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Review of Mgr. Alexander Fadeev's PhD Thesis: "Catalytic and photochemical cycloadditions of alkynes"

The submitted PhD thesis of Mgr. Alexander Fadeev is focused on the search for new synthetic approaches that use alkynes for cycloaddition reactions catalyzed by transition metals or photocatalysis.

First, a new chemo- and regioselective fully intermolecular [2+2+2]co-cyclootrimerization of internal alkynes with various alkynyl boronates via Ru catalysis was developed and its mechanism was investigated in collaboration with Dr. Gabriele Manca by DFT calculations.

Using this synthetic approach, a total of sixteen 1,4-diborylated benzenes were prepared. Some of these derivatives were then used for subsequent transformations (such as hydrolysis, Suzuki-Miyaura cross-coupling reaction, and various oxidation reactions). In addition, the developed method was used for the preparation of natural bioactive compounds such as mirandamycin, violaceoid C, and alboatrin analogues. The next work was devoted to the photochemical [2+2] cycloaddition reaction of variously substituted quinones with alkynes. In this case, this photocycloaddition was found to be highly chemo- and regioselective for selected derivatives and the corresponding cycloaddition derivatives could be obtained in good yields by simple irradiation of the reactants with blue light under air atmosphere. In this way, some highly reactive *p*-quinone methides as well as annulated cyclobutenes were prepared. It was further confirmed that the prepared *p*-quinone methides can be used for subsequent transformations with different nucleophiles to the corresponding *p*-hydroxyaryl ketones.

Formally, the dissertation is very well prepared. The thesis is written on 154 pages. The "State of the Art" part gives a good introduction to the studied problem of cycloaddition reactions of alkynes. It is sufficiently comprehensive and well elaborated with a minimum number of errors. The text is readable and logically organized. The experimental part and processing of experimental data are at a high level.

I have the following comments regarding the formal aspects of this PhD thesis:

1. The cumulative numbering for various compounds in the "State of the Art" chapter is inaccurate. Each compound should be assigned its own unique number. This issue is particularly misleading in specific examples, such as **Schemes 10, 41, and 53**. In these examples, various differently disubstituted alkynes (**22, 161, and 196**) are employed. Unfortunately, in these cases, the regioselectivity of these reactions and the structures of the resulting compounds (**25, 162, and 198**) cannot be discerned.
2. In **Scheme 21**, only the (*S*)-enantiomer **69** is intended to be formed. However, the depiction of compound **69** is inaccurate, and the location of the substituent R₁ is unclear.
3. In **Schemes 7 and 18**, R₃ is not defined.
4. In **Scheme 33**, products **116a-d** are formed. However, the regioselectivity of these reactions is not readily discernible from the scheme.

5. Regarding **Scheme 79** and **Table 8**, was compound **241a** formed as a mixture of regioisomers?
6. In the Experimental Part, it is unclear why the optical rotation was not measured for chiral molecules.

I have the following questions regarding the content of this PhD thesis:

1. **Scheme 69**: In this case, compound **226b** was synthesized as a mixture of diastereomers. Was compound **269b** also obtained as racemate?
2. **Schemes 72** and **73**: Was the reaction in the preparation of compound **232** enantioselective, or was compound **232** formed as a racemate? How can the formation of compound **239** as a mixture of diastereomers in a 3:2 ratio be explained?
3. In **Scheme 81** and **82** were prepared compounds **242a-i**. Were they obtained as a mixture of enantiomers? Additionally, do you have information on the enantiomeric excess for these compounds?
4. Chapter "Synthesis of cyclobutenes via the carbocycloaddition pathway": Cyclobutenes **241a-n** were synthesized, forming new chiral centers. Unfortunately, the author does not thoroughly discuss this aspect. Can the absolute or relative configuration be determined for some compounds? Could the author clarify whether this reaction was enantioselective and present analytical methods for solving this issue?
5. In the Experimental part, what should be the correct name of compound **241c** to express the configuration found at the chiral centers?

Finally, I would like to emphasize that the submitted dissertation is of a very high professional and formal level. It presents original results that have already been published in two established chemical journals during the study. In addition, the candidate is co-author of next three other publications. Therefore, I recommend that the dissertation of Mgr. Alexander Fadeev **be accepted for defense** as evidence for the degree of Ph.D.



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