

Chapter 3

The Use of MW in Organophosphorus Chemistry

György Keglevich, Erika Bálint and Nóra Zs. Kiss

Abstract The third chapter summarizes a special field, the application of the microwave (MW) technique in the synthesis of organophosphorus compounds. On the one hand, reactions are shown that are otherwise rather reluctant on traditional thermal heating. On the other hand, reactions are discussed, which, became more efficient (shorter reaction times and higher yields) on MW irradiation. Finally, the simplification of catalytic systems under MW conditions are surveyed.

Keywords Microwave · Organophosphorus chemistry · P-heterocycles · Direct esterification · Alkylating esterification · T3P[®] reagent · C-alkylation · Kabachnik–fields condensation · Arbuzov reaction · Hirao reaction

3.1 Introduction

The use of MW technique in general organic syntheses was spread revolutionarily in the last 35 years. As such, this novel approach was, of course, applied also in organophosphorus chemistry from the beginning (~1980), however, the real break-through happened much later. Guenin was the first, who collected the examples of MW-assisted organophosphorus reactions into a review article [1] that was followed by a few others compiled mainly by the author of this chapter [2–7].

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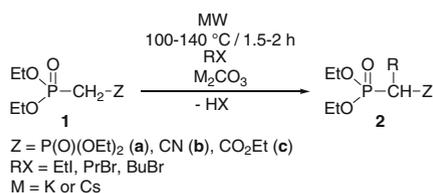
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3.2 Alkylation of Active Methylene Containing Substrates

3.2.1 Monoalkylation of P=O-Functionalized CH-Acidic Compounds

It was found that simple active methylene containing compounds underwent C-alkylation by reaction with alkyl halides in the presence of K_2CO_3 under solvent-free MW conditions. The message of this discovery is that the phase transfer catalyst can be substituted by MW irradiation [8, 9]. This method was then extended to the alkylation of tetraethyl methylenebisphosphonate (**1a**), diethyl cyanomethylphosphonate (**1b**) and diethyl ethoxycarbonylmethylphosphonate (**1c**) using K_2CO_3 or Cs_2CO_3 as the base to give the corresponding monoalkylated products (**2a-c**) in variable yields (Scheme 3.1, Table 3.1) [10–12].

The phase transfer catalyzed and MW-assisted alkylations of active methylene containing substrates were summarized [13–15].



Scheme 3.1 MW-assisted substitution of active methylene containing compounds

Table 3.1 Summary of the MW-assisted alkylation of CH-acidic compounds

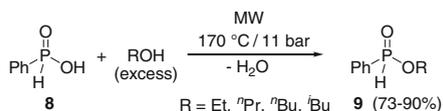
Entry	Starting material	RX	M_2CO_3	Solvent	Mode of heating	T/p ($^\circ\text{C}/\text{bar}$)	t (h)	Yield of 2	Ref.
1	1a	EtI	Cs_2CO_3	–	MW	140/11	1.5	80	[10]
2	1a	$^n\text{PrBr}$	Cs_2CO_3	–	MW	120/6	4	57 ^{a,b}	[10]
3	1b	$^n\text{PrBr}$	K_2CO_3	–	MW	100/2.5	2	64	[11]
4	1b	$^n\text{BuBr}$	K_2CO_3	–	MW	120/3	2	59	[11]
5	1c	EtI	Cs_2CO_3	–	MW	120	2	70	[12]
6	1c	$^n\text{PrBr}$	Cs_2CO_3	–	MW	120	2	71	[12]
7	1c	$^n\text{BuBr}$	Cs_2CO_3	–	MW	120	2	70	[12]

^aProportion in the mixture on the basis of GC

^bThe mixed esters with one or two PrO groups were also present in 33 % and 10 %, respectively

The generally applied esterification method (Scheme 3.3/B) has the disadvantage of requiring the use of relatively expensive *P*-chlorides (7). Moreover, the hydrogen chloride formed as the by-product should be removed by a base, and this method is not atomic efficient.

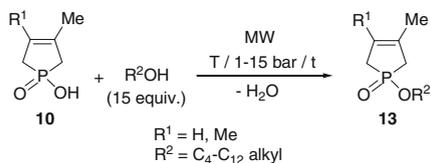
We have recently found that a series of phosphinic acids underwent direct esterification with longer chain alcohols on MW irradiation at around 170–220 °C [21]. The first example was the esterification of phenyl-*H*-phosphinic acid (8) at 170 °C to give the corresponding phosphinates (9) in yields of 73–90 % (Scheme 3.4).



Scheme 3.4 Direct esterification of phenyl-*H*-phosphinic acid under MW conditions

This esterification was assumed to take place via the tervalent tautomer of the phenyl-*H*-phosphine acid, but no evidence was presented [22].

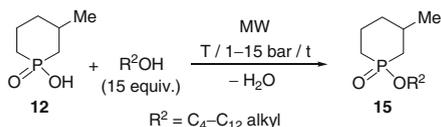
The MW-assisted esterification of cyclic phosphinic acids, such as 1-hydroxy-3-phospholene oxides (10), 1-hydroxyphospholane oxides (11) and 1-hydroxy-1,2,3,4,5,6-hexahydrophosphinine oxides (12) was carried out at 180–235 °C in the presence of *ca.* 15-fold excess of the alcohols to afford the corresponding alkyl phosphinates (13–15) in variable yields (Schemes 3.5, 3.6 and 3.7, Table 3.2) [23–26].



Scheme 3.5 MW-assisted direct esterification of 1-hydroxy-3-phospholene 1-oxides



Scheme 3.6 MW-assisted direct esterification of 1-hydroxyphospholane 1-oxides



Scheme 3.7 MW-assisted direct esterification of a 1-hydroxy-1,2,3,4,5,6-hexahydrophosphinine 1-oxide

Table 3.2 MW-assisted direct esterification of cyclic phosphinic acids (**10–12**)

Phosphinic acid	R ²	T (°C)	t (h)	Isomeric composition	Yield of 13–15 MW (%)	Entry
 10 (R ¹ = H)	ⁿ Bu	200	2	–	58 (11)	1
	ⁿ Pent	220	2.5	–	94	2
	ⁱ Pent	235	3	–	74	3
	ⁿ Oct	220	2	–	71	4
	ⁱ Oct	220	2	–	76 ^a	5
	ⁿ Dodec	230	2	–	95	6
 10 (R ¹ = Me)	ⁿ Pr	180	4	–	20	7
	ⁿ Bu	220	3	–	60 ^b	8
	ⁱ Bu	200	2	–	30	9
	ⁿ Pent	235	3	–	67	10
	ⁱ Pent	235	4	–	57	11
	ⁿ Oct	230	2	–	95	12
	ⁱ Oct	220	2.5	–	82 ^c	13
	ⁿ Dodec	230	2	–	95	14
 11 (R ¹ = H)	ⁿ Bu	230	3	~ 50–50	45	15
	ⁿ Pent	235	3	~ 50–50	79	16
	ⁱ Pent	235	4	~ 50–50	59	17
	ⁿ Oct	230	4	~ 50–50	74	18
	ⁱ Oct	220	3	~ 50–50	86	19
 11 (R ¹ = Me)	ⁿ Bu	210	3	~ 60–20–20	54	20
	ⁿ Pent	235	5	~ 70–15–15	60	21
	ⁱ Pent	235	6	~ 64–19–17	56	22
	ⁿ Oct	230	4	~ 60–20–20	70	23
	ⁱ Oct	220	4	~ 66–19–15	50	24
 12	ⁿ Bu	230	3	~ 69–31	45	25
	ⁿ Oct	235	4	~ 66–34	62	26
	ⁱ Oct	235	6	~ 69–31	54	27

^aIn the thermal variation, the yield was 22 %

^bIn the thermal variation, the yield was 13 %

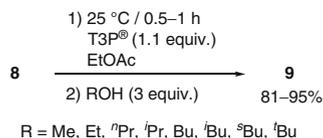
^cIn the thermal variation, the yield was 24 %

The method developed by us seems to be of more general value. It was also found that the esterification of phosphinic acids is thermoneutral and controlled kinetically. The reaction enthalpies were found to fall in the range of 0.1–4.0 kJ mol⁻¹, while the activation enthalpies were in the range of 102.0–161.0 kJ mol⁻¹ [25, 27]. Interestingly, the analogous thioesterifications were reluctant and incomplete under MW conditions [28].

3.3.2 Esterification in the Presence of the T3P[®] Reagent

The phenyl-*H*-phosphinic acid (**8**) could be esterified with simple alcohols efficiently and under mild conditions in the presence of 1.1 equivalents of the T3P[®] reagent as the activating agent (Scheme 3.8) [29].

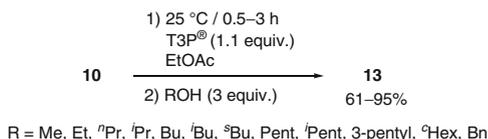
Scheme 3.8 T3P[®]-mediated esterification of phenyl-*H*-phosphinic acid



It was found that the use of only 0.66 equivalents of the T3P[®] reagent was also enough to reach yields of 78–91 % [29].

1-Hydroxy-3-phospholene 1-oxides (**10**) also underwent a similar T3P[®]-promoted direct esterification (Scheme 3.9) [29, 30].

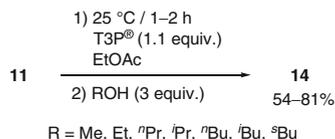
Scheme 3.9 T3P[®]-mediated esterification of 1-hydroxy-3-phospholene 1-oxides



However, the quantity of the T3P[®] reagent could be decreased to 0.66 equivalents only under MW conditions and working at 85 °C [29].

