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Phosphorus-containing amino acids with a P–C bond in the side chain or a P–O, P–S or P–N bond: from synthesis to applications

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Since the discovery of (L)-phosphinothricin in the year 1970, the development of α-amino acids bearing a phosphorus group has been of renewed interest due to their diverse applications, including their use in [^{18}F]-fluorolabeling, as fluorescent probes, as protecting groups and in the reversible immobilization of amino acids or peptide derivatives on carbon nanomaterials. Considerable progress has also been achieved in the field of antiviral agents, through the development of phosphoramidate prodrugs, which increase significantly the intracellular delivery of nucleoside monophosphate and monophosphonate analogues. This review aims to summarize the strategies reported in the literature for the synthesis of P(III), P(IV) and P(V) phosphorus-containing amino acids with P–C, P–O, P–S or P–N bonds in the side chains and their related applications, including their use in natural products, ligands for asymmetric catalysis, peptidomimetics, therapeutic agents, chemical reagents, markers and nanomaterials. The discussion is organized according to the position of the phosphorus atom linkage to the amino acid side chain, either in an α-, β-, γ- or δ-position or to a hydroxyl, thiol or amino group.

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1. Introduction

Heterosubstituted amino acids containing P, B, Si and F elements are important classes of unnatural compounds that have gained considerable attention in peptide engineering, because they improve stability toward enzymatic degradation, they can modulate bioactivity and they can also be used for labeling purposes. Among the available heterosubstituted amino acids, those containing a phosphorus atom in a tri-, tetra-, penta- or even hexavalent form are a source of structural diversity, as illustrated by compounds **1–7** in Fig. 1. α-Amino acids bearing a phosphate or a phosphinate group on the side chain give rise to biologically active scaffolds, because this type of functionality is isosteric with the carboxylate group in the transition state formed during hydrolysis. (L)-2-Amino-3-phosphonopropionic acid, (L)-AP3, **1** was identified as an antagonist of the metabotropic glutamate receptor (NMDAR) and was evaluated for the treatment of central nervous system disorders. A wide range of acyclic and cyclic derivatives, such as Selfotel **2** (CGS-19755), have also been identified as competitive antagonists to glutamate for binding to NMDAR. Besides these synthetic phosphonic α-amino acids, (L)-phosphinothricin **3** (glufosinate) is a natural phosphinic acid analogue of (L)-glutamate that exhibits herbicidal properties due to its ability to inhibit glutamine synthetase. In this latter case, (L)-phosphinothricin has engendered the development of numerous drugs for neurodegenerative disease treatment. The α-phosphonoglycinate **4** developed in the early 1990s has emerged as a powerful reagent for the synthesis of α,β-dehydroamino acids *via* the Horner–Wadsworth–Emmons (HWE) reaction. Those compounds led to enantiomerically enriched α-amino acids after asymmetric hydrogenation, which are key intermediates in the total synthesis of bioactive compounds. More recently, phosphine borane fullerene amino esters such as **5** were obtained *via* the hydrophosphination of [60]fullerene using *sec*-phosphine boranes under phase transfer catalysis. The electrochemical behavior of the C_{60} phosphine borane amino esters demonstrates that retro-hydrophosphination into free [60]fullerene is possible, thus offering a new strategy for the reversible immobilization of amino acid or peptide derivatives on carbon nanomaterials.

The synthesis of *o*-trifluoroborato phosphonium salts of (L)-amino acids **6** was achieved *via* quaternization, starting from *o*-(pinacolato)boronato phenylphosphine with γ-iodoamino ester followed by fluorination. The usefulness of this compound was demonstrated in fast nucleophilic [^{18}F]-radiolabeling, leading to [^{18}F]-**6** for peptide labeling *via* positron emission tomography (PET). Finally, the grafting of a fluorescent phosphole to an amino acid side chain led to the phospholyl sulfur amino ester **7**, which exhibits remarkable fluorescence emission at 535 nm (green) with a large Stokes shift of 160 nm. Such phospholyl amino acids constitute a new class of probe for the fluorescent labeling of peptides. In addition to the α-amino acids **1–7** mentioned above, which are useful in the fields of medicinal chemistry, organic synthesis and labeling, phosphoramidate prodrugs, such as the

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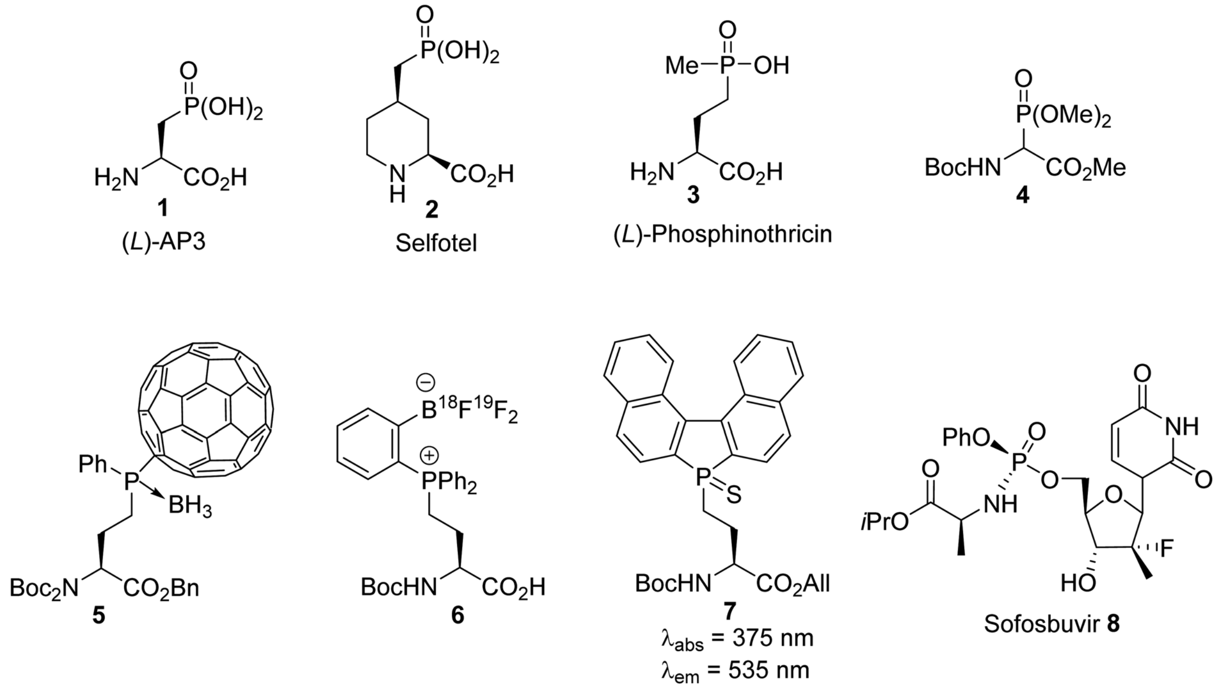


Fig. 1 Representative examples of recent phosphorus-containing amino acids.

anti-hepatitis C agent sofosbuvir **8** (Sovaldi), have been intensively developed for the intracellular delivery of nucleoside monophosphate and monophosphonate analogues.

This review aims to summarize the strategies reported in the literature for the synthesis of phosphorus-containing α- and β-amino acids with P–C, P–O, P–S or P–N bonds and it is organized according to the position of the phosphorus atom linkage to the amino acid side chain at an α-, β-, γ- or δ-position.

The preparation of other stable phosphino- and phosphono-amino acids is also reported in this review, along with their introduction into peptides; this provides ligands for asymmetric catalysis or tools for understanding the phosphorylation and dephosphorylation processes that regulate diverse cellular signalling pathways.

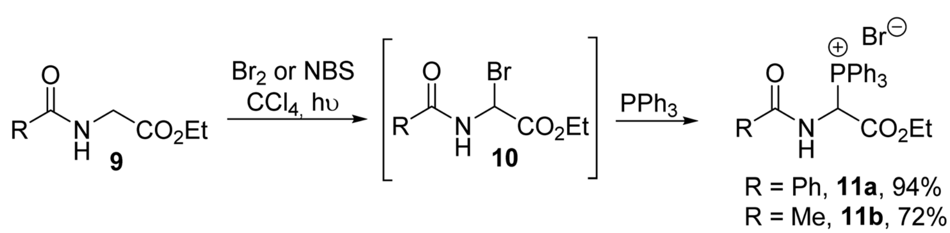
2. Phosphorus linked to carbon in the α-position

2.1. α-Phosphonium α-amino acids

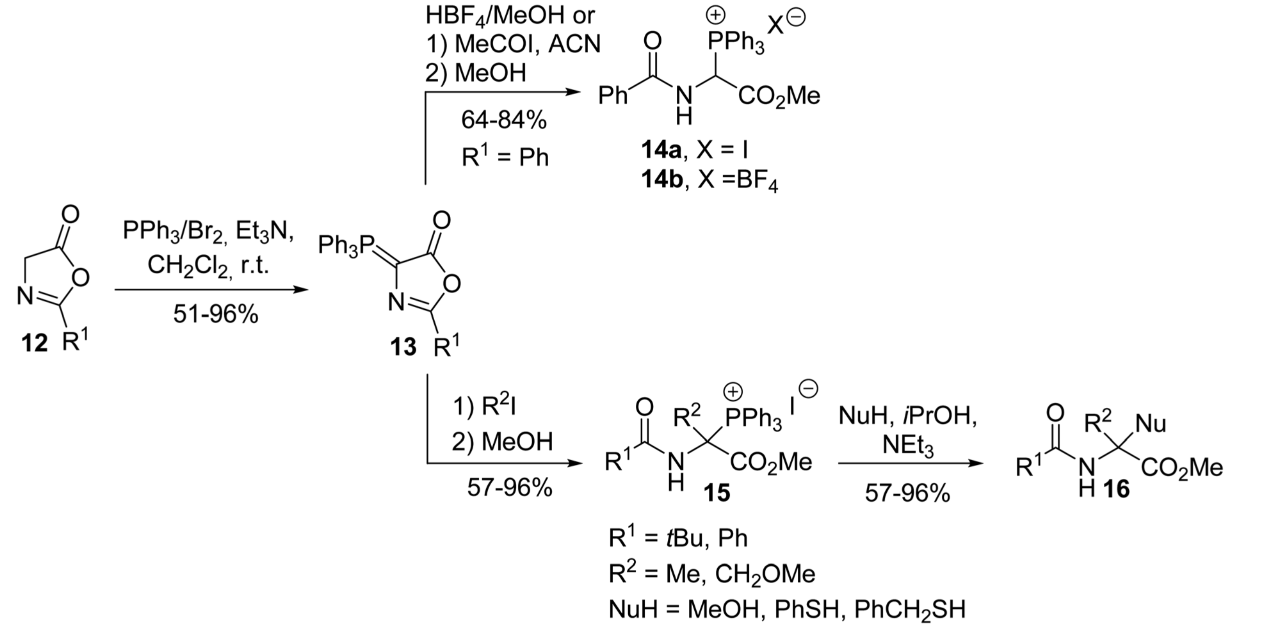
The *N*-acyl-α-triphenylphosphonium α-amino esters **11a–b** were reported for the first time by Kober and Steglich in 1983 and they were prepared *via* the quaternization of triphenylphosphine with *N*-acetyl-α-bromoglycinate **10**, which was previously generated *via in situ* photochemical bromination in the presence of bromine or *N*-bromosuccinimide (Scheme 1).[1]

Other strategies to access the α-triphenylphosphonium α-amino esters **14a–b** were later investigated by Mazurkiewicz *et al.*, involving the transformation of the phosphoranylidene oxazolone **13**, which resulted from the reaction of the oxazolone **12** with triphenylphosphine dibromide in the presence of triethylamine (Scheme 2).[2] Quaternary triphenylphosphonium amino esters **15** were prepared *via* the alkylation of the phosphoranylidene oxazolone **13** with alkyl halides, followed by ring-opening with methanol. These *N*-acyl-α-triphenylphosphonium α-amino esters **15** are stable and crystalline compounds and they can further lead to α,α′-disubstituted glycine **16** *via* the addition of a nucleophile.[3]

Such compounds are of great interest in organic synthesis due to their diverse reactivity, either as synthetic equivalents to glycine α-cations or as precursors to α,β-dehydroamino acid derivatives, involving their corresponding phosphonium ylides in Wittig olefination.[4,5] Thus, the treatment of α-triphenylphosphonium



Scheme 1 The synthesis of α-triphenylphosphonium α-amino esters 11 from the α-bromoglycinate 9.



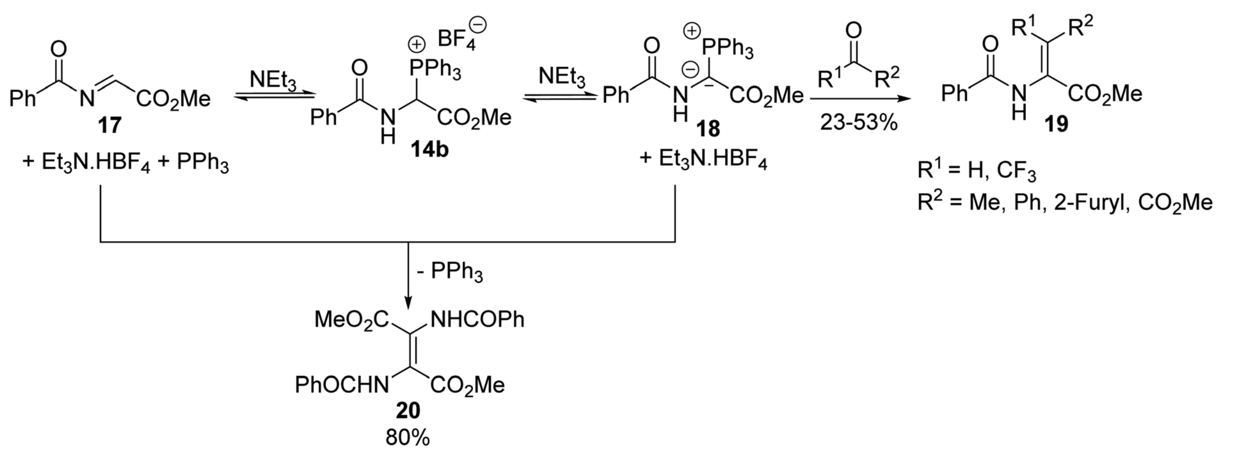
Scheme 2 The synthesis of the α-triphenylphosphonium α-amino esters 14 and 15 from the oxazolone 12.

glycinate **14b** with triethylamine resulted in the formation of its corresponding ylide **18** and *N*-acylimino acetate **17**, which are highly reactive compounds, both in equilibrium in solution. When the ylide **18** reacted with an aliphatic or aromatic aldehyde or ketone, the Wittig reaction proceeded under mild conditions, leading to α,β-dehydroamino esters **19** with yields of up to 53% and when the ylide **18** reacted *in situ* with *N*-acylimino acetate **17**, the dimer **20** was obtained with 80% yield (Scheme 3).[4] Reactions involving di- or tri-peptides have also been performed, illustrating the interest in this methodology for designing peptidic and non-peptidic structures as original tools to stabilize the three-dimensional folding of backbone chains in proteins.[5]

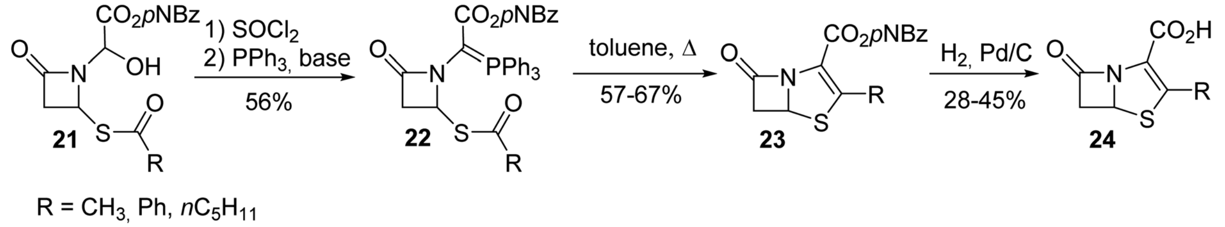
Compared to the ylide **18** reported above that could not be isolated because it was generated along with *N*-acylimino acetate **17**, the other phosphonium ylide **22** with a nitrogen atom inserted into a β-lactam ring was more stable and was used for the synthesis of the bicyclic β-lactam antibiotic **24** (Scheme 4).[6] The bicyclic β-lactam **24** was obtained *via* an intramolecular Wittig reaction with the thioester moiety, followed by the removal of the carboxylic acid protecting group *via* hydrogenation.

2.2. α-Phosphino α-amino acids

α-Phosphino α-amino acids and peptides are particularly useful ligands for a variety of transition metal catalyzed or organo-catalyzed chemical transformations and for providing water-soluble conjugates for biomedical applications. The first *N*-aryl α-diphenylphosphinoglycines were reported by Heinicke and coworkers *via* the one-pot three-component condensation of diphenylphosphine **25** with glyoxylic acid hydrate (GAH) in the presence of the aniline derivatives **26a–e**.[7,8] The reactions



Scheme 3 The Wittig reaction using the α-triphenylphosphonium glycinate 14b as a reagent.

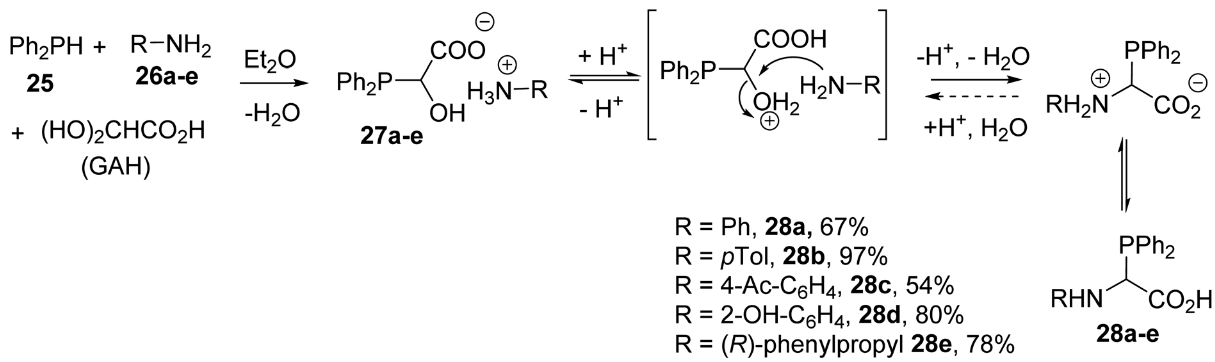


Scheme 4 The synthesis of the β-lactam **24** using the Wittig reagent **22**.

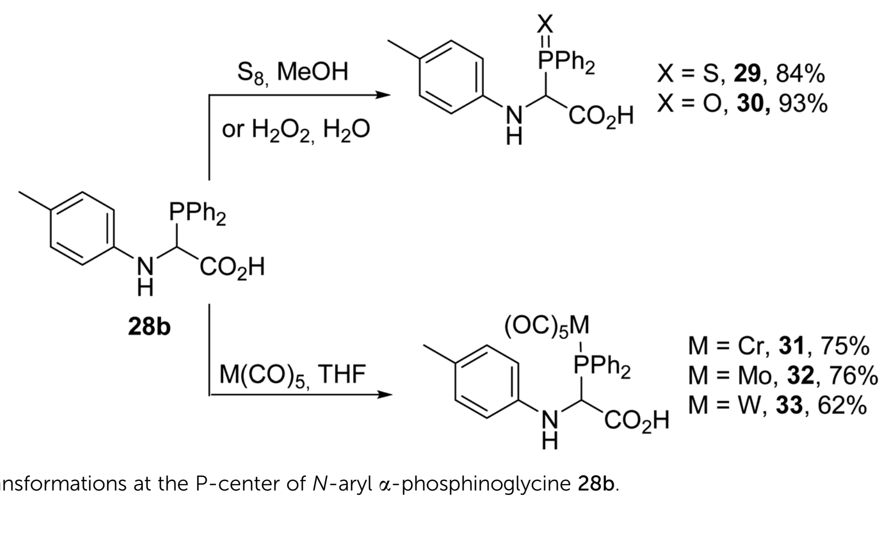
were performed at a 1 : 1 : 1 reagent ratio at room temperature *via* the addition of a mixture of diphenylphosphine and amine to an ethereal solution of GAH. The resulting ammonium salts **27a–e** led to the α-diphenylphosphinoglycines **28a–e** after dehydration, with yields of up to 97% (Scheme 5).

α-Phosphinoglycines possess two Lewis base *P*- and *N*-substituents at the α-carbon position; the presence of a carboxylic acid group destabilizes these compounds, leading to equilibrium in solution (Scheme 5). Another point to be mentioned is that α-phosphinoglycines are much more sensitive to decarboxylation and hydrolysis compared with conventional α-amino acids. *N*-Aryl derivatives are less sensitive to hydrolysis than those bearing *N*-alkylated substituents and can easily be stabilized either *via* sulfuration or oxidation with aqueous hydrogen peroxide, providing the corresponding P(V) compounds **29** and **30** with 84% and 93% yields, respectively (Scheme 6). Complexation with tungsten, chromium or molybdenum pentacarbonyl was also demonstrated to afford the transition-metal complexes **31–33**.[8] The complexation of such ligands with $Ni(cod)_2$ was successfully achieved, leading to highly active catalysts for the oligomerization of ethylene.

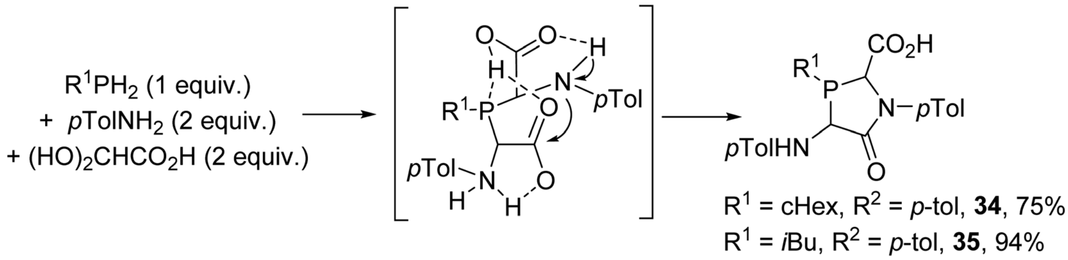
The influence of more basic alkylphosphines (PR^1H_2) on reactions with *p*-toluidine and glyoxylic acid was also studied; this did not afford phosphino-bis(amino acids) as expected, but the lactams **34–35** were formed (Scheme 7).[9] This could be explained based on the higher P-basicity of the



Scheme 5 The synthesis of *N*-aryl α-phosphinoglycines **28a–e** from glyoxylic acid *via* a one-pot three-component condensation.



Scheme 6 Chemical transformations at the P-center of *N*-aryl α-phosphinoglycine **28b**.



Scheme 7 One-pot three-component condensation from glyoxylic acid using primary alkylphosphines.

alkylphosphines, which are easily protonated, leading to intramolecular cyclization into a lactam ring at room temperature.

This reaction was also extended to *ortho*-phosphanylanilines **36**. Metallation and subsequent *P*-alkylation in liquid ammonia followed by cyclocondensation with GAH led to the 1,3-benzazaphospholine carboxylic acids **38a–b** (Scheme 8).[10] In spite of the presence of a bulky neopentyl substituent on the P-atom, low diastereoselectivity was observed in the ring closure step. Only the condensation of *N*-neopentyl-*o*-phosphanylaniline with glyoxylic acid in the presence of *p*-toluidine afforded the defined *trans* diastereoisomer phosphanyl-bis(amino acid) **40**, having the P-lone pair and carboxylic acid functionality on the same side (Scheme 8). This *N*-substituted benzazaphospholine 2-carboxylate, when complexed with nickel, allowed ethylene polymerization at a high conversion rate.

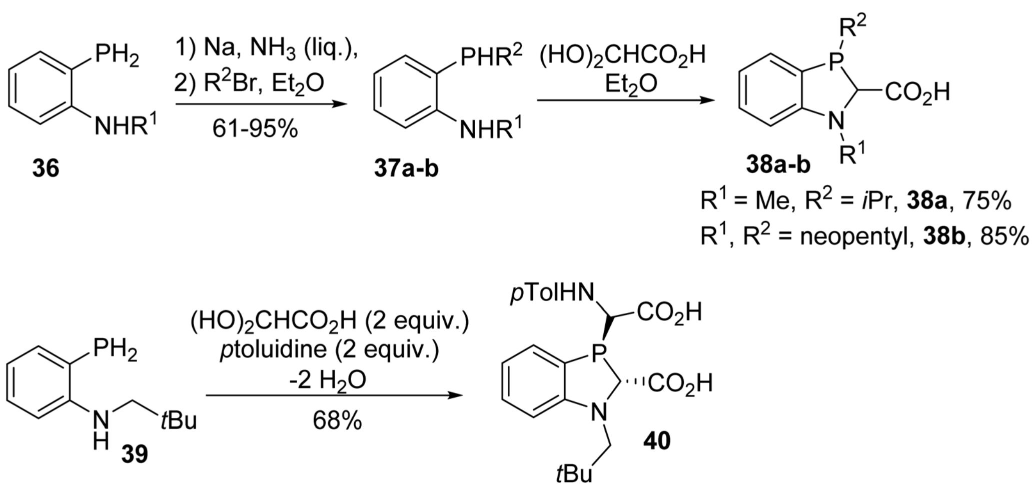
Among the α-amino acids bearing a phosphine group at the α-carbon position, the phenylphosphaprolines **42a–b** and **43a–b**, containing a trivalent phosphorus atom within the five-membered proline ring, were also reported by Heinicke *et al.* These compounds were obtained with up to 95% yields *via* the condensation of the 2-phenylphosphanyl ethylamines **41a–b** with an equimolar amount of glyoxylic acid or pyruvic acid in diethyl ether or 1,4-dioxane, respectively (Scheme 9).[11] The structures and diastereoisomeric ratios of these compounds were determined *via* ^{1}H, ^{31}P and ^{13}C NMR and the structures of *trans* **42a** and *trans* **43a** were assigned *via* X-ray diffraction.

2.3. α-Phosphono α-amino acids

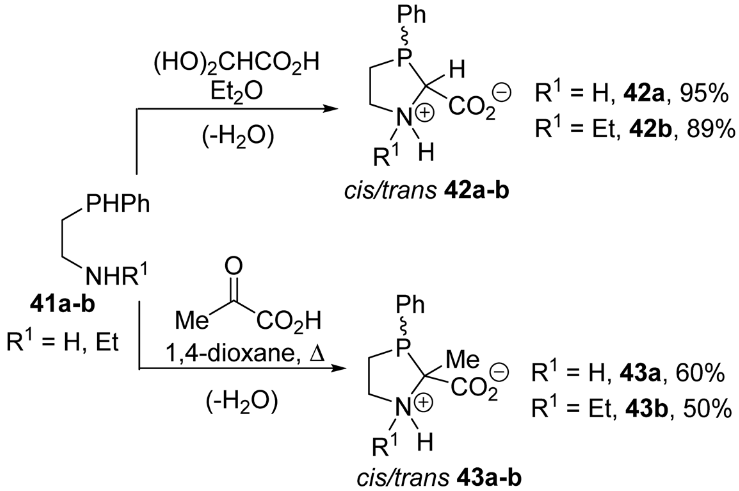
2.3.1. *Via* the Michaelis–Arbuzov reaction with α-chloroglycinates. One of the first synthesis procedures for the α-phosphonoglycinates **47a–e** was reported by Schmidt *et al.* in 1982 and consists of a Michaelis–Arbuzov reaction involving trimethyl phosphite and chloroglycinate **45**, which is more reactive than the methoxyamino ester precursor **44** (Scheme 10).[12,13] After the removal of the Cbz protecting group, the free amine was then transformed into a series of *N*-Boc, *N*-acetyl or *N*-formyl derivatives, with the dipeptides **47a–e** showing good yields from 78 to 91%.[13]

As an alternative to the chlorination step, α-methoxyglycinate **48** was activated with boron trifluoride etherate Lewis acid and dialkyl phosphites bearing *O*-trimethylsilyl as a leaving group were also used (Scheme 11).[14] Under these conditions, the α-phosphono α-amino esters **49a–c** were obtained with good to excellent yields, from 42 to 95%, depending on the reactivity of the phosphite.

