Final report

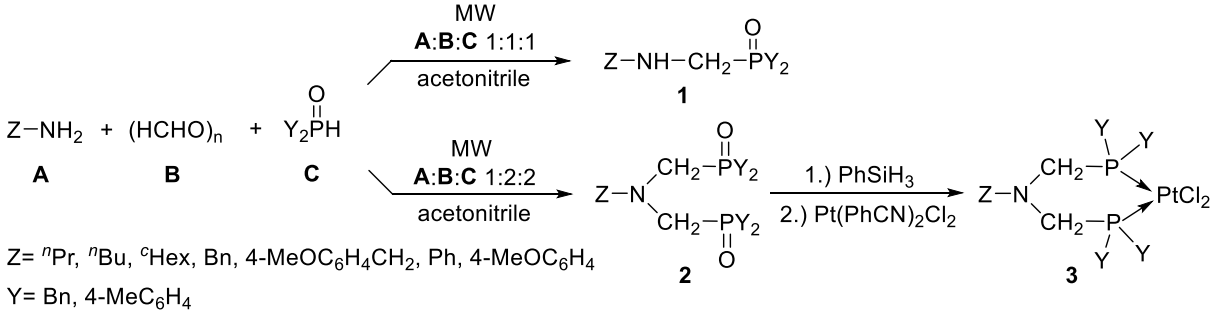
NKFIH - PD111895

Synthesis and utilization of aminophosphonate and aminophosphine oxide derivatives

According to the workplan, we conducted our researches in the field of organophosphorus and microwave (MW)-assisted chemistry. The main aim of our project was the MW-assisted synthesis of novel aminophosphonate and aminophosphine oxide derivatives. Furthermore, the utilization of the latter compounds as bidentate phosphine ligands in transition metal complexes after deoxygenation was also aimed at.

1.1.) Kabachnik-Fields reactions of primary amines with dialkyl- or diarylphosphine oxides and >P(O)H reagents with mixed groups

First, the Kabachnik-Fields reaction of primary amines with paraformaldehyde and secondary phosphine oxides, such as dibenzylphosphine oxide and di(*p*-tolyl)phosphine oxide was studied (Scheme 1) [1,2]. The double Kabachnik–Fields condensation was also investigated. In these cases, the primary amines were reacted with two equivalents of the paraformaldehyde and two equivalents of the P-reagents. The condensations were carried out under MW irradiation without using any catalyst in acetonitrile as the solvent to overcome the heterogeneity of the reaction mixture. All together 11 new (aminomethyl)phosphine oxides (**1**) and 8 novel *N*,*N*-bis(phosphinoylmethyl)amines (**2**) were synthesized in excellent yields (94–98%). After a double deoxygenation, the latter species (**2**) were utilized as bidentate phosphine ligands in the preparation of cyclic platinum(II) complexes (**3**).



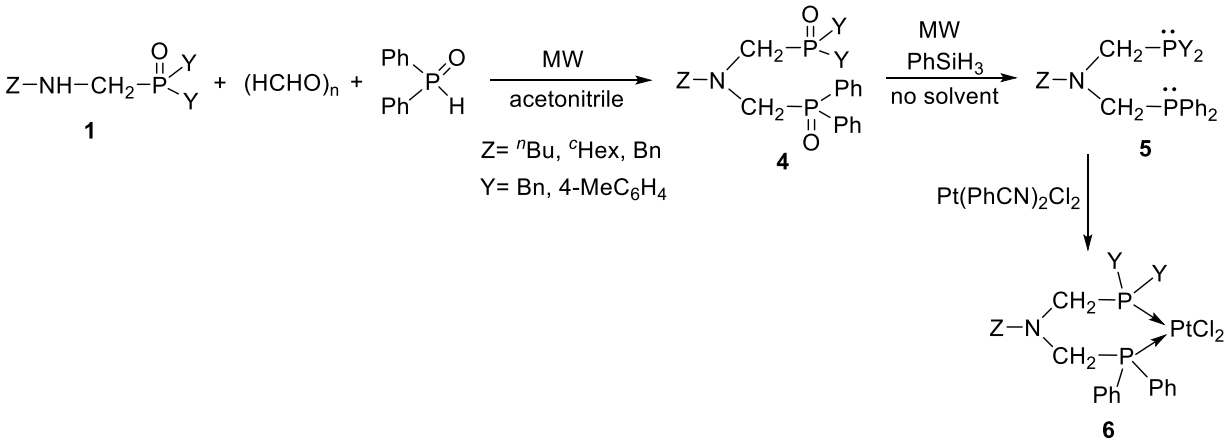
Scheme 1

The dependence of the energetics of the complexations on the substituents and the stereostructure of the complexes were evaluated by B3LYP/6-31G(d,p) and B3LYP/SDD(MWB60) calculations. Besides this, the crystal structures of

