



## Doctoral Thesis Review Report

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<b>Doctoral Thesis</b>	"Synthesis and Application of Helicene-Based N-Heterocyclic Carbene Ligands."
<b>Referee</b>	Assoc. Prof. RNDr. Jan Veselý, Ph.D.
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The submitted doctoral thesis deals with the preparation of enantiomerically pure oxa[5]helicene and oxa[6]helicene-based imidazolium salts as precursors of NHC ligands, and their evaluation in enantioselective Ni(0)-catalyzed [2+2+2] cycloisomerization. First, key helical building blocks, 2*H*-pyran-based helicenes bearing amino group, were prepared using diastereoselective Co(I)-catalyzed [2+2+2] cycloisomerization as a key step. Subsequently, helical building blocks were used for the preparation of various symmetrical and unsymmetrical imidazolium salts. Their evaluation in Ni(0)-catalyzed [2+2+2] cycloisomerization revealed a promising transfer of chirality in the case of symmetrical NHC precursors. Thus, a new set of symmetrical helicene-based imidazolium salts bearing sterically demanding substituents was designed, synthesized, and evaluated.

The thesis is traditionally constructed, consisting of six chapters (Introduction, Aim and Objectives, Results and Discussion, Conclusions, Experimental Section, and References) and covering 170 pages. It is written with a good level of English with the only minimum number of typos and misspellings. The text is logically constructed and sufficiently accompanied by the graphical material (figures, schemes, and tables). *Note 1:* Unfortunately, the size and the format of the schemes are not uniform.

The introduction part gives a detailed overview of the asymmetric synthesis of helicenes, their application, and the chemistry of N-heterocyclic carbenes. Goals are clearly formulated in chapter Aim and Objectives. Chapter 3 (Results and Discussion) is divided into five sections, following the works on the project. This part clearly formulates the main ideas of the work, describes experiment arrangements in detail and obtained results. It demonstrates a good level of applicant's knowledge of the studied area. *Note 2:* I would appreciate a deeper discussion of the results; for example, the effect of bulky substituents on the transfer of chirality in Ni(0)-catalyzed [2+2+2] cycloisomerization. The following chapter (Conclusions) summarizes the obtained results and contains a short outlook for further research in the study field. All the prepared compounds are characterized in a comprehensive way in the Experimental section, and the thesis contains 170 citations in a proper format.



The thesis stems from the recent findings in the group of Dr. Starý, and it is focused on the new area of research dealing with the use of helical ligands (NHC precursors) in asymmetric catalysis. Although it was not an easy task, the thesis's set goals (with specific objectives) were fulfilled. In total, the dissertant prepared twelve new helicene-based imidazolium salts, and some of them were found to be highly efficient ligands in Ni(0)-catalyzed cycloisomerization leading to the formation of dibenzo[7]helicene with high enantiocontrol (up to 86% ee). The results presented in the thesis are an important starting point for the development of asymmetric methods based on helicene-derived NHC ligands. I highly appreciate this work, and it was a real pleasure for me to be a referee.

Selected errors and inaccuracies appearing in the text:

- List of abbreviations    Instead of Abbreviations should be Abbreviations, and several abbreviations are missing, such as Xantphos, Mephos, Nf, Tf, and others.
- page 6, scheme 5        The yield of 99% in three-step transformation (including the resolution) of compound 14 is not realistic.
- page 18, scheme 18     The scheme does not contain X<sup>-</sup> in the catalyst's structure.
- page 19, scheme 19     Projection of menthyl should contain the correct configuration at all three stereocenters.
- page 60, line 4         Instead of enantioenriched should be enantioenriched.
- (The above list of errors is only indicative and not exhaustive.)

Questions and notes:

- 1) Several transformations, such as Sonogashira reaction, Mitsunobu reaction, and acid-catalyzed condensation affording imidazolium salts, were performed with various substrates, and the reaction conditions were modified, for example, the change of solvents, reaction temperature, and concentration of reagents. Could you please comment on why the conditions were changed and if the reported conditions were optimized? How did you measure the conversions?
- 2) Could you please describe the mechanism of reduction of Ni(+II) to Ni(0) in the presence of imidazolium salt using Grignard reagent? In addition, cyclotrimerizations were performed with 50 mol% of Co(I) or 20-30 mol% of Ni(0) catalyst. Have you tried to reduce the amount of catalysts and ligands?
- 3) In comparison to phenol derivatives, 1-iodo-2-naphthol **184** furnished upon Sonogashira reaction conditions mainly deiodinated product **185**. A slightly different situation was observed with regioisomeric 1-iodo-2-naphthol **196**. Do you have any explanation for the difference in reactivity of the substrates mentioned above?
- 4) Could you please comment on the selection of aryl substituents in oxa[5]helicenes **180a-f** and oxa[6]helicenes **207** and **208**? Why was not tested **180c** in the synthesis of



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dibenzo[7]helicene **161**? Based on the results mentioned in part 3.3.3 (Table 3), I would be interested if you plan to modify 2-methyl substituent (that is crucial for diastereoselective [2+2+2] cycloisomerization)?

In conclusion, I would like to note that the results of the thesis are original and with high scientific value. The aims stated in the thesis were reached, and the main results of the work were published in two peer-reviewed journals (*Chem. Commun.*, *J. Org. Chem.*). In my opinion, the thesis fulfills the requirements posed on the thesis aimed at obtaining the academic degree Ph.D. I recommend the submitted work as a basis for the defense.

Doc. RNDr. Jan Veselý, Ph.D.