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Prague, 20.05.2019

**Review of the Habilitation Thesis "Sulfur-based methodologies in the context of olefination and diversity-oriented synthetic methods"**

**Presented by RNDr. Jiří Pospíšil, Ph.D.**

**to the Faculty of Natural Sciences, Univerzita Palackého v Olomouci**

Dr. Pospisil presents a habilitation thesis that is based on his work in the Marko group and independent work, both performed at Université catholique de Louvain (Belgium, 2002-2006,2008-2012) as well as work at Palacký University Olomouc starting from 2012 until the present time. The habilitation work originates from his PhD studies on the development and application of the Julia olefination and its variants to the total synthesis of natural products. A part of these results has been included in the habilitation thesis and serves as a basis for the independent work during the second period in Louvain, which switches focus from strong total synthesis aspects to detailed mechanistic investigations of the widely used Julia-Kocienski olefination. After starting the next career step at Olomouc, the second large part of the thesis, the development of strategies toward diversity-oriented synthesis is introduced as a second leg of the major research interests. Both parts have been quite fruitful and a total of 12 publications forms the basis for the current thesis. In 2018 even more publications appeared in the context of this research.

Much work has been devoted to increase the substrate scope of several Julia olefination variants, notable are the sulfoxide-based variant and the method leading to allylic alcohol derivatives. The mechanistic investigations revealed many important factors that contribute to the outcome of Julia-type olefinations with respect to reaction efficacy and stereoselectivity and a consistent framework for performing them with best possible results has been laid out. Transition state models have been developed that allow prediction of reaction outcomes. A special value of the thesis is that the author tackled higher than 1,2-disubstituted alkenes and provided solutions for their selective synthesis. The aim for stereochemical diversity obtaining both, (E)- or (Z)-olefins electively, was also accomplished.

The second part of the thesis provides a different angle at sulfone-based methodology, namely to use them for the generation of diversity. The author introduces the concept and different approaches to accomplish the generation of scaffold diversity. The author aimed for an extension of the build-couple-pair strategy, in that a CORE structure serves as basis for attaching diverse fragments, which result in a parent molecule results after the build and couple stages, from which diversity can be introduced by a variety of reagents or their combinations. The author chose 2-(alkylsulfonyl)benzothiazoles as the CORE fragment, which were coupled by acylation reactions. The resulting β-keto sulfone parent molecules subsequently served in the pair phase for access to diverse ketones, esters, olefins or alkynes by various reagents.

A few fundamental scientific questions remain after reading the thesis that the candidate may address at a suitable occasion:

1) The habilitation thesis should of course be concise and concentrate on the achieved results, however they should also be critically discussed and judged in the bigger picture of organic chemistry. Here I miss a critical comparison of ylide or carbanion-based olefination methods developed by the author with the more recently and partly in parallel established new olefination strategies, ranging from metathesis (Two Nobel prizes), where a long-standing problem concerning the stereoselectivity of product formation existed, which however now becomes more and more solved with respect to (E)- or (Z)-selective methodology, up to carbonyl-olefin metathesis (Schindler et al. Nature 2016 and following publications).

2) Diversity oriented synthesis is a tool in drug discovery as the author correctly states. While the author indeed accomplishes generating scaffold diversity, none of the synthesized materials actually possesses drug-like properties. All products are small molecules falling out of the typically considered parameters typically proposed for drug-like molecules. Moreover, all compounds are linear, have no elements of stereocomplexity and most importantly have their largest complexity at the stage of the parent molecule, which is later lost again in the pair steps, which is also true for the most "drug-like" element, the benzothiazole ring. It is recognized that the author is here rather at the beginning of his investigations, but he may outline, how the strategy should be implemented beyond the proof-of-concept results into the drug-discovery process meeting the aims of diversity-oriented synthesis?

A habilitation should also have a high didactic value, since it will circle among students of the group for inspiration in their projects and colleagues for getting a shortcut into the field for quite some time. Even that it did not take too much effort to read the thesis for me, I see here shortcomings. Despite that the author provides an argument against perfection right away in the one but last quote of the acknowledgements, the thesis should be factually correct without large redundancies and provide all information in an easily understandable and organized way. Especially the latter is sometimes not given. This becomes very apparent in the discussion of the mechanisms on pages 19-21, where linking of text and scheme 12 and figure 4 is weak and the reader is basically left alone to make something out of table 3 and scheme 13. Much of this part is enlightened only much later when Scheme 12 is in large parts repeated as Scheme 28 and Scheme 30 and only then better explained. A less experienced student will certainly be lost in the treatment. Thus, a generally more audience-directed effort is strongly advised. Terms should also be properly used. Especially, in the discussion of transitions states correct terms are mandatory. The author uses several times the term "eclipsing interactions". Inspection of presented transition states cis-2-55, cis 2-132 or structure cis-2-47, cis 2-133 (Scheme 12, Scheme 28, Scheme 30) reveals, however, that the projections show staggered conformations and the substituents are in gauche orientation to each other, but not eclips(ed)(ing)!

Despite these formal shortcomings Dr. Pospiíšil provided a valuable habilitation thesis. He convincingly showed his ability to independently perform and direct valuable organic chemistry research. Since he is also active in several other organic chemistry fields, which have not been the topic of the here presented thesis, Dr. Pospiíšil demonstrates in perspective his ability to develop quality research projects and provide high quality results, which have impact in the field.

In summary, the by Dr. Pospiíšil submitted thesis fulfills all criteria and I recommend to accept it for further proceeding in the habilitation process.

For further information, please, do not hesitate to contact me.

Best regards

(Ullrich Jahn)