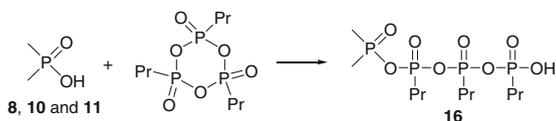
1-Hydroxyphospholane 1-oxides (**11**) were also converted to the corresponding phosphinates (**14**) in a similar way (Scheme 3.10) [29].

Scheme 3.10 T3P[®]-mediated esterification of 1-hydroxyphospholane 1-oxides



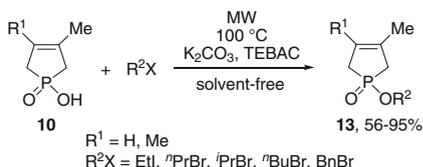
The use of only 0.66 equivalents of the T3P[®] reagent at 85 °C under MW conditions furnished the phosphinates (**14**) in somewhat lower (55–67 %) yields [29].

The role of the T3P[®] reagent is to activate the phosphinic acids (**8**, **10** and **11**) by converting them to the corresponding mixed anhydrides represented by general structure **16** (Scheme 3.11).

Scheme 3.11 Activation of phosphinic acids

3.3.3 Alkylating Esterification of Phosphinic Acids

Phosphinic esters may also be synthesized by alkylating esterification utilizing the MW and phase transfer catalytic (PTC) techniques. This is shown on the example of the alkylation of 1-hydroxy-3-phospholene oxides **10** (Scheme 3.12, Table 3.3) [24, 31]. During the alkylations, similarly to that of phenols, the combined application of MW irradiation and PTC was found to be synergistic [32, 33].

Scheme 3.12 Alkylating esterification of 1-hydroxy-3-phospholene 1-oxides**Table 3.3** Alkylating esterification of phospholene oxides under solvent-free MW conditions

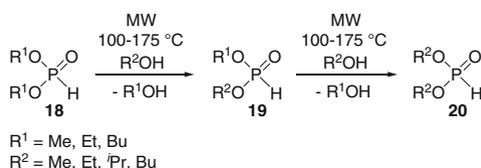
R ¹	R ² X	TEBAC (%)	t (h)	Yield of 13 (%)
H	EtI	–	1	80
H	EtI	5	1	90
H	ⁿ PrBr	–	1	73
H	ⁿ PrBr	5	1	94
H	ⁱ PrBr	–	1.5	42
H	ⁱ PrBr	5	1	65
Me	EtI	–	1	83
Me	EtI	5	1	95
Me	ⁿ PrBr	–	1	49
Me	ⁿ PrBr	5	1	90
Me	ⁱ PrBr	–	1.5	18
Me	ⁱ PrBr	5	1	56

The O-alkylations could, of course, be extended to 1-hydroxyphospholane oxides and to a 1-hydroxy-1,2,3,4,5,6-hexahydrophosphinine oxide [24].

The alkylation of thermally unstable cyclic phosphinic acids, such as a 1-hydroxy-3-phosphabicyclo[3.1.0]hexane 3-oxide and 1-hydroxy-1,2-dihydrophosphinine oxide was performed using K₂CO₃ in acetone at 63 °C [34].

3.3.4 Transesterification Reactions of Dialkyl Phosphites (H-Phosphonates)

It was found that dialkyl phosphites (**17**) underwent alcoholysis on exposing their alcoholic solutions to MW irradiation above 100 °C. In most cases, the three possible phosphites (**18**, **19** and **20**) were present in the mixture (Scheme 3.13, Table 3.4). The reaction could be controlled to give the dialkyl phosphite with two different alkyl groups (**19**) as the major component, or to provide the fully transesterified product (**20**) as an almost exclusive product. Comparative thermal experiments were also performed [35].



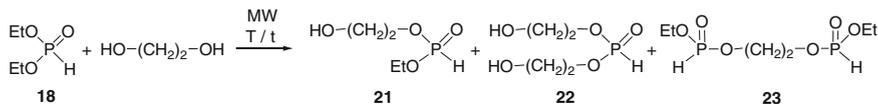
Scheme 3.13 Transesterification of dialkyl phosphites

Table 3.4 Results of the reactions of dialkyl phosphites with alcohols

R ¹	R ²	Equivalents of R ² OH	T (°C)	t (min)	p (bar)	Composition (%)		
						18	19	20
Me	Et	5	100	120	3	29	56	15
Me	Et	50	125	60	6	2	37	61
Me	Et	50	175	40	15	0	4	96
Et	Me	50	125	60	8	48	40	12
Et	Me	50	150	60	15	1	19	80
Et	Me	50	175	40	19	0	21	79
Me	Bu	25	125	60	3	0	40	60
Me	Bu	50	150	90	6	0	0	100
Et	Bu	25	125	60	3	25	54	21
Et	Bu	50	175	40	9	0	2	98

As can be seen from Table 3.4, the outcome of alcoholysis depended on the nature of the reagents, the molar ratio of alcohol and substrate, the temperature and reaction time. Using the alcohol in a less excess and applying lower temperatures, the proportion of the mixed dialkyl phosphites (**19**) was 40–56 %. Increasing the proportion of the alcohols and elevating the temperature, the fully transesterified *H*-phosphonate (**20**) became the predominating component. The dialkyl phosphites with mixed alkyl groups are valuable building blocks.

The alcoholysis of diethyl phosphite with ethylene glycol may principally lead to mixed ester **21**, fully transesterified product **22** and bis(*H*-phosphonate) **23** (Scheme 3.14, Table 3.5). The composition of the mixture depended on the ratio of the starting materials and the temperature [36].



Scheme 3.14 MW-assisted alcoholysis of diethyl phosphite with ethylene glycol

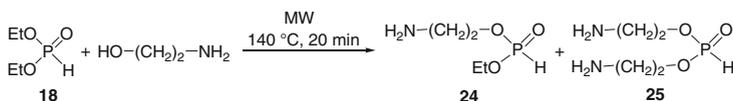
Table 3.5 MW-assisted alcoholysis of diethyl phosphite with ethylene glycol under different conditions

Entry	Molar ratio		T (°C)	t (h)	Conversion (%)	Product composition (%)		
	(EtO) ₂ P(O)H	(HOCH ₂) ₂				21	22	23
1	1	1	120	6	55	76	13	11
2	1	1	140	1 ^a	67	79	11	9
3	1	4	140	1	64	59	41	0
4	1	8	140	1	39	41	59	0
5	2	1	140	3	59	75	0	25

^aOn a prolonged heating (3 h), a considerable amount of by-products were formed

The maximum proportion (79 %) of the mixed ester (**21**) was obtained at 140 °C using the reactants in a 1:1 ratio. The bis(hydroxyethyl) derivative (**22**) was formed in a relative proportion of 59 %, if the glycol was measured in an eight-fold quantity. The bis(phosphono) derivative (**23**) was present in 25 % at a (EtO)₂P(O)H–(HOCH₂)₂ molar ratio of 2:1.

In the MW-assisted reaction with diethyl phosphite, ethanolamine acted as an O–nucleophile. However, when ethanolamine was applied in only a 1–2 equivalents quantity, not alcoholysis, but mono- and diethylation of the ethanolamine took place. Using ethanolamine in a 4–10-fold quantity at 140 °C for 20 min, different ratios of the mixed phosphinate (**24**) and the fully transesterified product (**25**) were obtained (Scheme 3.15, Table 3.6) [36].



Scheme 3.15 MW-assisted alcoholysis of diethyl phosphite with ethanolamine

Table 3.6 MW-assisted alcoholysis of diethyl phosphite with ethanolamine at 140 °C for 20 min

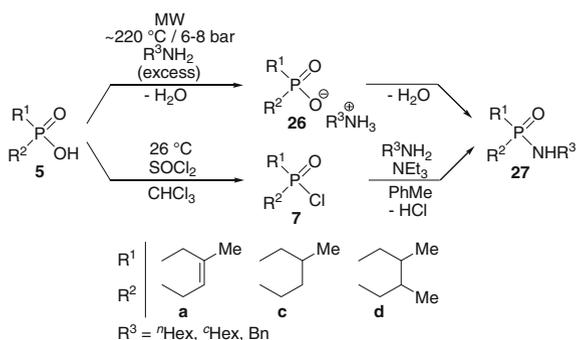
Entry	Molar ratio		Conversion (%)	Product composition (%)	
	(EtO) ₂ P(O)H	HO(CH ₂) ₂ NH ₂		24	25
1	1	4	100	45	55
2	1	8	100	22	78
3	1	10	100	15	85

From the point of view of bis(aminoethyl)phosphite (**25**), the best experiment was, when ethanolamine was measured in a 10 equivalents quantity and the reaction was performed at 140 °C for 20 min.

3.4 Amidation of Phosphinic Acids

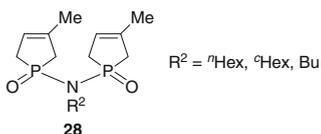
Phosphinic acids fail to undergo reaction with amines on heating. The usual synthesis of phosphinic amides (**27**) involves the reaction of phosphinic chlorides (**7**) with amines (Scheme 3.16). The direct amidations of phosphinic acids **5** attempted under MW irradiation remained incomplete with conversions of 30–33 % (Scheme 3.16) [37]. The ammonium salts of type **26** are intermediates in these amidations. The unreactivity even on MW is the consequence of the endothermicity of the direct amidations ($\Delta H^0 = 17.1\text{--}39.0 \text{ kJ mol}^{-1}$). It can be concluded that the amidation of phosphinic acids is controlled thermodynamically [25].

