Professor György Keglevich

A Tribute

This special issue of Arkivoc is dedicated to Professor György Keglevich on the occasion of his 65th birthday

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György Keglevich was born in Budapest, Hungary in 1957, and graduated from the Technical University of Budapest (TUB) in 1981 as a chemical engineer. He was awarded his PhD in 1990, DSc in 1994 and Dr Habil in 1995 in chemistry.

He was a Research Associate at Duke University (Durham/NC) with Prof. Louis D. Quin, then a Visiting Associate Professor at the University of Massachusetts (UMASS). He was appointed to Associate Professor (1993) and then Full Professor (1996) at the Department of Organic Chemical Technology where he served as the Head of Department of Organic Chemistry and Technology from 1999 to 2021.

He developed P-heterocyclic research in 6-, 7-membered, and bridged P-heterocycles. Additional research interests included the modification of the P-function and evaluation of mechanisms. He also dealt with environmentally friendly (green) chemistry embracing MW chemistry, ionic liquids, new catalysts, selective syntheses and collaborated in pharmaceutical projects as evidenced by 3 patents.

He was awarded the Zemplén Prize (1991), the Széchenyi Fellowship (1997) and an Award of the Hungarian Academy of Sciences (2004). He is the Editor-in-Chief of Current Organic Chemistry, founder E-I-C of Current Green Chemistry, and the Section E-I-C of the Symmetry/Asymmetry Section of Symmetry. He is Associate Editor for Current Organic Synthesis, Letters in Organic Chemistry, Letters in Drug Design and Discovery and Heteroatom Chemistry. He is an Editorial Board Member of Molecules, Green Processing and Synthesis, Phosphorus, Sulfur, Silicon and Current Microwave Chemistry. He was the Chair of Chemical Section 2 of the Hungarian Scientific Research Fund (HSRF) (1999–2002 and 2012–2015) and a member of the Collegium of the Natural Sciences for the HSRF (2003–2006 and 2016–2020). He was co-opted to the Steering Committee of International Conference of Phosphorus Chemistry (ICPC) in 2016. The 22nd ICPC took place in Budapest in 2018 under his chairmanship.

In addition, he is a member of the Advisory Board of the Rosztoczy Foundation and holds a number of positions at the Faculty of Chemical Technology and Biotechnology of Budapest University of Technology and Economics (BME).

He is the author or co-author of 630 papers including 40 review articles, 3 books and 51 book chapters. He has been an annual contributor to Specialists Periodical Reports on Organophosphorus Chemistry (edited by the RSC) since 2007. He organized 10 hot topic issues for Current Organic Chemistry and five other special issues for MDPI journals (Molecules and Symmetry – Symmetry/Asymmetry Section).

**Research Interests: Microwave-assisted organophosphorus syntheses, simplification of catalysts and utilization of organophosphorous compounds**

The microwave (MW) technique has become an important tool in organic chemistry in general,¹ and specifically in organophosphorus chemistry.²⁻⁴ Prof. Keglevich together with his co-workers elaborated the synthesis of P-heterocycles and other phosphinic, phosphonic and phosphine oxide derivatives utilizing the MW technique.⁵⁻¹¹ The reactions investigated by them are shown in Figure 1.
It is well-known that phosphinic acids do not undergo reaction with alcohols to afford phosphinates, and the widely used method (reaction of phosphinic chlorides with alcohols in the presence of a base) is neither atom efficient, nor environmentally friendly. Direct esterification of phosphinic acids with alcohols under MW conditions was a challenging task, but Keglevich found that a series of cyclic phosphinic acids, such as 1-hydroxy-3-phospholene oxides, 1-hydroxyphospholane oxides, and 1-hydroxy-1,2,3,4,5,6-hexahydrophosphinine oxides underwent esterification with propanol, butanol, isobutanol, octanol and dodecanol at around 200–230 °C on MW irradiation, and the phosphinates were isolated in 45–74% yields, after 2–4 h reaction time (Scheme 1).12–14

