



**BUDAPEST UNIVERSITY OF TECHNOLOGY AND ECONOMICS
FACULTY OF CHEMICAL AND BIOENGINEERING
GEORGE OLAH DOCTORAL SCHOOL**

**SYNTHESIS OF PHOSPHONATES, PHOSPHINATES AND
TERTIARY PHOSPHINE OXIDES BY ESTERIFICATION AND
P –C COUPLING REACTION**

PhD Thesis

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1. Introduction

Nowadays, the environmentally methods have become of increasing importance. The twelve principles¹ of green chemistry were described by *Anastas* and *Warner*, which were completed by twelve additional practical principles in 2003. According to these principles, synthetic methods should be designed to use renewable substances and to increase atomic and energy efficiency. Furthermore, unnecessary derivatization should be avoided and the shortest reaction path should be preferred. In the ideal case the green methods are economically favourable.

I started my PhD studies at the research group of *Prof. Dr. György Keglevich* at the Budapest University of Technology and Economics, Department of Organic Chemistry and Technology.

During my research work, new alternative methods were elaborated for the synthesis of phosphonates, phosphinates and tertiary phosphine oxides. These processes may be more economically-friendly and efficient approaches. My research work involves two main topics, “Synthesis of phosphinates by esterification of phosphinic acids” and “Synthesis of phosphonates, phosphinates and tertiary phosphine oxides by P–C coupling reaction”. These projects are focused on green chemical aspects.

It was found that applying the microwave (MW) technique the reactions become faster, and the yields and selectivity will be higher.² In addition, the use of solvents and catalysts can be avoided. Therefore, our reactions were performed primarily under MW conditions, and we studied the effects of MW irradiation.

Although, during my PhD work we synthesized valuable *P*-containing intermediates, the new simple and environmentally-friendly methods developed are considered to be more important from the point of view of our research work.

[1] Anastas, P. T.; Warner, J. C., In *Green Chemistry: Theory and Practice*; Oxford University Press: Oxford, **1998**.

[2] Keglevich, Gy., *Magy. Kém. Foly.* **2008**, 114, 81.

2. Background

2.1. Synthesis of phosphinic esters and amides

The classical method for the synthesis of phosphinic esters and amides involves the reaction of phosphinic chlorides with alcohols and amines, respectively. This method works well, but the use of expensive phosphinic chlorides cannot be regarded an environmentally-friendly approach.

Another strategy for the preparation of phosphinic acid derivatives is to activate the acids by derivatization, which easily reacts with nucleophiles.

Keglevich and *Kiss* found that the direct esterification of phosphinic acids with alcohols can be accomplished under MW conditions. The direct amidation of phosphinic acids was also studied, but it led only to low yields.

2.2. P–C coupling reactions

These days, coupling reactions are in the focus of interest. The P–C coupling of aryl-derivatives with dialkyl phosphites, *H*-phosphinates and secondary phosphine oxides became an important method for the synthesis of phosphonates, phosphinates and tertiary phosphine oxides, thus more and more publication can be found for these approaches. According to the original Hirao reaction, the P–C coupling reaction was carried out in the presence of expensive and air sensitive Pd(PPh₃)₄ as the catalyst using triethylamine or other bases in toluene. Many alternative approaches were described in the last three decades, which applied Pd, Ni or Cu salts combined with monodentate or bidentate *P*-ligands.

3. Experimental methods

The MW-assisted reactions were carried out in a 300 W CEM Discover microwave reactor equipped with a pressure controller.

The crude reaction mixtures were analysed by gas chromatography (GC), and in some cases by liquid chromatography (LC-MS). Purification of the products was carried out by flash column chromatography using silica gel.

The products were identified by ³¹P, ¹³C and ¹H NMR spectroscopic, HRMS spectrometric methods.

