



**BUDAPEST UNIVERSITY OF TECHNOLOGY AND ECONOMICS
FACULTY OF CHEMICAL TECHNOLOGY AND BIOTECHNOLOGY
GEORGE A. OLAH DOCTORAL SCHOOL**

**SYNTHESIS AND UTILIZATION OF AMINOPHOSPHINE
OXIDES, CYCLIC AMINOPHOSPHONATES AND THEIR
RELATED COMPOUNDS**

Summary of PhD theses

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Co-supervisor: **Dr. Erika Bálint**

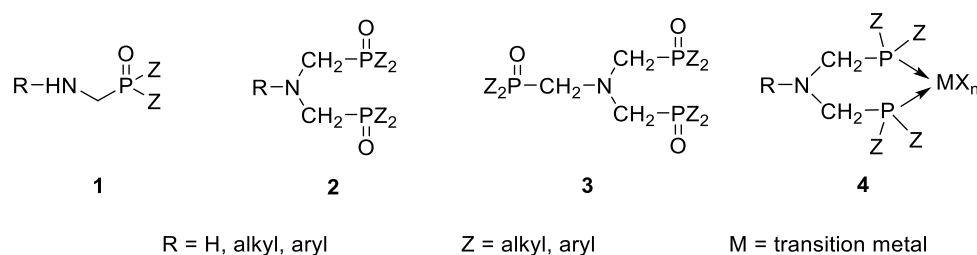
Department of Organic Chemistry and Technology

2020

1. Introduction

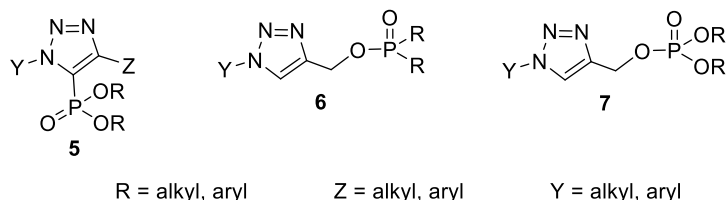
α -Aminophosphine oxides, as well as cyclic α -aminophosphonates, triazolyl phosphonates and their related phosphinate and phosphate derivatives have received significant attention within the field of organophosphorus chemistry.^{1,2} The wide range of their possible applications and their versatile biological activities have a stimulating effect on the continuous development of synthetic methods and the preparation of new derivatives.

I performed the research work for my PhD theses under the supervision of Dr. György Keglevich and Dr. Erika Bálint in the Green Chemical and Organophosphorus Research Group at the Department of Organic Chemistry and Technology. Our research focused on the synthesis of new α -aminophosphine oxides (**1**), bis- (**2**) and tris(phosphinoylmethyl)amine derivatives (**3**) (*Scheme 1*). Considering the aspects of green chemistry, the compounds were synthesized by the microwave-assisted and catalyst-free Kabachnik–Fields reaction. Our aims also included the utilization of the synthesized bis(phosphonomethyl)amines as ligand precursors for cyclic transition metal complexes (**4**).



Scheme 1 α -Aminophosphine oxides (**1**), bis(phosphinoylmethyl)amine (**2**), tris(phosphinoylmethyl)amine (**3**) and bis(phosphin) transition metal complexes (**4**)

We wish to develop methods for the preparation of cyclic α -aminophosphonates, 1,2,3-triazolyl phosphonates (**5**), triazolyl phosphinates (**6**), and phosphates (**7**) by copper(I)-catalysed domino and click reactions (*Scheme 2*). We also aimed to study the biological activity of the obtained 1,2,3-triazolyl phosphonates (**5**).



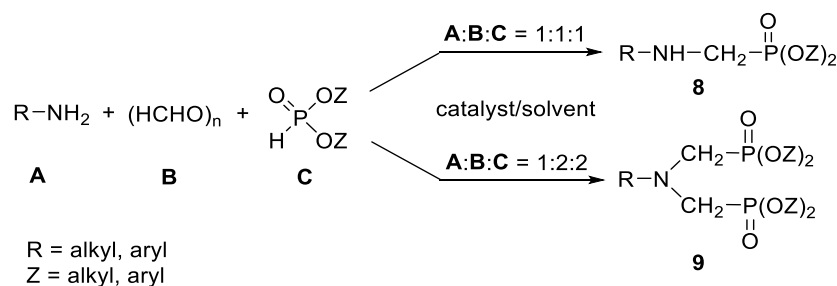
Scheme 2 1,2,3-Triazol-5-yl-phosphonates (**5**), (1,2,3-triazol-4-yl)methyl phosphinates (**6**) and (1,2,3-triazol-4-yl)methyl phosphates (**7**)

¹Hudson, H. R.; Kukhar, V. P. *Aminophosphonic and aminophosphinic acids: chemistry and biological activity*; Wiley: Chichester, 2000.

