MARIA CURIE-SKŁODOWSKA UNIVERSITY IN LUBLIN

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REVIEW

of doctoral thesis of Joseph Daniel Gbubele, M.Eng., entitled "Asymmetric synthesis of α-substituted phosphonates and phosphonic acids via hydrophosphonylation of substrates containing carbon-heteroatom bond with TADDOL-derived H-phosphonate", performed at the Department of Physical and Quantum Chemistry, Faculty of Chemistry, Wrocław University of Science and Technology under the supervision of Tomasz K. Olszewski, D.Sc.

For many years, organophosphorus compounds have been the target of scientific research by many research teams. This is due to the quite specific features of the phosphorus atom, which is capable of forming many types of bonds with carbon, oxygen, sulfur or nitrogen, as well as its ability to exist in two oxidation states (III) and (V). As a result, many classes of organophosphorus compounds are currently known, and continuous research leads to the discovery of newer combinations that are used not only in scientific research but also in commercial applications. The latter include their use as flame retardants and antioxidants in plastics, low compressibility fluids, friction-reducing additives in metal processing and mining, or initiators of radical reactions.

On the other hand, many organophosphorus compounds turned out to have interesting biological properties, especially those having an additional functional group in the molecule, most often hydroxyl or amine. Aminophosphonic acids, due to their similarity to amino acids, can act as mimetics, and the presence of the $P(O)(OH)_2$ residue, which differs from the carboxyl group in both structure (flat vs. tetrahedral structure) and electronic properties (different pKa values), has a large impact on the ability of this type of compounds to influence key processes occurring in biological systems. This is evidenced by fosfomycin, tenofovir, glyphosate and glufosinate, which have biocidal properties.

The structure of α-aminophosphonic acids, isosteric to α-amino acids, indicates that they may have a special type of isomerism, called stereoisomerism, which results in the existence of enantiomers due to the presence of a stereogenic center on the α carbon atom. When conducting research in biological systems, it is extremely important to work with compounds with precisely defined geometry, which in the case of enantiomers/diastereomers means working with single isomers. Therefore, in the case of α-aminophosphonic acids and their derivatives, it is important to develop convenient synthetic methods that would allow the synthesis of enantiomerically pure compounds on an appropriate scale. For this reason, it can therefore be concluded that the topic Mr. Gbubele was intended to develop, based on the development of the synthesis of chiral α-aminophosphonic acids using an easily available chiral auxiliary, such as TADDOL, is important from the application point of view and up-to-date due to the constant need to obtain new chiral compounds for their applications in biological systems.

The reviewed doctoral dissertation is prepared in a classic way, including an introduction, a literature part, a description and discussion of experimental data and an experimental part. In the literature part, the candidate presented a historical outline in the synthesis and characterization of this type of compounds, then conducted a discussion on the importance of aminophosphonic acids in biological systems, describing known cases of compounds with antimicrobial and antiviral activity. The next section presents examples of the use of this type of compounds as plant protection products, with particular emphasis on glyphosate and its safer analogues.

In the next chapter, Mr. Gbubele presented a literature outline regarding methods of synthesizing C-chiral α-substituted phosphonates using the Abramov, Kabachnik-Fields or Pudovik reactions, pointing to possible solutions. One

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of which was discussed in detail based on the use of chiral auxiliaries derived from easily available raw materials of natural or synthetic origin. The candidate then focused on the discussion of examples of the applications of three chiral auxiliaries: TADDOL, BINOL and menthol, which were used to synthesize chiral organophosphorus compounds subsequently used in C-P bond formation reactions. In the case of secondary phosphites based on TADDOL, Mr. Gbubele discussed its use in stereoselective Michael addition reactions, addition to *N*-functionalized imines and addition to carbonyl compounds. In the case of chiral organophosphorus compounds based on BINOL, Mr. Gbubele discussed examples related to the addition of a P(O)H-type compound to thiazolines or hydrazones and the conjugated addition to enynes substituted with a pyridyl group. Other applications included the derivatives of seleno and diselenephosphoric acid, which were used in radical alkylation reactions or reactions with organometallic reagents. In the case of organophosphorus compounds with an incorporated menthyl fragment, the candidate discussed the use of three classes of compounds: di-L-menthyl phosphite, L-mentyl phenylphosphonate and phenyl-L-menthylphosphine oxide, the preparation of which was developed by other research teams. In the case of these compounds, Michael addition reactions, nucleophilic substitution of MBH adducts, addition to nitriles and imines, and addition to carbonyl compounds were presented and discussed.

