1-Aminoalkylphosphonium Derivatives: Smart Synthetic Equivalents of \( N \)-Acyliminium-Type Cations, and Maybe Something More: A Review †

Jakub Adamek \(^{1,2,*} \), Mirosława Grymel \(^{1,2,3} \), Anna Kuźnik \(^{1,2} \) and Agnieszka Październiok-Holewa \(^{1,2} \)

1 Department of Organic Chemistry, Bioorganic Chemistry and Biotechnology, Silesian University of Technology, B. Krzywoustego 4, 44-100 Gliwice, Poland; mirosława.grymel@polsl.pl (M.G.); anna.kuznik@polsl.pl (A.K.); agnieszka.pazdzierniok-holewa@polsl.pl (A.P.-H.)
2 Biotechnology Center, Silesian University of Technology, B. Krzywoustego 8, 44-100 Gliwice, Poland
3 Department of Chemical Organic Technology and Petrochemistry, Faculty of Chemistry, Silesian University of Technology, B. Krzywoustego 4, 44-100 Gliwice, Poland
* Correspondence: jakub.adamek@polsl.pl; Tel.: +48-032-237-1724; Fax: +48-032-237-2094
† With a special dedication to Roman Mazurkiewicz in honor of the achievements within his career along with thanks from his scientific pupils.

Abstract: \( N \)-acyliminium-type cations are examples of highly reactive intermediates that are willingly used in organic synthesis in intra- or intermolecular \( \alpha \)-amidoalkylation reactions. They are usually generated in situ from their corresponding precursors in the presence of acidic catalysts (Brønsted or Lewis acids). In this context, 1-aminoalkyltriarylphosphonium derivatives deserve particular attention. The positively charged phosphonium moiety located in the immediate vicinity of the \( N \)-acyl group significantly facilitates \( C_\alpha-P^+ \) bond breaking, even without the use of catalyst. Moreover, minor structural modifications of 1-aminoalkyltriarylphosphonium derivatives make it possible to modulate their reactivity in a simple way. Therefore, these types of compounds can be considered as smart synthetic equivalents of \( N \)-acyliminium-type cations. This review intends to familiarize a wide audience with the unique properties of 1-aminoalkyltriarylphosphonium derivatives and encourage their wider use in organic synthesis. Hence, the most important methods for the preparation of 1-aminoalkyltriarylphosphonium salts, as well as the area of their potential synthetic utilization, are demonstrated. In particular, the structure–reactivity correlations for the phosphonium salts are discussed. It was shown that 1-aminoalkyltriarylphosphonium salts are not only an interesting alternative to other \( \alpha \)-amidoalkylating agents but also can be used in such important transformations as the Wittig reaction or heterocyclizations. Finally, the prospects and limitations of their further applications in synthesis and medicinal chemistry were considered.

Keywords: phosphonium salts; \( N \)-acyliminium cations; \( \alpha \)-amidoalkylation; \( \alpha \)-amidoalkylating agents; ylides; Wittig reaction

1. Introduction

\( \alpha \)-Amidoalkylation reactions play an increasingly important role in organic synthesis as convenient and effective methods for the formation of C-C and C-heteroatom bonds, particularly of the intramolecular type, allowing the synthesis of carbo- or heterocyclic systems. In most cases, \( N \)-acylimine 2 or \( N \)-acyliminium cations 3 are the correct \( \alpha \)-amidoalkylating agents and they are generated from precursors with the relevant structure 1 (Scheme 1) [1–23].

Many examples of \( \alpha \)-amidoalkylating agent precursors and their applications in \( \alpha \)-amidoalkylations have been reported in the literature. A brief summary is given in Table 1. Compared to the precursors described therein, 1-aminoalkylphosphonium derivatives are relatively unknown compounds. However, they have unique structural features...
which promote the generation of N-acyliminium-type cations. One of the most important is the presence of a positively charged phosphonium moiety (which easily departs as triarylphosphine PAr₃ in the immediate vicinity of the acyl group.

![Scheme 1](image)

Scheme 1. The α-amidoalkylation reaction.

Moreover, the reactivity of 1-amidoalkylphosphonium derivatives can be modulated by simple structural modifications, e.g., by changing the amino protecting group or by the introduction of electron-withdrawing substituents to the phosphonium moiety (replacing Ph₃P by (3-C₆H₄Cl)₃P or (4-C₆H₄CF₃)₃P; see Figure 1). Depending on the structure of the phosphonium salt used, the α-amidoalkylations may require a basic or acidic catalyst. However, the introduction of the abovementioned activating structural modifications allows one, in many cases, to conduct the reactions under milder and even catalyst-free conditions. Furthermore, such modifications not only affect the reactivity but also the course of the reaction (for example, to reduce side reactions), or even make it possible to change the type of reaction taking place (the α-amidoalkylation reaction vs the Wittig reaction).

![Figure 1](image)

Figure 1. Areas of potential structural modifications within phosphonium precursors of α-amidoalkylating agents.

The main purpose of this review paper is to organize and disseminate current knowledge about 1-amidoalkylphosphonium derivatives. To help understand the presented issues, three classes of these P-compounds have been distinguished. Three separate chapters
are dedicated to them, where general properties, the most important methods for preparation as well as synthetic applications are described. Particularly, the correlation between the structure and the reactivity of phosphonium derivatives I-III is discussed. Scheme 2 provides a classification and a brief summary of the chemistry of 1-aminoalkylphosphonium derivatives.

1-Aminoalkylarylphosphonium derivatives as synthetic equivalents of N-acyliminium-type cations:

\[
\begin{align*}
\text{I} & : \text{1-(N-acylimino)alkylphosphonium salts} \\
\text{II} & : \text{1-imidoalkylphosphonium salts} \\
\text{III} & : \text{N-acyl-1-phosphono-\(\alpha\)-amino acid esters}
\end{align*}
\]

Examples of nucleophiles used (NuI):

- SH
- NH₂
- OH
- P(OMe)₃
- DBU
- TBD
- PhP(OMe)₂
- ArSO₂Na
- O₃⁻
- CO₂Et
- A

Scheme 2. Classification and reactivity of 1-aminoalkylphosphonium derivatives.

| Structure of Precursor | Summary of Characteristics | Examples of Use in \(\alpha\)-Amidoalkylation (Selected Research or Review Literature) \(^\text{a}\) |
|------------------------|----------------------------|----------------------------------------------------------------------------------|
| \[
\begin{align*}
\text{I} & : \text{1-(N-acylimino)alkylphosphonium salts} \\
\text{II} & : \text{1-imidoalkylphosphonium salts} \\
\text{III} & : \text{N-acyl-1-phosphono-\(\alpha\)-amino acid esters}
\end{align*}
\] | limited structural diversity, limited reactivity, parent compounds for the other \(\alpha\)-amidoalkylating agents, activation with acidic catalysts, synthesis from amides (or imides) and aldehydes (mostly in situ)—only N-hydroxymethylamides (or -imides) can be easily isolated | [3,4,6–12] |
| \[
\begin{align*}
\text{R}^{1} & : \text{N-acyl-1-phosphono-\(\alpha\)-amino acid esters}
\end{align*}
\] | limited reactivity, high structural diversity, activation with acidic catalysts, main synthesis methods based on electrochemical alkoxylation | [5–9,12–14] |
| \[
\begin{align*}
\text{R}^{1} & : \text{N-acyl-1-phosphono-\(\alpha\)-amino acid esters}
\end{align*}
\] | high reactivity, rather low yields in \(\alpha\)-amidoalkylation reactions (lots of by-products), difficulties in the preparation, purification and storage | [6–9,12] |
| \[
\begin{align*}
\text{R}^{1} & : \text{N-acyl-1-phosphono-\(\alpha\)-amino acid esters}
\end{align*}
\] | high reactivity (good leaving group), high structural diversity, activation with acidic catalysts, easy to use and storage, diverse methods of synthesis, broad scope of application | [8,9,12,16–19] |
Table 1. Cont.

| Structure of Precursor | Summary of Characteristics | Examples of Use in α-Aminoalkylation (Selected Research or Review Literature) |
|------------------------|----------------------------|--------------------------------------------------------------------------|
| ![Structure](image)    | high reactivity (good leaving group), high structural diversity, activation with acidic catalysts, easy to use and storage, diverse methods of synthesis, broad scope of application, currently the most popular and convenient | [8,9,12,20–23] |

*R* Selected examples aimed at showing the most recent interest in α-amidoalkylation reactions.

2. 1-Aminoalkyltriarylphosphonium Derivatives

2.1. 1-(N-acylamino)alkylphosphonium Salts

Compounds with general formula 4 (Figure 2) are often called 1-(N-acylamino)alkylphosphonium salts, because a lot of the described models are amide derivatives (e.g., *R*₁ = H, Me, Et, t-Bu, Ph, Bn, etc.; *R*₃ = H). It is not an exact name because this group also includes lactams (e.g., *R*₁ = CH₃, *R*₃ = (CH₂)₃), carbamates (*R*₁ = t-BuO, BnO; *R*₃ = H) or urea derivatives (e.g., *R*₁ = NMe₂, *R*₃ = H). In the α-position, there may be hydrogen (*R*₂ = H), alkyl (*R*₂ = Me, Et, t-Bu, etc.), aryl (*R*₂ = Ph, 2-thienyl, 1-naphthyl, etc.) or more complex substituents (e.g., CH₂CO₂-t-Bu, CH₂C₆H₄OBn, PO(OEt)₂ etc.). The positively charged triarylphosphonium group PAR₃ (Ar = Ph, 3-C₆H₄Cl, 4-C₆H₄CF₂) is also directly bonded to Cα.

![General structure of 1-(N-acylamino)alkylphosphonium salts 4.](image)

1-(N-acylamino)alkyltriphenylphosphonium salts 4 (Ar = Ph) are crystalline, stable at room temperature compounds that can be stored under laboratory conditions for a long time. They are well soluble in DCM and MeCN, but insoluble in diethyl ether. The most effective method of their purification is crystallization from DCM/Et₂O or MeCN/Et₂O systems. 1-(N-acylamino)alkyltriarylphosphonium salts 4 which are derivatives of triarylphosphines with electron-withdrawing substituents (Ar = 3-C₆H₄Cl or 4-C₆H₄CF₂) are less stable. They are usually synthesized just before the reaction and used without purification. The type of phosphonium group used has a huge impact on the reactivity of the whole molecule, which will be discussed later in this review.

