FUNCTIONALIZATION OF P-HETEROCYCLES UTILIZING MICROWAVE IRRADIATION

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Abstract. *In this chapter, the recent results on the functionalization and refunctionalization of P-heterocycles, performed in most cases under microwave irradiation, are surveyed. During the esterifications, transesterifications, aminolyses, hydrolyses, deoxygenations and other transformations, green chemical approaches comprising atomic efficient, chlorine-free, catalyst-free, and, when possible, solvent-free accomplishments were applied.*

Contents

1. Introduction

Organophosphorus compounds including P-heterocycles find applications in synthetic organic chemistry as reactants, solvents (ionic liquids), catalysts or P-ligands, and, due to their biological activity, also as components of drugs and plant protecting agents.[1-3]

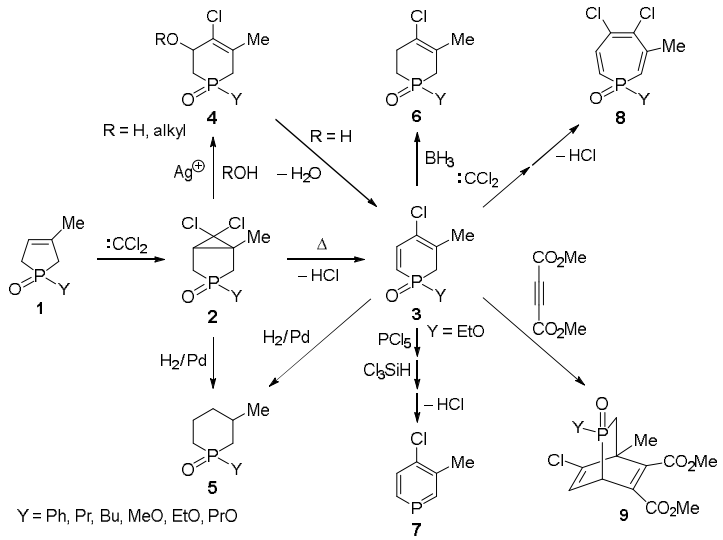
The Keglevich-group elaborated the ring expansion of easily available 3-phospholene 1-oxides **1** to simple 6-membered derivatives, such as 3-phosphabicyclo[3.1.0]hexane 3-oxides **2** and 1,2-dihydrophosphinine 1-oxides **3**.[4] Then, other P-heterocyclic derivatives, like 1,2,3,6-tetrahydrophosphinine oxides **4** and **6**, 1,2,3,4,5,6-hexahydrophosphinine oxides **5**, aromatic phosphinines **7**, phosphepine oxides **8**, bridged phosphabicyclo[2.2.2]octadiene **9** were synthesized (Scheme 1).[5,6] The chemistry and aromaticity of phospholes belonging to the family of pyrrole, furan and thiophene was also explored.[7,8]

The use of the microwave (MW) technique is widely used in organic chemistry for promoting a variety of syntheses, such as substitutions, additions, eliminations, condensations, acylations, esterifications, alkylations, C–C coupling reactions, cycloadditions, rearrangements and the formation of heterocycles, occasionally in multicomponent reactions.[9-10] The most common benefits from MW irradiation is the considerable shortening of reaction times and the increase in the selectivities. However, the most valuable benefit is when is it possible to perform a reaction that is otherwise impossible under traditional thermal conditions. This may be the consequence of the statistically occurring local overheating effects.[11,12] The utilization of MW irradiation in organophosphorus chemistry is a relatively new field.[13-15]

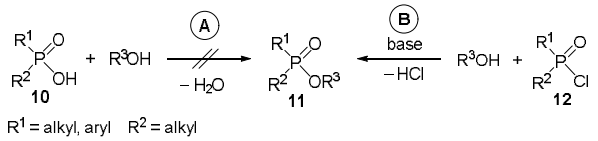
2. Direct esterification of cyclic phosphinic acids

It is well-known that phosphinic acids **10** do not undergo esterification with alcohols to afford phosphinates **11** (Scheme 2/**A**). For this reason, the esters of phosphinic acids **11** are synthesized by the reaction of phosphinic chlorides **12** with alcohols in the presence of a base (Scheme 2/**B**).[1] The generally applied esterification method (Scheme 2/**B**) has the drawback of requiring relatively expensive P-chlorides **12**

as the starting materials. In these cases, hydrogen chloride is formed as by-product and must be removed by a base. Hence, the method is not atomic efficient and is not environmentally-friendly.



Scheme 1. Ring expansion of 3-phospholene 1-oxides **1**, and utilization of 3-phosphabicyclo[3.1.0]hexane 3-oxides **2** and 1,2-dihydrophosphinine oxides **3** in the synthesis of other P-heterocycles.



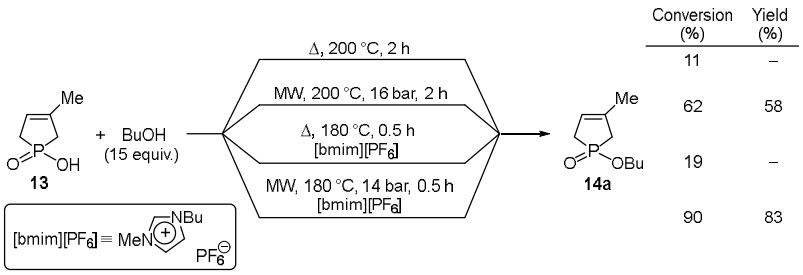
Scheme 2. The synthesis of phosphinates **11**.

Attempts on performing the direct esterification of phosphinic acids with alcohols under MW conditions, showed that the phosphinic acids underwent esterification above 200 °C.[16-19]

The reaction of 1-hydroxy-3-methyl-3-phospholene 1-oxide **13** with 15-fold of butanol was studied in detail (Scheme 3). It can be seen that a conversion of 62% could be reached at 200 °C under MW irradiation, while on conventional heating at the same temperature, the conversion was only 11%. Other alcohols, such as ethanol, propanol, pentanol and isooctanol could also be used in the esterifications to provide the corresponding phosphinates **14** in 30%, 30%, 82% and 76% yields, respectively (Table 1/Entries 1, 3, 5 and 7). It was also possible to extend the MW-assisted esterification to other cyclic phosphinic acids, like 1-hydroxy-3,4-dimethyl-3-phospholene oxide **15**, 1-hydroxy-3-methyl- and 3,4-dimethylphospholane oxides **17** and **19** and 1-hydroxy-3-methyl-1,2,3,4,5,6-hexahydrophosphinine oxide **21**. In the latter cases, pentanol was the alcoholic component, and the corresponding esters **16c**, **18c**, **20c** and **22c** were isolated in 31-79% yields (Table 2/entries 1, 3, 5 and 7).

