Asymmetric Synthesis of Chiral Amino Carboxylic-Phosphonic Acid Derivatives

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Asymmetric Synthesis of Chiral Amino Carboxylic-Phosphonic Acid Derivatives

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Abstract: Chiral amino acids featuring a phosphonate pendant arm are an important type of biologically active scaffold. Here in this review, we comprehensively summarize the modern synthetic methods towards asymmetric construction of chiral amino carboxylic-phosphonic acid derivatives. The main streams of such interesting compounds include phosphono-containing α-, β-, and γ-amino acid derivatives, amino acid fluorophosphonate derivatives, amino acid cyclopropanylphosphonate derivatives, and bisphosphono-amino acid derivatives. Chiral resolution protocols, chiral auxiliary-directed syntheses, and valorization of the pool of abundant chiral amino acid resources remain contemporary concerns, and meanwhile catalytic enantioselective synthesis has also emerged as a potent strategy as demonstrated by the latest advances.

Keywords: amino acids; amino phosphonic acids; asymmetric synthesis; fluorophosphonates; organophosphonates

1. Introduction

Protein phosphorylation is one of the most widespread and extensively explored post-translational modifications.[1] While it has been found that Nature mainly performs reversible *O*-phosphorylation at the side chain of serine, threonine or tyrosine residues, the artificial manufacturing of non-hydrolyzable *C*-phosphorylated amino acids represents an extremely interesting and meaningful topic. In fact, such stable amino

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Fa-Guang Zhang received his BS degree in 2009 and PhD in 2014 under the supervision of Prof. Jun-An Ma in Tianjin University. From 2014 to 2017, he was a postdoctoral fellow with Prof. Ilan Marek at Technion-Israel Institute of Technology. In late 2017, he joined Tianjin University as an Associate Professor. His research interests focus on fluorine chemistry, strained rings, and asymmetric synthesis.

Dominique Cahard joined the CNRS in 1996 as an Associate Researcher, completed his Habilitation in 2001, and was promoted to Director of Research in 2007. He received his PhD in 1994 at the University of Rouen, France; then, enjoyed two postdoctoral positions with Pr. Chris McGuigan in Southampton (UK) and in Cardiff (Wales), and with Pr. Tadashi Nakata at RIKEN, Tokyo (Japan). His research interests concern innovative methodologies for asymmetric synthesis of fluorinated molecules and the synthesis of fluorinated biomolecules.

Jun-An Ma received his PhD in 1999 at Nankai University, then stayed there to work with Qi-Lin Zhou before taking up postdoctoral fellowships with Dr D. Cahard (CNRS, France) and Professor M. T. Reetz (MPI, Germany) from 2003 to 2005. He also spent several months as a JSPS fellow with Professor M. Sodeoka (RIKEN, Japan). In July 2005, he joined Tianjin University as a full professor. His research interests focus on new methodologies in asymmetric synthesis and organofluorine chemisty, as well as biocatalysis.

carboxylic-phosphonic acids are widely distributed in many natural products and man-made bioactive molecules (Figure 1).[2] The introduction of a tetrahedral phosphonic acid moiety within the amino acid backbone could increase the acidity and steric bulk compared with their parent counterparts, thus often resulting in significant regulation of proteases activity.[3] This medicinal merit has been intensively leveraged in the design and development of potent inhibitors for various enzymes such as glutamine synthetase, protein tyrosine phosphatase, HIV protease, and human collagenase. Furthermore, chiral amino carboxylic-phosphonic acid derivatives also hold great promise as effective synthons in asymmetric catalysis, peptide synthesis, and functional material assembling.[4–6] Therefore, it is no wonder that numerous reports have focused on the development of asymmetric synthetic approaches towards chiral amino carboxylic-phosphonic acids over the past few decades. Among them (Figure 2), the major efforts have been made on the construction of chiral α-, β-, γ-, and δ-phosphono (P) α-amino acid derivatives (parts 2.1 to 2.4). In the meantime, P-functionalization on the framework of proline, tyrosine, phenylalanine, aspartic acid, pipecolic acid, and heteroaryl-based amino acids have also been intensively explored (parts 2.5 to 2.9).

It has been widely recognized that adding fluorine into amino acids represents a powerful and versatile approach to altering their lipophilicity, metabolic stability, and acidity or basicity at nearby sites.[7–9] Therefore, fluorine substitution at the methylene carbon of amino carboxylic-phosphonates was further introduced to afford more appropriate phosphate mimics, in particular the monofluorophosphonates have similar pK_{a2} values and retain potential hydrogen bonding interactions similar to the phosphate oxygen

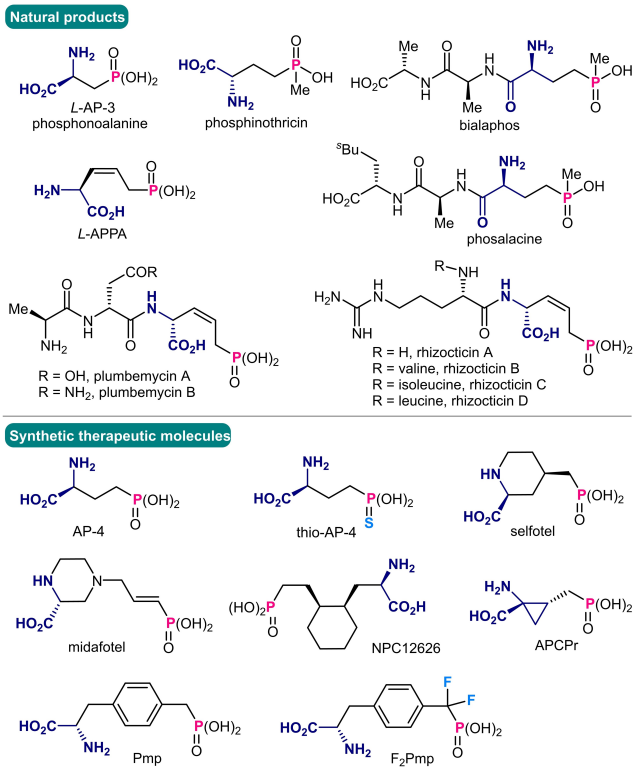


Figure 1. Naturally-occurring and representative man-made bioactive chiral amino carboxylic-phosphonic acid derivatives.

atoms. The interesting design of monofluorophosphonates and difluorophosphonates is discussed in part 3 of this review. Furthermore, the introduction of strained amino acids has been developed as a promising approach to construct conformationally constrained peptide-mimetics, among which the cyclopropane and bicycloalkane rings have emerged in specific efforts.[10–12] So this review also covers the asymmetric synthesis of P-cyclopropyl-, P-methylcyclopropyl-, and P-bicycloalkyl-amino acid derivatives (part 4). Finally, the endeavors in accessing chiral bis-P-amino acids, P-thioamino acids, as well as P-β-amino acids, and P-γ-amino acids are compiled in part 5. At the end of this review, we further point out the current challenges and possible directions in this rapidly evolving field.

While there are several reviews on the chemistry of amino phosphonic acid derivatives,[13–18] a focused overview of the chemistry of P-functionalized amino acids is surprisingly still lacking. Wardle *et al.* summarized the synthesis of ω-phosphinyl α-amino acids and their applications as therapeutic agents in 2007.[19] Very recently, Rémond, Cavelier *et al.* summarized the synthesis of selected phosphorus-containing α-amino acids.[20] However, a comprehensive analysis on this vigorous subject, especially on the asymmetric transformations to chiral molecules, has no precedence. Therefore, this review encompasses most if not all reported asymmetric synthetic methods towards chiral amino carboxylic-phosphonic acid derivatives that include chiral substrate exploitation, chiral resolution, chiral auxiliary use, and asymmetric catalysis (Figure 2). While the major attention is paid to the different stereocontrolled approaches, several reaction mechanisms and compound applications are also briefly discussed.

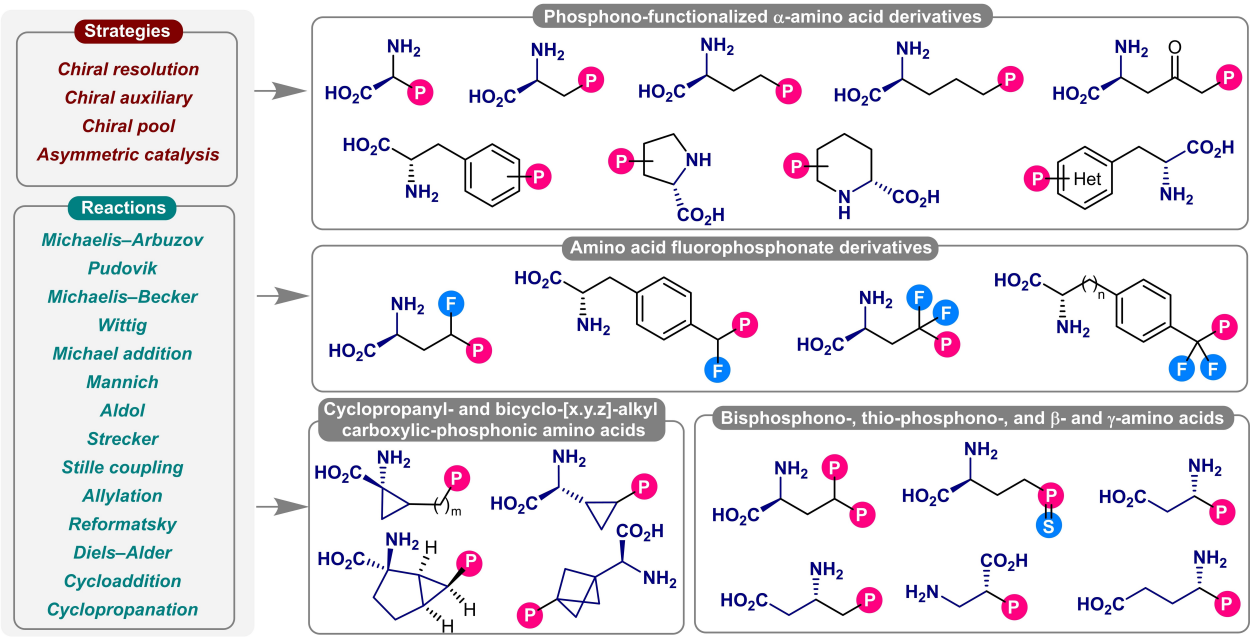


Figure 2. Representative chiral amino carboxylic-phosphonic acid derivatives, key strategies, and reactions.

2. Asymmetric Construction of Amino Acid Phosphonate Derivatives

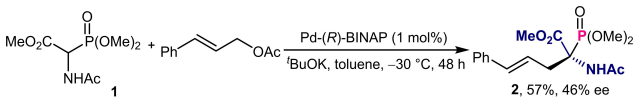
2.1. Chiral α-Phosphono-α-Amino Acids

By comparison with the abundant works on racemic α-phosphono-α-amino acids, only two asymmetric syntheses of such compounds have been reported to date. The first example of chiral non-racemic α-phosphono-α-amino acids was reported by Ito's group in 1999 (Scheme 1).[21] The racemic trimethyl *N*-acetylamino-phosphonoacetate **1** was subjected to an asymmetric allylation with cinnamyl acetate in the presence of (*R*)-BINAP and [Pd(π-allyl)(cod)]BF_4. The resulting α-phosphono-α-amino ester **2** was obtained in a synthetically useful yield, but the ee value was only 46%.

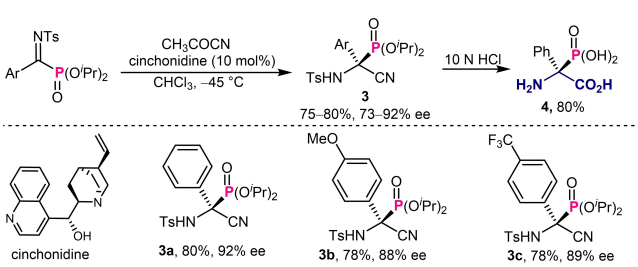
The Strecker reaction has been established as one of the most efficient methods to access chiral α-amino acids, and its application in the preparation of chiral α-phosphono-α-amino acids was first investigated by Palacios *et al.* in 2012 (Scheme 2).[22] Enantioenriched α-amino nitriles **3** were generated from α-ketimino-phosphonates with acetyl cyanide under the catalysis of cinchonidine. Furthermore, simple treatment of **3** with hydrochloric acid gave access to the tetrasubstituted phosphonated amino acid **4** in good yield.

2.2. Chiral β-Phosphono-α-Amino Acids

The simple β-phosphono-α-amino acid (3-phosphonoalanine), also called AP-3 (Figure 1), is a naturally-occurring compound that was initially found in *Zoanthus sociatus*.[23] AP-3 and its analogues have demonstrated potent activity as *N*-methyl-D-aspartate (NMDA) receptor modulators, thus their asymmetric syntheses have attracted significant attention. Enantiopure β-phosphono-α-amino acid derivatives could be obtained through three different approaches by using either a chiral auxiliary, a chiral substrate, or a chiral catalyst.



Scheme 1. Catalytic asymmetric allylation of racemic *N*-acetylamino-phosphonoacetate **1** with cinnamyl acetate.



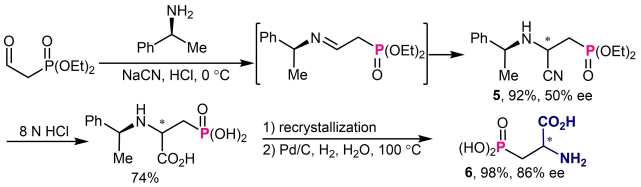
Scheme 2. Catalytic asymmetric Strecker reaction of α-ketimino-phosphonates.

2.2.1. Chiral Auxiliary Method

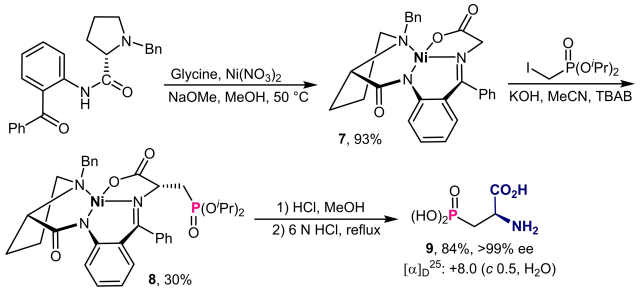
2.2.1.1. Chiral Schiff Base as the Auxiliary

As early as 1983, the first example of asymmetric synthesis of β-phosphono-α-amino acids was reported by Savignac's group (Scheme 3).[24] Enantiomerically enriched β-phosphono-amino nitrile **5** was prepared by Strecker reaction of the chiral imine in-situ generated from phosphonoacetaldehyde and (*S*)-α-methylbenzylamine. Acid hydrolysis and debenzylation proceeded without any epimerization, thus giving the corresponding β-phosphono-α-amino acid **6** with 86% ee.

Another example of using chiral Schiff base as the chiral auxiliary was developed by Kukhar's group in 1992 (Scheme 4).[25] The chiral nickel(II) complex **7** generated from *N*-benzyl-(*S*)-proline derivative and glycine was used as the key chiral building block. Stereoselective alkylation of **7** with iodomethyl diisopropylphosphite occurred under basic conditions to give alkylated Schiff base **8** as a single diastereoisomer, albeit in low yield. After hydrolysis, the β-phosphono α-amino acid **9** was obtained in 84% yield with 99% ee. In addition, most of the chiral proline auxiliary (60–85%) could be recovered after the reaction sequence.



Scheme 3. Asymmetric Strecker reaction for the synthesis of 3-phosphonoalanine.

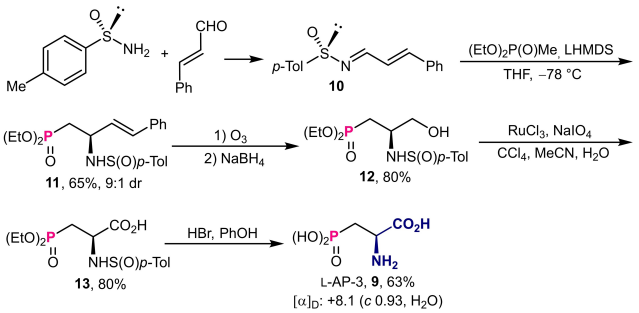


Scheme 4. Asymmetric alkylation of chiral nickel(II) complex **7** for the synthesis of 3-phosphonoalanine.

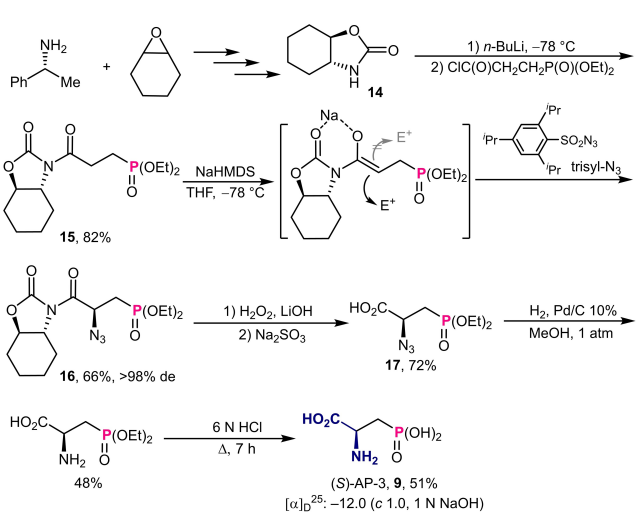
Enantiopure sulfinimine **10** prepared from (*S*)-4-methyl-benzenesulfinamide and cinnamaldehyde has also been used in the preparation of chiral AP-3 derivatives (Scheme 5).[26] The key step was a diastereoselective carbon-carbon bond formation reaction of α-phosphonate carbanion with imine **10** to give the corresponding adduct **11**. Subsequent process to chiral phosphono-amino acid **9** was completed after three additional steps (tandem ozonolysis/reduction, oxidation, and hydrolysis) via intermediates **12** and **13** in a 40% total yield. It is worth mentioning that both (*S*)- and (*R*)-enantiomers of β-phosphono amine **11** could be obtained by selecting the antipodal sulfinamide auxiliary.

2.2.1.2. Chiral Oxazolidinone as the Auxiliary

Enantiopure hexahydrobenzoxazolidin-2-ones **14** could be conveniently prepared from inexpensive cyclohexene oxide and (*S*)-α-phenylethylamine. The potential of **14** as an effective chiral auxiliary in the asymmetric synthesis of α-amino-β-phosphonocarboxylic acids was demonstrated by Juaristi *et al.* in 2006 (Scheme 6).[27] The phosphonate group was introduced by simple amidation with phosphono-carbonyl chloride in 82% yield. Then, the amide **15** was treated with NaHMDS to form the sodium enolate, which was azidated with trisyl azide with excellent diastereoselectivity. Removal of the chiral auxiliary of azido compound **16** gave the corresponding product **17**. Subsequent hydrogenation and hydrolysis of the azido phosphonate furnished the desired amino carboxylic-phosphonic acid (*S*)-AP-3 **9** in a satisfactory yield.



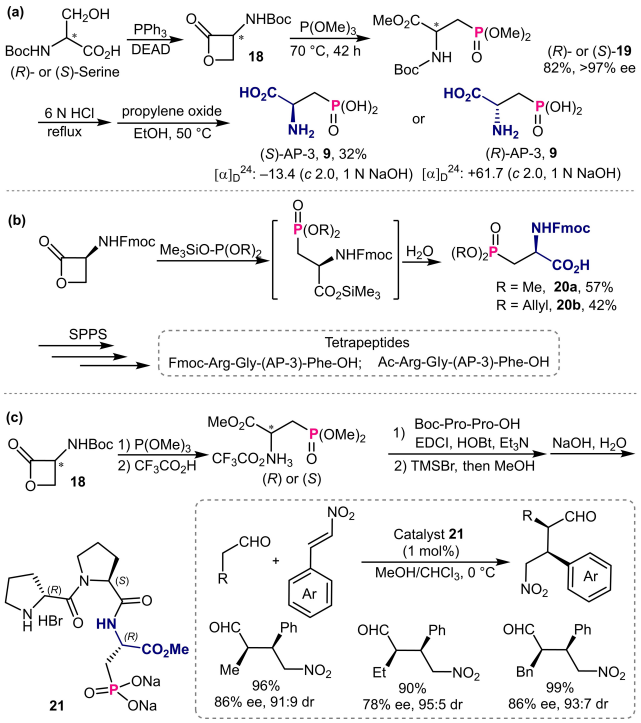
Scheme 5. Asymmetric 1,2-addition of $(EtO)_2P(O)Me$ to enantiopure sulfinimine for the synthesis of 3-phosphono-alanine.



Scheme 6. Asymmetric azidation of *N*-acylated oxazolidinone for the synthesis of (*S*)-AP-3.

2.2.2. Chiral Substrate Method

Enantiopure β-lactones could be easily obtained by an intramolecular Mitsunobu reaction of commercially available serine derivatives as originally developed by Vederas's group in 1985.[28,29] Importantly, versatile chiral amino acid derivatives could be smoothly afforded upon highly stereoselective ring-opening reactions of β-lactones with different nucleophiles. This practical strategy was extended to the synthesis of chiral amino carboxylic-phosphonic acids by Smith *et al.* in 1990 (Scheme 7a).[30] Nucleophilic ring-opening of (*S*)-β-lactone **18** with trimethyl phosphite produced the corresponding (*S*)-β-phosphono α-amino ester **19** in 82% yield; the (*R*)-enantiomer was similarly obtained according to the same procedure beginning from (*R*)-β-lactone. Acid hydrolysis, followed by treat-



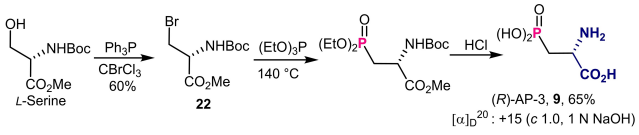
Scheme 7. Asymmetric ring-opening reactions of chiral α-amino-β-lactones for the synthesis of 3-phosphonoalanines.

ment with propylene oxide, produced both enantiomers of AP-3. In 1992, Hutchinson and Parkes used the more nucleophilic silyl phosphites to open the lactone and provided rapid access to optically pure Fmoc-D-AP-3 **20 a** (Scheme 7b).[31] In 1998, Lohse and Felber applied this strategy to the asymmetric synthesis of chiral amino carboxylic diallyl-phosphonate **20 b**, and this phosphonic acid isostere of aspartic acid was further successfully incorporated into two tetrapeptides via a general solid-phase peptide synthesis (SPPS) technique (Scheme 7b).[32] More recently, this chemistry has also been intensively explored by Lecouvey's group for the design of novel organocatalysts **21** featuring a polyfunctional tripeptide skeleton (Scheme 7c).[33–35] These organocatalysts behave efficiently in promoting enantioselective Michael addition reactions of nitroalkenes with aldehydes.