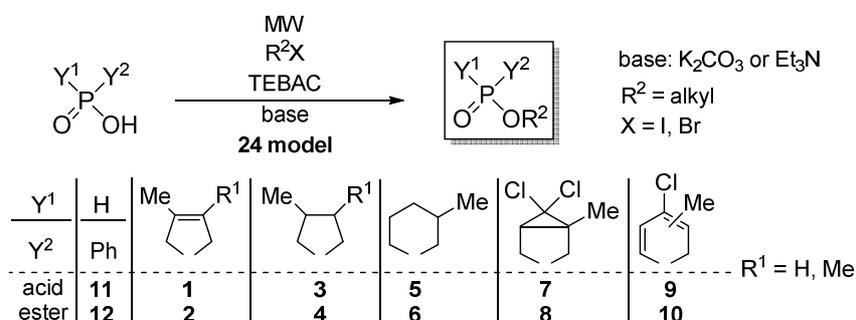
Quantum chemical calculations were carried out by the B3LYP/6-31G(d,p) method using the Gaussian09 program package. The PCM implicit method was applied taking into account the effect of solvent.

4. New scientific results

4.1. Alkylating esterification of phosphinic acids

The solid-liquid phase alkylating esterification of phosphinic acids (**1**, **3**, **5**, **7** and **9**) was carried out in the presence of K_2CO_3 , and the corresponding phosphinates (**2**, **4**, **6**, **8** and **10**) were formed in high yields. It was found, that the use of MW irradiation and PTC is beneficial in the reaction of 1-hydroxy-3-phospholene 1-oxide (**1**), 1-hydroxy-phospholane 1-oxide (**3**) and 1-hydroxy-3-methyl-1,2,3,4,5,6-hexahydrophosphinine 1-oxide (**5**) with alkyl halide of normal reactivity. In the case of thermally unstable phosphinic acids (**7** and **9**), the conventional heating was more effective, and the decomposition could be avoided using acetone as the solvent.

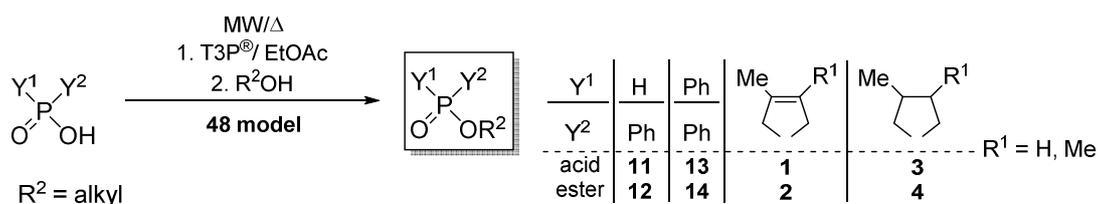
The alkylating esterification of acyclic phenyl-*H*-phosphinic acid (**11**) was carried out in homogenous phase in the presence of triethylamine.



The alkyl-phenyl-*H*-phosphinates (**12**) were utilized in P–C coupling reactions.

4.2. Esterification and amidation of phosphinic acid using T3P[®] reagent

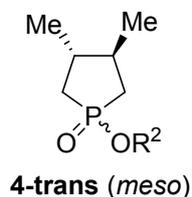
The esterifications of phenyl-*H*-phosphinic acid (**11**) and cyclic phosphinic acids (**1** and **3**) were carried out using 1.1 equivalent of T3P[®] under mild conditions (at 25 °C after 1-2 hours) and the corresponding products (**12**, **2** and **4**) were formed in good and high yields. The esterification of diphenylphosphinic acid (**13**) required higher temperature (85 °C) and MW irradiation, thus alkyl diphenylphosphinates (**14**) were obtained in yields of 45-49%.



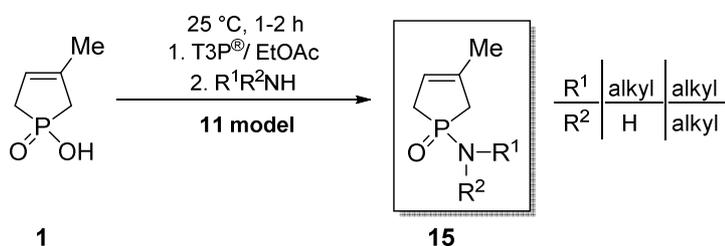
It was found that it is enough to apply the T3P[®] reagent in quantities of 0.44 or 0.66 equivalents in the reactions of more reactive phenyl-*H*-phosphinic acid (**11**) and 1-hydroxy-3-phospholene 1-oxides (**1**), but more forcing conditions are necessary in order to achieve good

yields. It can be concluded that from among the three “PrP(O)O” units of the T3P[®] reagents, more than one fragment can be utilized with reactive phosphinic acids.