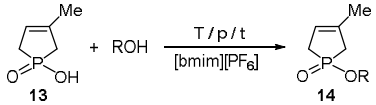
Later on, we experienced the beneficial effect of ionic liquids (ILs) as catalysts. It is a new trend to use ILs as additives or catalysts and not as solvents.[20–27] It was found that the MW-assisted direct esterifications were more efficient in the presence of 10% [bmim][PF_6]: the reactions took place already at lower temperatures (in most cases at 180-200 °C), in shorter reaction times (0.33-3 h) and, in most instances, with complete conversions (Scheme 3/case 4, Tables 1 and 2).[23] The application of [bmim][PF_6] without MW irradiation was not efficient (Scheme 3/case 3).

The order of the reactivity is shown below. Saturation of the ring, and the presence of methyl substituents decreased the reactivity.

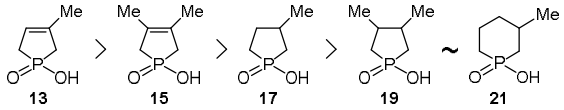


Scheme 3. The esterification of 1-hydroxy-3-methyl-3-phospholene oxide **13** with butanol under different conditions.

Table 1. MW-assisted esterification of 1-hydroxy-3-methyl-3-phospholene oxide **13** with a series of alcohols in the absence or presence of [bmim][PF_6]



Entry	R	[bmim][PF_6]	T (°C)	p (bar)	t (h)	Conversion (%)	Yield (%)
1	Et	–	160	17	4	38	30
2	Et	10%	160	17	3	86	60
3	Pr	–	180	15.5	4	40	30
4	Pr	10%	180	15.5	3	98	68
5	Pent	–	220	9	2.5	100	82
6	Pent	10%	180	5	0.5	100	94
7	^{i}Oct	–	220	3	1	100	76
8	^{i}Oct	10%	180	2	0.33	100	84



Our method was then extended to the esterification of 1-hydroxy-3-methyl-3-phospholene oxide **13** with phenol derivatives to furnish the corresponding aryl phosphinates **23** (Scheme 4).[24]

Thioalcohols could also be used in the esterification of hydroxy-3-phospholene oxides **13** and **15** under MW conditions. In these cases, the products were thioesters **24** (Scheme 5).[25] Theoretical calculations unfolded that the esterification with thioalcohols is endothermic (48.5 kJ mol^{-1}) and that the enthalpy of activation is rather high (145 kJ mol^{-1}), and higher than for esterifications (102 kJ mol^{-1}).[25]

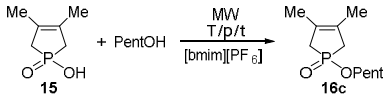
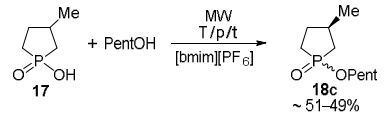
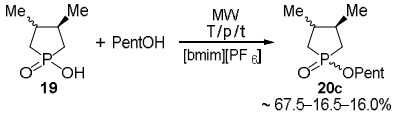
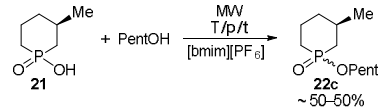
3. Attempts for the direct amidation of cyclic phosphinic acids

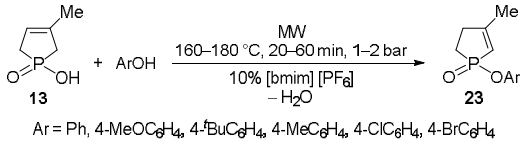
After the esterifications and thioesterifications, the direct amidation of cyclic phosphinic acids was also attempted. The reaction of 1-hydroxy-3-phospholene oxide **13** and 1-hydroxy-phospholane oxides **17** and **19** with primary amines under MW conditions took place with conversions of *ca.* 33% (Scheme 6). The amides **25** were isolated in yields of 23-29%.[26] As compared to the direct esterification of phosphinic acids, the amidations had a lower enthalpy of activation (79 kcal mol^{-1} vs. 102 kcal mol^{-1}), however amidations were significantly endothermic (33 kcal mol^{-1}).[26] It should be recalled that the esterifications are thermoneutral.[18]

It can be concluded that, in respect of the amidations, the MW-assisted reaction of phosphinic acids and amines is of limited use, and the traditional variation applying phosphinic chlorides **12** in reaction with amines

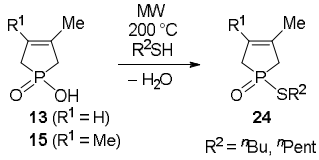
remains the method of choice (Scheme 6). Hence, 1-chloro-3-phospholene 1-oxides **26** are useful intermediates in the synthesis of aminophospholene oxides **27**. It was found that the order of addition of the reagents to each other and the molar ratio of the P-chloride **26** and the amine determines the result of the reaction. If the chlorophospholene oxide **26** was added to one equivalent of the amine, the expected aminophospholene oxide **27** was the product (Scheme 7/route A). However, when the amine was added to two equivalents of the P-chloride **26**, an imide type bis(phospholene oxide) **28** was formed in selective manner (Scheme 7/route B).[27] The latter method made available a new family of P-imides **28**.

Table 2. MW-assisted direct esterification of additional cyclic phosphinic acids **15**, **17**, **19** and **21** with pentanol

Entry	Model reaction	[bmim][PF_6]	T (°C)	p (bar)	t (h)	Yield (%)
1		–	235	11	3	67
2		10%	200	6	1	72
3		–	235	11	3	79
4		10%	220	9	1	89
5		–	235	11	5	60
6		10%	220	9	2	84
7		–	220	9	4	31
8		10%	200	9	2	42



Scheme 4. MW-assisted esterification of 1-hydroxy-3-methyl-3-phospholene 1-oxide **13** with phenol derivatives.

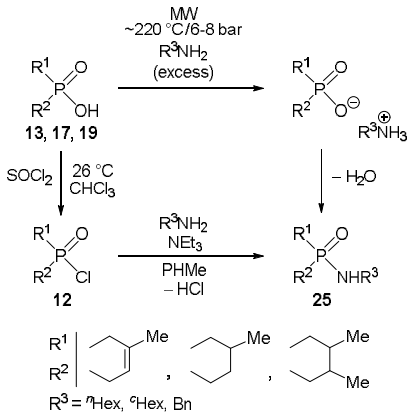


Scheme 5. The reaction of 1-hydroxy-3-phospholene 1-oxides **13** and **15** with thioalcohols.

