

Review Assessment of the PhD Thesis Entitled “The Combination of Organometallic, Transition-Metal Catalyzed, Radical and Carbocationic Reaction Steps to Domino Processes by Pratap Rampling Jagtap.

The doctoral work of P. R. Jagtap focuses on developing new tandem processes. Several reaction procedures leading to variety of target molecules were investigated. The thesis consist of a theoretical part (here unusually named as Introduction), which provides the reader with the fundamental aspects of cascade reactions and further focuses on the particular investigated procedures. The candidate further set the main Aims of the work, the largest chapter includes Results and Discussion terminated with Summary and followed by Experimental Part, References, and Appendix. Hence, the text is organized more or less as usual, well-written, completed with suitable illustrations and schemes and provides the reader with the current state of the art in the given field.

The work targets current and interesting topic, which is in accordance with the research activities of the candidate’s supervisor. The outcomes of this thesis were already published in one article in *Chem. Eur. J.* (2014) where the candidate acts as the first author. Since the doctoral studies were pursued from 2009 and despite the candidate claimed that two additional manuscripts are under preparation, I consider one finalized publication as insufficient. However, this depends on the rules applied at the Charles University.

Considering the formal and typographical aspects of the work, I have the following comments and recommendations:

1. The numbering of compounds is very confusing! I do not understand what or who forced the candidate to create such lunatic combination of numbers instead of simple linear extension 1, 2, 3, 4... The author’s numbering combines the chapter and the compound numbers, e.g. **1-7**. However, the candidate went even further and combines with small letters (e.g. **3-32a-c**), capitalized letters (e.g. **1-7A**, **1-7B**), stereochemical descriptors (**1-32Z**), use primed (e.g. **3-22g’** or **3-22g’’**), and finally also roman numerals (e.g. **I – XII**).
2. A short and non-informative last chapter on Antiviral Activity looks like a *deus ex machina*. There is no discussion addressing and rationalizing the testing, structure-property relationships elucidation or any comments on the data (reader is just referred to Appendix A, which contains a Table and description of the experiment).
3. Locants and stereochemical descriptors are inseparable parts of the chemical names and should not remain standing alone on the previous row (e.g. 1,4-diketone; (+)-; α,β -; *N*-; η^2 - and many others).
4. A row should not be terminated by a preposition.
5. *Iso* is written in italic.
6. In Scheme 1.8, the meaning of “s” is not explained (most likely solvent).

7. *p*-Cymene should read *p*-Cymene. According to IUPAC, *ortho*-, *meta*-, and *para*-locants should not be used anymore (see also the Experimental Part).
8. No enantiomeric excesses are given in Scheme 3.13 for the products of allylic substitution.
9. Compound **3-50b** is not 4-methoxybenzyl bromide but rather 4-methoxyphenyl bromide/1-bromo-4-methoxybenzene (p. 45).

I have also the following questions that should be addressed by the candidate during the defense:

1. Table 2, p. 27-28: The effect of the solvent replacement (THF vs. DME) is disputable. A clear trend of the reaction acceleration upon heating has been observed. Whereas the reactions in THF were carried out at 67 °C, in DME the temperature was elevated to 85 °C. Hence, the increased reaction rate is rather caused by the higher temperature?
2. The effect of an additional ligand (trimethyl phosphite or triphenylphosphine) and its amount are not clear to me. Could the candidate comment on it?
3. Scheme 3.4., p. 34: Knoevenagel reaction generally works well and provides the product in good to excellent yields. Why the author tested only Lehnert's reagent? This is considered as very harsh reagent generally used for inactive aldehydes and ketones (e.g. anthraquinones, see for instance *Eur. J. Org. Chem.* **2008**, 994). Did candidate attempt also milder conditions, for instance Al₂O₃/DCM system?
4. Scheme 3.15, p. 44-45: Where the asymmetric induction of the formed stereogenic centers comes from? Why compounds **3-53e-f** were prepared with opposite *syn/anti* ratio?
5. Scheme 3.15, p. 44: A selection of the substituted bromoaromates used as starting materials in the tandem reaction is not clear. Why only methyl and methoxy substituents were screened?
6. Scheme 3.16, p. 47: Would be possible to induce/terminate radicals in tandem processes, e.g. **3-61**, in a different way than using TEMPO or are these transformations to **3-53** spontaneous?
7. Scheme 3.22, p. 54: Were the alcohols formed upon N-O bond cleavage isolated or underwent direct lactonization?
8. Table 4, p. 60-61: Electron donating/withdrawing substituents in starting phenones **3-72a-g** affected the yield of the dimerization. How do they affect the reaction course?
9. p. 60: What was the product of decomposition/cyclization of diketone **3-69y** during purification by column chromatography?

The dissertation of P. R. Jagtap is certainly a very interesting contribution to the field of domino reactions. The candidate has developed very interesting methodologies and has prepared admirable number of new compounds (according to the Experimental Part). In fact, all aims were fulfilled. The aforementioned comments and questions rather reflect my interest during reading the work.

Provided the candidate will properly address all of my questions during defense, I

recommend

the Ph.D. thesis of Pratap Ramling Jagtap to be defended at the Faculty of Science, Charles University in Prague. Based on the successful defense I also

propose to award Pratap Ramling Jagtap academic title “philosophiae doctor, Ph.D.”.

In Pardubice, 14. 1. 2017.

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