Furthermore, it was noticed that the esterification of 1-hydroxy-3,4-dimethylphospholane 1-oxide (**3**, R¹ = Me) led to only to the trans (meso) diastereomer (**4-trans**, R¹ = Me). It can be concluded that using T3P[®] reagent the esterification became diastereoselective.



We have also studied the amidation of 1-hydroxy-3-methyl-3-phospholene 1-oxide (**1**, R¹ = Me) using the T3P[®] reagent. This method for the synthesis of phosphinic amides is a possible way to avoid the use of phosphinic chlorides.



The energetics of the T3P[®]-assisted esterification and amidation of 1-hydroxy-3-methyl-3-phospholene 1-oxid (**1**, R¹ = Me) with butanol and butylamine were evaluated by quantum chemical calculations which showed that both reactions are exothermic, and the esterification is energetically more favourable (Figure 1). Furthermore, it was found that the phosphinic acid (**1**, R¹ = Me) reacts with butanol in one-step fusion, while due to the intermediacy of the protonated *P*-amide, the amidation is a two-step process.

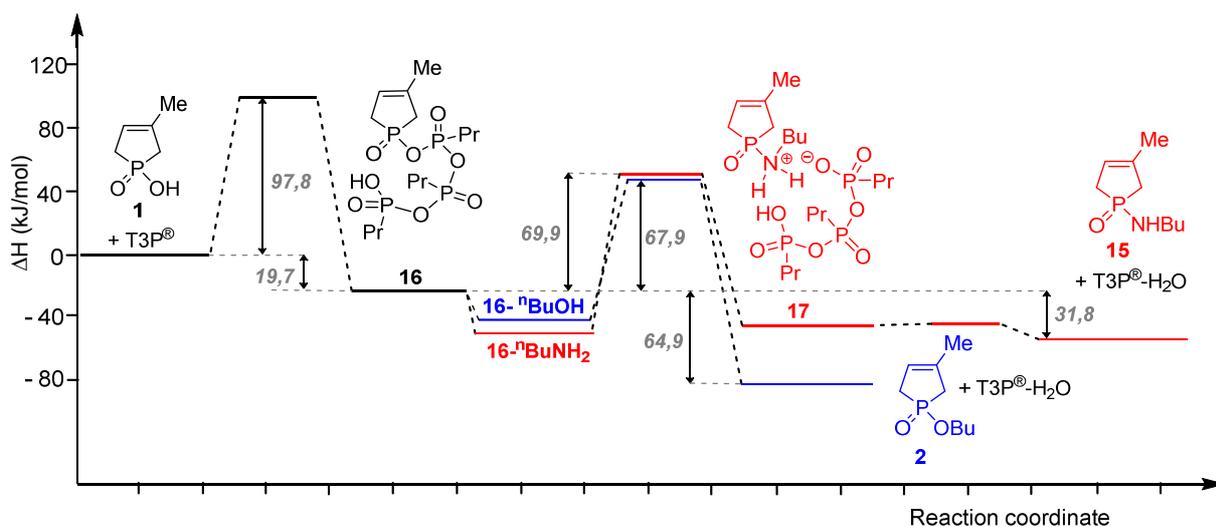
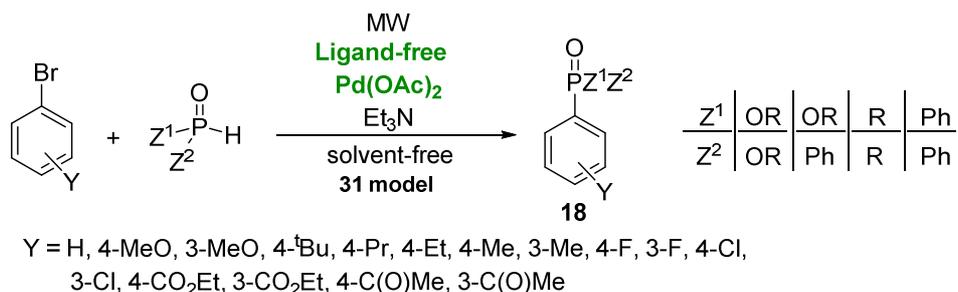


Figure 1 Mechanism of T3P[®]-assisted esterification and amidation

4.3. Ligand-free Pd-catalyzed P–C coupling reaction

The coupling reaction of aryl bromide with >P(O)H-reagents, such as dialkyl phosphites, alkyl phenyl-*H*-phosphinates and secondary phosphine oxides could be performed using Pd(OAc)₂ as the catalyst and triethylamine as the base without any ligand. The *P*-ligand-free Pd-catalyzed P–C coupling reactions were carried out in homogeneous phase under solvent-free MW conditions.