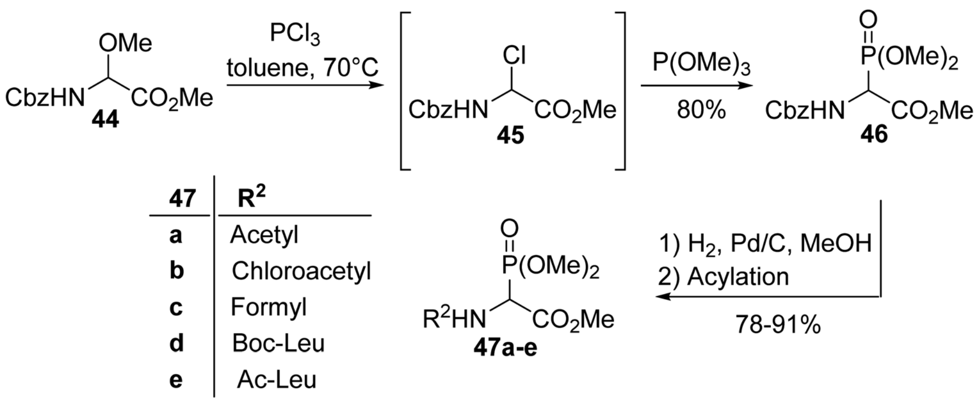
2.3.2. *Via* the rhodium catalyzed N–H insertion of diazaphosphonoacetate. In 1995, Moody *et al.* described an efficient strategy to prepare *N*-acyl phosphonoglycinate, starting with diethyl diaza-phosphonoacetate as a carbenoid precursor.[15] This method is based on an N–H insertion reaction involving



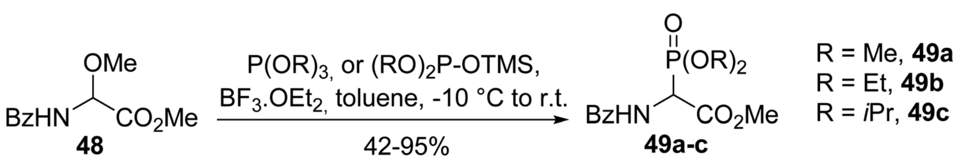
Scheme 8 The cyclocondensation of glyoxylic acid with the *ortho*-phosphanylanilines 36 and 39.



Scheme 9 The synthesis of the phenylphosphaprolines 42 and 43.



Scheme 10 The synthesis of the α-phosphono α-amino esters 47a–e from α-chloroglycinate 45.



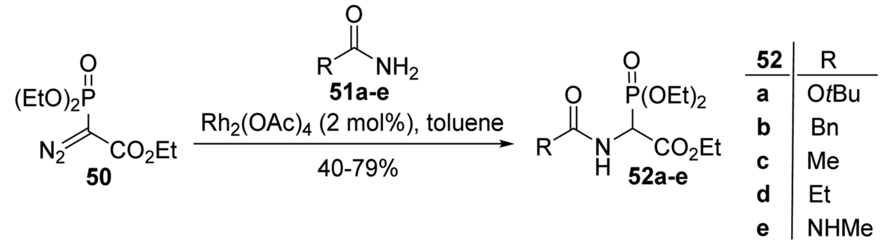
Scheme 11 The synthesis of the α-phosphono α-amino esters 49a–c from α-methoxyglycinate 48.

rhodium carbenoids derived from the readily available diazaphosphonate **50** and the amide, carbamate or urea compounds **51a–e.** This method is as similarly effective as the Michaelis–Arbuzov reaction described above and provides the *N*-acyl phosphonoglycinates **52a–e** with yields of up to 79% (Scheme 12).

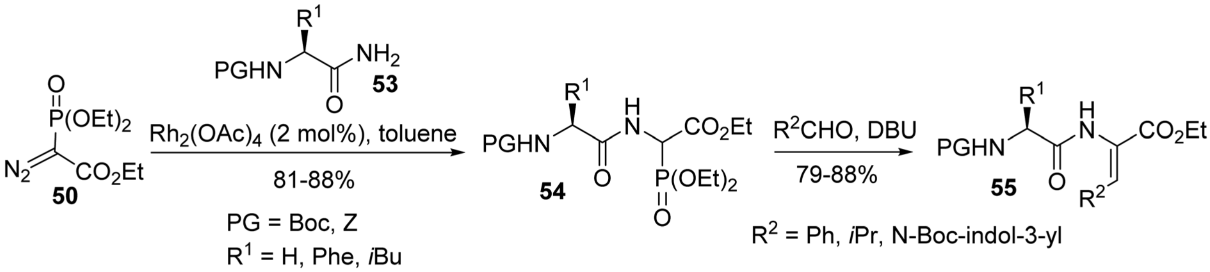
Later, this methodology was extended to a range of N-protected α-amino amides **53,** which were prepared from the corresponding acids. The N–H insertion reaction was performed in the presence of a Rh(II) catalyst and resulted in the formation of the phosphonate dipeptide derivatives **54** with 81% to 88% yields. Those phosphonates were subjected to the Horner–Wadsworth–Emmons (HWE) reaction with aldehydes to furnish a variety of dehydrodipeptides **55** (Scheme 13).[16,17]

2.3.3. *Via* the nucleophilic addition of dimethyl phosphonate to a Schiff base. The preparation of quaternary α-phosphonoglycinate was also possible *via* the addition of dimethyl phosphite **57** to the electrophilic trifluoromethyl *N*-(pyridin-2-yl) Schiff base **56.** This strategy allows the corresponding α-phosphonoglycinate **58** to be obtained with a good yield of 76% and it provides perspectives for the design of 2-aminopyridine derivatives, which are a structural fragment of many bioactive substances (Scheme 14).[18]

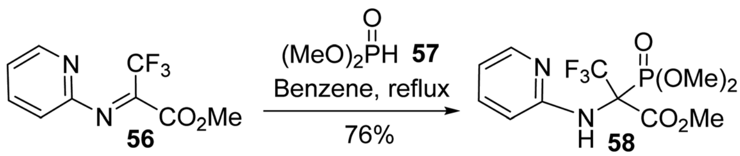
2.3.4. *Via* the asymmetric cyanation of α-ketiminophosphonates. While efficient preparations of racemic α-phosphonoglycinates were achieved according to the above



Scheme 12 The synthesis of the α-phosphonoglycinates **52a–e** from diethyl diaza-phosphonoacetate **50**.



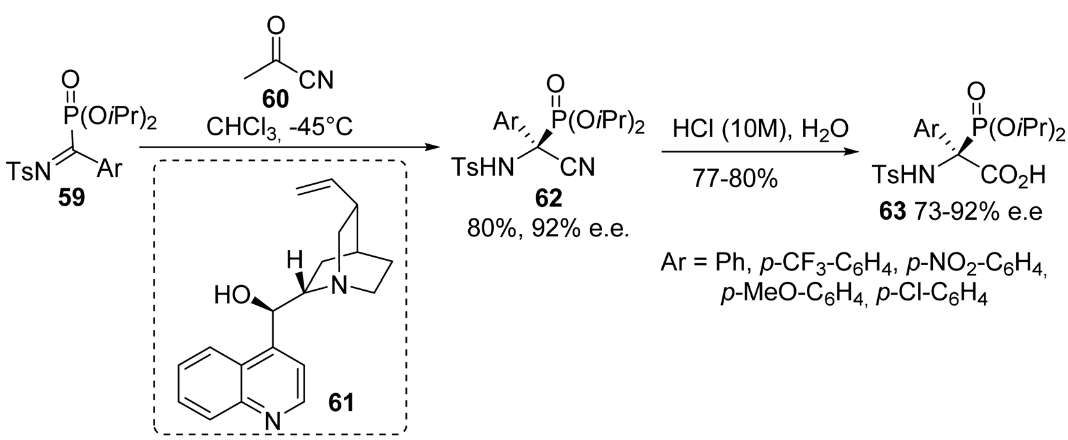
Scheme 13 The formation of dehydrodipeptides **55** *via* HWE olefination.



Scheme 14 The synthesis of α-phosphonoglycinate **58** *via* the hydrophosphonylation of the Schiff base **56**.

strategies (the Michaelis–Arbuzov reaction, the N–H insertion of rhodium carbenoids derived from diaza-phosphonates and the hydrophosphonylation of Schiff base), only one asymmetric synthesis of such compounds has been reported to date. In this context, Palacios *et al.* reported the asymmetric cyanation of α-ketiminophosphonates **59** with aryl cyanoformate, catalyzed by the *Cinchona* alkaloid **61**.[19] Tetrasubstituted (*S*)-α-amino nitriles **62** were obtained with good yields and enantioselectivities of up to 92%. Finally, treatment with hydrochloric acid afforded the corresponding (*S*)-phosphonated tetrasubstituted amino acids **63** bearing various aromatic substituents (Scheme 15).

2.3.5. The utilization of α-phosphonoamino acids. The use of α-phosphonoglycinates to afford α,β-dehydroamino acids *via* the Horner–Wadsworth–Emmons (HWE) reaction was first



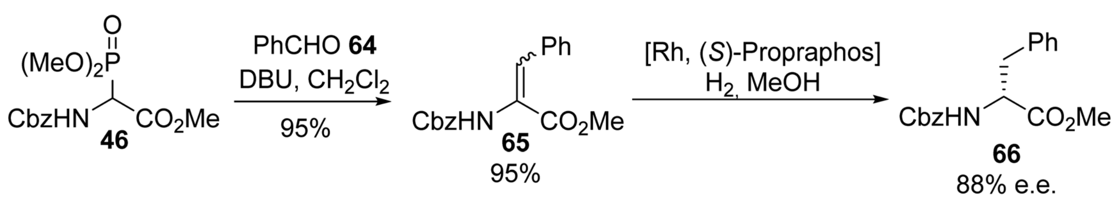
Scheme 15 The synthesis of α-phosphonoamino acids **63** *via* asymmetric cyanation.

reported in the early 1990s and it is still of great interest nowadays. This olefination, which proceeds between an aldehyde or a ketone and a phosphonate carbanion, has been widely explored, as illustrated by the following examples. The initial conditions developed by Schmidt *et al.* to generate α-phosphonoglycinate ylides in the presence of DBU as a base were also used by other authors for reactions with aldehydes or ketones to access a variety of α,β-dehydroamino acids and peptide derivatives.[20] Under these conditions, the HWE reaction involving the ylide obtained from α-phosphonoglycinate **46** was performed with benzaldehyde to furnish the corresponding α,β-dehydroamino ester **65** almost quantitatively and asymmetric hydrogenation catalyzed by rhodium led to the (D)-enantiomer of phenylalanine **66** with 88% e.e. (Scheme 16).[21]

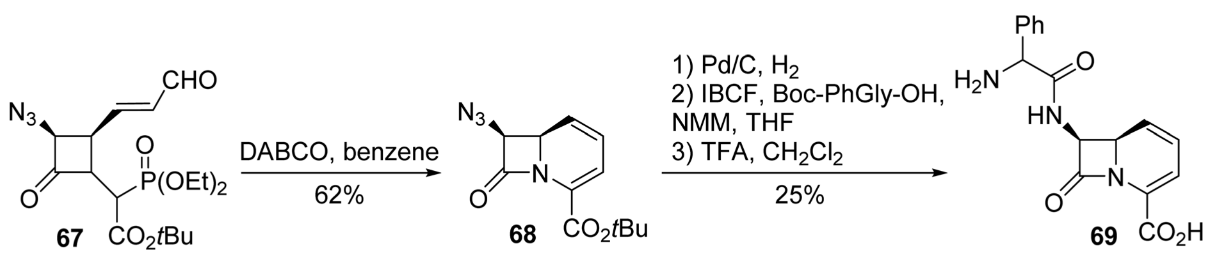
Cephalosporine is a β-lactamine antibiotic isolated from *Cephalosporium acremonium* and carbacephem **69** is an analogue in which the sulfur atom is substituted for a simple methylene isosteric group. It was obtained *via* an intramolecular HWE reaction starting from the phosphonate lactamine derivative **67**, followed by the reduction of the azido group and coupling with *N*-Boc phenylglycine, with 30% overall yield (Scheme 17).[22,23] Studies performed with this analogue demonstrate that the presence of a sulfur atom in the cephem nucleus is not essential for antimicrobial activity.

The azinomycins A and B, which exhibit antitumor properties, were isolated from a culture of *Streptomyces griseofuscus* S42227 in 1986. These densely functionalized molecules contain an aziridine motif and pyrrolidine ring connected to each other, making their synthesis challenging. In this context, Carpenter *et al.* found that HWE olefination involving α-phosphonoglycinate **70** and the aldehyde aziridine derivative **71** is a convenient method for the construction of the intermediate α,β-dehydroamino ester **72** (Scheme 18).[24] Then, radical bromination of the olefin, deprotection of the amine and intramolecular cyclization led successfully to the key building block **73** with 15% yield.

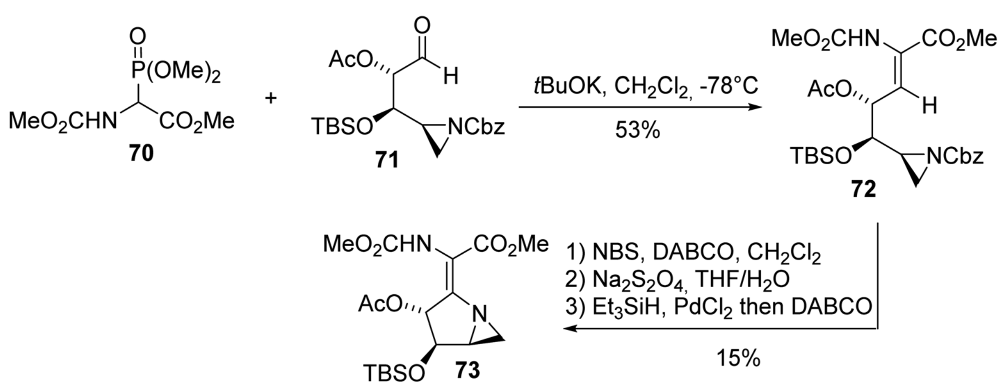
Gonadotropin-releasing hormone (GnRH) is a neurohormone that controls gonadotropin synthesis and is released with a very short half-life. It is therefore necessary to develop analogues that are stable enough *in vivo* to be administered to



Scheme 16 The formation of the dehydroamino acid **65** using the α-phosphonoglycinate **46** as the HWE reagent.



Scheme 17 The stereoselective synthesis of carbacephem **69** *via* an intramolecular HWE reaction.



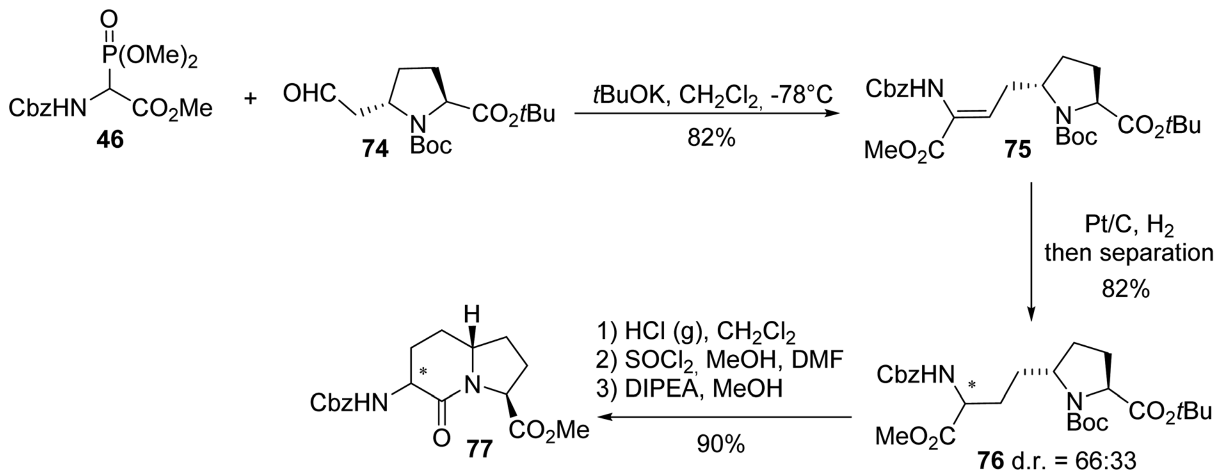
Scheme 18 The stereoselective synthesis of the dehydroamino acid **73** using the HWE reagent **70**.

patients who suffer from endocrine disorders. In line with this objective, the constrained dipeptide mimic AZABIC type I **77** was synthesized and its affinity towards the GnRH receptor was evaluated. First, the ylide of phosphonoamino ester **46** was reacted with the aldehyde derived from (L)-proline **74** to afford the unsaturated dipeptide **75** with 82% yield. Then, hydrogenation gave a mixture of the diastereoisomers of **76** in a 66 : 33 ratio, which were separated *via* column chromatography, deprotected and subjected to intramolecular cyclization to provide AZABIC type I **77** with 90% yield. The absolute configurations of each stereocenter were determined *via* X-ray diffraction analysis of the crystals (Scheme 19).[25]

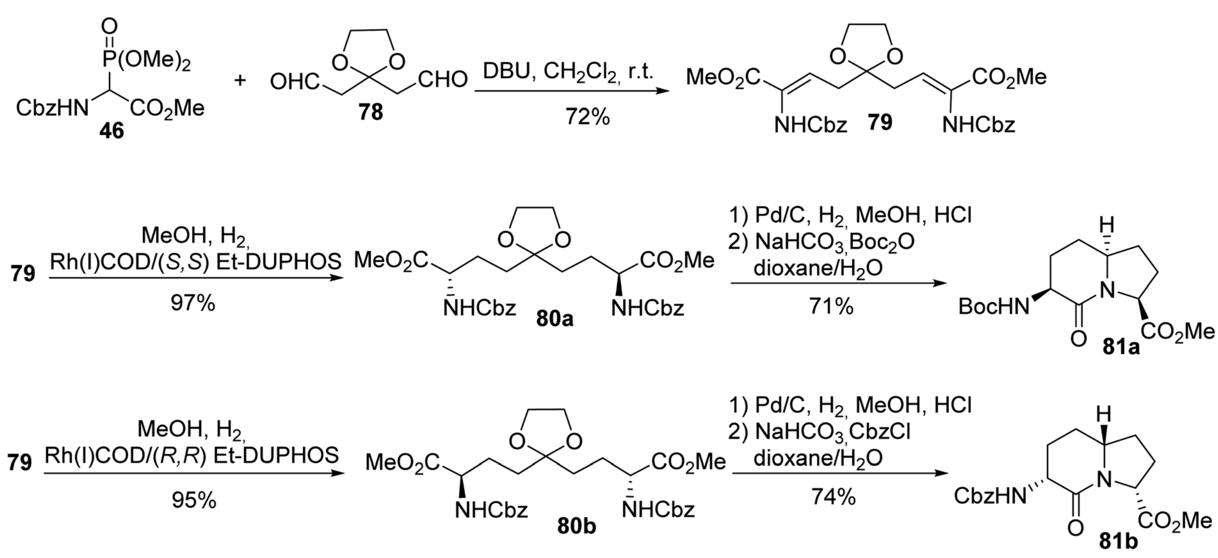
Two enantiomers of AZABIC were also prepared *via* HWE olefination using the ylide of phosphonoglycinate **46** and the dialdehyde **78**, followed by asymmetric hydrogenation of the unsaturated intermediate **79** catalyzed using a Rh(I)/Et-DUPHOS system.[26] Then, hydrogenolysis of the *N*-protected amine, removal of the acetal and intramolecular cyclization afforded both enantiomers (*S*,*S*)-**81a** and (*R*,*R*)-**81b** with 71% and 74% yields, respectively (Scheme 20).

The introduction of rigid non-natural amino acids into bioactive peptides induces conformational constraints into peptide backbones, tuning their pharmacological properties. Among those amino acids, an original synthesis of the conformationally restricted cubane alanine **84** was accomplished *via* HWE olefination under the conditions reported by Schmidt *et al.* The grafting of a cubane moiety onto the glycinate **4**, followed by the hydrogenation of the resulting α,β-dehydroamino ester **83**, the deprotection of the amine with TFA and the saponification of the methyl ester led to the cubane alanine **84** (Scheme 21).[27,28]

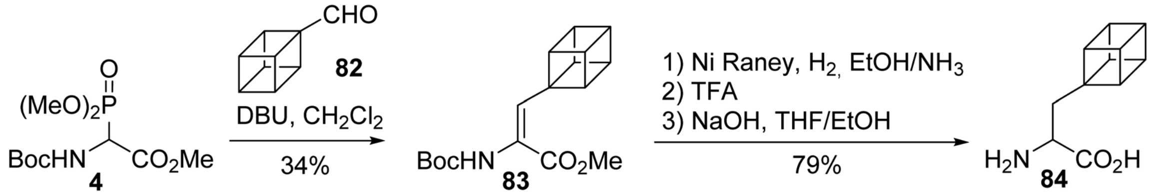
An approach for the treatment of chronic hepatitis C virus (HCV) infection consists of inhibiting the protein HCV NS5A with a small and highly potent molecule named BMS-986097.



Scheme 19 The synthesis of the constrained dipeptide mimic **77** *via* the HWE reaction using **46**.



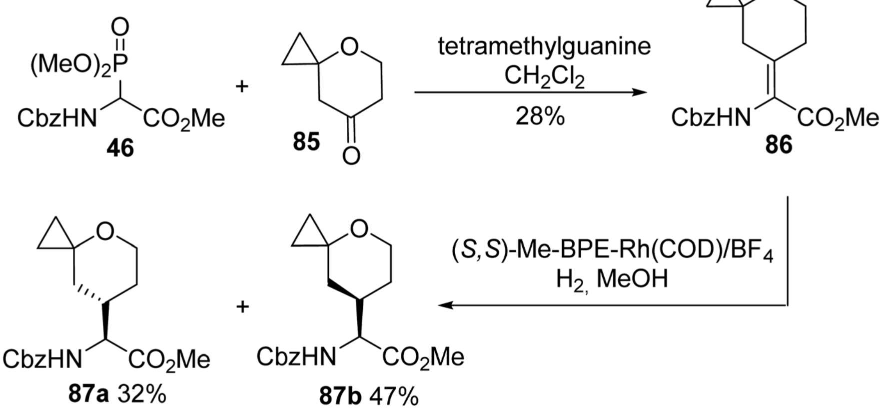
Scheme 20 The synthesis of constrained dipeptides **81** *via* the asymmetric hydrogenation of the dehydroamino acid **79** prepared using the HWE reagent **46**.



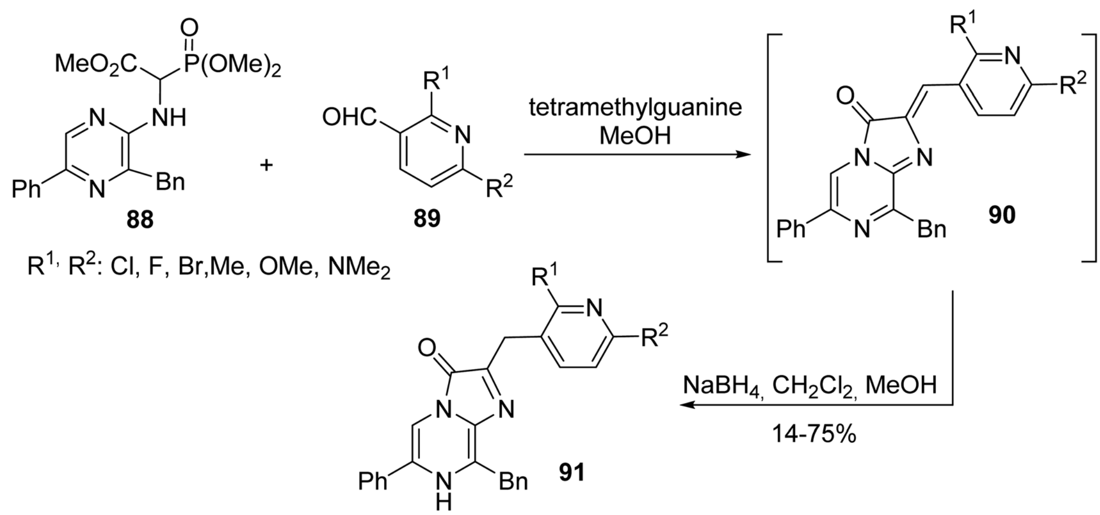
Scheme 21 The synthesis of the cubane alanine **84** *via* the hydrogenation of a dehydroamino ester prepared using the HWE reagent **4**.

This compound has been selected as a lead candidate for preclinical toxicology studies, requiring its synthesis on a large scale. In 2017, the key intermediates **87a** and **87b** were developed to access the BMS-986097 inhibitor, based on HWE olefination involving the ylide of the readily accessible α-phosphonoglycinate **46** with the cyclopropyl tetrahydropyran ketone **85**. Asymmetric hydrogenation of a *Z*/*E* mixture of **86** followed by separation provided the diastereoisomers **87a** and **87b** with 32% and 47% yields, respectively (Scheme 22).[29]

Coelenterazine is a luciferin found in many aquatic organisms and its analogues are of considerable interest for bioluminescence assays. While known methods employ drastic reaction conditions, limiting the access to such compounds, the recent work of Kirkland *et al.* has reported an efficient strategy based on a HWE reaction between α-phosphonoglycinate **88** and pyridyl aldehyde **89**, followed by the reduction of the olefin to afford the coelenterazine analogues **91** with a yield of up to 75% (Scheme 23).[30] Following this strategy, derivatives containing various heterocyclic motifs and substituted aromatic



Scheme 22 The synthesis of the tetrahydropyranoamino esters **87** *via* the asymmetric hydrogenation of the dehydro-precursor **86** prepared using the HWE reagent **46**.



Scheme 23 The synthesis of the coelenterazine analogues **91** *via* olefination using the HWE reagent **88**.

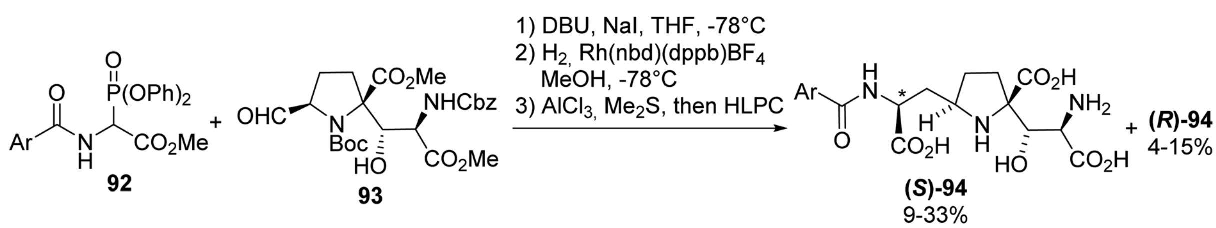
groups with diverse electronic R^2 substituents were characterized and used for the development of improved bioluminescence systems.

Among the known ionotropic glutamate receptors (iGluRs), the *N*-methyl-(D)-aspartate receptor (NMDAR) subtype is known to regulate signal transduction in the central nervous system. It has also been demonstrated that Alzheimer's and Huntington's neurodegenerative diseases are related to NMDAR dysfunction, due to their prolonged activation periods. Kaitocephalin (KCP), isolated form *Eupenicillium shearii* PF1191, was found to selectively antagonize NMDAR, displaying neuroprotective effects. Considering these results, the synthesis of the potent KCP analogues (*S*)-**94** and (*R*)-**94** was achieved to perform other structure–activity relationship studies.[31,32] The amino acid moiety was introduced *via* an olefination reaction between the α-phosphonoglycinate **92** and aldehyde **93**. Finally, reduction with a rhodium catalyst and deprotection using $AlCl_3$ and Me_2S led to the resulting mixture of diastereoisomers, which was further separated *via* chiral HPLC (Scheme 24).

