzed by a chiral ligand is a convenient method for creating a carbon-carbon bond. The products of the reaction can be used in a variety of fields - therapeutic preparations and dosage forms, cosmetics and perfumes, food additives, agrochemicals and others. Chiral amino alcohols have been used successfully in asymmetric synthesis as catalysts. The use of easily accessible natural compounds as sources of chirality is economically justified. In this regard, the topic is definitely relevant and the results achieved are in a promising scientific field. The main goal of the thesis is the development of new chiral amino alcohols and sulfur analogues with a menthane skeleton, as well as steroid analogues of aminomethylnaphthols of the "Betty bases" type and their application in asymmetric catalysis reactions. The set goals and objectives are in a logical sequence: synthesis and proof of the structure of the new compounds, evaluation of the synthesized diastereoisomerically pure amino alcohols and aminomethylnaphthols as ligands in the model reaction for enantioselective addition.

3. Knowledge of the problem

The literature review of the thesis covers 203 literature sources in renowned journals, which shows that the PhD student is well acquainted with the state of the problem. It is structured in four sections. The literature review in its first part considers the mechanism and stereoselectivity of the addition of dialkylzinc compounds to aldehydes. Historical data is given, the phenomena of ligand-induced amplification and chiral amplification are explained. The mechanism of the catalytic cycle of the addition reaction discovered by *Noyori* is described in detail. The following two sections systematize a large number of chiral β-, γ- and δ-amino alcohols as ligands in the model reaction. Particular attention is paid to the synthesis of chiral amino alcohols with a menthane skeleton and their use as chiral ligands for asymmetric syntheses. The last section of the literature review is the most extensive and is devoted to the synthesis of chiral aminonaphthols by three-component condensation of Betty type. Particular attention is paid to the use of "Betty bases" in reactions of enantioselective addition of diethylzinc to aldehydes, which emphasizes the relevance of the studies described in the thesis.

4. Research methodology

Within the thesis a significant experimental work is demonstrated. A complex of chemical synthesis techniques has been mastered: carrying out organometallic reactions in an inert atmosphere, synthesis of new chiral ligands for asymmetric transformations based on available source of chirality, conducting stereoselective reactions generating C-C bonds. The studies include the synthesis of chiral amino alcohols and sulfur analogues by addition reactions of organometallic reagents to (–)-menthone, as well as the synthesis of steroid analogues of aminomethylnaphthols by three-component condensation of Betty type with the participation of a steroid analogue of 2-naphtol, aromatic aldehydes and chiral amines and the corresponding 1,3-dihydrooxazines by reaction with formaldehyde. The synthesis of the steroid analogue of 2-naphthol, deoxy-isoequilenine, has been optimized by selective transformation of estrone. The

isolated compounds were characterized by appropriate physical and spectral methods: specific rotation, NMR spectroscopy (^{1}H NMR, ^{13}C NMR, DEPT, HSQC, HMBC and NOESY) and Mass spectrometry (electronic, chemical or electrospray ionization). The configurations of the newly formed stereogenic centers of the resulting aminomethylnaphthols were determined using NMR techniques and further confirmed by X-ray diffraction analysis. This is the achievement of the goal by performing the main tasks of the thesis using new synthetic procedures, developing techniques for isolation and purification, as well as instrumental methods for characterization and structural elucidation of organic compounds.

5. Characteristics and evaluation of the thesis

The thesis is well organized and structured and meets the established requirements. The exposition of the material in the thesis is formed on 149 pages and includes: introduction (3 pages), goals and tasks (1 page), literature review (42 pages), results and discussion (45 pages), conclusions (1 page), experimental part (37 pages) and literature (6 pages). 203 literature sources are cited. The results of the thesis are presented and discussed in two main sections: 1) Synthesis and application of amino alcohols and sulfur analogues with a menthane skeleton; 2) Synthesis of aminomethylnaphthols of the "Betty base" type by a three-component condensation reaction and their application in asymmetric catalysis.

The thesis is clearly written in good scientific language. A very good impression is made by the correct and detailed description of the synthetic experiments, as well as the detailed spectral characterization of the obtained compounds and the unambiguous establishment of the structure and stereochemistry of the new compounds by applying a combination of modern NMR techniques and X-ray diffraction analysis.

6. Contributions and significance of development for science and practice

The PhD thesis of Irena Zagranyarska has a fundamental character in the field of organic synthesis, although with a practical focus. The results of the conducted research on the methods of synthesis of functionalized chiral amino alcohols with menthane skeleton, as well as steroid analogues of aminomethylnaphthols of the type "Betty bases" are presented, with emphasis on their use as catalysts in reactions of enantioselective addition of diethylzinc zinc.