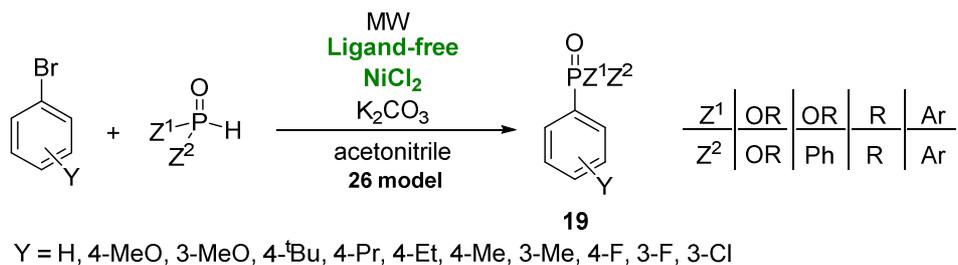


The effect of reaction conditions, such as amount of catalyst, temperature and reaction time were also studied. The reactions of bromobenzene and a >P(O)H-species, in almost all cases, were complete in the presence of 5% Pd(OAc)₂ at 150 °C after 5 min. In contrast to bromobenzene, the reaction of substituted aryl bromides required 10% Pd(OAc)₂ and a higher temperature (175/200 °C).

The *P*-ligand-free Pd-catalyzed reaction was utilized in course of the preparation of 31 model compounds (**18**) demonstrating its general value.

4.4. Ligand-free Ni-catalyzed P–C coupling reaction

A novel method was elaborated for the *P*-ligand-free Ni-catalyzed P–C coupling of aryl bromides with >P(O)H-species. These couplings were performed using NiCl₂ as the catalyst and K₂CO₃ as the base. Acetonitrile was applied to avoid the heterogeneity. The reaction of bromobenzene and diethyl phosphite was also studied on conventional heating, and in this case ethyl diphenylphosphinate was formed as the by-product. It can be seen that the MW irradiation allowed a chemoselective reaction.

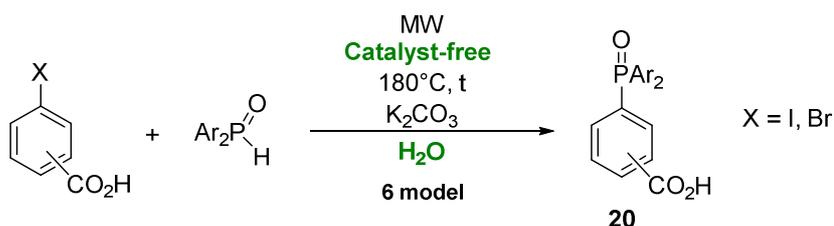


In many cases, the *P*-ligand-free Ni-catalyzed P–C couplings afforded the corresponding

products (**19**) in high yields at 150 °C after 0,75-2 hours. This method was applied for the preparation of 26 model compounds (**19**).

4.5. Catalyst-free P–C coupling reaction

It was found that the reaction of iodo- and bromobenzene with diarylphosphine oxide could be performed without any catalyst. The catalyst-free P–C coupling reactions were carried out in water under MW conditions and the phosphinoylated benzoic acids (**20**) were obtained at 180 °C after 1-3 hours in good yields which were isolated as the corresponding ethyl esters.



Although this method is a greener accomplishment, it works only for reaction of reactive water soluble compounds, such as halogenated benzoic acids and diarylphosphine oxides.

5. Theses

1. A simple and efficient method was elaborated by us for the solid-liquid alkylating esterification of 5- and 6-membered cyclic phosphinic acids in the presence of K_2CO_3 . It was found that the simultaneous use of MW irradiation and PTC is beneficial when alkyl halides of normal reactivity are applied. We extended the alkylating esterification to the derivatization of thermally unstable cyclic phosphinic acids. [1,2,3]
2. The alkylation of phenyl-*H*-phosphinic acid was accomplished by us in homogeneous phase using triethylamine as the base. [7]
3. A method was developed by us for the esterification of phosphinic acids using the T3P[®] reagent. We proved that under MW conditions less than a stoichiometric quantity is enough from the T3P[®] reagent when reactive phosphinic acids (*e.g.* phenyl-*H*-phosphinic acid, hydroxy-3-phospholene-1-oxide) are reacted. [4,5]
4. The T3P[®]-assisted derivatizations were extended by us to the preparation of phosphinic amides. [5]
5. We proved by quantum chemical calculation that the esterification and amidation of

phosphinic acids are exothermic in the presence of T3P[®] reagent, and that the esterification is energetically more favourable than the amidation.