To sum up this part of the dissertation, it can be stated that the PhD student clearly presented the main theses of his doctoral dissertation, carefully discussed the current knowledge on the use of organophosphorus compounds with a built-in chiral auxiliary in the synthesis of chiral α-functionalized organophosphorus compounds and presented the advantages and disadvantages of using each of the discussed chiral auxiliaries.

As a conclusion to this part of the doctoral thesis, I had a few questions and comments to which I would like to draw attention and ask the candidate to present his comment.

1. On pages 19 and 20, the Michael addition of a P(O)H compound with various Michael acceptors is discussed. What is interesting here, is the different absolute configuration of the newly created chiral center. The differences in the structure of the substrates are not large enough to have such a dramatic impact on the configuration. I would like to ask the candidate for his opinion here.
2. On page 21, lines 30-31, the candidate writes about an extremely reactive adduct between an organozinc compound and an organophosphorus compound. It seems to me that the zinc salt is a rather soft and therefore mild nucleophile due to the small difference in the electronegativity of both elements and the addition of TMEDA serves only to increase the solubility of this salt.
3. On page 22, lines 14-16, it is pointed out that the use of the opposite enantiomer of *N*-sulfinylimine resulted in a deterioration of the selectivity of the addition reaction. Please explain the reasons for this phenomenon.
4. On page 27, lines 15-20, the transesterification phenomenon is describes which occurs in the case of an organophosphorus compound based on BINOL. This observation is explained by the instability of the ring. Maybe the reason is simply that phenolate is a better leaving group and therefore undergoes nucleophilic substitution?
5. On page 32, Scheme 21, two alkylation products **74a** and **74e** are shown, which are actually the same compound but produced from different substrates. The most interesting thing, however, is the comparison of the reaction selectivity, which in the case of **74a** is 5:95 and in the case of **74e** - 50:50. I will ask the PhD student to explain the difference.
6. On Page 37, Scheme 26, a mechanism explaining the formation of product **91**, containing two phosphinoyl substituents, is presented. It seems to be highly unlike due to the high crowding at the phosphorus atom, and the proposed approximation of the olefin bond would possibly have to be achieved at the expense of a significant deformation of the phosphorus substituent. I would like to ask the PhD student to provide a comment here.

In the next part of the dissertation, Mr. Gbubele presented and discussed the results of his research. This part is divided into four chapters, corresponding to the various transformations studied by the candidate. Each chapter began with a very extensive literature introduction regarding the reaction under study, which, I admit, was difficult to follow and I do not know whether it would be worth including such extensive introductions in the literature part.

In the first part, the Mr. Gbubele described the results on the use of secondary phosphite based on TADDOL in the reaction with α-amidosulfones. α-Amidosulfones were prepared based on a known literature procesure. Initially, model α-amidosulfone was used to optimize the reaction with non-chiral diethyl phosphite. The author indicates that the best base turned out to be potassium carbonate, while pyridine, NEt_3, diisopropylamine and proline turned out to be ineffective. This seems obvious, because according to Bordwell's pKa tables, the pKa of carbamates lies within the range 20-24, which means that the bases mentioned above were too weak to effectively deprotonate α-amidosulfone, while proline occurs mainly in the form of a zwitterion and is not regarded as a base. The candidate also carried out a series of reactions with various α-amidosulfones and various phosphites in order to determine the scope of applicability of the developed method.

In the next step, Mr. Gbubele attempted to use optimized conditions for the reaction with chiral phosphite, but despite the high conversion of the substrate, the diastereomeric excess was rather low. Hence, it was necessary to perform additional optimization of the reaction conditions which was fortunately successful, affording products with high diastereoselectivity. The absolute configuration of the newly created chiral center was determined by X-ray analysis, and circular dichroism studies of the products obtained from TADDOL-based phosphites with opposite configurations of the TADDOL moiety confirmed the enantiomeric nature of the products.

The second chapter of the research discussion was devoted to the reactivity of chiral secondary phosphites towards imines. Here, the candidate also included a very large literature introduction, which should rather be moved to the literature part. At the beginning, Mr. Gbubele synthesized a number of imines which were obtained with good yields in the form of a mixture of E:Z isomers, and the Z isomer was present in a very small amount. Attempts to add chiral secondary phosphite based on TADDOL to the previously obtained imines were initially carried out with low yields, but by simple increase of the reaction temperature it was possible to obtain the appropriate derivatives of α-aminophosphonic acids with high yields, but at the expense of low diastereomeric excesses.