²K. Moonen, I. Laureyn, C. V. Stevens, *Chem. Rev.* **2004**, *104*, 6177–6215.

2. Background

The α -aminophosphonates (**8**), bis(phosphonomethyl)amines (**9**) and their derivatives may be prepared by the Kabachnik–Fields reaction (*Scheme 3*).³ In the three-component condensation a primary amine, an oxo compound (aldehyde or ketone) and a $>P(O)H$ reagent take part. Depending on the molar ratio of the reactants either α -aminophosphonates (**8**) or bis(phosphonomethyl)amines (**9**) could be selectively synthesized with good yields.



Scheme 3 The single and the double Kabachnik–Fields reactions of primary amines, paraformaldehyde and $>P(O)H$ reagents

The single and the double Kabachnik–Fields reactions, in most cases, were carried out in the presence of an additive (catalyst and/or solvent),⁴ however, in the last decades more and more publications discuss environmentally friendly methods, in which the condensations were investigated without expensive catalysts and solvents.⁵

One of the most noteworthy synthetic routes for triazolyl phosphonates and derivatives is the Huisgen 1,3-dipolar azide–alkyne cycloaddition (*Scheme 4*).⁶ 1,2,3-Triazol-4-yl-phosphonates (**10**) can be selectively synthesized by the Cu(I)-catalyzed reaction of azides and phosphorus-containing terminal acetylenes at room temperature,⁷ while the preparation of trisubstituted triazol-5-yl-phosphonates (**11**) can be accomplished by the reaction of azides and internal acetylenes.⁸

³G. Keglevich, E. Bálint, *Molecules* **2012**, *17*, 12821–12835.

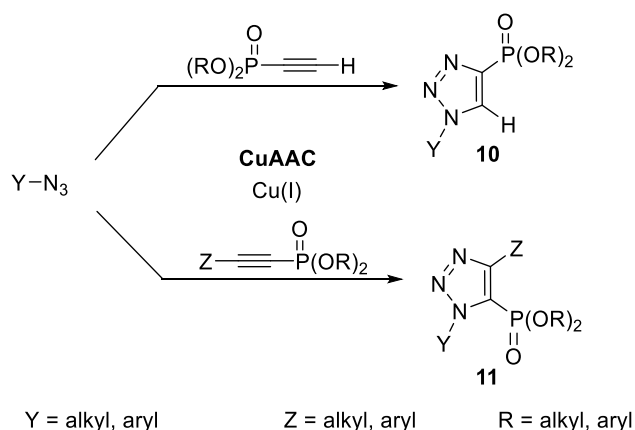
⁴N. S. Zefirov, E. D. Matveeva, *Arkivoc* **2008**, *2008*, 1–17.

⁵P. Kafarski, M. Gorny vel Gorniak, I. Andrasiak, *Curr. Green Chem.* **2015**, *2*, 218–222.

⁶V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chemie - Int. Ed.* **2002**, *41*, 2596–2599.

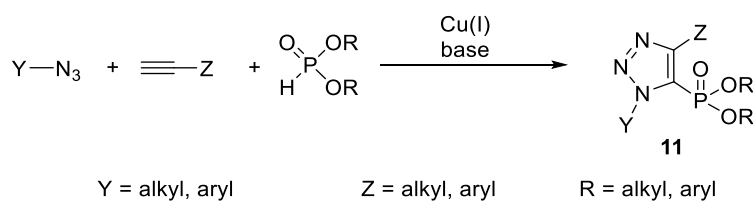
⁷S. Mukai, G. R. Flematti, L. T. Byrne, P. G. Besant, P. V. Attwood, M. J. Piggott, *Amino Acids* **2012**, *43*, 857–874.

⁸P. Huang, Q. Su, W. Dong, Y. Zhang, D. An, *Tetrahedron* **2017**, *73*, 4275–4284.



Scheme 4 The synthesis of 1,2,3-triazol-4-yl-phosphonates and 1,2,3-triazol-5-yl-phosphonates by 1,3-dipolar azide-alkyne cycloaddition

The trisubstituted triazol-5-yl-phosphonates (**11**) also can be synthesized by the Cu(I) catalysed domino reaction of azides, terminal alkynes and dialkyl phosphites (*Scheme 5*).⁹ One of the many advantages of the three-component reaction is that it avoids the isolation of intermediates.