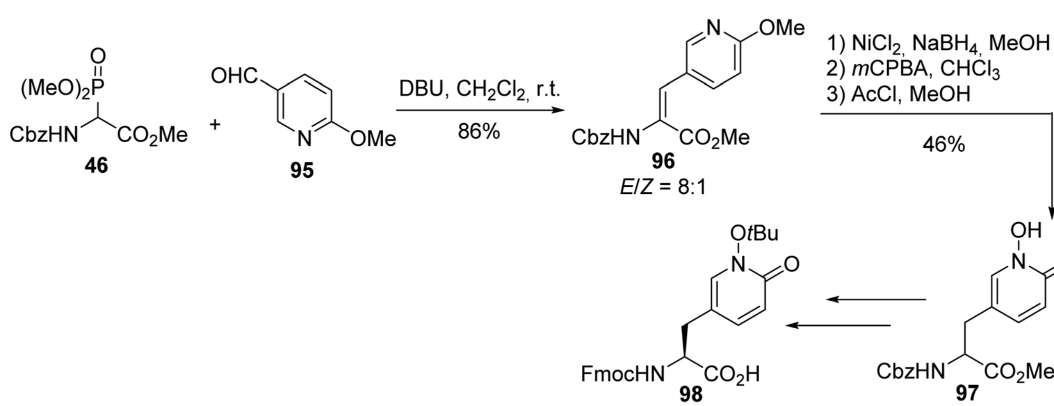
In the field of ligands designed to target receptors of the central nervous system that are related to neurodegenerative diseases, *N*-hydroxy-1,2-pyridone (Hop) amino acid, which exhibits similar metal-chelating properties to DOPA (3,4-dihydroxy phenylalanine) but without its unwanted redox activity, was readily obtained *via* a key HWE reaction between the ylide of α-phosphonoglycinate **46** and pyridyl aldehyde **95**. The C=C bond of the intermediate **96** was reduced and the nitrogen atom of pyridine was oxidized, to afford the hydroxy-1,2-pyridone derivative **97** (Scheme 25). This amino ester was further transformed into the desired enantiopure protected Fmoc-(L)-Hop(*t*Bu)-OH molecule **98** *via* enantioselective enzymatic hydrolysis and the product was used in peptide synthesis for the assembly of metallopeptides.[33]

Dysiherbaine, a natural product isolated from the Marine sponge *Dysidea herbacea*, is a selective agonist of CNS kainate subtype receptors. The enantioselective synthesis of (−)-dysiherbaine reported in 2015 by Gilbertson *et al.*[34] is based on HWE olefination involving the α-phosphonoglycinate **46** and aldehyde **99**, leading to the corresponding α,β-dehydroamino ester **100**. Then, asymmetric hydrogenation using rhodium DuPhos in ethanol provided the protected version of dysiherbaine **101**. Saponification with NaOH followed by ion exchange and reverse phase chromatography afforded (−)-dysiherbaine **102** with a quantitative yield (Scheme 26).[35]

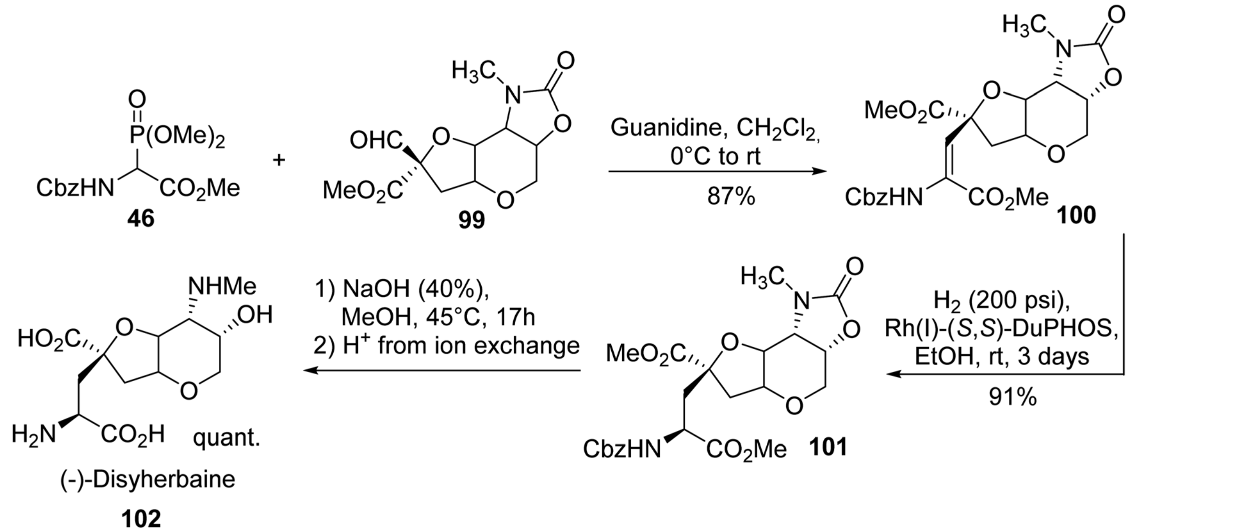
As exemplified above, the conditions developed by Schmidt *et al.* for HWE olefination provide a wide variety of α,β-dehydroamino ester derivatives efficiently, but usually, excess of organic base and low temperature are required for the deprotonation step. Alternatively, Lamaty *et al.* explored this reaction in the absence of solvent in a ball-mill for the synthesis of unsaturated amino esters. Under these conditions, α-phosphonoglycinate **4** was mixed with a series of aromatic and aliphatic aldehydes **103** in the presence of Cs_2CO_3 or K_2CO_3 as a base (Scheme 27). The corresponding α,β-dehydroamino esters **104** were obtained with good to excellent yields; however, two ketones, acetone and butanone, tested in this reaction were unreactive.[36]



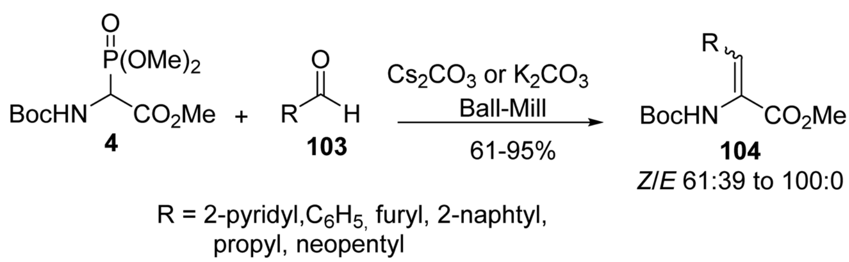
Scheme 24 The synthesis of the kaitocephalin analogue **94** *via* the asymmetric hydrogenation of a dehydro-precursor prepared using the HWE regent **92**.



Scheme 25 The synthesis of the *N*-hydroxy-1,2-pyridone amino acid **98** *via* HWE olefination with the α-phosphonoglycinate **46**.



Scheme 26 The synthesis of (−)-dysiherbaine **102** *via* the asymmetric hydrogenation of the dehydro-precursor **100** prepared using the HWE reagent **46**.



Scheme 27 The preparation of the dehydroamino acid **104** using the HWE reagent **4** *via* a ball-milling process.

3. Phosphorus linked to carbon in the β-position

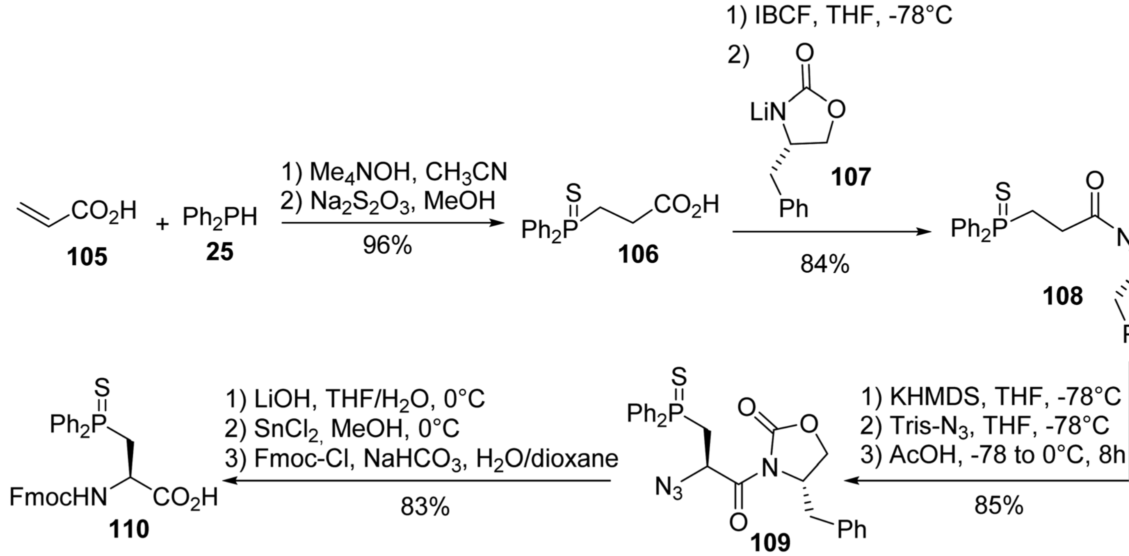
3.1. β-Phosphino and β-phospholyl α-amino acids

3.1.1. *Via* nucleophilic phosphination with secondary phosphines. The first synthesis of β-phosphino α-amino acids was reported by Gilbertson *et al.* and consists of the hydrophosphination of acrylic acid with diphenylphosphine **25** in the presence of tetramethylammonium hydroxide as a base, leading to the thiophosphine acid **106** with an almost quantitative yield. Then, it was coupled with the Evans oxazolidinone lithium salt **107** and the diastereoselective transfer of an azido group to the enolate of oxazolidinone **108** gave the corresponding azide oxazolidinone **109** with 85% yield. Cleavage of the chiral auxiliary and the reduction of the azide with tin(II) chloride afforded the amino acid, which was protected to form the *N*-Fmoc (L)-diphenylphosphinoserine sulfide **110**, which was ready for peptide synthesis (Scheme 28).[37]

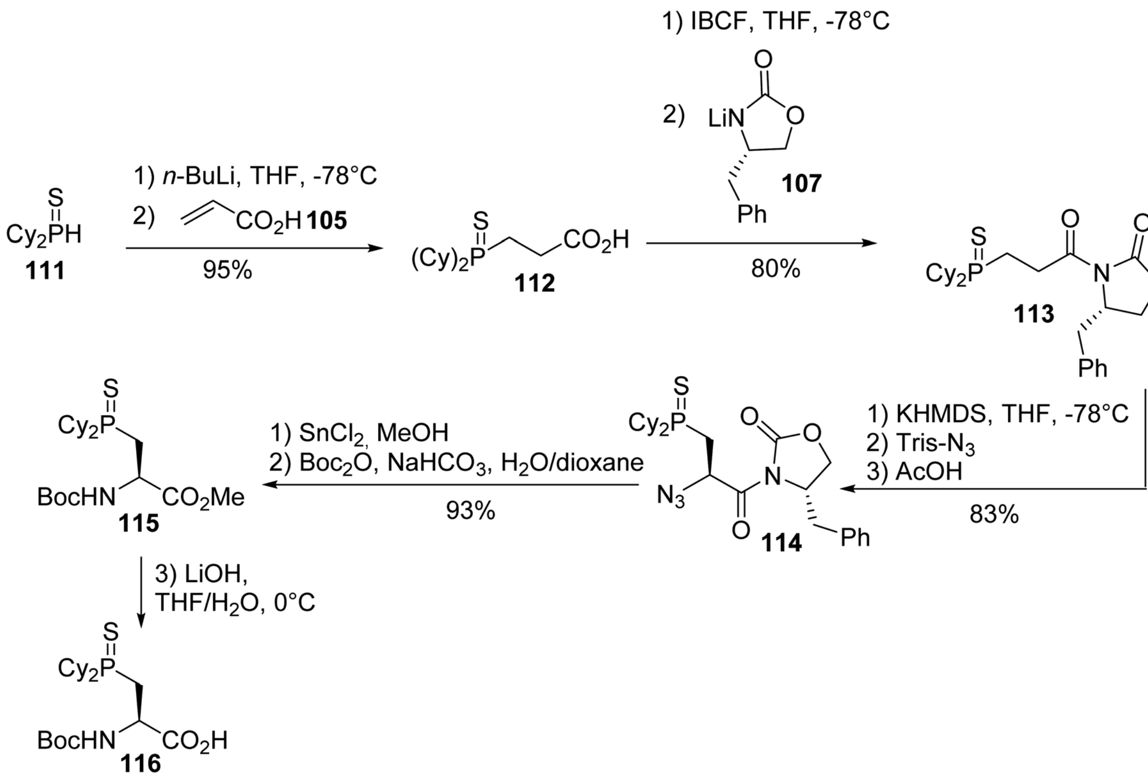
The same strategy was applied to the preparation of the dicyclohexylphosphinoserine sulfide **116**.[38] First, the 1,4-addition of the dicyclohexylphosphide sulfide **111** anion to acrylic acid **105** provided the thiophosphine acid **112** for coupling to the Evans oxazolidinone lithium salt **107**, according to the above-mentioned conditions. The treatment of compound **113** with Tris-N_3, the reduction of the azide oxazolidinone **114** and the protection of the resulting amine with *tert*-butyl anhydride afforded the corresponding α-amino ester **115** with 93% yield. Finally, hydrolysis with lithium hydroxide gave the *N*-protected (L)-amino acid **116**, a key building block in the syntheses of peptidomimetics with phosphine-containing side chains (Scheme 29).

Burgess reported another strategy based on the nucleophilic substitution of the tosyl oxazolidine **117** with the diphenylphosphide anion **118**, followed by the sulfuration of the phosphorus atom to furnish the corresponding thiophosphino oxazolidine **119** with 87% yield. Then, acidolysis cleaved the oxazolidine ring, but it also removed the *N*-Boc protection; this was reinstalled to give the alcohol **120**. Finally, the optimized conditions for the oxidation of the primary alcohol were found, using pyridinium dichromate to afford the enantiopure (D)-diphenylphosphinoserine **121** (Scheme 30).[39]

With the aim of preparing β-phosphinoamino acids on a larger scale compared to the multistage synthesis involving a chiral auxiliary reported by Gilbertson and Burgess, the nucleophilic substitution of the readily accessible (L)-iodoalanine **122**, using a phosphide anion generated *in situ* under solid–liquid phase transfer conditions, was performed.



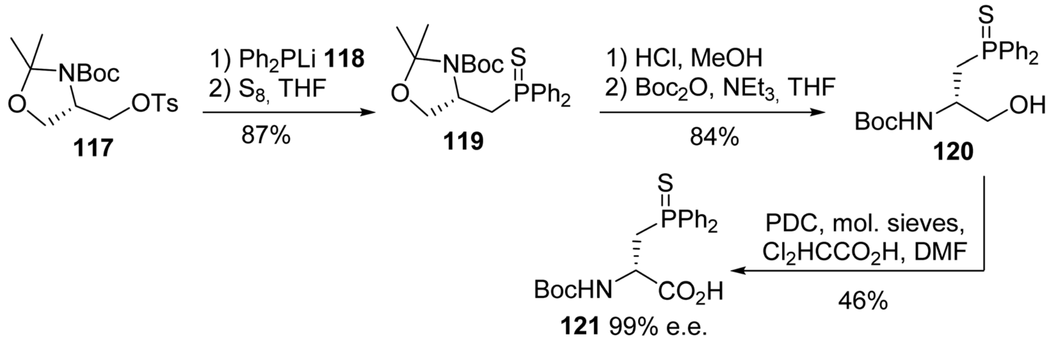
Scheme 28 The diastereoselective synthesis of (L)-diphenylphosphinoserine sulfide **110** using the Evans oxazolidinone **107**.



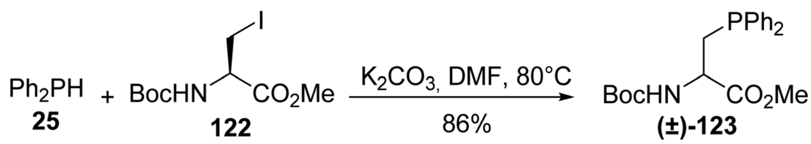
Scheme 29 The diastereoselective synthesis of (L)-dicyclohexylphosphinoserine sulfide **116** using the Evans oxazolidinone **107**.

Unfortunately, although the Ph_2PH/K_2CO_3 heterogeneous system provided phosphide anions only at a low concentration, extensive racemization at the α-carbon atom of the starting material occurred and the phosphinoamino ester (±)-**123** was observed (Scheme 31).[40]

Based on these results, Le Floch *et al.* examined this approach for the nucleophilic substitution of iodoalanine using phospholide species. While no reaction was observed with the lithium 2,5-diphenylphospholide anion, probably due to the stabilization of negative charge within the ring, satisfactory results were obtained using the more nucleophilic 3,4-dimethylphospholide anion **124′**. This anion was generated *via* the cleavage of the P–phenyl bond of the phenylphosphole **124** in the presence of lithium wires. After the removal of the metal excess, iodoalanine **122** was added to the anion and the tertiary phosphole was trapped with sulfur, leading to the



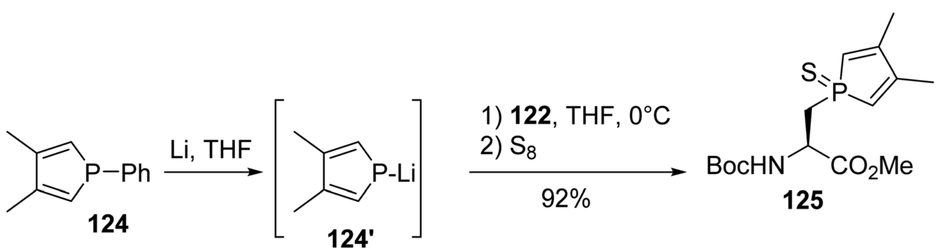
Scheme 30 The diastereoselective synthesis of the (D)-diphenylphosphinoserine **121** from the oxazolidine **117**.



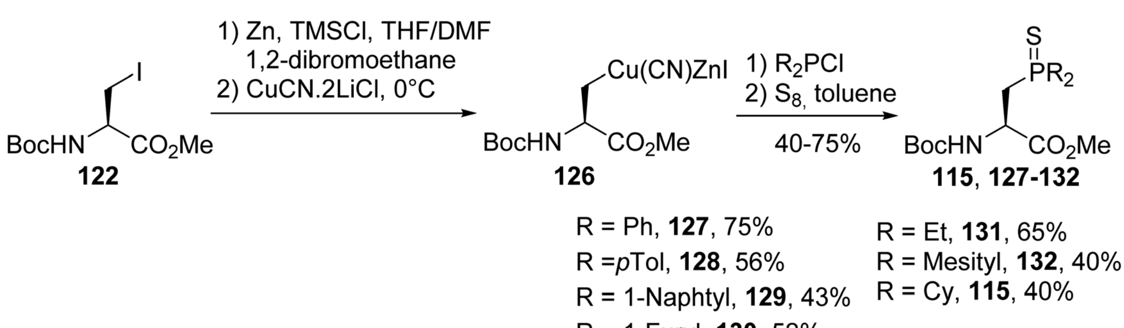
Scheme 31 The synthesis of the β-phosphinoamino ester **123** from sec-phosphine **25** under solid–liquid phase transfer conditions.

corresponding 3,4-dimethylphospholyl sulfide amino ester **125** with 92% yield (Scheme 32).[41] However, under these experimental conditions, where iodoalanine was in the presence of phospholide anion excess, racemization at the α-carbon position couldn't be excluded.

3.1.2. *Via* coupling a nucleophilic zinc/copper amino ester with chlorophosphine. In addition to methodologies based on using chiral oxazolidinones to prepare enantiopure β-phosphino α-amino acids, a more direct route consists in coupling a nucleophilic zinc/copper reagent derived from iodoalanine **122** with electrophilic chlorophosphine. This reaction proceeds with a range of aromatic and aliphatic chlorophosphines, except for when using the less reactive chloro-di-*tert*-butylphosphine. The resulting tertiary phosphines were derivatized with sulfur in order to avoid their oxidation. The corresponding enantiopure β-phosphinoamino esters were isolated with 52 to 75% yields, depending on the electrophilicity of the chlorophosphine (Scheme 33).[42,43]



Scheme 32 The stereoselective synthesis of the phospholyl amino acid **125** *via* P–C bond formation.

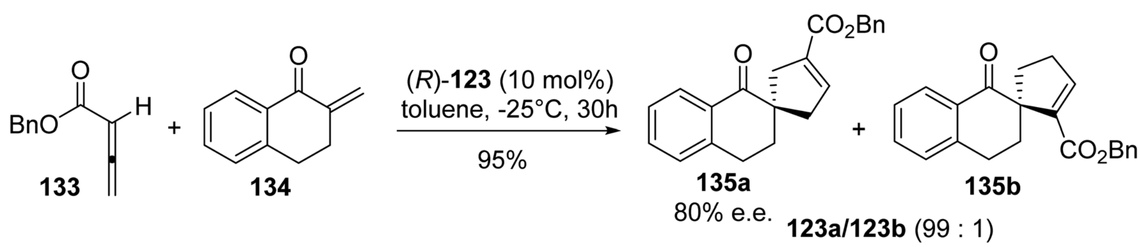


Scheme 33 The stereoselective synthesis of β-phosphinoamino esters *via* P–C coupling using the zinc/copper reagent **126**.

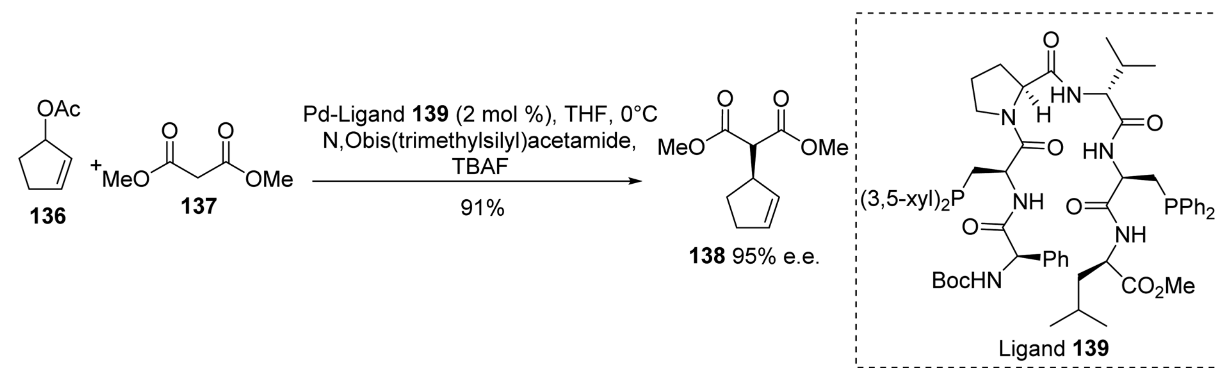
As phosphines are widely used either as ligands or as catalysts to promote organic reactions, the development of β-phosphino α-amino acids paves the way to a new class of highly selective transition-metal catalysts and organocatalysts. In this context, Miller *et al.* examined the [3 + 2]-cycloaddition of the allene **133** and enone **134** catalyzed using (*R*)-diphenylphosphinylalanine **123**. Indeed, this reaction is of particular interest for generating regioselectively in the conjugate-addition product or the cycloadduct **135a–b** *via* switching between amine and phosphine catalysts. Under optimized conditions, the cycloaddition of the allenic ester **133** and enone **134** was achieved with high regio- and enantio-selectivity using the catalyst (*R*)-**123** (Scheme 34).[44] The formation of the major regioisomer **135a** was rationalized using a transition state in which the enone approaches the zwitterion, which results from the addition of phosphine to the allene, *via* the π-face opposite to one of the phenyl rings of the catalyst.

A library of peptide-based bisphosphine ligands, which are expected to form β-turn secondary structures, was designed and evaluated for palladium-catalyzed reactions between cyclic allyl acetates and dimethyl malonate (Scheme 35). Ligands bearing modified amino acids at each end of the turn were first evaluated, then phosphines with various substituents on the aromatic moiety were introduced into the most promising sequences. The reactivity and selectivity of the ligands were determined either in solution or when immobilized on a solid support. As an example, the addition of 3-acetoxycyclopentene **136** to dimethyl malonate **137** catalyzed by ligand **139** was achieved with 90% yield and 85% enantiomeric excess, which is a comparable result to when the catalyst was immobilized on a resin support (91% yield and 86% e.e.). When this reaction was performed at 0 °C in THF, the alkylated malonate **138** was obtained with excellent enantioselectivity of 95%.[45–48]

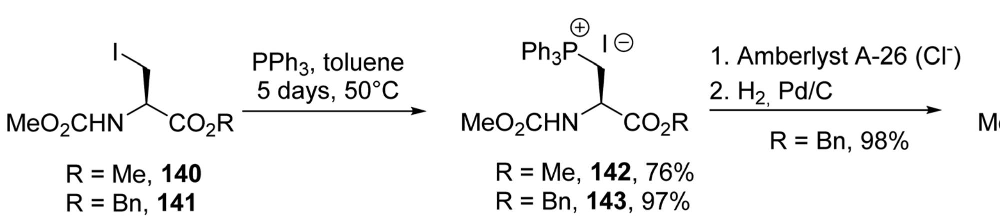
3.1.3. *Via* the quaternization of triphenylphosphine with β-halogenoalanines. Phosphonium salts derived from amino acids are of particular interest as Wittig reagents for preparing β,γ-unsaturated amino acids with a variety of substituents on the side chain. The pioneering work of Itaya *et al.* consists of the quaternization of triphenylphosphine with the iodoalanines **140** and **141** in toluene at 50 °C for several days to afford the corresponding triphenylphosphonium iodide amino esters **142** and **143** with good yields of 76% and 97%, respectively (Scheme 36).[49] Unfortunately, attempts to release the free carboxylic acid *via* the treatment of **142** with an aqueous



Scheme 34 The stereoselective [3 + 2]-cycloaddition reaction promoted by the diphenylphosphinylalanine (*R*)-**123**.



Scheme 35 Asymmetric Pd-catalyzed allylic alkylation using the bisphosphine peptide **139** as a chiral ligand.



Scheme 36 The synthesis of the phosphonium amino acid derivative **144** from β-iodoalanine.

solution of sodium hydroxide in methanol resulted in β-elimination. In addition, compound **143** can be converted into a chloride using an ion exchange resin to perform hydrogenolysis over Pd/C. In this case, the corresponding phosphonium amino acid **144** was obtained almost quantitatively.

Its utility as an equivalent of the nucleophilic alanine synthon was exemplified by Wittig olefination reactions that led to β,γ-unsaturated α-amino acid derivatives. This method was applied to the synthesis of (*S*)-wybutine, a fluorescent base isolated from yeast phenylalanine transfer ribonucleic acids. It was necessary to use a phosphonium salt bearing the free carboxylic acid because, under basic conditions, the resulting carboxylate ylide protects against racemization. Furthermore, when the phosphonium amino ester **142** was used, β-elimination was observed in preference to the Wittig reaction. Under optimized conditions, the Wittig reaction between the phosphonium chloride amino acid **144** and the aldehyde derived from the modified nucleic base **145**, followed by methylation, afforded the (*E*)-isomer of the β,γ-unsaturated amino ester **146** with 16% yield (Scheme 37). Finally, the C=C bond and imidazole ring were hydrogenated to provide the corresponding wyosine α-amino ester **147**.[50–53]

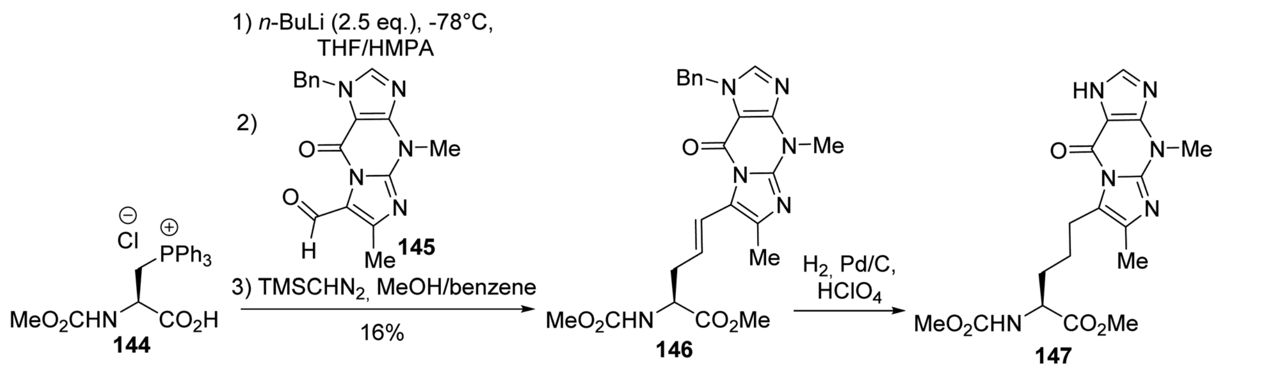
Subsequently, Jugé *et al.* reported a shorter synthesis protocol for the *N*-protected phosphonium salt amino acids **152** and **153**. *N*-Benzoyl-β-bromoalanine **150** or *N*-benzoyl-β-iodoalanine **151**, obtained from the ring-opening of oxazoline **149**, was refluxed with triphenylphosphine in chloroform (Scheme 38). The appeal of this strategy arises from the mild conditions used for the quaternization of triphenylphosphine with the β-halogeno amino acid. The desired phosphonium salts were obtained without side products or racemization, as demonstrated from ^{31}P NMR analysis with TRISPHAT as the chiral counter-anion and by comparison with a racemic sample.[54] Unfortunately, their use in Wittig reactions with aldehydes resulted in poor reactivity and the unsaturated amino acid was obtained as a racemic mixture.

3.2. β-Phosphono α-amino acids and peptides

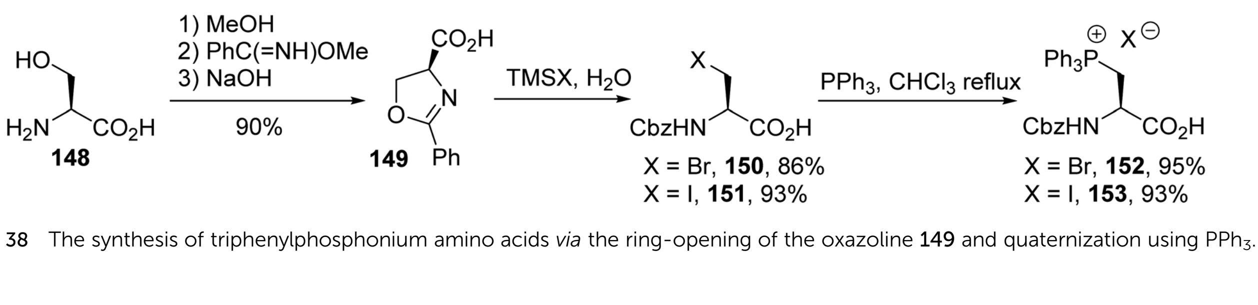
3.2.1. *Via* the reductive amination of phosphonopyruvate. The pioneering work of Savignac *et al.* in 1980 involved the synthesis of β-phosphono α-amino esters *via* the reductive amination of phosphonopyruvates **154** in the presence of $NaBH_3CN$ (Scheme 39). The substituents (OR) carried by the phosphorus atom have no influence on this reaction; however, the replacement of oxygen (X) with sulfur leads to lower yields, probably due to steric hindrance. Finally, the corresponding phosphonic α-amino acids **156a–e** were obtained after hydrolysis with hydrochloric acid (6 N) in satisfactory yields.[55]

3.2.2. *Via* the alkylation of a nickel(II) complex of a glycine Schiff base. Among the chiral auxiliaries commonly involved in the asymmetric synthesis of unnatural α-amino acids, a nickel(II) complex of a glycine Schiff base was used for the preparation of enantiopure β-phosphono α-amino acids.[56] When the complex **157** was deprotonated with potassium hydroxide, the resulting enolate reacted successfully with iodomethyl diisopropylphosphite **158** to afford the corresponding alkylated Schiff base as a single diastereoisomer. After hydrolysis, the β-phosphono α-amino acid (L)-**159** was obtained with 30% yield and excellent enantiomeric purity of 99% (Scheme 40).