Scheme 3.16 Possible ways for the amidation of phosphinic acids



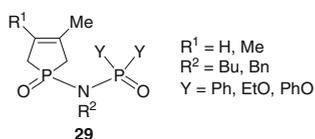
In the light of this fact, it is better to carry out the amidations under discussion via the traditional way, using phosphinic chlorides (**7**) as intermediates. However, it was observed that in the reaction of 1-chloro-3-methyl-3-phospholene oxide (**7a**)

with primary amines, bis(phosphinoyl)amine type side products (**28**) were also formed [38].



Moreover, fine-tuning the molar ratio of the components and the addition technique, it was possible to obtain the bis(phosphinoyl)amine (**28**) as the exclusive product.

It was also possible to utilize this protocol in the synthesis of mixed derivatives represented by structure **29** [39].

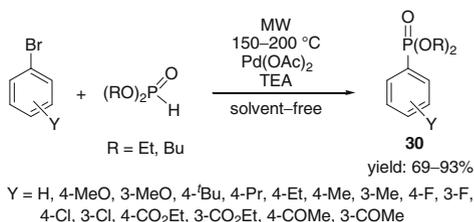


3.5 P–C Coupling Reactions

The Hirao-reaction comprising the P–C coupling of a vinyl halide/aryl halide/hetaryl halide and a $>\text{P}(\text{O})\text{H}$ species has become an important tool to synthesize phosphonates, phosphinates and phosphine oxides [40, 41]. This reaction model prompted many chemists to elaborate “green” variations.

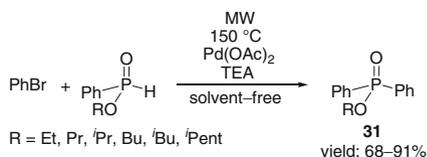
It was interesting to find that there is no need to use the expensive $\text{Pd}(\text{Ph}_3\text{P})_4$ catalyst in the coupling reaction of dialkyl phosphites with bromobenzene, as $\text{Pd}(\text{OAc})_2$ also catalyses the Hirao reaction in the absence of any added P-ligand. A MW-assisted solvent-free accomplishment was the best choice [42, 43]. The arylphosphonates (**30**) were obtained in 69–93 % yields (Scheme 3.17).

Scheme 3.17 Pd-catalyzed coupling reaction of dialkyl phosphites and aryl bromides



The use of alkyl phenyl-*H*-phosphinates in reaction with bromobenzene led to alkyl diphenylphosphinates (**31**) (Scheme 3.18).

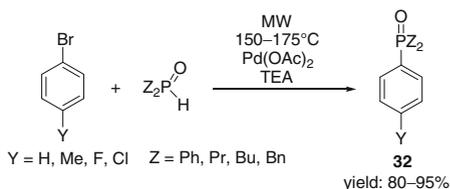
Scheme 3.18 Pd-catalyzed coupling reaction of alkyl phenyl-*H*-phosphinates and bromobenzene



Dibenzo[*c.e*][1,2]oxaphosphorine oxide was also utilized as a P-reagent.

Extending the reaction to secondary phosphine oxides, the products of the P–C coupling reaction are phosphine oxides (**32**) (Scheme 3.19).

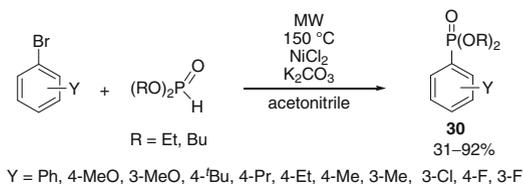
Scheme 3.19 Pd-catalyzed coupling reaction of secondary phosphine oxides and aryl bromides



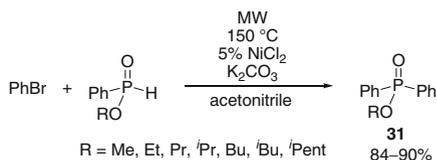
A P-ligand-free Pd-catalyzed method was also utilized in the reaction of 2-nitro-5-bromoanisole with diethyl phosphite using K_2CO_3 as the base and xylene as the solvent [44].

It was interesting to find that the MW-assisted P-ligand-free accomplishment worked also with $NiCl_2$ as the catalyst. In these variations, acetonitrile had to be used due to the heterogeneity of the reaction mixtures. The series of arylphosphonates (**30**), alkyldiphenylphosphinates (**31**) and diaryl-phenylphosphine oxides (**33**) were prepared as shown in Schemes 3.20, 3.21 and 3.22 [45].

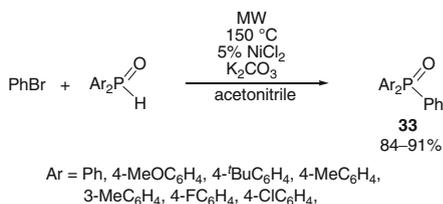
Scheme 3.20 Ni-catalyzed coupling reaction of alkyl phenyl-*H*-phosphinates and aryl bromides



Scheme 3.21 Ni-catalyzed coupling reaction of dialkyl phosphites and bromobenzene



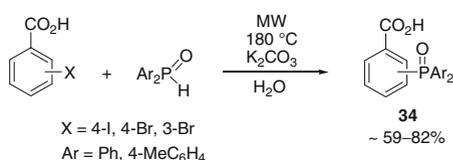
Scheme 3.22 Ni-catalyzed coupling reaction of secondary phosphine oxides and bromobenzene



The P-ligand-free approaches are environmentally-friendly as save costs and environmental burdens. Other MW-assisted variations of the Hirao-reaction were also described, but they applied P-ligands [46–49].

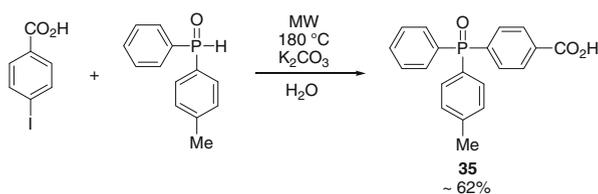
The P–C coupling of halobenzoic acids and diarylphosphine oxides was performed in the absence of any catalyst in the presence of K₂CO₃ in water under MW conditions (Scheme 3.23) [50].

Scheme 3.23 Catalyst-free coupling reaction of diarylphosphine oxides and halobenzoic acids



This protocol was then utilized for the synthesis of a mixed triarylphosphine oxide (**35**) (Scheme 3.24).

Scheme 3.24 Synthesis of trialkyl-substituted phosphine oxide with different aryl groups



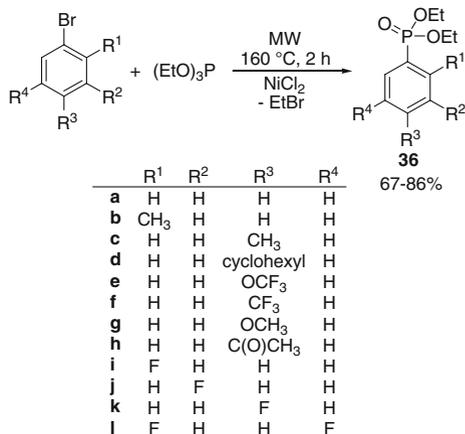
Till data, the P-ligand-free variation may be the most attractive protocol for the Hirao reaction. As a matter of fact, in the P-ligand-free cases, the trivalent tautomer form of the >P(O)H reagent may act as the ligand. The “green” accomplishments have been summarized [51, 52].

3.6 Arbuzov Reactions

Beside the Hirao-reaction, the Arbuzov-reaction is also a suitable method for the preparation of arylphosphonates [53]. However, special protocols are necessary to overcome the decreased reactivity of the aryl halides.

Arylphosphonates (**36**) are the products of the MW-assisted catalytic Arbuzov reaction of aryl bromides with triethyl phosphite. In the presence of a Ni salt catalyst, the phosphonates (**36**) could be prepared in yields of 67–86 % (Scheme 3.25) [54].

Scheme 3.25 MW-assisted Arbuzov reaction of aryl halides and triethyl phosphite



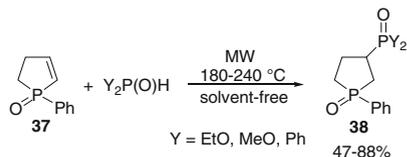
3.7 Phospha-Michael Additions

Simple phospha-Michael reactions, such as the addition of dialkyl phosphites or diphenylphosphine oxide to methyl vinyl ketone or cyclohexene-2-one were performed using NaOR/ROH (R = Me, Et), NaOH/H₂O under PTC or 1,8-diazabicycloundec-7-ene (DBU). There was no need to apply MW irradiation [55]. Phospha-Michael reactions of methyl vinyl ketone with *P*-heterocyclic nucleophiles deriving from a dibenzo-1,2-oxaphosphorine oxide or 1,3,2-dioxaphosphorine oxide were carried out in the presence of DBU [56]. However, the addition of dialkyl phosphites, dibenzo-1,2-oxaphosphorine oxide and diphenylphosphine oxide to the electron-poor double-bond of a 1,2-dihydrophosphinine oxide required a greater activation, so that first the >P(O)H

species had to be converted to the corresponding anion by deprotonation with trimethylaluminum [57, 58]. In these reactions, MW irradiation was unable to enhance the addition of the $>P(O)H$ species to the not too reactive $CH=CH-P(O)<$ unsaturation of the reactants.

However, MW irradiation was useful in the addition of dialkyl phosphites and diphenylphosphine oxide to the double-bond of 1-phenyl-2-phospholene 1-oxide (37) (Scheme 3.26) [59]. In these cases, the adducts (38) were formed as 1:1 mixtures of two isomers.