2.1.1. Preparation

In the last century, most of the methods for the synthesis of 1-(N-acylamino)alkyltriarylphosphonium salts 4 concerned 1-(N-acylamino)methyltriphenylphosphonium chlorides (4a, *R*₂ = H, Scheme 3). Between 1972 and 1991, Drach, Brovarets and co-workers [24–27] showed that 1-(N-acylamino)methylphosphonium chlorides (4a, X = Cl) can be obtained, in a simple reactions, by alkylation of triphenylphosphine (but also tributylphosphine PBu₃ or hexaethylphosphorus triamide P(NEt₂)₃) with N-(chloromethyl)amides (5, Z = Cl) (Scheme 3, Method A). They also used N-(hydroxymethyl)amides (5, Z = OH) as alkylating agents, that were N-(chloromethyl)amides precursors (Scheme 3, Method A) [27]. In 1974, Devlin and Walker reported similar reactions, which were carried out at room temperature, using AcOEt as a solvent. They obtained 1-(N-benzyolamino)methyltriphenylphosphonium bromide or chloride (4a, X = Br or Cl) from N-(bromomethyl)benzamide or N-(chloromethyl)
benzamide, respectively, in 54% and 69% yield (Scheme 3, Method A) [28]. Triphenylphosphine was also alkylated with N-(methoxymethyl)urea derivative 6 (Scheme 3, Method B). Reactions were carried out in methanol by bubbling HCl gas through the substrate solution or by treating it with aqueous HBr or HI [29]. 1-(N-alkoxycarbonyl)methyltriphenylphosphonium chlorides or bromides (4a, R1 = OR, X = Cl or Br) were obtained by Kozhushko et al. in the reaction of triphenylphosphine with chloromethylisocyanate or bromomethylisocyanate and further hydrolysis of the isocyanate group (Scheme 3, Method C) [30,31]. In analogous reactions, the corresponding triphenylphosphonium iodides (4a, R1 = OR, X = I) were also obtained by adding methyl iodide in the first step of the synthesis [32]. The same authors also described reactions in which phosphonium salts 4a (R1 = OR, X = Cl) were obtained by alklylation of triphenylphosphine with N-(chloromethyl)carbamates 10, that were previously generated from alcohol and methyl isocyanide (Scheme 3, Method D) [33]. In turn, Zinner and Fehlhammer described the two-stage method for the synthesis of 1-(N-formylamino)methyltriphenylphosphonium chloride 4a (R1 = H, X = Cl). Initially, they conducted the alkyllylation of triphenylphosphine using trimethylsilyl isocyanide in the presence of hexachloroethane in THF. The acidic hydrolysis of indirectly formed isocyanomethyltriphenylphosphonium chloride 11 finally yielded the expected phosphonium salt 4a (Scheme 3, Method E) [34]. However, the authors did not report the yield of the hydrolysis step.

Scheme 3. Methods for the synthesis of 1-(N-acylamino)methyltriphenylphosphonium salts 4a.

Only a few of the described methods for synthesizing 1-(N-acylamino)methyltriphenyl phosphonium salts 4a were based on other approaches than the alkylation of triphenylphosphine by N-(halomethyl)amides, their precursors or related compounds. One of these methods involved the alkylylation of methyl carbamate with hydroxymethyltriphenylphosphonium chloride 12, which resulted in the production of 1-(N-methoxycarbonyl)aminomethyltriphenylphosphonium chloride 4a (R1 = OMe, X = Cl) in 73% yield (Scheme 3, Method F) [35]. Devlin and Walker demonstrated that the treatment of 2-bromo-2-nitrostyrene 14 with triphenylphosphine in methanol gave the phosphonium salt 15 in 47% yield. The vacuum pyrolysis of salt 15 at 150 °C, reduction with NaHBF4 in methanol or refluxing in chloroform with addition of bromine led to a mixture containing 1-(N-benzoylamino)methyltriphenylphosphonium bromide 10, that was previously generated from alcohol and methyl isocyanide (Scheme 3, Method D) [33]. In turn, Zinner and Fehlhammer described the two-stage method for the synthesis of 1-(N-formylamino)methyltriphenylphosphonium chloride 4a (R1 = H, X = Cl). Initially, they conducted the alkyllylation of triphenylphosphine using trimethylsilyl isocyanide in the presence of hexachloroethane in THF. The acidic hydrolysis of indirectly formed isocyanomethyltriphenylphosphonium chloride 11 finally yielded the expected phosphonium salt 4a (Scheme 3, Method E) [34]. However, the authors did not report the yield of the hydrolysis step.
Enylphosphonium bromide 4a (R1 = Ph, X = Br) as the main product (Scheme 3, Method G) [28,36].

There are few data available in the literature on the synthesis of 1-substituted phosphonium salts 4. In 1975, Drach et al. demonstrated that the reaction of triphenylphosphine with N-(1-benzoyl-1-chloromethyl)amides 16 led to triphenylphosphonium salts 17 with a benzoyl group at the 1-position. However, salts 17 turned out to be hygroscopic and unstable. Thus, the authors decided to transform them into more stable oxazolones 18 (Scheme 4) [37].

![Scheme 4](image)

Scheme 4. Synthesis of 1-(N-acylamino)benzoylmethyltriphenylphosphonium chlorides 17.

Next, Drach et al. described the route for the synthesis of various 1-(N-acylamino)-substituted vinylphosphonium salts 22, which was based on the condensation of triphenylphosphine with N-polychloroalkylamides 19 [38,39]. As reported by the authors, in the first step, the salts 20 were probably formed, which further split off hydrogen chloride, resulting in the formation of the corresponding vinylphosphonium salts 22, typically in yields above 90% (Scheme 5). 1-(N-acylamino)vinylphosphonium salts (AVPOSs) 22 are unique reagents for various types of heterocyclization, which was comprehensively discussed by Drach, Brovarets, and co-workers in 2002 [39].

![Scheme 5](image)

Scheme 5. Synthesis of 1-(N-acylamino)vinylphosphonium salts (AVPOSs) 22.

At about the same time, Mazurkiewicz et al. started more extensive research on the synthesis of structurally diverse 1-(N-acylamino)alkyltriarylphosphonium salts 4. Wherein, the common feature of these methods was the raw materials, which was N-protected α-amino acids. The use of α-amino acids or their derivatives as substrates was greatly advantageous, due to almost unlimited availability and structural diversity of such compounds.

The first approach was based on using 4-triphenylphosphoranyliden-5(4H)-oxazolones 24 or 4-alkyl-4-triphenylphosphinopheno-5(4H)-oxazolones 25, obtained from glycine (Scheme 6) [40]. Phosphoranyliden-5(4H)-oxazolones 24, were hydrolyzed at room temperature in the presence of HBF4 to N-acyl-α-triphenylphosphinophenylglycines 26 (R2 = H, Scheme 6/A). Similarly, phosphonium iodides 25 were exposed to water in the mixture of THF/DCM, but without any acidic catalyst. Under these conditions, compounds 25 were transformed, in a few days, into N-acyl-1-triphenylphosphino-α-amino acids 26 (R2 = Me, Scheme 6/B). In the next stage, 1-triphenylphosphonio-α-amino acids 26 were heated at 105–115 °C under reduced pressure (5 mmHg) or treated with disopropylethylamine in DCM at 20 °C, which resulted in their decarboxylation to corresponding 1-(N-acylamino)alkyltriphenylphosphonium salts 4, usually in good yields (Scheme 6/C). The authors also showed, that in the case of hydrolysis of 4-alkyl-4-triphenylphosphinopheno-5(4H)-oxazolones 25 with a bulky substituent in the 4-position, the reaction proceeded with simultaneous decarboxylation and gave the expected 1-(N-acylamino)alkyltriphenylphosphonium salts 4 in one reaction step (Scheme 6/D) [41,42].
Scheme 6. Synthesis of 1-(N-acylamino)alkylphosphonium salts 4 from oxazolones.

However, the two most important and general methods for the synthesis of 1-(N-acylamino)alkylphosphonium salts 4 were developed by Mazurkiewicz and Adamek in the last 10 years (Scheme 7) [43,44].

**Method A**

![Diagram of Method A](image)

**Method B**

![Diagram of Method B](image)

Scheme 7. Modern strategy in the synthesis of 1-(N-acylamino)alkylphosphonium salts 4; Method A—Synthesis based on the electrochemical alkoxylation; Method B—Non-electrochemical synthesis based on the one-pot, three components coupling.

The first, three-stage method begins with the appropriate protection of \( \alpha \)-amino acid functional groups (the NH\(_2\) group and other groups susceptible to electrochemical oxidation). Next, electrochemical decarboxylative \( \alpha \)-methoxylation (or more generally, alkoxylation) takes place. As the authors noted, the electrochemical oxidations could be carried out in methanol with the addition of sodium methoxide as a base or in the presence of a solid-supported base (SiO\(_2\)-Pip); wherein the latter process (based on a solid-supported base) proceeded in excellent yields and had a less complicated work-up. Recently, a simpler and even more efficient, standardized method for preparation of \( N,N \)O-acetals 30 using the commercially available ElectraSyn 2.0 setup (graphite electrodes, Et\(_3\)N as a base, room temp.) was described [45].

The last step is the substitution of the methoxy group in the reaction of \( N,N \)O-acetals 30 with various types of phosphonium salts (Ar\(_3\)PHX, Scheme 7; Method A). The proposed method allows high yields (up to 99\%) to be obtained not only for the simplest 1-(N-acylamino)alkylphosphonium salts 4 (e.g., \( R^2 = H \)), but also for much more complex structure, including derivatives of phosphpine with various substituents (Ar = Ph, 3-C\(_6\)H\(_4\)Cl, 4-C\(_6\)H\(_4\)CF\(_3\)) [43,46]. Moreover, the raw material base can be expanded, since...
N-methoxyalkyl derivatives can be obtained by electrochemical oxidation of amides, carba-
mates or lactams. However, this is a less efficient process and an aqueous work-up of the
reaction mixture is necessary [47].

In 2021, a procedure for the preparation of N-protected aminoalkylphosphonium salts
(including 1-(N-acylamino)alkylphosphonium ones) in one reaction step from aldehy-
des and either amides, carboxamides, lactams, or urea in the presence of phosphonium
salts 33-Ar3P-HX (Scheme 7; Method B) was described [44]. Using a one-pot method-
ology, the simple work-up of the reaction mixture (no chromatography) makes 1-(N-
acylamino)alkylphosphonium salts obtainable in high yields under relatively mild condi-
tions (even at room temperature, but usually at 50 °C for 1 h). So far, it is the only general
method of obtaining N-protected aminoalkylphosphonium salts without the use of electro-
chemical techniques [44]. Mechanistic studies showed that in the first step of the transfor-
mation, aldehydes and phosphonium salts (Ar3P·HX) form 1-hydroxyalkylphosphonium salts
34, which then react with amide-type substrates 31 to give the desired 1-(N-acylamino)alkylphos-
honium salts 4 in good to excellent yields [44].