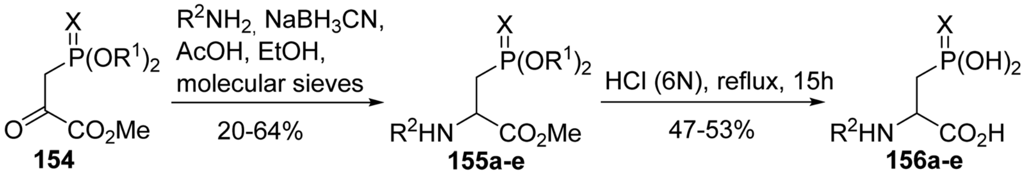
3.2.3. *Via* the reaction of trimethyl phosphite with serine β-lactone. Vederas *et al.* reported the addition of various nucleophiles to serine β-lactone to give products with the corresponding stereochemistry and this strategy was revisited by Smith *et al.* to prepare (D)- and (L)-AP3 enantiomers in an efficient way.[57] The nucleophilic addition of trimethyl phosphite to



Scheme 37 A Wittig reaction using the β-triphenylphosphonium amino acid **144**.

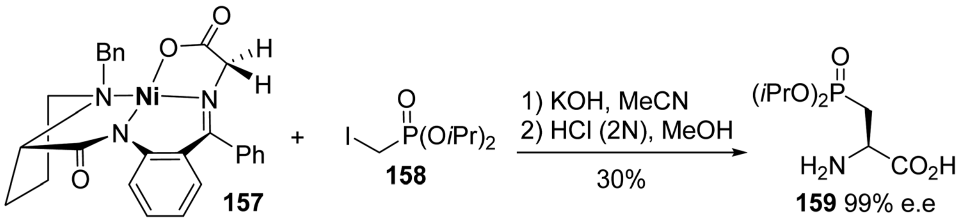


Scheme 38 The synthesis of triphenylphosphonium amino acids *via* the ring-opening of the oxazoline **149** and quaternization using PPh_3.



156	R^1	R^2	X	Yield (%)
a	Et	H	O	54
b	*i*Pr	H	O	40
c	Et	Me	O	64
d	Me	H	S	21
e	Et	H	S	20

Scheme 39 The synthesis of the β-phosphono α-amino esters **156a–e** from the phosphonopyruvates **154**.



Scheme 40 The synthesis of the β-phosphono α-amino acid (L)-**159** *via* the asymmetric alkylation of the Schiff base complex **157**.

N-Boc (L)-serine β-lactone **160** proceeded successfully upon heating at 70 °C to provide the (*R*)-β-phosphono α-amino ester **161** with 80% yield (Scheme 41). The (*S*)-enantiomer was also obtained following the same procedure, starting from (D)-serine β-lactone. The enantiomeric purity was confirmed *via* ^{1}H NMR studies with the chiral reagent (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol (TAE). Acidic hydrolysis, followed by treatment with propylene oxide, led to the (L)-AP3 **1** zwitterion.

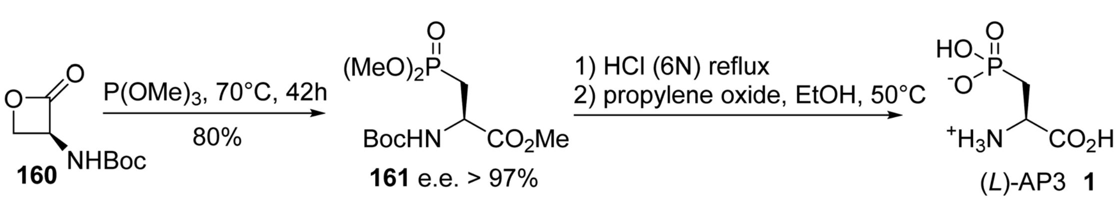
Lecouvey *et al.* reported a library of tripeptides combining both amino catalysis and phosphonic acid activation to promote the diastereo- and enantio-selective conjugate addition of aldehydes to nitroalkenes.[58,59] Opening the lactone (*R*)- or (*S*)-**160** with trimethyl phosphite led to both enantiomers of the resulting phosphono α-amino ester. Deprotection with TFA afforded the derivative pAla-OMe **163** with a free amine ready for peptide coupling. All diastereoisomers of the tripeptide H-Pro-Pro-pAla-OMe **166** were synthesized, varying the absolute configuration of the three stereogenic centers and the side chain length of the amino acid bearing the phosphonic acid moiety (Scheme 42). The influence of the catalyst structure on Michael addition between aldehydes and aromatic nitroalkenes was evaluated and the specific H-(*R*)-Pro-(*S*)-Pro-(*R*)-pAla-OMe sequence was crucial both for good selectivity and for fast intramolecular reactions.[60]

The Michael addition of propanal **167** to nitrostyrene **168** was catalyzed by the tripeptide H-(*R*)-Pro-(*S*)-Pro-(*R*)-pAla-OMe **166** to give the *syn* adduct **169** (Scheme 43).[60] This was isolated with a d.r. of up to 90 : 10 and opposite selectivity to that observed by Wennemers *et al.* using a H-(*R*)-Pro-(*S*)-Pro-(*R*)-Glu-NH_2 catalyst.

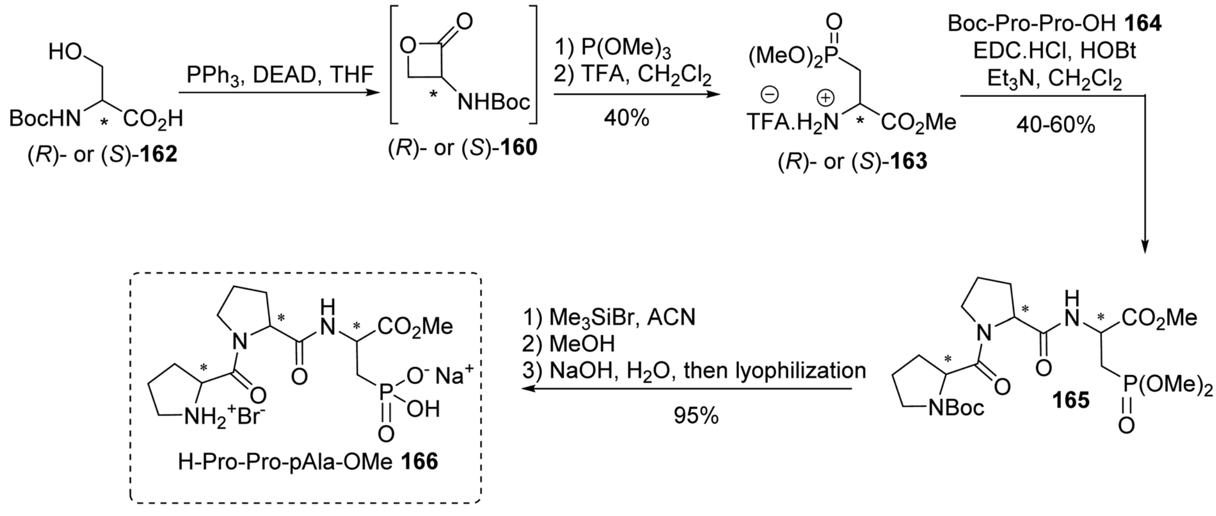
4. Phosphorus linked to carbon in the γ-position

4.1. γ-Phosphino and γ-phospholyl α-amino acids

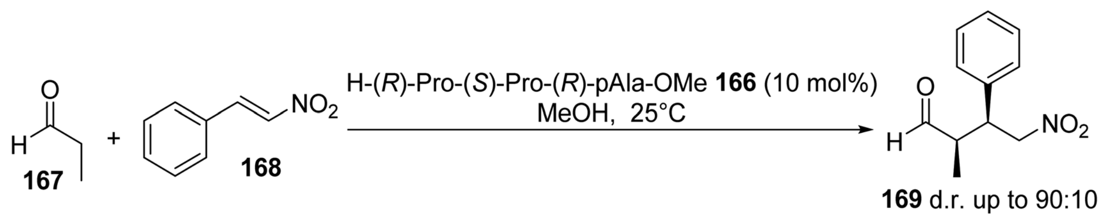
4.1.1. *Via* the quaternization of triphenylphosphine with γ-iodoamino esters. The synthesis procedures for β-phosphonium salt α-amino acids reported above involve demanding strategies. In addition, their use in Wittig reactions results in racemic mixtures of unsaturated amino acids with low yields. Considering these limitations, another class of α-amino acid Wittig reagent **172**, having both free carboxylic functionality and a phosphonium moiety in the γ-position on the lateral chain, was reported with the objective of avoiding racemization or eliminating the triphenylphosphine during Wittig



Scheme 41 The stereoselective synthesis of (L)-2-amino-3-phosphonopropionic acid **1** from the serine β-lactone **160**.



Scheme 42 The synthesis of the phosphono-tripeptide 166 from the 2-amino-3-phosphonopropionic acid 163.

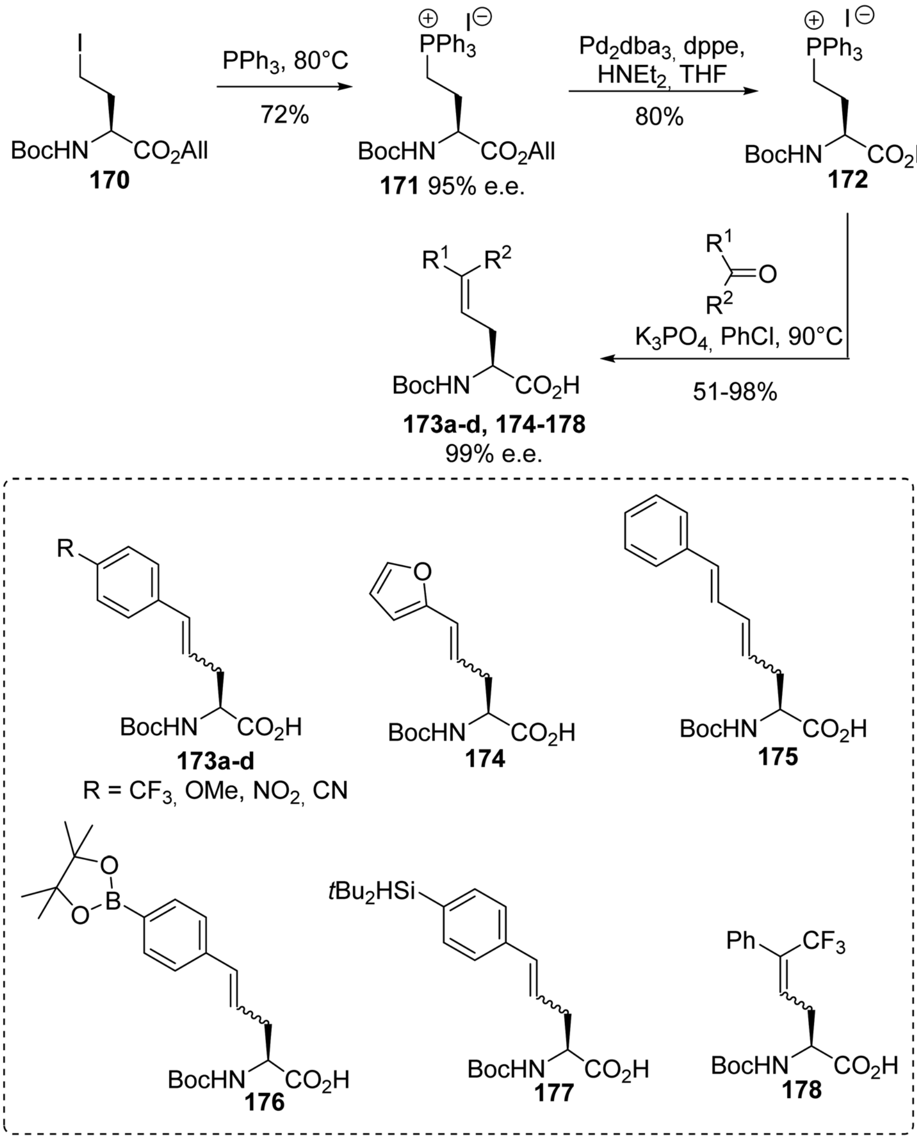


Scheme 43 Asymmetric Michael addition promoted by the tripeptide 166.

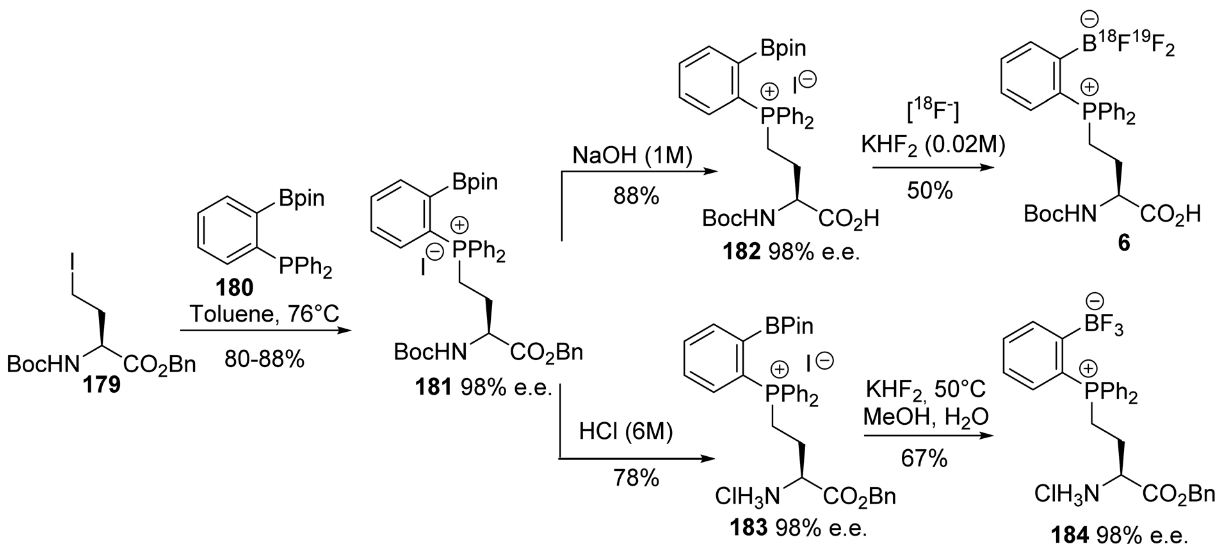
olefination. The stereoselective synthesis of the γ-phosphonium salt amino acid **172** was achieved with 58% overall yield *via* the quaternization of triphenylphosphine with the γ-iodoamino ester **170** at 80 °C without solvent, followed by deallylation with Pd_2dba_3. The enantiomeric excess was checked *via* ^{31}P NMR studies with BINPHAT as the chiral counter-anion, proving that no racemization occurred during the reaction.[61] Wittig reactions with aromatic or aliphatic aldehydes were performed under solid–liquid phase-transfer conditions in chlorobenzene and in the presence of K_3PO_4 as a weak base, affording the unsaturated amino acids **173a–d** and **174–178** as *Z*/*E* mixtures from 30 : 70 to 10 : 90, without racemization (Scheme 44). Under these conditions, the inorganic base deprotonated the carboxylic acid functionality and methylene substituent to form the ylide. In chlorobenzene, as a non-dissociative solvent, the phosphonium salt **172** favored the formation of an ion pair with the carboxylate moiety, enabling better solubility and reactivity of the ylide with the aldehyde. The amino acids **176** and **177**, bearing aryl boronate and silylated moieties on the side chains, were also obtained under these conditions and they are potentially useful for further functionalization or for ^{18}F-labeling (Scheme 44).[62,63]

Ortho-boronato-phenylphosphonium amino acids were also prepared according to this strategy *via* the quaternization of *ortho*-boronato-diphenylphosphine **180** with the γ-iodoamino ester **179**. Then, saponification led to compound **182** with a free carboxylic acid and the deprotection of the amine was performed *via* acidolysis into the corresponding ammonium salt **183** (Scheme 45). The feasibility of peptide coupling was demonstrated, as well as transformation into trifluoroborates. Finally, carrying out radiolabeling to obtain the [^{18}F]-trifluoroborato-phenylphosphonium α-amino acid **6** demonstrated the utility of such compounds for peptide labeling.[64]

4.1.2. *Via* the substitution of γ-iodoamino esters with a phosphide anion. A glycopeptide CSF114 (Glc) modified with an α-amino acid bearing a ferrocenyl thiophosphine substituent on its side chain was developed for the detection of autoantibodies in the serum of patients suffering from multiple sclerosis disease (MSD).[65] The ferrocenyl group of this marker allowed for the electrochemical detection of autoantibodies at potentials compatible with the biological medium and the thiophosphine substituent was attached to a gold surface for the development of a sensor. The diastereoselective synthesis of the amino acid marker **189** relies on the condensation of the enantio-enriched secondary ferrocenylphosphine borane **185** (86% e.e.), which was generated according to (−)-ephedrine methodology, with the *N*,*N*-diprotected γ-iodoamino ester **186**. The double protection of the amine with *tert*-butyloxycarbonyl (Boc) groups was necessary to avoid secondary reactions under basic conditions. The resulting phosphine borane amino ester was subjected to deprotection with DABCO and sulfurization to give the corresponding thiophosphine derivative **188** with 80% yield. Finally, the removal of one Boc-protecting group and the saponification of the benzyl ester led to the ferrocenyl



Scheme 44 The γ-phosphonium α-amino acid Wittig reagent 172: its synthesis and application to the preparation of γ,δ-dehydroamino acids.



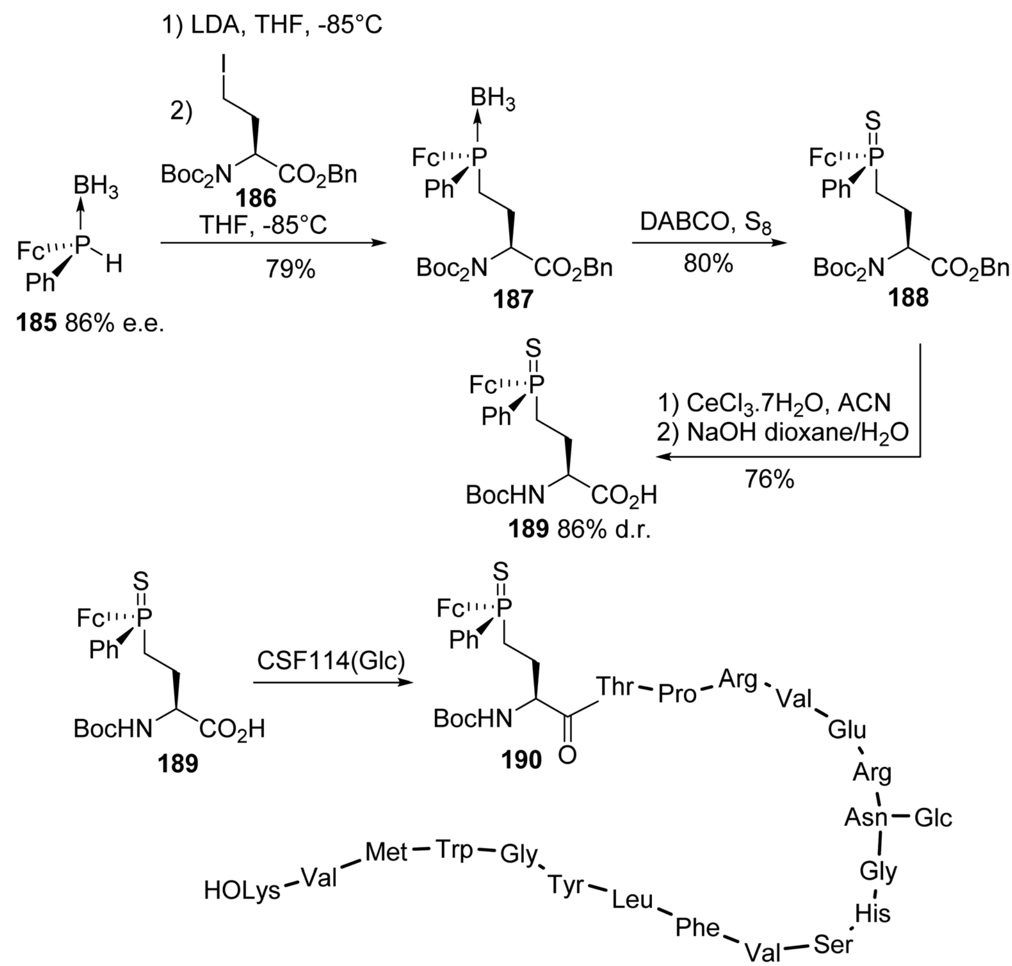
Scheme 45 The *ortho*-borato-phenylphosphonium α-amino acid 181: its synthesis and application to ^{18}F-radiolabeling.

thiophosphinoamino acid **189**, which was ready for peptide coupling with 76% yield and 86% diastereomeric purity (Scheme 46). After electrochemical grafting of the labeled antigen (FcPS-CSF114 (Glc)) **190** and incubation with autoantibodies, antigen/antibody recognition was possible *via* electrochemistry at very low concentrations, comparable to ELISA testing.

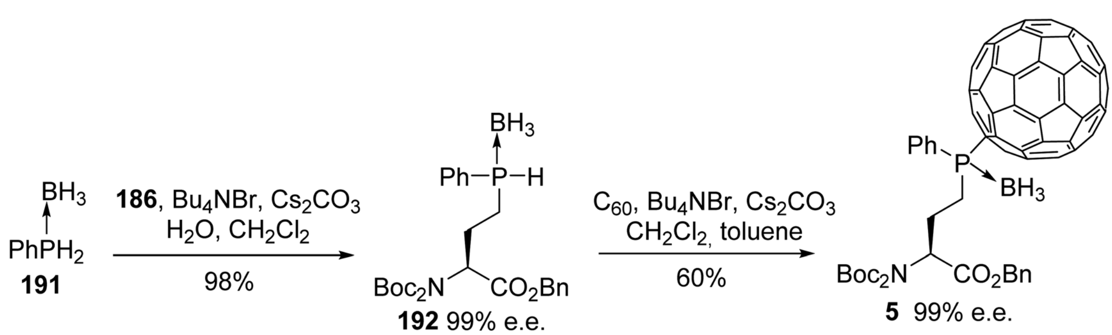
The examples reported above demonstrate the interest in phosphorus and boron chemistry for creating customized or labeled peptides. In the following examples, phosphine boranes are used as the precursors for grafting [60]fullerene to an amino acid side chain.[66] Fullerene derivatives have been studied for their biological activities and for medical diagnosis, as they are without known toxicity. Phenylphosphine borane **191** was linked to the side chain of the γ-iodoamino ester **186** under solid–liquid phase transfer conditions, leading to the corresponding phosphine borane amino ester **192** with 98% yield. The resulting *sec*-phosphine borane was subsequently grafted to [60]fullerene under the same conditions to give the [60]fullerene γ-phosphine borane α-amino ester **5** as an epimeric mixture (1 : 1), due to the existence of a P-chirogenic center without racemization (Scheme 47). The reversibility of the hydrophosphination was demonstrated *via* cyclic voltammetry, demonstrating the ability to immobilize and release amino acids or peptides on carbon nanomaterials.

For our part, we recently reported the first synthesis of phospholyl(borane) α-amino acids, as a new class of fluorescent amino acids, *via* the nucleophilic substitution of β- or γ-iodoamino esters with phospholide anions.[67] The phospholide anion **193′** was generated *via* the deprotonation of dibenzophosphole or *via* the cleavage of the P–phenyl bond starting from the phenylphosphole in the presence of potassium. After the removal of the excess metal, the anion was added to a solution of γ-iodoamino ester **170** and the resulting tertiary phospholyl amino ester was complexed *in situ* with BH_3.DMS (Scheme 48).[67] Under these conditions, the phospholyl(borane) (L)-α-amino ester derivatives **194–197** were isolated as stable compounds, which were easy to store and handle for further use.

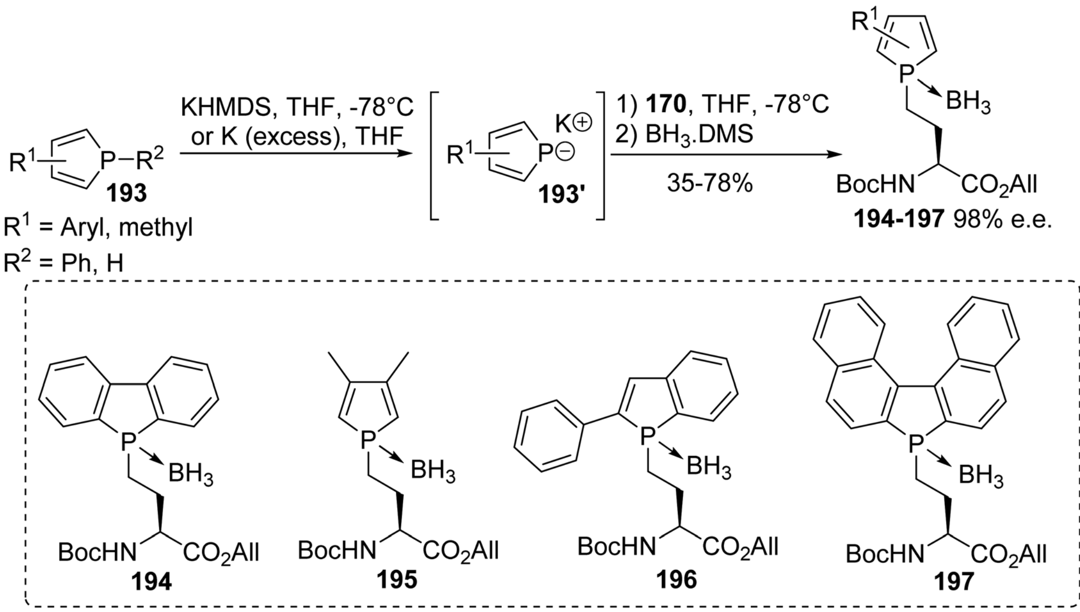
The phospholyl(borane) α-amino ester **194** was successfully transformed *via* decomplexation, oxidation, sulfuration, complexation with gold and quaternization, respectively, to provide the derivatives **198–202** with tunable fluorescence emission.[67] *Via* a tandem reaction involving decomplexation



Scheme 46 The ferrocenyl thiophosphinoamino acid **189**: its diastereoselective synthesis *via* P–C bond formation and application to the electrochemical detection of MSD autoantibodies.



Scheme 47 Grafting α-amino acids to [60]fullerene using phosphine borane as a linker.