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\begin{align*}
R^2PO_{(15 \text{ equiv.)}} + R^1OH & \overset{\text{MW}}{\underset{200-230 \, ^\circ\text{C}/2-20 \text{ bar}}{\rightarrow}} R^2POR^1 \\
\text{MePO} + R^1OH & \overset{\text{MW}}{\underset{220-230 \, ^\circ\text{C}/3-20 \text{ bar}}{\rightarrow}} \text{MePO}OR^1 \\
\text{MePO} + R^1OH & \overset{\text{MW}}{\underset{220-230 \, ^\circ\text{C}/3-20 \text{ bar}}{\rightarrow}} \text{MePO}OR^1 + \text{MePO}OR^1 \\
\text{MePO} + R^1OH & \overset{\text{MW}}{\underset{230 \, ^\circ\text{C}/\leq20 \text{ bar}}{\rightarrow}} \text{MePO}OR^1 \\
\end{align*}
\]

\(R^1 = \text{Pr, Bu, } t^\text{Bu, Pent, } t^\text{Pent, Oct, } t^\text{Oct, Dodec}\)

**Scheme 1.** MW-assisted direct esterification of cyclic phosphinic acids.

Phosphinic acids fail to undergo reaction with amines on heating and the usual synthesis of phosphinic amides involves the reaction of phosphinic chlorides with amines (Scheme 2/B). The direct amidations attempted at 220 °C under MW irradiation gave only incomplete conversions (~33%) (Scheme 2/A),15 and it is better therefore to carry out the amidations using phosphinic chlorides as the intermediates (Scheme 2/C).16 Mixed phosphinoylamide derivatives were also prepared in a similar way.17
**Scheme 2.** Preparation of 1-amino-3-methyl-3-phospholene oxides and related imide derivatives.

Applying the MW technique was extremely useful in the so-called inverse Wittig-type reaction of 2,4,6-trialkylphenyl-3-phospholene oxides, 2,4,6-trialkylphenylphospholane oxides, and 2,4,6-trialkylphenyl-1,2-dihydrophosphinine oxides with dialkyl acetylenedicarboxylate to form the corresponding β-oxophosphoranes (Scheme 3/(1)–(4)).

The interaction of a phosphine oxide and an unsaturated species affords a product containing a P=C moiety and a carbonyl function. Completion under thermal conditions required ca. two weeks heating at 150 °C, whereas on MW irradiation, the reactions were complete after 3–6 h at the same temperature. When the saturated, arylphospholane oxides and arylhexahydrophosphinine oxides were reacted (Scheme 3/(2) and (4)), it was unnecessary to use solvents. Using 3-phospholene oxide as the starting material, partial isomerization of the heteroring to 2-phospholene occurred (Scheme 3/(1)). Conversion of 1-aryl-1,2-dihydrophosphinine oxide to the corresponding β-oxophosphorane was efficient as the polymerization was suppressed under MW conditions. The synthesis from a suitable aryl-3-phosphabicyclo[3.1.0]hexane 3-oxide led to more modest results (Scheme 3/(3)). The β-oxophosphoranes were isolated in yields of 36–92%, and this inverse-Wittig type reaction is a transformation discovered by Keglevich and his co-workers.

In another field, potentially bioactive α-aminophosphonates and α-aminophosphine oxides were synthesized by the solvent-free and catalyst-free MW-assisted Kabachnik–Fields condensation of primary amines, aldehydes/ketones and suitable >P(O)H species, such as dialkyl phosphites and diphenylphosphine oxide. Earlier preparations utilized special catalysts, which were not environmentally friendly species, but Keglevich proved that under MW conditions, there is no need for either catalysts or solvents to obtain good yields (Scheme 4). By the use of heterocyclic amines, or heterocyclic >P(O)H species, the α-aminophosphonates and α-aminophosphine oxides synthesized included N-heterocyclic or P-heterocyclic derivatives, respectively.
Scheme 3. The inverse Wittig-type reaction of $P$-aryl cyclic phosphine oxides with dialkyl acetylenedicarboxylate.

Scheme 4. MW-assisted Kabachnik–Fields condensations.
In a novel extension of the Kabachnik–Fields reaction, primary amines were reacted with two equivalents of formaldehyde and the >P(O)H species to provide bis(phosphonomethyl)- or bis(phosphinoxido)-products (Scheme 5), which, could be used as bidentate P-ligands after double deoxygenation.24–28

![Scheme 5. The bis(Kabachnik–Fields) reaction.](image)