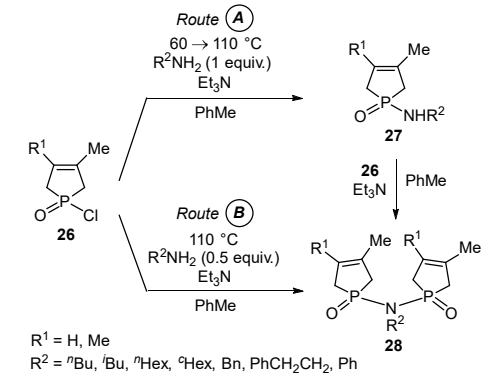
Then, the new approach was utilized in the preparation of mixed imides. A series of 1-aminophospholene 1-oxides **27** was allowed to react with diphenylphosphinoyl chloride and phosphoryl chlorides to afford mixed imides **29** and **30** (Scheme 8).[28]

The results of the esterification and amidation of cyclic phosphinic acids demonstrate well in which instances MW irradiation is advantageous. Our examples confirmed that MW assistance may be suitable to promote reactions having a relatively high enthalpy of activation. The statistically occurring local overheating effect[11] enhances to overcome the high activation barrier. It is, however, a criterion that the reaction should be

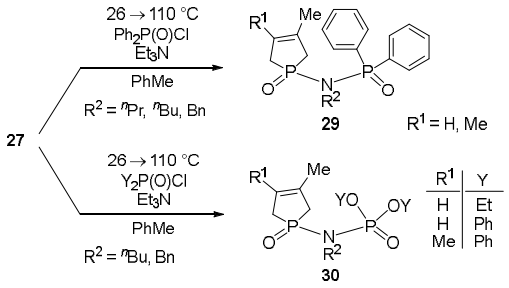
thermoneutral. This was the case with the direct esterification of cyclic phosphinic acids.[18] Regarding thioesterifications and amidations, the success was only partial, as the conversion remained incomplete due to the significant extent of endothermicity of these reactions.[25,26]



Scheme 6. Possible routes for the amidation of phosphinic acids **13**, **17** and **19**.



Scheme 7. The synthesis of phospholene-related amides **27** and imides **28**.

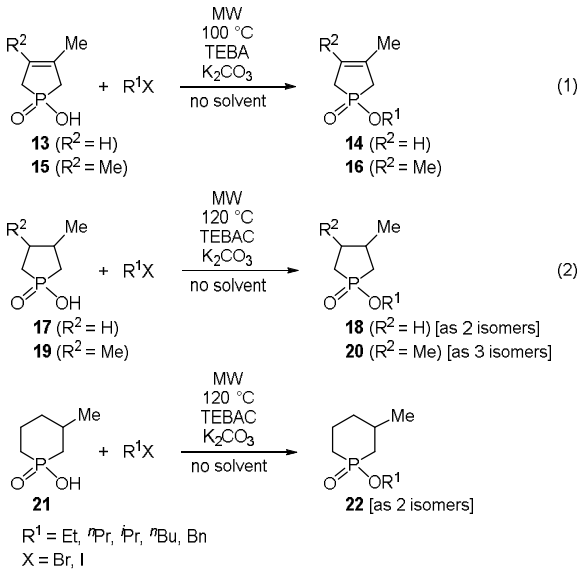


Scheme 8. The transformation of aminophospholene oxides **27** to mixed imides **29** and **30**.

4. Alkylating esterification of cyclic phosphinic acids

We wished to utilize the MW technique in the alkylating esterification of cyclic phosphinic acids, such as 1-hydroxy-3-phospholene oxides **13** and **15**, 1-hydroxyphospholane oxides **17** and **19** and

1,2,3,4,5,6-hexahydrophosphinine oxide **21**. The ring phosphinic acids **13**, **15**, **17**, **19** and **21** were reacted with different alkyl halides using K_2CO_3 under solvent-free and MW conditions to provide cyclic phosphinates **14**, **15**, **18**, **20** and **22**, respectively (Scheme 9). It was found that the application of TEBAC was beneficial, when an alkyl halide with a normal or decreased reactivity, such as ethyl iodide, *n*-propyl bromide, *n*-butyl bromide and isopropyl bromide was the reactant. At the same time, when an alkyl halide with an increased reactivity, like benzyl bromide was used, there was no need for the catalyst.[17,29,30]



Scheme 9. Alkylating esterification of cyclic phosphinic acids **13**, **15**, **17**, **19** and **21**.

However, in the case of thermally unstable cyclic phosphinic acids, like 3-hydroxy-3-phosphabicyclo[3.1.0]hexane 3-oxide and 1-hydroxy-1,2-dihydrophosphinine 1-oxide derivatives, the MW-assisted method was not suitable due to the occurrence of side reactions.[31]

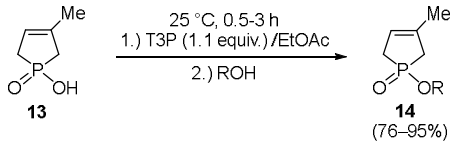
5. Propylphosphonic anhydride-promoted esterification of cyclic phosphinic acids

Propylphosphonic anhydride (T3P®) is a versatile cyclic P-reagent[32] that has a good solubility in various organic solvents.[32,33] Excess of the reagent, and the by-product formed may be easily removed from the reaction mixture by alkaline extraction. In addition to peptide chemistry, the T3P® reagent was successfully applied in different water elimination reactions, like esterification of carboxylic acids with alcohols, the direct conversion of carboxylic acid amides into nitriles, the *N*-benzylation of phenothiazine with benzyl alcohols, and the synthesis of heterocyclic compounds *via* cyclization. Additional examples include multicomponent reactions, and rearrangements.[34-37]

It was shown above that the direct esterification of phosphinic acids, that resists taking place on conventional heating, proceeds on MW irradiation.[18] The efficient esterification of 1-hydroxy-3-methyl-3-phospholene 1-oxide **13** with a series of acyclic alcohols was elaborated at room temperature applying 1.1 equivalents of the T3P® reagent (Scheme 10).[38]

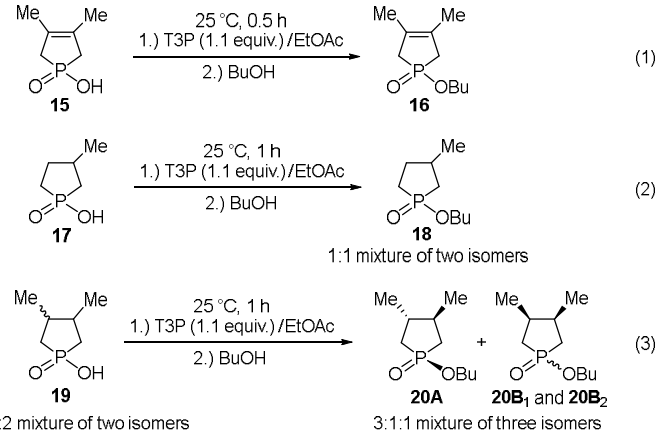
The use of 1.1 equivalents of the T3P® reagent led to high conversions. The utilization of a second unit of the T3P® reagent was also possible, but in the case, there was need to use less, 0.66 equivalents of the T3P® reagent, and to apply MW irradiation.[39] Then, the method developed by us could be extended to the esterification of the 1-hydroxy-dimethyl-3-phospholene oxide **15**, the 1-hydroxy-3-methylphospholane oxide **17**, and the 1-hydroxy-dimethylphospholane oxide **19** (Schemes 11).[39]

