
The thesis submitted by Pravinkumar Hansraj Mohite deals with synthesis of chiral benzo[d]imidazoles using amino acids as a source of chirality and their application as organocatalysts of stereoselective aldol type reactions.

Introductory part contains definition of aims of the thesis. In the theoretical part consisting of 8 chapters, synthetic approaches towards benzo[d]imidazoles and benzo[d]oxazoles are reviewed with the special focus to possible incorporation of an amino acid into the molecule of heterocycle. This relatively detailed review is accompanied by introduction to chemistry of amino acids, benzo[d]imidazoles and benzo[d]oxazoles including their biological properties. Finally modern applications of these heterocycles, namely in organocatalysis and in transition metal catalysis, are summarized. The next chapter contains experimental part. This location is not typical but it is possible. Nevertheless, for this type of work, Experimental located at the end of the thesis is more suitable as it does not disturb main story. In experimental, all procedures are clearly described, new compounds are adequately characterized by melting point, $^1$H and $^{13}$C NMR spectra and by elemental analysis or, alternatively by HR-MS which is usually acceptable in combination with clean $^{13}$C NMR spectra accompanying the work. These can be found in Supplement together with $^1$H NMR spectra, mass spectra and HPLC chromatograms.

Main part of the thesis is relatively short (20 pages), on the other hand it clearly comments the obtained results. In the first subchapter, design of benzo[d]imidazoles prepared in the thesis is explained in relation with previous studies in the group of supervisor. In the next part, synthesis and spectral characteristics are commented for the chiral catalysts. Finally, prove of efficiency of the prepared organocatalysts is presented on model substrates showing moderate enantioselectivities and good diastereoselectivities with 4-nitrobenzaldehyde and modest enantioselectivities with isatin which is justified by the proposed mechanism. The results are summarized in conclusion part.

The thesis is clearly written nevertheless it contains some typing errors and misspellings (see other comments). The text is logically constructed and sufficiently accompanied with graphical material. Style of presentation is on good level. Schemes, Figures and other illustrations meet standard criteria of publishing in the area of organic chemistry. The results were published in the form of one short communication and one full paper in impacted journals Synthetic Letters and Synthesis.

There are some comments and recommendations which should be addressed within the defense:

1. Branching of the substituent on the carbon next the stereogenic centre of amines seems to be crucial for enhanced stereoselectivity of aldol reactions. On the basis
of this conclusion, one should expect benzo[d]imidazole derived from tert-leucine could be the catalyst of choice. Have author tried to prepare this compound? Can author discuss the reactivity (even if it is only hypothetical) of such catalyst?

2. What is the role of benzene ring in benzoic acid found to be the best proton source? Could be positive effect of benzoic acid on the reaction even improved by its derivatization? Which group expect author to be suitable? Notably 4-nitrobenzoic acid is often used in both organocatalysis and transition metal catalysis.

Other comments:

In general procedure towards compounds 58, pH adjustment is not mentioned. However free bases are isolated from the solution containing an excess of trifluoroacetic acid. Is there any explanation?

How accurate is enantioselectivity calculated from HPLC analysis of compound 58g (pages 64 and 108). In this case, peaks in chromatogram are not fully separated.

Compounds numbers should be in parenthesis when full names are presented (e.g. page 18 or in Experimental)

Stereodescriptors D- and L- should be written by small capitals.

At least steps important for benzoimidazol formation should be shown in Scheme 13. Ten steps summarized in one are not too illustrative.

Cyclohexanone instead of acetone should be given in the caption to Table 15.

Selected typing errors: use of pKₐ instead of pKa is recommended (page 10), ethyl chloroformate should be used instead of of ethyl chloroformate (page 19), HOBT should be used instead of HOBT (page 19), α-ribazole is better than alpha-ribazole (page 36), phenole should be phenol (many places).

**Evaluation:**

In conclusion, I would like to note, that most presented comments are rather marginal. The results of the thesis are original and with significant scientific value. Student demonstrated ability to work independently in the area of organic chemistry. Therefore I recommend PhD. **thesis to be accepted** and doctoral degree to be awarded to author after successful defence.

Prague, November 30th 2016

Assoc. prof. Radek Cibulka, Ph.D.
Department of Organic Chemistry
University of Chemistry and Technology, Prague
Dr hab. Jarosław Romański, Associate Prof.

Review

on the PhD Thesis entitled

"Utilization of α-amino acids in the synthesis of nitrogen heterocycles"

by MSc. Pravinkumar Hansraj Mohite (University of Pardubice, Czech Republic)

The presented for review PhD thesis was prepared by the Candidate under supervision of Professor Filip Bureš, who is well known specialist in the field of synthesis and application studies on optically active organic compounds as well as organic material chemistry.

Submitted for review PhD Thesis of MSc. Pravinkumar Hansraj Mohite consists of 4 main parts (76 pages). In particular, the introduction with literature part (34 pages) contains the recent developments in the presented field of study, experimental part (18 pages) - description of procedures and spectral data; results and discussion part (19 pages) - comments and remarks of results and final conclusions; and cited literature (5 pages with 76 references). Moreover, in 'Attachment' part (35 pages) author add supplementary data with a series of reprints of NMR-, MS-spectra and HPLC chromatograms. In my opinion this part should rather be named as 'Supporting Information' or 'Annex'.