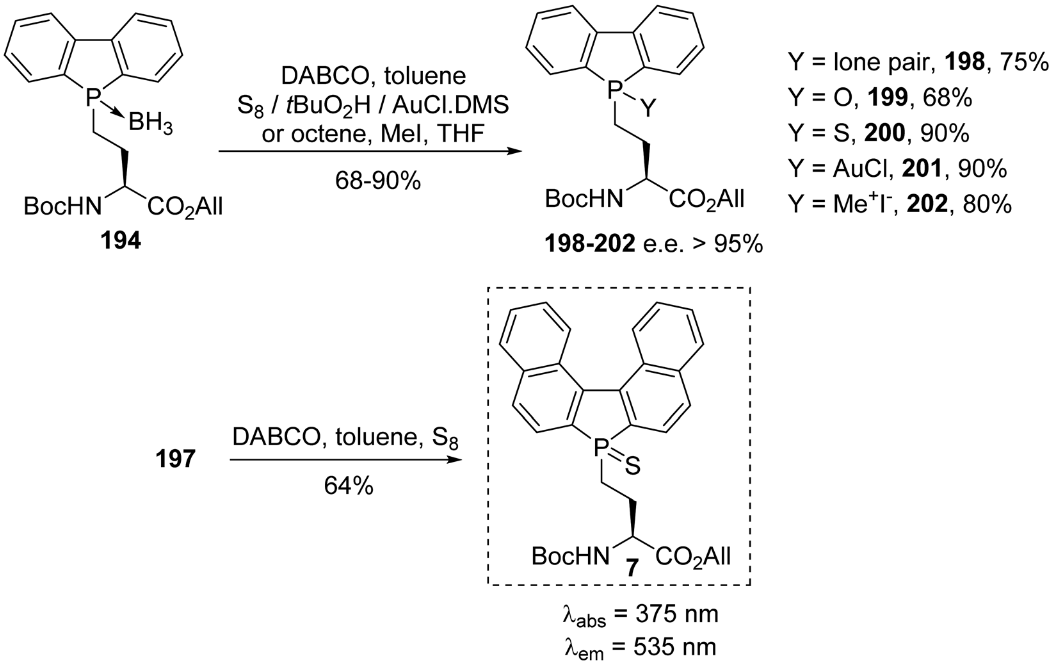
Scheme 48 The stereoselective synthesis of the phospholyl(borane) (L)-α-amino esters **194–197** *via* P–C bond formation.

and sulfuration, the binaphtyl sulfur amino ester **7** was obtained with 64% yield. It exhibits remarkable fluorescence emission in the green range at 535 nm, with a large Stokes shift of 160 nm. Such phospholyl amino acids were also selectively deprotected for carrying out peptide C- and N-coupling, either in solution or on a solid support. These molecules constitute a promising new class of probe for the fluorescence labeling of peptides (Scheme 49).[67]

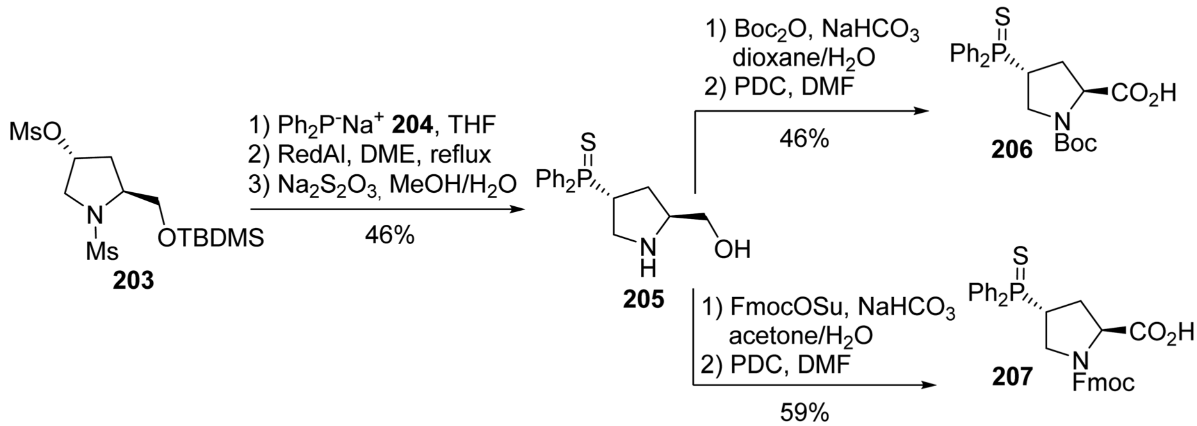
The incorporation of phosphino α-amino acids that can coordinate transition metals, such as rhodium, ruthenium, palladium and platinum, at specific positions into peptides provides a method to stabilize their secondary structures to control their reactivity. In this context, phosphine-containing proline derivatives were developed to coordinate with rhodium and ruthenium into β-turn structural motifs. This synthesis is based on the substitution of γ-mesylate prolinol **203** using the diphenylphosphide anion **204**, followed by the sulfuration of the phosphorus center. Then, the amine of the resulting phosphine sulfide prolinol was protected and the alcohol was oxidized, leading to the *N*-Boc- and *N*-Fmoc-γ-thiophosphinoprolines **206** and **207**, with 21% and 27% overall yields, respectively (Scheme 50). These phosphinoprolines and a diphenylphosphine alanine derivative were introduced at the *i* and *i* + 2 positions, forming a tetramer with a type II β-turn conformation in which both phosphines are on the same face to bind with transition metals.[68]

4.2. γ-Phosphinate and γ-phosphono α-amino acids

4.2.1. *Via* a Michaelis–Arbuzov reaction with phosphite and γ-bromoamino esters. (L)-Phosphinothricin is a natural phosphinic acid analogue of (L)-glutamate, which is isolated from two different *Streptomyces* species; it is shown to have antibiotic and herbicidal properties and to be an inhibitor of glutamine synthetase, blocking the incorporation of ammonia into amino acids and pyrimidines. Various γ-phosphonic α-amino acid analogues, (L)-AP4, were also developed for structure–activity relationship studies. Racemic (D,L)-phosphinotricin and one analogue were prepared *via* a Michaelis–Arbuzov reaction between diethyl methylphosphonite or triethyl phosphite and the γ-bromoamino ester **208**.[69] After heating in



Scheme 49 Chemical transformations at the P-center of the phospholyl(borane) amino acid **194**.



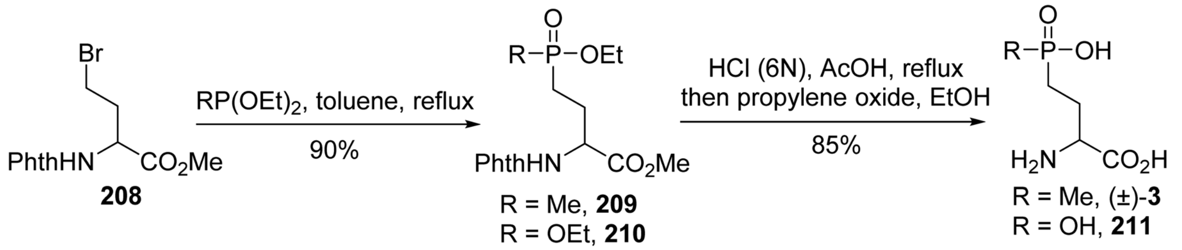
Scheme 50 The stereoselective synthesis of the diphenylphosphinoprolines **206** and **207**.

toluene, the resulting phosphonate was treated with HCl (6 N) to give the corresponding (D,L)-phosphinotricin (±)-**3** or its free phosphonic α-amino acid **211** with 85% yield (Scheme 51).

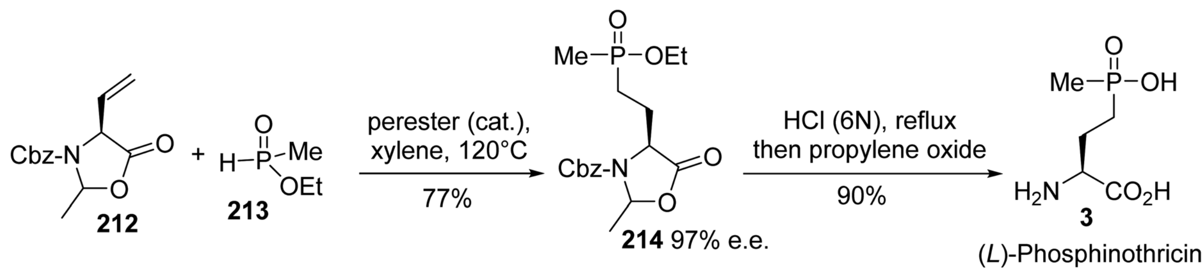
4.2.2. *Via* the hydrophosphination of vinyl oxazolidinone. Later, the enantiopure (L)-phosphinotricin was synthesized based on the regioselective hydrophosphination of the vinyl oxazolidinone **212** with methyl phosphonate **213**, in the presence of a perester catalyst.[70] The intermediate phosphonate oxazolidinone **214** was isolated with 77% yield. Acidic treatment led to the ammonium chloride, which was neutralized *via* the addition of propylene oxide to obtain the enantiopure (L)-phosphinothricin **3** (Scheme 52).

4.2.3. *Via* the palladium catalyzed C(sp^3)–H alkylation of aminoquinoline derivatives. In 2017, an efficient procedure for the construction of chiral γ-phosphono-α-amino acids *via* the Pd catalyzed C(sp^3)–H alkylation of alanine aminoquinoline derivatives was developed.[71] Coupling between the methylene C(sp^3)–H bond of the substrate **215** and phosphonated alkyl iodides led to the alkylated products **218** and **219** (Scheme 53). Then, the auxiliary group was removed *via* treatment with Boc_2O and DMAP and LiOH and H_2O_2 in two steps. Finally, after the removal of the phthaloyl and ester groups in the presence of HCl (6 N), (L)-phosphinothricin **3** and (L)-AP4 were obtained with 61 and 72% yields, respectively (Scheme 53).

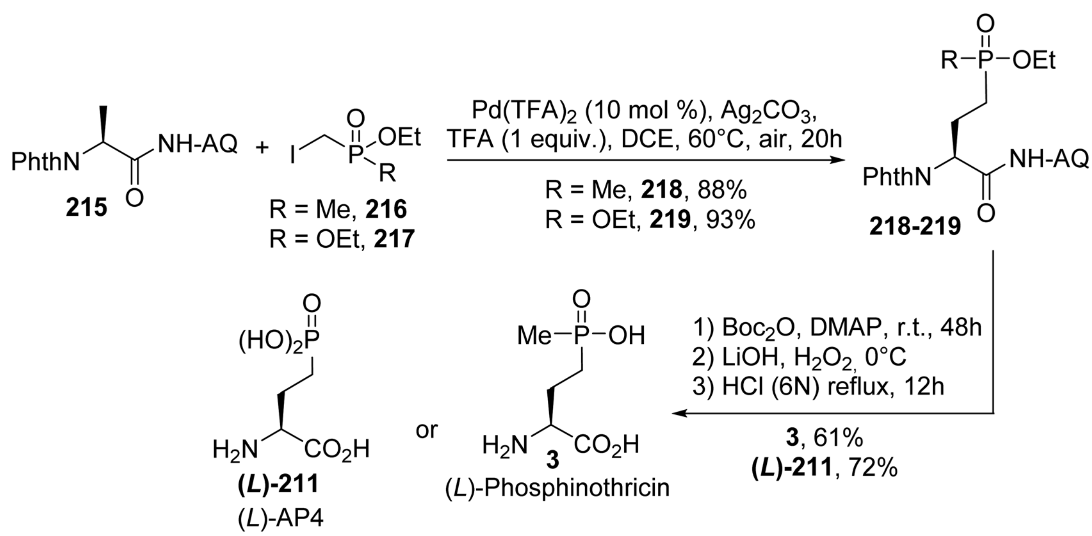
4.2.4. Diastereoselective synthesis *via* the Schöllkopf method. Another strategy for the asymmetric synthesis of γ-phosphono α-amino esters relies on the use of Schöllkopf bis-lactim ether as a chiral auxiliary.[72] After deprotonation by *n*-BuLi, the conjugate addition of the corresponding lithium salt to the vinyl phosphonate **222** leads exclusively to the



Scheme 51 The synthesis of phosphinotricin (±)-**3** *via* a Michaelis–Arbuzov reaction.



Scheme 52 The stereoselective synthesis of (L)-phosphinotricin **3** *via* the hydrophosphination of the vinyl oxazolidinone **212**.

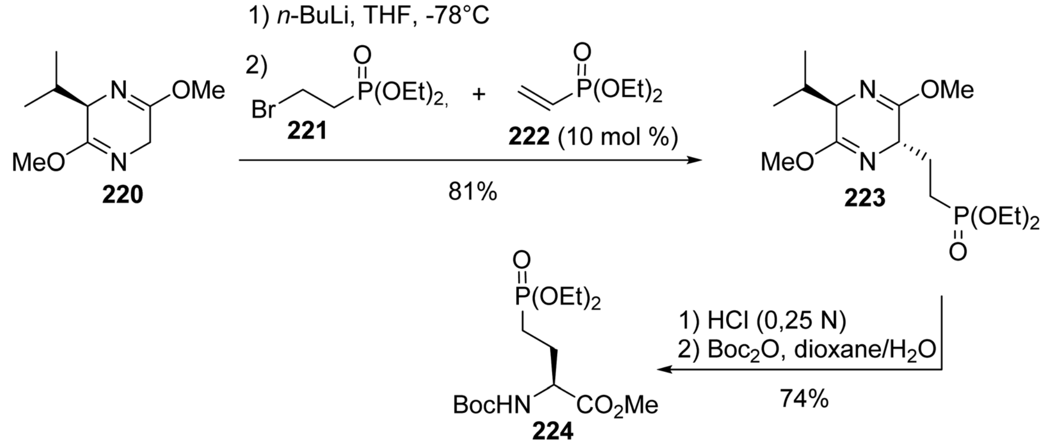


Scheme 53 The stereoselective synthesis of (L)-phosphinothricin **3** and (L)-AP4 **211** *via* alkylation at the β-position of the alanine derivative **215**.

diastereoisomer *trans*-**223** with 81% yield. In solution, the alkylation adduct was protonated by diethyl 2-bromoethylphosphonate **221**, which regenerated the vinyl phosphonate **222** *in situ* after dehydrobromination.[73] Acidolysis, followed by the protection of the amine with Boc_2O, led to the γ-phosphonate **224** with 74% yield (Scheme 54). This amino ester was used to prepare analogues of sphingosine-1-phosphate and sphinganine-1-phosphate, which are present in cell membranes as intermediates during the degradation of ceramide and the biosynthesis of sphingolipids, respectively.

Later, this methodology was applied to the synthesis of a variety of enantiomerically pure 4-substituted AP4 derivatives, which are useful for elucidating the role of metabotropic glutamate receptors in the central nervous system and for the development of potent and selective pharmacological agents.[74] When the electrophilic substitution of the phosphonate bis-lactim ether **225** was performed *via* trapping the anion at the α-position of the phosphonate with alkyl halides or other electrophile sources, compounds *syn*-**226** and *anti*-**226**, bearing a functional group, were obtained with up to 85% yield. Then, after separation, the bis-lactim ether of the intermediate *syn*-**226** was cleaved and the resulting phosphonate amino ester was treated with HCl (12 N) to provide the corresponding free phosphonic amino acid **228** (Scheme 55).

To explore the scope of these electrophilic substitutions, olefination reactions were examined involving α-stabilized

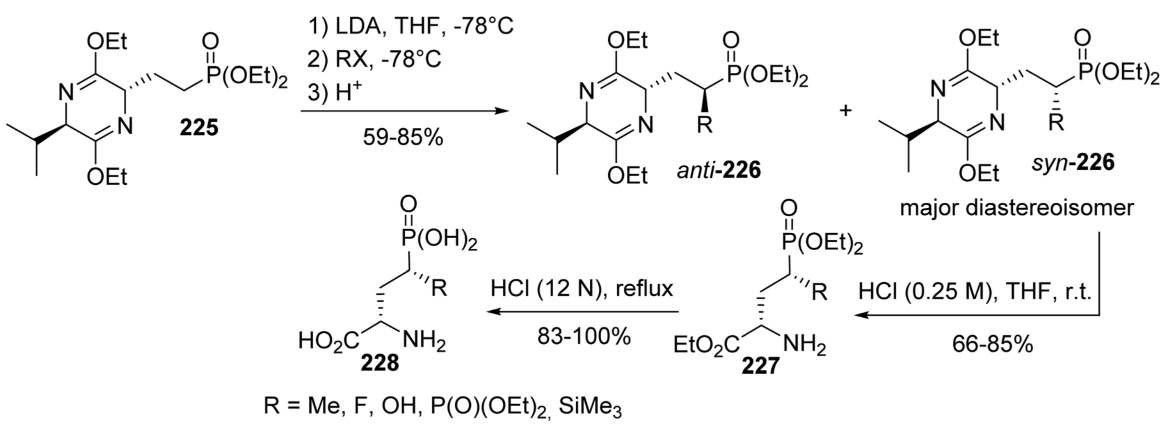


Scheme 54 The diastereoselective synthesis of the γ-phosphonoamino ester **224** from the Schöllkopf bis-lactim ether **220**.

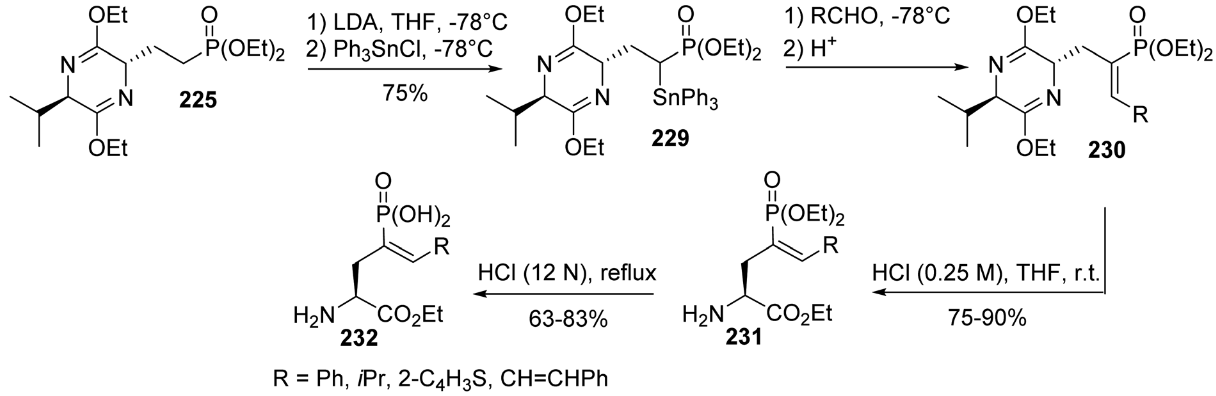
phosphonate carbanions. As an example, tin-Peterson olefinations with the α-triphenylstannyl derivative **229** and aryl or alkyl aldehydes were performed to give the (*Z*)-vinyl phosphonates **230** in moderate yields. Bis-lactim ether cleavage and a final deprotection step under strongly acidic conditions afforded the corresponding enantiopure unsaturated phosphonic α-amino acids **232** (Scheme 56).

4.2.5. *Via* the condensation of methylene bisphosphonate using Garner's aldehyde. An alternative synthetic route to AP4 derivatives was based on the Horner–Wadsworth–Emmons reaction *via* the condensation of a methylene bisphosphonate anion, using Garner's aldehyde **234** as the chiral pool. The resulting olefins **235a–b**, bearing α-methylene- or α-fluorophosphonates, were then reduced *via* hydrogenation over Pd/C to give **236a–b** with 99% and 88% yields, respectively. Finally, deprotection and oxidation steps using Jones reagent were simultaneously performed to afford the corresponding γ-phosphonoamino acids (*R*)-**237a–b** (Scheme 57).[75] Moreover, such amino acids are involved as key intermediates in the design of *N*-arylamide phosphonates, which are selective agonists or antagonists of sphingosine 1-phosphate (S1P) receptors.

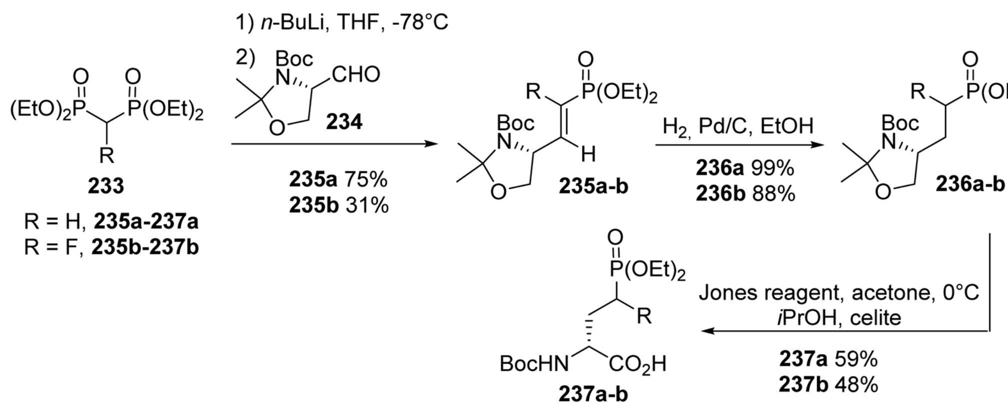
4.2.6. *Via* the Abramov reaction of phosphite with β-formylamino esters. Besides the asymmetric synthesis routes reported above for the preparation of (D)- and (L)-AP4 derivatives involving oxazolidinone, Schöllkopf bis-lactim ether and Garner's aldehyde as chiral auxiliaries, a hemisynthetic approach for accessing such compounds relies on the Abramov reaction of the aldehyde **238**, prepared from (L)-aspartic acid, with dimethyl trimethylsilylphosphite.[76,77] The resulting 4-hydroxy-4-dimethylphosphono derivative **239** was obtained with 98% yield after the *in situ* hydrolysis of the trimethylsilyl group. Hydride substitution of the hydroxyl group was achieved *via* homolytic deoxygenation through the treatment of the thiocarbonylimidazolide derivative with tributyltin hydride. Finally, the Boc and *tert*-butyl protecting groups were removed with TFA; Boc was then reintroduced under standard conditions, leading to the enantiopure γ-phosphono α-amino acids **242** and **243** with 63% and 68% yields, respectively (Scheme 58). The optical purity was determined *via* chiral HPLC in comparison with the dipeptides derived from (L)-leucine and the racemate using (D,L)-leucine.



Scheme 55 Functionalizing the α-position of the γ-phosphonoamino acid **228** obtained from the bis-lactim ether precursor **225**.

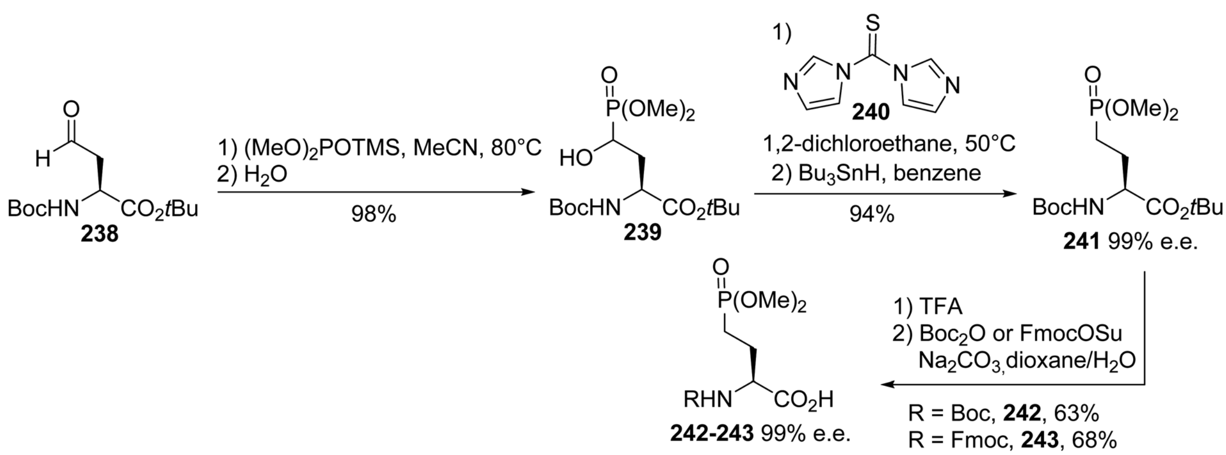


Scheme 56 The diastereoselective synthesis of the phosphonic α-amino acid **232** *via* the functionalization of the phosphono bis-lactim ether **225**.



Scheme 57 The stereoselective synthesis of γ-phosphonoamino acids **237a–b** from Garner's aldehyde **234**.

4.2.7. *Via* the enantioselective acylation of prochiral phosphonodiols. The enantiocontrolled syntheses of phosphonate α-amino acids in (L)- and (D)-forms have been considerably developed, but desymmetrization to provide chiral analogues of naturally occurring biological phosphates is less explored. For this purpose, Shibuya *et al.* reported the first desymmetrization of prochiral phosphono-l,3-propanediols, although this strategy was previously applied to other 2-substituted 1,3-propanediols.[78] The nucleophilic substitution of triflate **244** using the



Scheme 58 The stereoselective synthesis of the γ-phosphonoamino acids **242** and **243** *via* the Abramov reaction involving the β-formylamino ester **238**.

methyl phosphonate anion **245** afforded the phosphono ketal **246** with 70% yield. Then, this was subjected to transesterification with lipase forming the intermediate **247** with high enantioselectivity of 93%. The amino phosphonate **248** was obtained after Jones oxidation and amination with diphenylphosphoryl azide (DPPA), followed by protection with benzyl carbamate. Finally, the deprotection of the acetate and a second Jones oxidation step led to the γ-phosphonate (L)-amino acid **249** with 47% yield and 93% e.e. (Scheme 59).

Phosphopeptides are tools for understanding the biological functions of the phosphorylation regulating phosphoserine (pSer) and phosphothreonine (pThr) residues that are involved in protein–protein interactions. As phosphate moieties are easily hydrolyzed by phosphatases *in vivo*, several mimics containing non-hydrolysable methylene phosphonate or difluoromethyl phosphonate units with similar physicochemical properties to the phosphate moiety were developed. The synthesis of CF_2-substituted pSer and pThr mimics reported in 2018 by Chen *et al.* illustrates recent progress in this area.[79] The key step of this synthesis is the substitution of the iodine and bromine α,β-dehydroamino esters **250** and **255**, using the difluorophosphonate copper/zinc reagent **251**, to afford the unsaturated intermediates **252** and **256** with 85% and 70% yields, respectively. These were subjected to asymmetric hydrogenation catalyzed by a rhodium/DuPhos complex and deprotected using TFA or HCl (9 N). The resulting free amines were finally protected with FmocOSu, affording the corresponding *N*-Fmoc difluoro-substituted pSer **254** and pThr **258** mimics with high enantioselectivity (Scheme 60a and b). Furthermore, those amino acids were readily used in SPPS to provide phosphatase-resistant peptides that exhibit remarkable binding efficacy compared to the parent phosphopeptides.

4.2.8. *Via* the Michael addition of azalactone to vinylidene bisphosphonate.

Quaternary amino acids are relevant structures for improving stability when incorporated into peptides. Geminal bisphosphonates constitute another important class of pharmacologically active compounds and they are involved in the treatment of bone disorders such as Paget's disease, myeloma, bone metastases and osteoporosis.[80] In this context, Albrecht *et al.* developed a new class of quaternary α-amino acids bearing a bisphosphonate moiety on the side chain in order to improve the properties of both these compounds. The strategy consists of an enantioselective Michael reaction between the α-substituted azalactone **259** and vinylidene bisphosphonate **260** in the presence of *Cinchona* alkaloids as chiral Brønsted bases, followed by ring opening under acidic conditions (Scheme 61). Among the different *Cinchona* alkaloids evaluated, the highest enantioselectivity (37% e.e.) was obtained using catalyst **261**, which suggests that further optimization of this process is possible.

5. Phosphorus linked to carbon in the δ-position

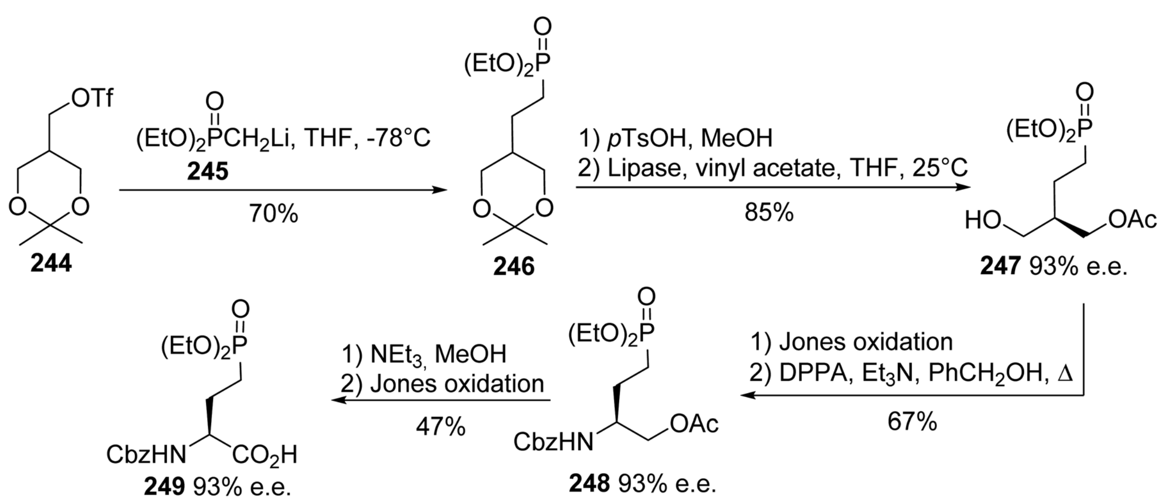
5.1. δ-Phosphono α-amino acids

5.1.1. *Via* four-component Ugi condensation.