The candidate also attempted to carry out a three-component reaction of a secondary phosphite with a carbonyl compound and an amine, where an imine initially would be formed under the reaction conditions, which would then undergo the addition of a P(O)H-type compound. The results indicated that, depending on the reaction conditions used, addition products to imines or carbonyl compounds were formed, and the diastereoselectivity of the process was much higher in the case of addition to a carbonyl compound. The reason for that was a much lower temperature the reaction was run compared to an addition to imine.

The third chapter was devoted to the addition of secondary phosphite based on TADDOL to carbonyl compounds. In this case, the PhD student also prepareded an extensive literature introduction. The research in this area was focused on the observation made by the candidate, where a three-component reaction between an aldehyde, a primary amine and a chiral phosphite at low temperatures led to the formation of a α-hydroxyalkylphosphonic acid derivative rather than an analogue with an amine group, and the reaction occurred with high diastereoselectivity. Based on this information, Mr. Gbubele carried out a series of additions of a P(O)H-type compound to various aldehydes, affording a series of adducts, usually with high diastereoselectivity. The main drawback of the developed methodology was the long reaction time and very low temperatures needed to conduct the addition with high degree of diastereoselectivity. Hence, further modifications of the reaction conditions were attempted, which allowed to determine that the use of a catalyst from the group of cinchona alkaloids allows the same reaction to be carried out at room temperature and in a shorter time without a significant loss of

diastereoselectivity. Although it turned out that this reaction can be carried out effectively for aldehydes only, and the use of a ketone as an electrophile led to the formation of an addition product with lower efficiency and lower diastereoselectivity.

In the last chapter, the candidate attempted to use hydrazones as electrophiles in the reaction with chiral phosphite. Initially, the idea was to use *N*-tosylhydrazones in a copper salt-catalyzed coupling reaction with chiral secondary phosphite. This reaction takes place through the stage of a diazo compound, which is coupled in the presence of a copper salt resulting in the formation of an alkylphosphonic acid derivative. The test reactions carried out by the PhD student using *N*-tosylhydrazone produced from acetophenone and secondary phosphite containing TADDOL led to the formation of the desired reaction product with high yields, but with very low diastereomeric excesses. Therefore, it was decided to use hydrazones as substitutes for imines in the synthesis of α-aminoalkylphosphonic acid derivatives. For this purpose, he used *N*-benzoylated hydrazones as substrates. Optimization of the reaction conditions allowed the preparation of appropriate adducts with chiral secondary phosphite with both good yields and diastereomeric excesses.

To summarize the part of the thesis devoted to the results and discussion, it can be stated that the candidate carried out a number of transformations using chiral secondary phosphite obtained from TADDOL with the intention to develop new synthetic methodology leading to C-chiral derivatives α-amino or α-hydroxyphosphonic acids or the acids themselves in a stereoselective manner. The factor inducing chirality at the newly created chiral center was a chiral TADDOL auxiliary bonded to the phosphorus atom. The assumed goal was achieved for the reaction of a chiral P(O)H type compound with α-amidosulfones, carbonyl compounds and *N*-benzoylated hydrazones, while the addition to imines and the reaction with hydrazones in the presence of copper salts turned out to be much more demanding required more detailed study. On the other hand, it must be taken into account that this may be a good reason to continue research in this field and perhaps even to submit a research project.

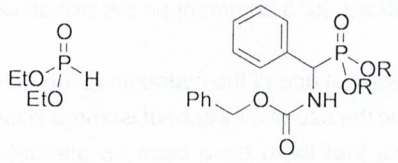
During the analysis of this part of dissertation, some comments and questions came to my mind I would like the PhD student to respond to.

1. On page 68, there is a diagram showing the reaction products of α-amidosulfones with diethyl phosphite. What I lack here is information about the efficiency of the process for meta- and para-substituted aromatic aldehydes and ketones. Have such attempts been made and what were the results?
2. On page 69, the candidate conducts a discussion on the use of various secondary phosphites as nucleophiles in the reaction with α-amidosulfones, pointing to the benzyl substituent as the more crowded one. This is not true, the benzyl substituent is less sterically encumbered than the *i*-propyl substituent.
3. On pages 78 and 79 and further, the candidate uses ^{13}C and ^{31}P NMR techniques to determine the diastereomeric excess of reaction products. It is known that these techniques give a much larger error compared to a regular ^{1}H NMR spectrum. Why weren't proton spectra used to determine reaction selectivity?
4. On page 79, when discussing the results from Scheme 58, PhD student indicates the 2-naphthyl substituent as sterically crowded. It is as large as the phenyl substituent and the second aromatic ring is placed "away" from the entire system and has little impact on steric crowding. The steric crowding generated by this substituent can be approximated to the *m*-substituted phenyl fragment.
5. On page 80, the results of the reaction of α-amidosulfones with chiral secondary phosphite are presented, where the compound with a pyridyl substituent was obtained with a significantly lower diastereomeric excess. Does the candidate have an explanation for this observation?
6. On page 88, a PhD student discusses the challenges associated with the use of unsubstituted imines, where one of the challenges is to ensure high selectivity due to the occurrence of E/Z isomerism. The hydrogen atom, despite its best intentions, is not able to make a crowd and its impact on stereochemistry is marginal.