Scheme 5 The domino reaction of azides, terminal alkynes and dialkyl phosphites

3. Experimental methods and equipment

The MW-assisted reactions were carried out in a CEM Discover[®] MW reactor (300 W), equipped with a pressure device.

The products were purified by column chromatography. The reactions were followed by gas chromatography (GC), high-pressure liquid chromatography (HPLC) and/or thin-layer chromatography (TLC). The products were identified by GC-MS and/or HPLC-MS measurements. Purification of the products was carried out by normal and/or reversed-phase flash column chromatography.

The compounds synthesized were characterized by ³¹P, ¹³C, and ¹H NMR spectroscopy, moreover, they were identified by HRMS. The crystal structures of a few derivatives were analyzed by X-ray diffraction measurements.

The quantum chemical calculations were carried out using Gaussian09 software package, B3LYP/6-31G(d,p), and B3LYP/SDD(MWB60) method.

⁹ L. Li, G. Hao, A. Zhu, X. Fan, G. Zhang, L. Zhang, *Chem. Eur. J.* **2013**, *19*, 14403–14406.

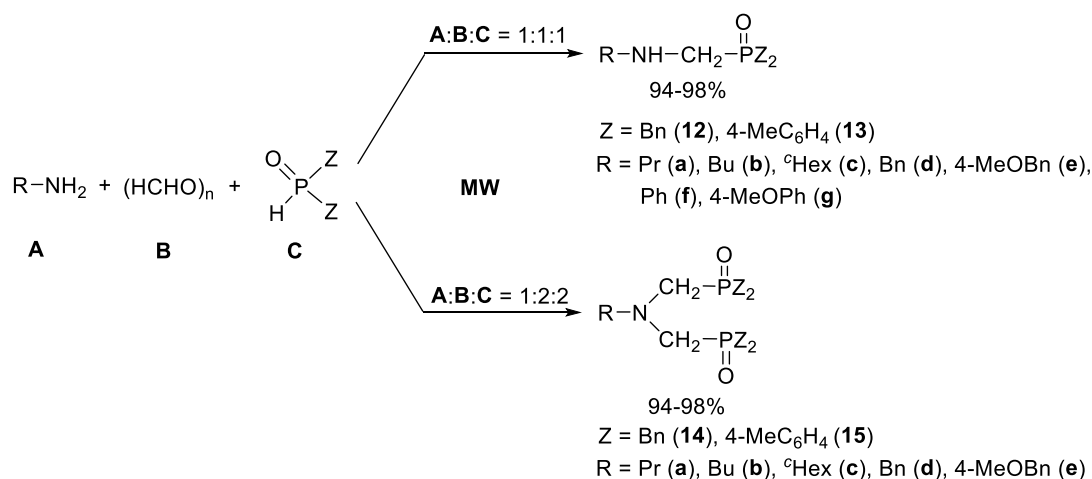
The IC₅₀ values for antibacterial and cytotoxicity studies were determined by fluorescence-based measurements.

4. New scientific results

4.1. α -Aminophosphine oxides and derivatives

4.1.1. The synthesis of α -aminophosphine oxides and bis(phosphinoylmethyl)amines^[1]

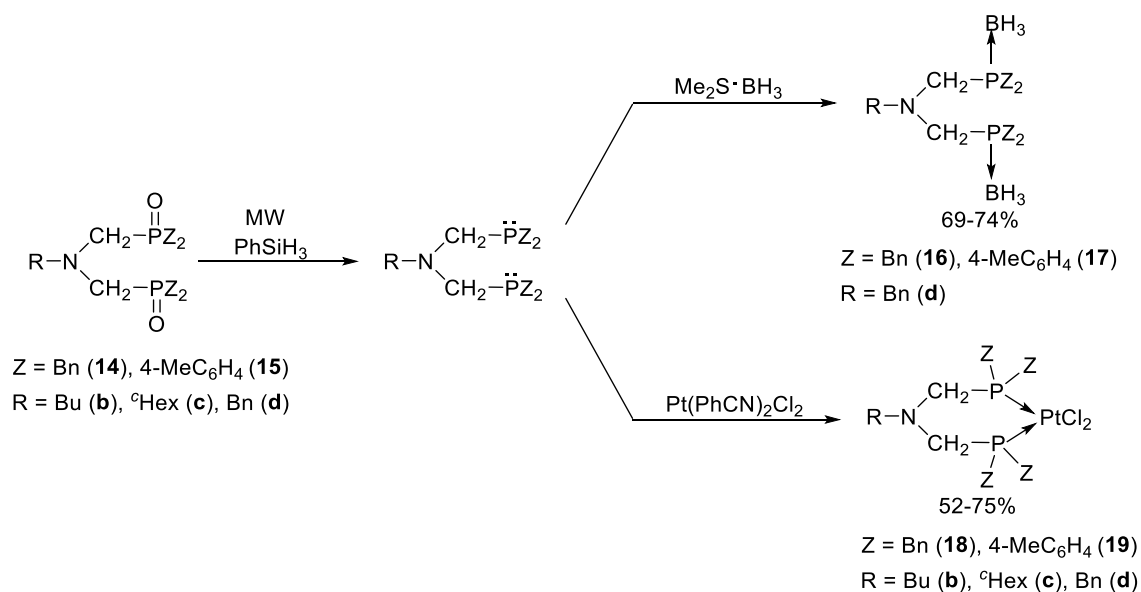
In the first approach, the single and double Kabachnik-Fields reactions of various primary amines, paraformaldehyde and secondary phosphine oxides were investigated (*Scheme 6*). In every case, the condensations were carried out under MW conditions in the absence of any catalyst. During the single and double Kabachnik-Fields reactions, 11 new α -aminophosphine oxides (**12a-g** and **13a-g**) and 8 new bis(phosphinoylmethyl)amines (**14b-e** and **15b-e**) were obtained in excellent yields.



