UNIVERSITY OF CHEMISTRY AND TECHNOLOGY, PRAGUE
Faculty of Chemical Technology
Department of Organic Chemistry

Expert opinion on Ph.D. thesis entitled: "The combination of organometallic, transition-metal catalyzed, radical and carbocationic reaction steps to domino processes"

The Ph.D. thesis submitted is focused on the development of novel domino processes for the synthesis of carbocyclic compounds. As per usual, the dissertation is divided into several parts (*Introduction*, *Aim of the Work*, *Results and Discussion*, *Summary*, *Experimental part*, *References*, *Appendix A–C*, and *Publications and Conferences*). The *Introduction* (24 pages) describes general terms and concepts that include cascade reaction, formation of enolates, SET tandem reaction and synthesis of lignans. The *Results and Discussion* consists of the most important part of the thesis (44 pages). Initially, starting dienes were prepared by Knoevenagel condensation, α-selenation/selenoxide elimination and cross-metathesis. Next, detailed results on tandem carbocyclization are presented along with mechanistic proposals. Then prepared carbocycles were modified under reductive or oxidative conditions. The *Results and Discussion* section ends with a discussion of the synthesis of lignans.

Overall, the formal level of the thesis fulfils general requirements. Basic terms and concepts are well explained in the introduction. Aims of the work are clearly defined. The thesis has outstanding performance in terms of accomplished experimental results. Schemes and tables are arranged in fashion typical for professional communication. All results and arising conclusions are logically and sufficiently formulated.

On the other hand, some inconsistencies can be found while reading the text. Surprisingly, no *E*/*Z* or *ee* ratio is provided during the preparation of starting alkenes (eg. scheme 3.8, 3.13). The compound **3-22g** (scheme 3.10) was prepared as a mixture of *E*/*Z* isomer, but no discussion of isomerization is provided. In some cases, several mechanistic routes for formation of products (eg. scheme 3.9) are described, but detailed explanations of predominant path are missing. The presentation of LAH reduction of 1,4-diketones and mechanistic course (schemes 3.31,3.32) is misleading because the substitution of aryls is not shown and substituents are appearing/disappearing depending on author's need.

The experimental part is well assembled but in rare cases important data are not provided (eg. compounds **3-22a**,**c–f** do not have ^{1}H NMR spectra). In my opinion, it will be difficult to repeat the preparation of compound **3-53v** (page 144) according to the general procedures outlined on page 101 because the general procedure does not cover aliphatic substrates.

The thesis contains minimal grammatical and typographical errors. Here are some examples:

Acknowledgements, line 8: Vaclav Chmela – Václav Chmela

Page 8, figure 1.4: the structure **1-20** does not represent the structure of (*S*)-ketorolac

Page 196: reference 55 should be: M. Holan, R. Pohl, I. Císařová, B. Klepetářová, P. G. Jones, U. Jahn *Chem. Eur. J.* **2015**, *21*, 9877-9888.

Page 14, line 18: Fenton reaction reported in 18th century – Fenton reaction reported in 19th century

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Page 15, the structure of Frémy's salt (**1-56**) is not correct
Page 20, figure 1.6: (–)-Maoecrystal v – (–)-Maoecrystal V
Page 21, line 9: hydroxyltion – hydroxylation
Page 28, line 9: prov to – prove to
Page 34, line 24: nucleophile.This – nucleophile. This
Page 45, line 10: 4-methoxybenzyl bromide – 4-methoxybromobenzene
Page 45, line 11: 2,4,6-trimethybromombenzene – 2,4,6-trimethylbromobenzene
Page 52, scheme 3.20: Selectivity Rationalization – Selectivity rationalization
Page 69, line 2: aryl-1,2-diol – arylpropan-1,2-diol

The following questions arose while reading this document:
1. *t*Buli was used for the preparation of aryllithium reagents but Br/Li exchange reaction can be also carried out with 1 equiv. of *n*BuLi. Why was the *t*BuLi used for lithiation of arylbromides?
2. Attempts to prepare compounds **3-76a** and **3-76b** (scheme 3.30) using 1) LAH reduction and 2) MsCl, TEA cyclization failed, giving **3-77** as major product in only 40% yield. What were the other products isolated from/or detected in the reaction mixture?
3. I do not understand the statement (page 71, line 1): "All the results prove that, formation of trimethylsilyl enol ether **3-82a** and **3-85** takes place at faster rate in a one-pot reaction …" because I do not see any clear evidence that the silylation in a one-pot reaction proceeds faster. Could you also comment on the low yield of phosphate **3-84** (25%, scheme 3.35)? Usually, preparation of disubstituted enolphosphates via enolization–phosphorylation sequence is high yielding.
4. The formation of carbocycles **3-53** (scheme 3.18) by a tandem reaction proceeds with good diastereoselectivity only in case of aryllithium reagents. When butyllithium was used, radical cyclization afforded cyclopentane derivative **3-53v** without any diastereoselectivity. Do you have any indications why there is no diastereoselectivity in the case of aliphatic substrate?

Let me conclude the report by saying that the presented Ph.D. thesis is a collection of high quality original results. The aims of the thesis were reached, and part of the results have already been published in a peer-reviewed journal (*Chem. Eur. J.*). Therefore, I recommend accepting this Ph.D. thesis as the basis for defending the Ph.D academic degree.

In Prague 11. 1. 2017

doc. Ing. Tomáš Tobrman, Ph.D.

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