Next, it was shown that by conducting the reaction step-by-step and changing the
order of the reacting compounds, 1-(N-acylamino)alkylphosphonium salts 4 could also be
obtained. However, the procedure is effective only for formaldehyde (or paraformalde-
hyde). Hydroxymethylamides 35, already mentioned in the introduction (see also Table 1),
are generated during such a transformation (Scheme 8). This method works well for the
synthesis of N-protected aminomethyltriarylphosphonium salts 4a, but requires a catalyst
(NaBr) and elevated temperatures (70–135 °C) [48].

\[ R'N\text{H} + \text{CH}_2\text{O} \rightarrow R'N\text{OH} + Ar_3P\text{HX} \rightarrow R'\text{N}P\text{Ar}_3X \]

**Scheme 8.** Step-by-step procedure for the synthesis of N-protected aminomethylphosphonium
salts 4a.

The presented methods (Schemes 7 and 8) are based on a wide and diverse base of raw
materials (α-amino acids, amide-type compounds, aldehydes), and provide easy access to
structurally diverse 1-(N-acylamino)alkylphosphonium salts 4 also in the synthesis on a
larger gram-scale [44,48].

2.1.2. Synthetic Utilization

Synthetic applications of 1-(N-acylamino)alkylphosphonium salts 4 are summarized
in Figure 3. The high reactivity of such compounds is mainly related to the possibility of
easy cleaving of the Cα-P+ bond (Scheme 9).

The strength of the Cα-P+ bond can be further reduced by introducing electron-
withdrawing substituents to the phosphonium moiety (Scheme 10, Ar = 3-C6H4Cl and
4-C6H4CF3). The equilibrium in such systems was examined and described in 2018 [46]. As
can be seen, it is shifted toward more stable and less reactive 1-(N-acylamino)alkylphospho-
ium salts (reactivity: PS-CF3 > PS-CI > PS-H; stability: PS-CF3 < PS-CI < PS-H).

The ease of formation of iminium-type cations 3 from phosphonium salts 4 was es-
sential in the α-amidoalkylation reactions of various types of nucleophiles (C-nucleophiles
and heteronucleophiles). In many cases, the generation of such reactive intermediates
can proceed without the use of any catalysts, which is an amazing advantage compared to
other α-amidoalkylating agents described in the literature (e.g., N-(1-methoxyalkyl)amides,
α-amido sulfones, or N-(benzotriazolylalkyl)amides) [12,20].
One of the most widely described α-amidoalkylation reactions involving 1-(N-acylamino)alkylphosphonium salts is the reaction with P-nucleophiles: phosphites, phosphonites, or phosphinites. The products of these transformations are called phosphorus analogs of α-amino acids (more precisely: 1-aminoalkenephosphonic acid derivatives, 1-aminoalkenephosphinic acid derivatives, or 1-aminoalkylphosphate oxide derivatives), and they are extremely interesting in terms of their biological activity [49].

Initially, the Michaelis–Arbuzov-type reaction with a double catalytic system was used for the synthesis of such compounds. A base (e.g., the Hüning’s base-(i-Pr)2EtN) facilitates the cleavage of the C-α-P⁺ bond and the formation of corresponding N-acylimine. In turn, the iodide anion (introduced as methyltriphenylphosphonium iodide) enables dealkylation of the intermediate alkoxyphosphonium salt 36 (Scheme 11) [50–52]. Further studies showed that the reaction could be carried out also under a catalytic-free conditions [46,52].
It was also possible, for the first time, to isolate and characterize one of the intermediates 36 (R¹ = t-Bu; R² = Me; R³, R⁴ = OR = OEt, Scheme 11), thus proving the reaction mechanism [46].

Unfortunately, the major disadvantage of these reactions is the complete racemization of the products. However, two solutions were proposed to overcome this drawback. The first was enzymatic kinetic resolution of products using Penicillin G acylase from Escherichia coli (Scheme 12, Method A) [53,54]. The second was changing the synthetic approach and to conduct organocatalytic α-amidoalkylation of P-nucleophiles (e.g., dimethyl phosphite; Michaelis–Becker-type reaction) by 1-(N-acylamino)alkyltriphenylphosphonium salts in PTC systems using Cinchona alkaloid derivatives 38 and 39 as catalysts (Scheme 12, Method B) [55].

![Scheme 11. Michaelis–Arbuzov-type reaction of 1-(N-acylamino)alkylphosphonium salts 4 with P-nucleophiles.](image)

![Scheme 12. Methods for the obtaining of enantiomerically enriched phosphorus analogs of α-amino acids 37 via 1-(N-acylamino)alkyltriphenylphosphonium salts 4 based on enzymatic kinetic resolution (Method A) or organocatalytic α-amidoalkylation of P-nucleophiles in PTC systems (Method B).](image)

Further research on phosphorus analogs of α-amino acids 37 revealed the possibility of transforming them into bisphosphoric acid esters 43, which also exhibit important biological activity (Scheme 13) [56,57].
Molecules 2022, 27, 1562

Scheme 13. Synthesis and applications of 1-(N-acylamino)-1-triphenylphosphoniumalkylphosphonates 42. Reagents and conditions: (A) R1R2R3POR (e.g., P(OEt)3, MeP(OEt)2, Ph2P(OEt), etc.), (i-Pr)2EtN, Ph3P+MeI−, 20–60 °C, 0.3–6 h; (B) KCN, 18-crown-6, 20 °C, 24 h; (C) (i-Pr)2EtN, 20 °C, 5 h; (D) MeC(O)CF3, K2CO3, 18-crown-6, 50 °C, 4 h.

Electrochemical alkoxylation of compounds 37 followed by substitution of the alkoxy group leads to 1-(N-acylamino)-1-triphenylphosphoniumalkylphosphonates 42. They can be also synthesized in a multi-stage procedure from imidate hydrochlorides 40 (Scheme 13).

As shown, the high reactivity of the phosphonium salts 42 can be used not only in the α-amidoalkylation reactions of phosphorus or carbon nucleophiles (Scheme 13, route A and B) but also in the elimination (Scheme 13; route C) or Wittig reaction (Scheme 13, route D) [57].

In the years between 2012 and 2021, Mazurkiewicz (triphenylphosphonium derivatives) and then Adamek (phosphonium salts with weakened Cα-P+ bond) explored the possibility of α-amidoalkylation of various other heteronucleophiles (Scheme 14) [46,51,58]. They demonstrated that, under appropriate conditions, N-protected 1-aminoalkyltrialkylphosphonium salts 4 react with a wide variety of nucleophiles including mercaptans (PhCH2SH), phenol (PhOH), amines (PhCH2NH2), phthalimide, benzotriazole (BtH) or its salts (BtNa), and sodium aryl sulfonates (Ar2SO2Na) [46,51].

Initially, reactions were carried out at an elevated temperature (60 °C) in the presence of Hüning’s base (for 1-(N-acylamino)alkyltriphenylphosphonium salts 4, Ar = Ph, Scheme 14) [51]. The use of 1-(N-acylamino)alkyltrialkylphosphonium salts 4 with a weakened Cα-P+ bond strength (Ar = 3-C6H4Cl, 4-C6H4CF3, Scheme 14) made it possible to conduct these reactions at room temperature without the use of catalysts [46].

The extraordinary α-amidoalkylation properties of 1-(N-acylamino)alkylphosphonium salts 4 also allow the α-amidoalkylation of “non-nucleophilic” bases, such as DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), DBN (1,5-diazabicyclo[4.3.0]non-5-ene) or TBD (1,5,7-triazabicyclo[4.4.0]dec-5-ene; Scheme 14). The corresponding 1-(N-acylamino)alkylamidinium or guanidinium salts 52 are products in these reactions. They can be isolated but show limited stability; for example, salts 52 with a hydrogen at the β-position underwent transformation to enamides 53. As shown, enamides 53 can also be obtained directly from phosphonium salts 4 with an appropriate structure (hydrogen at the β-position) by an elimination reaction (Scheme 14) [58].

Interestingly, the 1-(N-acylamino)alkylphosphonium salts 4 can be converted to other α-amidoalkylating agents such as N-[1-(benzotriazol-1-yl)alkyl]amides 50 or α-amido sulfoxides 51. So far, they have been synthesized mainly in a three-component condensation of aldehyde with an amide-type substrate (amides, lactams, urea derivatives, etc.) in the presence of benzotriazole (BtH) or aryl sulfonates, respectively [12,20].
The proposed methodology extended the base of raw materials with N,O-acetals 30 obtained from α-amino acids or amide-type substrates in electrochemical oxidation (alkoxylation). As shown, 1-(N-acylamino)alkylphosphonium salts 4 do not have to be isolated in this type of transformation (Scheme 15A, see also Section 2.1.1, Scheme 7) [47,59].

Scheme 14. Reactivity of 1-(N-acylamino)alkyltriphenylphosphonium salts 4 with nucleophiles.

The extraordinary α-amidoalkylating properties of 1-acylamino)alkylphosphonium salts 4 allow the α-amidoalkylation of various other heteronucleophiles (Scheme 14). The corresponding 1-acylamino)alkylphosphonium salts 4 can react with a wide variety of nucleophiles including mercurials and organotin reagents. Interestingly, the 1-acylamino)alkylphosphonium derivatives 4 can be converted to other α-amidoalkylating agents such as N-[1-(benzotriazol-1-yl)alkyl]amides 50 or α-amido sulfones 51. So far, they have been synthesized mainly in a three-step procedure, but they can be used not only in C-nucleophiles leading to the formation of β-amino carbonyl systems 58 but also in N,O-desamido sulfones 51. The extraordinary α-amidoalkylating properties of 1-acylamino)alkylphosphonium salts 4 allow the α-amidoalkylation of various other heteronucleophiles (Scheme 14).

Such transformations gained attention and were used for the preparation of substrates for α-amido sulfone-based intermolecular Mannich addition in the stereodivergent synthesis of lankacyclinol (Lankacidin antibiotics; Scheme 15/B) [60–62].

High reactivity of 1-(N-acylamino)alkylphosphonium salts 4 is also revealed in reactions with C-nucleophiles leading to the formation of β-aminocarbonyl systems 58 and 60. In the case of 1,3-dicarbonyl compounds 57 (dimethyl or diethyl malonate, ethyl acetocetate, and ethyl 2-methylacetocetate), it was necessary to use bases (DBU or LDA-lithium diisopropylamide) as catalysts to produce enolate anions [46,51]. However, the use of...
1-(N-acylamino)alkyltriarylphosphonium salts 4 with a weakened Cα-P+ bond made it possible to conduct the reaction under slightly milder conditions (Scheme 16/A). This was similar in the reaction with 1-morpholinocyclohexene 59; replacing the triphenylphosphonium residue (Ar = Ph) with a triarylphosphonium group (Ar = 3-C6H4Cl or 4-C6H4CF3) facilitates the transformation (Scheme 16B) [46,51].

The spontaneous generation of reactive N-acyliminium cations from 1-(N-acylamino)alkyltriarylphosphonium salts 4 (under catalyst-free conditions) was also used in reactions with silyl enolates 66 or 67, to provide N-protected β-amino esters 68, as well as N-protected β-amino ketones 69 in good to excellent yields (Scheme 18/A). As Październiok-Holewa et al. demonstrated, the process can be carried out in THF at 50 °C or 60 °C using conventional heating or microwave irradiation. The proposed mechanism of the transformation included, in the first stage, the formation of the reactive N-acyliminium cation 3, which further reacts with the silyl enolate to give silyloxy-substituted carbenium ion 70, which fast undergoes a desilylation reaction to give β-amino carbonyl compounds 68 or 69 (Scheme 18/B) [64].
Scheme 17. Reaction of 1-(N-acylamino)alkyltriarylphosphonium salts 4 with aromatic compounds: (A) synthetic routes, (B) plausible mechanism. 