Beside the above esterifications, the amidation of 1-hydroxy-3-methylphospholene oxide **13** to product **31** was also developed using primary or secondary amines together with the T3P® reagent (Scheme 12).[39]

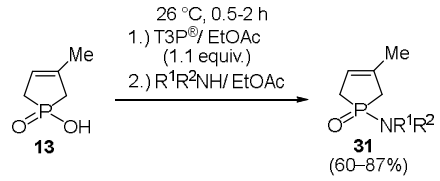


R= Me, Et, Pr, ^{i}Pr, Bu, ^{i}Bu, ^{s}Bu, Pent, ^{i}Pent, 3-pentyl, ^{c}Hexyl, Bn, 2-phenylethyl, 2-(1-naphthyl)ethyl, menthyl

Scheme 10. T3P®-promoted esterification of 1-hydroxy-3-methyl-3-phospholene 1-oxide **13**.



Scheme 11. The T3P®-promoted esterification of 5-ring phosphinic acids **15**, **17** and **19**.



R^1	Pr	^{i}Pr	^{n}Bu	^{i}Bu	^{s}Bu	^{n}Hex	^{c}Hex	Bn	Et	Pr	Bu
R^2	H	H	H	H	H	H	H	H	Et	Pr	Bu

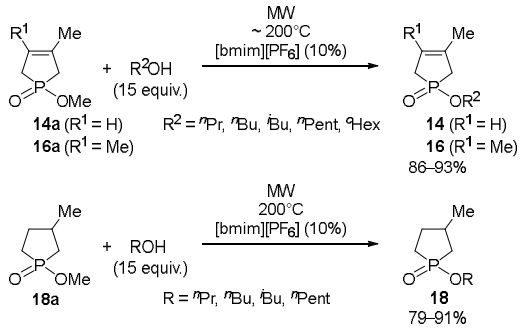
Scheme 12. Amidation of 1-hydroxy-3-methyl-3-phospholene 1-oxide **13** using the T3P® reagent.

This was the first T3P®-promoted conversion of phosphinic acids to phosphinic amides. Mechanism of the T3P®-assisted esterifications and amidations was also evaluated by quantum chemical calculations.[40]

6. Transesterification of cyclic phosphinates

If certain carboxylic acid esters are available in nature, alcoholysis (transesterification) is a good method to convert them to esters with other alkyl chain. This is not only important in the production of biodiesel, but also in the case of P-esters.[41,42] We developed the MW-assisted alcoholysis of dialkyl phosphites,[43] in which case the intermediates with two different alkoxy groups may be valuable species.[44] 1-Methoxy-3-phospholene 1-oxides **14a** and **16a**, as well as a 1-methoxyphospholane oxide **18a**, also underwent alcoholysis under MW conditions at 200 °C to provide alkoxyphospholene oxides **14** and **16** and alkoxyphospholane oxides **18**, respectively (Scheme 13). The application of 10% of [bmim][PF_6] as the catalyst was highly beneficial.[45]

The catalytic effect of ILs, *e.g.* [bmim][PF_6] was also observed in the transesterification of alkyl diphenylphosphinates.[46] The application of other ILs, such as [emim][HSO_4] and [bmim][Cl] in the alcoholysis of dialkyl phenylphosphonates led to the corresponding ester-acid or to the diacid after the fission of the ester function(s).[47] Continuous flow MW-assisted transesterification of the P-esters was also reported.[48]

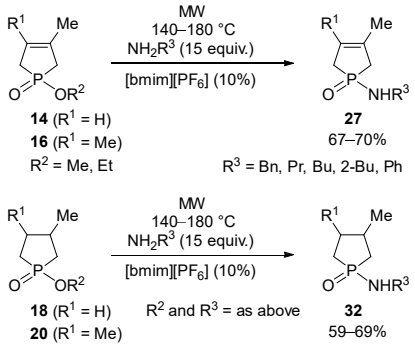


Scheme 13. Alcoholysis of 1-methoxy- and 1-ethoxy-3-phospholene oxides **14a** and **16a**, as well as 1-methoxy-3-methylphospholane oxide **18a**.

7. Aminolysis of cyclic phosphinates

According to a literature survey, the seemingly practical and halogen-free aminolysis of phosphinic esters to give amides is a neglected field. Only a few cases were described, mostly kinetic studies on the aminolysis of aryl phosphinates with electron-withdrawing substituents in the phenyl ring.[49,50] The factors influencing the course of the aminolyses were also explored.[51,52]

It was a challenge for us to investigate the aminolysis of 1-methoxy- and 1-ethoxy-3-phospholene 1-oxides **14** and **16**, as well as that of 1-alkoxyphospholane oxides **18** and **20** using primary amines in a 15-fold quantity at 140-180 °C on MW irradiation in the presence of 10% of a suitable ionic liquid (Scheme 14). In this way, the corresponding cyclic phosphinic amides **27** and **32** were obtained in yields of 59-70%.[53] The reverse reaction, the alcoholysis of phosphinic amides is also possible, however, there is need for somewhat more forcing conditions.[53]



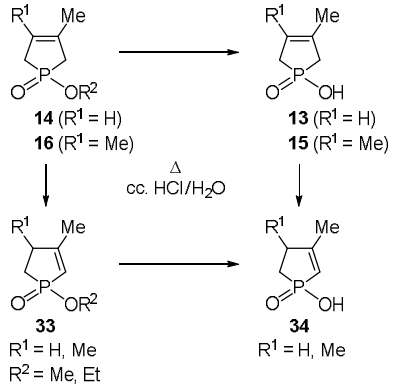
Scheme 14. Aminolysis of cyclic phosphinates **14**, **16**, **18** and **20**.