The literature part clearly outlined aims of the research and concise summary of characterization, synthetic methods and application of benzo[d]imidazoles and additionally, for comparison, benzo[d]oxazoles. This part helps the reader to get insight into recent problems related to the chemistry of described compounds. However, it is necessary to notice that in this part there are a few deficiencies. On
page 10 in point 4 Candidate point out that 'selected asymmetric reactions' will be examined, but only one aldol reaction was used as a model process. The Figure 3 show the structure of benzo[d]imidazole where the electron pair is out of the imidazole ring which indicates basic character of this nitrogen atom and, of course is not true, because this electron pair must be placed inside the ring in order to underline the aromaticity of a compound. In organic chemistry the electron pairs play a very significant role and it is highly important to add in all structures (Scheme 1, Fig. 4 and many others) and the position of electron pair also shows the character of molecule. On the page 14 author write 'isoelectric point at which is in neutral/zwitterionic form (insoluble).’ which I do not understand, especially the term ‘(insoluble)’. It should be explained that at this point that the equilibrium between ‘zwitterionic’ and ‘neutral’ form shows mostly ionic form but neutral form is only a minor. On the page 18 the Candidate express that ‘compounds 12 and 13 in poor yields of 32 and 51 %' but in his reactions the overall yields are lower (see page 61, Table 11 and further comment).

The classical form of experimental part contains the details of all requested procedures for preparation of starting materials and desired compounds. All compounds are described according to the standard protocols. However, instead 'white solid' I preferred to use 'colorless solid'.

The most important part of the PhD thesis is 'Results and discussion' which summarized the scientific research of the Candidate. MSc. Mohite focused on the synthesis of ligands/organocatalysts based mainly on the natural L-amino acids in which the reader can find the description of synthesis of benzoimidazoles derivatives and their usage in the aldol reaction. In the introduction for this part on the page 57, author repeated the Fig. 9 and give a new number Fig. 21 which was not necessary. In the case of preparation of benzo[d]imidazoles derived from amino acids the alternative sequence of reactions is well documented, however author in the Table 11 will not give the overall yields, which are not very impressive (approx. 15-20%). In comparison the direct reaction of amino acid with o-phenylenediamine (method I)
gives better result. The usefulness of obtained ligands in the aldol condensation was described in the next chapters. In the first example, the acetone and p-nitrobenzaldehyde were used for the reaction in the presence of 9 mol% ligand. For comparison the results of Vincent (ref. 37) is cited, however Candidate will not give yields and enentiooneric excess described in this paper. There is also no explanation why the 9 mol%, not as usually 10 mol% of ligand was used for this reaction (in the reaction with isatin is again 10 mol%). The reaction with cyclohexanone gives the mixture of diastereoisomers which are well described, however in Table 13 only syn:anti or de could be presented to describe the ratio of isomers. On the page 69 in the sentence ‘reaction of isatin with acetone using 10 % of dipeptide’ the 10 mol% should be used. Additionally, I do not understand the sentence ‘Such standard condition allowed investigation of the structure-catalytic activity’ what does it mean ‘structure-catalytic activity’, and it should be explained in details.

The proposed mechanism, supported by Kočovský’s theoretical calculations (ref. 46) is reasonable and can explain the enantiomorphic excess in the reaction with acetone. However, there is almost no deeper comment for the reaction performed with cyclohexanone and what means the sentence ‘This most likely accounts for the low stereochemical performance of this derivative.’ In addition, it is not logic to describe the reaction concerning cyclohexanone after the discussion of the mechanism of the reaction. The Candidate has tried to find an appropriate catalyst (ligand) the one model asymmetric aldol reaction and in this case the results are good, however I recommend further in-depth investigation and use obtained benzoimidazoles in other reactions such as, Henry nitroaldol condensation or diethylzinc addition. Therefore, there is a still open space in order to design and prepare the best catalyst for enantioselective synthesis. In conclusion, on the end of this part of PhD Thesis, the Candidate clearly summarized his achievements using adequate spectroscopic and analytical methods.

In the general scope the English language could be more fluent. In details, the expression ‘with yield(s)’ is repeated many times but in English it should be given ‘in
yield(s); page 68 'motive' should be changed into 'motif'; page 69 what author means to use 'operational method' which is not clear for me, etc. There are also a few editorial errors and one is important. The numbering of compounds which is used in the schemes should be used in the text (see e.g., Conclusions). Other mistakes are less important.

It is important to mention, that the major part of the work performed by the Candidate has already been published in two full papers in peer-reviewed journals Synlett (2014) and Synthesis (2016, accepted).

In summary, the work presented in the PhD Thesis of MSc. Pravinkumar Hansraj Mohite can be treated as a well done contribution for better understanding of action of nitrogen-containing heterocycles used as catalysts. Collected results are important not only from the point of view of fundamental characteristics of this class of heterocycles but also enables the chemists better understanding the influence of the structural factor, especially in the scope of asymmetric synthesis.

Despite my comments and remarks in my opinion, the reviewed PhD Thesis fulfils requirements expected for a scientific elaboration, which should be considered as a adequate base for graduation with doctor title in chemistry at University of Pardubice and opens the way to the planned defense. The Candidate is recommended to admit the 'PhD defense' regarding to applicable rules, which planned for a end of the year 2016.

/J. Romański/

Łódź, December 1st, 2016