1-(N-acylamino)alkyltriarylphosphonium salts 4 are bifunctional compounds and their reactivity is not related only to the phosphonium moiety. Already in the 1980s, the transformation of N-acylaminoethyltriphenylphosphonium salts 4a into imidoyl chlorides 71 was described [26]. They turned out to be valuable reagents in cyclization reactions, in which heterocyclic systems such as oxazole, imidazole, tetrazole, or quinazolinone derivatives 72–76 can be obtained (Scheme 19/A–D) [26,65,66]. The presence of a triphenylphosphonium group enables further modification of the synthesized heterocycles, which was demonstrated in the example of the quinazolinones 75 (a structural motif of N-acylaminoalkylphosphonium salt can also be indicated here). These compounds undergo a reduction under mild conditions (Scheme 19/E). They can also be used as ylide precursors in the Wittig reaction with 4-nitrobenzaldehyde (Scheme 19/F) [26,65,66].
Scheme 18. Reaction of 1-(N-acylamino)alkyltriarylphosphonium salts 4 with silyl enolates—(A) conditions and yields, (B) plausible mechanism.

Scheme 19. Synthesis of imidoyl chlorides 71 and their further transformations.
2.2. 1-Imidoalkyltriarylphosphonium Salts

Structures of the 1-imidoalkylphosphonium salts 79 described in the literature are based on a phthalimide (A = 1,2-C₆H₄) or succinimide (A = (CH₂)₃) ring (Figure 4). Two electron-withdrawing carbonyl groups connected to the nitrogen atom reduce the electron density at Cₓ, thus increasing its electrophilicity. In the α-position there may be hydroxy (R² = H), alkyl (R² = Me, Et, i-Bu) or aryl (R² = Ph) substituent. Cₓ is also directly bonded to the triarylphosphonium group PAr₃ (Ar = Ph, 4-C₆H₄Cl, 3-C₆H₄Cl, 4-C₆H₄CF₃), which is positively charged and can act as a nucleofugal group.

![Structure of 1-imidoalkylphosphonium salts 79](image)

R² = H, Me, Et, i-Bu, Ph; Ar = Ph, 3-C₆H₄Cl, 4-C₆H₄Cl, 4-C₆H₄CF₃, 4-C₆H₄OMe; X = BF₄, Br, Cl, I.

Figure 4. General structure of 1-imidoalkylphosphonium salts 79.

In most cases, the 1-imidoalkylphosphonium salts are stable solids that can be stored under laboratory conditions for a long time. Interestingly, some of them also show biological activities such as cytotoxic or antimicrobial properties [67–69].

2.2.1. Preparation

In general, there is not much information in the literature on the methods for synthesis of 1-imidoalkylphosphonium salts 79, and most of them concern the simplest ones—imidomethylphosphonium salts (R² = H). To the best of our knowledge, the first attempt to prepare imidomethylphosphonium salts was reported in 1961 by Hellmann and Schumacher [70]. It consisted in the reaction of phthalimidomethyltrimethylammonium iodide to prepare imidomethylphosphonium salts reported in 1961 by Hellmann and Schumacher [70].

The first one consisted of three stages: (A) the protection of amino group (from amino acids) by smelting phthalic, succinic or 1,8-naphthalic anhydride with the corresponding amino acid at 140–170 °C; (B) electrochemical decarboxylative α-methoxylation of the intermediate dehydrated product P·HX (Scheme 7).

Next, 1-imidoalkylphosphonium salts 79 (X = Br) is also formed as a by-product in the reaction with Pd(PPh₃)₄ (Scheme 19).

| Entry | Substrate 80 X | Solvent | Conditions | Yield of 79, % | Refs. |
|-------|----------------|---------|------------|---------------|------|
| 1     | (Me₃N)⁺ I⁻    | methanol| reflux, 4 h| 58            | [70] |
| 2     | Cl             | benzene | reflux, 2 h|               | [70] |
| 3     | Br             | acetone | reflux, 3 min| 80            | [24] |
| 4     | Br             | benzene | reflux, 22 h| 68            | [67,71] |
| 5     | Br             | toluene | reflux, 24 h|               | [72] |

* Compound 79 (X = Br) is also formed as a by-product in the reaction with Pd(PPh₃)₄ (rt, benzene).

After several decades, general methods for the synthesis of imidoalkylphosphonium salts appeared. The first one consisted of three stages: (A) the protection of amino group (from amino acids) by smelting phthalic, succinic or 1,8-naphthalic anhydride with the corresponding amino acid at 140–170 °C; (B) electrochemical decarboxylative α-methoxylation of the intermediate dehydrated product P·HX (Scheme 7).
of 1-imidoalkanecarboxylic acids 81; (C) the displacement of the methoxy group by the triarylphosphine by smelting of the N-(1-methoxyalkyl)imides 82 with triarylphosphonium tetrafluoroborates in the presence of NaBr as catalyst (Scheme 20) [73].

Scheme 20. Three-step synthesis of 1-imidoalkylphosphonium salts 79 from amino acids.

Next, 1-imidoalkylphosphonium salts 79 were prepared in the three-component coupling of aldehydes and imides in the presence of triarylphosphonium salts Ar3P·HX (Scheme 21). An interesting fact is the formation of an intermediate hydroxyalkylphosphonium salt 34 in situ from aldehyde and triarylphosphonium salt (Ar3P·HX) during the reaction (see also Section 2.1.1, Scheme 7) [44].

Scheme 21. Three-component coupling of aldehydes, imides, and triarylphosphonium salts in the synthesis of 1-imidoalkylphosphonium salts 79.

As it was demonstrated, 1-imidomethylphosphonium salts 79 can also be obtained in the step-by-step procedure. This time, at first, formaldehyde (reactions with other aldehydes are ineffective) and imides form hydroxymethylimides 84 which, after isolation and purification, are reacted with triarylphosphonium salts 33 (Ar3P·HX) in the last stage (Scheme 22). The use of NaBr as a catalyst had a positive effect on the reaction (both on reaction time and yield) when Ar3P·HBF4 was used (for Ar3P·HBr no catalyst is needed) [48].

Scheme 22. Step-by-step method for the synthesis of 1-imidoalkylphosphonium salts 79 from imides.

The last two methods allow for the fast synthesis of 1-imidoalkylphosphonium salts 79 (especially 1-imidomethylphosphonium salts) from readily available substrates, even on a larger scale (5–20 g). Besides, the advantage of both strategies is that they rely on non-electrochemical procedures, thus they are an interesting complement to previously described method.
2.2.2. Synthetic Utilization

The most important synthetic applications of 1-imidoalkylphosphonium salts 79 are summarized in Figure 5. Due to certain structural features (dicarbonyl protecting group and thus no NH proton), 1-imidoalkylphosphonium salts 79 can be considered as potential precursors of ylides in the Wittig reaction. These properties of phthalimidomethyltriphenylphosphonium bromide 79 were used by Tan and co-workers in the first stage of multi-step synthesis of compounds 85 and 86, which are known to modulate the activity of the TAAR1 receptor (the trace amine-associated receptor 1, see Table 3) [72].

![Figure 5. Applications of 1-imidoalkylphosphonium salts 79.](image)

Table 3. Application of phthalimidomethyltriphenylphosphonium bromide as ylide precursors.

| Phosphonium Salt 79 | Carbonyl Components | Conditions | Intermediate Compound | Targeted Compound |
|---------------------|---------------------|------------|-----------------------|-------------------|
| ![Phosphonium Salt](image) | ![Carbonyl Components](image) | KHMDS, THF, 0 °C→RT, 86% | ![Intermediate Compound 85](image) | ![Targeted Compound 86](image) |
| ![Phosphonium Salt](image) | ![Carbonyl Components](image) | KHMDS, THF, 0 °C→RT, 77% | ![Intermediate Compound 85](image) | ![Targeted Compound 86](image) |

Recently, the possibilities of using 1-imidoalkylphosphonium salts in imidoalkylation reactions with carbon- or heteronucleophiles have been explored.

In 2017, the Friedel–Crafts-type reaction of 1-imidoalkylphosphonium salts with various aromatic compounds was described. N-(1-arylalkyl)imides 87 were the main products of these transformations (Scheme 23) [73].

The presence of the dicarbonyl protection increases the electrophilicity of the Cα. In addition, the use of phosphonium salts which were derivatives of triarylphosphines with electron-withdrawing substituents make it easier to cleave the Cα-P+ bond (first step of the reaction, Scheme 23). Such structural modifications facilitated reactions with aromatic systems, also with weakly activated anisole and toluene (see Scheme 23 and compare the relation between the required reaction temperature and the type of phosphonium moiety).
It is worth noting that, contrary to the reaction of the 1-(N-acylamino)alkylphosphonium salts 4 with arenes described in this review (Section 2.1.2), no consecutive reaction leading to the so-called non-classical α-amidoalkylation products (1-arylalkylphosphonium salts 63, see also Scheme 17) was observed. The only exception was the reaction of phosphonium salts 79-CF₃ with 1,3,5-trimethoxybenzene (Scheme 24).

![Scheme 23](image)

**Selected, representative examples:**

- **Scheme 23.** Friedel–Crafts-type reaction of 1-imidoalkylphosphonium salts 79 with various aromatic compounds–conditions and yields (MW–microwave assisted reaction).

- **Scheme 24.** Unusual course of the reaction of 1-imidoalkylphosphonium salt 79-CF₃ with a highly activated aromatic system–1,3,5-trimethoxybenzene.

1-Imidoalkylphosphonium salts have also been used in the synthesis of imidoalkanephosphonates, imidoalkanephosphinates, and imidoalkylphosphine oxides. Generally, these compounds exhibit interesting biological properties, including antibacterial and antifungal activities or can be used in the synthesis of many bioactive compounds such as phosphapeptides (acting as enzyme inhibitors), oligonucleotides, cytotoxic agents (for example Cryptophycin 52) or 2,4,5-imidazolidinetriones (herbicides and plant growth regulators) [74,75].

The strategy for preparation of P-compounds 90 from phosphonium salts 79 was based on the Michaelis–Arbuzov-type reaction with the appropriate phosphorus nucleophiles (Scheme 25) [76].
They were prepared for the first time in 1983 by Kober and Steglich from ethyl phosphorus nucleophiles.

In the literature are based on a glycinate skeleton (R = Me, OMe, CH₂Bt) or carbamate (R¹ = MeO, t-BuO, PhCH₂O) moiety. The most common counterion to the positively charged phosphonium group is the tetrafluoroborate, bromide or iodide anion (X = BF₄ − , Br, I).