6. We observed that MW-assisted coupling reaction of aryl bromides with dialkyl phosphites, alkyl phenyl-*H*-phosphinates or secondary phosphine oxides may be performed without *P*-ligand using Pd(OAc)₂ as the catalyst to afford the corresponding phosphonates, phosphinates or tertiary phosphine oxides. [6,7]
7. A NiCl₂ catalyzed *P*-ligand-free variation for the coupling reaction was also elaborated by us resulting in the formation of phosphonates, phosphinates and tertiary phosphine oxides. The couplings were carried out in the presence of K₂CO₃ in acetonitrile under MW conditions. [8]
8. A green method was developed for the reaction of iodo- and bromobenzoic acid with diarylphosphine oxides that was performed without any catalyst in the presence of K₂CO₃ as the base in water and under MW conditions. [9]

6. Application possibilities

The phosphinic acids can be converted directly to the corresponding phosphinates by alkylating and T3P[®]-assisted esterification. These methods are generally applicable for the synthesis of phosphinates. The T3P[®]-assisted esterification becomes more favourable due to the use of less than stoichiometric amount of the T3P[®] reagent, when reactive compounds are esterified. Therefore the not so cheap T3P[®] may be applied in industrial scale and the method is more environmentally-friendly.

In the course of *P*-ligand-free P–C coupling reactions, we proved that the reaction of aryl bromides with dialkyl phosphites, alkyl phenyl-*H*-phosphinates and secondary phosphine oxides can be performed in the presence of Pd and Ni salts. These ligand-free P–C coupling reactions can be more environmentally-friendly than traditional P–C couplings. The cost can be decreased by the use of Pd and Ni salts without any additional ligands, and the processing of the reaction mixture is also more simplified. These experiences can be utilized in other Pd- and Ni-catalyzed syntheses as well.

Noteworthy, it was found, that positive effects of the MW irradiation could be observed in all cases of the alkylating esterification, of T3P[®]-assisted esterification and of P–C couplings, as in most of the cases the transformations were incomplete under traditional heating. These experiences demonstrate that the use of MW technique may be effective in a wide range of chemical reactions.

7. Publications

7.1. Full scientific publications related to the PhD Thesis

- [1] Bálint E., **Jablonkai E.**, Bálint M., Keglevich Gy.: Alkylating Esterification of 1-Hydroxy-3-phospholene Oxides under Solventless MW Conditions; *Heteroatom Chem.* **2010**, *21*, 211-214. [IF: **1,044**; JE: **45%**; I: **2**]
- [2] Keglevich G., Bálint E., Kiss N. Zs., **Jablonkai E.**, Hegedűs L., Grün A., Greiner I.: Microwave-Assisted Esterification of Phosphinic Acids; *Curr. Org. Chem.* **2011**, *15*, 1802-1810. [IF: **3,064**; JE: **33%**; I: **1**]
- [3] **Jablonkai E.**, Bálint E., Balogh Gy. T., Drahos L., Keglevich Gy.: Cyclic phosphinates by the alkylation of a thermally unstable 1-hydroxy-1,2-dihydrophosphinine 1-oxide and a 3-hydroxy-3-phosphabicyclo[3.1.0]hexane 3-oxide, *Phosphorus, Sulfur, Silicon* **2012**, *187*, 357-363. [IF: **0,601**, JE: **70%**]
- [4] **Jablonkai E.**, Milen M.; Drahos L., Keglevich Gy.: Esterification of five-membered cyclic phosphinic acids under mild conditions using propylphosphonic anhydride (T3P[®]); *Tetrahedron Lett.* **2013**, *54*, 5873-5875. [IF: **2,391**, JE:**100%**; I: **2**]
- [5] **Jablonkai E.**, Keglevich Gy.: *P*-ligand-free, microwave-assisted variation of the Hirao reaction under solvent-free conditions; the P-C coupling reaction of >P(O)H species and bromoarenes, *Tetrahedron Lett.* **2013**, *54*, 4185-4188. [IF: **2,391**, JE: **100%**; I: **4**]
- [6] Keglevich Gy., **Jablonkai E.**, Balázs L. B.: A „green” variation of the Hirao reaction: the P-C coupling of diethyl phosphite, alkyl phenyl-*H*-phosphinates and secondary phosphine oxides with bromoarenes using a *P*-ligand-free Pd(OAc)₂ catalyst under microwave and solvent-free conditions; *RSC Adv.* **2014**, *4*, 22808-22816. [IF: **3,708**, JE: **70%**; I: **1**]
- [7] **Jablonkai E.**, Henyecz R., Milen M., Kóti J., Keglevich Gy.: T3P[®]-assisted esterification and amidation of phosphinic acids; *Tetrahedron* **2014**, *70*, 8280-8285. [IF: **2,817**, JE: **60%**]
- [8] Jablonkai E., Balázs L. B., Keglevich Gy.: A *P*-ligand-free Ni-catalyzed variation of the Hirao reaction under MW condition; *Curr. Org. Chem.* **2015**, *19*, 197-202. [IF: **2,537**, JE: **85%**]
- [9] **Jablonkai E.**, Keglevich Gy.: Catalyst-free P-C coupling reactions of halobenzoic acids and secondary phosphine oxides under microwave irradiation in water, *Tetrahedron Lett.*