8. Hydrolysis of cyclic phosphinates

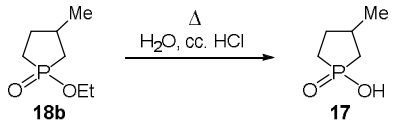
The hydrolysis of phosphinates, phosphonates and phosphoric esters is of importance. In most cases, the acid-catalyzed hydrolysis is applied, when the respective P-ester is refluxed in aqueous hydrochloric acid. However, the hydrolyses were not optimized, and excessive conditions were applied.[54-56] 1-Alkoxyphospholane oxides were hydrolyzed in 3 M hydrochloric acid under reflux for 5-8 h to give the cyclic phosphonic acids in yields of 60-68%.[57] It is also possible to perform hydrolyses using aqueous NaOH or KOH.[58] According to a special approach, the phosphinate is converted to the corresponding phosphinic chloride by reaction with PCl_5, and then the P-chloride so obtained is hydrolyzed.[59] Last but not least, a microwave (MW)-assisted protocol was elaborated for the HCl-catalyzed hydrolysis of phosphonate diesters.[60]

The research group of the author of this chapter developed the hydrochloric acid-catalyzed hydrolysis of cyclic phosphinates, such as 1-alkoxy-3-phospholene 1-oxides **14**/**16**, 1-ethoxy-3-methylphospholane

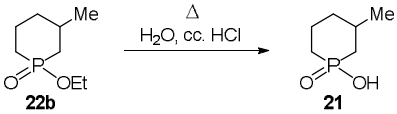
1-oxide **18b**, and 1-ethoxy-3-methyl-1,2,3,4,5,6-hexahydrophosphinine 1-oxide **22b** (Schemes 15-17).[61] The optimum conditions were explored. During the hydrolysis of 1-alkoxy-3-phospholene oxides **14**/**16**, migration of the double-bond was also observed. Either the starting cyclic phosphinate **14**/**16**, or the cyclic phosphinic acid **13**/**15** formed as an intermediate underwent double-bond isomerization to afford species **33** or **34**, respectively. The hydrolyses were characterized by rate constants. It is noteworthy that the double-bond isomerization was more significant in case of the monomethylphospholene oxide derivatives **14**/**13**. The MW-assisted hydrolysis at 140 °C in the presence of *p*-toluenesulfonic acid as the catalyst offers another option.



Scheme 15. Hydrolysis of 1-alkoxy-3-phospholene 1-oxides **14**/**16**.

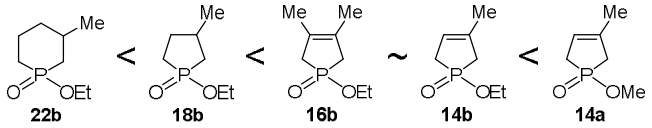


Scheme 16. Hydrolysis of 1-ethoxy-3-methylphospholane 1-oxide **18b**.



Scheme 17. Hydrolysis of 1- ethoxy-3-methyl-1,2,3,4,5,6-hexahydrophosphinine 1-oxide **22b**.

The reactivity of the cyclic phosphinates showed the following order:



It means that the phosphinates with saturated ring are less reactive than the 3-phospholene derivatives. A second Me group on the skeleton decreases the reactivity, and the methyl ester is more reactive than the ethyl analogue.

It was possible to accomplish the MW-promoted hydrolysis of 1-alkoxy-3-methyl- and 3,4-dimethyl-phospholane 1-oxides **18** and **20** to cyclic phosphinic acids **17** and **19**, respectively, using a commercially available flow cell and a HPLC pump together with a back pressure regulator. The catalyst was *p*-toluenesulfonic acid and the temperature applied was 160 °C (Figure 1).[62]

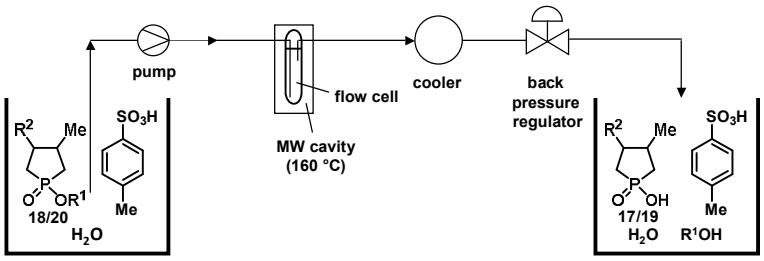
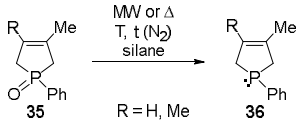


Figure 1. The flow MW equipment used for the hydrolysis of cyclic phosphinates.

9. Deoxygenation of 2,5-dihydro-1*H*-phosphole 1-oxides

Deoxygenation of phosphine oxides represent a hot topic, as, on the one hand, the phosphines so obtained are important ligands in transition metal complexes, on the other hand, the regeneration of phosphines from phosphine oxides formed *e.g.* in the Wittig- or the Mitsunobu reactions is a green chemical task. Reduction of the phosphine oxides have been reviewed.[63] A special field is the deoxygenation of cyclic phosphine oxides by different silanes. Earlier methods on the reduction of different 1-phenyl-2- or 3-phospholene oxides comprised the use of trichlorosilane with trimethylamine in benzene at the boiling point, the application of phenylsilane at 26 °C or at 80 °C in the absence of a solvent, or the use of polymethylhydrosiloxane ([–O–SiH(Me)–]$_n$, PMHS) at 250 °C under solvent-free conditions to provide the corresponding cyclic phosphines in variable (24-97%) yields.[64,65]

We investigated, among other model compounds, the deoxygenation of 3-methyl- and 3,4-dimethyl-1-phenyl-3-phospholene 1-oxides **35**, 3-methyl-1-phenyl-2-phospholene oxide **37**, and 3-methyl-1-phenylphospholane 1-oxide **39** under different conditions (in aromatics or in the absence of any solvent) applying different silanes, such as trichlorosilane, phenylsilane tetramethyldisiloxane ([Me_2SiH]$_2$O, TMDS) and PMHS at different temperatures ensured by conventional heating or MW irradiation.[66–69] We wished to replace the rather corrosive Cl_3SiH and the user-friendly, but expensive $PhSiH_3$ by the cheap, but less reactive TMDS and PMHS. The best conditions involved MW assistance and avoiding the use of solvents. The optimum set of parameters elaborated for the reduction of 1-penyl-3-phospholene oxide **35** to cyclic phosphine **36**, together with the results of the comparative thermal experiments are shown in Scheme 18.



Heating source	Silane	Equiv.	T (°C)	t (h)	Conv. (%)	Yield (%)
MW	$PhSiH_3$	3	80	1	100	91
MW	TMDS	4	110	3	100	92
MW	PMHS	2	110	2	100	92
Δ	$PhSiH_3$	3	80	2	100	95
Δ	TMDS	4	110	5	100	92
Δ	PMHS	2	110	4	100	91

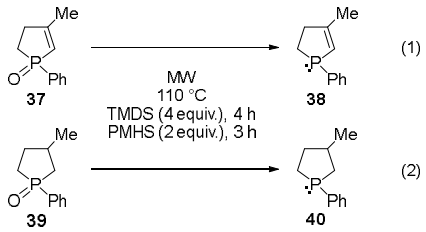
Scheme 18. Deoxygenation of 1-phenyl-3-phopsholene 1-oxides **35**.