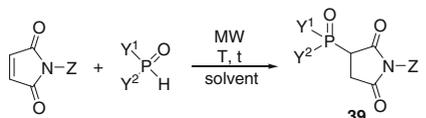
Scheme 3.26 Michael addition of $>P(O)H$ species to 1-phenyl-2-phospholene 1-oxide



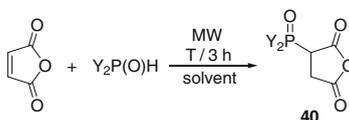
Using dialkyl phosphites pre-reacted with trimethylaluminum, the above additions took place more efficiently (in 89–93 % yields), and were selective leading to only one isomer.

MW addition promoted the addition of dialkyl phosphites, ethyl phenyl-*H*-phosphinate and diphenylphosphine oxide to the reactive unsaturation of *N*-phenyl and *N*-methylmaleimide, as well as maleic anhydride (Schemes 3.27 and 3.28) [60]. In most cases, the reactions were performed in the absence of any solvent. Products 39 and 40 were obtained, with one exception, in good yields.

Scheme 3.27 Michael addition of $>P(O)H$ species to maleimide derivatives



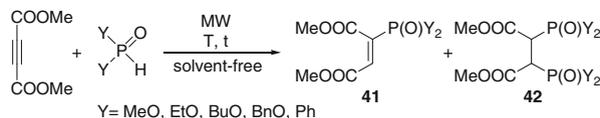
Z	Y ¹	Y ²	T (°C)	t (h)	solvent	yield of 39 (%)
Ph	EtO	EtO	175	2.5	-	83
Ph	MeO	MeO	175	2.5	-	81
Me	EtO	EtO	175	3	-	95
Me	MeO	MeO	175	3	-	71
Ph	Ph	EtO	175	2.5	-	92
Me	Ph	EtO	175	3	-	80
Ph	Ph	Ph	120	3	MeCN	97
Me	Ph	Ph	120	3	MeCN	98



Y	T (°C)	solvent	yield of 40 (%)
EtO	120	-	49
Ph	175	MeCN	66

Scheme 3.28 Michael addition of $>P(O)H$ species to maleic anhydride

Depending on the molar ratio of the reactants and the conditions (temperature and reaction time), the addition of dialkyl phosphites or diphenylphosphine oxide to the triple bond of dimethyl acetylenedicarboxylate resulted in the formation of a comparable mixture of the corresponding monoadduct (**41**) and bisadduct (**42**), or the bisadduct (**42**) as the predominating or exclusive product (Scheme 3.29, Table 3.7) [61].

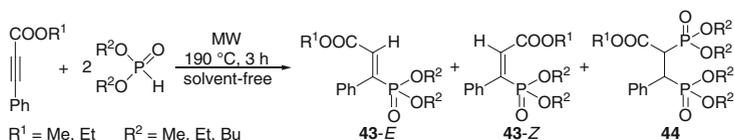


Scheme 3.29 MW-assisted addition of dialkyl phosphites and diphenylphosphine oxide to dimethyl acetylenedicarboxylate

Table 3.7 The MW-assisted addition of dialkyl phosphites and diphenylphosphine oxide to dimethyl acetylenedicarboxylate

Entry	Y	$\frac{n_{\text{Y}_2\text{P(O)H}}}{n_{\text{(MeO}_2\text{C)C}_2}}$	T (°C)	t (h)	Product composition (%)		Yield (%)
					41	42	
1	MeO	0.5	90 → 100	5.5	55	45	45 (41 (Y = MeO))
2	MeO	2	100	3.5	5	95	90 (42 (Y = MeO))
3	EtO	0.5	90 → 100	5.5	51	49	46 (41 (Y = EtO))
4	EtO	2	100	3.5	7	93	87 (42 (Y = EtO))
5	BuO	0.5	90 → 100	5.5	50	50	44 (41 (Y = BuO))
6	BuO	2	100	3.5	6	94	90 (42 (Y = BuO))
7	BnO	0.5	90 → 100	5.5	43	57	39 (41 (Y = BnO))
8	BnO	2	100	3.5	0	100	96 (42 (Y = BnO))
9	Ph	0.5	26	0.25	58	42	53 (41 (Y = Ph))
10	Ph	2	80	0.75	4	96	94 (42 (Y = Ph))

The similar reaction of alkyl phenylpropiolates and two equivalents of dialkyl phosphites at 190 °C afforded a mixture of *E* and *Z* alkyl 3-(dialkoxyphosphoryl)-3-phenylacrylates (**43**), and in a few cases some of the bisadducts (**44**). Within the phosphoryl-phenylacrylates (**43**) the *E* isomer predominated (Scheme 3.30, Table 3.8) [62].



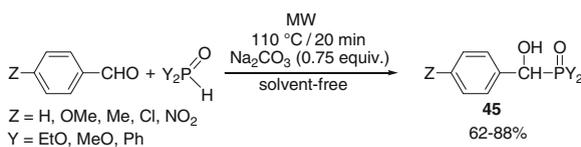
Scheme 3.30 MW-assisted addition of dialkyl phosphites to methyl- and ethyl phenylpropiolate

Table 3.8 The MW-assisted addition of dialkyl phosphites to alkyl phenylpropiolates

Entry	R ¹	R ²	Product composition (%)			Yield (43-E) (%)
			Monoadduct (43)		Bisadduct (44)	
			<i>E</i>	<i>Z</i>		
1	Me	Me	73	13	14	60
2	Me	Et	90	10	0	84
3	Me	Bu	89	11	0	83
4	Et	Me	74	14	12	66
5	Et	Et	86	14	0	80
6	Et	Bu	85	15	0	72

3.8 The Addition of >P(O)H Species to Carbonyl-Compounds

α -Aryl- α -hydroxyphosponates and α -aryl- α -hydroxyphosphine oxides (**45**), potentially bioactive substrates, were synthesized in a catalytic and solvent-free MW-assisted reaction comprising the addition of >P(O)H species to aryl aldehydes (Scheme 3.31, Table 3.9) [63].



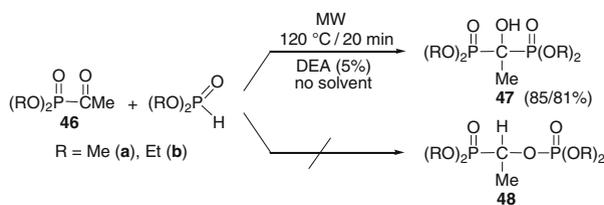
Scheme 3.31 MW-assisted synthesis of α -hydroxyphosponates and α -hydroxyphosphine oxides

Table 3.9 Summary of the MW-assisted synthesis of α -hydroxyphosphonates and α -hydroxyphosphine oxides

Entry	Y	Z	Yield of 45 (%)
1	EtO	H	85
2	MeO	H	87
3	Ph	H	88
4	EtO	MeO	82
5	MeO	MeO	84
6	Ph	MeO	78
7	EtO	Me	87
8	MeO	Me	62
9	Ph	Me	80 ^a
10	EtO	Cl	84
11	MeO	Cl	72
12	Ph	Cl	79 ^a
13	EtO	NO ₂	86 ^b
14	MeO	NO ₂	71
15	Ph	NO ₂	80

^a110 °C, 0.5 h^b150 °C, 1 h

Dialkyl phosphites were also added to the carbonyl function of α -ketophosphonates (**46**) to result in the formation of dronate analogue α -hydroxybisphosphonates (**47**) in the presence of diethylamine and in the absence of any solvent. Under optimum conditions, the formation of the rearranged by-product **48** could be avoided (Scheme 3.32) [64, 65].

**Scheme 3.32** MW-assisted reaction of α -ketophosphonates and dialkyl phosphites

It was interesting to find that on MW irradiation, α -ketophosphonate **46b** was converted to α -hydroxybisphosphonate **47b**. Half of the starting material (**46b**) served as the precursor for diethyl phosphite which then reacted with the unchanged **46b** to afford bisphosphonate **27b** (Scheme 3.33) [65].

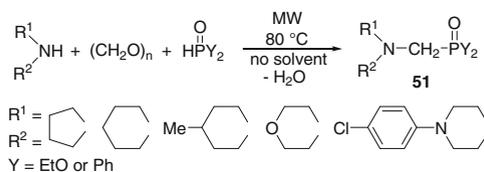
Table 3.10 Summary of the MW-assisted Kabachnik–Fields reactions

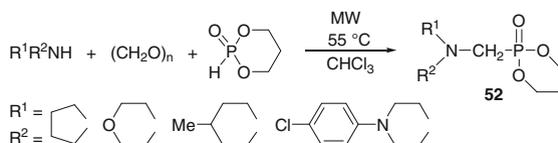
Entry	R ¹	R ²	R ³	Y	T (°C)	t (min)	Yield of 50 (%)
1	Ph	H	H	EtO	80 ^a 100 ^b	15 ^a 30 ^b	91
2	Ph	H	H	MeO	80 ^a 80 ^b	15 ^a 60 ^b	80
3	Ph	H	H	Ph	80	30	94
4	Bn	H	H	EtO	100	30	81
5	Bn	H	H	Ph	80	30	88
6	Ph	H	Ph	EtO	100	30	93
7	Ph	H	Ph	MeO	100	30	86
8	Ph	H	Ph	Ph	80	30	87
9	Bn	H	Ph	EtO	100	20	83
10	Bn	H	Ph	MeO	100	20	87
11	Ph	Me	Ph	EtO	120	40	80
12	Bn	Me	Ph	EtO	120	30	84
13	Bn	Me	Ph	Ph	100 ^a 120 ^b	30 ^a 30 ^b	80
14	Ph			EtO	120	40	81
15	Bn			EtO	120	30	91
16	Bn			MeO	120	30	85
17	Bn			Ph	100 ^a 120 ^b	30 ^a 30 ^b	80

^aCondensation of the oxo-component and the amine^bAddition of the >P(O)H species to the Schiff-base

MW-assisted phospho-Mannich condensations were also performed in an excess of diethyl phosphite. Due to the use of domestic MW ovens, the reaction temperatures were not reported [71, 72].