2015, 56, 1638-1640. [IF: 2,391, JE:100%]

7.2. Proceedings and short publications related to the PhD Thesis

- [10] Keglevich Gy., Kiss, N. Zs., Bálint E., **Jablonkai E.**, Grün A., Milen M., Frigyes D., Greiner I.: Microwave-Assisted Esterification of Phosphinic Acids by Alcohols, Phenols, and Alkyl Halogenides; *Phosphorus, Sulfur and Silicon*, **2011**, 186, 802-803. [IF: 0,716; JE: 33%]
- [11] Keglevich Gy., Kiss N. Zs., Bálint E., Kovács R., **Jablonkai E.**, Fazekas E., Takács J., Kaszás A., Blastik Zs., Grün A.: Synthesis of Organophosphorus Compounds under Microwave Conditions, *IFMBE Proc.* **2011**, 37, 1350-1353. [IF: –, JE: 15%]
- [12] **Jablonkai E.**, Balázs L. B., Keglevich Gy.; MW-Assisted P-C coupling reaction using P-ligand-free Pd(OAc)₂ catalyst; *Phosphorus, Sulfur, Silicon* **2015**, 190, 660-663. [IF: 0,827, JE: 70%]
- [13] Keglevich Gy, Kiss N. Zs., **Jablonkai E.**, Bálint E., Mucsi Z.: The potential of microwave in organophosphorus syntheses; *Phosphorus, Sulfur, Silicon* **2015**, 190, 647-654. [IF: 0,827, JE: 50%]

7.3. Review and mini-review articles related to the PhD Thesis

- [14] Keglevich Gy., Grün A., Bálint E., Kiss N. Zs., **Jablonkai E.**: Microwave-Assisted Organophosphorus Syntheses; *Curr. Org. Chem.* **2013**, 17, 545-554. [IF: 2,537; JE: 50%; I: 2]
- [15] **Jablonkai E.**, Keglevich Gy.: P-C Formation by Coupling Reactions Utilizing >P(O)H Species as the Reagents; *Curr. Org. Synth.* **2014**, 11, 429-453. [IF: 2,439, JE: 100%]
- [16] **Jablonkai E.**, Keglevich Gy.: Advances and New Variations of the Hirao Reaction; *Org. Prep. Proc. Int.* **2014**, 46, 281-316. [IF: 1,185, JE: 100%; I: 1]
- [17] Keglevich Gy., Grün A., Bagi P., Bálint E., Kiss N. Zs., Kovács R., **Jablonkai E.**, Kovács T., Fogassy E., Greiner I.: Environmentally friendly chemistry with organophosphorus syntheses on the focus, *Period. Polytech.* **2015**, 59, 82-95. [IF: 0,130, JE: 20%]
- [18] Keglevich Gy., Kiss N. Zs., Mucsi Z., **Jablonkai E.**, Bálint E.: The Synthesis of Phosphinates – Traditional Versus Green Chemical Approaches; *Green Proc. Synth.* **2014**, 3, 103–110. [IF: 1,125, JE: 50%]