α-Aryl-α-hydroxyphosphonates and α-aryl-α-hydroxyphosphine oxides, potentially bioactive substrates,29 were synthesized advantageously in a catalytic and solvent-free MW-assisted Pudovik reaction involving the addition of the >P(O)H species to aryl aldehydes in the presence of 5% of Na₂CO₃ (Scheme 6).30 In a variation of this reaction, dialkyl phosphites added to the carbonyl group of α-ketophosphonates to form α-hydroxybisphosphonates.31,32 The greenest protocol for the preparation of α-hydroxyphosphonates was elaborated by Keglevich, in which a benzaldehyde derivative and dialkyl phosphite were refluxed in the presence of triethylamine in a minimum quantity of acetone; the crystalline product precipitated on the addition of pentane.33 It was also found that α-hydroxyphosphonates could readily be transformed to the corresponding aminophosphonates by reaction with amines under MW conditions at 100 °C,34 and the reaction was promoted by the neighboring group effect of the adjacent P=O moiety.34,35

![Scheme 6. MW-assisted synthesis of α-hydroxyphosphonates and α-hydroxyphosphine oxides.](image)

The Hirao reaction is an important method to establish P–C bonds.36–38 It was found by Keglevich that under MW-assisted, solvent-free conditions, there is no need to use the expensive and environment-burdening Pd(Ph₃P)₄ catalyst in the reaction of dialkyl phosphites with bromobenzene derivatives, since Pd(OAc)₂ also catalyses the reaction. When the >P(O)H reagent is used in excess (Scheme 7), the arylphosphonates were obtained in ca. 85% yield.39,40 It was also found that NiCl₂ could replace Pd(Ph₃P)₄,41,42 and H-phosphinates or secondary phosphine oxides could be used as the P-reagents (Schemes 8 and 9).40,41,43
Scheme 7. Pd-catalyzed coupling reaction of dialkyl phosphites with aryl bromides under MW irradiation.


Interestingly, the substituted aryl halide being soluble in water, there was no need to use any catalyst under MW conditions (Scheme 10). It was found that during the reaction, Pd(OAc)$_2$ might be reduced to Pd(0) by the $>P(O)H$ reagent, and the Pd(0) formed might be complexed by two molecules of the trivalent tautomeric form of the $>P(O)H$ species (Scheme 11). These new findings proved that, in certain cases, there is no need to add expensive and environment burdening P-ligands and it may represent a breakthrough in catalysis.

Scheme 10. Catalyst-free coupling reaction of diarylphosphine oxides with halobenzoic acids.
Scheme 11. In situ formation of Pd(PY₂(OH))₂ catalyst from Pd(OAc)₂ and the excess of Y₂P(O)H reagent under the conditions of the Hirao reaction.

During the catalyst-free deoxygenation of phosphine oxides it was found that trichlorosilane and phenylsilane are the best reagents to reduce phosphine oxides to phosphines.⁴⁶ This reaction is important to regenerate the by-products of, among others, the Wittig reaction and the Mitsunobu reaction. To replace the corrosive Cl₃SiH and expensive PhSiH₃, a MW-assisted solvent-free procedure utilizing cheap (Me₂SiH)₂O (TMDS) and polymethyilsiloxane (–(OSiMeH)ₙ–, PMHS) was developed by Keglevich. In addition, they proved that there was no need to use catalysts suggested by other authors. The applicability of this approach is illustrated by the example of the reduction of 1-phenyl-3-methyl-3-phospholene 1-oxide by three silanes (Scheme 12)⁴⁷⁻⁵⁰. Under MW irradiation, the selected deoxygenation could effectively be performed by applying TMDS or PMHS in 4 or 2 equivalents, at 110 °C for 3 h and 2 h, respectively.

Scheme 12. Catalyst-free deoxygenation of 1-phenyl-3-methyl-3-phospholene oxide by user-friendly silanes under solvent-free MW-assisted conditions.

Transition metal complexes containing P-heterocyclic ligands, depending on the systematically modified P-heterocycles, enable the fine-tuning of the chemo-, regio-, and (in appropriate cases) enantioselectivities of homogeneous catalytic reactions.⁵¹ Keglevich also studied some phospha-Michael reactions which involve P-heterocyclic nucleophiles, such as dibenzo-1,2-oxaphosphorine oxide or 1,3,2-dioxaphosphorine oxide, with methyl vinyl ketone as the unsaturated acceptor molecule, in the presence of 1,8-diazabicycloundec-7-ene (DBU).⁵² However, the addition of dibenzo-1,2-oxaphosphorine oxide or other >P(O)H species including dialkyl phosphites and diphenylphosphine oxide to the electron-poor double-bond of a 1,2-dihydrophosphinine oxide
required a greater activation; hence the \( \text{P(O)H} \) species had to be transformed to the corresponding anion by reaction with trimethylaluminum prior to the addition (Scheme 13/step 1).\(^{52-54}\) In these reactions, MW irradiation alone was insufficient to promote the addition of the \( \text{P(O)H} \) reagent to the \( \text{CH}=\text{CH}–\text{P(O)}< \) moiety of the \( \text{P} \)-heterocyclic compound.