Scheme 6 Kabachnik-Fields reaction of primary amines, paraformaldehyde and secondary phosphine oxides

4.1.2. The utilization of bis(phosphinoylmethyl)amines as bidentate phosphine ligands^[1]

We wished to study the utilization of *N,N*-bis(phosphinoylmethyl)amines as bidentate phosphine ligands (*Scheme 7*). After the optimization of the double deoxygenation, the synthesis of boron and platinum complexes was investigated from the obtained bisphosphines. The preparation of new boron (**16d** and **17d**) and new cyclic platinum complexes (**18b-d** and **19b-d**) was accomplished. The structures of 3 platinum derivatives were investigated by X-ray diffraction analysis as well as quantum chemistry calculations.

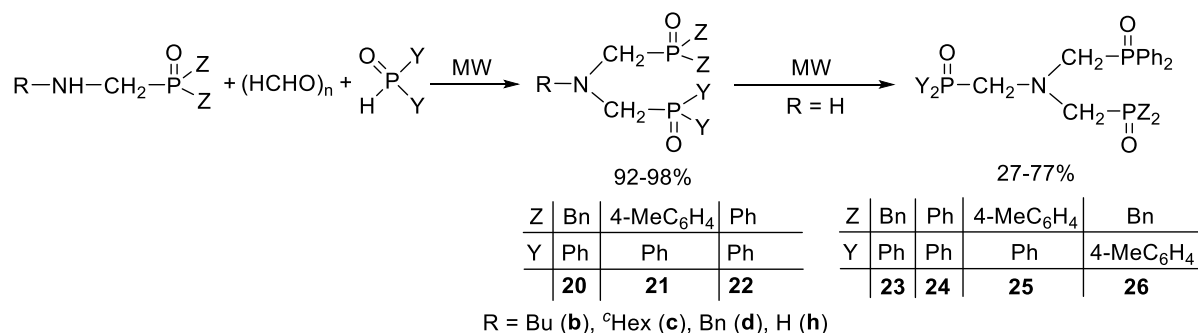


Scheme 7 The double deoxygenation and utilization of *N,N*-bis(phosphinoylmethyl)amines as phosphine ligands

The platinum complexes (**18b-d** and **19b-d**) were tested as novel catalyst in the hydroformylation of styrene. Out of the studied platinum complexes, the [bis[di(*p*-(tolyl)phosphonomethyl)] derivatives (**19b-d**) proved to be more effective. In the experiments, high conversion, chemoselectivity, and unusual regioselectivity were achieved. The formation of branched aldehyde predominated in all cases.

4.1.3. Kabachnik-Fields reactions starting from aminophosphine oxides^[2]

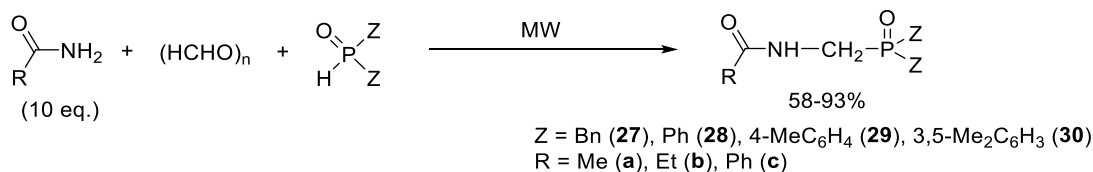
We have also developed an efficient, catalyst-free process for the synthesis of bis(phosphinoylmethyl)alkylamines (**20b-d** and **21b-d**), bis(phosphinoylmethyl)amines (**20h**, **21h** and **22h**), and tris(phosphinoylmethyl)amines (**23-26**) bearing identical or different substituents on their phosphorus atoms (*Scheme 8*). With this approach the Kabachnik–Fields reactions afforded altogether 13 new derivatives.