7. On pages 106 and 107, the spectra of imines are presented, where the signals from the second isomer are clearly visible. Was this information taken into account when considering the stereoselectivity of the reaction, and what possible impact would the presence of the second isomer have on the diastereoselectivity of the process?
8. On page 110 of the thesis, Mr. Gbubele presented the optimization of the addition of chiral secondary phosphite to imine. I would like to ask for a comment on the comparison of the diastereoselectivity of this process with the diastereoselectivities obtained in the reaction with α-amidosulfones, because in this reaction the intermediate product is imine so the selectivity should be more or less the same.
9. On page 115, the PhD student analyzes the change in the reactivity of a three-component reaction carried out at -30 °C. This seems obvious to me because to produce imine effectively, it is necessary to remove water from the reaction mixture, otherwise the imine will undergo hydrolysis. Hence, at 110 °C, the only product is the α-aminoalkylphosphonic acid derivative, while at low temperatures this product is absent.
10. On page 116, poor ketimine reactivity is discussed, and sterical crowding was pointed to as a possible cause. It seems to me that crowding is less important here due to the sp^2 hybridization of the electrophilic center. The problem is the lower electrophilicity of ketimine compared to aldimine. It can be increased by adding a Lewis acid to the mixture, for example magnesium, zinc or aluminum salts. Have such attempts been made?
11. On page 136 there is a scheme with the set of the addition reaction products. Please explain the unusual behavior of aldehydes containing a nitro group in the aryl fragment, as I was unable to find the explanation in the dissertation.
12. On page 139, the PhD student presents the results of the addition of phosphite to aromatic aldehydes with various substitution patterns, assigning the methoxy group to the EWG group, which is supposed to explain the lower diastereoselectivity of the process. There must be another reason here, because the methoxy group is not an electron-withdrawing substituent.
13. On page 156, the proposed catalytic cycle for the reaction of *N*-tosylhydrazones in the presence of copper salts is given. I would like to ask for a comment on the oxidation states of copper at individual stages of this cycle.
14. On pages 158-159, the spectra of one of the hydrazones are presented, with two isomers visible. I would like to ask for a comment on how the use of a mixture of isomers influences the diastereoselectivity of the addition reaction, because I assume that there have been no attempts to use only one hydrazone isomer in the addition reaction.
15. On page 160 optimization of a reaction of *N*-tosylhydrazones with secondary phosphite in the presence of copper salts is presented. The conversion of substrates to the product was high in most of cases, while diastereoselectivity was weak or very poor. It seems that the high temperature is responsible for the low diastereoselectivity of the process. The solution could be the use of stronger bases. There is literature data indicating that for NaOMe as a base this process occurs already at temperatures of 30-40 oC. Of course, it is a matter of selecting the optimal base, but so far there is a lot of potential reagents to choose. The second issue is the choice of catalyst. Rhodium(II) complexes would work well or even better here and they could be used in a chiral form. Have such attempts been made?
16. Regarding the reaction of *N*-benzoylated hydrazones with chiral secondary phosphite, I would like to ask why they were used in the reaction and not the *N*-tosylated hydrazones obtained a moment earlier?