the Pt(II) complexes were solved by X-ray investigation. The complexes were tested as novel catalysts in the hydroformylation of styrene, where tin(II) chloride was used as a cocatalyst, and toluene served as the solvent. Comparing the effect of the substituents on the P atoms, it was found that the *P*-(4-methylphenyl) complexes were more active, than the *P*-benzyl derivatives. Regarding the *N*-substituent, a benzyl group on the nitrogen atom increased the activity as compared to the butyl and cyclohexyl groups.

The *N*,*N*-bis(di-*p*-tolylphosphinomethyl)amines were also converted to ring palladium(II) complexes using dichlorodibenzonitrile palladium(II) as the precursor, and the corresponding *cis* chelate complexes were obtained in yields of 40–49%.

The (aminomethyl)dibenzyl- and (aminomethyl)di(*p*-tolyl)phosphine oxides (**1**) synthesized were reacted further with one equivalent of paraformaldehyde and one equivalent of diphenylphosphine oxide in acetonitrile under MW conditions (Scheme 2). The corresponding new asymmetric *N*,*N*-bis(phosphinoylmethyl)amines (**4**) were prepared in high yields (92–97%). After the MW-assisted double deoxygenation of these derivatives with phenyl silane, the asymmetric *N*,*N*-bis(phosphinomethyl)amines (**5**) were converted to cyclic platinum(II) complexes (**6**) applying dichlorodibenzonitrile platinum(II) as the precursor.



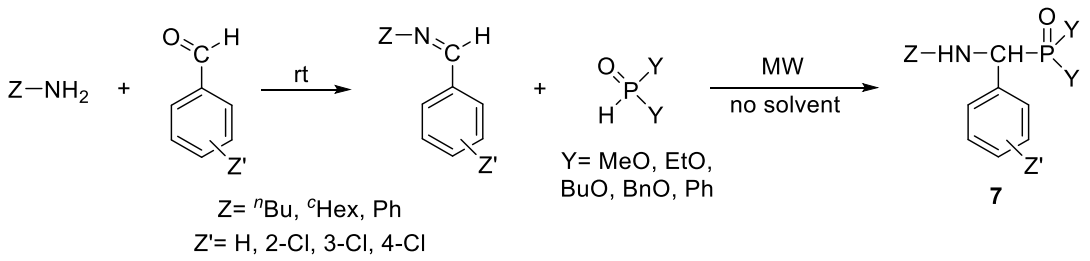
Scheme 2

The Kabachnik-Fields condensations were extended using >P(O)H reagents with different alkoxy substituents on the P-atom, such as ethyl octyl phosphite [2,3]. More than 14 new aminophosphonate and bis(aminophosphonate) derivatives were synthesized in good to high yields under catalyst-free and solvent-free MW-assisted conditions. The bisphosphonates were formed as a 1:1 mixture of two diastereomers due to the two P-stereogenic centers in the P-functionalities.

Alkyl phenyl-*H*-phosphinates were also applied as novel P-reagents in the Kabachnik–Fields reaction [2,4]. Twenty-seven new alkyl α-aminomethyl-phenylphosphinates and bis(alkoxyphenylphosphinylmethyl)amines were prepared in moderate or high yields under MW irradiation in the absence of catalyst and solvent. The formation of the *N*-methylated aminomethyl-phenylphosphinate by-products was also investigated. The *N*,*N*-bis(alkoxyphenylphosphinylmethyl)amines were formed as a mixture of two diastereomers in a ratio of 1:1.

1.2.) Synthesis of α-aryl-α-aminophosphonates and α-aryl-α-aminophosphine oxides

A series of α-aryl-α-aminophosphonate and α-aryl-α-aminophosphine oxide was prepared by the MW-assisted addition of dialkyl phosphites and diphenylphosphine oxide to imines obtained from primary amines and benzaldehyde derivatives (Scheme 3) [2,5]. All together 21 α-aminophosphonates and 3 α-aminophosphine oxides were synthesized in yields of 68–97% under catalyst- and solvent-free conditions. Except 3, all compounds were new. One of the reactions was monitored by the *in situ* FT-IR spectroscopy. The reactivity was mapped by optimization, while the fine mechanism was evaluated by DFT calculations.