Scheme 8 The synthesis of bis(phosphinoylmethyl)amines and tris(phosphinoylmethyl)amines

4.1.4. The Kabachnik-Fields reaction of amides and secondary phosphine oxides^[3]

We have shown that the Kabachnik-Fields condensation can be extended to amides that have lower reactivity than primary amines (*Scheme 9*). The reactions were carried out in a MW reactor, using the amides in excess to afford the new acylaminophosphine oxides with good yields. Altogether 12 new acylaminophosphine oxides (**27a-c**, **28a-c**, **29a-c** and **30a-c**) were synthesized by the condensation of three different amides, paraformaldehyde and secondary phosphine oxides.

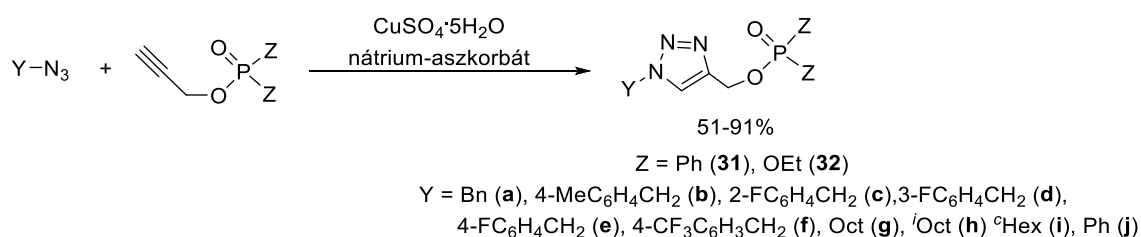


Scheme 9 Kabachnik-Fields reaction of amides, paraformaldehyde and secondary phosphine oxides

4.2. (1,2,3-Triazol-4-yl)methyl phosphinates, phosphates and 1,2,3-triazoyl phosphonates

4.2.1. Synthesis of (1,2,3-triazol-4-yl)methyl phosphinates and phosphates by click reaction^[4]

As a continuation of my research, the Cu(I)-catalyzed click reaction was investigated through a model reaction of propynyl phosphinates, propynyl phosphates – which can be easily prepared by esterification – and organic azides (*Scheme 10*). After the optimization of the click reaction, the synthesis of 20 new (1,2,3-triazol-4-yl)methyl phosphinates (**31a-j**) and phosphates (**32a-j**) was performed.

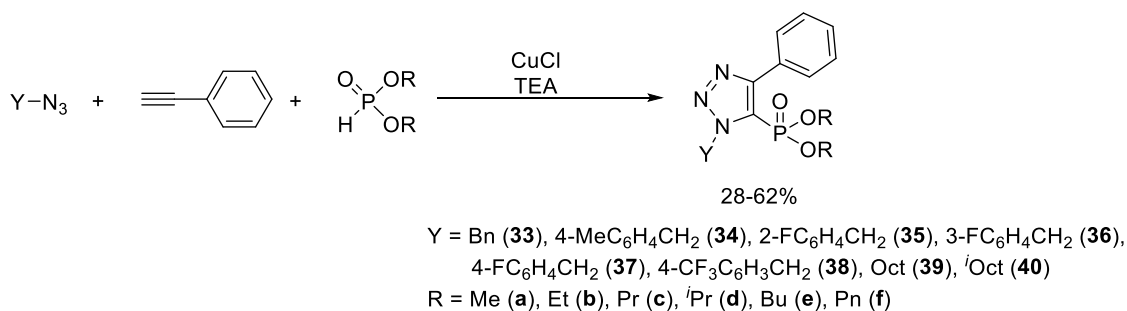


Scheme 10 Synthesis of (1,2,3-triazol-4-yl)methyl phosphinates and (1,2,3-triazol-4-yl)methyl phosphates by click reaction

4.2.2. The synthesis of 1,2,3-triazolyl phosphonates by domino reaction^[5]

In the next part of our work, the synthesis of cyclic aminophosphonates and their derivatives was studied. As a first step related to the preparation of triazol-5-yl phosphonates, we optimized the Cu(I)-catalyzed domino reaction through a model reaction of phenylacetylene, benzyl azide, and dibutyl phosphite. The reaction was extended to various

organic azides and dialkyl phosphites to give 17 cyclic aminophosphonates (**33a-f**, **34a,b,e**, **35e**, **36e**, **37e**, **38e**, **39a,b,e** and **40e**) (Scheme 11).