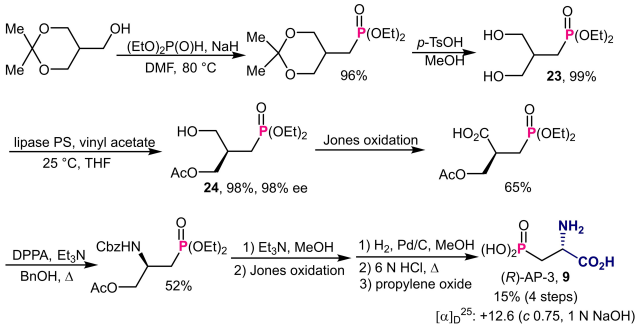
Alternatively, L-serine could also be converted into chiral β-phosphono-α-amino acid AP-3 without the formation of lactone. In 2010, this complementary protocol was reported by Kolodyazhnaya and Kolodyazhnyi who used the brominated intermediate **22** to undergo Michaelis–Arbuzov reaction for the formation of the key C–P bond (Scheme 8).[36]

2.2.3. Chiral Catalytic Method

Catalytic asymmetric synthesis generates chiral stereocenters with a small amount of chiral inductor, thus avoiding the use of stoichiometric amount of chiral material or auxiliary. The first catalytic asymmetric approach to chiral β-phosphono-α-amino acids was



Scheme 8. The Michaelis–Arbuzov reaction of brominated L-serine for the synthesis of (*R*)-AP-3.



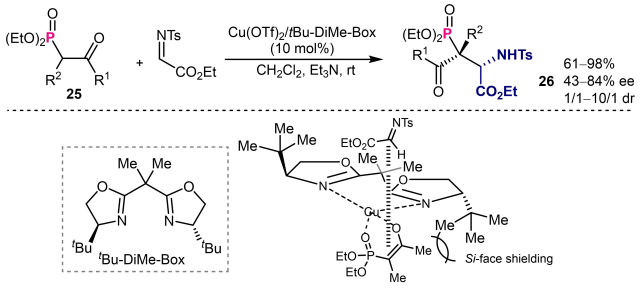
Scheme 9. Lipase-catalyzed enantioselective desymmetrization of 2-phosphonomethyl-1,3-propanediol for the synthesis of (*S*)-AP-3 **9**.

reported by Shibuya *et al.* in 1996 (Scheme 9).[37] The phosphono-1,3-propanediol **23** was prepared from easily available triol derivative via Michaelis-Becker reaction followed by simple acidic deprotection. Then, a bio-catalytic enantioselective transesterification of **23** with vinyl acetate was scrutinized by using diversified commercially available lipases. The desired monoacetate **24** was obtained via this enantioselective desymmerization reaction in up to 98% yield with 98% ee in the presence of lipase PS in THF at 25 °C. Subsequent oxidation of **24** with Jones reagent brought in the carboxyl group, which was transformed into the amino group with diphenyl-phosphoryl azide (DPPA) by virtue of the Curtius rearrangement. Afterwards, Jones oxidation was operated again to regenerate the carboxylic moiety on the other side chain. Finally, hydrogenolysis and acid hydrolysis produced the β-phosphono-α-amino acid (*R*)-AP-3 **9** in a good overall yield.

An example of organometallic Lewis acid-catalyzed asymmetric synthesis of β-phosphono-α-amino acid derivatives was disclosed by Jørgensen's group in 2005 (Scheme 10).[38] By adding β-keto phosphonates **25** to *N*-tosyl-α-imino ester in the presence of a chiral copper-bisoxazoline complex, an array of β-phosphono-α-amino esters **26** could be obtained in high yields with moderate diastereoselectivities and good enantioselectivities. A bidentate coordination mode of the nucleophile to the copper complex causes shielding of the *Si*-face leaving the *Re*-face open to approach by *N*-tosyl-α-imino ester.

2.3. Chiral γ-Phosphono-α-Amino Acids

Phosphinothricin (glufosinate) is a C–P-containing natural product, and has been universally used as herbicide worldwide by acting as a potent inhibitor of glutamine synthetase (GS) in high plants (Figure 1).[39,40] AP-4 (2-amino-4-phosphonobutyric acid) is known as the first selective agonist for group III metabotropic glutamate receptors (Figure 1), and itself along with its numerous analogues have been investigated as potential therapeutic agents for central



Scheme 10. Cu-catalyzed asymmetric synthesis of β-phosphono-α-amino acid derivatives.

nervous system diseases.[41] The remarkable biological activities of these γ-phosphono-α-amino acids make them attractive synthetic targets for organic chemists, particularly when it comes to asymmetric versions.

2.3.1. Chiral Substrate Method

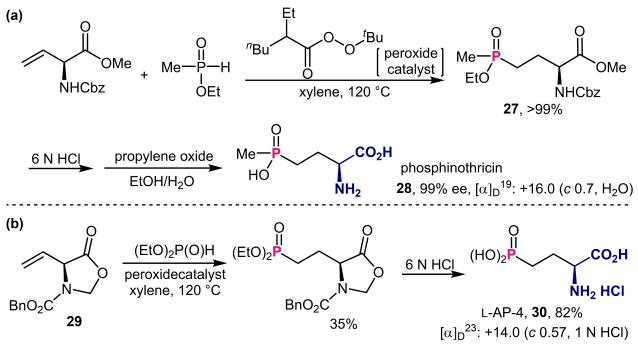
To produce optically pure γ-phosphono-α-amino acids, chiral substrate transformation is the most widely employed strategy, which takes advantage of the chiral information from easily available starting materials involving C–P, C–C, or C–N bond connection.

2.3.1.1. C–P Bond Connection

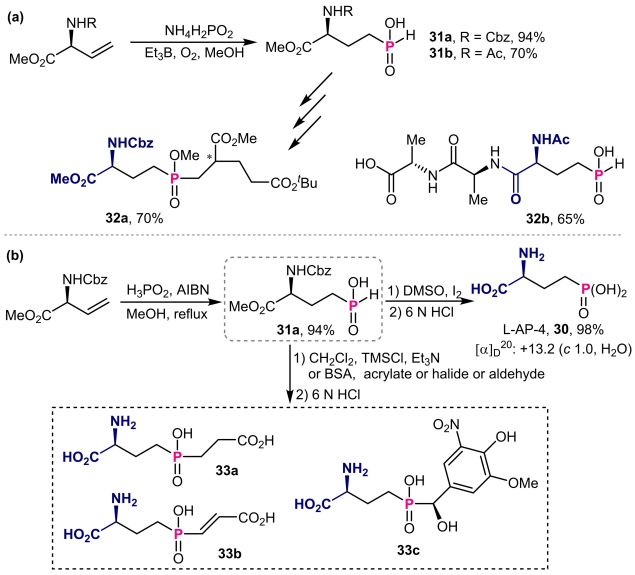
Apart from their numerous biological activities, abundant amino acid derivatives are enjoying renewed popularity as practical chiral synthons. Because the carboxylic and amino groups are already present in the molecular skeletons with accessibility of the antipodal absolute configurations, the key step is to build the C–P bond to introduce a phosphate group.

L-(+)-Methionine-derived vinylglycines are common and useful building-blocks in the asymmetric synthesis of γ-phosphono-α-amino acids. For example, Zeiss described the facile application of vinylglycine to prepare enantiopure L-phosphinothricin **28** and L-AP-4 **30** (Scheme 11).[42] Radical P-aza-addition reaction of methylphosphinate to vinyl glycine, executed under catalysis by means of peroxides, produced the adduct **27** in quantitative yield. Subsequent hydrolysis gave L-phosphinothricin **28** with more than 99% ee (Scheme 11a). A similar procedure could also be used to synthesize L-AP-4 **30** from protected vinylglycine **29**, albeit in relatively low yield and enantiopurity (Scheme 11b).

In 2005, Bartley and Coward employed ammonium hypophosphite as the phosphorylation reagent of vinylglycines under Et_3B/O_2 conditions for the asymmetric synthesis of phosphinothricin **31 a** (Scheme 12a).[43] Further nucleophilic transformation of **31 a** and conjugate addition to 2-methyleneglutaric acid derivative furnished the phosphinate pseudopeptide **32 a**. Subsequently, Liu *et al.* used this protocol for the asymmetric synthesis of phosphinothricin **31 b** and phosphinothricin tripeptide **32 b** (Scheme 12a).[44] Notably, Acher *et al.* devised a more practical H_3PO_2/AIBN combination to construct the central C–P bond of **31 a** in high yield (Scheme 12b).[45–47] Oxidation of **31 a** in DMSO with a catalytic amount of iodine led to the formation of L-AP-4 **30** in excellent yield. Based on this procedure, a series of the group III metabotropic glutamate receptor agonists (such as **33 a**–**c**) were prepared in good yields.

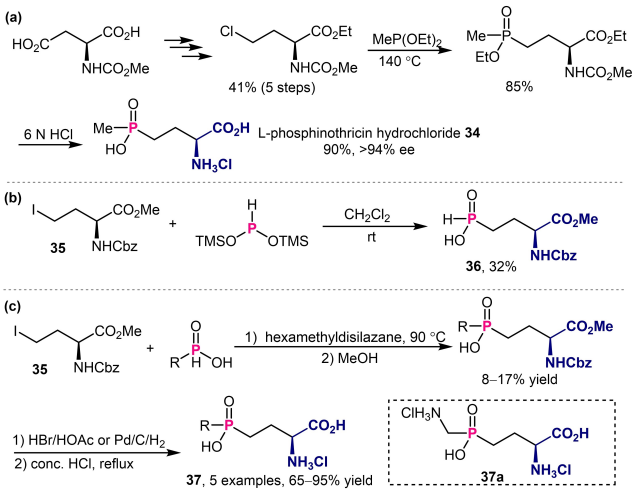


Scheme 11. Asymmetric transformation of vinylglycines into γ-phosphono-α-amino acid derivatives.



Scheme 12. Asymmetric transformation of vinylglycines into phosphinothricin derivatives.

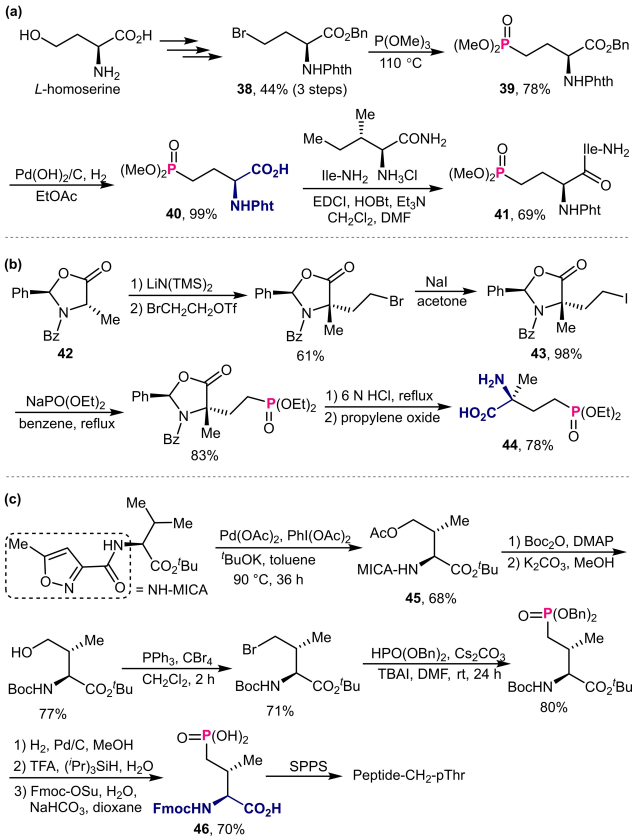
The Michaelis–Arbuzov reaction is a general strategy to build C–P bond, and has also been frequently used in the preparation of phosphono-derivatives from amino acid halides. For example, Hoffmann and Zeiss employed the inexpensive L-aspartic acid as the starting material to produce amino acid chloride in 41% yield within 5 steps (Scheme 13a).[48] Then, the key Arbuzov reaction of with diethyl methylphosphonite proceeded well under heating conditions. Final hydrolysis furnished the L-phosphinothricin hydrochloride **34** in 90% yield with over 94% ee. Amino acid iodide **35** was used by Tanner *et al.* to react with in-situ generated bis(trimethylsilyl)phosphonite to produce the chiral γ-phosphinic acid **36** under mild conditions, albeit in low yield (Scheme 13b).[49] In 2005, Kafarski *et al.* further modified this protocol by using hexamethyldisilazane as the base (Scheme 13c).[50] After hydrolysis, several phosphinothricin analogues **37** were obtained and **37 a** proved to be equipotent to phosphinothricin as a competitive inhibitor of glutamine synthetase.



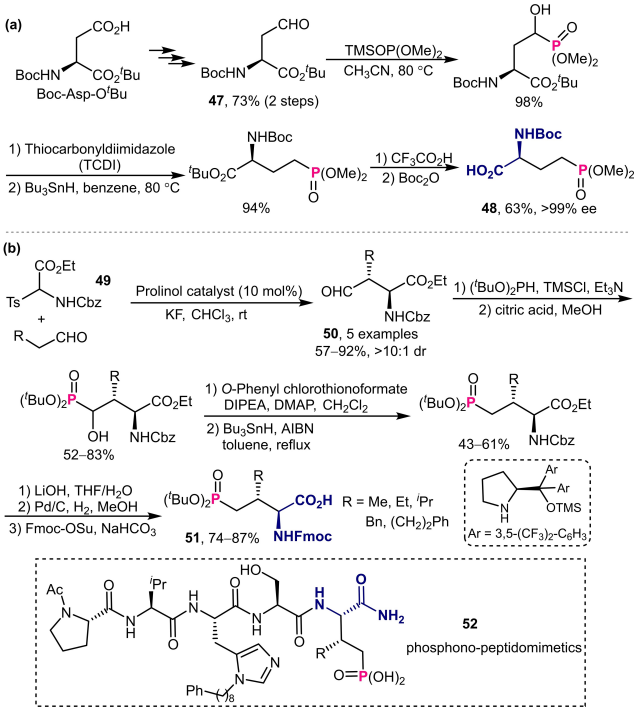
Scheme 13. The Michaelis–Arbuzov reaction for the asymmetric construction of γ-phosphono-α-amino acids.

The use of amino acids featuring a bromoalkyl chain to make AP-4 derivatives was descried by Hangauer *et al.* (Scheme 14a).[51] Bromide **38** was prepared from commercially available L-homoserine in 44% yield after 3 steps, and subjected to Michaelis-Arbuzov reaction conditions to give the phosphonate **39** in 78% yield. Coupling of phosphono-amino acid **40** with Ile-NH_2 delivered the dipeptide **41** in good yield. The construction of quaternary carbon stereocenters has been a significant challenge in asymmetric synthesis. In this context, Ma *et al.* reported an asymmetric entry to chiral methylated AP-4 derivative MAP-4 **44** (Scheme 14b).[52] 2-Phenyloxazolidinone **42** was first converted into the iodide **43**, and then the C–P bond was forged via the Michaelis–Becker reaction. Subsequently, Chen *et al.* further applied this strategy to the asymmetric synthesis of the chiral phosphono-threonine derivative **46** (Scheme 14c).[53] The homothreonine **45** was generated from the protected valine via a palladium-catalyzed γ-methyl C (sp^3)–H bond activation. The C–P bond was constructed via the Michaelis–Becker reaction with HP(O)$(OBn)_2$ under basic conditions. Subsequent functional group interconversions gave the Fmoc-pThr **46** in good yield, which was further subjected to SPPS to access two phosphono-peptide inhibitors.

The Pudovik reaction could introduce the phosphonate group into aldehydes or imines to afford α-hydroxyl- or amino-phosphonates. Johns' group applied this protocol for the asymmetric synthesis of chiral AP-4 derivatives (Scheme 15a).[54] Amino carboxylic aldehyde **47** derived from *N*-Boc tert-butyl aspartate was phosphonylated in excellent yield by the



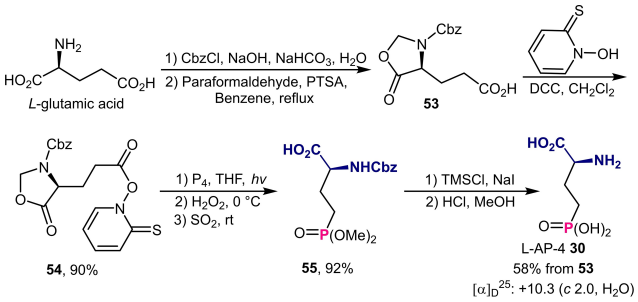
Scheme 14. The Michaelis–Becker reaction for the asymmetric synthesis of γ-phosphono-α-amino acids.



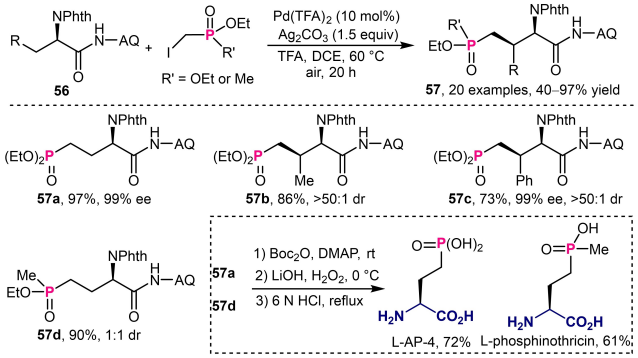
Scheme 15. The Pudovik reaction for the asymmetric synthesis of γ-phosphono-α-amino acid derivatives.

Pudovik reaction using trimethylsilyl methyl phosphonate. Following Barton-McCombie deoxygenation and hydrolysis gave the phosphonate amino acid **48** in good overall yield with >99% ee. With the aid of a similar strategy, Hymel and Burke achieved an efficient synthesis of a group of pThr-containing peptides that could bind to the polo-box domain (PBD) of polo-like kinase 1 (Scheme 15b).[55] A prolinol-catalyzed stereoselective Mannich-type reaction of imine precursor **49** with aldehyde was used to produce the optically pure aldehydes **50**. Then, the Pudovik reaction of **50** with di-tert-butyl phosphite gave the adduct, which was subjected to radical deoxygenation to cleave the hydroxyl group. Five substituted γ-phosphono amino acids **51** were obtained on gram-scale in 22–25% overall yield (8 steps). Notably, these phosphothreonine analogues were successfully incorporated into peptide sequence **52** and exhibited enhanced activity as PBD-binding inhibitors.

Alternatively, Barton and Embse developed an interesting radical phosphonylation approach to L-AP-4 with white phosphorus (Scheme 16).[56] L-Glutamic acid was first protected as an oxazolidinone **53**, and the carboxylic acid was converted to the pyridine thione intermediate **54** (Barton ester). Photolysis of this ester and radical phosphorylation with elemental phosphorus were conducted followed by a two-step oxidation procedure to yield the phosphono amino acid **55** in good yield. This protocol provided a simple and efficient method to access L-AP-4 **30** with improved yield.



Scheme 16. Asymmetric transformation of L-glutamic acid to L-AP-4.



Scheme 17. Pd-catalyzed C(sp^3)–H alkylation for the asymmetric synthesis of γ-phosphono-α-amino acid derivatives.

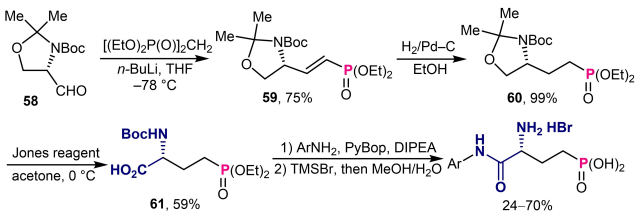
2.3.1.2. C–C Bond Connection

In 2017, Yang's group devised an interesting method to construct chiral γ-phosphono-α-amino acids via an 8-aminoquinoline (AQ)-directed C(sp^3)–H alkylation of α-amino acid derivatives under palladium catalysis conditions (Scheme 17).[57] The methylene C(sp^3)–H site of substrates **56** was connected with phosphono-alkyl iodides with excellent diastereoselectivity and enantioselectivity, thus offering facile access to a diverse array of chiral phosphono-amino amides **57**. Furthermore, asymmetric preparation of L-AP-4 **30** and L-phosphinothricin **28** on a gram-scale was also operated to showcase the synthetic utility of this transformation.

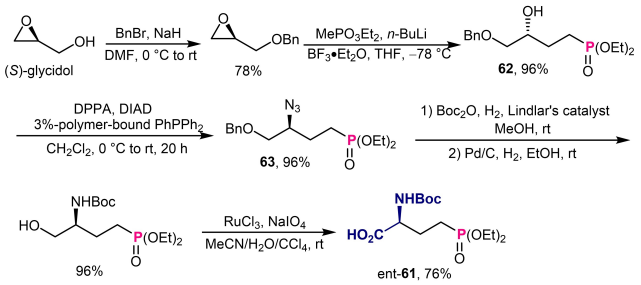
L-serine-derived Garner's aldehyde **58** was reacted with nucleophilic methylene bisphosphonate anion to give the vinyl phosphonate product **59** in good yield (Horner-Wadsworth-Emmons reaction, Scheme 18).[58] The resulting alkene function in **59** was then hydrogenated over Pd/C to furnish **60**, which was further treated with Jones reagent to afford the corresponding γ-phosphono amino acid **61**. Moreover, the Macdonald group also coupled **61** with aryl amines to give a series of *N*-arylamide phosphonates, which are selective agonists or antagonists of sphingosine 1-phosphate (S1P) receptors.