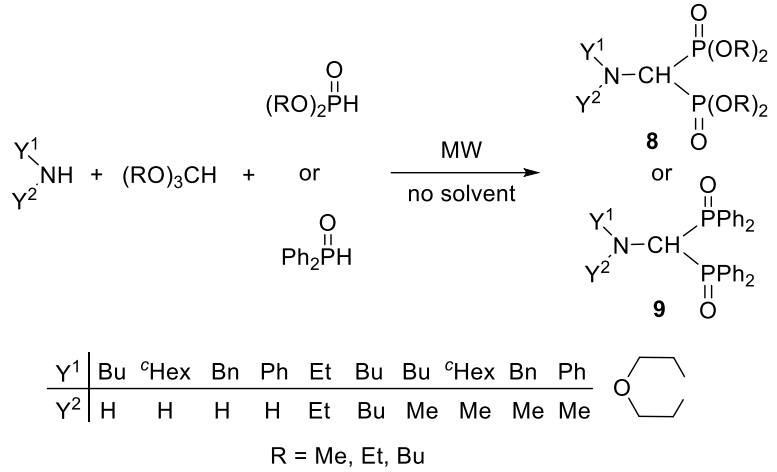


Scheme 3

1.3.) Synthesis of aminomethylene bisphosphonates by Kabachnik-Fields reaction

A facile, solvent- and catalyst-free MW-assisted method was developed for the synthesis of amino-methylenebisphosphonates (**8**) and amino-methylenebisphosphine oxides (**9**) by the condensation of a primary or secondary amine, an orthoformate, and a dialkyl phosphite or diphenylphosphine oxide was developed (Scheme 4) [6-8]. This method is a novel approach for the preparation of amino-methylenebisphosphine oxides (**9**) and an optimized process for the synthesis of amino-methylenebisphosphonates (**8**). Twenty-two derivatives were isolated with good to high yields and characterized, except two, they are new compounds. Furthermore, a few intermediates, supporting the mechanism of the condensation, and several by-products were also identified. Our purpose was to investigate the utilization of amino-

methylenebisphosphine oxides (**9**) as P-ligands after double deoxygenation, however unfortunately, the deoxygenation step of this type of phosphine oxides were not totally success, probably due to the proximity of the two phosphorus atoms.