Scheme 11 The synthesis of 1,2,3-triazolyl phosphonates by domino reaction

4.2.3. The antibacterial activity and *in vitro* cytotoxicity of 1,2,3-triazol-5-yl-phosphonates^[5]

The antibacterial activity of the synthesized 1,2,3-triazol-5-yl-phosphonates was tested on Gram-positive (*Bacillus subtilis*) and Gram-negative (*Escherichia coli*) bacterial cells, and the *in vitro* cytotoxicity assessments were performed on three different cell lines. According to the results, modest antibacterial activity was detected against the more sensitive *Bacillus subtilis* strain. Several triazolyl phosphonates (**33c**, **33e**, **33f**, **34a**, **35e**, **36e**, **37e**, **38e** and **40e**) showed activity against mouse fibroblast (NIH/3T3) and human promyelocytic leukemia (HL-60) cells. The IC₅₀ values fall in the range of 9.7 and 27.5 μM.

In conclusion, the production of the targeted new α-aminophosphine oxides (**12a-g**, **13a-g**, **27a-c**, **28a-c**, **29a-c** and **30a-c**), bis(phosphinoylmethyl)amines (**14b-e**, **15b-e**, **20b-d,h**, **21b-d,h** és **22h**) tris(phosphinoylmethyl)amines (**23-26**) was successfully achieved. The synthesis of the compounds was performed by single, double and multi-step Kabachnik-Fields reactions under MW conditions. After double deoxygenation, the bis(phosphinoylmethyl)amines (**14b-d** and **15b-d**) were utilized as bidentate phosphine ligands in the synthesis of borane (**16d**, **17d**) and platinum complexes (**18b-d**, **19b-d**). We also performed the preparation of cyclic aminophosphonates, 1,2,3-triazolylphosphonates (**33a-f**, **34a,b,e**, **35e**, **36e**, **37e**, **38e**, **39a,b,e** és **40e**), (1,2,3-triazol-4-yl)methyl phosphinates (**31a-j**) and phosphates (**32a-j**) by copper(I)-catalyzed domino and click reactions. In the course of my research, I have expanded the family of aminophosphine oxides, triazolyl phosphonates, and their related compounds with nearly 100 new compounds.

5. Theses

1. A new, environmentally friendly synthesis of α -aminophosphine oxides and *N,N*-bis(phosphinoylmethyl)amines was accomplished by the MW-assisted single and double Kabachnik-Fields reactions.^[1]
2. The double deoxygenation of new bis(phosphinoylmethyl)amine derivatives was optimized, and the synthesized phosphines were utilized as bidentate ligands. The prepared platinum complexes afforded high conversion, chemoselectivity, and unusual regioselectivity in the hydroformylation of styrene.^[1]
3. The synthesis of new non symmetric bis(phosphinoylmethyl)amines and tris(phosphinoylmethyl)amines was elaborated by the MW-assisted Kabachnik-Fields condensation of secondary phosphine oxides, paraformaldehyde and (aminomethyl)phosphine oxides.^[2]
4. An efficient method was developed for the Kabachnik-Fields reaction of amides. We proved it first, that the acylated α -aminophosphine oxides can be prepared in good yield using an amide excess, under MW conditions.^[3]
5. The (1,2,3-triazol-4-yl)methyl phosphinates and phosphates can be synthesized with good yields by the copper(I)-catalyzed click reaction of organic azides and propynyl phosphinates or propynyl phosphates.^[4]
6. Formation of the 5-H-substituted triazole and alkynyl phosphonate besides the desired 1-benzyl-4-phenyl-1,2,3-triazol-5-ylphosphonate during the domino reaction of phenylacetylene, benzyl azide and dibutyl phosphite was confirmed. Appropriate conditions were elaborated to promote the formation of 1-benzyl-4-phenyl-1,2,3-triazol-5-ylphosphonate as the main product.^[5]
7. The domino reaction was extended to a number of organic azides and dialkyl phosphites. Several of the synthesized new 4-phenyl-1,2,3-triazol-5-yl phosphonates showed mild antibacterial activity as well as moderate *in vitro* cytotoxicity.^[5]

6. Application possibilities

During my PhD work, we have elaborated generally applicable syntheses for α -aminophosphine oxides, and triazolyl phosphonate, phosphinate and phosphate derivatives. New families of compounds were made available.