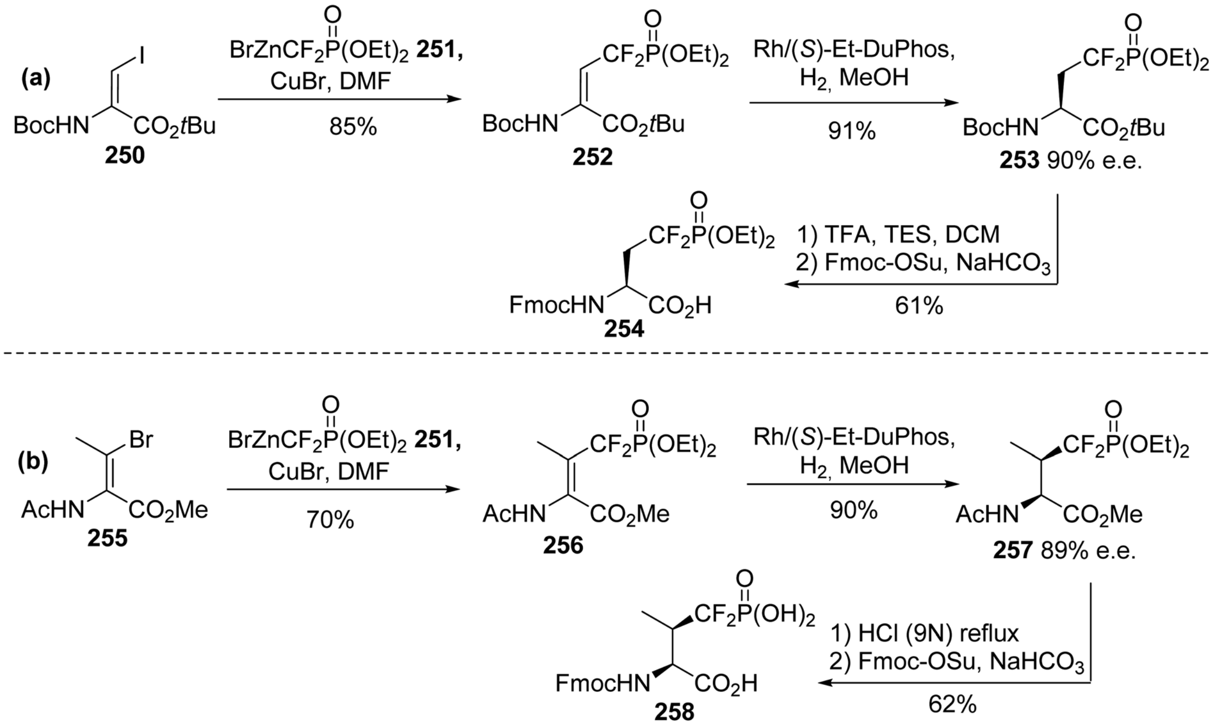
One of the first synthetic route for δ-phosphonic α-amino acids was reported in 1988 by Natchev *et al.* The key step for introducing the phosphorus moiety is based on a Michaelis–Arbuzov reaction between the bromopropene acetal **265**, readily obtained from the aldehyde **264** and triethyl phosphite.[81] The corresponding unsaturated phosphonate **266** was obtained and the acetal was deprotected into the aldehyde **267**. Finally, compound **267** was condensed with ammonium formate, cyclohexyl isonitrile and sodium hydroxide to provide the unsaturated δ-phosphonic α-amino acid **269** in a single step with 79% yield. Enzymatic approaches were used to separate the (L)- and (D)-isomers (Scheme 62).

5.1.2. *Via* the diastereoselective alkylation of Seebach's imidazolidinone.

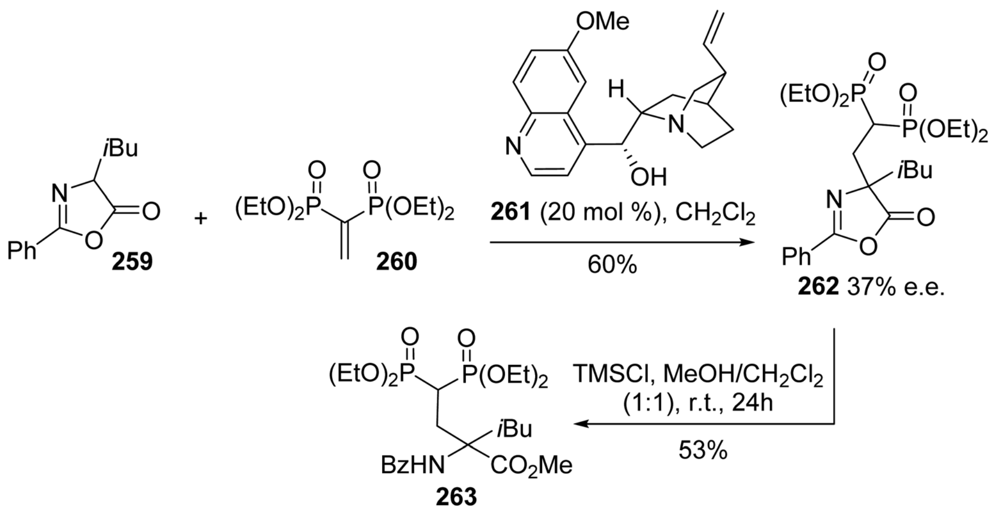
(*S*)-2-Amino-5-phosphonopentanoic acid, (L)-AP5, is a potent antagonist for the *N*-methyl-(D)-aspartic acid receptor (NMDAR) and can be synthesized starting from Seebach's imidazolidinone.[82] The resulting enolate, obtained *via* the treatment of the imidazolidinone **270** with LDA, was added



Scheme 59 The asymmetric synthesis of the γ-phosphonoamino acid **249** *via* the enzymatic desymmetrization of the substrate **246**.



Scheme 60 The synthesis of the difluorophosphonoamino acids **254** and **258** *via* cross-coupling reactions using the difluorophosphonate copper/zinc reagent **251** (a) or **255** (b).

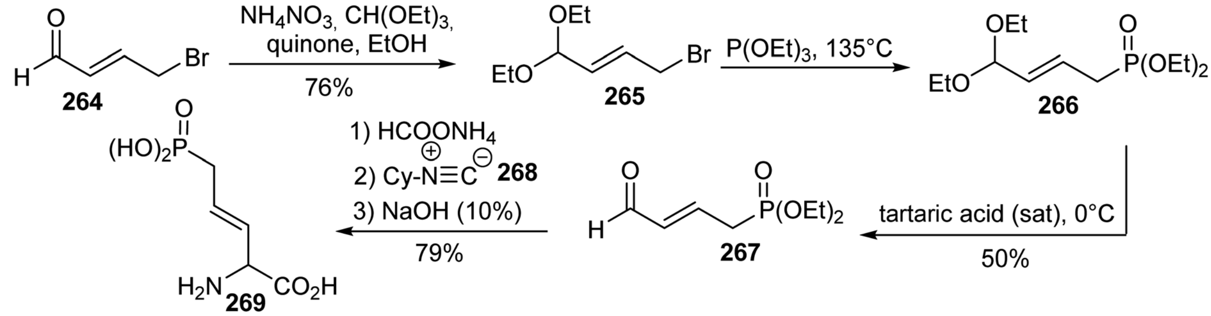


Scheme 61 The asymmetric synthesis of the bisphosphonate amino ester **263** *via* an organocatalyzed Michael-type reaction.

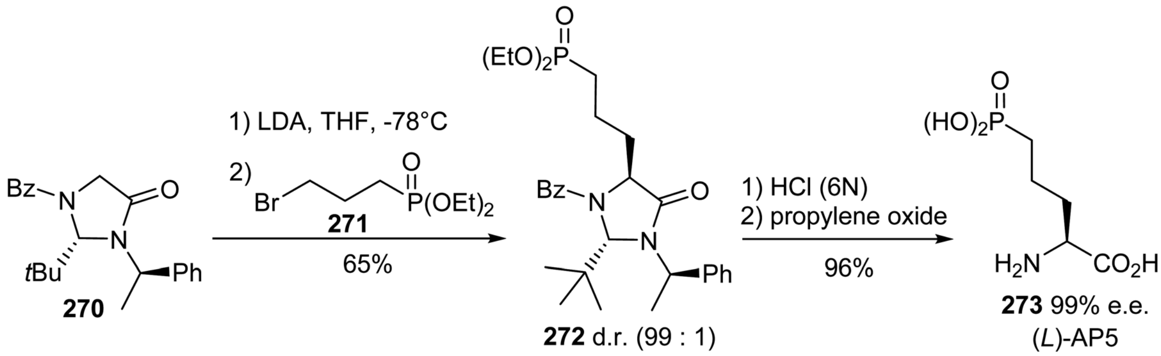
to 3-bromopropyl phosphonate **271** to obtain the *trans*-substitution product **272** with 65% yield and high diastereoselectivity, as assigned *via* ^{1}H NMR. Hydrolysis under acidic conditions led to the enantiopure aminophosphonic acid **273** (Scheme 63). This strategy was also applied to the preparation of the enantiomer (D)-AP5, taking care with the choice of chiral inductor; this is because when starting from *N*-methyl imidazolidinone, racemization due to the assistance of the neighbouring phosphonate group was observed during hydrolysis.

5.2. β-Keto-δ-phosphonate α-amino acids

5.2.1. *Via* the addition of cuprate phosphonate to acid chloride oxazolidinone. The (L)-AP5 antagonist exhibits suitable affinity (IC_{50} = 5.5 μM) towards NMDAR, but its weak blood–brain barrier crossing ability results in weak systemic activity. Considering this limitation and on the basis of molecular modeling studies, the analogue (*R*)-4-oxo-5-phosphononorvaline **278** was identified as a potent ligand and it was prepared *via* a convergent synthesis procedure



Scheme 62 The synthesis of the δ-phosphonic α-amino acid **269** *via* the four-component Ugi condensation of the phosphonoaldehyde **267**.

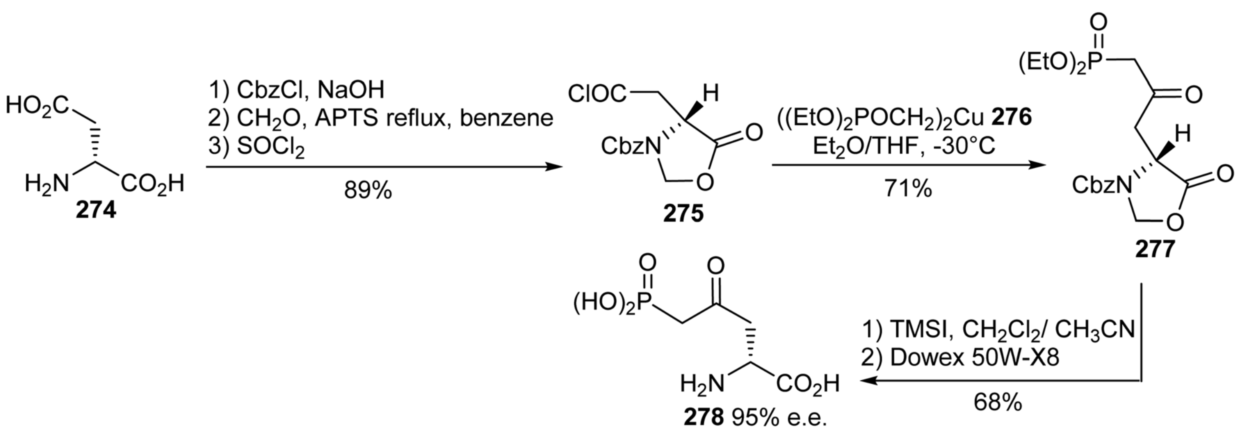


Scheme 63 The diastereoselective synthesis of the δ-phosphonic α-amino acid **273** *via* the alkylation of the Seebach imidazolidinone **270**.

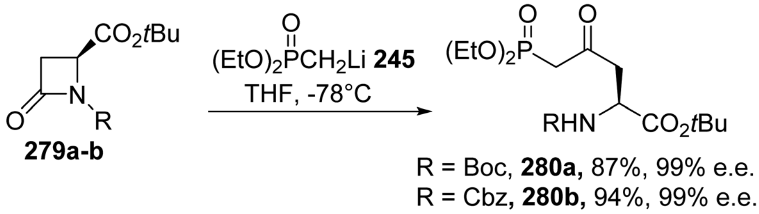
reported by Whitten *et al.*[83] The *N*-protected oxazolidinone acid chloride **275**, obtained from (D)-aspartic acid **274**, reacted with the nucleophilic diethyl methylphosphonate cuprate **276** to provide the alkylated imidazolidinone **277** with 71% yield. Finally, ring opening with TMSI and ion exchange gave the (*R*)-γ-keto-δ-phosphonic α-amino acid **278** with 68% yield and 95% e.e. (Scheme 64).

A more straightforward strategy consists of opening the β-lactam with the diethyl methylphosphonate lithium salt **245**.[84] Under these conditions, the enantiopure δ-phosphono-γ-ketoamino esters **280a–b**, bearing Boc and Cbz protecting groups, respectively, were obtained with yields of up to 94% (Scheme 65). The optical purity was determined *via* ^{19}F and ^{1}H NMR studies on the Mosher salts after deprotection of the amine.

Sutherland *et al.* exploited another approach based on the nucleophilic addition of the methyl diethylphosphonate lithium salt **245** to the methyl ester on the side chain of the aspartate derivative **281**. It must be noted that a sterically hindered trityl protecting group is necessary for regioselective addition to the ester of the side chain (Scheme 66).[85–87] These authors also reported the synthesis of optically active β-pyridyl



Scheme 64 The stereoselective synthesis of the γ-keto-δ-phosphonic α-amino acid **278** *via* P–C bond coupling with the acid chloride **275**.



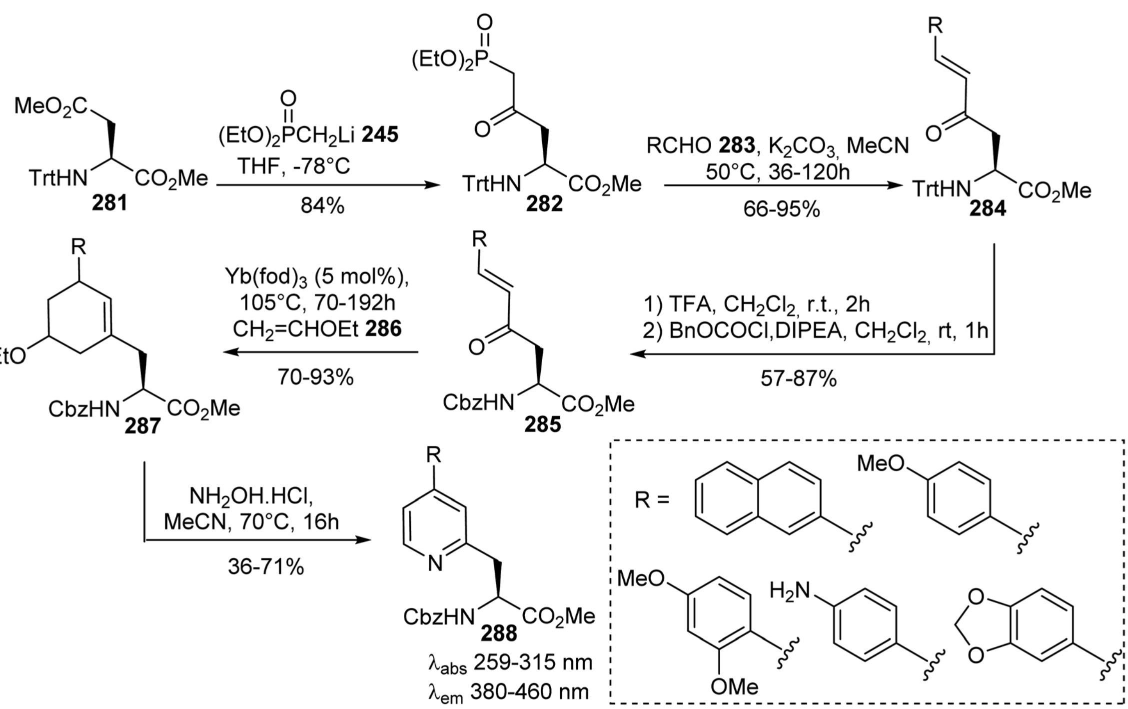
Scheme 65 The stereoselective synthesis of the δ-phosphono-γ-ketoamino esters **280** from the β-lactam **279**.

α-amino acids displaying fluorescence properties.[88] First, (*E*)-enones **284** were obtained *via* Horner–Wadsworth–Emmons reactions between the δ-phosphono-γ-keto α-amino ester **282** and various substituted benzaldehydes **283**. Then, the trityl group was removed and replaced by an *N*-protecting group (Cbz) under standard conditions. A regioselective hetero-Diels–Alder reaction between the enone derived from the α-amino ester **285** and ethyl vinyl ether **286** was performed using an ytterbium catalyst. Finally, a modified Knoevenagel–Stobbe reaction with hydroxylamine hydrochloride at 70 °C led to pyridines **288** bearing various aromatic substituents with good yields from 58% to 71% (Scheme 66). The removal of both the amine and carboxylic acid protecting groups was performed to give the free amino acids. These amino acids exhibit fluorescence emission from 380 to 460 nm, with large Stokes shifts and intensities that depend on the nature of the electron-deficient or -rich substituents.

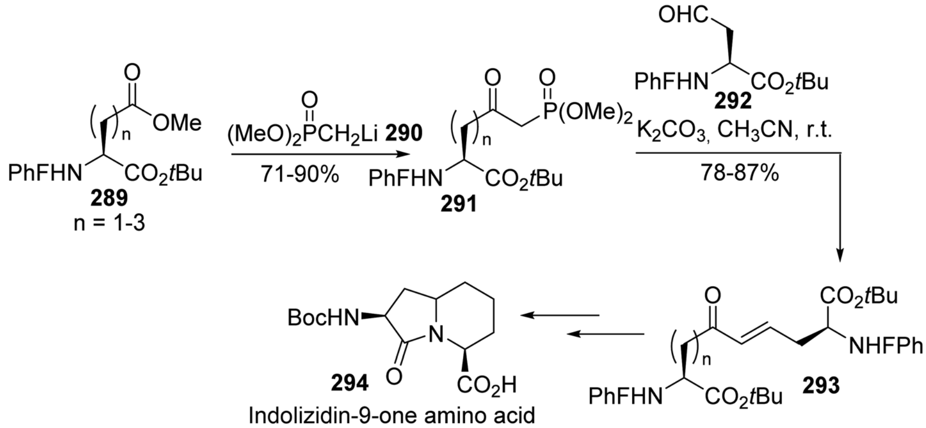
The same method was employed by Lubell *et al.* to prepare the δ-phosphono-γ-ketoamino ester **291** *via* the addition of the dimethyl methylphosphonate anion **290** to aspartates **289**.[89] Then, Horner–Wadsworth–Emmons olefination reactions with the aldehyde **292** led to the corresponding α,ω-diamino dicarboxylates **293** with carbon chain lengths of nine to eleven and 78% to 87% yields (Scheme 67). These dimers were involved in the preparation of the bicyclic indolizidin-9-one derivative **294**, which could introduce rigidity into peptide structures.

5.2.2. *Via* the phosphatation of vinyl aziridines. As exemplified above, efficient phosphonation and phosphatation reactions involving α-amino acids have been reported in the literature, however divergent and stereoselective methodologies have not been explored. In 2018, a regiodivergent approach for the ring-opening of vinyl aziridines using phosphorus nucleophiles, depending on the catalyst and the reaction atmosphere, was reported.[90] The regioselective addition of the P-radical obtained from diphenylphosphine oxide **296** enabled the S_N2' ring-opening of vinyl aziridines to afford the δ-phosphinoamino esters **297** with 70% yield and 97% e.e. at room temperature (Scheme 68).

On the other hand, when phosphate anions generated *in situ* from a dialkylphosphite reagent and a Ag catalyst were used



Scheme 66 The stereoselective synthesis of fluorescent β-pyridyl α-amino acids **288** *via* a Knoevenagel–Stobbe type reaction from the aspartate precursor **281**.



Scheme 67 The stereoselective synthesis of the indolizidinone amino acid **294** *via* a HWE reaction.

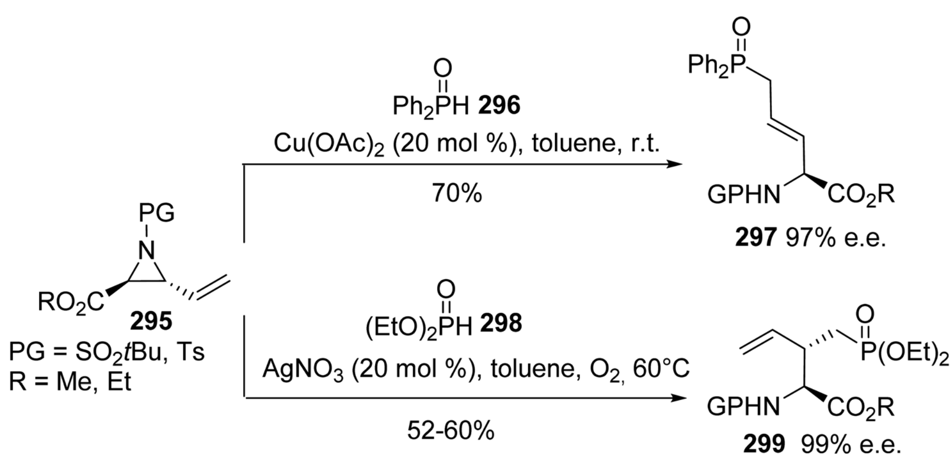
under an oxygen atmosphere, the S_N2 phosphonation of vinyl aziridines led to the enantiopure branched α-amino esters **299** (Scheme 68). *Via* this divergent strategy, it is possible to access various optically active phosphorus-containing α-amino acids, which can act as useful building blocks for the design of more relevant compounds in the field of medicinal chemistry.

5.2.3. *Via* Hirao cross-coupling starting from bromomethylpicolinate. Selfotel (CGS 19755) is one of the most potent NMDAR antagonists, but it was finally rejected during clinical trials due to its toxic side effects. In this context, the synthesis of Selfotel analogues with limited side effects has been explored according to a procedure developed by Kafarski *et al.*[91] The first step consists of palladium-catalyzed Hirao cross-coupling between the bromomethylpicolinate regioisomers **300** and diethyl phosphite **298** to give a series of phosphorylpyridyl carboxylates with isolated yields of up to 92% (Scheme 69). Acidic hydrolysis with HCl (12 N) led to the desired acids **302**, which were then subjected to hydrogenation over PtO_2. The reaction proceeded smoothly and the aliphatic acids **303** were obtained as a mixture of stereoisomers, identified *via* NMR, with the *cis* addition product being the major one. This methodology was also extended to piperidyl diphosphinic acid derivatives.

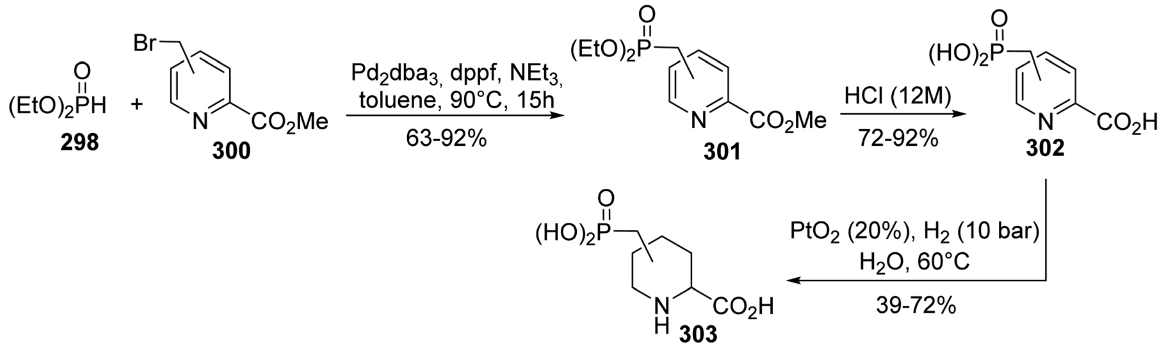
6. Phosphorus-containing phenylalanine derivatives

6.1. *Via* palladium-catalyzed cross-coupling reactions

Amino acids containing functionalized aromatic substituents are interesting building blocks for the design of modified peptides with unusual properties. In connection with their research in the field of peptide-based phosphine ligands, Gilbertson *et al.* developed a catalytic method to convert the phenol moiety of tyrosine into the corresponding arylphosphine α-amino acids.[92] *N*-Protected hydroxyphenylglycine or tyrosine was transformed into a triflate to act as a suitable reagent for palladium-catalyzed Stille cross-coupling *via* a reaction with *N*-phenyltrifluoromethane sulfonamide and diisopropylethylamine. While the first attempts using triflate and (trimethylstannyl)diphenylphosphine reagents in the presence of a palladium catalyst were unsuccessful, the use of diphenylphosphine and $Pd(OAc)_2$ led to the corresponding phosphine α-



Scheme 68 The regiodivergent hydrophosphonation of vinyl aziridines **295**.



Scheme 69 The synthesis of the Selfotel analogue **303** *via* P–C Hirao cross-coupling.

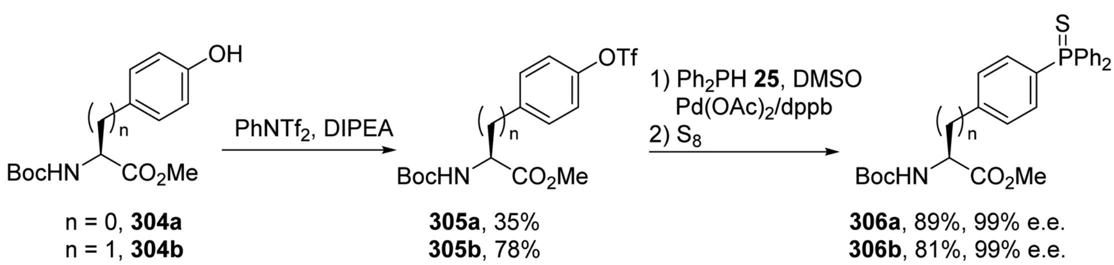
amino esters. Besides, the choice of protecting group is important for the stereoselectivity because starting from *N*-Boc hydroxyphenylglycine or tyrosine **304a–b**, this reaction proceeds without racemization, unlike in the case of *N*-acetyl precursors (Scheme 70). Under optimized conditions, this reaction was also extended to the *ortho* and *meta* isomers of tyrosine and to hydroxyphenylglycine to provide new phosphine ligands. Finally, the air-sensitive phosphine groups were protected in the form of the phosphine sulfur derivatives **306a–b**, which are convenient for purification *via* chromatography and removable with RANEY® nickel. The method was also performed on a pentapeptide containing a tyrosine residue, leading to the corresponding phosphine peptide with 78% yield (Scheme 70).

Alternatively, Kraatz *et al.* reported similar conditions for the cross-coupling of the *N*-acetyl iodophenylalanine methyl ester **307** with diphenylphosphine in the presence of triethylamine as a base.[93] In this case, the free phosphine derived from phenylalanine **308** was isolated with an almost quantitative yield after purification *via* column chromatography in a glove box, without racemization (Scheme 71).

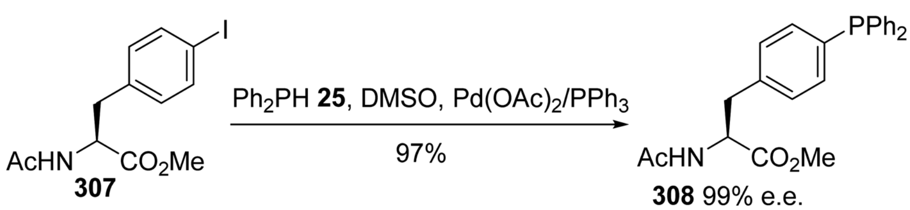
Considering the extensive use of phospholes as ligands that can bind a large variety of transition metals for applications in catalysis and optoelectronics, the incorporation of such compounds into the side chains of phenylalanine and tyrosine was investigated.[94] While the Stille cross-coupling of tyrosine triflate failed with stannylphosphole **310**, the reaction with *N*-protected 4-iodophenylalanine **309** was successfully achieved in the presence of Pd_2dba_3 (Scheme 72). Then, the phosphole was protected with elemental sulfur and purified *via* column chromatography to generate the phosphole sulfur phenylalanine **311** with 78% yield as a mixture of two diastereoisomers due to the chirality of the P-center.

6.2. *Via* aromatic nucleophilic substitution starting from fluorophenylglycine

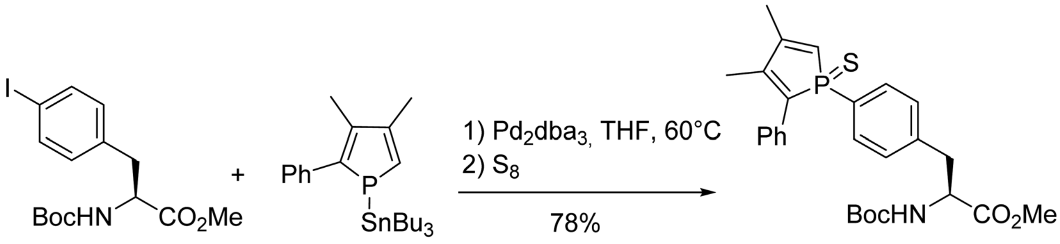
Compared to methods wherein a palladium catalyst or stannyl reagent was required to promote P–C bond formation between the phosphorus moiety and aryl triflate or halide amino esters, the reaction involving sodium 2-fluorophenylglycinate **312**



Scheme 70 The synthesis of the arylphosphine ligands **306a–b** *via* a palladium-catalyzed P–C cross-coupling reaction.



Scheme 71 The synthesis of the diphenylphosphine (L)-phenylalanine **308** *via* a palladium-catalyzed P–C cross-coupling reaction.