- [19] **Jablonkai E.**, Keglevich Gy.: A survey of the palladium-catalyzed Hirao reaction with emphasis on green chemical aspects. *Curr. Green Chem.* **2015** (nyomdában). [IF: –, JE:100%]
- [20] **Jablonkai E.**, Keglevich Gy.: P-C coupling Reactions under environmentally-friendly conditions, in *Advances in Engineering Research* (Eds. Victoria M. Petrova), Nova Science Publishers, **2015**, vol. 10, ISBN: 978-1-63482-815-4. [IF: –, JE:100%]

7.4. Additional publication

- [21] **Jablonkai E.**, Drahos L., Drzazga Z., Pietrusiewicz M. K., Keglevich Gy.: 3-P=O-Functionalized Phospholane 1-Oxides by the Michael Reaction of 1-Phenyl-2-phospholene 1-Oxide and Dialkyl Phosphites, *H-Phosphinates*, or Diphenylphosphine Oxide, *Heteroatom Chem.* **2012**, 23, 539-544. [IF: 1,577, JE: 100%]

7.5. Oral presentations

1. **Jablonkai E.**, Bálint E., Keglevich Gy.: Foszfinsavak alkilező észterezésének vizsgálata, *Kémiai Előadói Napok*, Szeged, 2012.
2. **Jablonkai E.**, Bálint E., Keglevich Gy.: *P*-heterociklusok funkcionálizálása: Alkilezés, Észterezés és Michael-addíció, *Heterociklusos és Elemorganikus Kémiai Munkabizottság ülése*, Balatonszemes, 2013.
3. **Jablonkai E.**, Balázs L. B., Keglevich Gy.: Hirao-reakció megvalósítása Pd(II) só jelenlétében *P*-ligandum alkalmazása nélkül, *Kémiai Előadói Napok*, Szeged, 2013.
4. **Jablonkai E.**, Keglevich Gy.: A mikrohullámú technika alkalmazásának lehetőségei katalitikus reakciókban, *X. Oláh György Doktori Iskola Konferenciája*, Budapest, 2013.
5. **Jablonkai E.**, Henyecz R., Balázs L. B., Keglevich Gy.: Foszfor-heterociklusok és más analóg vegyületek funkcionálizálása észterezési és P-C kapcsolási reakciókkal, *Heterociklusos és Elemorganikus Kémiai Munkabizottság ülése*, Balatonszemes, 2014.

7.6. Poster presentations

1. **Jablonkai E.**, Keglevich Gy.: MW-assisted Alkylating Esterification and Michael addition, *IX. Oláh György Doktori Iskola Konferenciája*, Budapest, 2012.
2. **Jablonkai E.**, Keglevich Gy.: >P(O)H-funkciót tartalmazó reagensek Michael-addíciója 2-foszfolén-oxidra, *Vegyészkonferencia*, Hajdúszoboszló, 2013.

3. **Jablonkai E.**, Balázs L. B., Keglevich Gy.: P-C kapcsolás *P*-ligandummentes Pd katalizátorral, *Vegyészkonferencia*, Hajdúszoboszló, 2013.
4. **Jablonkai E.**, Balázs L. B., Keglevich, Gy.: A *P*-Ligand-Free Palladium-Catalyzed Version of the Hirao Reaction, *15. Österreichische Chemietage*, Graz, 2013.
5. **Jablonkai E.**, Balázs L. B., Keglevich Gy.: MW-Assisted P-C Coupling Reaction Using *P*-Ligand-Free Pd(OAc)₂ Catalyst, *International Conference Phosphorus Chemistry*, Dublin, 2014.
6. **Jablonkai E.**, Keglevich Gy.: P-C kapcsolás *P*-ligandummentes mikrohullámú körülmények között, *Vegyészkonferencia*, Hajdúszoboszló, 2015.
7. **Jablonkai E.**, Henyecz R., Ábrányi-Balogh P., Milen M., Keglevich Gy.: Foszfinsavészterek és amidok szintézise T3P[®] reagens alkalmazásával, *Vegyészkonferencia*, Hajdúszoboszló, 2015.