Figure 6. General structure of N-acyl-1-phosphonio-α-amino acid esters 91.

2.3. N-acyl-1-phosphonio-α-amino Acid Esters

The general structural formula of N-acyl-1-phosphonio-α-amino acid esters 91 is shown in Figure 6. In most cases, structures of this kind of phosphonium salts described in the literature are based on a glycinate skeleton (R² = H), although derivatives of other proteinogenic and non-proteinogenic α-amino acids, containing in the α position alkyl (R² = Me, CH₂OMe, CH₂CN, CH₂CH=CH₂) or alkyl-aryl substituent (R² = CH₂Ph, CH₂Bt) are also known. Cα is most often directly bonded to the positively charged triphenylphosphonium group (R = Ph), and less often tributylphosphonium group (R = Bu). In the structure of the phosphonium salts in question, the carboxyl group is protected as an amide (R¹ = Me, t-Bu, Ph) or carbamate (R¹ = MeO, t-BuO, PhCH₂O) moiety. The most common counterion to the positively charged phosphonium group is the tetrafluoroborate, bromide or iodide anion (X = BF₄ − , Br, I).

R¹ = Me, t-Bu, Ph, MeO, t-BuO, BrO;
R² = H, Me, CH₂OMe, CH₂CN, CH₂CH=CH₂, Bn, CH₂Bt;
R³ = Me, Et;
R = Ph, Bu; X = BF₄ − , Br, I.

Figure 6. General structure of N-acyl-1-phosphonio-α-amino acid esters 91.

2.3.1. Preparation

For a wide group of compounds belonging to N-acyl-1-triphenylphosphonio-α-amino acid esters 91, N-acyl-1-triphenylphosphonioglycimates (R² = H) are the best known ones. They were prepared for the first time in 1983 by Kober and Steglich from ethyl N-acyl-1-bromoglycinates 93 by their reaction with triphenylphosphine. The starting 1-bromoglycine derivatives 93 were previously obtained in situ in the reaction of photochemical bromination of N-acylglycine ethyl esters 92 with bromine or N-bromosuccinimide carried out in tetrachloromethane (Scheme 26) [77].
Molecules 2022, 27, 1562

Scheme 26. Method for the synthesis of N-acyl-1-triphenylphosphonioglycinate bromides 91 from glycine derivatives 92 via 1-bromoglycinates 93.

In 1996, Mazurkiewicz and Pierwocha developed a simple route for the transformation of N-acylated glycine 94 into the 4-phosphoranylidene-5(4H)-oxazolones 24 [40]. The corresponding 5(4H)-oxazolone, obtained here as an intermediate in the reaction of the starting compound with DCC (N,N'-dicyclohexylcarbodiimide), is phosphorylated in situ with dibromotriphenylphosphorane (R3PBr2) in the presence of triethylamine. The resulting phosphoranylidene-5(4H)-oxazolones 24 can be further effectively converted into N-acyl-1-triphenylphosphonioglycinates (R2 = H), as well as esters of other N-acyl-1-triphenylphosphonio-α-amino acids 91 (Scheme 27).

Scheme 27. Synthesis of N-acyl-1-triphenylphosphonio-α-amino acid esters 91 via phosphoranylidene-5(4H)-oxazolones 24.

However, the most convenient procedure for the synthesis of N-acyl-1-triphenylphosphonoglycinate tetrafluoroborates (91, X = BF4) is to treat a solution of phosphoranylidene-5(4H)-oxazolones 24 in methanol with an ethereal solution of tetrafluoroboric acid [78]. An alternative method for the synthesis of N-acyl-1-triphenylphosphonioglycinates with an iodide counterion (91, X = I) is a two-stage procedure that consists in the reaction of phosphoranylideneoxazolone 24 with acetyl iodide performed in acetonitrile, followed by the subsequent reaction of the acylation product with methanol [78,79]. Similarly, the synthesis of N-acyl-1-triphenylphosphonio-α-amino acids 91 with an alkyl substituent at the α-position (R2 ≠ H) by alkylation of 4-phosphoranylidene-5(4H)-oxazolones 24 with alkyl halides [80], and the next opening of the oxazolone ring under the treatment with methanol or methanol in the presence of an acidic catalyst was also described (Scheme 27) [81].

In 2004, three methods for the tranformation of N-alkoxycarbonyl-1-hydroxyglycinates 96 into especially interesting N-alkoxycarbonyl-1-triphenylphosphonioglycinates 91 (R1 = MeO, t-BuO, BnO) were developed by Mazurkiewicz et al. The proposed synthetic routes included the following transformations: phosphorylation of N-alkoxycarbonyl-1-hydroxyglycinates 96 with Ph3P·Br2 in the presence of Et3N (Procedure A), the reaction of N-alkoxycarbonyl-1-hydroxyglycinates 96 with DCC and Ph3P-HBF4 in the presence of an acidic catalyst.
of Ph₃P as a catalyst (Procedure B), and a new kind of the Mitsunobu reaction using Ph₃P-HBF₄ as a nucleophile conjugated acid (Procedure C, Scheme 28) [82].

Scheme 28. Methodology for the synthesis of N-acyl-1-triphenylphosphoranylglycinates 91 via α-hydroxyglycinates. Reagents and conditions: Procedure A: Ph₃P·Br₂, Et₃N, Ph₃P, DCM, rt; Procedure B: DCC, Ph₃P-HBF₄, Ph₃P, DCM, rt; Procedure C: DEAD (diethyl azodicarboxylate), Ph₃P-HBF₄, Ph₃P, THF, rt.

2.3.2. Synthetic Utilization

N-Acyl-1-triphenylphosphonio-α-amino acid esters 91 are, in most cases, crystalline compounds, stable at room temperature, moderately sensitive to moisture, and well soluble in DCM and MeCN, but insoluble in diethyl ether. They can be easily purified by crystallization consisting of dissolution in DCM or MeCN at room temperature and precipitation with diethyl ether [78–82]. It is worth emphasizing that they are easily accessible from N-acylglycine even at kilogram scale (Schemes 26 and 27). All of these features of N-acyl-1-triphenylphosphonio-α-amino acid esters, as well as their diverse reactivity make these compounds interesting reagents in organic syntheses (Figure 7).

The directions of N-acyl-1-triphenylphosphonio-α-amino acid esters reactivity, and thus, the possibility of their further applications, were recognized during comprehensive research on their behavior in the presence of organic bases [83]. Reactions of N-acyl-1-triphenylphosphonio-α-amino acid methyl esters 91 with DBU and triethylamine were investigated then as the crucial step of the base catalysed displacement of the triphenylphosphonium group by various nucleophiles. Initially, this was observed by Kober, and Steglich, and later confirmed by Mazurkiewicz and Grymel, that N-acyl-1-triphenylphosphonio glycines 91, upon treatment with bases, were converted into a mixture of the corresponding N-acyliminoacetate 97 and N-acyl-1-triphenylphosphoranylidenglycinate 98. Both the iminoacetate 97 and the ylide 98 turned out to be highly reactive, instable compounds that remained in an equilibrium and reacted slowly with each other providing the fumaric acid derivative 99. In the case of N-acyl-1-triphenylphosphonio-α-amino acid esters 91 with the quaternary α-carbon, the α-substituted homologues of N-acyliminoacetate 97 can undergo further tautomerization into the corresponding enamine 100 (Scheme 29) [83].
The displacement of triphenylphosphonium ylides. Initially, this was observed by Kot.

**Scheme 29.** Various pathways for synthetic applications of N-acyl-1-triphenylphosphonio-α-amino acid esters 91 in the presence of a base (Et3N or DBU).

The application of N-acyl-1-triphenylphosphonogiycinates 91 as the precursors of phosphonium ylides 98 in the Wittig reaction with aliphatic or aromatic aldehydes in the presence of Et3N allowed the development of a simple and efficient procedure for the synthesis of α,β-dehydro-α-amino acid derivatives 101 (Scheme 29) [84].

On the other hand, methods for the displacement of the triphenylphosphonium group with a variety oxygen, sulfur and carbon nucleophilic agents, consisting in the addition of a nucleophile to the activated C=N double bond of the N-acylimino intermediate 97, opened up new routes for the synthesis of biologically important natural and unnatural non-proteinogenic α-amino acids by double functionalization of the glycine α-position with electrophilic and nucleophilic reagent (Scheme 30) [78,79,81].

**Scheme 30.** Synthetic applications of N-acyl-1-triphenylphosphonio-α-amino acid esters 91 in reactions with heteronucleophiles.

N-acyl-1-triphenylphosphonio-α-amino acid esters 91 react easily with a wide variety of oxygen, sulphur and nitrogen nucleophiles including phenol (PhOH), mercaptons (t-BuSH, PhSH, PhCH2SH), imidazole, 4-nitroimidazole, pyrazole, benzotriazole,
phthalimide, cyclohexylamine (Scheme 30) [78,81] and two kinds of carbon nucleophiles: enolates 103 of activated carbonyl compounds or enamines 105 (Scheme 31) [79]. Reactions were conducted in acetonitrile or methanol at room temperature in the presence of DBU or triethylamine, and the corresponding α-amino acid derivatives 102, 104, and 106 (including α,α-difunctionalized derivatives) were usually obtained in good to excellent yields [78,79,81].

This great interest in natural non-proteinogenic α-amino acids results from their diverse biological activities as antibiotics, pharmaceuticals, natural pesticides, and growth regulators, as well as their use in the synthesis of enzymes, hormones, new chemotherapeutics, synthetic immunostimulants, and other protein structured compounds [85,86]. The importance of α,α-disubstituted α-amino acids has been comprehensively discussed by many authors [87,88].

As demonstrated by Mazurkiewicz and Kuźnik, N-acyl-1-triphenylphosphonio-glycinate tetrafluoroborates 91 are also convenient starting compounds for the transformation into N-acyl-α-(dialkoxyphosphoryl)glycinates 108 by the Michaelis–Arbuzow-type reaction with trimethylphosphite in the presence of methyltriphenylphosphonium iodide as a catalyst (Scheme 32) [89]. Among others, α-(dialkoxyphosphoryl)glycinates became the crucial synthetic tool commonly used for the synthesis of many natural products (including β-lactam antibiotics) or α,β-dehydro-α-amino acids by the Wadsworth-Emmons reaction [90–96]. As is known, hydrogenation of the latter compounds using chiral catalysts is considered to be one of the most general methods for the enantioselective synthesis of α-amino acids, including non-proteinogenic α-amino acids of diverse biological activities [97–100].
Although N-acyl-1-triphenylphosphonioglycines 91 are relatively stable, they undergo interesting transformations at high temperatures. Thermogravimetric investigations revealed that during the process of the melting of salts 91, they underwent demethoxy-carbonylation, providing N-acylaminoethyltriphenylphosphonium salts 4a (18–50%), along with methyltriphenylphosphonium salts (22–68%). When this reaction was performed in the presence of Ph3P and Ph3P-HX (X = Br, BF4, I) the process of demethoxy-carbonylation for N-acyl-1-triphenylphosphonioglycinate bromides and iodides (X = Br, I) occurred at 95–130 °C in good to excellent yields (79–100%); whereas for N-acyl-1-triphenylphosphonioglycinate tetrafluoroborates 91 (X = BF4) as starting compounds, the analogous transformation occurred at about 170–175 °C, giving the corresponding phosphonium tetrafluoroborates 4a in much lower yields (34–67%; Scheme 33) [101]. The practical significance of this process is due to the fact that the obtained 1-(N-acylamino)alkyltriphenylphosphonium salts 4a can be used as valuable α-amidoalkylating agents (see also Section 2.1.2).

