**Review of the PhD. Thesis entitled „Synthesis and Application of Helicene-based *N*-Heterocyclic Carbene Ligands" submitted by Ms. Isabel G. Sánchez**

The structure of the Thesis is consistent with that of research papers in the field, ie. individual chapters include Introduction, Aims, Results and discussion, Experimental part and References. According to WoS data, Ms. Sánchez has made a contribution to two experimental publications. Specifically, she is a co-author of a paper in *J. Org. Chem.*, and the first author of another paper in *Chem. Commun.* Since both papers report results that are clearly related to the Thesis, the conditions required by the Czech legislation as well as internal regulations of Charles University have been met.

In general, the Thesis deals with the design and preparation of novel *N*-heterocyclic carbene derivatives based on the chiral helicene scaffold for possible application as ligands in metal catalysis. While the array of *N*-heterocyclic carbenes that have found applications in catalysis is relatively wide, the preparation of their chiral, helicene-based versions has remained underdeveloped. In this regard, the candidate has chosen a demanding topic, since the identification of a novel ligand with the potential to enjoy real applications is rarely a matter of a single dissertation unless he/she is extremely lucky.

The quality and quantity of original research in a demanding area of synthetic manipulation is very good. The strategy used by the candidate was based on the facile assembly of enantiopure oxahelicenes bearing a pendant primary amino group via the venerable [2+2+2] cyclotrimerization of acyclic precursors. The precursors had been obtained by the combination of Sonogashira coupling and Mitsunobu nucleophilic substitution from halophenolic building blocks and readily available chiral propargylic alcohols. The pendant primary amino group then served as the foundation stone for the attachment of an imidazolium ring, the deprotonation of which furnished the desired *N*-heterocyclic carbene.

The candidate prepared several generations of novel *N*-heterocyclic helicene-based carbenes, which were tested as ligands to $Ni^0$ in two model [2+2+2] cyclotrimerizations leading to helical structures. As regards the first generation, Ms. Sánchez found out that NHC ligands generated from the *bis*(oxahelicenyl)imidazolium salts gave much better ee values compared to those obtained from the imidazolium salt precursors with just one oxahelicenyl moiety. Hence, the structures of the former were further varied in the second series, where the relationship between the distance of the stereogenic carbons of the NHC ligands from the imidazolium core and enantioselection was investigated. Not surprisingly, closer distance resulted in somewhat more optimistic ee values. The third series was prepared with the aim of increasing the steric

demands of the oxa[5]helicene-based ligands via the attachment of bulky aryl substituents. These ligands gave good to excellent yields in the model reactions, and enantioselectivity up to a promising 86 per cent. However, going to sterically even more crowded oxa[6]helicene-based scaffolds with an attached aryl (Ph, *bis*-3,5-(*t*-Bu)Ph) did not bring any improvement in the cyclization of model triyne **43**. In fact, the phenyl-substituted compound gave even worse enantioselection than its parent oxa[6]helicene ligand. However disappointing this may be, it is certainly not the fault of the candidate. Whenever structural modifications are used in quest for improvement of selectivity or biological activity, it is not unusual that a plateau level without a sign of improvement is reached. I am therefore wondering about future prospects and possible direction of further modifications of these structures, since, in addition, I also noted that the catalyst loadings used in the screening experiments were relatively high (20 % Ni).

The Thesis is well written in idiomatic English, and logically guides the reader through the strategical and tactical development of the research. There are only few typographical and factual errors and none serious enough to require correction.

Formal points:

1. Nomenclature, whenever amine is the functional goup of the highest priority, its presence should be reflected in the suffix (not prefix). Thus, for example correct name of 2-aminooxa[5]helicene is oxa[5]helicene-2-amine.
2. Page 23, Scheme 25, *bis*-ester **100** is *S*, but the configuration at the centre of chirality is not depicted.

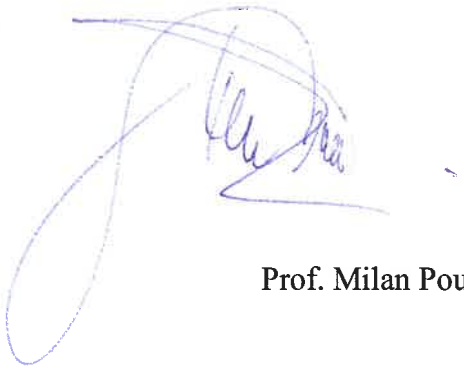
The following points might be raised in a discussion:

1. I am wondering why the conversions of compounds **134** and **135** into *mono*(helicenyl) imidazolium salts **138a** and **139a** proceeded with lower yields compared to the preparation of bis(helicenyl) imidazolium salts.
2. For what reason was chloride **181** functionalized with *bis*-3,5-*tert*-butylphenyl moiety, while the regioisomeric chloride **182** with just an unsubstituted phenyl ring?
3. The last two ligands, **207** and **208**, were probed only in the cyclization of triyne **43** (Table 7, pg 73), but the compound, which had inspired their preparation, oxahelicene **180b**, fared best in the cyclization of triyne **160** (Table 6, pg 63).

In summary, the work makes a substantial contribution to knowledge, shows a good knowledge of the most recent literature, demonstrates the ability to conceive and execute

excellent chemical research, and has then been reasonably well communicated. Therefore it provides evidence that, after a successful defence, the candidate is worthy of unconditional admission to the degree of Doctor of Philosophy.

In Hradec Králové 12. 1. 2021



Prof. Milan Pour