2.3.1.3. C–N Bond Connection

Alternatively, Macdonald *et al.* developed a C–N bond connection strategy for the asymmetric synthesis of the anti-enantiomer of **61** (Scheme 19).[58] (*S*)-Glycidol was employed as chiral starting material and transformed into monoprotected phosphonodiol **62** via a nucleophilic ring-opening of epoxide with lithiated diethyl methylphosphonate in the presence of $BF_3{\cdot}Et_2O$. The key C–N bond formation was realized by the Mitsunobu reaction using DPPA as the nitrogen source. The azide **63** was then subjected to the



Scheme 18. Asymmetric transformation of Garner's aldehyde into γ-phosphono-α-amino acid derivatives.



Scheme 19. Mitsunobu reaction for the asymmetric synthesis of γ-phosphono-α-amino acid.

sequential reduction/deprotection/oxidation process to furnish the target phosphono-amino acid (ent-**61**) in 40% overall yield from (*S*)-glycidol.

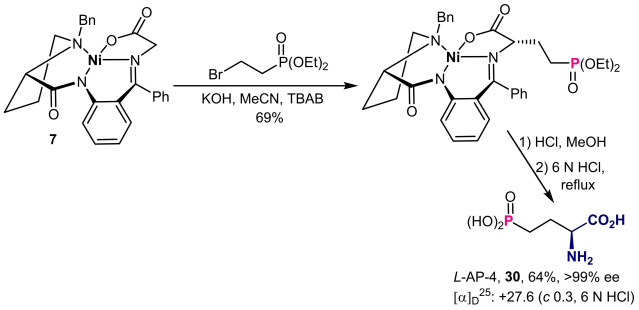
2.3.2. Chiral Auxiliary Method

Published examples for the asymmetric synthesis of γ-phosphono-amino acids involving the use of chiral auxiliaries can be classified into three major types: Schiff bases, Schöllkopf bis-lactim ethers, and oxazolidinones.

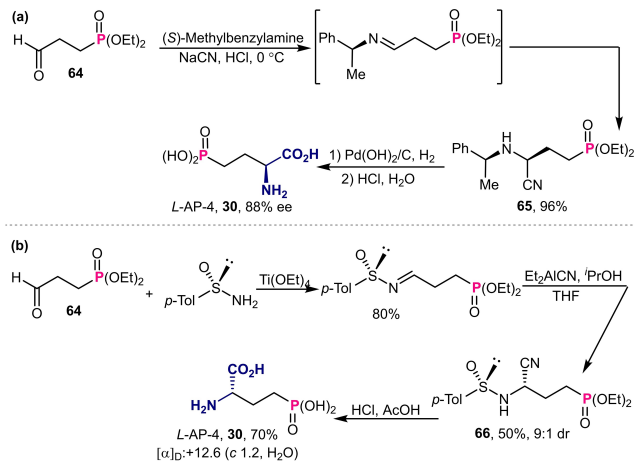
2.3.2.1. Chiral Schiff Base as the Auxiliary

The Strecker reaction of phosphono-containing chiral Schiff base was developed to access enantiomerically pure phosphono-amino acids. For instance, by using phosphono-aldehyde **64**, the corresponding amino nitrile **65** was obtained in 96% yield (Scheme 20a).[24] Then, direct debenzylation and hydrolysis furnished L-AP-4 **30** with 88% ee. In a similar manner, the chiral sulfinamide could also be employed as the directing group as reported by Mikołajczyk *et al.* (Scheme 20b).[59] Diethylaluminum cyanide was used as the nucleophile to react with Schiff base to provide the adduct **66** in 9:1 diastereomeric ratio. Simple hydrolysis delivered the desired L-AP-4 **30** in good yield. Chiral nickel complex **7** was previously shown to be an effective precursor for the synthesis of AP-3 derivatives (see Scheme 4).[25] This approach could also be modified with a longer chain-possessing phosphonate bromide, thus offering another rapid route to L-AP-4 **30** (Scheme 21).

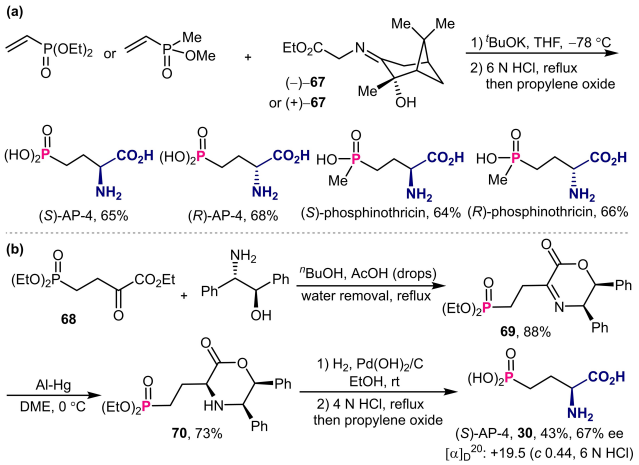
Minowa *et al.* made use of chiral glycine Schiff bases (−)-**67** and (+)-**67** as the nucleophilic donors to undergo the Michael addition reactions with vinyl phosphonates in the presence of ^{t}BuOK.[60] After hydrolysis, both enantiomers of AP-4 and phosphinothricin were all obtained in good yields with high optical purities (Scheme 22a). In addition, Hu *et al.* reported the condensation of phosphono-α-carbonyl ester **68** with chiral amino alcohol to yield the cyclic ketimine **69**.[61] The key step of this method was a diastereoselective Al–Hg reduction of **69** to give the amino ester **70**. After chiral auxiliary removal, the



Scheme 21. Asymmetric alkylation of chiral nickel(II) complex **7** for the synthesis L-AP-4.



Scheme 20. Strecker reaction for the asymmetric synthesis of L-AP-4.

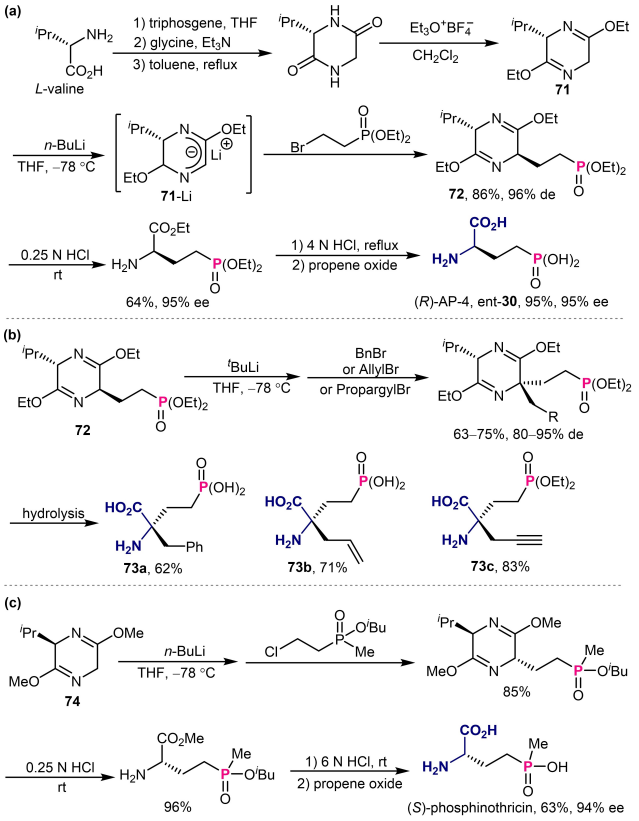


Scheme 22. Asymmetric transformation of chiral Schiff bases into AP-4 and phosphinothricin.

desired AP-4 **30** was provided with moderate ee value (Scheme 22b).

2.3.2.2. Chiral Schöllkopf Bis-lactim Ether as the Auxiliary

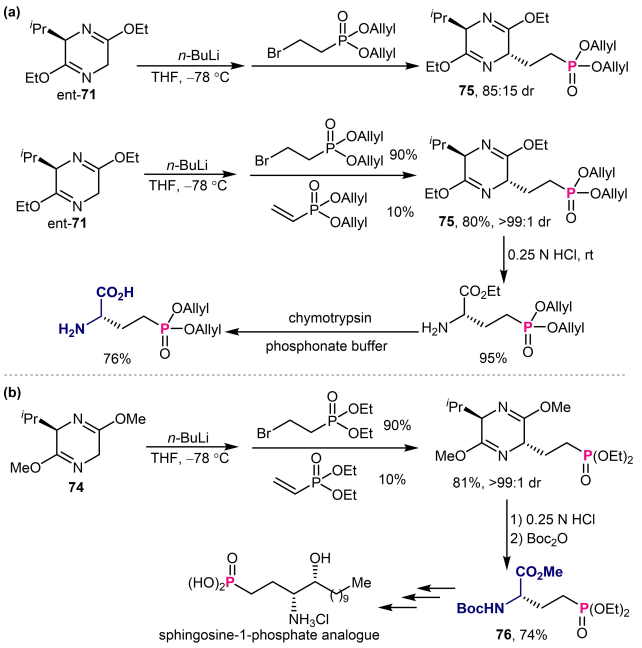
Another chiral auxiliary that is also commonly used for the asymmetric construction of γ-phosphono α-amino esters is the Schöllkopf bis-lactim ether, which is easily prepared from valine and glycine (Scheme 23).[62] In 1986, Schöllkopf *et al.* first reported the utilization of lithiated bis-lactim ether **71**-Li as the nucleophile to undergo diastereoselective alkylation reaction with different alkyl halides. After hydrolysis, this method offered an efficient route to chiral AP-4 (ent-**30**) with 95% ee (Scheme 23a). Interestingly, the intermediate **72** could be further treated with tert-butyl lithium and alkylated to form challenging quaternary carbon stereocenters with high diastereoselectivity (Scheme 23b). Subsequent acid hydrolysis provided the chiral γ-phosphono α-amino acids **73**. Furthermore, Zeiss applied Schöllkopf bis-lactim ether **74** as the chiral auxiliary to produce (*S*)-phosphinothricin (Scheme 23c).[63]



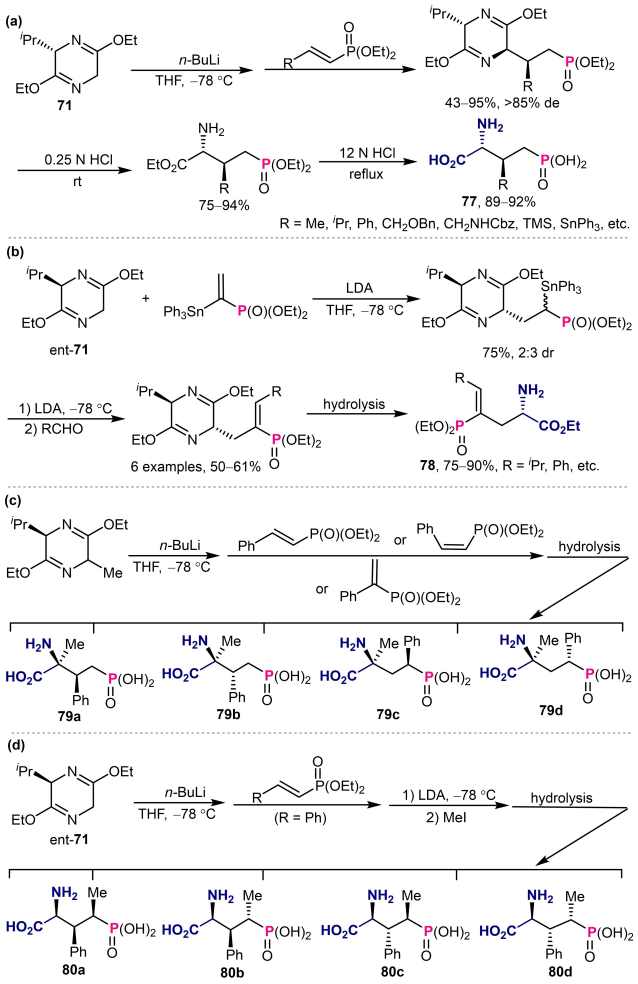
Scheme 23. Asymmetric alkylation of Schöllkopf bis-lactim ethers for the construction of γ-phosphono-α-amino acid derivatives.

Shapiro *et al.* conducted the alkylation of Schöllkopf bis-lactim ether (ent-**71**) with diallyl bromoethylphosphonate to produce **75**, but only with 85:15 dr (Scheme 24a).[64] Interestingly, enhanced diastereoselectivity was observed when a mixture of bromoethylphosphonate and vinylphosphonate (90:10) was employed as the electrophiles. A similar result was also reported by Sandhoff's group, in which the obtained phosphonic amino acid **76** was further transformed to a sphingosine-1-phosphate analogue (Scheme 24b).[65] The Michael addition of lithiated Schöllkopf bis-lactim with vinylphosphonate was proposed to proceed faster than the competitive alkylation process with bromoethylphosphonate, thus accounting for the observed improved diastereoselectivity.

Inspired by these primary findings, Ojea and Ruiz *et al.* substantially extended the scope and practical application of this method for the asymmetric preparation of various γ-phosphono α-amino acids **77**, such as the β-alkyl-, β-aryl-, and β-silyl-substituted ones (Scheme 25a).[66,67] In addition, a series of 4-alkylidene-AP-4 derivatives **78** were also obtained by the *Z*-selective olefination of α-stannyl-stabilized carbanions with carbonyl electrophiles (Scheme 25b).[68,69] An array of tetrasubstituted amino acids **79** were also easily accessible via the Michael conjugate addition of substituted-Schöllkopf agents to vinylphosphonates (Scheme 25c).[70] Furthermore, the enantiomerically pure β,γ-disubstituted AP-4 derivatives **80** were constructed via a tandem Michael addition/alkylation sequence with good results (Scheme 25d).[71]



Scheme 24. Asymmetric addition of Schöllkopf bis-lactim ethers for the construction of γ-phosphono-α-amino acid derivatives.



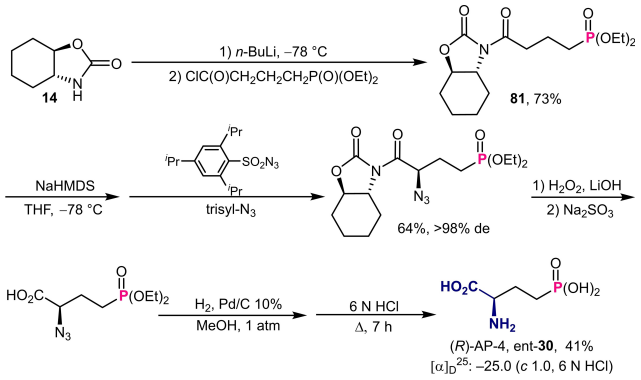
Scheme 25. Asymmetric synthesis of substituted AP-4 analogues.

2.3.2.3. Chiral Oxazolidinone as the Auxiliary

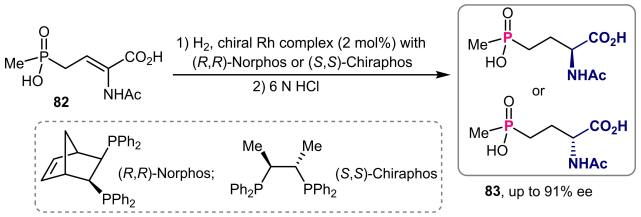
The enantiopure hexahydrobenzoxazolidin-2-one **14** was used by Juaristi *et al.* to produce chiral AP-4 (Scheme 26).[27] The phosphonate group was introduced by an amidation reaction of phosphono-carbonyl chloride in good yield. The stereoselective azidation of **81** was achieved after deprotonation at low temperature (> 98% de). Subsequently, non-racemizing auxiliary cleavage, hydrogenation, and hydrolysis gave the free amino carboxylic-phosphonic acid AP-4 (ent-**30**) in 12% overall yield.

2.3.2.4. Catalytic Asymmetric Synthesis

Zeiss described a catalytic asymmetric entry to both enantiomers of phosphinothricin **83** via a Rh-catalyzed enantioselective hydrogenation of phosphorylated dehydro-amino acid derivative **82** (Scheme 27).[72] A highly diluted solution of the substrate (0.0125 M in



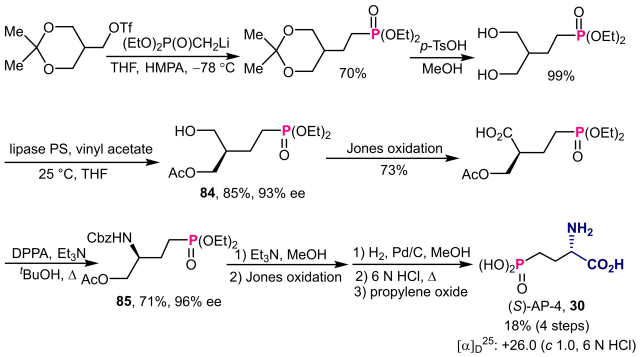
Scheme 26. Asymmetric transformation of chiral oxazolidinone into (*R*)-AP-4.



Scheme 27. Rh-catalyzed asymmetric synthesis of both enantiomers of phosphinothricin.

methanol) was found to be beneficial for the improvement of the enantiocontrol.

In a complementary fashion, a lipase-catalyzed enantioselective acylation reaction was applied to the asymmetric preparation of chiral phosphono-diol derivative **84** in good yield with 93% ee (Scheme 28).[37] Then, a sequence of Jones oxidation and Curtius rearrangement transformations provided the phosphono-amino alcohol precursor **85** without any loss of enantiopurity. Further Jones oxidation and hydrolysis gave the chiral AP-4 **30** in a practical overall yield.



Scheme 28. Lipase-catalyzed enantioselective synthesis of (*S*)-AP-4.

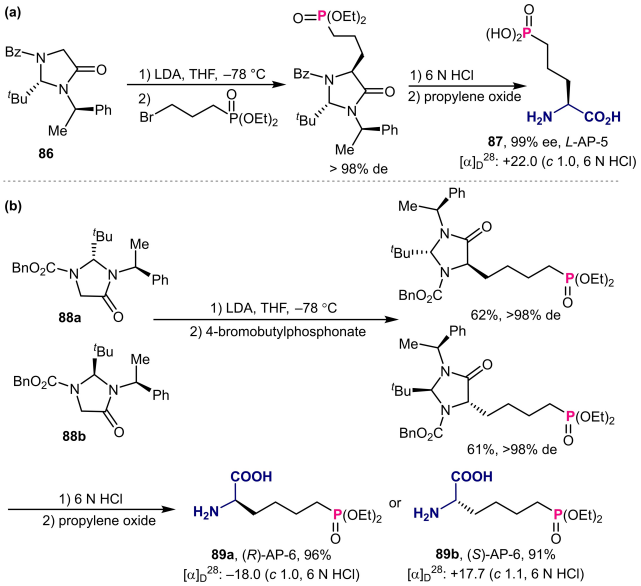
2.4. Chiral δ- and ε-Phosphono-α-Amino Acids

Amino acid 2-amino-5-phosphono-pentanoic acid (AP-5) represents an important class of antagonists of NMDA receptors, which plays a key role in the development of drugs for the central nervous system. In this context, Juaristi reported the asymmetric preparation of δ-phosphonic α-amino acid **87** (AP-5) from Seebach imidazolidinone **86**.[73] The key process was a diastereoselective alkylation of in-situ formed enolate with 3-bromopropyl phosphonate, thus delivering the corresponding intermediate in 65% yield with high diastereoselectivity. Simple acid hydrolysis led to the desired enantiopure aminophosphonic acid **87** (Scheme 29a). This practical protocol was also utilized to the synthesis of the enantiomer D-AP-5 by appropriate choice of the chiral inductor. In addition, 2-amino-6-phosphono-hexanoic acids (AP-6) are members of the phosphonate analogues of glutamic acid and have also been investigated as potent NMDA receptor agonists. By using a similar chiral imidazolidinone auxiliary **88**, Juaristi's group synthesized both enantiomers of AP-6 (Scheme 29b).[74] The key step is a highly diastereoselective alkylation of in-situ formed chiral enolate with 4-bromobutylphosphonate. Removal of the auxiliary gave access to both *R* and *S*-enantiomers of **89** (AP-6) in more than 90% yield.

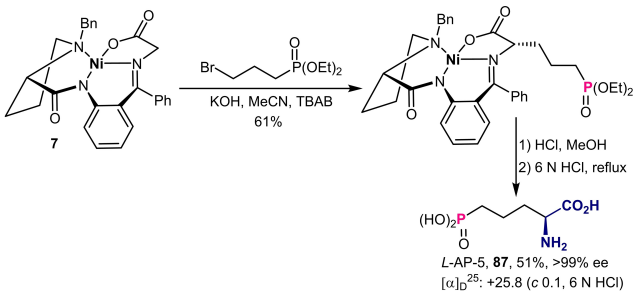
As mentioned above in the text, Kukhar *et al.* reported the use of chiral nickel complex **7** as a unique Schiff base to undergo alkylation reactions for the synthesis of AP-3 and AP-4 derivatives (see Schemes 4 and 21).[25] This elegant protocol was also practized for the asymmetric preparation of δ-phosphono-α-amino acids by using $BrCH_2CH_2CH_2P(O)(OEt)_2$ as the electrophile, thus leading to L-AP-5 **87** in good yield with excellent enantiopurity (Scheme 30).