The crucial structural motif for N-acyl-1-triphenylphosphonio-α-amino acid esters 91 can be a part of more complex systems. In this regard, 3-triphenylphosphonio-2,5-piperazinedione 111, 114 can be considered as structurally similar compounds to the phosphonium salts 91. They can be obtained from dipeptides in multistep procedure described by Mazurkiewicz and Gorewoda in 2011 [102]. The retention of configuration (position 6) results in the formation of chiral glycine cation equivalents 111, 114 which can be used for a diastereoselective nucleophilic substitution of the triphenylphosphonium group with S-, N-, P-, and C-nucleophiles (Scheme 34). Reactions were conducted at 0 or 25 °C in the presence of a base (i-Pr2EtN or DBU) and were particularly effective (high yields and high de%) for the proline derivative 111 [102].
aminoalkylphosphonium salts derivatives, but also some phosphonium salts themselves which are very important because of their valuable biological and chemical properties. This was used in the synthesis of such compounds as phosphorus analogs of α-amino acids (Figure 8—new challenges/biological activity).

The structure of such phosphonium salts is easy to modify by changing the N-protecting group or introducing electron-withdrawing or electron-donating substituents to the phosphonium moiety by using appropriately modified phosphines in the key stage of the synthesis. It allows for the control and, more interestingly, the targeting of the reactivity of these phosphonium compounds (α-amidoalkylation reaction vs. Wittig reaction).

All these factors make the 1-aminoalkylphosphonium derivatives an interesting group of “smart-reagents” with great potential as precursors of reactive intermediates such as N-acyliminium-type cations (generated without the need for any catalysts), or ylides. This was used in the synthesis of such compounds as phosphorus analogs of α-amino acids, β-aminocarbonyl systems, 1-aryalkylphosphonium salts or α,β-dehydro-α-amino acids, which are very important because of their valuable biological and chemical properties. However, most of the described reactions were intermolecular (did not lead to cyclization) and were not conducted in a stereocontrolled manner. These two aspects require further research because such transformations are of great importance in the synthesis of natural, biologically active compounds. It seems that, especially in this field, the easy ability to control the Cα-P+ bond strength and introduce structural modifications within phosphonium salts may be crucial (Figure 8—new challenges/asymmetric synthesis/cyclization). Studies on cyclization and stereocontrol of reactions involving 1-aminoalkylphosphonium salts are in progress.

It is worth adding that, not only many of the described compounds obtained from 1-aminoalkylphosphonium salts derivatives, but also some phosphonium salts themselves show interesting biological properties. However, in this case, the area of potential application should also be much more explored. 1-Aminoalkylphosphonium salts derivatives can be an ideal tool for the modification of already known structures with proven biological activity. Furthermore, recent reports on mitochondria-targeted phosphonium salts inspire the design and synthesis of molecular hybrids or conjugates that will use the targeting properties of the triphenylphosphonium (TPP) group, its biological properties, or both (Figure 8—new challenges/biological activity).

Scheme 34. Synthetic use of 3-triphenylphosphonio-2,5-piperazinedione 111, 114-chiral glycine cation equivalents.

3. Conclusions
We hope that the presented data will encourage further research on 1-aminoalkylphosphonium salt derivatives and will contribute to discovering their full potential.

Author Contributions: Conceptualization, J.A.; data curation, J.A., M.G., A.K. and A.P.-H.; writing—original draft preparation, J.A., M.G., A.K. and A.P.-H.; writing—review and editing, J.A., M.G., A.K. and A.P.-H.; supervision, J.A. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported under the Rector’s Habilitation Grant, Silesian University of Technology (Poland), No. 04/020/RGH20/1006. This research was also supported by Silesian University of Technology (Poland) Grant BK No. 04/050/BK_21/0116.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Neto, B.A.D.; Rocha, R.O.; Rodrigues, M.O. Catalytic Approaches to Multicomponent Reactions: A Critical Review and Perspectives on the Roles of Catalysis. Molecules 2022, 27, 132. [CrossRef]
2. Kokkala, P.; Rajeshkumar, T.; Mpakali, A.; Stratikos, E.; Vogiatzis, K.D.; Georgiadis, D. A Carbodiimide-Mediated P–C Bond-Forming Reaction: Mild Amidocyclolation of P-Nucleophiles by Boc-Aminals. Org. Lett. 2021, 23, 1726–1730. [CrossRef]
3. Heravi, M.M.; Zadsirjan, V.; Heydari, M.; Masoumi, B. Organocatalyzed Asymmetric Friedel-Crafts Reactions: An Update. Chem. Rec. 2019, 19, 2236–2340. [CrossRef]
4. Aranzamendi, E.; Sotomayor, N.; Lete, E. Phenolic Activation in Chiral Bronsted Acid-Catalyzed Intramolecular α-Aminocyclolation Reactions for the Synthesis of Fused Isoquinolines. ACS Omega 2017, 2, 2706–2718. [CrossRef]
5. Huang, Y.-Y.; Cai, C.; Yang, X.; Lv, Z.-C.; Schneider, U. Catalytic Asymmetric Reactions with N,O-Aminals. ACS Catal. 2016, 6, 5747–5763. [CrossRef]
6. Kataja, A.O.; Masson, G. Imine and iminium precursors as versatile intermediates in enantioselective organocatalysis. Tetrahedron 2014, 70, 8783–8815. [CrossRef]
7. Maryanoff, B.E.; Zhang, H.C.; Cohen, J.H.; Turchi, I.J.; Maryanoff, C.A. Cyclizations of N-acyliminium ions. Chem. Rev. 2004, 104, 1431–1628. [CrossRef]
8. Yazici, A.; Pyne, S.G. Intermolecular addition reactions of N-acyliminium ions (Part I). Synthesis 2009, 339–368. [CrossRef]
9. Yazici, A.; Pyne, S.G. Intermolecular addition reactions of N-acyliminium ions (Part II). Synthesis 2009, 513–541. [CrossRef]
10. Aranzamendi, E.; Arrasate, S.; Sotomayor, N.; Gonzalez-Diaz, H.; Lete, E. Chiral Bronsted Acid Catalyzed Enantioselective α-Aminocyclolation Reactions: A Joint Experimental and Predictive Study. ChemistryOpen 2016, 5, 540–549. [CrossRef]
11. Zhang, S.; Shi, X.; Li, J.; Hou, Z.; Song, Z.; Su, X.; Peng, D.; Wang, F.; Yu, Y.; Zhao, G. Nickel-Catalyzed Amidocyclolation Reaction of γ-Hydroxy Lactams: An Access to 3-SubstitutedIsoindoliones. ACS Omega 2019, 4, 19420–19436. [CrossRef]
12. Mazurkiewicz, R.; Pażdzierniok-Holewa, A.; Adamek, J.; Zielińska, K. α-Aminoalkylating agents: Structure, synthesis, reactivity and application. Adv. Heterocycl. Chem. 2014, 111, 43–94. [CrossRef]
13. Touati, B.; El Bouakher, A.; Taillier, C.; Othman, R.B.; Trabelsi-Ayadi, M.; Antoniotti, S.; DuÇach, E.; Dalla, V. Enolizable Carboxyls and N,O-Acetals: A Rational Approach for Room-Temperature Lewis Superacid-Catalyzed Directa-Amidoalkylation of Ketones and Aldehydes. Chem. Eur. J. 2016, 22, 6012–6022. [CrossRef] [PubMed]

14. Schneider, A.E.; Manolikakes, G. Bi(OTf)2-Catalyzed Multicomponent α-Amidoalkylation Reactions. J. Org. Chem. 2015, 80, 6193–6212. [CrossRef] [PubMed]

15. Smolii, O.B.; Brovarets, V.S.; Pirozhenko, V.V.; Drach, B.S. Cyclocondensation of [CrossRef]

16. Brovarets, V.S.; Lobanov, O.P.; Vinogradova, T.K.; Drach, B.S. Preparation and Properties of 2-Chloro-1-Acylaminovinyltriphenylphosphonium Chlorides. Zh. Obshch. Khim. 2007, 77, 1110–1118. [CrossRef]

17. Katritzky, A.R.; Manju, K.; Singh, S.K.; Meher, N.K. Benzotriazole-mediated amino- , amido- , alkoxy- and alkylthioalkylation. Tetr Hedron 2005, 61, 2555–2581. [CrossRef]

18. Katritzky, A.R.; Mehta, S.; He, H.Y. Syntheses of Pyrrolo- and Indoloisoquinolinones by Intramolecular Cyclizations of 1-(2-Arylethyl)-3-benzotriazoloylpyrrolidin-2-ones and 3-Benzotriazolyl-2-(2-arylethyl)-1-isoindolinones. J. Org. Chem. 2006, 71, 148–152. [CrossRef] [PubMed]

19. Zinner, G.; Fehlhammer, W.P. Isocyanomethylenetriphenylphosphorane. Angew. Chem. Int. Ed. Engl. 1985, 24, 979–980. [CrossRef]

20. Russ. Chem. Rev. 2007, 76, 58–72. [CrossRef]

21. Shokol, V.A.; Kozushko, B.N.; Gumenyuk, A.V.; Smolii, O.B.; Pirozhenko, V.V.; Drach, B.S. Substituted Methylphosphonium Salts with an Imidoyl Chloride Group. Zh. Obshch. Khim. 1986, 56, 2802–2803.

22. Shokol, V.A.; Brovarets, V.S.; Pirozhenko, V.V.; Drach, B.S. Cyclocondensation of N-Substituted Imidoyl Chlorides Containing a Phosphonium Group. Zh. Obshch. Khim. 1988, 58, 2465–2471.

23. Shokol, V.A.; Silina, E.B.; Kozushko, B.N.; Golik, G.A. Bromomethyl Isocyanate and Its Phosphorylated Derivatives. Zh. Obshch. Khim. 1977, 49, 312–319.

24. Shokol, V.A.; Kozushko, B.N.; Gumenyuk, A.V.; Turov, A.V.; Shokol, V.A. Triaryl(isocyanatomethyl)Phosphonium Iodides. Zh. Obshch. Khim. 1980, 50, 2210–2215.

25. Shokol, V.A; Kozushko, B.N.; Gumenyuk, A.V. Trialkyl- And Aryldialkyl(isocyanatomethyl)Ammonium Chlorides. Zh. Obshch. Khim. 1977, 47, 1110–1118.