\[
\begin{align*}
\text{Cl}\text{Me} & \quad Z_2\text{P(O)H} \quad \text{step 1} \\
\text{Y} = \text{Ph}, \text{EtO} & \quad \text{Me}_3\text{Al} \quad \text{CHCl}_3 \\
\text{Z} = \text{Ph}, \text{EtO}, \text{MeO} & \quad \text{step 2} \quad 26^\circ \text{C} \quad \text{Cl}_2\text{SiH} (2 \text{ equiv.}) \\
\text{PhH} & \quad \text{pyridine} \\
\text{Y} = \text{Z} = \text{Ph} & \quad \text{step 3} \quad 26^\circ \text{C} \\
\text{PhCN}_2\text{PtCl}_2 & \quad \text{PhMe}
\end{align*}
\]

**Scheme 13.** Phospha-Michael additions to 1,2-dihydroporphinine oxides together with the utilization of one of the adducts.

However, MW irradiation was also beneficial in the addition of dialkyl phosphites or diphenylphosphine oxide to the double-bond of 1-phenyl-2-phospholene 1-oxide (Scheme 14/step 1).\(^{55}\) The resultant bis(phosphine oxides) served as precursors for bidentate \( \text{P} \)-ligands, and were converted to the corresponding \textit{cis} chelate Pt(II) complexes after double deoxygenation followed by complexation. This is exemplified by the transformation of 3-phosphinoyl-1,2,3,6-tetrahydrophosphinine oxide (Scheme 13/steps 2 and 3),\(^ {56}\) and by the conversion of a 3-phosphinoylphospholane oxide (Scheme 14/steps 2 and 3).\(^ {57}\)

\[
\begin{align*}
\text{PhMe} & \quad 1., 26^\circ \text{C} \\
\text{PhP(O)H} & \quad \text{NaOMe/MeOH} \\
\text{PhMe} & \quad 2., 26^\circ \text{C} \quad \text{Me}_3\text{Al/heptane} \\
\text{CH}_2\text{Cl}_2 & \quad 3., \text{MW} \\
180^\circ \text{C} & \quad \text{trans} \\
& \quad 0 \rightarrow 25^\circ \text{C} \\
\text{Cl}_2\text{SiH} & \quad \text{PhH} \\
\text{trans} & \quad 26^\circ \text{C} \\
\text{PtCl}_2(\text{PhCN})_2 & \quad \text{PhH}
\end{align*}
\]

**Scheme 14.** Phospha-Michael addition to 1-phenyl-2-phospholene oxide, and the conversion of the adduct to the corresponding \textit{cis} chelate Pt(II) complex.

**Teaching**

Throughout his career, Prof. Keglevich has been a dedicated and effective teacher. He has created, developed and taught several subjects related to organic chemical technology, environmentally friendly chemistry and technology, as well as organophosphorus chemistry for chemical engineer (BSc), environmental engineer (BSc) and pharmaceutical engineer (MSc) students. To date 19 PhD degrees have been awarded under his supervision, along with numerous undergraduate and postdoctoral research associates. Keglevich’s alumni have gone on to...
successful careers in academia throughout the world, industrial research and scientific management. Recognition of the quality of Keglevich’s teaching ability includes the *Erdei László Award* for outstanding scientific achievements, and the *Csűrös Zoltán Award* for technological educational work, the *Master Teacher Decoration* and the *Memorial Plaquette* for the scientific supervision of the students, and the *Teacher of the Year* for educational work in foreign language. He is decorated with the *Knight’ Cross of Hungarian Order of Merit* (2021) for his outstanding research, research organization, educational and leadership activities performed throughout decades.

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### Selected Publications

   [https://doi.org/10.1002/tcr.201800006](https://doi.org/10.1002/tcr.201800006)
   [https://doi.org/10.2174/1385272811317050009](https://doi.org/10.2174/1385272811317050009)
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