Several natural unsaturated δ-phosphono-α-amino acids represent a class of interesting compounds and possess antibacterial activities, such as rhizocticins, plumbemycins and phosacetamycin (Figure 1). The first report about the synthesis of unsaturated δ-phosphonic α-amino acids was disclosed in 1988 by Natchev's group (Scheme 31).[75] The first step was to introduce the phosphorus atom by virtue of the Michaelis-Arbuzov reaction between the bromopropene acetal and triethyl phosphite. The resulting acetal was converted into aldehyde, which was reacted with ammonium formate, cyclohexyl isonitrile, and sodium hydroxide to give the unsaturated δ-phosphonic α-amino acid **90** in a single pot in 79% yield. Enzymatic systems were then developed to separate the L- and D-enantiomers.

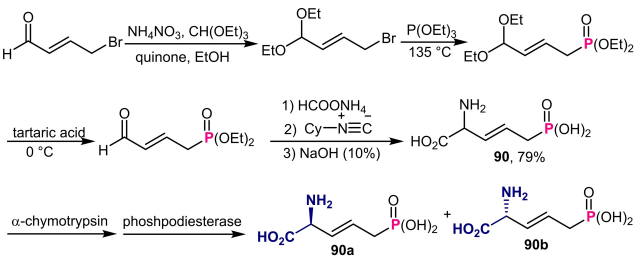
Luxen *et al.* presented a chemical synthesis of the 2-amino-5-phosphonopent-3-enoic acid (APPA **93**) and further transformation into the natural products rhizocticin A and plumbemycin A.[76] (*S*,*Z*)-APPA **93** was synthesized in seven steps as shown in Scheme 32. The first key step was the stereoselective formation of the ester **91** starting from (*R*)-Garner's aldehyde ent-**58** and Still–Gennari reagent $[(CF_3CH_2O)_2P(O)CH_2CO_2Me]$. Direct reduction, bromination, and Michaelis–Arbuzov reaction of this ester gave rise to the formation of the corresponding intermediate **92**. Sub-



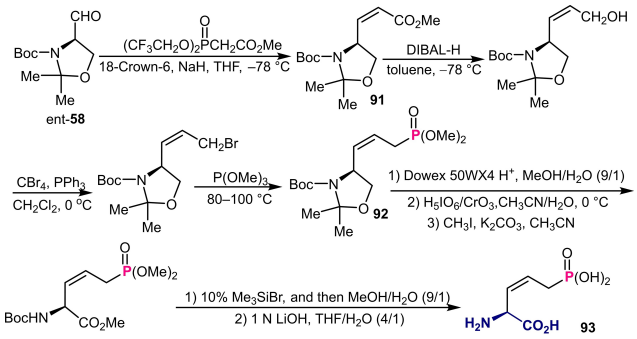
Scheme 29. Asymmetric transformation of chiral imidazo-lidinones into δ- and ε-phosphono-α-amino acid derivatives.



Scheme 30. Asymmetric transformation of chiral Schiff base Ni-complex into δ-phosphono-α-amino acid L-AP-5.



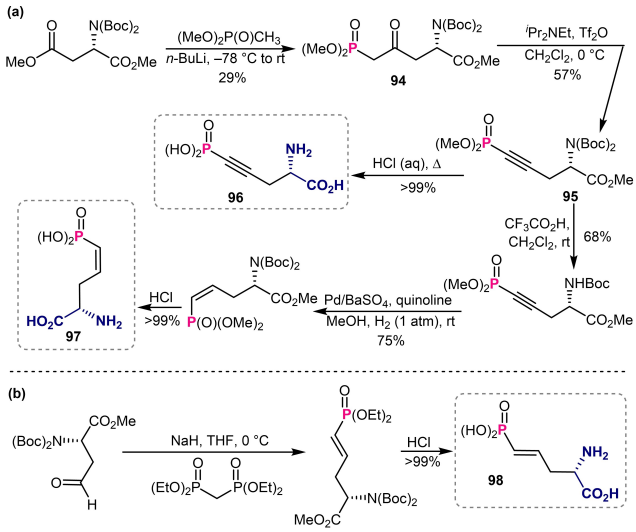
Scheme 31. Enzymatic asymmetric construction of unsaturated δ-phosphono-α-amino acids.



Scheme 32. Asymmetric synthesis of the (*Z*)-2-amino-5-phosphonopent-3-enoic acid.

sequent ring-opening, oxidation, and hydrolysis delivered the desired (*S*,*Z*)-APPA. Whereupon, the group of Luxen elaborated two natural peptides rhizocticin A and plumbemycin A by condensing (*S*,*Z*)-APPA with appropriate amino acids. Oligopeptides were also prepared using liquid phase peptide synthesis (LPPS) and were tested against selected bacteria and fungi.

Acetylenic and *Z*/*E*-olefinic analogues of AP-5 were prepared as candidate inhibitors of aspartate semialdehyde dehydrogenase (ASA-DH).[77] As illustrated in Scheme 33, L-aspartic acid dimethyl ester was reacted with $LiCH_2P(O)(OMe)_2$ to introduce the phosphonate moiety on the intermediate **94**, which was then converted into the acetylene **95**. Further hydrogenation of **95** gave *Z*-olefinic phosphonate in 75% yield (Scheme 33a). The *E*-olefinic phosphonate analogue was constructed from corresponding starting chiral aldehyde via the Horner-Wadsworth-Emmons olefination (Scheme 33b). Finally, deprotection and hydrolysis furnished the desired products **96**, **97**, and **98** in quantitative yields.



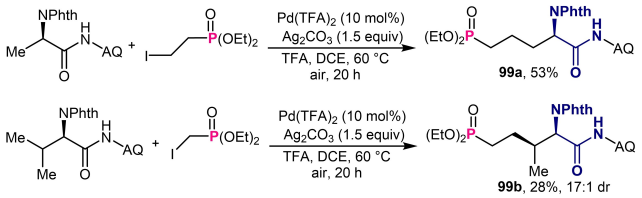
Scheme 33. Asymmetric synthesis of chiral acetylenic and *Z*/*E*-olefinic analogues of AP-5.

As previously mentioned in Scheme 17, C(sp^3)–H bond activation of AQ-functionalized amino acid derivatives could be achieved under palladium catalysis conditions to produce valuable chiral phosphono amino acids.[57] Yang *et al.* also applied this C(sp^3)–H functionalization reaction to the synthesis of δ-phosphono amino acid derivatives **99** via the β- and γ-C(sp^3)–H bond alkylation with phosphono iodides (Scheme 34).

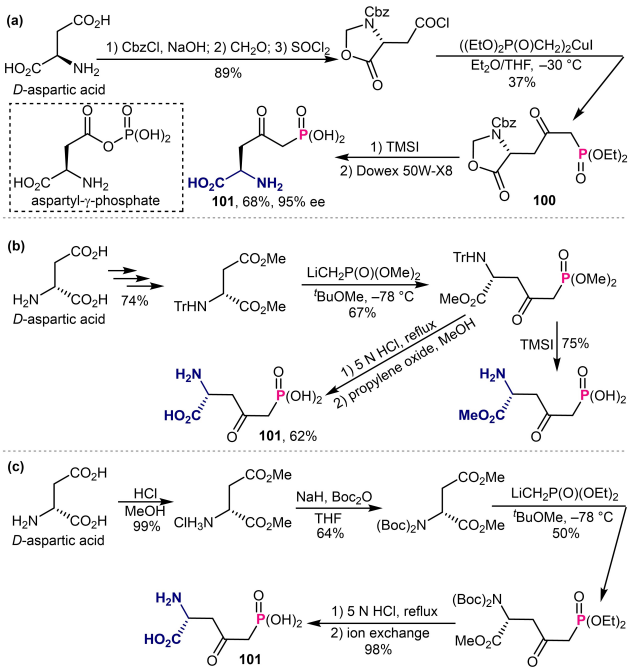
2.5. Aspartic-Based Derivatives

As analogues of AP-5, γ-keto-δ-phosphono-α-amino acids derived from aspartic acid have been developed as selective antagonists of NMDA receptors. By mimicking aspartyl-γ-phosphate activity towards the enzyme aspartate-semialdehyde dehydrogenase (ASA-DH), aspartic-based phosphono-amino acid derivatives could also be a group of promising inhibitors for ASA-DH. The stereoselective synthesis of γ-keto-δ-phosphono-α-amino acid **101** was developed by Whitten (Scheme 35a).[78] D-Aspartic acid-derived *N*-protected oxazolidinone acid chloride was coupled with the nucleophilic diethyl methylphosphonate cuprate to give the phosphono-functionalized imidazolidinone **100**. Finally, deprotection with TMSI and ion exchange treatment provided the (*R*)-γ-keto-δ-phosphonic α-amino acid **101** in high enantio-purity. To solve the purification problem of viscous acid chloride intermediate, Rudisill and Whitten reported an improved synthetic procedure to **101** (Scheme 35b).[79] The use of triphenylmethyl (Tr) group as amino-protecting group was found to be crucial to enable the coupling step with good yield and stereoselectivity. Both amino acid ester and free phosphonic α-amino acid **101** were obtained after different deprotection conditions. In a similar fashion, Cox *et al.* reported a modified protocol to **101** again from aspartic acid in four steps in high overall yield (Scheme 35c).[80]

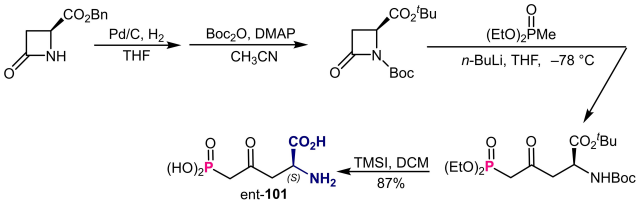
In addition, Smith *et al.* developed a ring-opening approach of easily available optically pure lactam to the (*S*)-enantiomer ent-**101** (Scheme 36).[81] Lithiated diethylmethyl-phosphonate served as the nucleophile for selective ring-opening of lactam to give the chiral



Scheme 34. Pd-catalyzed asymmetric synthesis of δ-phosphono amino acid derivatives.



Scheme 35. Asymmetric transformation of D-Aspartic acid into (*R*)-γ-keto-δ-phosphonate α-amino acid **101**.



Scheme 36. Asymmetric transformation of chiral lactam into (*S*)-γ-keto-δ-phosphonate α-amino acid.

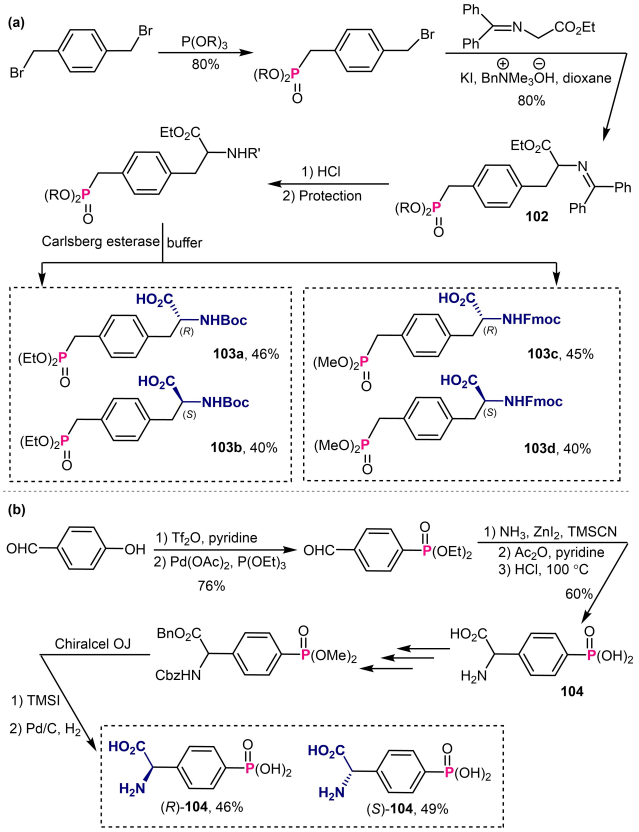
phosphono-aspartic acid derivative in good yield. After deprotection with TMSI, free phosphonic acid ent-**101** was obtained in 87% yield.

2.6. Phenylalanine-Based Derivatives

Protein phosphorylation provides precise and flexible control of complex information transfer events within cells acting as a switch via phosphorylation and dephosphorylation of crucial proteins. Among these, phosphorylation on tyrosine residues plays an important role in cellular signal transduction by facilitating recognition and binding necessary for critical protein-protein interactions.[82] On the other hand, The replacement of the O–P bond by the stronger C–P bond bestows hydrolytic stability to phosphotyrosyl (pTyr) mimetics and thus makes them useful tools for the study of cellular signal transduction processes and attractive candidate in the development of signalling antagonists.[83] Phosphonomethyl-phenylalanine (Pmp) is a nonhydrolyzable analogue of phosphotyrosine and the carbon-phosphorus bond of Pmp is stable to chemical and enzyme-catalyzed hydrolysis. According to origin of chirality, the synthetic methods for Pmp can be briefly classified into four distinct categories as follows: chiral resolution, chiral auxiliary, chiral substrate, and chiral catalyst method.

2.6.1. Chiral Resolution Method

Roques *et al.* described an interesting protocol via monophosphorylation of 1,4-bis(bromomethyl)benzene and alkylation of glycine imines for the preparation of racemic Pmp **102**.[84] Then, in the presence of subtilisin Cartsberg esterase, a chiral resolution furnished both enantiomers **103 a** and **103 b** in high yields with optical purity (Scheme 37a). Aiming for the applications in peptide synthesis, both enantiomers (**103 c** and **103 d**) of *N*-Fmoc-Pmp were prepared via a similar enzymatic resolution protocol.[85] Gasparini *et al.* proposed a HPLC resolution procedure to obtain each enantiomer of phosphonophenylglycine (PPG) (Scheme 37b).[86] The racemic phosphono-amino acid **104** was obtained in good yield from 4-hydroxy-benzaldehyde involving Pd-catalyzed phosphorylation and Strecker reaction as



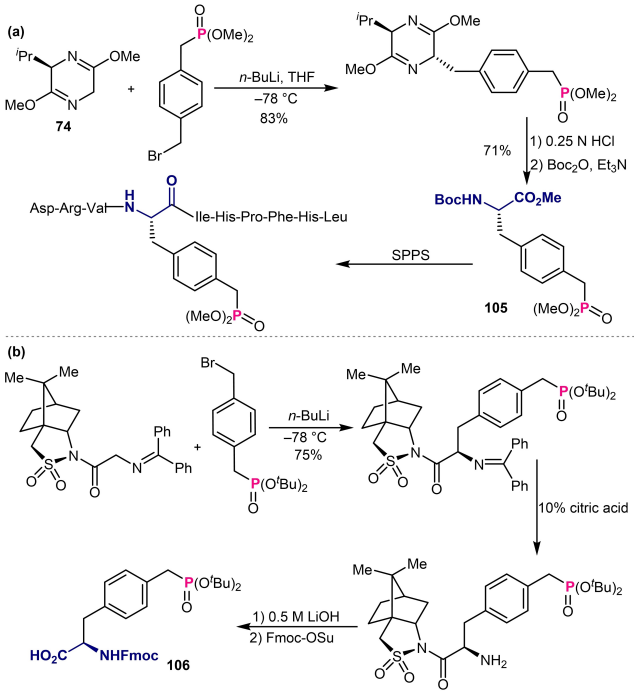
Scheme 37. Chiral resolutions for the preparation of enantiomers of Pmp and PPG.

the key steps. The protected PPG was separated on chiral preparative HPLC, thus giving the two enantiomers with >99% ee on gram-scale.

2.6.2. Chiral Auxiliary Method

Four types of chiral auxiliaries have been employed to couple with phosphonomethyl benzyl bromide in order to introduce the amino acid moiety, including Schöllkopf bis-lactim ether, camphor sultam imine, Seebach's imidazolidinone, and diphenyloxazinone.

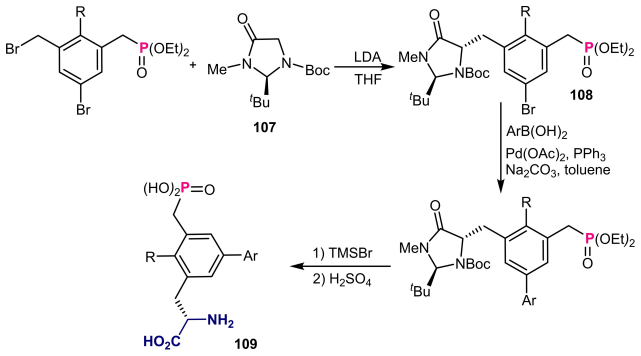
Cushman and Lee reported the nucleophilic substitution reaction of Schöllkopf bis-lactim ether **74** (Williams lactone) with phosphonomethyl benzyl bromide to afford the alkylated compound in 83% yield with excellent diastereoselectivity (Scheme 38a).[87] Hydrolysis and protection of the amino group produced the unnatural amino acid **105**, which was further incorporated into peptide sequence by SPPS. Another elegant work to Fmoc-L-Pmp(^{t}Bu)$_2$-OH **106** has been disclosed by Roques as shown in Scheme 38b.[88] The chiral camphor sultam imine in anhydrous THF was treated with *n*-BuLi at −78 °C for 30 minutes, and then alkylated with phosphonomethyl benzyl bromide to provide the expected product in 75% yield. Smooth hydrolysis with 10% aqueous citric acid and removal of the chiral auxiliary afforded the desired compound **106** with very good enantiomeric purity (>97% ee).



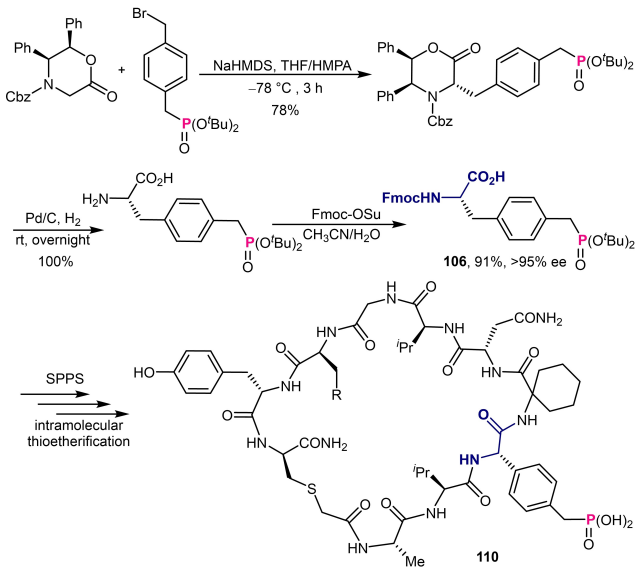
Scheme 38. Schöllkopf bis-lactim ether and camphor sultam imine-induced asymmetric synthesis of Pmps.

Seebach's (*S*)-imidazolidinone auxiliary **107**, via its lithium enolate, was used to control the stereochemical outcome of the displacement of variously decorated phosphonomethyl benzylic bromides providing the coupled adducts **108** in yields ranging from 53 to 81% (Scheme 39).[89] Subsequent Suzuki cross-coupling with aryl boronic acids produced the biphenyl-linked phosphonates in good yields. A broad scope of such biaryl phosphono-amino acids **109** were obtained with more than 98% ee. By employing a similar strategy, a series of enantiomerically pure Pmp derivatives were also prepared by Bigge *et al.* as competitive NMDA receptor antagonists.[90]

Fmoc-Pmp(^{t}Bu)$_2$-OH **106** was designed and prepared for incorporating the L-Pmp residue into peptides and peptidomimetics (Scheme 40).[91] In this concise approach, the chiral amino acid moiety was built via a diphenyloxazinone-directed alkylation reaction, and



Scheme 39. Chiral imidazolidinone-induced asymmetric synthesis of Pmps.

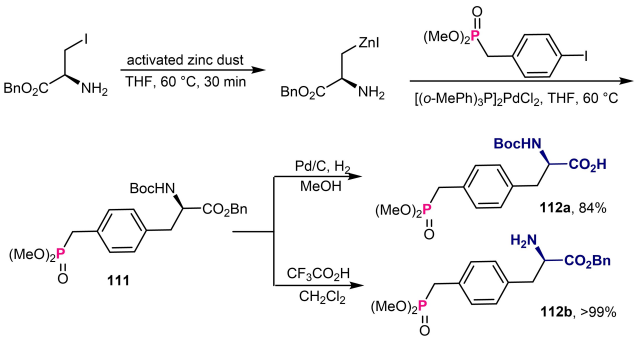


Scheme 40. Chiral diphenyloxazinone-induced asymmetric synthesis of Pmp and cyclotide.

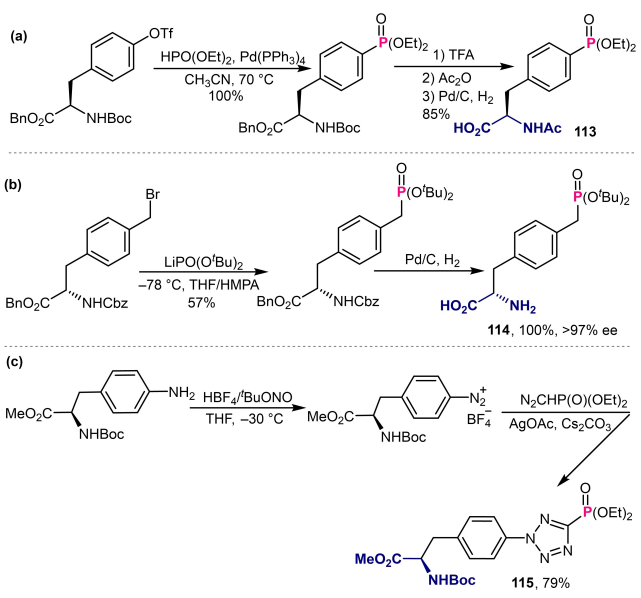
followed by hydrogenolysis and Fmoc protection. The key building block **106** was obtained in a 45% overall yield in five steps with very good enantiomeric purity (>95% ee). More importantly, a series of potent Pmp-containing Grb2-SH2 domain antagonists **110** were further synthesized and evaluated as chemotherapeutic leads in treating erbB2-overexpressed breast cancer.