26. Zinner, G.; Fehlhammer, W.P. Isocyanomethylenetriphenylphosphorane. Angew. Chem. Int. Ed. Engl. 1985, 24, 979–980. [CrossRef] [PubMed]

27. Frank, A.W.; Drake, G.L. Synthesis and properties of carbamate derivatives of tetrakis(hydroxymethyl)phosphonium chloride. J. Org. Chem. 1975, 40, 4040–4045. [CrossRef]

28. Zinner, G.; Fehlhammer, W.P. Isocyanomethylenetriphenylphosphorane. Angew. Chem. Int. Ed. Engl. 1985, 24, 979–980. [CrossRef] [PubMed]

29. Russ. Chem. Rev. 2007, 76, 58–72. [CrossRef]

30. Russ. Chem. Rev. 2007, 76, 58–72. [CrossRef]

31. Russ. Chem. Rev. 2007, 76, 58–72. [CrossRef]

32. Russ. Chem. Rev. 2007, 76, 58–72. [CrossRef]

33. Russ. Chem. Rev. 2007, 76, 58–72. [CrossRef]

34. Russ. Chem. Rev. 2007, 76, 58–72. [CrossRef]

35. Russ. Chem. Rev. 2007, 76, 58–72. [CrossRef]

36. Russ. Chem. Rev. 2007, 76, 58–72. [CrossRef]

37. Russ. Chem. Rev. 2007, 76, 58–72. [CrossRef]

38. Russ. Chem. Rev. 2007, 76, 58–72. [CrossRef]

39. Russ. Chem. Rev. 2007, 76, 58–72. [CrossRef]

40. Russ. Chem. Rev. 2007, 76, 58–72. [CrossRef]
Molecules 2022, 27, 1562

41. Mazurkiewicz, R.; Październik-Holewa, A.; Grymel, M. Synthesis and decarboxylation of N-acyl-α-triphenylphosphonio-α-amino acids: A new synthesis of α-(N-acylamino)alkyltriphenylphosphonium salts. Tetrahedron Lett. 2008, 49, 1801–1803. [CrossRef]

42. Mazurkiewicz, R.; Październik-Holewa, A.; Grymel, M. N-Acyl-α-triphenylphosphonio-α-amino Acids: Synthesis and Decarboxylation to α-(N-Acylamino)alkyltriphenylphosphonium Salts. Phosphorus Sulfur Silicon Relat. Elem. 2009, 184, 1017–1027. [CrossRef]

43. Mazurkiewicz, R.; Adamek, J.; Październik-Holewa, A.; Zielińska, K.; Zielińska, K.; Gajos, A.; Szymura, K. α-Amidoalkylating Agents from N-Acyl-α-amino Acids: 1-(N-Acylamino)alkyltriphenylphosphonium Salts. J. Org. Chem. 2012, 77, 1952–1960. [CrossRef] [PubMed]

44. Adamek, J.; Zieleźny, P.; Erfurt, K. N-protected 1-aminoalkylphosphonium salts from amides, carbamates, lactams, or imides. J. Org. Chem. 2021, 86, 5852–5862. [CrossRef]

45. Walęcka-Kurczyk, A.; Walczak, K.; Kuźnik, A.; Stecko, S.; Październik-Holewa, A. The Synthesis of 1-(N-Acylamino)alkyltriphenylphosphonium Salts. Phosphorus Sulfur Silicon Relat. Elem. 2013, 188, 205–212. [CrossRef]

46. Adamek, J.; Węgrzyk, A.; Kończewicz, J.; Walczak, K.; Erfurt, K. 1-(N-Acylamino)alkyltriarylphosphonium Salts with Weakened C₈₋P Bond Strength—Synthetic Applications. Molecules 2018, 23, 2453. [CrossRef] [PubMed]

47. Adamek, J.; Mazurkiewicz, R.; Walczak, K.; Michalak, M.; Październik-Holewa, A. Non-Kolbe electrolysis of 1-(N-Acylamino)alkyltriphenylphosphonium Salts. Beilstein J. Org. Chem. 2012, 8, 10991–11005. [CrossRef]

48. Kozicka, D.; Zieleźny, P.; Erfurt, K.; Adamek, J. Amide-type substrates in the synthesis of α-amino Acids: A new synthesis of α-acylamino)alkylphosphonic and 1-(N-Acylamino)alkyltriphenylphosphonium Salts. Phosphorus Sulfur Silicon Relat. Elem. 2013, 188, 967–980. [CrossRef]

49. Mucha, A.; Kafarski, P.; Berlicki, L. Remarkable Potential of the α-Aminophosphonate/Phosphinate Structural Motif in Medicinal Chemistry. J. Med. Chem. 2011, 54, 5955–5980. [CrossRef] [PubMed]

50. Październik-Holewa, A.; Kononienko, A. A Novel Synthesis of 1-Aminoalkanephosphonic Acid Derivatives from 1-(N-Acylamino)alkyltriphenylphosphonium Salts. Phosphorus Sulfur Silicon Relat. Elem. 2010, 185, 1986–1992. [CrossRef]

51. Październik-Holewa, A.; Adamek, J.; Mazurkiewicz, R.; Zielińska, K. Amidoalkylating Properties of 1-(N-Acylamino)alkyltriphenylphosphonium Salts. Phosphorus Sulfur Silicon Relat. Elem. 2013, 188, 205–212. [CrossRef]

52. Adamek, J.; Październik-Holewa, A.; Zielińska, K.; Mazurkiewicz, R. Comparative Studies on the Amidoalkylating Properties of N-(1-Methoxyalkyl)Amides and 1-(N-Acylamino)alkyltriphenylphosphonium Salts in the Michaelis–Arbuslov-Like Reaction: A New One-Pot Transformation of N-(1-Methoxyalkyl)Amides into Phosphonic or Phosphinic Analogs of N-Acyl-α-Amino Acids. Phosphorus Sulfur Silicon Relat. Elem. 2013, 188, 967–980. [CrossRef]

53. Zielińska, K.; Mazurkiewicz, R.; Szymańska, K.; Jarzębski, A.; Magiera, S.; Erfurt, K. Penicillin G Acylase-Mediated Kinetic Resolution of Racemic 1-(N-Acylamino)alkylphosphonic and 1-(N-Acylamino)alkylphosphinic Acids and Their Esters. J. Mol. Catal. B Enzym. 2016, 132, 31–40. [CrossRef]

54. Zielińska, K.; Mazurkiewicz, R.; Szymańska, K.; Jarzębski, A. Batch and in-flow kinetic resolution of racemic 1-(N-Acylamino)alkylphosphonic and 1-(N-Acylamino)alkylphosphinic acids and their esters using immobilized penicillin G acylase. Tetrahedron Asymmetry 2017, 28, 146–152. [CrossRef]

55. Walęcka-Kurczyk, A.; Walczak, K.; Kuźnik, A.; Stecko, S.; Październik-Holewa, A. The Synthesis of α-Aminophosphonates via Enantioselective Organocatalytic Reaction of 1-(N-Acylamino)alkylphosphonium Salts with Dimethyl Phosphite. Molecules 2020, 25, 405. [CrossRef]

56. Kuźnik, A.; Mazurkiewicz, R.; Grymel, M.; Zielińska, K.; Adamek, J.; Chmielewska, E.; Bochno, M.; Kubica, S. New method for the synthesis of α-aminokylenebiphosphonates and their asymmetric phosphonyl-phosphinyl and phosphonyl-phosphinoyl analogues. Beilstein J. Org. Chem. 2015, 11, 1418–1424. [CrossRef]

57. Kuźnik, A.; Mazurkiewicz, R.; Ziemia, M.; Erfurt, K. 1-(N-Acylamino)-1-triphenylphosphoniumalkylphosphonates: General synthesis and prospects for further synthetic applications. Tetrahedron Lett. 2018, 59, 3307–3310. [CrossRef]

58. Październik-Holewa, A.; Adamek, J.; Zielińska, K.; Piernikarczyk, K.; Mazurkiewicz, R. N-(1-Acetoaminoalkyl)amidinium salts derived from DBU or related bases as reactive intermediates in α-amidoalkylation reactions. Arkivoc 2012, 4, 314–329. [CrossRef]

59. Adamek, J.; Mazurkiewicz, R.; Październik-Holewa, A.; Kuźnik, A.; Grymel, M.; Zielińska, K.; Simka, W.N.—[1-(Benzotriazol-1-yl)alkyl]amides from N-acyl-α-amino acids or N-alkylamides. Tetrahedron 2014, 70, 5725–5729. [CrossRef]

60. Zheng, K.; Shen, D.; Zhang, B.; Hong, R. Stereodivergent Synthesis of Lankacyclinol and Its C2/C18-Congeneres Enabled by a Bioinspired Mannich Reaction. J. Org. Chem. 2021, 86, 10991–11005. [CrossRef]

61. Zheng, K.; Shen, D.; Zhang, B.; Hong, R. Landscape of Lankacidin Biomimetic Synthesis: Structural Revisions and Biogenetic Implications. J. Org. Chem. 2020, 85, 13818–13836. [CrossRef]

62. Zheng, K.; Hong, R. The Fruit of Gold: Biomimicry in the Syntheses of Lankacidsins. Acc. Chem. Res. 2021, 54, 3438–3451. [CrossRef]

63. Adamek, J.; Węgrzyk, A.; Krawczyk, M.; Erfurt, K. Catalyst-free Friedel-Crafts reaction of 1-(N-acylamino)alkyltriarylphosphonium salts with electron-rich arenes. Tetrahedron 2018, 74, 2575–2583. [CrossRef]

64. Październik-Holewa, A.; Walęcka-Kurczyk, A.; Musioł, S.; Stecko, S. Catalyst-free Mannich-type reaction of 1-(N-acylamino)alkyltriphenylphosphonium salts with silyl enolates. Tetrahedron 2019, 75, 732–742. [CrossRef]
65. Smolii, O.B.; Brovarets, V.S.; Drach, B.S. Reaction of the Chloride of N-(Triphenylphosphoniomethyl)benzimidoyl chloride with Sodium Rhodanide. Zh. Obsch. Khim. 1987, 57, 2145–2146.

66. Smolii, O.B.; Brovarets, V.S.; Drach, B.S. Reaction of the Chloride of N-(Triphenylphosphoniomethyl)benzimidoyl chloride with Carboxylic Acid Chlorides. Zh. Obsch. Khim. 1988, 58, 1670–1671.

67. Dubois, R.J.; Lin, C.-C.; Beisler, J.A. Synthesis and antitumor properties of some isoindolyllalkylphosphonium salts. J. Med. Chem. 1978, 21, 303–306. [CrossRef]

68. Tessier, D.; Filteau, M.; Radu, I. New Antimicrobial Compositions and Uses Thereof. U.S. Patent US 2015/0201622 Al, 23 July 2015.