The main contributions and merits of the thesis can be summarized as follows:

- New chiral amino alcohols and sulfur analogues with a menthane skeleton have been synthesized by stereoselective addition of nitrogen- and sulfur-functionalized organolithium reagents to (–)-menthone. The ligands were used in the addition reaction of diethylzinc to various aldehydes with a maximum enantioselectivity of 80%.

- The synthesis of steroid analogues of 2-naphthol, isoequilenine and deoxo-isoequilenine is optimized by selective transformation of estrone.

- Synthesized and isolated in diastereoisomerically pure form are a large number of chiral steroid analogues of aminomethylnaphthols by three-component Betty condensation of deoxy-isoequilenine, various aromatic aldehydes and chiral amines. The structure and configurations of the newly formed stereogenic centers were unambiguously determined by using NMR techniques and confirmed by X-ray diffraction analysis of three of the synthesized compounds.

- Chiral aminomethylnaphthols were evaluated as ligands in the model reaction of enantioselective addition of diethylzinc to various aldehydes, with enantioselectivity up to 98% *ee*.

7. Assessment of the publications and personal participation of the PhD student

The scientific results of the thesis have been published in two articles in *Bulg. Chem. Comm.* and *Molecular diversity*. Irena Zagranyarska is the first author in both publications, which confirms her personal participation in the elaboration and interpretation of the published results. One citation of the first article was noticed. The results of her scientific work were presented at nine international and five national scientific forums with poster presentations and one report. In eight of the posters, the doctoral student is the first author.

I have no doubts about the personal participation of Irena Zagranyarska in the implementation of the tasks and the achievement of scientific results and contributions to the thesis, of course under the guidance of her supervisors.

8. Abstract

The abstract of the thesis is 40 pages long. It is written in accordance with the established rules and accurately and correctly reflects the main results achieved in the thesis in summary form. The conclusions and scientific contributions, publications and participation in scientific forums in connection with the thesis are noted.

9. Critical remarks and recommendations

In general, the thesis is well-done and carefully written. However, some technical errors and inaccuracies are noted. I have a few remarks and recommendations.

- References to literary quotations are usually placed at the end of the sentence, and when many consecutive quotations are listed as numbering, it is adopted to write with a dash from the smallest to the largest number.

- In most of the schemes in the "Results and discussion" section the yields of the products are not specified, and when a mixture of diastereoisomers is obtained, the ratio between them. Illustrating the schemes with this information would make it easier for the reader.

- The description of experimental data on the product purification in the "Results and Discussion" section in some cases is too detailed. Their place is in the "Experimental part". Furthermore, I consider that in describing the isolation of the individual compounds by column chromatography, it is not correct to give percentage yields of the reisolated starting compounds, especially when they are not in equimolar ratios.

- It would be good to present some typical NMR spectra, which, although illustrative, would be valuable for easier understanding of methods for assignment of the ^{1}H and ^{13}C NMR spectra.

- According to literature data, the compounds of the type "Betty base" show a variety of biological activity. Have you considered researching your compounds in this regard? Such a study would further enrich the work.

The observed inaccuracies and technical errors are insignificant and do not affect my excellent impression of the research and the scientific level of the thesis.

10. Personal impressions

I have known Irena Zagranyarska personally since her employment at IOCCP-BAS and I have followed her scientific career. Her experimental training, confirmed by many years of work in the laboratory "OSS", has helped her to realize the research work, carried out under the guidance of Assoc. Prof. Kalina Kostova and Prof. Vladimir Dimitrov.

CONCLUSION

The PhD thesis contains **scientific and scientific-applied results, which represent an original contribution to science and meet all the requirements** of the Law for Development of the Academic Staff in the Republic of Bulgaria (LDASRB), the Regulations for application of LDASRB and the respective Regulations of BAS and IOCCP-BAS. The presented materials **fully** comply with the specific requirements of IOCCP -BAS.

The thesis unequivocally shows that the Ph.D. student **Irena Bocheva Zagranyarska** has theoretical knowledge and professional skills in the scientific specialty "Organic Chemistry" by demonstrating qualities and skills for independent research.

Based on the above, I give my **positive assessment** of the PhD thesis **and propose to the esteemed academic board to award the educational and academic degree "Doctor"** of Irena Bocheva Zagranyarska in the field of higher education: 4. Natural sciences, mathematics and informatics; 4.2. Chemical sciences; Scientific Specialty "Organic Chemistry".

03.08.2020 Reviewer:……

Sofia Assoc. Prof. Irena Philipova