

Referees opinion on the PhD thesis of **MSc. Nikola Topolovčan: Development of new pathways for syntheses of sesquiterpenoids**

The main aim of the dissertation is to develop new on transition metals based methods for the synthesis of fused polycyclic compounds and also to work out new synthetic approach to 1,2-disubstituted cyclopentadienes. Since fused polycycles are part of many naturally occurring compounds and cyclopentadienyl is common ligand in organometallic chemistry these aims are of considerable synthetic interest.

From the formal point of view, the thesis is written by the classical way. In the first section of the thesis author clearly describes zirconocene chemistry and its use in organic synthesis, especially for the synthesis of carbocycles and the applications in total syntheses. Also the reported syntheses and applications of 1,2-disubstituted cyclopentadienes are mentioned. The section “Results and discussion” is divided into four parts. The first part of thesis deals with the synthesis of fused functionalized 5-7-6(aryl) and 6-7-6(aryl) membered ring systems. The approach is based on the sequential formation of zirconacyclopentenes from 1,6- or 1,7-enynes, their reaction with *ortho*-halobenzaldehydes followed by the intramolecular coupling of the sp^2 -Zr bond with the halogen in the pendant chain that should form the required tricyclic system. The first two steps were successful giving predominantly one diastereoisomer of the product, which structure was predicted by stereochemical analysis and by theoretical calculations, and in two cases confirmed by single crystal x-ray analysis. The yields of the third step were rather modest and the product was accompanied by numerous side-products. Mechanism of the formation of the ketone corresponding to the starting compound was studied and elucidated in detail. To overcome these problems, conversion to diiododerivatives and subsequent Pd-catalyzed cyclization was also attempted, however, the yields were not better.

The second part is devoted to the formation of fused 5-8 and 6-8 membered carbocycles. The chosen strategy was based on the formation of bicyclic zirconacyclopentenes, their Cu-mediated bis-allylation followed with ring-closing metathesis. This approach was successful giving the desired compounds mainly in high yields. Only attempts to introduce two different allyl groups by sequential allylation have not been successful. The synthesis has been finally solved by introducing of ethoxycarbonyl group instead of the second allyl group and the subsequent allylation of the corresponding enolate. This allowed the preparation of functionalized carbocycles.

The obtained experience with the synthesis of fused 5-8 and 6-8 membered carbocycles were used to attempt the synthesis of *Asteriscanolide*. The synthesis of the starting enyne, containing the protected terminal alkyne, protected hydroxy and ester groups was not easy and required much effort. However, subsequent formation of zirconacyclopentene was not successful as well as the attempts to form titanacycle using low valent titanium reagents. The last part of the thesis describes new approach to the synthesis of 1,2-disubstituted cyclopentadienes. The synthesis is based on successive haloallylation of internal alkynes, cross-coupling with vinyl organometallics followed by ring-closing metathesis. For that, number of symmetrical, nonsymmetrical, and functionalized internal alkynes were prepared. The Pd-catalyzed bromoallylation afforded the products of *cis*-addition in most cases. The cross-coupling step had to be optimized. Finally, two procedures one employing Suzuki and the second one Stille coupling were developed giving the desired trienes in high yields except of that containing two trifluoromethyl groups. The obtained trienes were smoothly converted to the 1,2-disubstituted cyclopentadienes by ring-closing metathesis using Grubbs I catalyst. Only the preparation of cyclopentadienes containing ester group have failed. Finally, several prepared symmetrical and nonsymmetrical 1,2-disubstituted cyclopentadienes were converted to the corresponding ferrocenes, cyrhetrenes and cymantrenes. The experimental is written as it is common in publications, and new compounds are suitably described, List of references contains 132 references.

In my opinion, the thesis is written carefully, but the language might be better. Like in all theses, it is possible to find typing errors and inaccuracies, some of them are listed below.

Pg. 11: Halogenes cannot be consider as nucleophiles.

Pg. 14, Scheme 2.2.3: Compounds **XX** and **XXI** are not cycloheptene derivatives. The same holds for **XXVI** in Scheme 2.2.4.

Pg. 16, and other places in the text: Should be Negishi reagent not Negishi's.

Pg. 24, Scheme 2.3.1: **LVI** is not arylmetal.

Pg. 42, Scheme 2.4.1: Should be *i*-Pr not *i*-Bu.

Pg. 57: Should be 1,3-disubstituted cyclobutadiene, not *p*-substituted.

Pg 58, Scheme 2. 4. 19: H₂PO₄

Pg. 78, Scheme 2.6.11: Structure **CCCVI** is wrong.

Pg. 87, Table 4.1.1 and other tables: For clarity it would be beneficial to introduce also R. It holds especially in the case when only electronic version of the thesis is available.

Pg. 127, Table 4.4.2: For clarity, it would be beneficial to introduce comment, what are conditions A, B.

Pg. 132, Table 4.4.3: The structure **53k** contains Me instead of Ph.

Nevertheless, the above imperfections do not lower the scientific quality of the thesis of MSc. Nikola Topolovčan, which is in my opinion valuable scientific work. He explored several new approaches to fused carbocycles as well as new synthesis of 1,2-disubstituted cyclopentenes. I appreciate, that he did not focused only to the syntheses of target compounds but he also found time for the elucidation of the mechanism of the unexpected formation of the ketone **13ae**.

I have following question:

In the attempt to obtain bis-allylated product containing two different allyl groups by sequential addition of allyl and crotyl chlorides to the zirconacyclopentene **16a** only homo bisallylated product **20a** was obtained in 45% yield. How can you explain the fact, that when (according to the text on pg 104) 1.0 equivalent of allyl chloride was used in the first step and the mono-allylated product was formed quantitatively?

Nikola Topolovčan proved that he is a good synthetic chemist with the broad practical and theoretical knowledge and he is able of an independent scientific work. This can be documented by the fact, that the obtained results have been already published in three respected scientific journals. Therefore, **I recommend** his thesis for further processing **to obtain PhD degree**.

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