2.6.3. Chiral Substrate Method

Derivatives of natural optically active amino acids could play a very appropriate role as substrate source towards Pmp compounds. Yet, a key feature of the installation of the phosphonate moiety should not affect the integrity of the α-amino acid stereogenic center. For example, an early asymmetric synthesis of L-Pmp from amino acid iodide derived from serine was described by Dow and Bechle (Scheme 41).[92]



Scheme 41. Asymmetric transformation of iodo-derived serine into chiral Pmps.



Scheme 42. Direct functionalization on the backbones of tyrosine and phenylalanine derivatives.

Organozinc reagent underwent palladium-catalyzed cross-coupling with dimethyl 4-iodobenzyl-phosphonate to form the key intermediate **111**. After hydrolysis or deprotection, the desired phosphono-amino acid derivatives **112** were obtained with more than 95% ee.

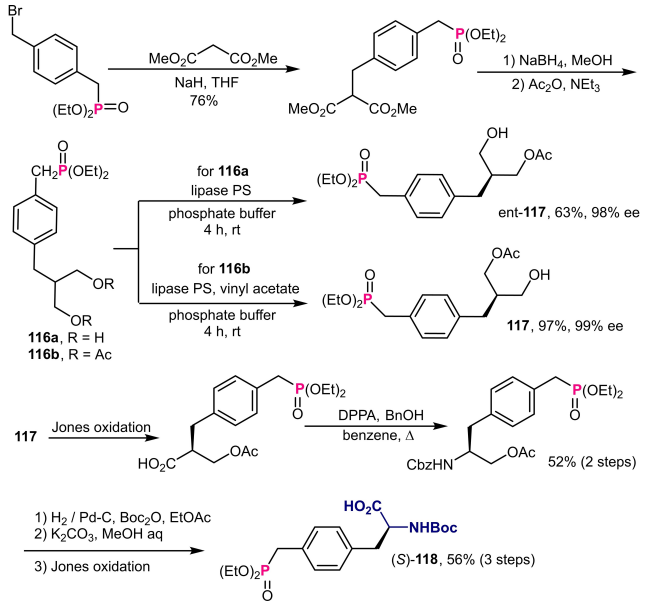
Direct functionalization on the backbones of tyrosine and phenylalanine derivatives would be an attractive approach to rapidly introduce the phosphonate moiety. In this context, Stankovic *et al.* accomplished a straightforward C–P bond formation reaction of tyrosine triflate under palladium catalysis conditions (Scheme 42a).[93] Subsequent deprotection and hydrolysis gave Ac-PmpEt$_2$-OH **113** in good overall yield, which has been incorporated into dipeptide prodrugs. The Arbuzov reaction was also utilized to introduce the phosphonate group to phenylalanine-derived benzyl bromide. This protocol enabled the efficient synthesis of chiral PmpCH$_2$^{t}Bu$_2$-OH **114** with retention of the stereochemical information (Scheme 42b).[94] Very recently, Ma *et al.* reported an interesting approach to fix phosphonate moiety on the chiral amino acid scaffold by employing a Ag-catalyzed [3+2] cycloaddition reaction between aryl diazonium salts and Seyferth–Gilbert reagent (Scheme 42c).[95] 4-NH$_2$-Phenylalanine was smoothly converted into the diazonium salt and then cycloadded with Seyferth–Gilbert reagent with exclusive regioselectivity, thus furnishing the tetrazole-linked phosphono-amino ester **115**.

2.6.4. Chiral Catalyst Method

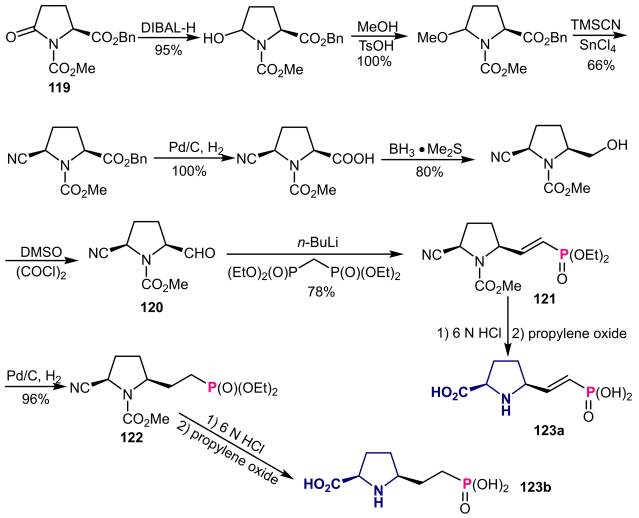
An enantioselective enzymatic desymmetrization reaction has been developed by Shibuya's group for the synthesis of chiral Pmp derivatives (Scheme 43).[96] The prochiral 1,3-propanediol substrates **116** were easily obtained from phosphonomethyl benzyl bromide and dimethyl malonate. Importantly, by slightly switching the reaction conditions, transesterification and deacetylation were realized with excellent enantioselectivity under the catalysis of lipase PS to give the antipodal products **117**. Subsequently, functional group transformations afforded the enantiopure phosphono-phenylalanine derivative **118** in good overall yield.

2.7. Proline-Based Derivatives

Proline-based phosphonate derivatives represent a unique type of conformationally constrained analogues of pharmaceutically important amino phosphonic acids. Langlois *et al.* pioneered the asymmetric synthesis of several semi-rigid proline-derived chiral phosphonic acids (Scheme 44).[97] The reported procedure took benzyl (*S*)-pyroglutamate **119** as the starting chiral material, through selective reduction with DIBAL–H, methylation with methanol, cyanation with TMSCN promoted by $SnCl_4$, reduction of carboxylic acid with BH_3·Me_2S, and Swern oxidation, giving the



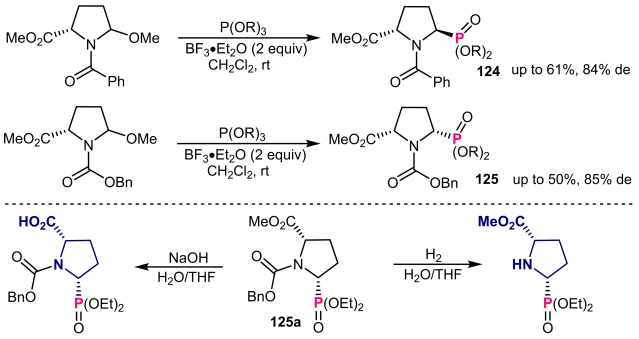
Scheme 43. Enzymatic desymmetrization for enantioselective synthesis of Pmp.



Scheme 44. Asymmetric transformation of (*S*)-pyroglutamate into chiral proline-based phosphonic acids.

aldehyde intermediate **120** as a single diastereomer in good overall yield. The incorporation of the phosphonate moiety was realized by means of an *E*-selective Horner–Wadsworth–Emmons (HWE) reaction without touching the cyano group. Finally, direct hydrogenation of vinylphosphonate **121** under Pd/C catalysis gave saturated phosphonate **122** without epimerization. The authors further hydrolyzed both **121** and **122** to provide proline-functionalized phosphonic acids **123** in 90–99% yields.

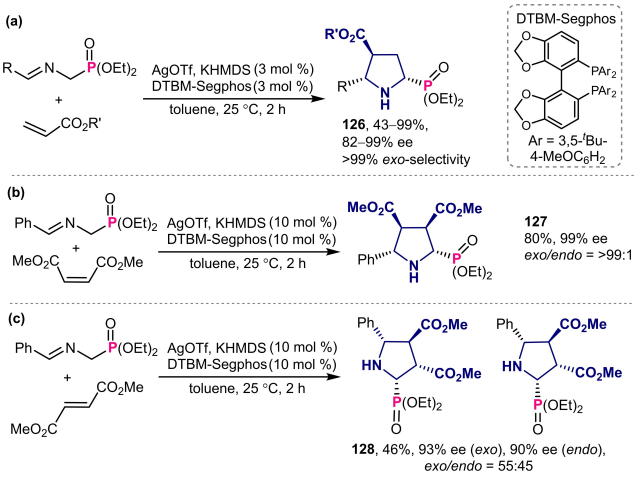
Direct phosphorylation on the proline core was reported by the Onomura's group (Scheme 45).[98]



Scheme 45. Asymmetric synthesis of chiral 5-phosphonate proline derivatives.

Interestingly, *N*-benzoyl prolinate underwent the $BF_3{\cdot}Et_2O$-promoted Arbuzov reaction to give *trans*-phosphorylated product **124**, whereas changing the substrate's *N*-protecting group to benzyloxycarbonyl (Cbz) led to the formation of *cis*-isomer **125** as the major product under otherwise identical conditions. Alkaline hydrolysis of **125a** with sodium hydroxide produced free carboxylic acid, whereas the Cbz group could be easily removed under hydrogenation conditions.

While the above strategies started with pre-existing proline framework, it is no doubt that enantioselective construction of the pyrrolidine ring to further expand the molecular diversity would be more challenging. In this context, Kobayashi *et al.* made significant progress in catalytic asymmetric preparation of chiral proline phosphonic analogues (Scheme 46a).[99,100] α-Imino-phosphonates were engaged into [3 + 2] cycloaddition reaction with acrylates catalyzed by an in-situ formed chiral silver-amide complex. This protocol was well compatible with different functionalities and almost



Scheme 46. Catalytic asymmetric cycloaddition reactions for the synthesis of chiral phosphonic proline-analogues.

exclusively yielded exo-cycloadducts **126** with excellent ee values (>94% in most cases). The suggested concerted cycloaddition mechanism was evidenced by two comparison experiments between fumarate and malate under same conditions to give the cycloadducts **127** and **128** (Scheme 46b, c).

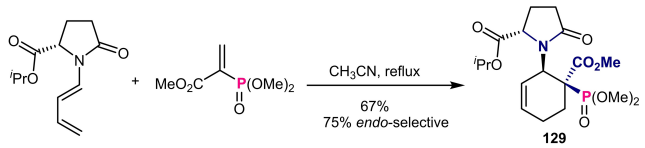
2.8. Cyclohexyl- and Pipecolic-Based Derivatives

Robiette and Marchand-Brynaert devised a Diels–Alder reaction for the asymmetric construction of chiral pyroglutamate-derived phosphonate **129** (Scheme 47).[101] Optically pure aminodiene was reacted with the phosphonodienophile under simple heating conditions to afford the *endo*-stereoisomer as major product. The relative and absolute configurations of stereogenic centers in the cycloadduct **129** were ascribed by combined NMR and theoretical analysis.

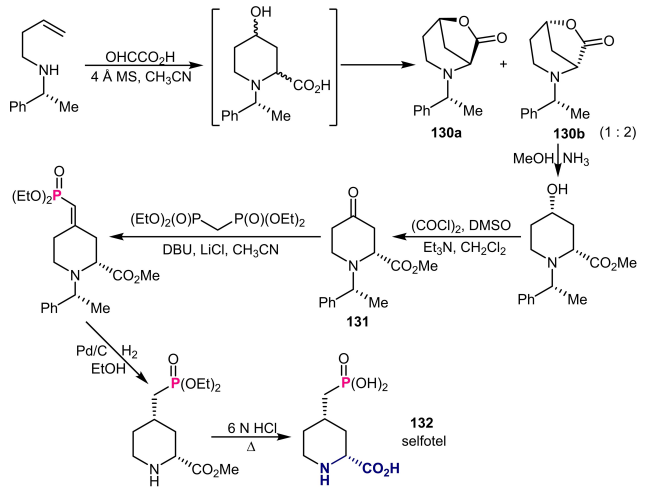
Selfotel (CGS-19755) has been investigated as a potential drug for the treatment of stroke by acting as a competitive NMDA antagonist.[102,103] In this context, Skiles *et al.* reported a chiral auxiliary-induced asymmetric synthesis of enantiomerically pure pipecolic-based phosphonic acid selfotel **132** (Scheme 48).[104] The key piperidine ring was formed via iminium ion cyclization of chiral homoallylic amine with glyoxylic acid. Although the diastereoselectivity of lactones **130** was not satisfactory (**130a**/**130b** = 1/2), the desired *cis*-isomer **130b** could be easily obtained after recrystallization. Simple ring-opening and oxidation transformations afforded chiral ketone **131**, which was then treated with $[(EtO)_2P(O)]_2CH_2$ under basic conditions to introduce the phosphonate group. Finally, diastereoselective reduction and hydrogenolysis with $Pd/C/H_2$ and hydrolysis with 6 N HCl produced the desired selfotel **132**.

While the above approach to chiral selfotel is inspiring, no yield nor experimental procedure were described in the original paper. Aiming to provide a more practical and reproducible protocol, Gálvez *et al.* described the stereodivergent preparation of both *cis* and *trans*-chiral isomers of selfotel (Scheme 49).[105] The Danishefsky's diene was reacted with chiral imine in the presence of ZnI_2 to generate cyclic enaminone **133** in good yield. Subsequent selective reduction of the double bond with L-Selectride and HWE olefination with phosphonate building block gave the key vinyl phosphonate intermediate **134**. At this stage, further hydrogenation with PtO_2/H_2 produced the *cis*-saturated phosphonate, whereas switching the reductant to L-Selectride delivered *trans*-isomer with exclusive diastereoselectivity. Sequential deprotection, oxidation, and hydrolysis of both isomers were carried out, thus providing the corresponding chiral pipecolic-based phosphonic acids **132** and *trans*-**132**, respectively.

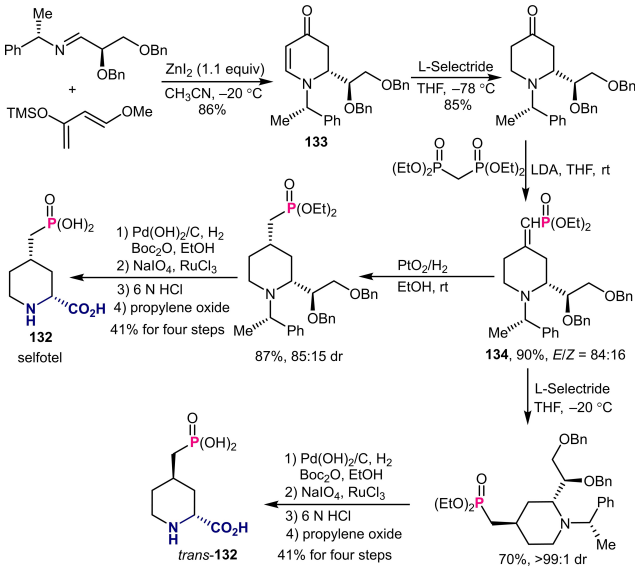
The catalytic asymmetric synthesis of selfotel was realized by Maruoka's group (Scheme 50).[106] The key chiral piperidine-2-carboxylic acid **132** was obtained through the enantioselective alkylation of glycine imine under phase-transfer-catalysis (PTC) of chiral BINOL-derived quaternary ammonium salt. Subse-



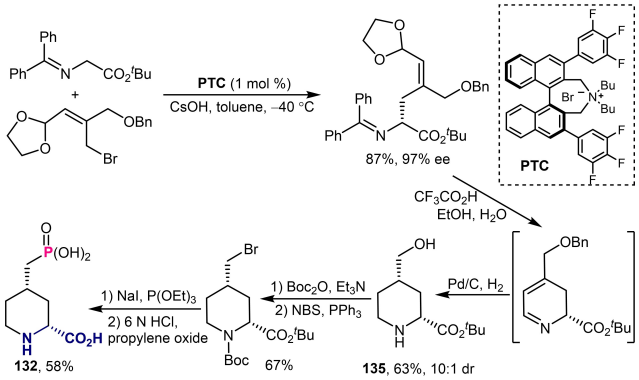
Scheme 47. Asymmetric [4 + 2] cycloaddition for the synthesis of chiral phosphonated 2-aminocyclohex-3-ene-1-carboxylate.



Scheme 48. Chiral auxiliary-induced asymmetric synthesis of selfotel.



Scheme 49. Asymmetric stereodivergent synthesis of selfotel.



Scheme 50. Catalytic asymmetric synthesis of selfotel.

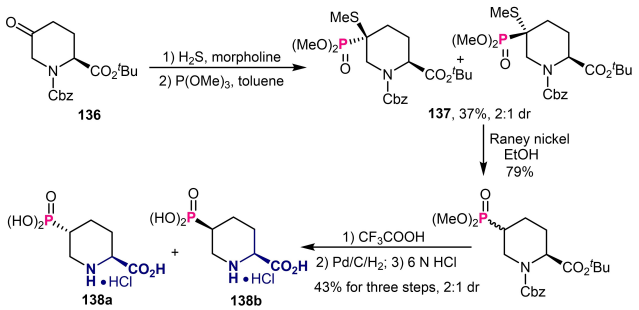
quent one-pot deprotection-cyclization-reduction transformation led to the formation of the corresponding alcohol **135** in 63% yield with good diastereoselectivity (10:1 dr). The phosphonate group was incorporated at late stage with the aid of the Arbuzov reaction of bromide intermediate. Final hydrolysis delivered the selfotel **132** in good overall yield.

Evitt and Cox employed (*S*)-5-oxopiperidine-2-carboxylic acid as chiral starting material for the asymmetric construction of pipecolic-5-phosphonic acids featuring the phosphonate motif directly attached on the piperidine ring (Scheme 51).[107] (*S*)-5-Oxopiperidine-2-carboxylate **136** was treated with H_2S and P$(OMe)_3$ in toluene to give the adducts **137**, albeit with moderate diastereoselectivity. Subsequently, removing the thioether group with Raney nickel, isolation, deprotection, and hydrolysis provided two diastereoisomers **138a** and **138b**. Importantly, these conformationally restricted analogues of linear AP-5 demonstrated increasing inhibitory activity for aspartate semialdehyde dehydrogenase.

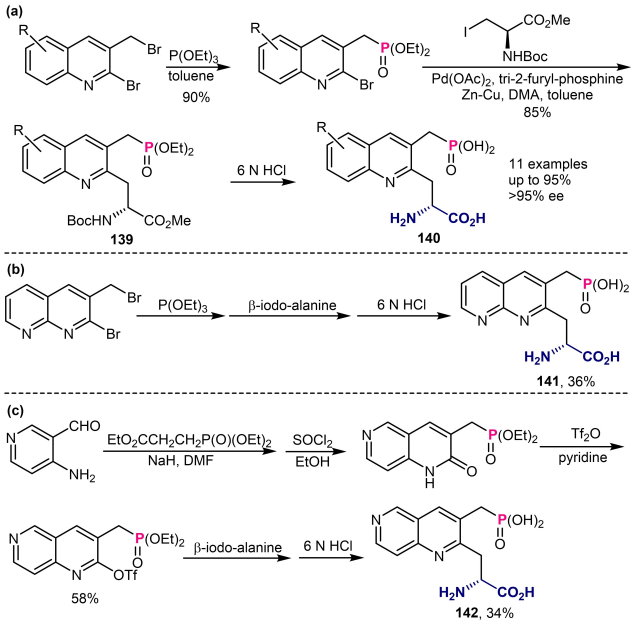
2.9. Heteroaryl-Based Phosphono-α-Amino Acids

Heteroaryl-based phosphono-α-amino acids could be regarded as a particular class of phosphono-phenylalanine analogues. Claesson *et al.* disclosed the asymmetric synthesis of quinoline and naphthyridine derivatives from easily available chiral amino acid building-blocks (Scheme 52).[108] Quinoline-dibromide was first phosphorylated with triethyl phosphite and then underwent palladium-catalyzed cross-coupling with β-iodo-alanine to give 6-phosphono-amino ester **139** in good yield. After hydrolysis, a broad scope of mono and di-substituted quinoline-linked chiral amino carboxylic phosphonic acids **140** were prepared (Scheme 52a). Using a similar procedure could also smoothly give access to chiral 1,8-naphthyridine-based phosphonic acid **141** in 36% overall yield (Scheme 52b). For the preparation of 1,6-naphthyridine derivative **142**, a one-pot phosphorylation/cyclization method was devised to construct the central framework (Scheme 52c). Subsequent transformations via triflation, cross-coupling, and hydrolysis, gave birth to the corresponding phosphono-α-amino acid **142**.