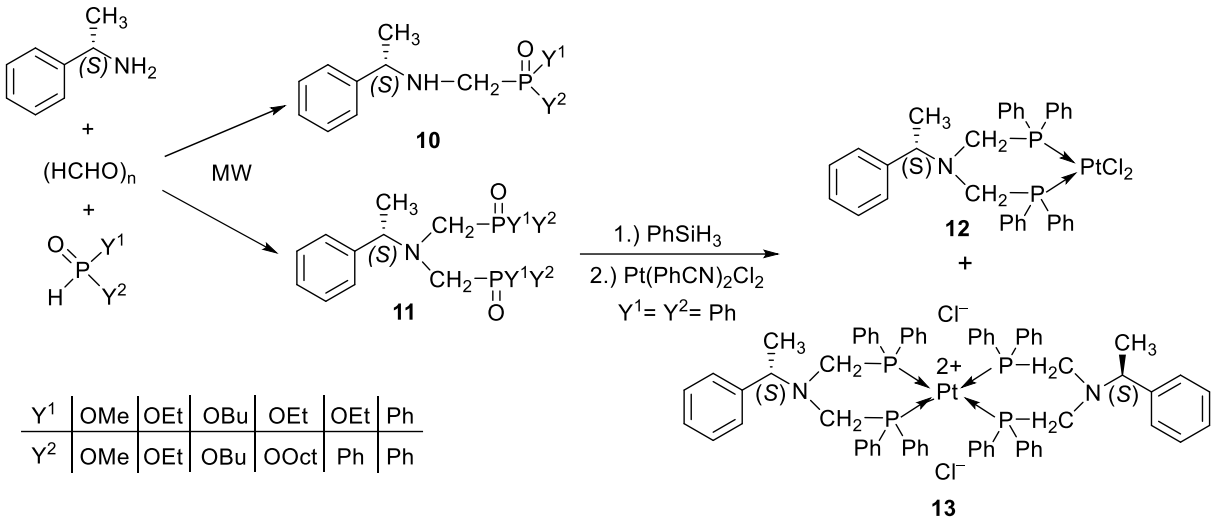


Y^1	Bu	^{c}Hex	Bn	Ph	Et	Bu	Bu	^{c}Hex	Bn	Ph
Y^2	H	H	H	H	Et	Bu	Me	Me	Me	Me

Scheme 4

1.4.) Preparation of optically active α-aminophosphonate derivatives

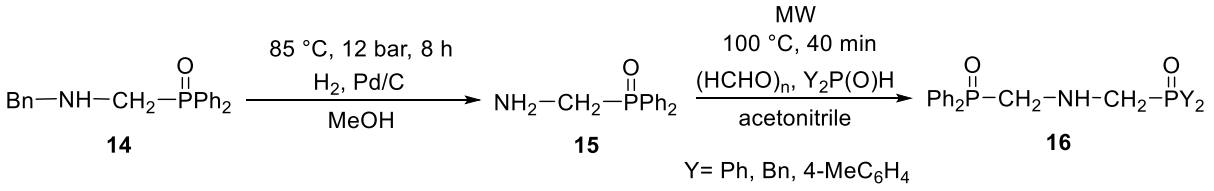
In this part of the project, the Kabachnik-Fields reactions of (*S*)-α-phenylethylamine, paraformaldehyde and various >P(O)H reagents were studied (Scheme 5) [8,9]. All together, 11 new optically active mono- and bis(α-aminophosphonate) derivatives (**10** and **11**) were prepared in high yields (71–97%) by the catalyst- and mostly solvent-free MW-assisted condensations. The (*S*)-bis(diphenylphosphinoyl)-α-phenylethylamine was converted to an optically active bidentate phosphine ligand, which was utilized in the synthesis of a chiral cyclic platinum(II) complex. A unique bicyclic platinum(II) complex, formed as a by-product, was also identified. The ensuing crystal shows not only a highly solvated complex salt structure, but also a curious pseudo-centrosymmetric disposition of most of the atoms of a chiral molecular complex in a chiral crystal lattice.



Scheme 5

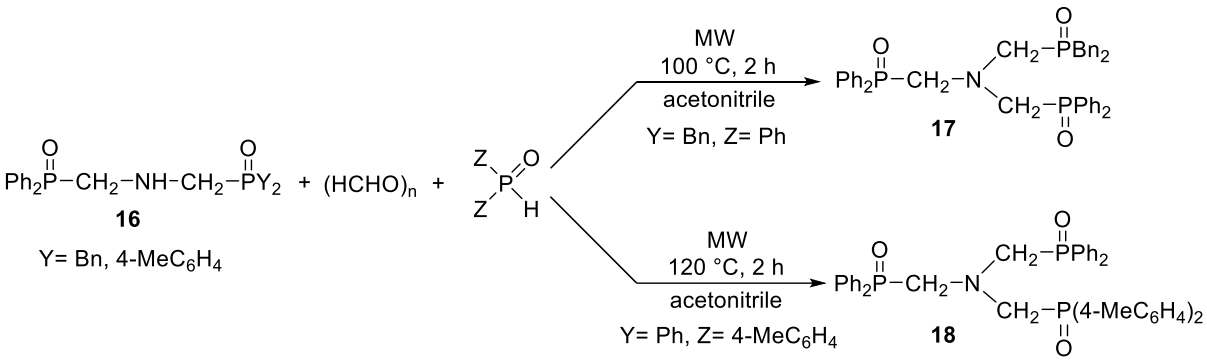
1.5.) Extension of the Kabachnik-Fields condensation using (aminoalkyl)phosphine oxide as strating material

(Aminomethyl)diphenylphosphine oxide (**15**), which was synthesized by the hydrogenation of (benzylaminomethyl)diphenylphosphine oxide (**14**), proved to be a suitable starting material in the Kabachnik-Fields reaction (Scheme 6). The condensation of (aminomethyl)diphenylphosphine oxide (**15**), paraformaldehyde and different secondary phosphine oxides, such as dibenzyl-, diphenyl- or di(*p*-tolyl)phosphine oxide was investigated under MW irradiation in the absence of catalyst, and three new symmetric and asymmetric *N*,*N*-bis(phosphinoylmethyl)amines (**16**) were synthesized in excellent yields (95–97%).