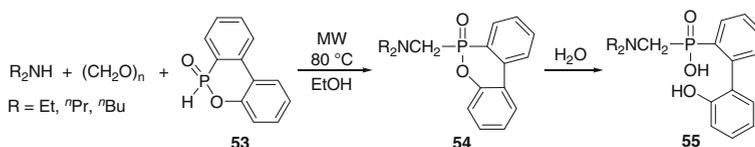
The use of heterocyclic amines pyrrolidine, piperidine derivatives, morpholine and piperazine derivatives or heterocyclic >P(O)H species (e.g. 1,3,2-dioxaphosphorine oxide) led to *N*-heterocyclic [73] and *P*-heterocyclic [74] α -aminophosphonates (**51**, Y = EtO and **52**) and α -aminophosphine oxides (**51**, Y = Ph) (Schemes 3.36 and 3.37).

**Scheme 3.36** Kabachnik–Fields reactions with *N*-heterocycles as the amine component



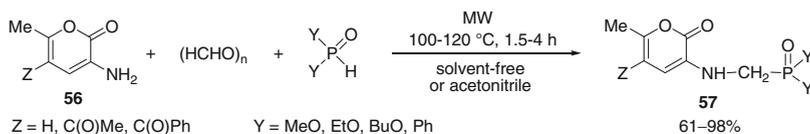
Scheme 3.37 Kabachnik–Fields reactions with 1,3,2-dioxaphosphorine oxide as the P-reactant

In the reaction of dialkylamines, paraformaldehyde and dibenzo[*c.e*][1,2]-oxaphosphorine oxide (**53**), the heterocyclic ring underwent ring opening by reaction with water formed in the condensation to result in end-product **55** (Scheme 3.38) [74].



Scheme 3.38 Kabachnik–Fields reaction with a dibenzooxaphosphorine oxide as the P-reactant

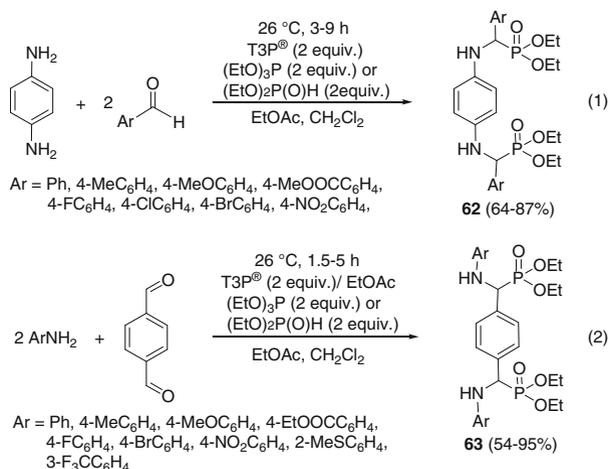
Then 3-amino-6-methyl-2*H*-pyran-2-ones (**56**) were utilized in the Kabachnik–Fields reaction with formaldehyde and dialkyl phosphites or diphenylphosphine oxide (Scheme 3.39) [75].



Scheme 3.39 The synthesis of phosphono- or phosphinoylmethylamino-2*H*-pyran-2-ones

Phospha-Mannich-condensations are also known to proceed with trialkyl phosphites in water as the solvent. In this respect, the reaction of benzylamine, benzaldehyde and triethyl phosphite was investigated in comparison with the variation using diethyl phosphite as the P-reagent. The first version was practically complete at room temperature, but the conversion with diethyl phosphite remained uncomplete (Scheme 3.40) [76]. This experience justifies again the MW-assisted and solvent-free accomplishment of the Kabachnik–Fields reactions utilizing dialkyl phosphites [70].

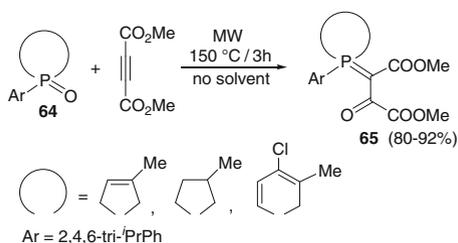
equivalents of arylamine and P-reagent (as above) (Scheme 3.43/(2)). The bis-products **62** and **63** were obtained in variable yields [83].



Scheme 3.43 Further variations of the bis(phospha-Mannich) reactions

3.11 Inverse Wittig-Type Reactions

The use of the MW technique was rather advantageous in the inverse Wittig-type reaction of 2,4,6-triisopropylphenyl-3-phospholene oxides, 2,4,6-triisopropylphenyl-phospholane oxides and 2,4,6-triisopropylphenyl-1,2-dihydrophosphinine oxides (all represented by formula **64**) and dimethyl acetylenedicarboxylate to furnish β -oxophosphoranes **65** (Scheme 3.44). Completion under thermal conditions required a *ca.* 2 week's heating at 150 °C, while on MW irradiation, the reactions were complete already after 3 h at the same temperature. No solvent had to be used in either case [84, 85].

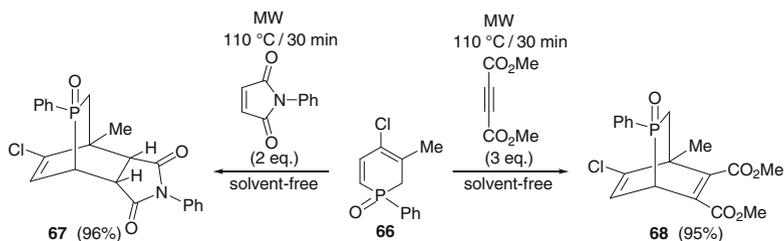


Scheme 3.44 The inverse Wittig-type reaction of P-aryl substituted cyclic phosphine oxides with dimethyl acetylenedicarboxylate

It should be noted that in case of the *P*-mesityl substituent (Ar = 2,4,6-Me₃Ph), the inverse Wittig-type reaction shown in Scheme 3.44 took place exclusively under MW irradiation.

3.12 Diels–Alder Cycloaddition Reactions

The reaction of 1-phenyl-1,2-dihydrophosphinine oxide **66** with dienophiles, such as *N*-phenylmaleimide and dimethyl acetylenedicarboxylate took place according to the [4+2] Diels–Alder protocol to provide the corresponding phosphabicyclo[2.2.2]octene oxide (**67**) or phosphabicyclo[2.2.2]octadiene oxide (**68**), respectively [86]. The MW technique was useful in shortening the reaction times [30 min (MW) versus 2 days (thermal heating) under solvent-free conditions] and in providing the cycloadducts (**67/68**) in almost quantitative yields (Scheme 3.45) [87].

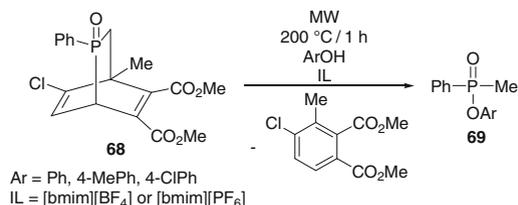


Scheme 3.45 Diels–Alder reactions of a 1,2-dihydrophosphinine oxide with different dienophiles

The absorption of MW irradiation was more efficient in the presence of onium salts, when a solvent was also used [88].

3.13 Fragmentation-Related Phosphorylations

The bridged *P*-heterocycles, such as phosphabicyclo[2.2.2]octadiene oxide **68** are useful in fragmentation-related phosphorylations [86]. On thermal influence or photochemical irradiation, the bridging methylenephosphine oxide [PhP(O)(CH₂)] unit of precursor **68** is ejected, and may phosphorylate a nucleophile e.g. a phenol added to the mixture prior to the fragmentation [89]. An alternative mechanism comprising a pentacoordinate intermediate was also proposed and proved [86]. It was found that the fragmentation-related phosphorylations are more efficient under MW conditions using ionic liquids as the solvent. The phosphorylated phenols (**69**) were obtained in somewhat better yields than in earlier experiments (Scheme 3.46) [90].



Scheme 3.46 Fragmentation-related phosphorylations utilizing phosphabicyclo[2.2.2]octadiene precursor

3.14 Conclusions

In summary, a number of organophosphorus reactions were performed under MW conditions. The transformations studied embraced esterifications, amidations, alcoholyses, cycloadditions, additions, substitutions and condensations. In most cases, the role of MW irradiation was to make the reactions faster, or to make them more efficient and selective. In a few instances, the reactions took place only under MW conditions. It also occurred that MW irradiation substituted for the catalyst, or simplified catalyst systems. The examples shown demonstrate the potential of MW irradiation in organophosphorus synthesis.