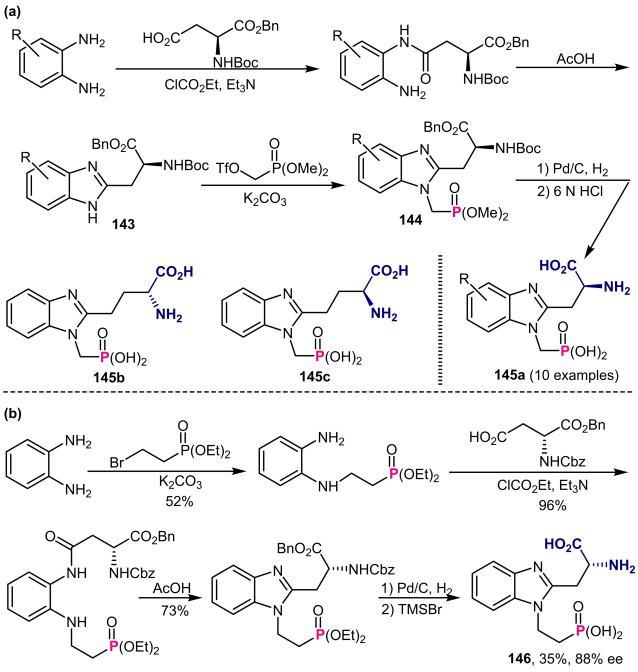
In an extending effort to discover new NMDA antagonists, Baudy *et al.* reported the design and synthesis of several benzimidazole-based chiral phosphono-amino acid derivatives (Scheme 53).[109] Aspartic acid building-block was first condensed with various 1,2-diaminoarenes and then cyclized to give benzimidazole-functionalized amino acids 143. Nucleophilic alkylation under basic conditions allowed the introduction of phosphonate group to give the corresponding compound **144**. After hydrogenation and hydrolysis, a series of enantiomerically pure phosphono-containing amino acids **145a** were obtained (Scheme 53a). A similar procedure could also



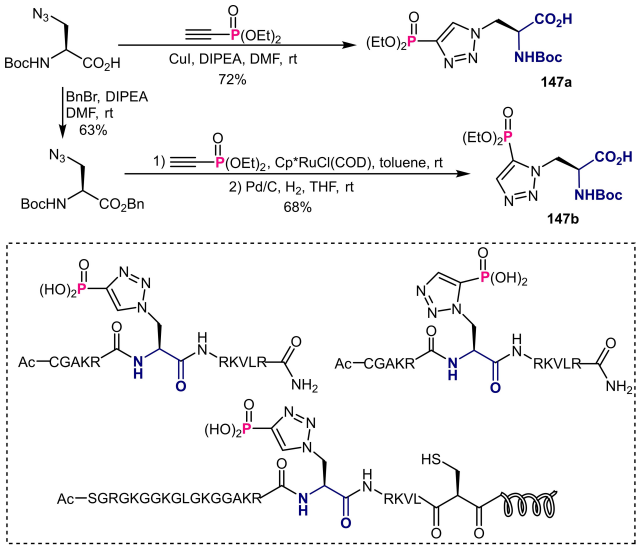
Scheme 51. Chiral substrate-induced asymmetric synthesis of 5-phosphonate pipecolic acids.



Scheme 52. Asymmetric synthesis of chiral quinolone- and naphthyridine-based phosphono-α-amino acids.



Scheme 53. Asymmetric synthesis of chiral benzimidazole-based phosphono-α-amino acids.



Scheme 54. Asymmetric synthesis of chiral triazole-based phosphono-α-amino acid and the corresponding peptides.

smoothly give access to both enantiomers of phosphono-amino acids **145b** and **145c** possessing one more carbon on the amino carboxylic side chain. For phosphono-amino acid with one more carbon on the phosphonic side chain, the phosphorylation reaction of bromoethylphosphonate with benzene-1,2-diamine was performed at early stage to afford the corresponding intermediate. Subsequently, intermolecular amidation, intramolecular cyclization, and deprotection led to the formation of benzimidazole-functionalized amino acid **146** with good ee values (Scheme 53b). Noteworthy is that 5-chloro-substituted benzimidazole-based phosphono amino acid **145a** (R = 5-Cl) exhibited high potency as NMDA antagonist towards a potential neuroprotective agent.

To mimic the geometry and electronics of phosphohistidine (pHis), Muir *et al.* designed 4- and 5-phosphono-triazole-based amino acids.[110] The synthetic route was quite concise that employed azidoalanine as the chiral source to undergo Cu- or Ru-catalyzed [3 + 2] cycloaddition reaction with a phosphono-alkyne. Importantly, both amino acids **147a** and **147b** have been successfully embedded into peptides via SPPS method (Scheme 54).

3. Asymmetric Construction of Amino Acid Fluorophosphonate Derivatives

Phosphonates are relevant phosphate mimics in medicinal chemistry as they cause minimal perturbation both in terms of electronic properties and spatial arrangement while increasing stability and bioavailability. However, preserving cell permeability is not often satisfactory and biological activity is sometimes limited. Fluorine substitution at the methylene carbon of phosphonate was introduced as a new generation of phosphate mimics for which there is mounting evidence of higher efficiency. A comparison of pK_{a2} values for phosphates, phosphonates, and fluorinated analogues provides the necessary clues to properly understand the design of appropriate mimics (Figure 3).[111] The pK_{a2} value of a phosphate group is ca. 6.4. The CH_2-phosphonate has a pK_{a2} value of ca. 7.5 and is much less acidic. The presence of two electron-withdrawing fluorine atoms on the CF_2-phosphonate significantly lowers the pK_{a2} value to ca. 5.6 while the installation of a single fluorine atom for the CHF-phosphonate results in a pK_{a2} value of ca. 6.5 nearly identical to that of the natural phosphate. It means that under physiologic conditions, CHF- and CF_2-phosphonates are di-ionic and matches the natural phosphates. Moreover, CH_2 to CHF or CF_2 substitution restores potential hydrogen bonding interactions similar to the phosphate oxygen atoms that are often at the origin of binding affinities.

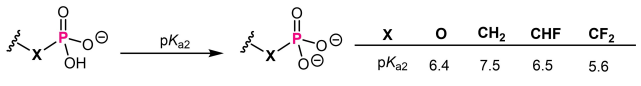


Figure 3. A comparison of pK_{a2} values for phosphates, phosphonates, and fluorinated analogues.

3.1. Monofluorophosphonates

Compared to α,α-difluorophosphonates (see later in the text), the evaluation of α-monofluorophosphonates as biological phosphate mimics, albeit the fact that their pK_{a2} values are nearly the same as the parent phosphates, has been less explored. This is probably because of a higher synthetic challenge caused by the inclusion of a new stereogenic carbon center featuring the fluorine atom. Obviously, the new chirality element introduced within monofluorophosphonates can potentially affect the bioactivity.

3.1.1. β-Monofluorophosphonomethyl-α-Amino Acids

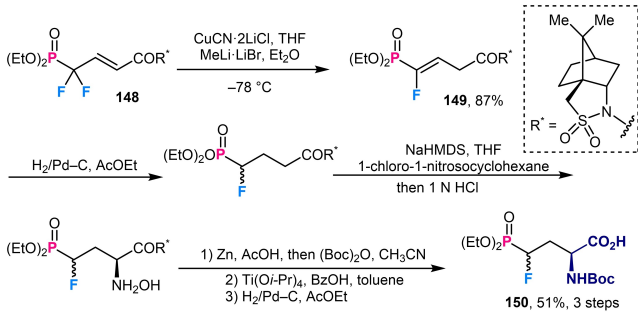
The synthesis of the monofluorophosphonomethyl-serine derivative, 2-amino-4-fluoro-4-phosphonobutanoic acid (FPab), in the appropriately *N*-Boc-protected form **150** for direct assembly of pSer mimetic containing peptides was described by the group of Otaka via a diastereoselective approach exploiting Oppolzer's chiral sultam (Scheme 55).[112] The first step was an organocopper-mediated reduction of γ,γ-difluoro-α,β-sultam imide **148** yielding the corresponding (*E*)-γ-fluoro-β,γ-sultam imide **149** in 87% yield. Note that the conjugate methylation product was not observed under these conditions. Subsequent steps included a non-stereoselective hydrogenation at the γ-position and a high diastereoselective electrophilic amination of the sodium enolate using 1-chloro-1-nitrosocyclohexane. Then, sultam cleavage and *N*-Boc protection ended up with the FPab derivative **150** as a mixture of two diastereoisomers. This compound was incorporated into the peptide sequence (H–Gly–FPab–Val–Pro–Met–Leu) in the aim to serve as inhibitor against kinases and phosphatases.

Towards the synthesis of *N*-arylamide phosphonates as potent, subtype selective agonists and antagonists of sphingosine L-phosphate receptors ($S1P_{1-5}$), the synthesis of phosphoserine mimetic FPab was also described by Macdonald exploiting Garner's aldehyde **58**, easily prepared from L-serine, as chiral resource (Scheme 56).[58] After a Horner-Wadsworth-Emmons olefination carried out with the aid of tetraethyl monofluoromethylene bisphosphonate, the fluoroolefin **151** was reduced by hydrogenation over Pd/C. Here again, the hydrogenation was non-stereoselective leading to a mixture of diastereoisomers of **152** and the impact of the fluorinated carbon center couldn't be evaluated. Finally, *N*-Boc-protected FPab **153** was obtained by oxidation of **152** with Jones reagent.

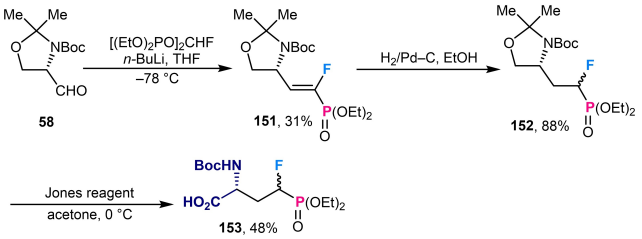
A regio- and diastereoselective electrophilic fluorination at the α-position of the phosphonate ester was proposed by the group of Ruiz and Ojea on lithiated Schöllkopf's bis-lactim ethers derived from cyclo-[L-AP4-D-Val] (Scheme 57).[71] Although the diastereoselectivity was poor, the diastereoisomers of **154a** and **154b** were separated by chromatography (>98% de) and subjected separately to a deprotection/reprotection sequence in order to obtain the desired *N*-Fmoc-protected pSer and pThr mimetics ready for solid phase peptide synthesis. These enantiopure compounds **155a** and **155b** were prepared as potential tools for studying the molecular pharmacology of group III metabotropic glutamate receptors (mGluRs).[113]

3.1.2. Monofluorophosphonomethyl Tyrosine Analogues

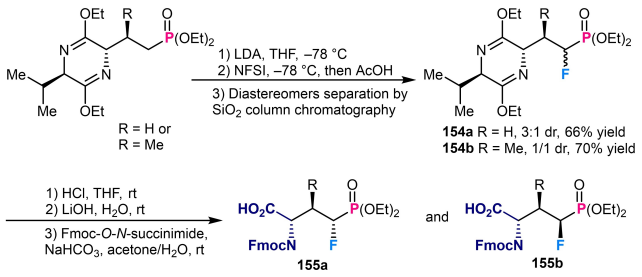
The stereoselective synthesis of 4-phosphonofluoromethyl-phenylalanine (FPmp), a pTyr analogue, was attempted by the group of Shibuya in the aim to study its binding affinity with Src homology



Scheme 55. Oppolzer's chiral sultam-induced asymmetric synthesis of monofluorophosphonomethyl-(*S*)-serine.



Scheme 56. Chiral Garner's aldehyde-induced asymmetric synthesis of monofluorophosphonomethyl-(*R*)-serine derivative.



Scheme 57. Chiral Schöllkopf bis-lactim ether-induced asymmetric construction of monofluorophospho-α-amino acids.

2 (SH2) protein interaction domains (Scheme 58).[114] The SH2 domains participate in protein tyrosine kinase-mediated cellular signal transduction through their high ability to bind to pTyr-containing protein sequences. Peptides containing pTyr competitively inhibit the binding but are quickly dephosphorylated by cellular phosphatases. This study was directed toward SH2 inhibitory peptides featuring phosphatase resistant pTyr mimetics. Prior to this work, only a racemic FPmp analogue was investigated.[115–118] Starting from methyl *N*-Cbz-L-tyrosinate, triflation followed by a palladium-catalyzed coupling reaction with tri-*n*-butylvinylstannane gave the styrenic compound, which was subjected to ozonolysis and transacetalization with (*2R,4R*)-pentanediol to afford acetal **156**. Next, stereoselective ring-opening with triethyl phosphite under Lewis acid catalysis afforded **157** (97:3 dr and >99:1 after SiO_2 column chromatography). Ether cleavage provided the 4-phosphonohydroxymethylphenylalanine (OHPmp) **158** on which the absolute configuration was determined by X-ray analysis. Unfortunately, the ultimate step consisting in the nucleophilic fluorination by means of DAST ended up with a 3:2 ratio of diastereoisomers **159** supposedly through a S_N1 pathway. To conclude, research efforts are still in need to have access to enantiopure FPmp.

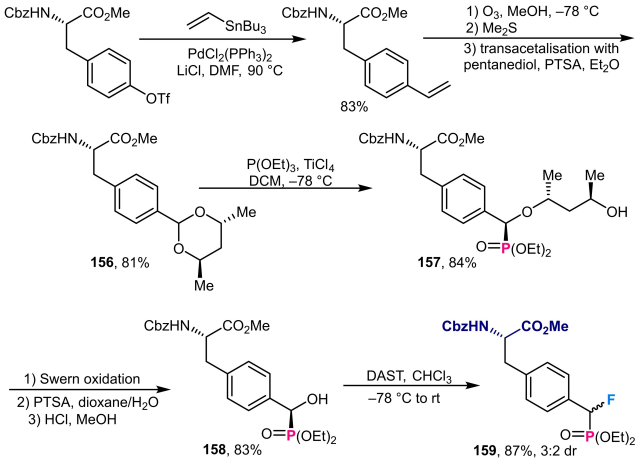
3.1.3. Monofluorophosphonomethyl Aspartic Acid Derivatives

Monofluorinated analogues of aspartyl-β-phosphate were designed as potential inhibitors of the bacterial aspartate semialdehyde dehydrogenase (ASA-DH), an enzyme that catalyzes the reductive dephosphorylation of aspartyl phosphate. The hydroxyl group of the γ-carboxylic acid was replaced by a monofluorophosphonomethyl group as in **161** (Scheme 59a) or a monofluoro olefinic phosphonate was constructed as carboxylic acid surrogate as in **162** (Scheme 59b).[119] L-Aspartic acid dimethyl ester was reacted with $LiCH_2P(O)(OMe)_2$ to introduce the phosphonate moiety and the corresponding sodium salt was added to Selectfluor to afford a 1:1 diastereomeric mixture of monofluorophosphonate **160** along with 10% of its enol form, which is indicative of an epimerization of the stereocenter; consequently, no effort was made to separate the diastereoisomers. Further deprotection and hydrolysis furnished the desired product **161** (Scheme 59a). The monofluoro olefinic phosphonate was constructed from chiral aldehyde by a Horner-Wadsworth-Emmons olefination in a low yield; further deprotection ended up with free phosphonate **162** (scheme 59b). The inhibitory activity of the monofluoromethylphosphonate **161** was similar to that of the difluoromethylene phosphonate (see 3.2.4), while the monofluoro olefinic phosphonate **162** showed poorly competitive inhibition of ASA-DH.

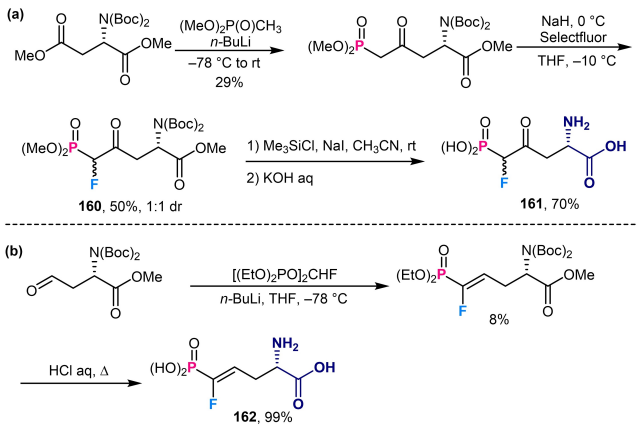
3.2. Difluorophosphonates

3.2.1. β-Difluorophosphonomethyl-α-Amino Acids

The protein phosphoserine/threonine phosphatases (PPs) are important enzymes responsible for mediating cellular signal transduction events by the control of the phosphorylation of several proteins in eukaryotic cells. For that reason, PPs are important targets for drug development. Peptides featuring an effective, but hydrolytically stable, phosphoserine/threonine mimic, have the capacity to inhibit this class of enzymes. Many studies have been conducted to synthesize pSer and pThr mimics having a difluoromethylene group in place of the phosphate ester oxygen and to incorporate them into small peptides for inhibition



Scheme 58. Asymmetric transformation of tyrosine into 4-phosphonofluoromethyl-phenylalanine.



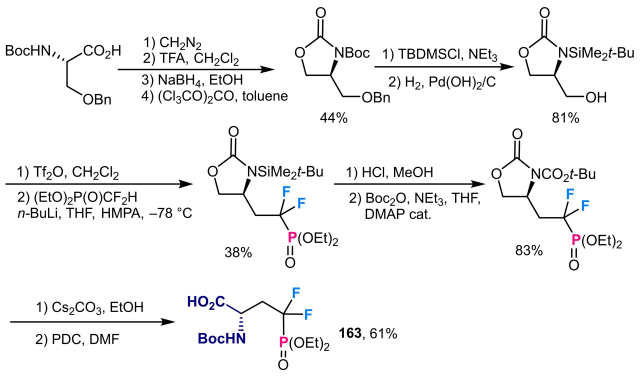
Scheme 59. Asymmetric transformation of chiral substrates into monofluorophosphonomethyl aspartic acid derivatives.

evaluation.[120–124] It requires the stereocontrol of one carbon center in pSer and two carbon centers in pThr.

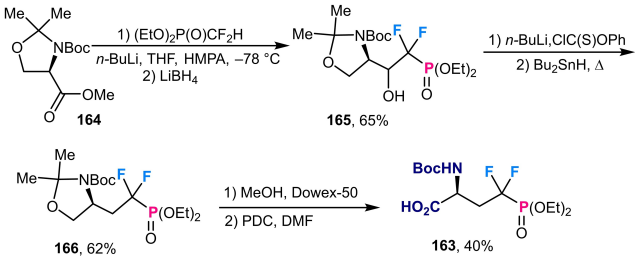
3.2.1.1. Difluorophosphonomethyl pSer Analogues

Methods for the synthesis of pSer analogues often start from chiral pool available natural amino acid L-serine. Berkowitz *et al.* developed a route from *N,O*-protected L-serine derivative, which was further transformed into the *N*-silylated oxazolidinone by standard reactions (Scheme 60). A triflate displacement procedure by means of diethyl lithio (*α,α*-difluoromethylene)phosphonate anion was then applied to introduce the difluoromethylphosphonate moiety followed by the nitrogen transprotection. Subsequent oxazolidinone ring-opening and oxidation ended up with the desired pSer mimic **163**.[125–126] The stereointegrity of the initial stereogenic center is retained all along the several synthetic steps.

The same group also reported the condensation of lithio (α,α-difluoromethylene)phosphonate anion with D-serine-derived Garner's ester **164** (Scheme 61). Reduction of the resulting β-keto(α,α-difluoromethylene)phosphonate into alcohol **165** with $LiBH_4$ proceeded chemoselectively, and subsequent deoxygenation with Bu_3SnH afforded **166**, which was further transformed into the final pSer mimic **163** under conditions already described.[127] The group of Otaka



Scheme 60. Asymmetric transformation of L-serine into β-difluorophosphonomethyl-α-amino acid.

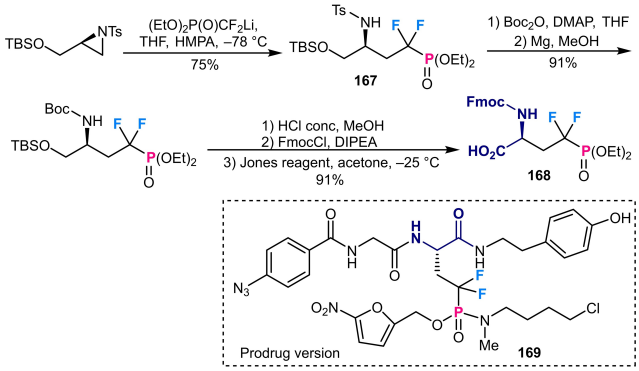


Scheme 61. Asymmetric transformation of D-serine-derived Garner's ester into β-difluorophosphonomethyl-α-amino acid.

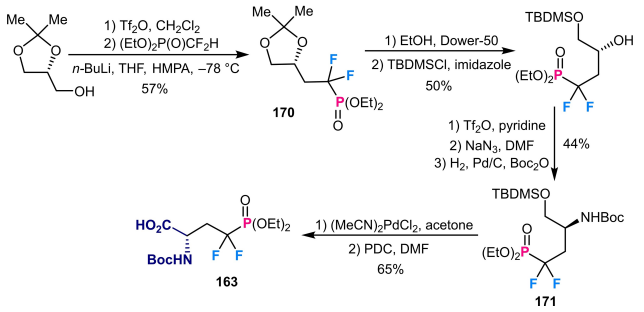
developed basically the same synthetic route to access **163**, which was incorporated into a difluoromethyl-substituted phosphoserine mimetic peptide by solid-phase synthesis.[128]

Enantiomerically pure aziridine having a pendant masked hydroxyl group is a useful synthon towards pSer mimics as demonstrated by Borch *et al.* (Scheme 62).[129] In this approach, the aziridine ring-opening by α,α-difluoromethylene diethylphosphonate anion performed stereospecifically to furnish the product **167** in 75% yield. The remainder of the sequence leading to the desired Fmoc protected phosphonoamino acid proceeded smoothly. Direct conversion of the *N*-tosyl to *N*-Boc protecting group was realized via the doubly protected *N*-Boc *N*-Ts amine and detosylation with magnesium powder. The TBS and *N*-Boc groups were removed under acidic conditions and the amine reprotected as *N*-Fmoc. Finally, the oxidation of the alcohol with Jones reagent afforded the desired product **168**. This small molecule that features a nonhydrolyzable difluoromethylenephosphoserine was designed to make prodrug inhibitors of 14-3-3 proteins. The prodrug **169** was prepared to generate a phosphoserine peptidomimetic in cells. Of particular importance, the rather stable diethylphosphonate moiety was replaced by a phosphoramidate that is more amenable to release in vivo the free phosphate.

Alternatively, (*R*)-solketal was used as starting chiral material (Scheme 63).[125] This approach differs from the precedent one in that the nitrogen atom was installed late in the synthetic plan, after the difluoromethylene phosphonate motif. Indeed, the free hydroxyl group in (*R*)-solketal was first converted into triflate for substitution with the lithio (α,α-difluoromethylene)phosphonate anion. Intermediate **170** was ring-opened and the secondary alcohol displaced with sodium azide via the triflate; the azide hydrogenolysis in the presence of Boc_2O gave directly compound **171**. Finally, Lipshutz's conditions for the



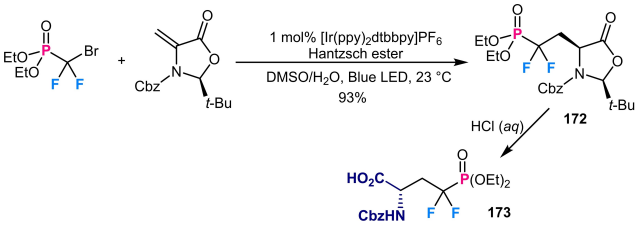
Scheme 62. Asymmetric transformation of enantiomerically pure aziridine into chiral phosphoserine.