The optimized method was also applied for the deoxygenation of 1-phenyl-3-methyl-2-phospholene oxide **37** and 1-phenyl-3-methylphospholane oxide **39** to phosphines **38** and **40**, respectively (Scheme 19). Utilizing MWs allowed performing the reductions without any catalyst that was otherwise suggested by Beller *et al.*[70]

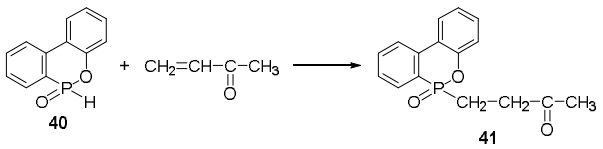
10. Other P-functionalizations

Phospha-Michael reactions are useful to establish a P–C bond. The addition of >P(O)H species (*e.g.* dialkyl phosphites and secondary phosphine oxides) at the end of electron-poor double-bonds may be facilitated by bases, like NaOR, NaOH or DBU.[71] The addition of P-heterocyclic nucleophiles was also

studied. It was found that dibenzo-1,2-oxaposphorine oxide **40** added easily on the double-bond of methyl vinyl ketone under MW conditions to provide product **41** (Scheme 20).[72] No solvent was used.

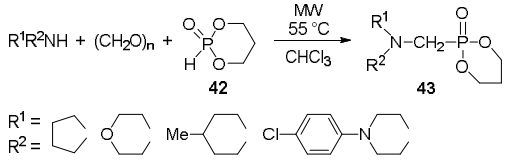


Scheme 19. MW-assisted deoxygenation of additional cyclic phosphine oxides **37** and **39**.



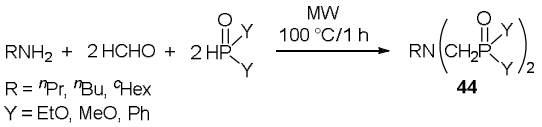
Scheme 20. Phospha-Michael addition of dibenzo[*c.e*][1,2]oxaphosphorine oxide (DOPO) **40** to methyl vinyl ketone.

In another investigation, potentially bioactive α-aminophosphonates and α-aminophosphine oxides were synthesized by the solventless and catalyst-free MW-assisted Kabachnik–Fields condensation of primary amines, aldehydes/ketones and >P(O)H species. Earlier preparations utilized special catalysts (*e.g.* $BiNO_3$[73], phthalocyanine[74], and Lantanoid$(OTf)_3$[75]) that cannot be regarded environmentally friendly species. We proved that under MW conditions there is no need for any catalyst. Moreover, the syntheses can be carried out without the use of a solvent.[76] A nice example is the phospha-Mannich condensation of 1,3,2-dioxaphosphorine 2-oxide **42** paraformaldehyde and secondary amines including 5- and 6-membered *N*-heterocycles to provide novel heterocyclic derivatives **43** (Scheme 21).[77]



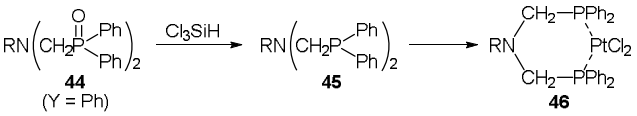
Scheme 21. A heterocyclic variation of the Kabachnik-Fields reaction using a heterocyclic P-reagent.

Double Kabachnik-Fields condensations leading to bis(phosphonoylmethyl)- and bis(phosphinoylmethyl)amines **44** were also developed using two equivalents of the formaldehyde and the >P(O)H species to one equivalent of the primary amine (Scheme 22).[78-80]



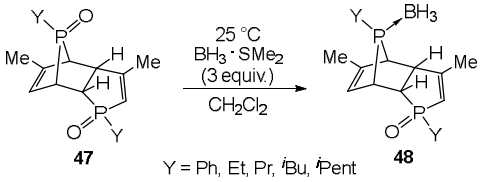
Scheme 22. Double Kabachnik-Fields reaction.

The bis(phosphinoylmethyl)amines **44** (Y=Ph) were useful precursors of bidentate P-ligands **45** after double deoxygenation that could be used for the synthesis of ring platinum complexes **46** (Scheme 23).[78-80] Ring Pt-complexes are special heterocycles.



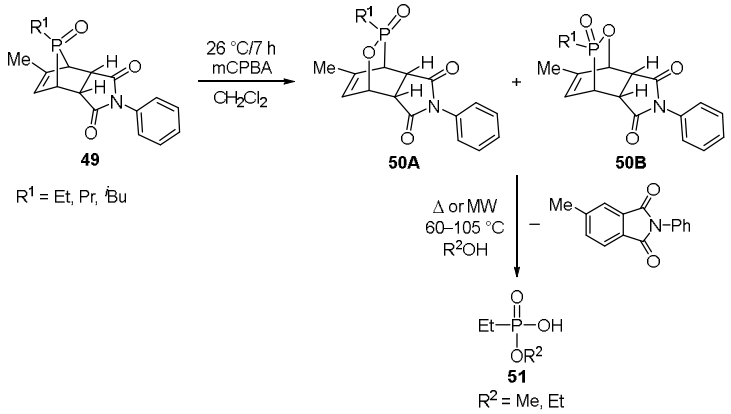
Scheme 23. The synthesis of ring platinum complexes **46** from bis(phospha-Mannich) products.

Earlier transformation of P-phenyl phosphole oxide dimer **47** (Y=Ph) to the species containing a phosphine-borane function on the bridging P-atom **48** (Y=Ph) involved heating of the starting material and three equivalents of borane-dimethyl sulfide in a diluted chloroform solution at the boiling point for 24 h.[81] The selective monoboration of a phenylphosphole oxide dimer **47**, (Y=Ph) could be performed even at room temperature in a concentrated solution, and the optimized protocol could be extended to the conversion of a series of P-alkyl analogues **48** (Y=alkyl) (Scheme 24).[82]



Scheme 24. Refunctionalization of 7-phosphanorbornene oxides **47**.

P-Alkyl derivatives of 2,3-oxaphosphabicyclo[2.2.2]octene 2-oxides **49A** and **49B** were synthesized as new bridged P-heterocycles by Baeyer-Villiger oxidation, and the stability of the regioisomers was mapped. The precursors **49** could be utilized well in fragmentation-related phosphonylations to afford, eventually, alkylphosphonic acid-esters **50** (Scheme 25). MW irradiation was a novel way to bring about the ejection of the bridging moiety as a reactive alkylmethaphosphonate.[83]



Scheme 25. Oxidation of 7-phosphanorbornene oxides **49** and use of the product so obtained in fragmentation-related phosphorylations.

11. Conclusion

It was shown on the example of P-heterocycles, how their P-function may be modified in esterification, alcoholysis, aminolysis hydrolysis, deoxygenation and other transformations keeping in mind and applying the “green” criterions. MW irradiation, in certain cases, may be a good substitute for catalysts, or may act as a co-catalyst. A part of the procedures presented developed in the Keglevich laboratory is brand new, another part represents optimized syntheses according to the “green” requirements. The methods elaborated are of general applicability.

