



Doctoral Thesis Review Report

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| PhD student | Miguel Alexandre Gomes Mateus |
| Doctoral Thesis | „Synthesis and Application of Transition Metal Complexes Bearing <i>N</i> -Heterocyclic Carbene Ligands“ |
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Doctoral thesis submitted by Miguel Alexandre Gomes Mateus, Msc. deals with synthesis and application of silver, nickel, and palladium complexes bearing *N*-heterocyclic carbene (NHC) ligands. Initially, the synthetic work led to the preparation of suitable imidazolium salts which can be transformed into carbenes capable of chelating silver(I) cations. The thesis also describes the synthesis of nickel and palladium complexes through the transmetalation of NHC-silver complexes. The prepared complexes were characterized using standard analytical methods, and their conformational stability was studied. Further, a search to use silver, nickel, and palladium complexes in catalysis resulted in several promising applications. Some products of the A³ coupling reaction were utilized for data storage, thereby expanding the range of applications enabled by silver complexes. Finally, the expected antimicrobial activity of silver complexes was evaluated.

The thesis was written in more than 138 pages in a conventional format and is supported by 149 references. The introductory part consists of three main chapters. Firstly, I have to appreciate the comprehensible structure of the thesis, as outlined in the first chapter. The second chapter, State of the art, described the milestones in the development of NHCs, explained intelligibly the classes of NHCs and their electronic and steric properties. Further, the reader was provided with relevant information about other transition metal complexes with NHC ligands, the applications of silver complexes in medicinal chemistry and catalysis, and the use of small molecules in data storage. The standard chapter, aims of the project, clearly defined the goals.



The main part of the thesis, Results and Discussion, began with the proposal of the chelating ligands for silver complexes. Several attempts failed, but the synthesis presented in Scheme 24 (page 35) proved to be viable to get desired imidazolium salts in very good or nearly quantitative yields. This successful synthesis of precursors for NHC ligands cleared the way for the preparation of silver complexes. In addition to the desired chelate complexes **106**, **107**, and **109**, an unprecedented tetranuclear complex **108** with an interesting structure was synthesized. Furthermore, the developed transmetalation method enabled the preparation of nickel and palladium complexes, including some whose syntheses had previously been reported as unsuccessful or with very low yields. The synthesized ligands and complexes were characterized by standard analytical methods such as NMR, X-ray, and HRMS. The key information of the collected analytical data was effectively used in a logical manner to elucidate the structure of the complexes. The PhD candidate demonstrated a good level of knowledge in interpreting complex analytical data, which was also useful in the studies of conformational stability of the prepared nickel and palladium complexes. Figures 20 and 21 clearly convey substantial information by comparing complexes **110** and **111**. Here, I would appreciate to add the numbering of the complexes depicted in Figure 21 to get better reader-friendly information.

The expected antimicrobial activity of silver complexes was confirmed by very good minimal inhibitory concentration values. Although the antimicrobial activity is unequivocally associated with the release of the silver cations, I would suggest showing the structure of silver complexes **106a** and **107a** in this chapter again, as it would be more effective to view the structure and activity on the same page.

The search to identify application in the catalysis for nickel or palladium complexes resulted in one promising application of a nickel complex to catalyze the Michael addition, which was evident from the effort focused on the synthesis of a chiral ligand. Concurrently, the main attention was paid to silver complexes **107a** and **107c**, which were successfully used in A^3 and KA^2 coupling reactions. It was possible to use a catalyst loading of less than 5 mol%. However, important information about molar ratios of the reactants is not obvious from Tables 4 and 5 and Figures 23 and 24. Fortunately, the gram-scale synthesis of compound **150** in Scheme 34 (page 67) indicated an equimolar ratio and the experimental part confirmed this assumption. Moreover, in the case of the KA^2 coupling reaction, it is unclear which conditions were applied from Table 5 to study the reaction scope; only information about the catalyst was provided, while other reaction conditions can be found in the experimental section.