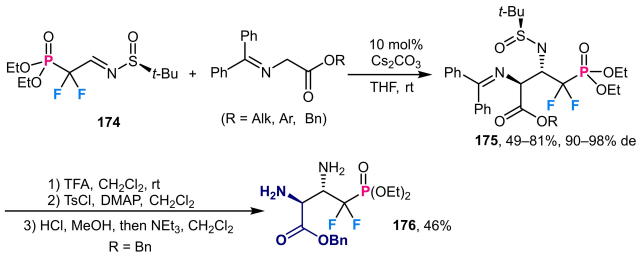
Scheme 63. Asymmetric transformation of (*R*)-solketal into the CF_2-pSer mimic.

catalytic Lewis acid-mediated chemoselective deprotection of the silyl ether and oxidation of the resulting alcohol yielded the pSer mimic **163**.

The methods described so far exploited the chirality of the starting material in which the stereogenic center remained unchanged or was inverted through stereospecific substitutions. In a different way, Jui *et al.* proposed a diastereoselective approach using a removable chiral auxiliary (Scheme 64).[130] Activation of diethyl (bromodifluoromethyl)-phosphonate via single electron reduction using blue LED excited photoredox catalyst $[Ir(ppy)_2(dtbbpy)]PF_6$ resulted in the generation of the difluoromethyl radical that was engaged in the conjugate addition onto the chiral *tert*-butyl oxazolidinone. Oxazolidinone adduct **172** was obtained as a single diastereoisomer. A deprotection step will still be required to yield the pSer surrogate **173**.



Scheme 64. Chiral auxiliary-induced asymmetric synthesis of the CF_2-pSer surrogate.

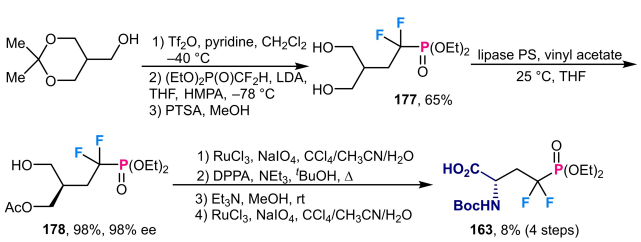


Scheme 65. Chiral auxiliary-induced asymmetric construction of a β-amino-β-difluorophosphonomethyl-α-amino acid.

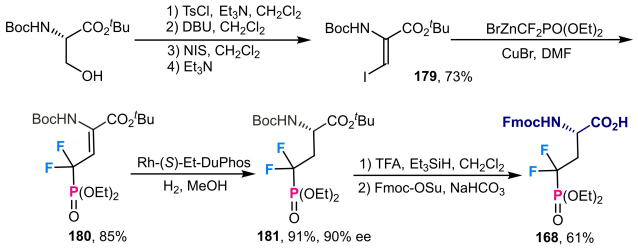
A different diastereoselective approach offers access to unique β-amino functionalized β-difluorophosphonomethyl-α-amino acids **176**. The source of chirality came from (S_S)-*N*-(*tert*-butylsulfinyl)difluoro(phosphoryl)imine **174**, which reacted with the glycine Schiff base simply at room temperature in THF catalyzed by Cs_2CO_3 to give the Mannich products **175** (Scheme 65).[131] High diastereoselectivity was measured in most cases and amine deprotection was demonstrated to occur without racemization.

The asymmetric enantioselective synthesis of **163** was achieved by the Shibuya group starting from prochiral isopropylidene-2-hydroxymethyl-1,3-propanediol by a lipase PS-catalyzed transesterification of 2-(diethylphosphono)-methyl-1,3-propanediol **177** (Scheme 66).[37] The enantioselectivity of the transesterification reaction by means of the lipase PS was very high (>98% ee) within one hour in THF. The enantiomeric excess of **178** was determined by HPLC analysis of the corresponding Mosher ester while the absolute configuration of the stereogenic center was assigned after transformation into the known pSer mimic **163**. The free alcohol group in **178** was converted into the corresponding acid through a Ru-catalyzed oxidation, and a Curtius rearrangement with DPPA and ^{t}BuOH gave the carbamate with high stereospecificity (>94% ee). Deacetylation of the masked hydroxyl group and a second Ru-catalyzed oxidation gave the desired pSer mimic **163** in a low overall yield.

A recent contribution from Chen group described an efficient enantioselective preparation of *N*-Fmoc-protected CF_2-pSer **168** starting from *N*-Boc-protected L-serine α-*tert*-butyl ester (Scheme 67).[132] The initial stereogenic carbon center was destroyed in favour of an iodo olefin **179** required for a Cu(I)-mediated coupling to introduce the CF_2-phosphonate moiety in **180** and for a rhodium-catalyzed asymmetric hydrogenation, which regenerated the stereogenic center in **181** with up to 90% ee. Next, chiral molecule **168** was successfully incorporated into phosphatase-resistant peptides by solid-phase peptide synthesis, and displayed similar inhibition to the 14-3-3 ζ protein as the parent pSer peptides.



Scheme 66. Enzymatic desymmetrization for the asymmetric synthesis of the CF_2-pSer mimic.



Scheme 67. Catalytic asymmetric hydrogenation for the construction of *N*-Fmoc-protected CF_2-pSer.

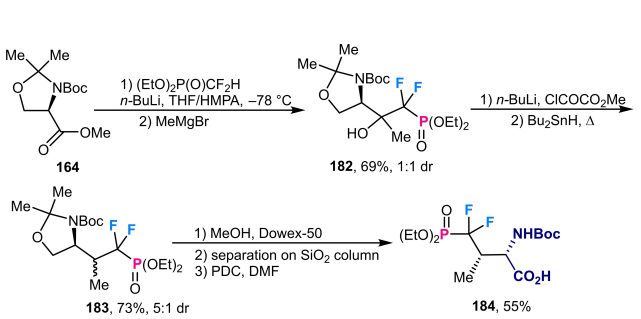
3.2.1.2. Difluorophosphonomethyl pThr Analogues

The protein serine/threonine phosphatases generally show a pronounced preference for phosphothreonine-containing peptides relative to phosphoserine-containing peptides. This different behaviour has been exploited to distinguish PP activity from general acido-basic dephosphorylation. The higher propensity for PP's to dephosphorylate phosphothreonine is somewhat counter intuitive based on the greater steric hindrance at the β-carbon of threonine; however, it raises the question of the impact of the configuration of the β-carbon stereocenter and its influence in the binding to PP-active sites. Consequently, several routes to difluoromethyl phosphonate analogues of L-phosphoserine have been reported.

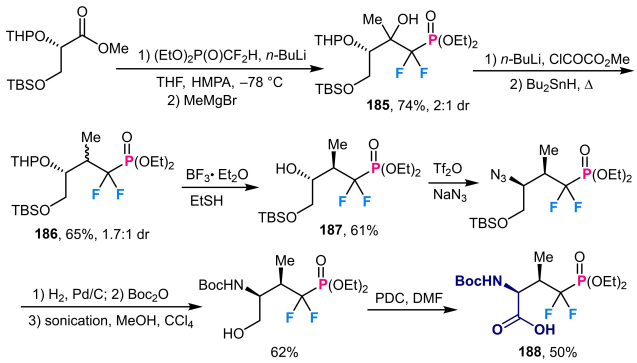
The Berkowitz group who already reported pSer mimics (see 3.2.1.1) applied a similar strategy for the preparation of L-phosphoallothreonine analogue (F_2pThr) as a CF_2-substituted pThr mimetic (Scheme 68).[127] After condensation of the lithio (α,α-difluoromethylene)phosphonate anion with Garner's ester **164**, the β-keto(α,α-difluoromethylene)phosphonate was reacted with methyl magnesium bromide in a non-stereoselective manner. The mixture of tertiary alcohols **182** was deoxygenated via a modified Dolan-MacMillan procedure to yield predominantly the allothreonine isomer **183** (5:1 dr). The *N,O*-acetal was cleaved, followed by the separation of the allothreo and threo diastereoisomers by silica gel chromatography, and finally the oxidation with pyridinium dichromate (PDC) yielded **184** as the desired *N*-Boc-protected L-phosphoallothreonine analogue.

A strategy was next elaborated to reach exclusively the diastereoisomer L-phosphothreonine analogue **188**. Starting from the differentially protected L-glycerate derivative, the tertiary alcohol intermediate **185** was obtained as a 2:1 mixture of diastereomers via (difluoromethylene)phosphonate condensation and Grignard addition, and after deoxygenation intermediate **186** as a 1.7:1 (allothreo:threo) mixture of diastereoisomers. Then, the THP deprotection by means of $BF_3{\cdot}Et_2O$ gave only the allothreo alcohol **187** on which the secondary alcohol was inverted via triflation / displacement with sodium azide. The remainder steps towards **188** paralleled those employed in the synthesis of the L-phosphoallothreonine **184** (Scheme 69). In this fashion, the (α,α-difluoroalkyl)-phosphonate analogues of both L-phosphoallothreonine and L-phosphothreonine were synthesized in forms appropriate for solid phase peptide synthesis, from D-serine and L-methylglycerate, respectively.[127]

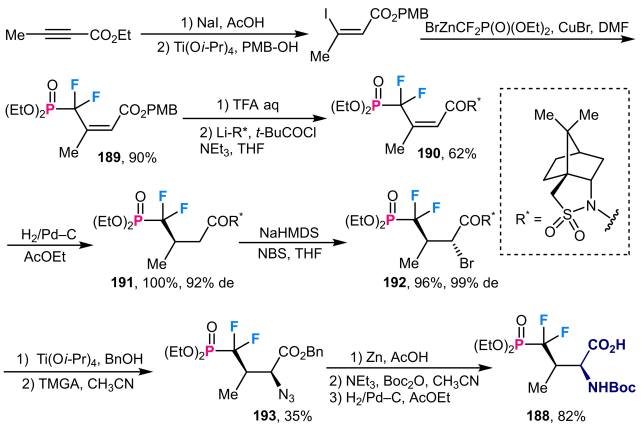
Another synthesis of chiral enantiopure 2-amino-4,4-difluoro-3-methyl-4-phosphonobutanoic acid (F_2pThr) was explored through consecutive diastereoselective hydrogenation and diastereoselective amination by Otaka *et al.* (Scheme 70).[133–134] The overall sequence started with the reaction of ethyl 2-butynoate with sodium iodine in acetic acid to give regio- and stereoselectively ethyl (*Z*)-3-iodo-2-butenoate. A transesterification gave the *p*-methoxybenzyl ester on which the introduction of the difluoromethylphosphonate unit was carried out by Cu(I)-mediated coupling. In this way, **189** was obtained in 90% yield with retention of the C=C bond geometry. The ester was cleaved and the (*2R*)-bornane-10,2-sultam condensed to afford the conjugated sultam-imide **190** as substrate in the diastereoselective hydrogenation. This diastereoselective step was carried out with H_2/Pd–C in EtOAc to yield **191** quantitatively with 92% de. The major diastereoisomer was purified by column chromatography, crystallized and its absolute configuration ascer-



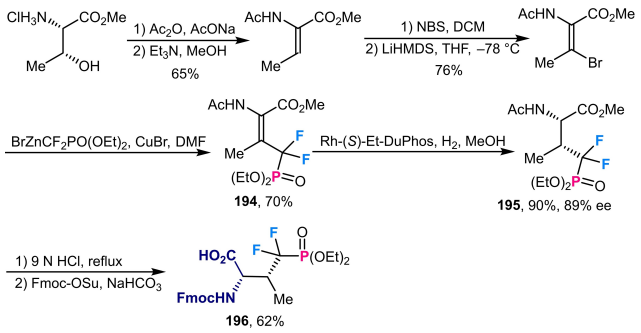
Scheme 68. Asymmetric transformation of chiral Garner's ester into difluorophosphonomethyl pThr derivative.



Scheme 69. Asymmetric transformation of methyl L-glycerate into *N*-Boc-protected CF_2-pThr.



Scheme 70. Chiral auxiliary-induced asymmetric synthesis of *N*-Boc-protected CF_2-pThr.



Scheme 71. Catalytic asymmetric hydrogenation for the synthesis of *N*-Fmoc-protected CF_2-pThr.

tained. The subsequent step was the introduction of an amino group. Direct electrophilic amination by means of 1-chloro-1-nitroso-cyclohexane showed some limitations in particular to access the threo derivatives; on the other hand, diastereoselective bromination and azide substitution with inversion of configuration appeared as an appropriate pathway to achieve the diastereoselective preparation of all four isomers of protected F_2pThr. Deprotonation of **191** with NaHMDS followed by bromination with NBS gave the brominated compound **192** in excellent yield and de value. At this stage, the chiral auxiliary was removed prior to the substitution with tetramethylguanidinium azide (TMGA); this later reaction proceeded with complete inversion of configuration at the α-stereocenter. However, the yield of **193** was only 35% because of competitive E2-elimination side-product. To conclude, the azide was reduced, *N*-Boc protected and a catalytic hydrogenation yielded the desired F_2pThr **188**. The full sequence was applied to all four isomers using the enantiomeric chiral auxiliaries and chromatographic separation of diastereoisomers.

In section 3.2.1.1, we have seen that the Chen group has described an enantioselective rhodium-catalyzed hydrogenation for the synthesis of *N*-Fmoc-protected CF_2-pSer; the authors also applied such approach for the synthesis of *N*-Fmoc protected CF_2-pThr **196** starting from L-threonine methyl ester (Scheme 71).[132] After Cu(I)-mediated coupling to introduce the CF_2-phosphonate motif, the E olefin **194** was hydrogenated in the presence of Rh-(*S*)-Et-DuPhos to give **195** in 89% ee with high control of two chiral centers in one step.

3.2.2. Difluorophosphonomethyl Tyrosine Analogues (F_2Pmp)

Phosphotyrosine (pTyr) is an essential phosphorylated amino acid for cellular signal transduction as it plays a role in protein-protein interactions at the origin of a wide range of cell functions. In whole-cell systems, pTyr-containing peptides suffer from phosphate cleavage by protein-tyrosine phosphatases. To thwart this metabolization, the (phosphono-methyl)phenylalanine (Pmp) was introduced as well as the 4-(phosphonodifluoromethyl)phenylalanine (F_2Pmp); this latter having proved to be superior to Pmp as a non-hydrolyzable pTyr mimetic.[135] F_2Pmp demonstrated widespread uses when incorporated into peptides that bind to SH_2 domains.[136] For instance, F_2Pmp-containing peptides exhibit biological activity as inhibitors of protein tyrosine phosphatase PTP-1B, its closest related enzyme T-cell PTP (TC-PTP), and PTP-MEG2 in the treatment of type 2 diabetes, obesity, and cancer;[124,137–146] they are also involved in the regulation of protein-tyrosine phosphatase SHP-1.[147] Not surprisingly, several synthetic approaches were studied towards convenient and stereo-controlled access to F_2Pmp and its derivatives. Four disconnections cover the ways of making F_2Pmp (Figure 4). Disconnection **A** consists of a functional group interconversion starting from tyrosine in which the phenolic hydroxyl group is substituted by the difluoromethylphosphonate moiety. Disconnection **B** is a C–C bond formation operated by convergent palladium-catalyzed coupling. Unlike the former two approaches, disconnections **C** and **D** touches directly the stereogenic center and require the asymmetric formation of a C–C bond or a C–N bond, respectively.

Disconnection **A** (Figure 4) obviously exploits tyrosine as source of chirality and syntheses of F_2Pmp

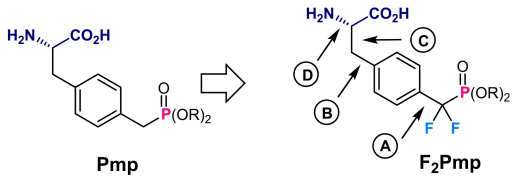
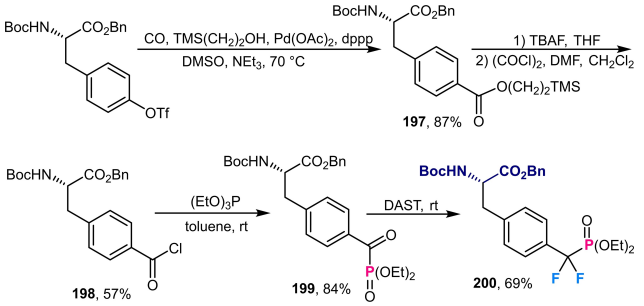


Figure 4. Structures of (phosphonomethyl)phenylalanine (Pmp) and (phosphonodifluoromethyl)phenylalanine (F_2Pmp).

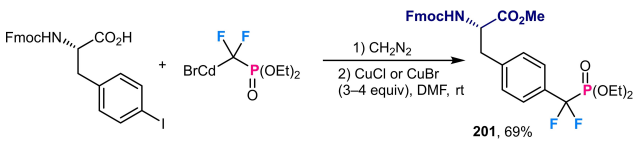
derivatives consist primarily in the installation of the difluorophosphonate moiety while retaining the integrity of the α-amino acid stereogenic center. Wrobel and Dietrich started from *N*-Boc-L-tyrosine benzyl ester whose hydroxyl group was transformed into the corresponding triflate to be engaged in a Pd-catalyzed alkoxycarbonylation in the presence of 1,3-bis(diphenylphosphino)propane (dppp) under an ambient CO pressure (Scheme 72).[148] The trimethylsilylethyl ester **197** was cleaved with *n*-tetrabutylammonium fluoride (TBAF) and the resulting acid transformed into acid chloride **198** by means of oxalyl chloride and catalytic DMF. Next, an Arbuzov reaction with triethylphosphite led to the acylphosphonate **199** and the carbonyl function was difluorinated with (diethylamino)sulfur trifluoride (DAST) to afford L-(*S*)-4-(phosphonodifluoromethyl)-phenylalanine derivative **200**. The optical purity of **200** was demonstrated by derivatization into a single diastereoisomeric form.

Instead of a coupling reaction via an aryl triflate, commercially available *N*-Fmoc-L-4-iodophenylalanine was first esterified with diazomethane followed by a CuCl-mediated coupling to (diethylphosphonyl) difluoromethylcadmium bromide under Burton's conditions (Scheme 73).[149–150] A good yield of 87% (**201**, R = Fmoc) was obtained only when excess CuCl was used (3–4 equiv.). It was later found that excess CuBr performed slightly better in the coupling reaction.[151] This protocol proved to be as efficient on L-4-iodoPhe-containing peptides in order to provide F_2Pmp-containing peptides.

Methyl *N*-Ac-L-4-iodophenylalanine can be converted into the corresponding unsymmetrical iodonium salt and diethyl bromodifluoromethylphosphonate into



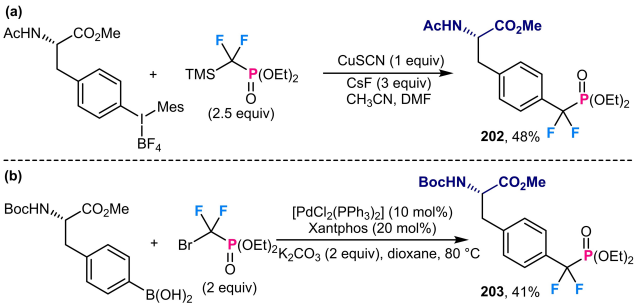
Scheme 72. Asymmetric transformation of natural L-tyrosine into the F_2Pmp derivative.



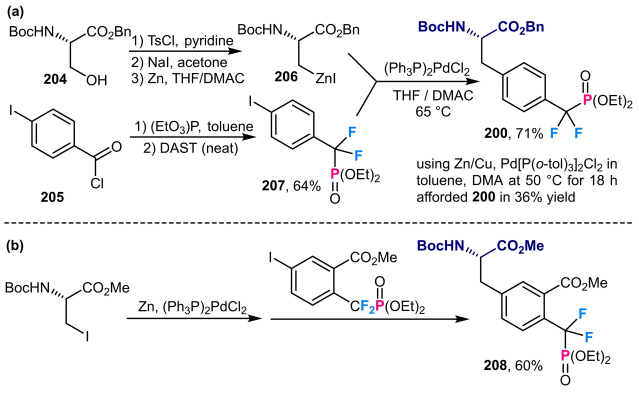
Scheme 73. Cu-mediated cross-coupling of L-4-iodophenylalanine and $(EtO)_2POCF_2CdBr$ for the synthesis of F_2Pmp.

diethyl [(trimethylsilyl)-difluoromethyl]phosphonate to be engaged in a copper/fluoride-mediated coupling reaction (Scheme 74a). Although, these additional steps provided an interesting approach, the F_2Pmp derivative **202** was obtained only in a moderate yield.[152] For a truly catalytic coupling reaction, tyrosine-derived aryl boronic acid was coupled with diethyl bromodifluoro-methylphosphonate under the palladium (II) catalysis in the presence of the bidentate ligand Xantphos to afford the F_2Pmp derivative **203** in a moderate yield (Scheme 74b).[153]

Disconnection **B** differs from **A** (Figure 4) in that the newly created C–C bond allows to install the aromatic moiety onto the β-carbon of α-amino acids. Burke *et al.* constructed the two halves from *N*-Boc L-serine benzyl ester **204** and 4-iodobenzoyl chloride **205** (Scheme 75a). Initial tosylation of **204** was followed by nucleophilic displacement with sodium iodide and zincation by means of zinc dust afforded the first fragment **206**. An Arbuzov reaction of triethyl phosphite with **205** and conversion of the carbonyl group into the difluoromethylene motif with DAST furnished the second fragment **207**. Then, a palladium (II)-catalyzed coupling reaction (with 5 mol% of Pd) of the organozinc reagent with the aryl iodide gave the



Scheme 74. The cross-coupling of 4-substituted phenylalanines and $(EtO)_2POCF_2TMS/Br$ for the asymmetric synthesis of F_2Pmps.