Acknowledgement

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References

1. Quin, L. D. *A Guide to Organophosphorus Chemistry*, Wiley & Sons, New York, **2000**.
2. Mathey, F., Ed., *Phosphorus-Carbon Heterocyclic Chemistry: The Rise of a New Domain*, Pergamon, Amsterdam, **2001**.
3. Keglevich, G., Ed., *Organophosphorus Chemistry - Novel Developments*, De Gruyter, Berlin, **2018**.
4. Keglevich, G. *Synthesis* **1993**, *1993*, 931-942.
5. Keglevich, G. in *Topics in Heterocyclic Chemistry*, Gupta, R. R., Ed., Bansal, R. K. (Vol. Ed.), Springer, Dordrecht, **2009**, *20*, 65-98.
6. Keglevich, G. *Current Org. Chem.* **2006**, *10*, 93-111.
7. Keglevich, G. in *Topics in Heterocyclic Chemistry*, Gupta, R. R., Ed., Bansal, R. K. (Vol. Ed.), Springer, Heidelberg, **2010**, *21*, 149-173.
8. Keglevich, G. in *Targets in Heterocyclic Systems*, Attanasi, O. A.; Spinelli, D.; Eds., Italian Society of Chemistry, Rome, **2002**, *6*, 245-269.
9. *Microwaves in Organic Synthesis*, Loupy, A., Ed., Wiley-VCH, Weinheim. **2002**.
10. *Milestones in Microwave Chemistry - SpringerBriefs in Molecular Science*, Keglevich G.; Ed., Springer, Switzerland, **2016**.
11. Kranjc, K.; Kočevar, M. *Curr. Org. Chem.* **2010**, *14*, 1050-1074.
12. Keglevich, G.; Mucsi, Z. in: *Microwave Chemistry*, Cravotto, G.; Carnaroglio, D., Eds., De Gruyter, Berlin, **2017**, 53-64.
13. Guénin, E.; Meziane, D. *Curr. Org. Chem.* **2011**, *15*, 3465-485.
14. Keglevich, G.; Grün, A.; Bálint, E.; Kiss, N. Z.; Jablonkai, E. *Curr. Org. Chem.* **2013**, *17*, 545-554.
15. Keglevich, G.; Greiner, I. *Curr. Green Chem.* **2014**, *1*, 2-16.
16. Kiss N. Z.; Ludányi, K.; Drahos, L.; Keglevich, G. *Synth. Commun.* **2009**, *39*, 2392-2404.
17. Keglevich, G.; Bálint, E.; Kiss, N. Z.; Jablonkai, E.; Hegedűs, L.; Grün, A.; Greiner, I. *Curr. Org. Chem.* **2011**, *15*, 1802-1810.
18. Keglevich, G.; Kiss, N. Z.; Mucsi, Z.; Körtvélyesi, T. *Org. Biomol. Chem.* **2012**, *10*, 2011-2018.
19. Kiss, N. Z.; Böttger, É.; Drahos, L.; Keglevich, G. *Heteroatom Chem.* **2013**, *24*, 283-288.
20. Olivier-Bourbigou, H.; Magna, L.; Morvan, D. *Appl. Catal. A: Gen.* **2010**, *373*, 1-56.
21. Zhang, Q.; Zhang, S.; Deng, Y. *Green Chem.* **2011**, *13*, 2619-2637.
22. Rádai, Z.; Kiss, N. Z.; Keglevich, G. *Curr. Org. Chem.* **2018**, *22*, 533-556.
23. Kiss, N. Z.; Keglevich, G. *Tetrahedron Lett.* **2016**, *57*, 971-974.
24. Kiss, N. Z.; Rádai, Z.; Tihanyi, I.; Szabó, T.; Keglevich, G. *Mendeleev Commun.* **2018**, *28*, 31-32.
25. Keglevich, G.; Kiss, N. Z.; Drahos, L.; Körtvélyesi, T. *Tetrahedron Lett.* **2013**, *54*, 466-469.
26. Keglevich, G.; Kiss, N. Z.; Körtvélyesi, T. *Heteroatom Chem.* **2013**, *24*, 91-99.
27. Kiss, N. Z.; Simon, A.; Drahos, L.; Huben, K.; Jankovski, S.; Keglevich, G. *Synthesis* **2013**, *45*, 199-204.
28. Kiss, N. Z.; Rádai, Z.; Mucsi, Z.; Keglevich, G. *Heteroatom Chem.* **2015**, *26*, 134-141
29. Bálint, E.; Jablonkai, E.; Bálint, M.; Keglevich, G. *Heteroatom Chem.* **2010**, *21*, 211-214.
30. Keglevich, G.; Kiss, N. Z.; Bálint, E.; Jablonkai, E.; Grün, A.; Milen, M.; Frigyes, D.; Greiner, I. *Phosphorus, Sulfur, Silicon* **2011**, *186*, 802-803.
31. Jablonkai, E.; Bálint, E.; Balogh, G. T.; Drahos, L.; Keglevich, G. *Phosphorus Sulfur* **2012**, *187*, 357-363.
32. Wissmann, H.; Kleiner, H.-J. *Angew. Chem. Int. Ed.* **1980**, *19*, 133-134.
33. Glauder, J. *Speciality Chemicals Magazine* **2004**, *24*, 30-31.
34. Basavaprabhu; Vishwanatha, T. M.; Panguluri, N. R.; Sureshbabu, V. V. *Synthesis* **2013**, *45*, 1569-1601.
35. Waghmare, A. A.; Hindupur, R. M.; Pati, H. N. *Rev. J. Chem.* **2014**, *4*, 53-131.
36. Schwarz, M. *Synlett* **2000**, *2000*, 1369.
37. García, A. L. L. *Synlett* **2007**, *2007*, 1328-1329.
38. Jablonkai, E.; Milen, M.; Drahos, L.; Keglevich, G. *Tetrahedron Lett.* **2013**, *54*, 5873-5875.
39. Jablonkai, E.; Henyecz, R.; Milen, M.; Kóti, J.; Drahos, L.; Keglevich, G. *Tetrahedron* **2014**, *70*, 8280-8285.