Scheme 72 The synthesis of the phosphole (L)-phenylalanine **311** *via* Stille cross-coupling.

proceeds directly with phosphide anions.[95] Indeed, the presence of fluorine as a good leaving group enhances the reactivity of the aromatic ring towards the nucleophilic diphenylphosphide potassium salt **313**, without the need for a transition metal catalyst, to provide the 2-diphenylphosphine phenylglycine **314** with 89% yield (Scheme 73).

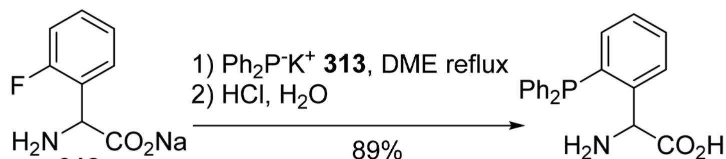
6.3. *Via* the diastereoselective alkylation of iminolactone

The development of non-hydrolyzable phosphotyrosine analogues that could be introduced into peptides is of considerable interest for studying the cellular signaling events involved in diseases such as diabetes and cancer. For this purpose, the efficient asymmetric synthesis of phosphonodifluoromethyl (L)-phenylalanine **321** was reported using the commercially available diphenyloxazinone **318** as a chiral auxiliary. The alkylating reagent **317** was obtained *via* two steps: the reaction of triethyl phosphite with a benzoic acid bromide reagent **316**, generated *in situ via* the treatment of toluic acid with PBr_3, followed by the addition of (diethylamido)sulfur trifluoride (DAST) to the resulting ketophosphonate **316**. The enolate of the chiral auxiliary **318** was then alkylated in the benzylic position, leading to compound **319** with 78% yield. The hydrogenation and protection of the amine with an Fmoc-NHS ester, followed by the deprotection of the phosphonate, provided the *N*-Fmoc phosphonic (L)-phenylalanine derivative **321** with a quantitative yield (Scheme 74).[96,97] Analysis of compound **320** *via* HPLC after derivatization with a chiral amine proves that no racemization occurs during the alkylation step.

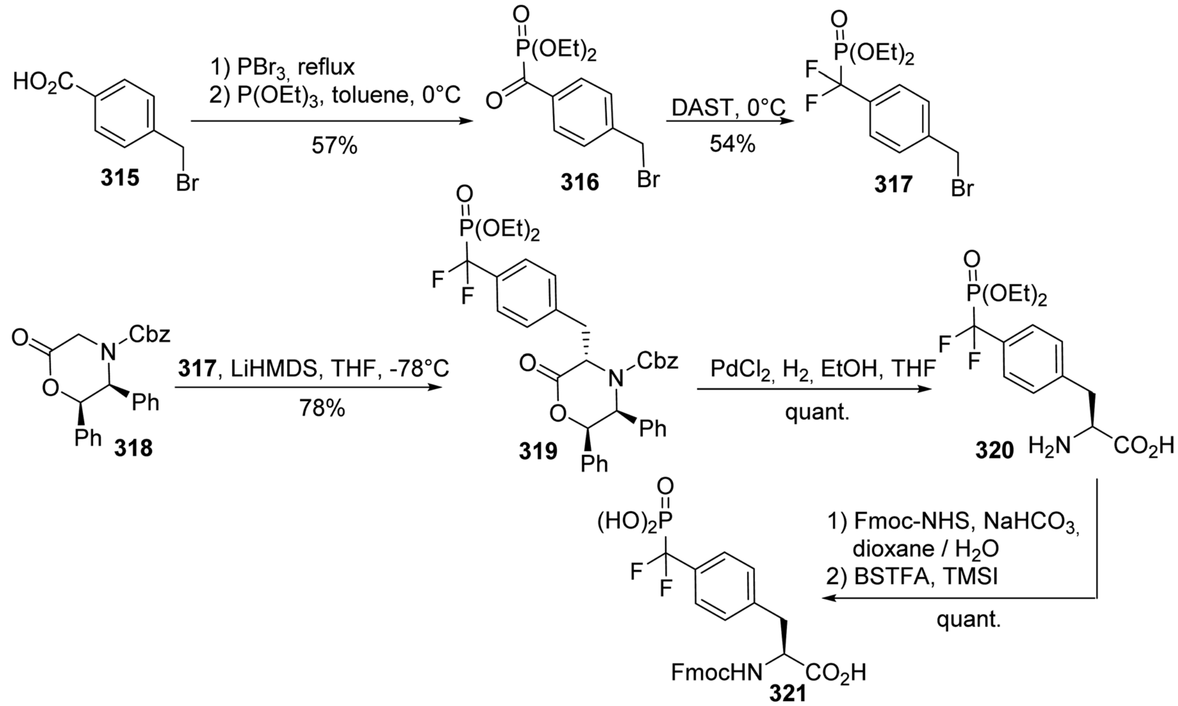
A similar approach was also employed for the synthesis of the (L)-phosphonomethyl phenylalanine **326**, a phosphatase-resistant phosphotyrosine analogue that exhibits similar biological properties to phosphotyrosine.[98] The phosphonate motif was obtained *via* the reaction of 4-methylbenzyl bromide with nucleophilic sodium di-(*tert*-butyl)phosphite **323**, followed by bromination with *N*-bromosuccinimide. The enolate of the chiral auxiliary **318** was generated under the conditions reported above and, then, *trans*-alkylation was performed in the presence of HMPA as a solvating agent, leading to the compound **325** with 78% yield. Finally, the (L)-phosphonomethyl phenylalanine **326** was obtained with high enantioselectivity (e.e. > 95%) after hydrogenolysis and Fmoc-protection of the free amine (Scheme 75).

7. Phosphohistidine analogues

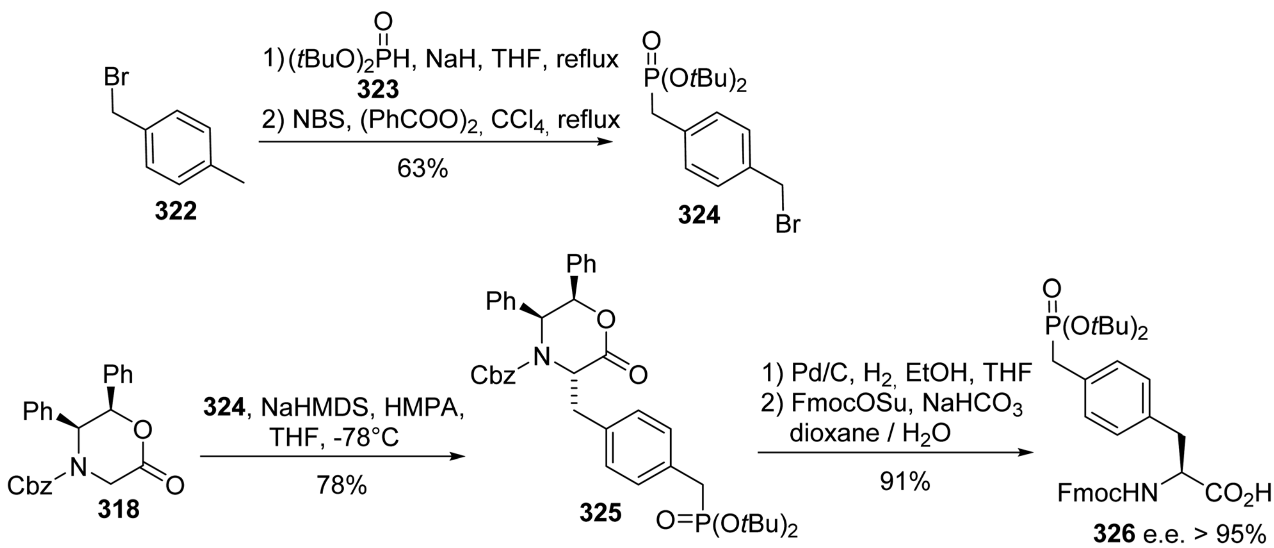
Protein phosphorylation is one of the most studied post-translational modifications. Compared to serine, threonine and tyrosine *O*-phosphorylation, obtaining an understanding of histidine phosphorylation is more difficult due to the instability and isomerism of phosphohistidine (pHis), making its detection and isolation from biological sources challenging. On the basis of molecular modeling, isomers **329** and **331**, having non-hydrolysable C–P bonds as replacements for the labile P–N bond, are expected to mimic the geometry and electronic properties of phosphohistidine. The principle of the synthesis is based on the cycloaddition of the azide alanine derivative **327** with ethynyl phosphonate **328**. When CuI was used as a catalyst, the regioisomer **329** was directly obtained with 72% yield, while for the Ru-catalyzed cycloaddition, it was necessary to protect carboxylic acid with benzyl bromide. After the reaction and debenzylation, the isomer **331** was isolated with 68% yield (Scheme 76).[99] These stable analogues were then incorporated into peptides *via* solid-phase peptide synthesis using a Boc-strategy to study histidine phosphorylation in histones.



Scheme 73 The synthesis of the phosphinophenylglycine **314** *via* P–C bond formation using S_NAr.



Scheme 74 The synthesis of the phosphonodifluoromethyl phenylalanine **321** *via* the diastereoselective alkylation of the diphenyloxazinone **318**.

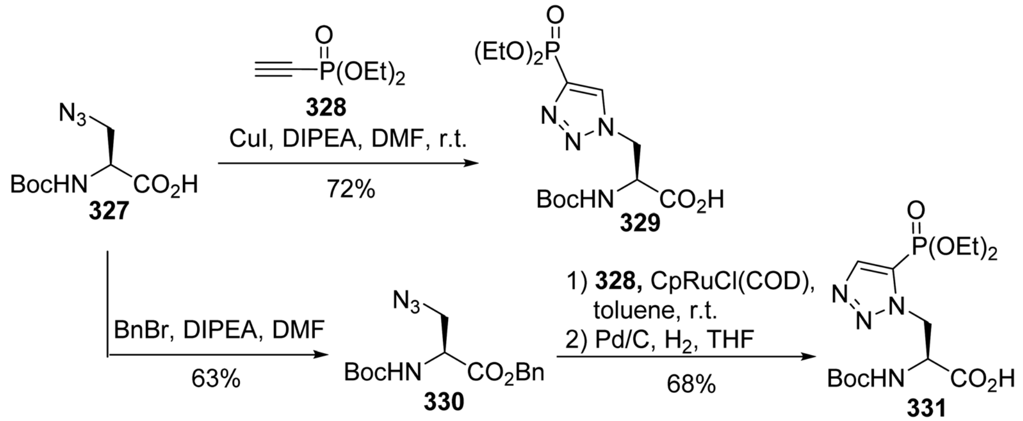


Scheme 75 The synthesis of the phosphonomethyl phenylalanine **326** *via* the diastereoselective alkylation of the diphenyloxazinone **318**.

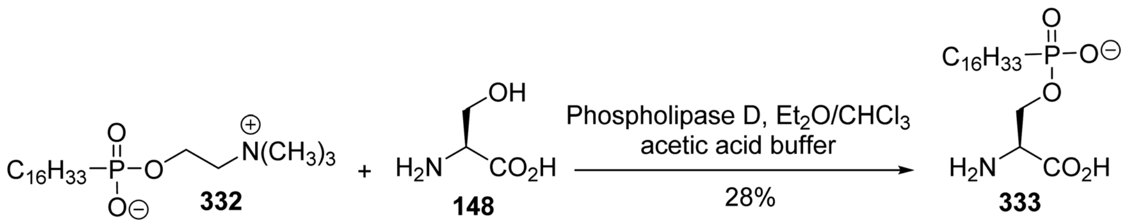
8. The phosphorylation and phosphination of hydroxyamino acids with a P–O bond

Serine phospholipid analogues are of crucial interest for understanding the physiological activity of phosphatidylserine (PS), a naturally occurring amphiphilic phospholipid that is involved in the activation of several membrane-associated enzymes. In addition, recent studies have reported the interactions of such negatively charged phospholipids with polynuclear platinum anticancer agents to facilitate cellular uptake.[100]

The synthesis of hexadecylphosphono-(L)-serine **333** was reported by Brachwitz *et al.* The transesterification reaction was carried out by stirring a mixture of hexadecyl phosphonocholine **332** and excess (L)-serine, at a ratio of 1 : 100, with phospholipase D, which is known to convert phosphatidylcholine into phosphatidylserine (Scheme 77).[101] After treatment, the crude



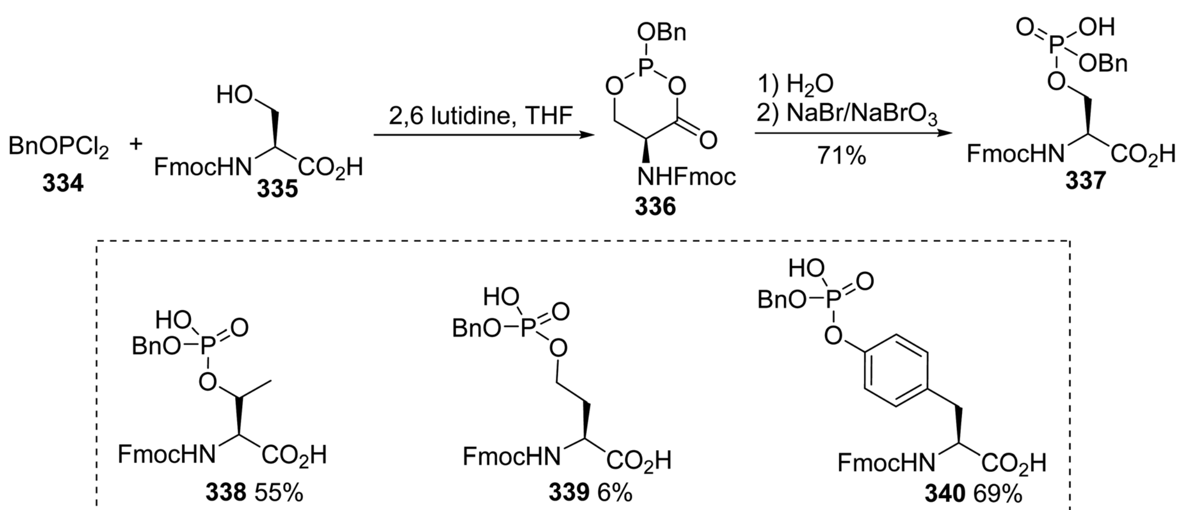
Scheme 76 The stereoselective synthesis of the phosphohistidine analogues 329 and 331 *via* click chemistry.



Scheme 77 The synthesis of the lipophilic phosphonoserine 333 *via* enzymatic transesterification.

substance was purified *via* chromatography on cellulose to furnish the phosphonoserine **333** with 28% yield.

The one-pot synthesis of another important building block, Fmoc-*O*-benzyl-(L)-phosphoserine **337**, bearing convenient protecting groups for solid-phase peptide synthesis, was reported more recently by Petrillo *et al.*; its incorporation into the phosphopeptide Forigerimod was also studied for the treatment of systemic lupus erythematosus (SLE).[102] It must also be noted that the use of a monobenzyl protecting group was necessary to avoid the elimination of the phosphate into dehydroalanine under the basic conditions required for Fmoc deprotection. The reaction between phosphorus trichloride and benzyl alcohol afforded benzyl dichlorophosphite **334**, which reacted efficiently with Fmoc-(L)-serine **335** in the presence of 2,6-lutidine as a base without the deprotection of the amine. When the cyclic intermediate **336** was observed *via* ^{31}P NMR studies, hydrolysis was performed in the presence of NaBr, leading to the acyclic phosphite **337** with 71% yield (Scheme 78). As an



Scheme 78 The synthesis of the *O*-phosphorylated amino acids 337–340.

alternative to phosphoramidite chemistry, the phosphorylation of other Fmoc-hydroxyamino acids was also performed based on this one-pot strategy.

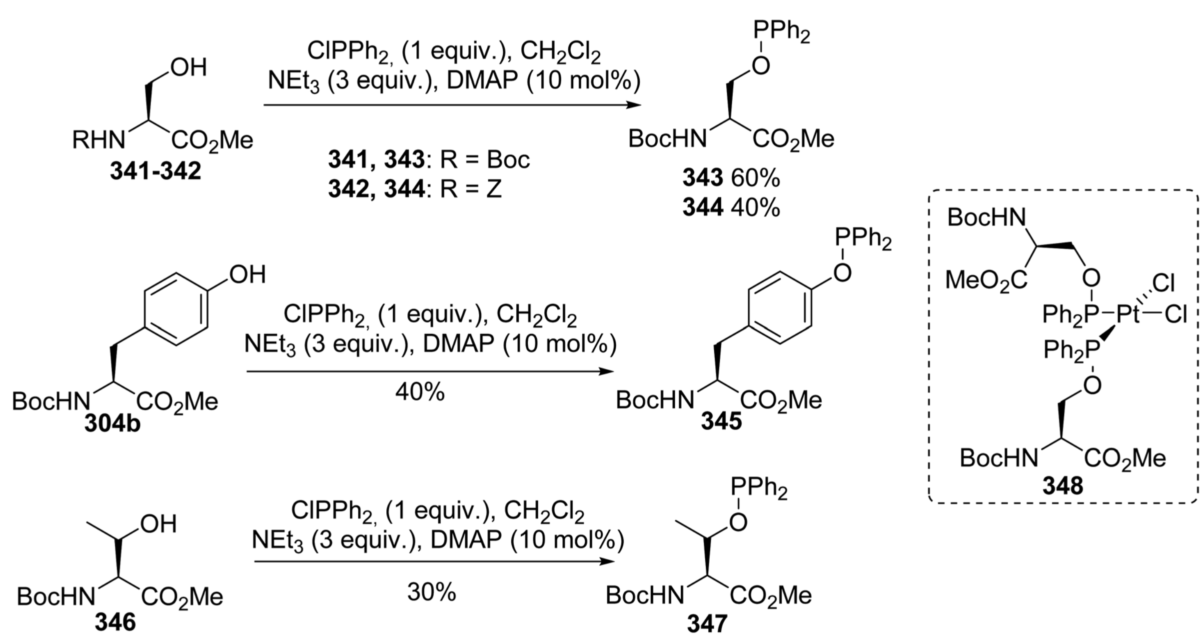
Phosphinites constitute a class of phosphorus-based ligands, leading to robust complexes for transition metal catalysis. They exhibit stronger metal-phosphorus bonds compared with the related phosphines, due to the presence of the electron-withdrawing alkoxy group. Phosphinite ligands derived from naturally occurring (L)-hydroxyamino acids were conveniently prepared by reacting an alcoholic amino acid with one equivalent of chlorodiphenylphosphine in the presence of NEt_3 and a catalytic amount of DMAP.[103,104] After purification on basic alumina, phosphinites based on serine **343–344**, on tyrosine **345** and on threonine **347**, were obtained with up to 60% yield (Scheme 79). Then, a platinum complex of a phosphinite ligand **348** was also prepared with a quantitative yield and X-ray structure analysis indicates a square planar coordination environment around the metal center, with phosphinite amino acids positioned *cis* to each other.

Cidofovir (HPMPC) **349** is an antiviral agent for the treatment of human cytomegalovirus (HCMV) retinitis, aimed at immune-suppressed individuals, which contains an ionisable $P(O)(OH)_2$ moiety at physiological pH, resulting in low internalization and biodisponibility. To address these limitations, prodrugs based on cyclic Cidofovir (cHPMPC) conjugated to serine and dipeptides have been developed.[105] The interest in this approach arises from the possibility of coupling a variety of amino acids with serine to fine-tune the prodrug, minimize its toxicity and improve its lipophilicity, which is necessary for its transportation in the gastrointestinal tract. The cHPMPC conjugates **350**, **352** and **354** were obtained using PyBOP to promote the intramolecular cyclization of Cidofovir **349** into cHPMPC, followed by the grafting of serine or dipeptides and Boc-deprotection with TFA (Scheme 80). The target compounds **352** and **354** were isolated after purification as a pair of diastereoisomers, owing to the chiral phosphorus atom. This strategy was also applied to the synthesis of an adenine conjugate (cHPMPA) but, in this case, the amine functionality of serine was anchored to a solid support. Studies with a peptide-specific intestinal transporter (hPEPT1) suggest that the presence of a dipeptide in the conjugate is necessary to increase its affinity towards the transporter and that (L)-amino terminal prodrugs are stereospecifically recognized by hPEPT1 but not transported due to steric hindrance or the polar properties.

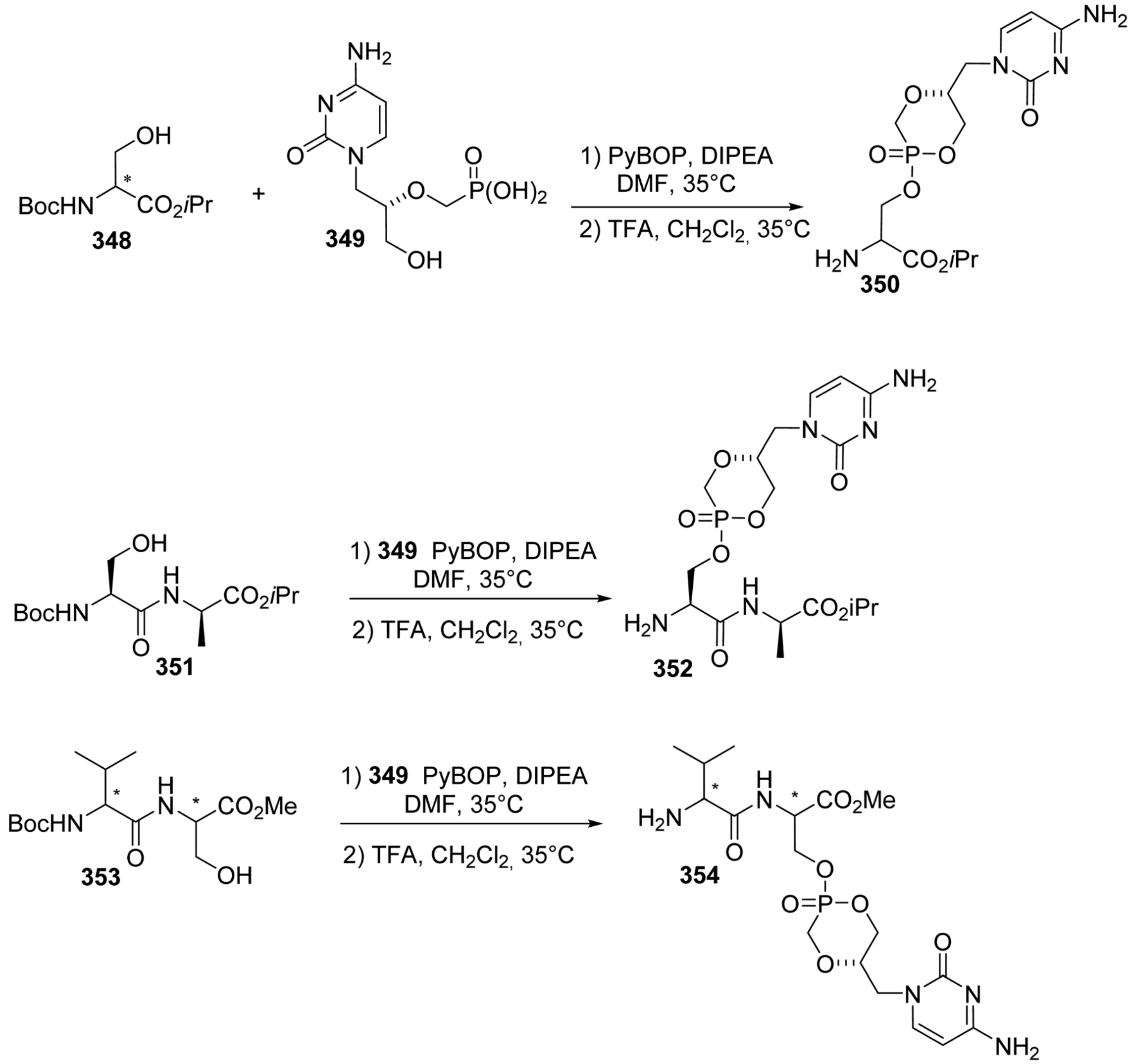
9. Phosphocysteine and its derivatives with a P–S bond

S-Phosphocysteine is one of the lesser-known phosphoamino acids, discovered in both prokaryotic and eukaryotic systems, which is involved in mechanisms related to protein tyrosine phosphatases (PTPases) that are responsible for the dephosphorylation of tyrosine side chains. It is of major importance to understand the role of *S*-phosphocysteine in the regulation of tyrosine phosphorylation, which is associated with cell growth and division processes and is therefore of interest to cancer researchers.[106–108] Only a few methodologies have been developed for the synthesis of *S*-phosphocysteine derivatives. The first strategy is based on a Michaelis–Arbuzov reaction involving a readily available disulfanyl derivative and trimethyl phosphite, leading to the corresponding phosphorothioate **356** with an almost quantitative yield after purification (Scheme 81).[109,110]

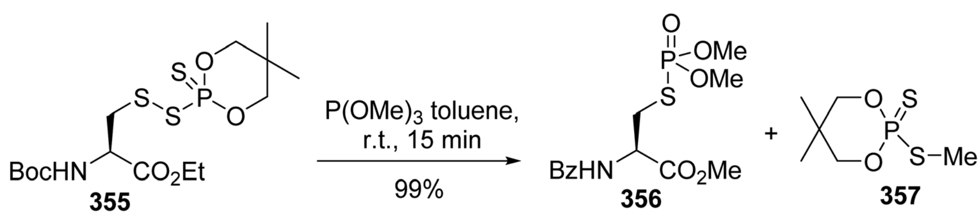
A more recent strategy that consists of reactions between *S*-nitrosothiols and phosphite esters was reported last year.[111] Interestingly, this reaction led to two different products, thiophosphoramidates and phosphorothioates, depending on the



Scheme 79 The stereoselective synthesis of phosphinite ligands from (L)-hydroxyamino acids.



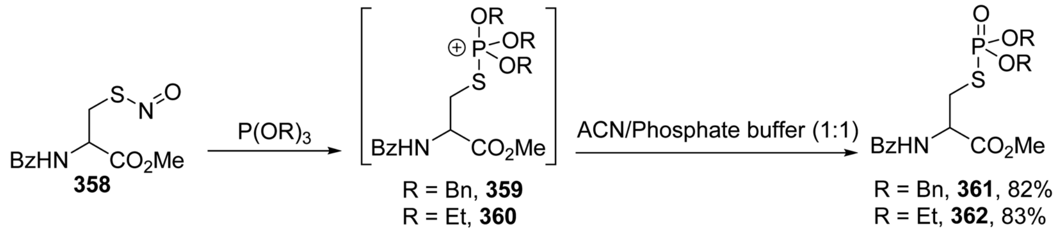
Scheme 80 The synthesis of cyclo-Cidofovir conjugates with serine to obtain the prodrugs **352** and **354**.



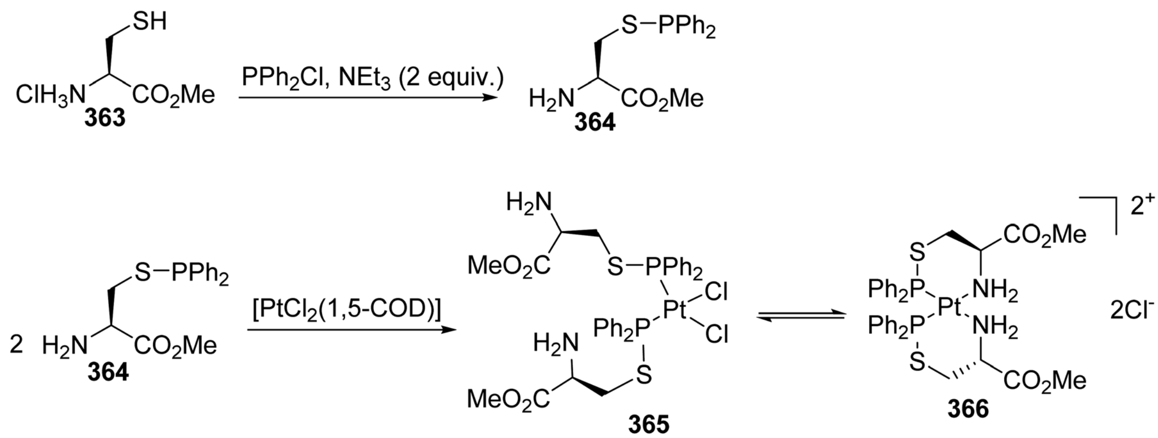
Scheme 81 The synthesis of the *S*-phosphocysteine derivative **356** *via* a Michaelis–Arbuzov type reaction.

structure of the *S*-nitrosothiol reagent. When *S*-nitrosocysteine **358** was used, the phosphite directly attacks the sulfur atom of the S–N bond, leading to the thiophosphonium salt intermediates **359–360**, which produced the corresponding phosphocysteine derivatives **361** and **362** with 82% and 83% yields, respectively, after hydrolysis (Scheme 82). The derivative **362** was also obtained with a higher yield of 90% through the reaction of nucleophilic $P(OEt)_3$ with a cystine precursor.