Scheme 6

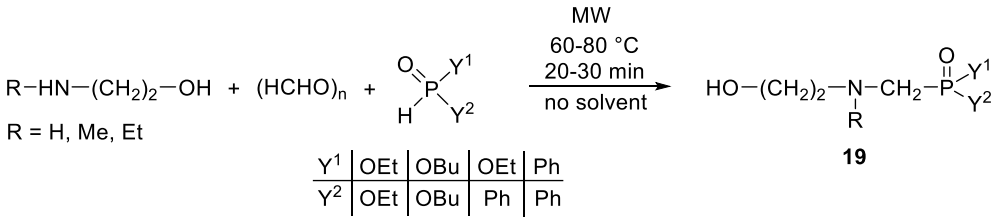
The two asymmetric *N*,*N*-bis(phosphinoylmethyl)amines (**16**) were reacted further with paraformaldehyde and diphenylphosphine oxide or di(*p*-tolyl)phosphine oxide in acetonitrile under MW irradiation (Scheme 7). The corresponding tris(phosphinoylmethyl)amine derivatives were obtained in 61% and 78%, respectively.



Scheme 7

1.6.) Kabachnik-Fields reactions of amino alcohols

The synthesis of α-aminophosphonates containing amino alcohol moiety (**19**) was studied under MW conditions. In terms of selectivity, 2-aminoethanol was not a suitable starting material in the condensation with paraformaldehyde and dialkyl phosphite (Scheme 8). Beside the expected aminophosphonates (**19**), *N*-alkylated by-products and bis derivatives were also formed. Starting from *N*-methyl- or *N*-ethyl-substituted amino alcohols, such as 2-(methylamino)ethanol or 2-(ethylamino)ethanol, the corresponding aminophosphonates (**19**) were obtained selectively. Applying diphenyl phosphine oxide as the P-reagent, the condensation was selective with all the three type of amino alcohols. The reactions were carried out efficiently in the absence of catalyst and solvent, and nine new derivatives were synthesized in yields of 52–98%.



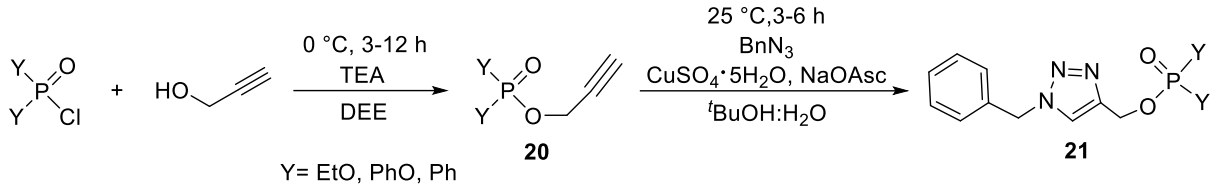
Y^1	OEt	OBu	OEt	Ph
Y^2	OEt	OBu	Ph	Ph

Scheme 8

2.) Synthesis of derivatives containing a triazole ring by click reaction

The click reaction of phosphorous-containing acetylenes and benzyl azide was also studied (Scheme 9). First the preparation of the starting materials (**20**) was carried out. The synthesis of >P(O)-C-acetylenes was not efficient due to decomposition problems, instead of these, >P(O)-O-C-acetylene derivatives (**20**) were prepared by the esterification of diethyl- and diphenyl chlorophosphate, as well as diphenylphosphinic chloride with propargyl alcohol. After that, the click reactions were performed with benzyl azide at room temperature in the presence

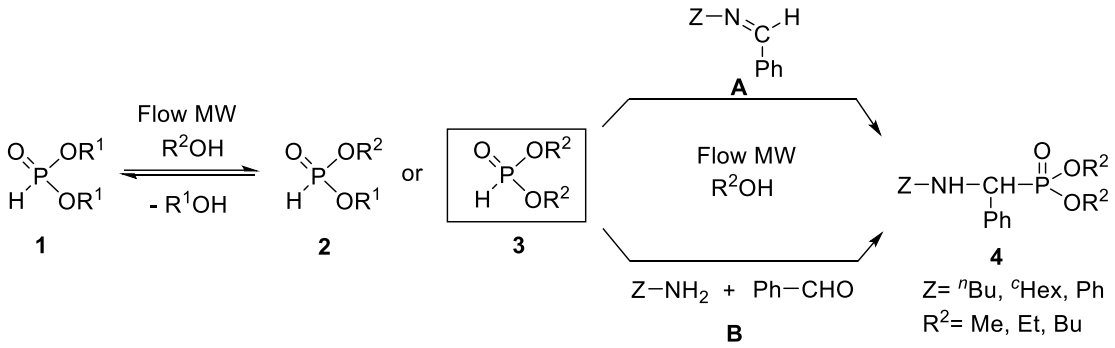
of copper(II) sulphate and sodium ascorbate. The corresponding triazole-based derivatives were obtained in yields of 60–76%.