Towards the end of the chapter, Results and Discussion, an interesting application of synthesized propargylamines from the A^3 coupling reaction for data storage was demonstrated. A simple TLC method and software were used to translate information from digital form to 96-well plates and back. The method is attractive because it does not require expensive machinery, and mistakes in the translation process can be corrected.

The chapter, Conclusions, briefly summarized and assessed the experimental results and outlined potential future research directions. The experimental section covered all prepared compounds with procedures and relevant NMR, HRMS, and IR data. However, it would be reasonable to include more details about DFT calculation used to explain the transition state and energy barrier of the configurational flip depicted in Figure 22 (page 50).

The thesis contains some errors and typos. For example, the correct name for the reagent, isothiocyanates, was mistakenly written as isocyanites in Scheme 1 (page 2). Another name, 4-methoxyacetylene (page 65, line 17), was inconveniently abbreviated. Non-systematic nomenclature was used for amines **85** and **86** (page 33), but the structure of reactants was still evident from these names. A classical typo, R-Xay, was overlooked on page 47, line 3. A hydrogen atom located at the pyrazole ring is missing in complex 45 (page 16, Scheme 11). Furthermore, it is desirable to reference Figures 12 and 13 whenever the graphics originate from a published article. I believe, the reference adverting to Figure 18 (the last sentence, the second paragraph, page 47) would be more appropriate for Figure 21. Proper numbering of compounds is important as well. Incorrect numbering was used for product **41** in the text discussing Scheme 10 (page 15). The numbering is inconsistent for boronic acid **114** in the text and Scheme 28 (page 51) and for compound **119** with regard to Scheme 30 (page 52), and two different numbers (**113** and **128**) were assigned to pyrrolidine (Tables 4 and 5, pages 59 and 64). However, the incorrect numbering was not systematic, and it was still possible to follow the presented data. I would also recommend adding numbering for the complexes illustrated in Table 1 (page 41), as I previously suggested for Figure 21. Additionally, some numbers were not formatted in bold (e.g., complexes **106a** and **107a** on page 56). In general, I have to note that the number of errors did not exceed the acceptable level.

Questions

- 1) Several attempts failed to prepare a chiral ligand for the nickel complex used in the Michael addition, as illustrated in Scheme 31 (page 52). Please, have you also considered to follow your successful synthesis of ligand precursors depicted in Scheme 24, but this time using a chiral imidazole? The first synthetic step in Table 2 (page 55) indicates that the synthesis of



imidazole with a chiral substituent is viable. Figure 20 (page 46) shows that these chiral substituents should be in close proximity, which I believe might have an impact on helicity to favour one stereoisomer of the nickel complex. I also understand that you might have abandoned this idea due to the detection of abnormal carbenes during the synthesis of complex **110c**.

- 2) Please, could you disclose more details on the successful start of the optimization of the A3 coupling reaction? Was there any literature precedent?
- 3) Please, could you comment on the drop in yield presented in Entries 6 and 7 compared to Entries 4 and 5 (Table 4, page 59)?
- 4) What was the decisive factor in choosing silver complex **107c** over **107a** for the KA² coupling reaction? Was it only the yield and better isolation conditions? The complexes seem comparable according to Entries 6 and 9 in Table 5 (page 64). The chapter, Results and Discussion, mentioned that complex **107c** was used for the optimization and study of the reaction scope, but it is not clear from the general procedure in the experimental section (page 112) which complex was used.
- 5) What could be the upper limit of the deposited propargylamines in one well you can use for data storage with regard to the TLC method?

In conclusion, it was a pleasure to read this submitted work. The PhD candidate accomplished the aims declared in the thesis. I would highlight the development of the silver catalysts, which broadened the scope of A³ and KA² coupling reactions, as well as the interesting application of propargylamines for data storage. The extensive work of the PhD candidate was communicated in two thesis-related (one submitted recently) and three additional publications in peer-reviewed journals. In my opinion, the thesis fulfils the criteria for a successful defense to obtain the academic degree Ph.D.

Olomouc 21.8.2024

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