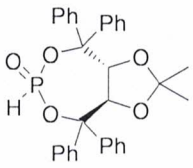
The experimental part is written clearly, and the inclusion of compound structures greatly facilitates the analysis of the attached data. Generally, the description of NMR spectra is correct, although there are some issues that require clarification or correction. For example, for compound **141f** and several others, the signal at 16.41 ppm belonging to the CH_3 carbon atom of the ethoxy substituent is described as a singlet, although in other cases the signals of these types of carbons are described as doublets. In turn, for compound **141h**, the signal at 16.45 ppm was described as a doublet of doublets, which is rather impossible. For compound **141j** and several others derived from diisopropyl phosphite, the chemical shifts of methyl carbon atoms have very small coupling constants (approx. 3 Hz) in ^{13}C NMR spectra. Shouldn't they be larger, especially since the coupling constants for other methyl groups are larger? In turn, for the compound (*R,R*)-**29**, the description of the ^{1}H NMR spectrum lacks the shift and coupling constant value of the hydrogen atom directly bonded to the phosphorus atom. Starting with the compound (*R,R,R*)-**148a**, footnotes relating to the coupling atoms begin to appear in the description of ^{13}C NMR spectra with the coupling designation (J). The question arises why it has started here. This notification should be used with care, as I am afraid that unless these are compounds enriched in ^{17}O oxygen, C-O coupling will not be observed. For or C-Cl coupling, I must admit I have never heard about. For the compound (*S,S,S*)-**148b**, in the ^{13}C NMR analysis for the signal at a 163.87 ppm a coupling constant $^{1}J_{C\text{-}F}$ = 3.1 Hz was assigned. Generally, the values for this type of coupling exceed 200 Hz. Moreover, in the case of compounds containing both phosphorus and fluorine atoms, a double splitting of signals in the ^{13}C NMR spectrum would be expected, which I did not find when analyzing any of the compounds. In some cases, there is also no description of the coupling constants between phosphorus and carbon in aromatic systems, like in compound **205a'** but also in other compounds. Generally, a thorough inspection of these analyzes should be made, especially in case a publication will be prepared.

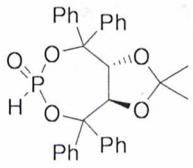
The editorial side of the work is at a good level, although I would like to draw attention to two aspects related to drawing compounds which, as a person involved in the chemistry of phosphorus compounds, I cannot get over. The first issue concerns the way of drawing non-cyclic organophosphorus compounds, but also sulfone groups. In the work they are drawn in different ways, it is certainly not uniform. In my opinion, the way of drawing should be uniform, preferably as shown below.



This way of drawing allows to maintain the tetrahedral structure of the phosphorus fragment and fit all the substituents around. I think this is reasonable, especially since phosphorus is the leitmotif of this work, so it should deserve appropriate respect :)

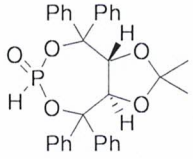
The second issue concerns the drawing of secondary phosphite obtained from TADDOL. When reading the dissertation, I counted three ways of drawing this molecule, two are acceptable and one is misleading.





Misleading absolute configurations

Can be found in the literature,
the absolute configuration is correct



In accordance with IUPAC

The first two molecules on the left are often found in the literature. This is not 100% correct, but the configurations on carbon atoms are consistent with the actual situation. The molecule on the right has its stereochemical bonds drawn incorrectly, and in ChemDraw this causes a configuration change on the chiral atom. Moreover, trying to imagine a molecule drawn in this way is very hard work and unintuitive. IUPAC guidelines here are clear - stereochemical bonds are drawn in such a way that the thinner end is placed on a chiral atom. However, the most correct version is the molecule drawn at the bottom. In this case, the rings are drawn flat and the bond to the sole substituent is drawn using a stereochemical bond.

Apart from these issues, mistakes are found on the schemes, such as:

- page 16, Fig. 9 - Corey's chiral auxiliary certainly does not look like this, and Schöllkopf's chiral auxiliary lacks the element of chirality
- page 17, Fig. 10 – redundant hydrogen atoms in phosphites derived from TADDOL and BINOL
- page 30, Scheme 18 – interesting diastereomer ratio for **65a**
- page 31, Scheme 20 – with a 50:50 diastereoisomer ratio, there is a major diastereomer
- page 36, Scheme 25, path B - the diagram is cut off, one stage is missing
- page 37, Scheme 26 and a few others below - compounds seem to have a different formatting style
- page 45, Scheme 35 – compound **84** has an excess hydrogen atom, and the mentoxy substituents are written in a strange way
- page 48, Scheme 38 - triple bonds should be drawn in accordance with the hybridization of atoms
- page 98, Scheme 70 – missing phenyl substituents in the products and a strange N_2 fragment

The language of the doctoral dissertation is good, although there is a tendency to use high-flown phrases, chemical jargon and unusual syntax. Due to the length of this review, I will refrain from detailing examples. However, this does cause any problems in understanding the data collected in the dissertation.

To sum up the review, I would like to emphasize that the substantive value of the dissertation, despite various shortcomings, is high. The goals set at the beginning of the dissertation were largely achieved, which clearly allows me to state that it meets the requirements for this type of dissertations. Therefore, I am applying to the Council of the Scientific Discipline of Chemical Sciences to allow the dissertation to proceed to the next stages of the doctoral process.

Prof. Marek Stankevič