69. Tessier, D.; Filteau, M.; Radu, I. Antimicrobial Solution Comprising a Metallic Salt and a Surfactant. International Patent WO 2006105669 A1, 12 October 2006.

70. Hellmann, H.; Schumacher, O. Quartäre Phosphoniumsalze aus tertiären Phosphinen und quartären Ammoniumsalzen. Justus Liebigs Ann. Chem. 1961, 640, 79–84. [CrossRef]

71. Enzmann, A.; Eckert, M.; Ponikwar, W.; Polborn, K.; Schneiderbauer, S.; Beller, M.; Beck, W. Aminomethyl and Aminoacetyl Complexes of Palladium(II), Platinum(II), Iron(II) and Rhenium(II) with N-phthaloyl as Amino Protecting Group and Mechanistic Studies on the Palladium-Catalyzed Amidocarbonylation. Eur. J. Inorg. Chem. 2004, 6, 1330–1340. [CrossRef]

72. Tan, E.S.; Naylor, J.C.; Groban, E.S.; Bunzow, J.R.; Jacobson, M.P.; Grandy, D.K.; Scanlan, T.S. The Molecular Basis of Species-Specific Ligand Activation of Trace Amine-Associated Receptor 1 (TAAR1). ACS Chem. Biol. 2009, 4, 209–220. [CrossRef] [PubMed]

73. Adamek, J.; Wegrzyk-Schlieter, A.; Steć, K.; Walczak, K.; Erfurt, K. Michaelis-Arbuzov-Type Reaction of 1-Imidoalkyltriarylphosphonium Salts with Selected Phosphorus Nucleophiles. Monatsh. Chem. 2019, 24, 3405. [CrossRef]

74. Clavé, G.; Reverte, M.; Vasseur, J.-J.; Smietana, M. Modified internucleoside linkages for nuclease-resistant oligonucleotides. RSC Chem. Biol. 2021, 2, 94–150. [CrossRef]

75. Nahrwold, M.; Bogner, T.; Eissler, S.; Verma, S.; Sewald, N. “Clicktophycin-52”: A Bioactive Cryptophycin-52 Triazole Analogue. Liebigs Ann. Chem. 2004, 135, 33–43. [CrossRef]

76. Adamek, J.; Wegrzyk-Schlieter, A.; Steć, K.; Walczak, K.; Erfurt, K. Michaelis-Arbuzov-Type Reaction of 1-Imidoalkyltriarylphosphonium Salts with Modulated Cα-P” bond strength: Synthesis and application as new active α-imidoalkylating agents. Beilstein J. Org. Chem. 2017, 13, 1446–1455. [CrossRef] [PubMed]

77. Kobcr, R.; Steglich, W. Untersuchungen zur Reaktion von Acylniminobrommalonestern und Acylnominobrommessigestern mit Trialkylphosphiteneine einfache Synthese von 2-Amino-2-(diethoxyphosphoryl) Essigsäure Ethylester. Liebigs Ann. Chem. 1983, 4, 599–609. [CrossRef]

78. Mazurkiewicz, R.; Grymel, M.; Kuznik, A.; Mazurkiewicz, R.; Grymel, M. A new synthesis of α-amino acid derivatives by reaction of N-acetyl-α-triphenyolphosphinoglycinates with carbon nucleophiles. Phosphorus Sulfur Silicon. 2000, 164, 33–43. [CrossRef]

79. Mazurkiewicz, R.; Pierwocha, A.W. 4-Phosphoranylidene-5(4H)-oxazolones II. Reactions with alkylating agents. Monatsh. Chem. 1997, 128, 893–900. [CrossRef]

80. Mazurkiewicz, R.; Grymel, M. N-Acyl-α-triphenylphosphinoglycinates: A Novel Cationic Glycine Equivalent and its Reactions with Heteroatom Nucleophiles. Monatsh. Chem. 1999, 130, 597–604. [CrossRef]

81. Mazurkiewicz, R.; Grymel, M. A new synthesis of α-amino acid derivatives by reaction of N-acetyl-α-triphenyolphosphinoglycinates with carbon nucleophiles. Phosphorus Sulfur Silicon. 2000, 164, 33–43. [CrossRef]

82. Mazurkiewicz, R.; Grymel, M. α-Amino acid derivatives with a Cα-P bond: Mechanism of the Base-Catalyzed Nucleophilic Substitution of the Triphenylphosphonium Group. Monatsh. Chem. 2002, 133, 1197–1204. [CrossRef]

83. Mazurkiewicz, R.; Grymel, M. Reaction of N-Acyl-α-triphenylphosphinopheno-α-amino Acid Esters with Organic Bases: Mechanism of the Base-Catalyzed Nucleophilic Substitution of the Triphenylphosphonium Group. Monatsh. Chem. 2004, 135, 799–806. [CrossRef]

84. Mazurkiewicz, R.; Grymel, M.; Kuznik, A.; Mazurkiewicz, R. N-Acyl-α-triphenylphosphino-α-amino acid esters as synthetic equivalents of α-amino acid α-cations. Phosphorus Sulfur Silicon. 2015, 190, 429–439. [CrossRef]

85. Mazurkiewicz, R.; Grymel, M.; Kuznik, A. Three New in situ Syntheses of N-Acyl-α-triphenylphosphinoglycinates. Monatsh. Chem. 2004, 135, 799–806. [CrossRef]

86. Mazurkiewicz, R.; Grymel, M.; Kuznik, A.; Mazurkiewicz, R. N-Acyl-α-triphenylphosphinoglycinates in the Synthesis of α,β-Dehydro-α-amino Acid Derivatives. Monatsh. Chem. 2004, 135, 807–815. [CrossRef]

87. Gentilucci, L.; De Marco, R.; Cerisoli, L. Chemical Modifications Designed to Improve Peptide Stability: Incorporation of Non-Natural Amino Acids, and Cyclization. Curr. Pharm. Des. 2010, 16, 3185–3203. [CrossRef]

88. Meester, W.J.N.; van Maarseveen, J.H.; Schoemaker, H.E.; Hiemstra, H.; Rutjes, F.P.J. T. Glyoxylates as Versatile Building Blocks for the Synthesis of α-Amino Acid Derivatives and α-Alkoxo Acid Derivatives via Cationic Intermediates. Eur. J. Org. Chem. 2003, 2003, 2519–2529. [CrossRef]

89. Heimgartner, H.; Braun, K.; Linden, A. Synthesis and conformational analysis of pentapeptides containing enantiomerically pure 2,2-disubstituted glycines. Helv. Chim. Acta. 2008, 91, 526–588. [CrossRef]

90. Ohfune, Y.; Shinada, T. Enantio- and Diastereoselective Construction of α,α-Disubstituted α-Amino Acids for the Synthesis of Biologically Active Compounds. Eur. J. Org. Chem. 2005, 2005, 5127–5143. [CrossRef]

91. Mazurkiewicz, R.; Kuznik, A. A new convenient synthesis of N-acetyl-2-(dimethoxyphosphoryl)glycinates. Tetrahedron Lett. 2006, 47, 3439–3442. [CrossRef]

92. Kobayashi, K.; Tanaka, K.; Kogen, H. Recent topics of the natural product synthesis by Horner-Wadsworth-Emmons reaction. Tetrahedron Lett. 2018, 59, 568–582. [CrossRef]

93. Mazurkiewicz, R.; Kuznik, A.; Grymel, M.; Pzdzierniok-Holewa, A. α-Amino acid derivatives with a Cα-P bond in organic synthesis. Arkivoc 2007, 6, 193–216. [CrossRef]
92. Pfefferkorn, J.A.; Nugent, R.A.; Gross, R.J.; Greene, M.L.; Mitchell, M.A.; Reding, M.T.; Funk, L.A.; Anderson, R.; Wells, P.A.; Shelly, J.A.; et al. Inhibitors of HCV NS5B polymerase. Part 2: Evaluation of the northern region of (2Z)-2-benzoylamino-3-(4-phenoxy-phenyl)-acrylic acid. *Bioorg. Med. Chem. Lett.* 2005, 15, 2812–2818. [CrossRef] [PubMed]

93. Shangguan, N.; Joullié, M.M. Total synthesis of isoroorquefortine E and phenylalaistin. *Tetrahedron Lett.* 2009, 50, 6755–6757. [CrossRef] [PubMed]

94. Wang, W.; Xiong, C.; Zhang, J.; Hruby, V.J. Practical, asymmetric synthesis of aromatic-substituted bulky and hydrophobic tryptophan and phenylalanine derivatives. *Tetrahedron* 2002, 58, 3101–3110. [CrossRef]

95. Cativiela, C.; Diaz de Villegas, M.D.; Galvez, J.A.; Su, G. Horner-Wadsworth-Emmons reaction for the synthesis of unusual alpha, beta-didehydroamino acids with a chiral axis. *Arkivoc* 2004, 4, 59–66. [CrossRef]

96. Aguado, G.P.; Moglioni, A.G.; Ortuño, R.M. Enantiodivergent synthesis of cyclobutyl-(Z)-α,β-dehydro-α-amino acid derivatives from (−)-cis-pinononic acid. *Tetrahedron Asymmetry* 2003, 14, 217–223. [CrossRef]

97. Etayo, P.; Vidal-Ferran, A. Rhodium-catalysed asymmetric hydrogenation as a valuable synthetic tool for the preparation of chiral drugs. *Chem. Soc. Rev.* 2013, 42, 728–754. [CrossRef] [PubMed]

98. Adamczyk, M.; Akireddy, S.R.; Reddy, R.E. Nonproteinogenic amino acids: An efficient asymmetric synthesis of (S)-(−)-acromelobic acid and (S)-(−)-acromelobinic acid. *Tetrahedron* 2002, 58, 6951–6963. [CrossRef]

99. Blaskovich, M.A. *Handbook on Syntheses of Amino Acids, General Routes to Amino Acids*; American Chemical Society & Oxford University Press: New York, NY, USA, 2010.

100. Yasuno, Y.; Mizutani, I.; Sueuchi, Y.; Wakabayashi, Y.; Yasuo, N.; Shimamoto, K.; Shinada, T. Catalytic Asymmetric Hydrogenation of Dehydroamino Acid Esters with Biscarbamate Protection and Its Application to the Synthesis of xCT Inhibitors. *Chem. Eur. J.* 2019, 25, 5145–5148. [CrossRef]

101. Adamek, J.; Mrowiec-Białon, J.; Październik-Holewa, A.; Mazurkiewicz, R. Thermogravimetical investigations of the dealkoxy-carbonylation of N-acyl-α-triphenylphosphonoglycinates. *Thermochim. Acta* 2011, 512, 22–27. [CrossRef]

102. Gorewoda, T.; Mazurkiewicz, R.; Simka, W.; Młostoń, G.; Schroeder, G.; Kubicki, M.; Kuźnik, N. 3-Triphenylphosphonio-2,5-piperazinediones as new chiral glycine cation equivalents. *Tetrahedron Asymmetry* 2011, 22, 823–833. [CrossRef]