Scheme 9

3.) Continuous flow microwave-assisted synthesis

The scale up of MW-assisted reactions is limited. In order to synthesize higher amount of products, the use of continuous flow MW reactors can be a suitable solution. During this research project, a continuous flow MW system was also developed using a commercially available flow cell immersed into a batch MW reactor. The first model reactions investigated were the direct esterification of benzoic acid with different aliphatic alcohols [10]. The research was extended to the investigation of the alcoholysis of dialkyl phosphites [11]. Our aim was to optimize the conditions to obtain the mixed esters (**2**) or the fully transesterified products (**3**). The symmetric dialkyl phosphites (**3**) were utilized in the continuous flow synthesis of α-aminophosphonates (**4**). The latter species were synthesized by the Pudovik reaction (**A**) or the Kabachnik-Fields condensation (**B**), in the absence of any catalyst [11].



The results of the project were also summarized in two papers [12,13] and in two bookchapters [14,15].

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Submitted manuscript:

1. **Bálint, E.**; Tajti, Á; Tripolszky, A.; Keglevich G. Synthesis of platinum, palladium and rhodium complexes of α-aminophosphine ligands. *Dalton Trans.* **2018** – submitted.

Manuscript before submission:

1. **Bálint, E.**; Tripolszky, A.; Hegedűs, L.; Keglevich, G. Synthesis and utilization of asymmetric *N,N*-bis(phosphinoylmethyl)amines by the Kabachnik-Fields reaction of (aminomethyl)phosphine oxides.
2. Tajti, Á.; **Bálint, E.**; Szatmári, E.; Keglevich, G. Kabachnik-Fields reaction of aminoalcohol derivatives.

List of presentations:

1. **Bálint, E.**; Tajti, Á.; Kangyal, R.; Tóth, R. E.; Ádám, A.; Horváth, J.; Tripolszky, A.; Keglevich G.: Kabachnik-Fields reakciók különféle megvalósításai. MKE 2. Nemzeti Konferencia, Hajdúszoboszló, 2015. augusztus 31. – szeptember 2. (oral presentation)
2. **Bálint, E.**; Tripolszky, A.; Kollár, L.; Keglevich, G.: α-Aminofoszfin-oxidok előállítása és P-ligandumként történő hasznosítása. MKE 2. Nemzeti Konferencia, Hajdúszoboszló, 2015. augusztus 31. – szeptember 2. (poszter előadás)
3. **Bálint, E.**; Tripolszky, A.; Tajti, Á.; Tóth, R. E.; Keglevich, G.: Aminofoszfonátok és aminofoszfin-oxidok szintézise és hasznosítása. XXI. Nemzetközi Vegyészkonferencia, Csíksomlyó, Románia, 2015. szeptember 23-27. (oral presentation)
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5. **Bálint, E.**; Tripolszky, A.; Ádám, A.; Tajti, Á.; Keglevich, G.: Synthesis and utilization of α-aminophosphine oxides and related derivatives. 21st International Conference on Phosphorus Chemistry, Kazan, Russia, June 5-10, 2016. (poster presentation)
6. **Tajti, Á.**; Tóth, R. E.; Kalocsai, D.; Keglevich, G.; Bálint, E.: Formation of P-C-N moiety by microwave-assisted condensation reactions. 21st International Conference on Phosphorus Chemistry, Kazan, Russia, June 5-10, 2016. (poster presentation)
7. **Bálint, E.**; Tajti, Á.; Ádám, A.; Keglevich, G. Dialkil-foszfitok és difenilfoszfin-oxid Pudovik-reakciója iminekkel mikrohullámú körülmények között. Vegyészkonferencia 2017, Hajdúszoboszló, 2017. június 19-21. (oral presentation)

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14. **Bálint, E.**; Tajti, Á.; Ladányi-Pára, K.; Keglevich, G.: Microwave-assisted synthesis of α-aminophosphonates under continuous flow conditions. 6th Conference on Frontiers in Organic Synthesis Technology, Budapest, Hungary, October 18-20, 2017. (poster presentation)
15. Tajti, Á.; Tóth, N.; Keglevich, G.; **Bálint, E.**: Direct esterification of benzoic acid and alcoholysis of dialkyl phosphites in a continuous flow MW reactor. 6th Conference on Frontiers in Organic Synthesis Technology, Budapest, Hungary, October 18-20, 2017. (poster presentation)
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