40. Ábrányi-Balogh, P.; Jablonkai, E.; Henyecz, R.; Milen, M.; Keglevich, G. *Curr. Org. Chem.* **2016**, *20*, 1135-1142.
41. Froneman, M.; Modro, T. A. *Tetrahedron Lett.* **1988**, *29*, 3327-3330
42. Singh, R.; Nolan, S. P. *Chem. Commun.* **2005**, *37*, 5456-5458
43. Bálint, E.; Tajti, Á.; Drahos, L.; Ilia, G.; Keglevich, G. *Curr. Org. Chem.* **2013**, *17*, 555-562
44. Tajti, Á.; Bálint, E.; Keglevich, G. *Curr. Org. Synth.* **2016**, *13*, 638-645
45. Harsági N.; Kiss N. Z.; Drahos L.; Keglevich G. *Synthesis* **2022**, *54*, 3899-3905.
46. Harsági N.; Szőllősi B.; Kiss N. Z.; Keglevich G. *Green Process. Synth.* **2021**, *10*, 1-10.
47. Harsági, N.; Bertha, C.; Kiss, N. Z.; Henyecz, R.; Varga, P. R.; Ábrányi-Balogh, P.; Drahos, L.; Keglevich, G. *Curr. Org. Chem.* **2021**, *25*, 842-848.
48 Kiss N. Z.; Henyecz R.; Keglevich G. *Molecules* **2020**, *25*, 719.
49. Cook, R. D.; Daouk, W. A.; Hajj, A. N.; Kabbani, A.; Kurku, A.; Samaha, M.; Shayban, F.; Tanielian, O. V. *Can. J. Chem.* **1986**, *64*, 213-219.
50. Um, I. H.; Shin, Y. H.; Han J. Y.; Mishima, M. *J. Org. Chem.* **2006**, *71*, 7715-7720.
51. Um, I. H.; Han, J. Y.; Shin, Y. H. *J. Org. Chem.* **2009**, *74*, 3073-3078.
52. Dey, N. K.; Kim C. K.; Lee, H. W. *Org. Biomol. Chem.* **2011**, *9*, 717-724.
53. Keglevich G.; Harsági N.; Szilágyi S. *Green Chem.* **2023**, *25*, 10372-10380.
54. Desai, J.; Wang, Y.; Wang, K.; Malwal, S. R.; Oldfield, E. *Chem. Med. Chem.* **2016**, *11*, 2205-2215.
55. Tcarkova, K. V.; Artyushin, O. I.; Bondarenko, N. A. *Phosphorus Sulfur* **2016**, *191*, 1520-1522.
56. Keglevich, G.; Grün, A.; Bölcskei, A.; Drahos, L.; Kraszni, M.; Balogh, G. T. *Heteroatom Chem.* **2012**, *23*, 574-582.
57. Gavande, N.; Yamamoto, I.; Salam, N. K.; Ai, T-H.; Burden, P. M.; Johnston, G. A. R.; Hanrahan, J. R.; Chebib, M. *ACS Med. Chem. Lett.* **2011**, *2*, 11-16.
58. Wróblewski, A. E.; Verkade, J. G. *J. Am. Chem. Soc.* **1996**, *118*, 10168-10174.
59. Keglevich, G.; Kovács, A.; Tőke, L.; Újszászy, K.; Argay, G.; Czugler, M.; Kálmán, A. *Heteroatom Chem*. **1993**, *4*, 329-335.
60. Jansa, P.; Baszczyński, O.; Procházková, E.; Dračínský, M.; Janeba, Z. *Green Chem.* **2012**, *14*, 2282-2288.
61. Keglevich, G.; Rádai, Z.; Harsági, N.; Szigetvári, Á.; Kiss, N. Z. *Heteroatom Chem.* **2017**, *28*, e21394.
62. Harsági N.; Keglevich G. *Green Process. Synth.* **2022**, *11*, 176-183.
63. Kovács, T.; Keglevich, G. *Curr. Org. Chem.* **2017**, *21*, 569-585.
64. Fritzsche, H.; Hasserodt, U.; Korte, F.; Friese, G.; Adrian, K. *Chem. Ber.* **1965**, *98*, 171-174.
65. Fritzsche, H.; Hasserodt, U.; Korte, F.; Friese, G.; Adrian, K.; Arenz, H. J. *Chem. Ber.* **1964**, *97*, 1988-1993.
66. Keglevich, G.; Kovács, T. *Curr. Green Chem.* 2014, *1*, 182-188.
67. Keglevich, G.; Kovács, T.; Csatlós, F. *Heteroatom Chem.* **2015**, *26*, 199-205.
68. Kovács, T.; Urbanics, A.; Csatlós, F.; Binder, J.; Falk, A.; Uhlig, F.; Keglevich, G. *Curr. Org. Synth.* **2016**, *13*, 148-153.
69. Kovács, T.; Keglevich, G. *Phosphorus Sulfur* **2016**, *191*, 359-366.
70. Li, Y. H.; Das, S.; Zhou, S. L.; Junge, K.; Beller, M. *J. Am. Chem. Soc.* **2012**, *134*, 9727-9732.
71. Keglevich, G.; Sipos, M.; Takács, D.; Greiner, I. *Heteroatom Chem.* **2007**, *18*, 226-229.
72. Keglevich, G.; Sipos, M.; Takács, D.; Ludányi, K. *Heteroatom Chem.* **2008**, *19*, 288-292.
73. Bhattacharya, A. K.; Kaur, T. *Synlett* **2007**, *2007*, 745-748.
74. Matveeva, E. D.; Podrugina, T. A.; Tishkovskaya, E. V.; Tomilova, L. G.; Zefirov, N. S. *Synlett* **2003**, *2003*, 2321-2324.
75. Lee, S.; Park, J. H.; Kang, J.; Lee, J. K. *Chem. Commun.* **2001**, *2001*, 1698-1699.
76. Keglevich, G.; Szekrényi, A. *Lett. Org. Chem.* **2008**, *5*, 616-622.
77. Keglevich, G.; Szekrényi, A.; Sipos, M.; Ludányi, K.; Greiner, I. *Heteroatom Chem*. **2008**, *19*, 207-210.
78. Keglevich, G.; Szekrényi, A.; Szöllősy, Á.; Drahos, L. *Synthetic Commun.* **2011**, *41*, 2265-2272.
79. Bálint, E.; Fazekas, E.; Pintér, G.; Szöllősy, Á.; Holczbauer, T.; Czugler, M.; Drahos, L.; Körtvélyesi, T.; Keglevich, G. *Current Org. Chem.* **2012**, *16*, 547-554.

80. Bálint, E.; Fazekas, E.; Pongrácz, P.; Kollár, L.; Drahos, L.; Holczbauer, T.; Czugler, M.; Keglevich, G. *J. Organomet. Chem.* **2012**, *717*, 75-82.
81. Keglevich, G.; Chuluunbaatar, T.; Ludányi, K.; Tőke, L. *Tetrahedron* **2000**, *56*, 1-6.
82. Kovács, T.; Cseresnyés, D.; Drahos, L.; Keglevich, G. *Phosphorus Sulfur* **2017**, *192*, 695-699.
83. Kovács, T., Fülöp, L. S., Keglevich, G. *Heteroatom Chem.* **2016**, *27*, 83-90.