The bis(phosphinoylmethyl)amines (**14b-d** and **15b-d**) were utilized after double deoxygenation as bidentate phosphine ligands for the synthesis of borane and platinum complexes. In the hydroformylation of styrene, high conversion, chemoselectivity, and unusual regioselectivity were achieved with the synthesized platinum complexes. As the formation of branched aldehyde predominated in all cases, our complexes may be suitable for the possible replacement of more expensive rhodium-containing catalysts after further development.

During the biological activity studies, we found that the 1,2,3-triazol-5-yl phosphonate derivatives have low antibacterial activity and modest *in vitro* cytotoxicity compared to commercially available drugs. However, the results obtained against human myeloid leukemia (HL-60) cell lines suggest, that the developed methods may provide a good possibility for the preparation of additional potentially bioactive compounds.

7. Publications

7.1. Full scientific publications related to the PhD Thesis

- [1] E. Bálint, **A. Tripolszky**, E. Jablonkai, K. Karaghiosoff, M. Czugler, Z. Mucsi, L. Kollár, P. Pongrácz, G. Keglevich, *J. Organomet. Chem.* **2016**, *801*, 111–121. DOI: 10.1016/j.jorganchem.2015.10.029. [IF: 2,184, FI: 9, TA: 100%]
- [2] E. Bálint, **A. Tripolszky**, L. Hegedűs, G. Keglevich, *Beilstein J. Org. Chem.* **2019**, *15*, 469–473. DOI: 10.3762/bjoc.15.40. [IF(2018/2019): 2,595, FI: 1, TA: 100%]
- [3] **A. Tripolszky**, L. Zoboki, E. Bálint, J. Kóti, G. Keglevich, *Synth. Commun.* **2019**, *49*, 1047–1054. DOI: 10.1080/00397911.2019.1584675. [IF(2018/2019): 1,439, FI: 2, TA: 60%]
- [4] **A. Tripolszky**, K. Németh, P. T. Szabó, E. Bálint, *Molecules* **2019**, *24*, 2085–2098. DOI: 10.3390/molecules24112085. [IF(2018/2019): 3,060, FI: 1, TA: 90%]
- [5] **A. Tripolszky**, E. Tóth, P. T. Szabó, L. Hackler, B. Kari, L. G. Puskás, E. Bálint, *Molecules* **2020**, *25*, 2643–2659. DOI: 10.3390/molecules25112643. [IF(2018/2019): 3,060, FI:0, TA: 70%]

7.2. Short preliminary and summary publications, review articles and book chapters related to the PhD Thesis

- [6] **A. Tripolszky**, E. Bálint, G. Keglevich, *Phosphorus. Sulfur. Silicon Relat. Elem.* **2019**, *194*, 345–348. DOI: 10.1080/10426507.2018.1541898. [IF(2018/2019): 0,781, FI:0, TA: 100%]
- [7] **A. Tripolszky**, E. Tóth, E. Bálint, *Phosphorus. Sulfur. Silicon Relat. Elem.* **2019**, *194*, 377–378. DOI: 10.1080/10426507.2018.1547727. [IF(2018/2019): 0,781, FI: 0, TA: 70%]
- [8] **A. Tripolszky**, G. Keglevich, *Lett. Org. Chem.* **2018**, *15*, 387–393. DOI: 10.2174/1570178615666171227144555. [IF(2018/2019): 0,723, FI: 1, TA: 100%]
- [9] E. Bálint, Á. Tajti, **A. Tripolszky**, G. Keglevich, *Dalt. Trans.* **2018**, *47*, 4755–4778. DOI: 10.1039/C8DT00178B. [IF(2018/2019): 4,052, FI: 11, TA: 30%]
- [10] E. Bálint, Á. Tajti, **A. Tripolszky**, Synthesis of α -aminophosphonates by the Kabachnik-Fields reaction and by the Pudovik reaction, In: *Organophosphorus Chemistry*; Keglevich, G. (ed.); Walter de Gruyter: Berlin, 2018, p 108. (ISBN 978-3-11-053583-9) [FI: 2, TA: 50%]

7.3. Publications indirectly related to the PhD Thesis

- [11] E. Bálint, **A. Tripolszky**, A. Ádám, Á. Tajti, G. Keglevich, *Phosphorus, Sulfur, Silicon Relat. Elem.* **2016**, *191*, 1539–1540. DOI: 10.1080/10426507.2016.1212860. [IF: 0,809, FI: 0, TA: 60%]
- [12] E. Bálint, E. Fazekas, **A. Tripolszky**, R. Kangyal, M. Milen, G. Keglevich, *Phosphorus. Sulfur. Silicon Relat. Elem.* **2015**, *190*, 655–659. DOI: 10.1080/10426507.2014.984022. [IF: 0,723, FI: 11, TA: 60%]