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References

1. Guenin E, Meziane D (2011) Microwave assisted phosphorus organic chemistry: A review. *Curr Org Chem* 15:3465–3485. doi:[10.2174/138527211797374724](https://doi.org/10.2174/138527211797374724)
2. Keglevich G, Grün A, Bálint E, Kiss NZ, Jablonkai E (2013) Microwave-assisted organophosphorus synthesis. *Curr Org Chem* 17:545–554. doi:[10.2174/1385272811317050009](https://doi.org/10.2174/1385272811317050009)
3. Keglevich G, Greiner I (2014) The meeting of two disciplines: organophosphorus and green chemistry. *Curr Green Chem* 1:2–16. doi:[10.2174/221334610101131218094831](https://doi.org/10.2174/221334610101131218094831)
4. Keglevich G, Kiss NZ, Mucsi Z, Jablonkai E, Bálint E (2014) The synthesis of phosphinates: traditional versus green chemical approaches. *Green Process Synth* 3:103–110. doi:[10.1515/gps-2013-0106](https://doi.org/10.1515/gps-2013-0106)
5. Keglevich G (2014) Microwave-assisted synthesis of P-heterocycles. *Phosphorus, Sulfur Silicon Relat Elem* 189:1266–1278. doi:[10.1080/10426507.2014.885974](https://doi.org/10.1080/10426507.2014.885974)
6. Keglevich G, (2015) Application of microwave irradiation in the synthesis of P-heterocycles. In: Brahmachari G (ed) *Green synthetic approaches for biologically relevant heterocycles*. Elsevier, Amsterdam, pp 559–570. doi:[10.1016/B978-0-12-800070-0.00020-7](https://doi.org/10.1016/B978-0-12-800070-0.00020-7)

7. Keglevich G, Grün A, Bagi P, Bálint E, Kiss N, Kovács R, Jablonkai E, Kovács T, Fogassy E, Greiner I (2015) Environmentally friendly chemistry with organophosphorus syntheses in focus. *Per Polytechn Chem Eng* 59:82–95. doi:[10.3311/PPCh.7317](https://doi.org/10.3311/PPCh.7317)
8. Keglevich G, Novak T, Vida L, Greiner I (2006) Microwave irradiation as an alternative to phase transfer catalysis in the liquid-solid phase, solvent-free C-alkylation of active methylene containing substrates. *Green Chem* 8:1073–1075. doi:[10.1039/B610481A](https://doi.org/10.1039/B610481A)
9. Keglevich G, Majrik K, Vida L, Greiner I (2008) Microwave irradiation as a green alternative to phase transfer catalysis: solid-liquid phase alkylation of active methylene containing substrates under solvent-free conditions. *Lett Org Chem* 5:224–228. doi:[10.2174/157017808783955754](https://doi.org/10.2174/157017808783955754)
10. Greiner I, Grün A, Ludányi K, Keglevich G (2011) Solid-liquid two-phase alkylation of tetraethyl methylenebisphosphonate under microwave irradiation. *Heteroatom Chem* 22:11–14. doi:[10.1002/hc.20648](https://doi.org/10.1002/hc.20648)
11. Keglevich G, Grün A, Blastik Z, Greiner I (2011) Solid-liquid phase alkylation of P=O-functionalized CH acidic compounds utilizing phase transfer catalysis and microwave irradiation. *Heteroatom Chem* 22:174–179. doi:[10.1002/hc.20673](https://doi.org/10.1002/hc.20673)
12. Grün A, Blastik Z, Drahos L, Keglevich G (2012) Microwave-assisted alkylation of diethyl ethoxycarbonylmethylphosphonate under solventless conditions. *Heteroatom Chem* 23:241–246. doi:[10.1002/hc.21009](https://doi.org/10.1002/hc.21009)
13. Keglevich G, Grün A (2015) Microwave irradiation as a substitute for phase transfer catalyst in C-alkylation reactions. *Curr Green Chem* 3:254–263. doi:[10.2174/2213346102666141215212108](https://doi.org/10.2174/2213346102666141215212108)
14. Grün A, Bálint E, Keglevich G (2015) Solid-liquid phase C-alkylation of active methylene containing compounds under microwave conditions. *Catalysts* 5:634–652. doi:[10.3390/catal5020634](https://doi.org/10.3390/catal5020634)
15. Keglevich G, Grün A, Bálint E (2013) Microwave irradiation and phase transfer catalysis in C-, O- and N-alkylation reactions. *Curr Org Synth* 10:751–763. doi:[10.2174/1570179411310050006](https://doi.org/10.2174/1570179411310050006)
16. Grün A, Blastik Z, Drahos L, Keglevich G (2014) Dialkylation of diethyl ethoxycarbonylmethylphosphonate under microwave and solventless conditions. *Heteroatom Chem* 25:107–113. doi:[10.1002/hc.21142](https://doi.org/10.1002/hc.21142)
17. McBride JJ Jr, Grange L, Mais A (1963) Preparing esters of phosphinic acids. USA Patent US3092650, 04/20/1961
18. Quin LD (2000) A guide to organophosphorus chemistry. Wiley, New York
19. Kiss NZ, Keglevich G (2014) An overview of the synthesis of phosphinates and phosphinic amides. *Curr Org Chem* 18:2673–2690. doi:[10.2174/1385272819666140829011741](https://doi.org/10.2174/1385272819666140829011741)
20. Keglevich G, Kiss NZ, Mucsi Z (2014) Synthesis of phosphinic acid derivatives; traditional versus up-to-date synthetic procedures. *Chem Sci J* 5:1–14. doi:[10.4172/2150-3494.1000088](https://doi.org/10.4172/2150-3494.1000088)
21. Kiss NZ, Ludányi K, Drahos L, Keglevich G (2009) Novel synthesis of phosphinates by the microwave-assisted esterification of phosphinic acids. *Synth Commun* 39:2392–2404. doi:[10.1080/00397910802654880](https://doi.org/10.1080/00397910802654880)
22. Troev KD (2006) Reactivity of H-phosphonates. In: *Chemistry and application of H-phosphonates*. Elsevier, Amsterdam, pp 23–105. doi:[10.1016/B978-044452737-0/50004-1](https://doi.org/10.1016/B978-044452737-0/50004-1)
23. Keglevich G, Kiss NZ, Körtvélyesi T, Mucsi Z (2013) Direct esterification and amidation of phosphinic acids under microwave conditions. *Phosphorus, Sulfur Silicon Relat Elem* 188:29–32. doi:[10.1080/10426507.2012.743542](https://doi.org/10.1080/10426507.2012.743542)
24. Keglevich G, Bálint E, Kiss NZ, Jablonkai E, Hegedűs L, Grün A, Greiner I (2011) Microwave-assisted esterification of phosphinic acids. *Curr Org Chem* 15:1802–1810. doi:[10.2174/138527211795656570](https://doi.org/10.2174/138527211795656570)
25. Keglevich G, Kiss NZ, Mucsi Z, Körtvélyesi T (2012) Insights into a surprising reaction: The microwave-assisted direct esterification of phosphinic acids. *Org Biomol Chem* 10:2011–2018. doi:[10.1039/C2OB06972E](https://doi.org/10.1039/C2OB06972E)
26. Kiss NZ, Böttger É, Drahos L, Keglevich G (2013) Microwave-assisted direct esterification of cyclic phosphinic acids. *Heteroatom Chem* 24:283–288. doi:[10.1002/hc.21092](https://doi.org/10.1002/hc.21092)

27. Mucsi Z, Kiss NZ, Keglevich G (2014) A quantum chemical study on the mechanism and energetics of the direct esterification, thioesterification and amidation of 1-hydroxy-3-methyl-3-phospholene 1-oxide. *RSC Adv* 4:11948–11954. doi:[10.1039/C3RA47456A](https://doi.org/10.1039/C3RA47456A)
28. Keglevich G, Kiss NZ, Drahos L, Körtvélyesi T (2013) Direct esterification of phosphinic acids under microwave conditions: extension to the synthesis of thiophosphinates and new mechanistic insights. *Tetrahedron Lett* 54:466–469. doi:[10.1016/j.tetlet.2012.11.054](https://doi.org/10.1016/j.tetlet.2012.11.054)
29. Jablonkai E, Henyecz R, Milen M, Kóti J, Keglevich G (2014) T3P[®]-assisted esterification and amidation of phosphinic acids. *Tetrahedron* 70:8280–8285. doi:[10.1016/j.tet.2014.09.021](https://doi.org/10.1016/j.tet.2014.09.021)
30. Jablonkai E, Milen M, Drahos L, Keglevich G (2013) Esterification of five-membered cyclic phosphinic acids under mild conditions using propylphosphonic anhydride (T3P[®]). *Tetrahedron Lett* 54:5873–5875. doi:[10.1016/j.tetlet.2013.08.082](https://doi.org/10.1016/j.tetlet.2013.08.082)
31. Bálint E, Jablonkai E, Bálint M, Keglevich G (2010) Alkylating esterification of 1-hydroxy-3-phospholene oxides under solventless MW conditions. *Heteroat Chem* 21:211–214. doi:[10.1002/hc.20596](https://doi.org/10.1002/hc.20596)
32. Keglevich G, Bálint E, Karsai É, Grün A, Bálint M, Greiner I (2008) Chemoselectivity in the microwave-assisted solvent-free solid–liquid phase benzylation of phenols: O- versus C-alkylation. *Tetrahedron Lett* 49:5039–5042. doi:[10.1016/j.tetlet.2008.06.051](https://doi.org/10.1016/j.tetlet.2008.06.051)
33. Keglevich G, Bálint E, Karsai É, Varga J, Grün A, Bálint M, Greiner I (2009) Heterogeneous phase alkylation of phenols making use of phase transfer catalysis and microwave irradiation. *Lett Org Chem* 6:535–539. doi:[10.2174/157017809789869500](https://doi.org/10.2174/157017809789869500)
34. Jablonkai E, Bálint E, Balogh GT, Drahos L, Keglevich G (2012) 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 Relat Elem* 187:357–363. doi:[10.1080/10426507.2011.613876](https://doi.org/10.1080/10426507.2011.613876)
35. Bálint E, Tajti Á, Drahos L, Ilia G, Keglevich G (2013) Alcoholysis of dialkyl phosphites under microwave conditions. *Curr Org Chem* 17:555–562. doi:[10.2174/1385272811317050010](https://doi.org/10.2174/1385272811317050010)
36. Keglevich G, Bálint E, Tajti Á, Mátravölgyi B, Balogh György T, Bálint M, Ilia G (2014) Microwave-assisted alcoholysis of dialkyl phosphites by ethylene glycol and ethanolamine. *Pure Appl Chem* 86:1723–1728. doi:[10.1515/pac-2014-0601](https://doi.org/10.1515/pac-2014-0601)
37. Keglevich G, Kiss NZ, Körtvélyesi T (2013) Microwave-assisted functionalization of phosphinic acids; amidations versus esterifications. *Heteroat Chem* 24:91–99. doi:[10.1002/hc.21068](https://doi.org/10.1002/hc.21068)
38. Kiss NZ, Simon A, Drahos L, Huben K, Jankowski S, Keglevich G (2013) Synthesis of 1-amino-2,5-dihydro-1H-phosphole 1-oxides and their N-phosphinoyl derivatives, bis(2,5-dihydro-1H-phosphol-1-yl)amine P, P'-dioxides. *Synthesis* 45:199–204. doi:[10.1055/s-0032-1316830](https://doi.org/10.1055/s-0032-1316830)
39. Kiss NZ, Rádai Z, Mucsi Z, Keglevich G (2015) Synthesis of bis(phosphinoyl)amines and phosphinoyl-phosphorylamines by the N-phosphinoylation and N-phosphorylation of 1-alkylamino-2,5-dihydro-1H-phosphole 1-oxides. *Heteroat Chem* 26:134–141. doi:[10.1002/hc.21229](https://doi.org/10.1002/hc.21229)
40. Jablonkai E, Keglevich G (2014) P-C bond formation by coupling reaction utilizing >P(O)H species as the reagents. *Curr Org Synth* 11:429–453. doi:[10.2174/15701794113109990066](https://doi.org/10.2174/15701794113109990066)
41. Jablonkai E, Keglevich G (2014) Advances and new variations of the Hirao reaction. *Org Prep Proc Int* 46:281–316. doi:[10.1080/00304948.2014.922376](https://doi.org/10.1080/00304948.2014.922376)
42. Jablonkai E, Keglevich G (2013) 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* 54:4185–4188. doi:[10.1016/j.tetlet.2013.05.111](https://doi.org/10.1016/j.tetlet.2013.05.111)
43. Keglevich G, Jablonkai E, Balázs LB (2014) 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* 4:22808–22816. doi:[10.1039/C4RA03292F](https://doi.org/10.1039/C4RA03292F)

