STATEMENT

in regard to the dissertation submitted for awarding the educational and scientific degree
DOCTOR

field of higher education **4. Natural Sciences, Mathematics and Informatics,**
professional field **4.2. Chemical Sciences,** Doctoral Programme **Organic Chemistry**

Author: Krassimira Petkova Dikova
Title: Betty condensation – an instrument for preparation of chiral aminomethylnaphthols
Supervisors: Prof. Vladimir Dimitrov, Institute of Organic Chemistry, BAS, Sofia
Assoc. Prof. Dr. Kalina Kostova, Institute of Organic Chemistry, BAS, Sofia
Member of the scientific jury: Prof. Dr. Ilian Ivanov, Plovdiv University "Paisii Hilendarski"

With administrative act РД-09-179/03.07.2020 signed by the Director of The Institute of Organic Chemistry with Centre of Phytochemistry (IOCCP) I. was appointed as a member of the scientific jury to prepare an opinion/statement on dissertation with title " Betty condensation – an instrument for preparation of chiral aminomethylnaphthols " for obtaining the educational and scientific degree "Doctor" in the field of higher education **4. Natural sciences, mathematics and informatics**, professional field **4.2. Chemical sciences**, doctoral program **Organic chemistry**. The author of the dissertation is Assistant Professor Krasimira Dikova – PhD student at Laboratory of Organic Synthesis and Stereochemistry - IOCCP BAS.

The set of materials presented in electronic format by Assistant Professor Dikova is in full compliance with the requirements of the Law for Development of the Academic Staff in the Republic of Bulgaria and the regulations for its application, as well as Regulation on the Terms and Procedure for Acquisition of Academic Degrees and the Occupation of IOCCP.

In 2001 Assistant Professor Dikova graduated with honors from Master's degree in Organic and Analytical Chemistry at the Faculty of Chemistry, Sofia University. Since 2002 she has been working at IOCCP BAS, successively holding the position of chemist-specialist and assistant professor.

During the period of her training, Assistant Professor Dikova has fully completed the educational part of her individual PhD plan. She has successfully passed the doctoral exam with a grade of Very good 5.25.

The results of the research are described in a dissertation presented on 165 pages, including 34 tables, 10 figures and 76 diagrams. The bibliography covers 165 literary sources in the period between 1900 and 2013. The dissertation is structured in the classical way - introduction, goals and objectives, literature review, results and discussion, conclusions, experimental part and references.

The topic of the presented dissertation is of emphasized relevance and significance. The importance of the use of chiral amino alcohols as catalysts in the reaction of addition of dialkylzinc compounds to aldehydes is briefly, clearly and with specific examples substantiated. The possibility of their synthesis by three-component *Betti* condensation is indicated.

I consider the level of knowledge of the state of the problem to be very good. Based on the presented literature review in which the doctoral student shows good awareness and in-depth

understanding of the problem. Each separate part of the review ends with a short summary, which allows the correct formulation of the set goals and objectives for their achievement.

The solution of the set tasks in connection with the set goal has allowed its realization in full.

According to the stated purpose, by application in the Betti type reaction of ferrocene carbaldehyde, ruthenocene carbaldehyde, 1-pyrenecarbaldehyde and 2-fluorenecarbaldehyde, (S)-(-)-phenylethylamine and 2-naphthol or 3-methoxy-2-naphthol with high diastereoselectivity five new chiral aminomethylnaphthols were synthesized for first time.

A possible mechanism and explanation of the diastereoselectivity of the reaction for the obtaining of ferrocenyl-aminomethylnaphthol are proposed.

The possibility of converting the obtained aminonaphthols into the corresponding oxazine derivatives by reaction with an aqueous solution of formaldehyde under different reaction conditions has been shown. Numerous attempts to obtain tertiary derivatives by N-alkylation (reduction of the obtained oxazines or by alkylation) with various reagents and reaction conditions have unfortunately been unsuccessful.

Functionalized chiral amines prepared by reduction of α-aminocarboxylic acids have been successfully used in the Betti reaction. New chiral aminomethylnaphthol was synthesized by condensation of (S) -leucinol, 1-naphthaledehyde and 2-naphthol.

Using modern techniques (COSY, HSQC, HMBC, NOESY) in NMR spectroscopy, the possibility of determining the configuration of the newly formed stereogenic centers of chiral aminomethylnaphthols has been shown. The applicability of the approach has been confirmed by X-ray diffraction studies.

A series of experiments were performed for the application of the obtained new aminomethylnaphthols as catalysts in a model reaction of enantioselective addition of diethylzinc to aldehydes. The obtained results show the achievement of a high degree of enantioselectivity - up to 93% ee.

The possibility of application of diethylzinc as catalysts in the reaction of enantioselective addition to ferrocene carbaldehyde and benzaldehyde of the alkaloids quinine and (-) - ephedrine, of the amino acids L-proline and L-phenylalanine, as well as of amino alcohols has been studied. The addition reactions were found to proceed with acceptable yields and low to moderate enantioselectivity. In the addition reactions to ferrocenecarbaldehyde, the obtaining of by-products (ferrocenylmethanol and 1-ferrocenyl-1-propanone) was registered, and a hypothesis for their preparation was proposed.

In the experimental section, the synthesis of more than thirty compounds, mostly obtained for first time, is accurately described.

All synthesized compounds are characterized in detail using classical analytical and modern spectral methods and techniques - mass spectrometry, NMR spectroscopy - ^{1}H, ^{13}C, DEPT, COSY, NOESY, HSQC, HMBC, elemental analysis, X-ray diffraction analysis.

The main results obtained in the dissertation are popularized among the scientific community through two scientific reports - one publication in Polyhedron (Q2) journal and one in the journal of Bulgarian Chemical Communications (Q4).

The results of the research are presented via poster presentation in eleven scientific forums, seven of which abroad.

One citation was noticed at the time of submitting the documents under the procedure based on data provided by Assistant Professor Dikova.

The autoreferat contains the most important parts and accurately covers the main contributions and achieved results of this work.

In conclusion, I believe that the candidate has in-depth theoretical knowledge in the field of organic synthesis and the ability for independent research. The dissertation work of Assistant Professor Dikova contains scientific and scientific-applicable results, which represent the expansion of existing knowledge, meets the requirements for awarding the educational and scientific degree "Doctor" according to the Law for Development of the Academic Staff in the Republic of Bulgaria and meets the criteria laid down in the Regulations for the acquisition of scientific degrees and for holding academic positions in IOCCP BAS.

In accordance with the above and in connection with Article 10, paragraph 1 of the Law for Development of the Academic Staff in the Republic of Bulgaria, I kindly recommend the scientific jury **to grant the PhD degree** to Krassimira Petkova Dikova.

Plovdiv
22 August 2020

Member of the SJ:
Prof. Iliyan Ivanov