7.4. Conference proceedings

1. **A. Tripolszky**, E. Bálint, *Tavaszi Szél 2016 Konferenciakötet* **2016**, 132. Budapest, Magyarország, 2015.04.15-16. (ISBN 978-615-5586-09-5) [TA:100%]
2. **A. Tripolszky**, E. Bálint, In: B. Bohner, E. Mesterházy (szerk.) XXXVIII. Kémiai előadói napok Program és előadás-összefoglalók, 2015, pp. 198. Szeged, Magyarország, 2015.10.26-28. (ISBN: 978-963-9970-64-9) [TA:100%]

3. **A. Tripolszky**, E. Tóth, E. Bálint, In: A. A. Ádám, Sz. Ziegenheim, (szerk.) I. FKF Szimpózium, F fiatal Kémikusok Fóruma Konferencia kiadvány, 2019, pp. 6. Debrecen, Magyarország, 2019.04.3-5. (ISBN: 978-615-6018-00-7) [TA: 70%]

7.5. Oral presentations

1. **A. Tripolszky**, E. Bálint, G. Keglevich, *Microwave-assisted synthesis of α -aminophosphine oxides*. The 22nd International Conference on Phosphorus Chemistry, Budapest, 2018.7.8-13.
2. **A. Tripolszky**, E. Tóth, E. Bálint, *Klick és dominó reakciók tanulmányozása foszfortartalmú reagensekkel. I. FKF Szimpózium*, Debrecen, 2019.4.3-5.
3. **A. Tripolszky**, E. Bálint, *Foszfin-oxid és foszfonát oldalláncot tartalmazó triazolok szintézise klick és dominó reakciókkal*. BME, XVI. Oláh György Doktoráns Konferencia, Budapest, 2019.1.31.
4. **A. Tripolszky**, *α -Aminofoszfin-oxidok szintézise és P-ligandumként történő felhasználása*. XXXIII. Országos Tudományos Diákköri Konferencia, Miskolc, 2017.3.29-31.
5. **A. Tripolszky**, E. Bálint, G. Keglevich, *α -Aminofoszfin-oxidok szintézise és hasznosítása*, Vegyészkonferencia, Hajdúszoboszló, 2017.6.19-21.
6. **A. Tripolszky**, E. Bálint, *α -Aminofoszfin-oxidok szintézise és hasznosíthatóságuk vizsgálata*. Tavaszi Szél Konferencia, Budapest, 2016.4.15-17.
7. **A. Tripolszky**, E. Bálint, *Kabachnik–Fields-reakciók szekunder foszfin-oxidokkal; a termékek P-ligandumként történő felhasználása*. V. Interdiszciplináris Doktorandusz Konferencia, Pécs, 2016.5.27-29.
8. **A. Tripolszky**, E. Bálint, *Kabachnik–Fields-reakciók szekunder foszfin-oxidokkal; termékek hasznosíthatóságának vizsgálata*. XXXVIII. Kémiai Előadói Napok, Szeged, 2015.10.26-28.

7.6. Poster presentations

1. **A. Tripolszky**, E. Tóth, E. Bálint, *Synthesis of triazolyl-phosphonate derivatives by click and domino reactions*. 18th Blue Danube Symposium on Heterocyclic Chemistry, Ljubjana, 2019.9.18-21.

2. **A. Tripolszky**, E. Tóth, E. Bálint, *Synthesis of triazole derivatives with phosphorus side chain*. The 22nd International Conference on Phosphorus Chemistry, Budapest, 2018.7.8-13.
3. **A. Tripolszky**, E. Bálint, G. Keglevich, *Synthesis of α -Aminophosphine Oxide Derivatives: Kabachnik-Fields and "click" reactions*. 15th European Workshop in Phosphorus Chemistry, Uppsala, 2018.3.14-16.
4. **A. Tripolszky**, E. Bálint, G. Keglevich, *Synthesis and utilization of α -aminophosphine oxides*. 17th Blue Danube Symposium on Heterocyclic Chemistry, Linz, 2017.8.30. – 9.2.
5. E. Bálint, **A. Tripolszky**, A. Ádám, Á. Tajti, G. Keglevich, *Synthesis and utilization of α -aminophosphine oxides and related derivatives*. 21st International Conference on Phosphorus Chemistry, Kazan, 2016.6.5-10.
6. **A. Tripolszky**, E. Bálint, G. Keglevich, *α -Aminofoszfín-oxidok szintézise mikrohullámú körülmények között*. XXI. Bolyai Konferencia, Budapest, 2016.3.19-20.