44. Amaya T, Abe Y, Inada Y, Hirao T (2014) Synthesis of self-doped conducting polyaniline bearing phosphonic acid. *Tetrahedron Lett* 55:3976–3978. doi:[10.1016/j.tetlet.2014.04.115](https://doi.org/10.1016/j.tetlet.2014.04.115)
45. Jablonkai E, Balázs L, Keglevich G (2015) A P-ligand-free nickel-catalyzed variation of the Hirao reaction under microwave conditions. *Curr Org Chem* 19:197–202. doi:[10.2174/1385272819666150114235413](https://doi.org/10.2174/1385272819666150114235413)
46. Kalek M, Ziadi A, Stawinski J (2008) Microwave-assisted palladium-catalyzed cross-coupling of aryl and vinyl halides with H-phosphonate diesters. *Org Lett* 10:4637–4640. doi:[10.1021/ol801935r](https://doi.org/10.1021/ol801935r)
47. Andaloussi M, Lindh J, Sävmarker J, Sjöberg PJR, Larhed M (2009) Microwave-promoted palladium(II)-catalyzed C-P bond formation by using arylboronic acids or aryltrifluoroborates. *Chem Eur J* 15:13069–13074. doi:[10.1002/chem.200901473](https://doi.org/10.1002/chem.200901473)
48. Villemain D, Jaffrès P-A, Siméon F (1997) Rapid and efficient phosphonation of aryl halides catalysed by palladium under microwaves irradiation. *Phosphorus, Sulfur Silicon Relat Elem* 130:59–63. doi:[10.1080/10426509708033697](https://doi.org/10.1080/10426509708033697)
49. Rummelt SM, Ranocchiaro M, van Bokhoven JA (2012) Synthesis of water-soluble phosphine oxides by Pd/C-catalyzed P-C coupling in water. *Org Lett* 14:2188–2190. doi:[10.1021/ol300582y](https://doi.org/10.1021/ol300582y)
50. Jablonkai E, Keglevich G (2015) Catalyst-free P-C coupling reactions of halobenzoic acids and secondary phosphine oxides under microwave irradiation in water. *Tetrahedron Lett* 56:1638–1640. doi:[10.1016/j.tetlet.2015.02.015](https://doi.org/10.1016/j.tetlet.2015.02.015)
51. Jablonkai E, Keglevich G (2015) A survey of the palladium-catalyzed Hirao reaction with emphasis on green chemical aspects. *Curr Green Chem* 2:379–391. doi:[10.2174/2213346102999150630114117](https://doi.org/10.2174/2213346102999150630114117)
52. Jablonkai E, Keglevich G (2015) P-C coupling reactions under environmentally-friendly conditions. In: Petrova V (ed) *Advances in engineering research*, vol 10. Nova Science Publishers Inc, pp 99–125
53. Dzielak A, Mucha A (2015) Catalytic and MW-assisted Michaelis-Arbuzov reactions. *Curr Green Chem* 2:223–236. doi:[10.2174/2213346102666150128195001](https://doi.org/10.2174/2213346102666150128195001)
54. Keglevich G, Grün A, Bölskei A, Drahos L, Kraszni M, Balogh GT (2012) Synthesis and proton dissociation properties of arylphosphonates; a microwave-assisted catalytic Arbuzov reaction with aryl bromides. *Heteroat Chem* 23:574–582. doi:[10.1002/hc.21053](https://doi.org/10.1002/hc.21053)
55. Keglevich G, Sipos M, Takács D, Greiner I (2007) A study on the Michael addition of dialkylphosphites to methylvinylketone. *Heteroat Chem* 18:226–229. doi:[10.1002/hc.20266](https://doi.org/10.1002/hc.20266)
56. Keglevich G, Sipos M, Takács D, Ludányi K (2008) Phospha-Michael reactions involving P-heterocyclic nucleophiles. *Heteroat Chem* 19:288–292. doi:[10.1002/hc.20421](https://doi.org/10.1002/hc.20421)
57. Keglevich G, Sipos M, Imre T, Ludányi K, Szieberth D, Tőke L (2002) Diastereoselective synthesis of 1,2,3,6-tetrahydrophosphinine 1-oxides with an exocyclic P-function by a Michael type addition. *Tetrahedron Lett* 43:8515–8518. doi:[10.1016/S0040-4039\(02\)02081-6](https://doi.org/10.1016/S0040-4039(02)02081-6)
58. Keglevich G, Sipos M, Szieberth D, Nyulászi L, Imre T, Ludányi K, Tőke L (2004) Weak intramolecular interactions as controlling factors in the diastereoselective formation of 3-phosphinoxido- and 3-phosphono-1,2,3,6-tetrahydrophosphinine 1-oxides. *Tetrahedron* 60:6619–6627. doi:[10.1016/j.tet.2004.05.090](https://doi.org/10.1016/j.tet.2004.05.090)
59. Jablonkai E, Drahos L, Drzazga Z, Pietrusiewicz KM, Keglevich G (2012) 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. *Heteroat Chem* 23:539–544. doi:[10.1002/hc.21047](https://doi.org/10.1002/hc.21047)
60. Bálint E, Takács J, Drahos L, Keglevich G (2012) Microwave-assisted phospha-Michael addition of dialkyl phosphites, a phenyl-H-phosphinate, and diphenylphosphine oxide to maleic derivatives. *Heteroat Chem* 23:235–240. doi:[10.1002/hc.21007](https://doi.org/10.1002/hc.21007)
61. Keglevich G, Bálint E, Takács J, Drahos L, Huben K, Jankowski S (2014) The addition of dialkyl phosphites and diphenylphosphine oxide on the triple bond of dimethyl acetylenedicarboxylate under solvent-free and microwave conditions. *Curr Org Synth* 11:161–166. doi:[10.2174/1570179411999140304142747](https://doi.org/10.2174/1570179411999140304142747)