Chiral thiophosphinite ligands derived from cysteine and their stable complexes with platinum(II) have been prepared and characterized. The reaction of (L)-cysteine methyl ester hydrochloride with chlorodiphenylphosphine in the presence of NEt_3 proceeds quantitatively, leading to the corresponding thiophosphinite derivative **364**, as shown by ^{31}P NMR analysis (Scheme 83).[112,113] The platinum complex **365** was prepared *via* the direct addition of $[PtCl_2(1,5\text{-}COD)]$ at a ratio of 2 : 1 to the



Scheme 82 The synthesis of the phosphocysteines **361** and **362** using *S*-nitrosocysteine **358**.



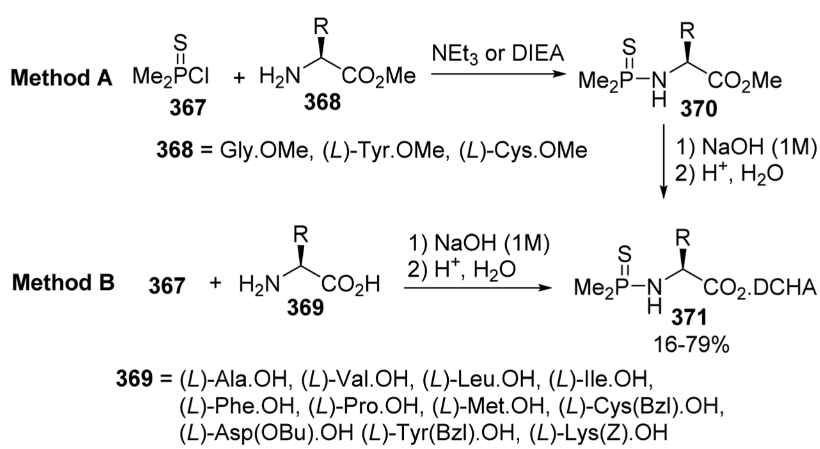
Scheme 83 The synthesis of the β-thiophosphinito amino acid ligands used in Pt-coordination chemistry.

non-isolated ligand and equilibrium with the bis-chelate **366** was observed in solution.

10. Phosphorus-containing α-amino acids with a P–N bond

10.1. *N*-Phosphinothioyl α-amino acid derivatives

Diphenylphosphinothioyl (Ppt) and dimethylphosphinothioyl (Mpt) groups were used to protect the amine groups of α-amino acids, taking advantage of the P–N bond lability under acidic conditions. While the removal of the Ppt group *via* hydrogen chloride is inappropriate for the synthesis of peptides on a large scale, more efforts have been devoted to the preparation of Mpt-amino acids and their deprotection under mild conditions.[114] They were obtained either *via* the alkaline hydrolysis of Mpt-amino esters (Method A) or *via* the direct phosphinothioylation of the free amino acids (Method B) (Scheme 84). The chloride **367** reacted more efficiently with the amino esters **368**, which were subsequently hydrolyzed using aqueous sodium hydroxide into Mpt-amino acids and isolated as dicyclohexylamine (DCHA) salts **370**, compared to direct synthesis using the amino acids **371** due to the partial hydrolysis of **367** under basic conditions.



Scheme 84 The preparation of *N*-phosphinothioyl protected α-amino acids.

The removal of the Mpt group was successfully performed using PPh_3/HCl in dichloromethane. Interestingly, Mpt removal was increased by a factor of 60 compared to the *tert*-butoxycarbonyl (Boc) group.[114] Considering the stability of the P–O bond under acidic conditions, a good orthogonal relationship between the *N*- and *O*-phosphinothioyl groups was observed. The N-Mpt group was also selectively removed to give H-(L)-Cys(Mpt)-OH with 89% yield. Mild conditions for the deprotection of the S-Mpt group, suitable for use with a Boc-strategy, were found when using tetrabutylammonium fluoride hydrate (TBAF·H_2O).[115,116] These conditions present an interesting alternative to the use of heavy metal catalysts such as $AgNO_3$ and $Hg(OAc)_2$.

10.2. *N*-Phosphoramidate α-amino acid derivatives

Nucleoside analogues have been developed for a number of decades to treat various cancers and viral infections.[117,118] The *in vivo* activation of such nucleosides is based on their phosphorylation into active di- or tri-phosphate counterparts. However, several limitations are associated with their administration as drugs, due to poor cellular permeability and because the first phosphorylation step into 5′-*O*-monophosphate derivatives is the rate-limiting step. To overcome these limitations, one of the most applied phosphate prodrug approaches is ProTide technology, which consists in masking the hydroxyl moieties of the monophosphate or monophosphonate groups using an aryl motif and an amino ester.[119,120] Then, the ProTides are metabolized inside cells by the action of an esterase and a phosphoramidase enzyme to release the free nucleoside monophosphate and monophosphonate. ProTide prodrug technology has led to the discovery of two FDA-approved antiviral drugs, sofosbuvir (Sovaldi) **8** and tenofovir alafenamide (TAF) **372** for clinical use against hepatitis C (HCV) and for human immunodeficiency virus (HIV) therapy, respectively (Fig. 2). Other ProTide prodrugs bearing various esters of (L)-alanine and aryloxy substituents in a phosphoramidate system have also been approved by the FDA and are being subjected to clinical trials for the treatment of cancers and the Ebola virus.

As the biological activity of phosphoramidate prodrugs depends on the $(S)_P$ or $(R)_P$ configuration at the phosphorus center, the development of stereoselective synthesis procedures is of major importance. The conventional preparation of phosphoramidates involves a chlorophosphoramidate electrophilic reagent **373**, which is subjected to nucleophilic substitution with a nucleoside to give a diastereomeric mixture of isomers **375** that are further separated *via* column chromatography (Scheme 85a).[121] Another approach consists of the reaction of the stereochemically pure phosphordiamidate $(S)_P$ or $(R)_P$ **376**, derived from the chiral auxiliary (*S*)-4-isopropylthiazolidine-2-thione, with the nucleoside analogue **377**. *Via* this strategy, the almost diastereomerically pure $(S)_P$ or $(R)_P$ phosphoramidate prodrug **378** (95% d.e.) was obtained (Scheme 85b).[122]

Highly stereoselective and regioselective nucleoside 5′-phosphorylation was recently reported without the use of a protecting group.[123] The strategy consists of the activation of stable chiral pentafluorophenyl reagents **379** by a dimethylaluminium chloride Lewis acid to afford the ProTides without employing 3′ protection. Optimization of 5′-selective phosphorylation was first performed to regioselectively target sofosbuvir **8** without the undesired 3′,5′-bis-ProTide. In the presence of Me_2AlCl (0.5 equiv.) and pyridine as a solvent, sofosbuvir was obtained with 84% yield and excellent diastereo- and regio-selectivity (>500 : 1; 110 : 1) (Scheme 86). This method was extended to other relevant phosphoramidate prodrugs that have been investigated for the treatment of viral infections or cancer. Methyl and benzyl phosphoryl-(L)-alaninates were used to access AZT ProTide **381** and Acelarin **382** with 94% and 80% yields, respectively. Finally, INX-08189 **383**, which is a liver targeting prodrug in phase II of clinical studies, was obtained with 81% yield and with excellent diastereo- and regio-selectivities.

10.3. Phosphoramidate peptide derivatives *via* Staudinger reactions

Phospholysine (pLys) is one of the less studied phosphorylated amino acids due to the lability of the P(O)–N bond under acidic conditions, which is an obstacle both for its identification and its synthesis. To overcome this issue, a strategy based on the chemoselective Staudinger reaction of an azidonorleucine-containing peptide was reported by Hackenberger *et al.*[124] Considering the stability of the phosphoramidate bond under alkaline conditions, it was envisaged that the Staudinger reaction could be performed starting from the azidonorleucine peptide **384**, fixed on base-labile 4-hydroxymethyl benzoic acid

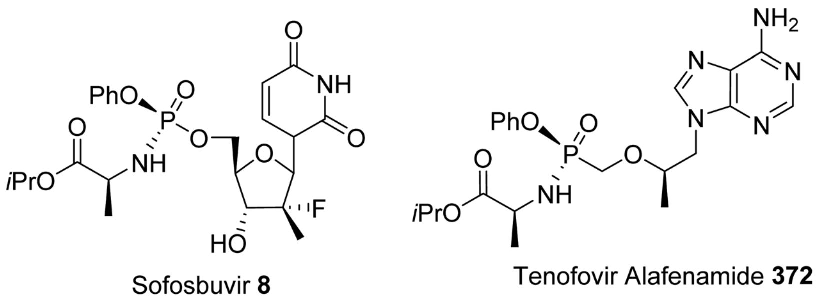
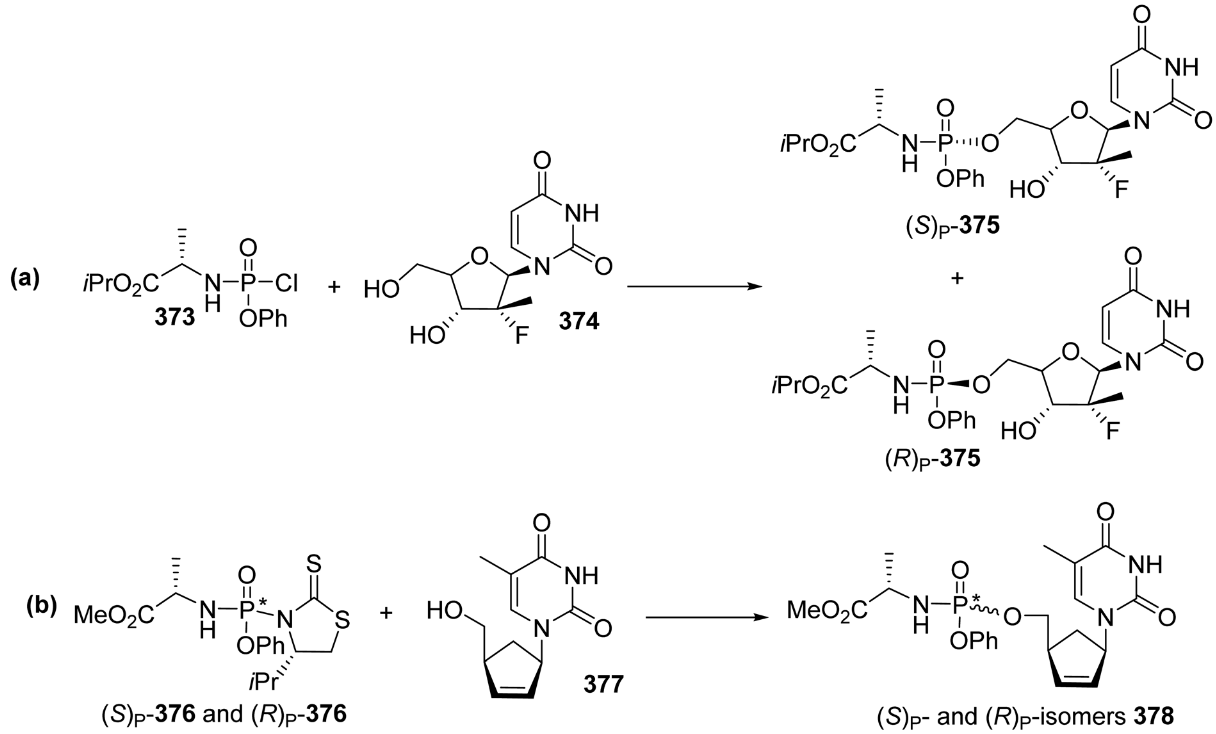
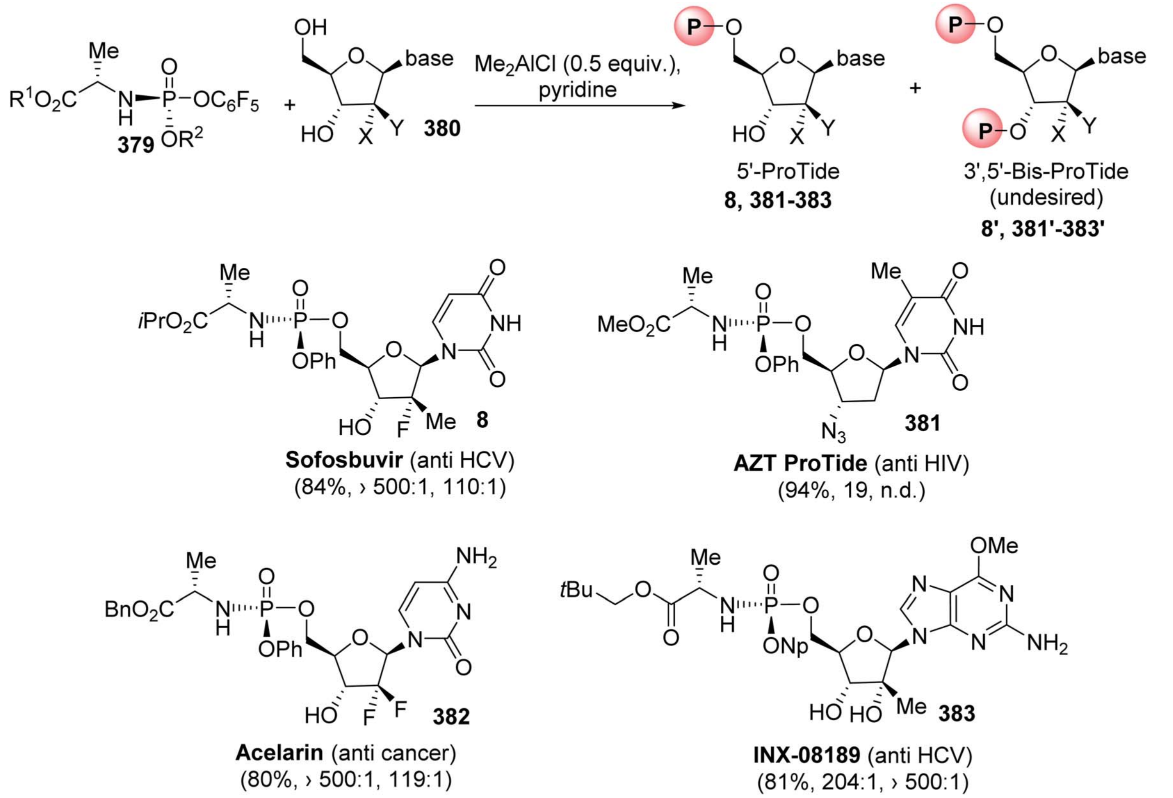


Fig. 2 Representative FDA-approved antiviral ProTides.



Scheme 85 The stereoselective synthesis of aryloxy phosphoramidate prodrugs 375 (a) and 378 (b).

(HMBA) TG resin and *ortho*-nitrobenzylphosphite (Scheme 87). The amine side chain was first deprotected by treatment with TFA in the presence of triisopropylsilane (TIS), then the unprotected peptide was subjected to the Staudinger reaction *via* incubation for 48 h with phosphite. The excess reagent was removed and the peptide was cleaved from the resin using



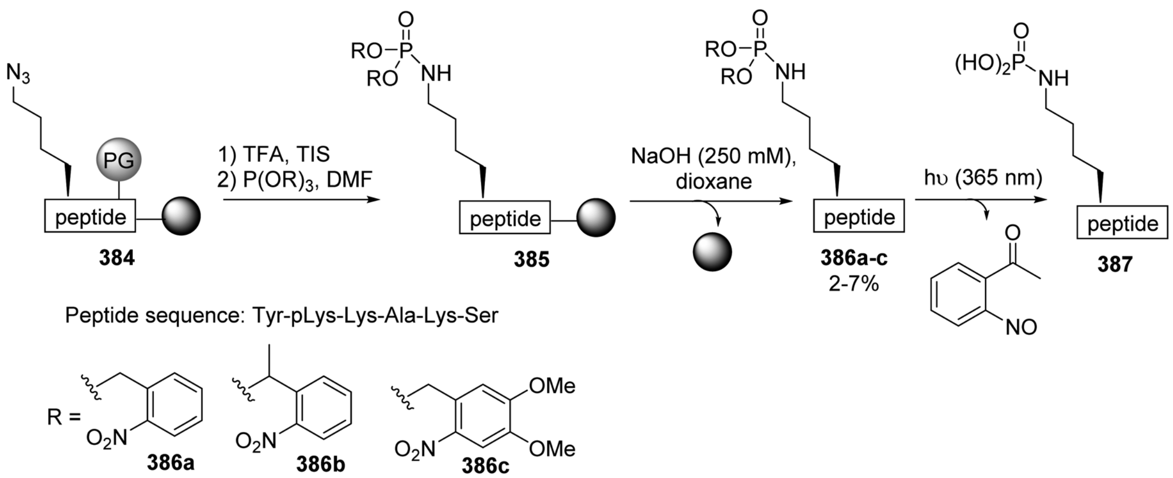
Scheme 86 The regioselective synthesis of ProTides using the pentafluorophenyl phosphoramidate reagents 379.

NaOH (250 mM). After neutralization with HCl, the corresponding phosphoramidate esters **386a–c** were identified *via* LCMS analysis and the *ortho*-nitrobenzyl moieties were released upon UV light irradiation to provide the expected phospholysine peptide **387** (Scheme 87).

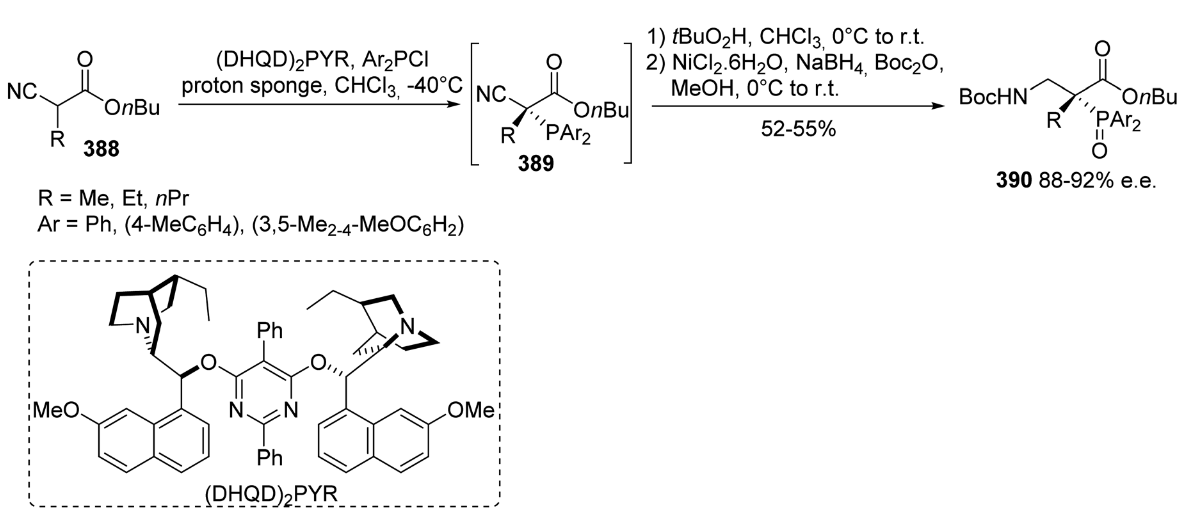
11. Phosphorus-containing β-amino acids

A few examples of β-amino acids containing a phosphorus moiety have been reported in the literature to date. To access such amino acids, asymmetric organocatalysis has been considered, owing to the efficacy of this approach in the development of optically active organophosphorus compounds. Herein, the reaction of the substituted cyanoacetates **388** with electrophilic diarylphosphine chloride led to the corresponding optically active α-phosphinocyano acetates **389**, which were further transformed into the quaternary α-phosphino β-amino acids **390** *via* a one-pot procedure (Scheme 88).[125] A *Cinchona* alkaloid $(DHQD)_2PYR$ catalyst was used in the presence of 1,8-bis(dimethylamino)naphthalene as a scavenger to consume the hydrochloric acid formed during the reaction; otherwise the catalyst would become protonated and remain inactive. Under the optimized conditions, various substituents on the cyanoacetate and different diaryl phosphines were tolerated in this reaction, providing the β-amino esters **390** with yields from 52% to 55% and enantioselectivities ranging from 88% to 92% (Scheme 88).

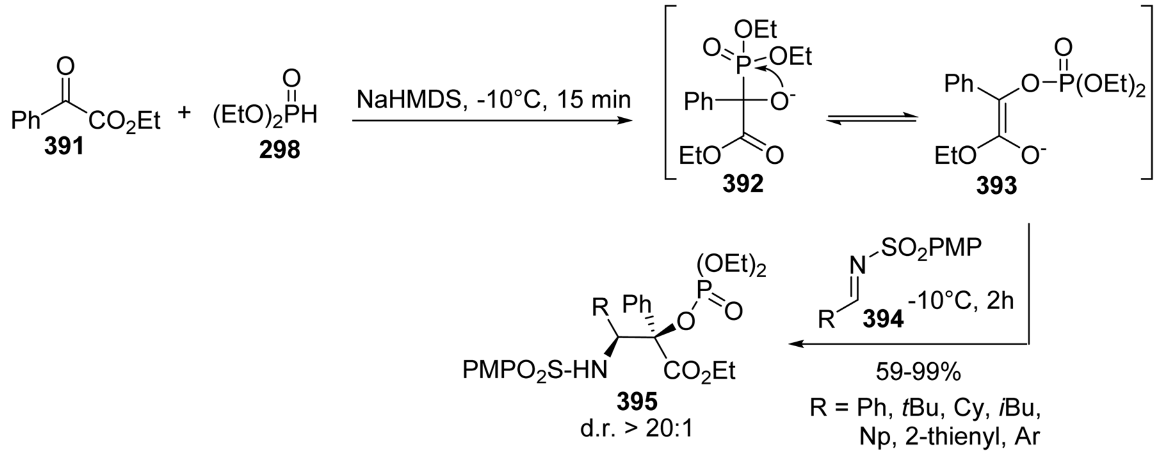
As the formation of a P–C bond could be achieved *via* the nucleophilic addition of phosphites to hybridized sp^2 carbon atoms in polarized π-bond electrophiles, this strategy was applied to the coupling of α-ketoesters with imines in the presence of phosphite under basic conditions.[126] The addition of the diethyl phosphite anion to the α-ketoester **391** followed by the [1,2]-phospha-Brook rearrangement of the intermediate **392** generated the α-phosphonyloxy enolate **393**, which was subsequently trapped by imines **394** through Mannich reactions. The use of aryl and heteroaryl *N*-sulfonyl imines as coupling partners permits the *syn* α-hydroxy-β-amino esters **395** to be selectively obtained with excellent diastereoselectivities (d.r. > 20 : 1)



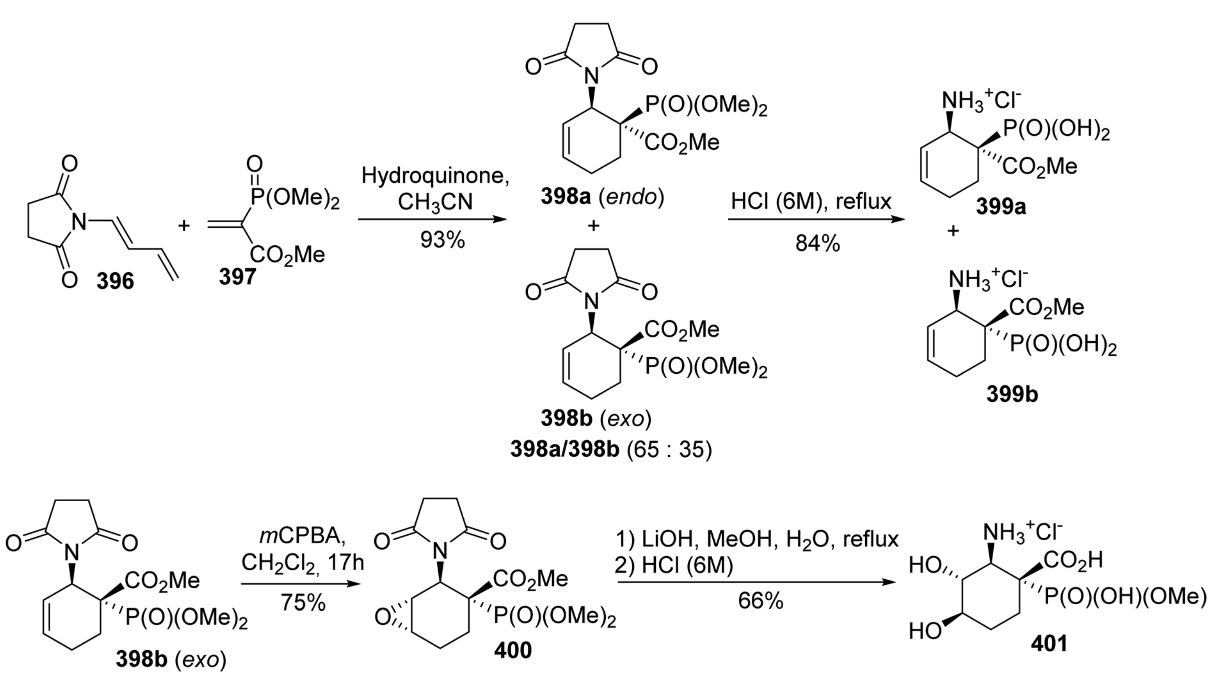
Scheme 87 The synthesis of phospholysine-containing peptides *via* the Staudinger reaction.



Scheme 88 The asymmetric synthesis of the α-phosphino β-amino acids **390** *via* the phosphination of the α-cyanoacetates **389**.



Scheme 89 The synthesis of the α-phosphonyloxy-β-amino esters **395** from the phenylglyoxylate **391** using a three-component reaction.



Scheme 90 The synthesis of cyclo-β-aminophosphonic acid derivatives using Diels–Alder cycloaddition.

(Scheme 89). This reaction was also successfully performed using aliphatic imines and heteroaromatic ketoesters and constitutes a tunable approach, since trapping the intermediate from the phosphate addition/[1,2]-phospha-Brook rearrangement with *N*-diphenylphosphinyl imine results in an aziridine derivative.

[4 + 2] Diels–Alder cycloaddition is a method of choice for the construction of regio- and stereo-selective six-membered rings. In this context, this strategy was exploited for the reaction of aminodienes with phosphonate dienophiles to afford β-aminophosphonic acids.[127] The cycloaddition of the succinimide diene **396** to the activated vinyl phosphonate dienophile **397** bearing an electron-withdrawing ester led to the cycloadducts **398a–b** with 93% yield as a mixture of *endo*/*exo* stereoisomers at a ratio of 65 : 35. Then, hydrolysis of the succinimide and the phosphonate gave the corresponding ammonium salts **399a–b** with 84% yield (Scheme 90). Functionalization of the C=C bond in the cyclohexene ring was also reported *via* oxidation with *m*-chloroperbenzoic acid, resulting in the *trans*-oxirane **400**. This was finally transformed into the *trans*-dihydroxycyclohexane **401** *via* the nucleophilic opening of the oxirane with lithium hydroxide, followed by acidic hydrolysis of the protected functional groups.

12. Conclusions

The chemistry of amino acids containing a phosphorus atom emerged as a field of study fifty years ago and it is still subject to developments that provide reagents for hemisynthesis, ligands for coordination chemistry and asymmetric catalysis, precursors for peptide labeling and bioactive compounds and bioconjugates.

Such amino acids are obtained *via* P–C, P–O, P–S or P–N bond formation. In the former case, phosphorus amino acids were reported based on phosphorus atoms in the α-, β-, γ- and δ-positions of the side chain. α-Amino acids with a C_α–P bond have been extensively used as HWE reagents to obtain α,β-dehydro-α-amino acids, which are key intermediates in the total synthesis of biomolecules, dehydropeptides or β-lactam antibiotics. Considerable efforts have been made relating to the synthesis of enantiopure alanine and proline derivatives containing a phosphine moiety in the β-position for use as chiral ligands in asymmetric catalysis with transition metal complexes. Since the discovery of the natural product (L)-phosphinothricin, numerous phosphonic analogues of aspartic and glutamic acid have been developed for their application as antagonists of the ionotropic glutamate receptors associated with neurodegenerative diseases. More recent developments concern the stereoselective synthesis of amino acids bearing a phosphorus group in the γ-position, leading to stable phosphine borane, trifluoroboronato phosphonium salt and phospholyl derivatives. Such compounds have been used as electrochemical markers or for the radio- and fluorescence-labeling of peptides. The synthesis of phosphine phenylalanine derivatives has also been investigated either through palladium-catalyzed cross coupling or *via* the direct nucleophilic substitution of halogenophenyl moieties.

In the α-amino acid series containing P–O bonds, those obtained *via* the phosphorylation of hydroxyamino acids have been extensively studied, as this is one of the most important post-translational modifications. Conjugates with serine and dipeptide derivatives based on the cyclic Cidofovir antiviral agent have been developed for minimizing its toxicity and improving its lipophilicity.

Recent methodologies to access stable analogues of phosphohistidine (pHis) and *S*-phosphocysteine, associated with signaling processes in living cells, have also recently been achieved.

Among the α-amino acids containing a P–N bond, the synthetic utility of *N*-phosphinothioyl derivatives has been demonstrated in solid-phase peptide synthesis. Also, the linkage of a phosphoryl group to the nitrogen atom of an amino acid in the form of phosphoramidate ProTides, highly potent antiviral and anticancer agents, constitutes one of the major forms of progress in the prodrug field over the last twenty years.

Conflicts of interest

There are no conflicts to declare.

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