62. Bálint E, Takács J, Bálint M, Keglevich G (2015) The catalyst-free addition of dialkyl phosphites on the triple bond of alkyl phenylpropiolates under microwave conditions. *Curr Catal* 4:57–64. doi:[10.2174/2211544704666150303232225](https://doi.org/10.2174/2211544704666150303232225)
63. Keglevich G, Róza Tóth V, Drahos L (2011) Microwave-assisted synthesis of α -hydroxy-benzylphosphonates and -benzylphosphine oxides. *Heteroat Chem* 22:15–17. doi:[10.1002/hc.20649](https://doi.org/10.1002/hc.20649)
64. Grün A, Molnár IG, Bertók B, Greiner I, Keglevich G (2009) Synthesis of α -hydroxy-methylenebisphosphonates by the microwave-assisted reaction of α -oxophosphonates and dialkyl phosphites under solventless conditions. *Heteroat Chem* 20:350–354. doi:[10.1002/hc.20558](https://doi.org/10.1002/hc.20558)
65. Keglevich G, Grün A, Molnár IG, Greiner I (2011) Phenyl-, benzyl-, and unsymmetrical hydroxy-methylenebisphosphonates as dronic acid ester analogues from α -oxophosphonates by microwave-assisted syntheses. *Heteroat Chem* 22:640–648. doi:[10.1002/hc.20727](https://doi.org/10.1002/hc.20727)
66. Kiss NZ, Kaszás A, Drahos L, Mucsi Z, Keglevich G (2012) A neighbouring group effect leading to enhanced nucleophilic substitution of amines at the hindered α -carbon atom of an α -hydroxyphosphonate. *Tetrahedron Lett* 53:207–209. doi:[10.1016/j.tetlet.2011.11.026](https://doi.org/10.1016/j.tetlet.2011.11.026)
67. Bhattacharya A, Kaur T (2007) An efficient one-pot synthesis of alpha-amino phosphonates catalyzed by bismuth nitrate pentahydrate. *Synlett* 5:745–748. doi:[10.1002/chin.200730153](https://doi.org/10.1002/chin.200730153)
68. Matveeva ED, Podrugina TA, Tishkovskaya EV, Tomilova LG, Zefirov NS (2003) A novel catalytic three-component synthesis (Kabachnik-Fields reaction) of alpha-aminophosphonates from ketones. *Synlett* 2003:2321–2324. doi:[10.1055/s-2003-42118](https://doi.org/10.1055/s-2003-42118)
69. Lee S, Park J, Kang J, Lee J (2001) Lanthanide triflate-catalyzed three component synthesis of alpha-amino phosphonates in ionic liquids. A catalyst reactivity and reusability study. *Chem Commun*:1698–1699. doi:[10.1016/j.tetlet.2005.12.027](https://doi.org/10.1016/j.tetlet.2005.12.027)
70. Keglevich G, Szekrényi A (2008) Eco-friendly accomplishment of the extended Kabachnik-Fields reaction; a solvent- and catalyst-free microwave-assisted synthesis of α -aminophosphonates and α -aminophosphine oxides. *Lett Org Chem* 5:616–622. doi:[10.2174/157017808786857598](https://doi.org/10.2174/157017808786857598)
71. Kabachnik MM, Zobnina EV, Beletskaya IP (2005) Catalyst-free microwave-assisted synthesis of alpha-aminophosphonates in a three-component system: (RC)-C-1(O)R-2-(EtO)(2)P(O)H-RNH₂. *Synlett* 2005:1393–1396. doi:[10.1055/s-2005-868519](https://doi.org/10.1055/s-2005-868519)
72. Mu X-J, Lei M-Y, Zou J-P, Zhang W (2006) Microwave-assisted solvent-free and catalyst-free Kabachnik-Fields reactions for α -amino phosphonates. *Tetrahedron Lett* 47:1125–1127. doi:[10.1016/j.tetlet.2005.12.027](https://doi.org/10.1016/j.tetlet.2005.12.027)
73. Prauda I, Greiner I, Ludányi K, Keglevich G (2007) Efficient synthesis of phosphono- and phosphinodimethylated N-heterocycles under solvent-free microwave conditions. *Synth Commun* 37:317–322. doi:[10.1080/00397910601033856](https://doi.org/10.1080/00397910601033856)
74. Keglevich G, Szekrényi A, Sipos M, Ludányi K, Greiner I (2008) Synthesis of cyclic aminomethylphosphonates and aminomethyl-arylphosphinic acids by an efficient microwave-mediated phospho-Mannich approach. *Heteroat Chem* 19:207–210. doi:[10.1002/hc.20387](https://doi.org/10.1002/hc.20387)
75. Bálint E, Takács J, Drahos L, Juranovič A, Kočevár M, Keglevich G (2013) α -Aminophosphonates and α -aminophosphine oxides by the microwave-assisted Kabachnik-Fields reactions of 3-amino-6-methyl-2H-pyran-2-ones. *Heteroat Chem* 24:221–225. doi:[10.1002/hc.21086](https://doi.org/10.1002/hc.21086)
76. Keglevich G, Bálint E, Kangyal R, Bálint M, Milen M (2014) A critical overview of the Kabachnik-Fields reactions utilizing trialkyl phosphites in water as the reaction medium; a study on the benzaldehyde-benzylamine triethyl phosphite/diethyl phosphite models. *Heteroat Chem* 25:282–289. doi:[10.1002/hc.21192](https://doi.org/10.1002/hc.21192)
77. Cherkasov RA, Garifzyanov AR, Talan AS, Davletshin RR, Kurnosova NV (2009) Synthesis of new lipophilic functionalized aminomethylphosphine oxides and their acid-base and membrane-transport properties toward acidic substrates. *Russ J Gen Chem* 79:1835–1849. doi:[10.1134/S1070363209090114](https://doi.org/10.1134/S1070363209090114)

78. Keglevich G, Szekrényi A, Szöllősy Á, Drahos L (2011) Synthesis of bis(phosphonomethyl)-, bis(phosphinatomethyl)-, and bis(phosphinoxidomethyl)amines, as well as related ring bis(phosphine) platinum complexes. *Synth Commun* 41:2265–2272. doi:[10.1080/00397911.2010.501478](https://doi.org/10.1080/00397911.2010.501478)
79. Bálint E, Fazekas E, Pintér G, Szöllősy A, Holczbauer T, Czugler M, Drahos L, Körtvélyesi T, Keglevich G (2012) Synthesis and utilization of the bis(>P(O)CH₂)amine derivatives obtained by the double Kabachnik–Fields reaction with cyclohexylamine; quantum chemical and X-ray study of the related bidentate chelate platinum complexes. *Curr Org Chem* 16:547–554. doi:[10.2174/138527212799499822](https://doi.org/10.2174/138527212799499822)
80. Bálint E, Fazekas E, Pongrácz P, Kollár L, Drahos L, Holczbauer T, Czugler M, Keglevich G (2012) N-Benzyl and N-aryl bis(phospha-Mannich adducts): synthesis and catalytic activity of the related bidentate chelate platinum complexes in hydroformylation. *J Organomet Chem* 717:75–82. doi:[10.1016/j.jorganchem.2012.07.031](https://doi.org/10.1016/j.jorganchem.2012.07.031)
81. Bálint E, Fazekas E, Drahos L, Keglevich G (2013) The synthesis of N, N-bis(dialkoxylphosphinoylmethyl)- and N, N-bis(diphenylphosphinoylmethyl)glycine esters by the microwave-assisted double Kabachnik–Fields reaction. *Heteroat Chem* 24:510–515. doi:[10.1002/hc.21126](https://doi.org/10.1002/hc.21126)
82. Bálint E, Fazekas E, Kóti J, Keglevich G (2015) Synthesis of N, N-bis(dialkoxylphosphinoylmethyl)- and N, N-bis(diphenylphosphinoylmethyl)-β- and γ-amino acid derivatives by the microwave-assisted double Kabachnik–Fields reaction. *Heteroat Chem* 26:106–115. doi:[10.1002/hc.21221](https://doi.org/10.1002/hc.21221)
83. Milén M, Ábrányi-Balogh P, Kangyal R, Dancsó A, Frigyes D, Keglevich G (2014) T3P[®]-mediated one-pot synthesis of bis(α-aminophosphonates). *Heteroat Chem* 25:245–255. doi:[10.1002/hc.21170](https://doi.org/10.1002/hc.21170)
84. Keglevich G, Dudás E, Sipos M, Lengyel D, Ludányi K (2006) Efficient synthesis of cyclic β-oxophosphoranes by the microwave-assisted reaction of cyclic phosphine oxides and dialkyl acetylenedicarboxylate. *Synthesis* 2006:1365–1369. doi:[10.1055/s-2006-926395](https://doi.org/10.1055/s-2006-926395)
85. Keglevich G, Forintos H, Körtvélyesi T (2004) Synthesis and reactions of β-oxophosphoranes/yliides containing a cyclic or acyclic P-moiety. *Curr Org Chem* 8:1245–1261. doi:[10.2174/1385272043370023](https://doi.org/10.2174/1385272043370023)
86. Keglevich G, Szelke H, Kovács J (2004) Fragmentation-related phosphinylation and phosphorylation of nucleophiles utilising the bridging P-unit of 2-phospha-bicyclo[2.2.2]oct-5-ene derivatives. *Curr Org Synth* 1:377–389. doi:[10.2174/1570179043366521](https://doi.org/10.2174/1570179043366521)
87. Keglevich G, Dudás E (2007) Microwave promoted efficient synthesis of 2-phospha-bicyclo[2.2.2]octadiene- and octene 2-oxides under solvent-free conditions in Diels–Alder reaction. *Synth Commun* 37:3191–3199. doi:[10.1080/00397910701547532](https://doi.org/10.1080/00397910701547532)
88. Hohmann E, Keglevich G, Greiner I (2007) The effect of onium salt additives on the Diels–Alder reactions of a 1-phenyl-1,2-dihydrophosphinine oxide under microwave conditions. *Phosphorus, Sulfur Silicon Relat Elem* 182:2351. doi:[10.1080/10426500701441473](https://doi.org/10.1080/10426500701441473)
89. Keglevich G, Szelke H, Dobó A, Nagy Z, Toke L (2001) Phosphorylation of phenols and naphthols by phenyl-methylenephosphine oxide generated by the thermolysis of a 2-phospha-bicyclo[2.2.2]octa-5,7-diene 2-oxide. *Synth Commun* 31:1737–1741. doi:[10.1081/scc-100104403](https://doi.org/10.1081/scc-100104403)
90. Keglevich G, Kovács R, Drahos L (2011) Diels–Alder cycloadditions of 1,2-dihydrophosphinine oxides and fragmentation-related phosphorylations with 2-phospha-bicyclo[2.2.2]octadiene oxides under green chemical conditions—the role of microwave and ionic liquids. *Phosphorus, Sulfur Silicon Relat Elem* 186:2172–2179. doi:[10.1080/10426507.2011.597807](https://doi.org/10.1080/10426507.2011.597807)