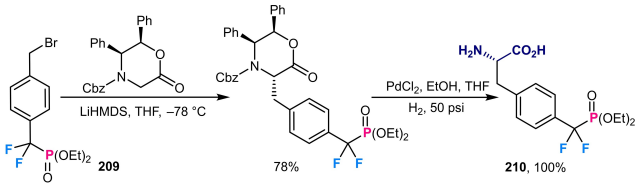
Scheme 75. Pd-catalyzed coupling of L-serine-derived zinc reagents with aryl iodide for the synthesis of F_2Pmps.

desired *N*-Boc-L-F_2Pmp(OEt_2)-OBn compound **200** in 71%. The Fmoc derivative as well as methyl esters and free acids were also prepared.[154–155] Percy *et al.* used different reaction conditions [Zn/Cu, $Pd[P(o\text{-tol})_3]_2Cl_2$ in toluene and dimethylacetamide (DMA)] to obtain **200** in 36% yield.[156] This synthetic route was further employed for the preparation of derivatives containing an additional functional group on the aromatic ring as shown in Scheme 75b. The F_2Pmp surrogate **208** was produced in 60% yield by the Burke palladium-catalyzed coupling.[157]

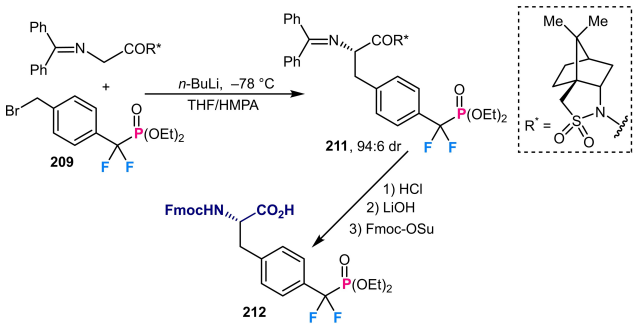
Disconnection **C** (Figure 4) was made possible via a diastereoselective alkylation of a chiral substrate bearing a removable chiral auxiliary. Solas *et al.* exploited the Williams lactone as source of chirality in the diastereoselective addition of benzylic bromide **209** prepared from 4-(bromomethyl)-benzoic acid in three steps (Scheme 76).[158] After deprotonation by LiHMDS, alkylation of Williams lactone proceeded in 78% yield for a single diastereoisomer of the product. The cleavage of the auxiliary into the free amino acid L-F_2Pmp **210** was done quantitatively by hydrogenation.

A different chiral auxiliary, as in the camphorsultam glycine Schiff base derivative, was evaluated by Roques *et al.* (Scheme 77).[159] The acyclic nature of the substrate is more flexible than the Williams lactone and it resulted in a lower diastereoselectivity of 88% de for the benzylated product **211** (the yield was not provided). The alkylated compound was further transformed into *N*-Fmoc-protected L-F_2Pmp **212** under the standard conditions.

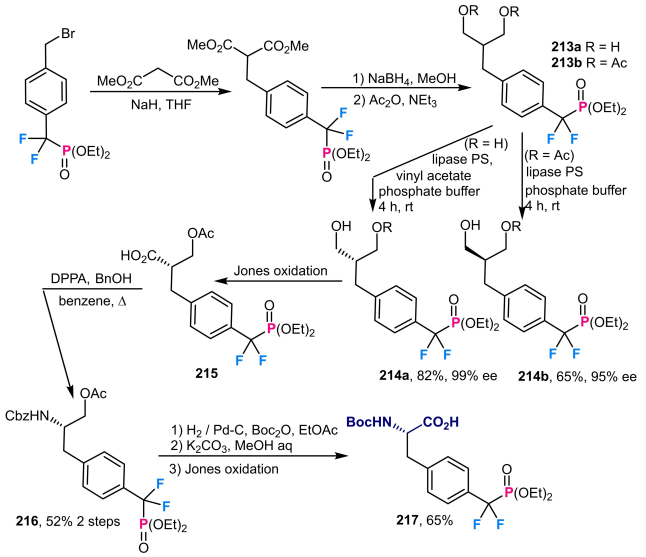
Disconnection **D** (Figure 4) is certainly the most challenging as it is based on a C–N bond formation directly at the α-stereogenic carbon atom. Shibuya *et al.* have elaborated an elegant pathway toward F_2Pmp derivative **217** via an enzymatic enantioselective (trans)esterification and a stereospecific Curtius rearrangement (Scheme 78).[96] The sequence started with a condensation of dimethyl malonate and diethyl ((4-(bromomethyl)phenyl)difluoromethyl)-phosphonate to give the new malonate followed by the reduction of the two esters moieties into diol **213a** (R = H) with $NaBH_4$ and acetylation of the two hydroxyl functions to end up with **213b** (R = Ac). Two options were next examined, either the PS lipase (Pseudomonas cepacia)-catalyzed hydrolysis of the diacetate **213b** or the transesterification of the diol **213a** mediated by the lipase PS in the presence of vinyl acetate. The former approach gave the monoacetylated compound **214b** in 65% yield with 95% ee while the second one gave its antipode **214a** in 82% yield with 99% ee. A Jones oxidation led to the chiral acid **215**, which was exposed to a stereospecific Curtius rearrangement for the installation of a nitrogen atom leading to the amino derivative **216**. The remainder of the sequence to install the final functions and protecting groups amenable to the peptide synthesis gave the desired compound **217** in three steps in 65% yield. Note that from the same intermediates **213**, homologues of **217** having a β-amino acid structure were also synthesized via a Mitsunobu reaction (see 5.3).



Scheme 76. Chiral Williams lactone-induced asymmetric synthesis of L-F_2Pmp.



Scheme 77. Chiral camphorsultam glycine imine-induced asymmetric synthesis of *N*-Fmoc-protected L-F_2Pmp.



Scheme 78. Enzymatic desymmetrization for enantioselective synthesis of *N*-Boc-protected L-F_2Pmp.

3.2.3. Difluorophosphonomethyl Aspartic Derivatives

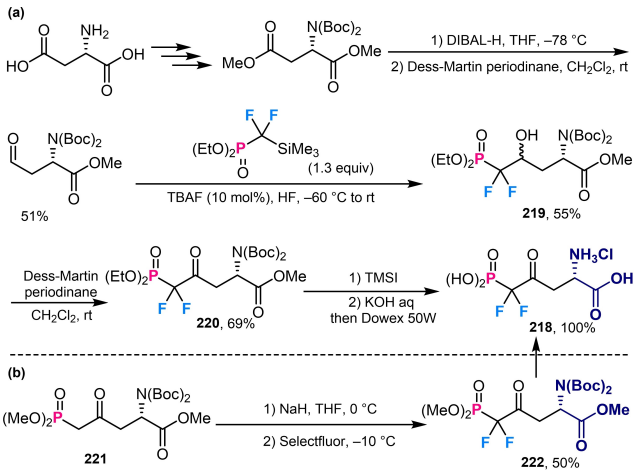
As mentioned earlier in the text, L-aspartate-β-semialdehyde dehydrogenase (ASA-DH) is an enzyme that catalyzes the dephosphorylation of β-aspartyl phosphate to L-aspartate semialdehyde. Since the aspartate biosynthetic pathway is only present in plants and microbes, ASA-DH is a relevant biological target for developing the next generation of antibiotics. The Cox's group was particularly active in the design of phosphonic aspartic derivatives including phosphoramidates, phosphonates (see 2.5), monofluorophosphonates (see 3.1.3), and difluorophosphonates.[160] Aspartyl β-difluorophosphonate (β-AFP) of **218**, was identified as a lead compound and used to understand the molecular recognition interactions with ASA-DH.[161–162] The synthesis of **218** was reported via different routes that all exploited aspartic acid as starting chiral substrate.

The diester-*N*-$(Boc)_2$ aspartate, routinely prepared from aspartic acid, was reacted with diethyl lithio (α,α-difluoromethylene)phosphonate anion, but only a very low yield of the adduct was obtained. Alternatively, the diester was converted into the aldehyde in a two-step sequence in 51% yield. When this aldehyde was treated with diethyl [(trimethylsilyl)difluoromethyl] phosphonate in the presence of TBAF, the desired adduct **219** was obtained in a moderate 55% yield. A 3:1 mixture of diastereoisomeric alcohols was obtained and converted to the single ketone **220** by oxidation in 69% yield (Scheme 79a).[163–164] Note that the authors investigated a reverse approach by late introduction of the fluorine en route to the mono- (see 3.1.3) and difluoro phosphonates. In this way, the dimethyl phosphonate **222** (analogue of **220**) was accessible by Selectfluor addition onto the sodium salt of phosphonate **221** (Scheme 79b).[119] Subsequent treatment with TMSI and hydrolysis gave rise to the corresponding phosphono-α-amino acid **218**.

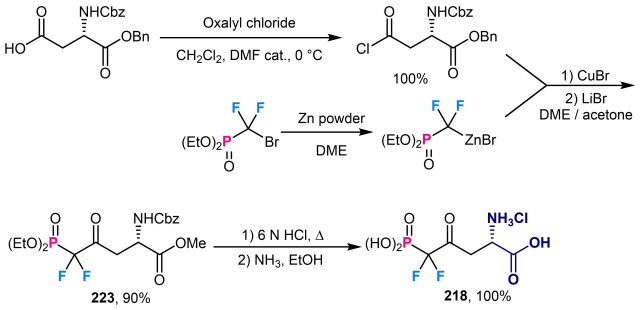
A shorter and more efficient synthesis was claimed by Viola *et al.* (Scheme 80).[165] Based on the fact that the addition of the diethyl lithio (α,α-difluoromethylene)phosphonate anion to the γ-ester function in diester-*N*-$(Boc)_2$-aspartate gave the adduct in a poor yield, it was proposed a coupling reaction between the carbonyl function of the L-aspartate acid chloride and the bromozinc-difluoromethylene phosphonate. This pathway afforded the protected product **223** in 90% yield. Full deprotection of the phosphonate, ester, and amine functions was achieved to afford **218** quantitatively. Preincubation of ASA-DH from various infectious microorganisms with β-AFP **218** led to potent time-dependent enzyme inactivation.

3.2.4. Glutamic-based Derivatives

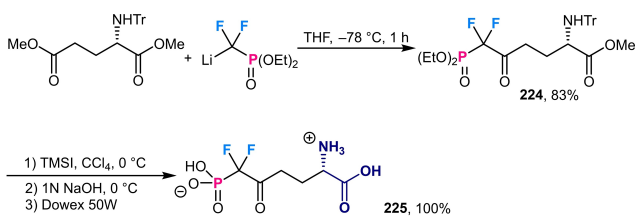
One carbon elongation allows to go from aspartic to glutamic acid and it is reasonable to think that methods used to make aspartyl difluorophosphonate could be applied to glutamic homologues (Scheme 81).[166] Surprisingly in this case and contrary to what other groups observed, the addition of the diethyl lithio (α,α-difluoromethylene)phosphonate anion onto the δ-ester function of the *N*-trityl-L-glutamic acid dimethyl ester worked well in THF at −78 °C, and gave the adduct **224** in a pretty good yield. After the deprotection by trimethylsilyl iodide (TMSI), alkaline hydrolysis, and cation-exchange chromatography, the corresponding



Scheme 79. Asymmetric transformation of aspartic acid into difluorophosphonomethyl aspartic acid analogues.



Scheme 80. Cu-mediated asymmetric coupling of L-aspartate acid chloride and bromozinc-difluoromethylenephosphonate.



Scheme 81. Asymmetric transformation of *N*-trityl-L-glutamic acid ester into difluorophosphonomethyl glutamate analogue.

product **225** was obtained quantitatively. It was then engaged in a study as inhibitor of γ-glutamylcysteine synthetase and glutamine synthetase. Unfortunately, **225** turned out to be a poor inhibitor of both enzymes.

4. Asymmetric Construction of Cyclopropane and Bicyclo-[x.y.z]-Alkane Amino Acid Phosphonate Derivatives

4.1. Phosphonomethylcyclopropanecarboxylic Acids

As mentioned in part 2.3, L-AP-4 is a potent and selective agonist for group III mGlu receptors. Therefore, the synthesis of L-PA-4 and its analogues are of great significance. 1-Amino-2-phosphonomethylcyclopropanecarboxylic acid (APCPr), a structural analogue of L-AP-4, was first reported by Acher *et al.* in 2007 (Scheme 82).[167] The authors initially used chiral substrate **226** introduced by Burgess in his pioneering work.[168] The bromide **227** was prepared by Appel reaction in 56% yield, and the amine protective group (Boc) in **227** was preferentially substituted by a more electron-withdrawing group (trifluoroacetyl) to give the corresponding intermediate in 93% yield. Subsequently, the Arbuzov reaction was performed to introduce the phosphonate functionality to give the product **228**. Ultimately, (1*S*,2*R*)-APCPr **229** was obtained by acid hydrolysis and ionic chromatography purification in 96% yield. According to this method, starting from each stereoisomer of hydroxymethylcyclopropyl amino acid derivative **226**, the four stereoisomers **229a–d** of APCPr have been smoothly accessed, among which (1*S*,2*R*)-APCPr **229a** displayed the best activity for the group III mGlu receptors.

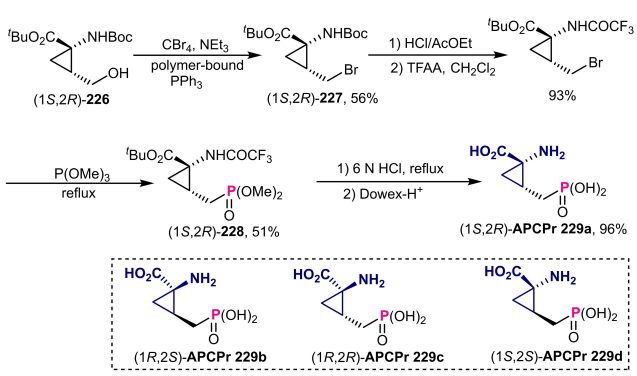
4.2. Fluorocyclopropane Analogues

As discussed in part 3, it is well known that the introduction of fluorine atoms can effectively change the physical and chemical properties of the parent molecules. In 2012, the Jubault's group synthesized the racemic 1-amino-2-fluoro-2-(phosphono-methyl)cyclopropane-1-carboxylic acid (FAP4), which exhibited better activity compared to the non-fluorinated counterpart.[169] Three years later, four optically pure stereoisomers of FAP4 were obtained by the same group, and the biological study showed that both the (−)-(*Z*)-FAP4 and (−)-(*E*)-FAP4 have a good agonist activity against mGlu4.[170] As depicted in Scheme 83, 3-chloro-2-fluoropropene was converted into diethyl 2-fluoro-allylphosphonate **230** by the Arbuzov reaction in 77% yield. A Rh-catalyzed cyclopropanation of diethyl 2-fluoroallyl-phosphonate with ethyl nitrodiazoacetate led to cyclopropane **231** with *E*-stereochemistry (determined ^{19}F NMR). Further reduction and protection afforded the corresponding compound (*E*)-**232**, whose stereochemistry was determined by NOESY NMR. After chiral resolution by preparative supercritical fluid chromatography (SFC), deprotection with HCl/AcOH, both (−)-(*E*)-FAP4 **233** and (+)-(*E*)-FAP4 **233** were obtained in yields of 67% and 72%, respectively. The use of *p*-methoxyphenyl (PMP) nitrodiazoacetate gave preferential access to the phosphonate cyclopropane (*Z*)-**234** in 78% yield with 87:13 diastereoselectivity. For the next steps, a similar protocol as above was performed with (*E*)-**233** to give the desired products: (−)-(*Z*)-FAP4 and (+)-(*Z*)-FAP4.

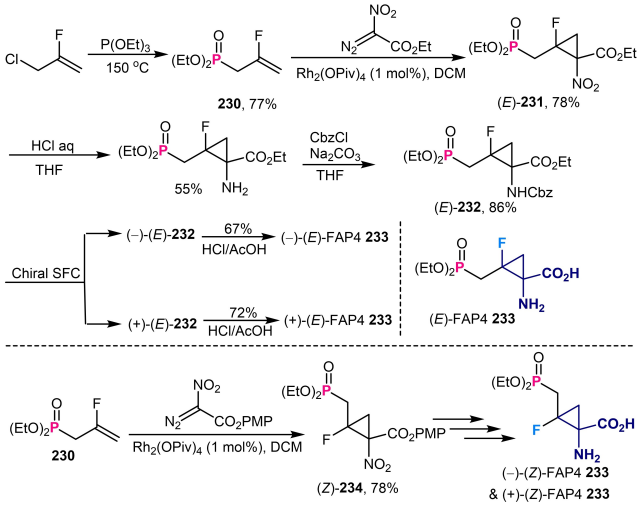
4.3. Phosphonocyclopropyl-α-Amino Acids

4.3.1. Disubstituted Phosphonocyclopropyl-α-Amino Acids

In 2006, the Pellicciari's group presented an interesting synthesis of phosphonocyclopropyl-α-amino acid by virtue of a diastereoselective Strecker reaction under



Scheme 82. Asymmetric transformation of chiral cyclopropyl α-amino acids into enantiopure APCPrs.



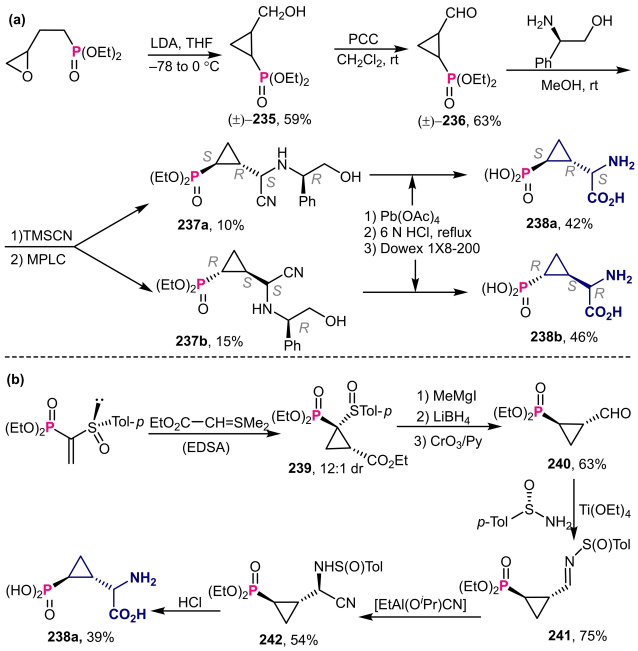
Scheme 83. Diastereoselective synthesis of 1-amino-2-fluoro-2-(phosphonomethyl)cyclopropane-1-carboxylic acids.

the assist of a chiral auxiliary (Scheme 84a).[171] Starting from readily available diethyl γ,δ-epoxybutylphosphonate, a unique LDA-induced epoxide ring-opening and intramolecular cyclopropanation gave the *trans*-diethyl 2-(hydroxymethyl) cyclopropyl phosphonate **235**.[172] Subsequent oxidation with PCC afforded the corresponding aldehyde **236** in 63% yield. Then, *R*-(−)-phenylglycinol-tethered imine underwent the Strecker reaction with trimethylsilyl cyanide to generate the mixture of amino nitriles **237**. After separation and purification on silica gel and MPLC, the two enantiopure diastereoisomers **237 a** and **237 b** were obtained in 10% and 15% yield over 2 steps, respectively. The ultimate deprotected phosphonocyclopropyl-α-amino acids **238** were synthesized through Pb-oxidative cleavage, acid hydrolysis, and separation by ion-exchange resin chromatography. In a similar fashion, Midura *et al.* prepared these chiral phosphonocyclopropyl glycine (PCG) derivatives by the use of a chiral sulfinyl auxiliary (Scheme 84b).[173] Enantiopure phosphono-cyclopropanyl ester **239** was obtained via a cyclopropanation reaction of chiral vinyl sulfoxide with ethyl (dimethyl-sulfuranylidene) acetate (EDSA) in 12:1 dr. Following desulfurization, reduction, and oxidation gave the aldehyde **240**, which was further condensed with (*S*)-(+)-*p*-toluenesulfinamide to form the Schiff base **241**. Then, ethylaluminum cyanoisopropoxide [EtAl(O^{i}Pr)CN] in-situ formed from diethylaluminum cyanide and ^{i}PrOH, was used as the nucleophile to produce the amino nitrile **242**. Although the diastereoselectivity of the Strecker step was moderate (5:2), the major isomer could be easily separated via column chromatography. Final hydrolysis provided the desired PCG **238 a** in 39% yield, and its antipode PCG **238 b** was also prepared in an identical sequence.

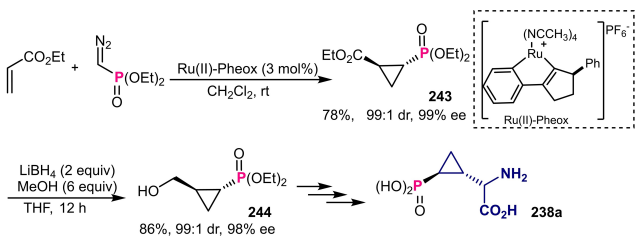
A catalytic asymmetric entry to phosphonocyclopropyl amino acid was reported by Iwasa *et al.* in 2014. The key reaction development was a Ru(II)-Pheox-catalyzed stereoselective cyclopropanation of olefins with diazomethyl-phosphonates (Scheme 85).[174] This method was successfully applied to the preparation of optically active cyclopropylphosphonate **243** in 78% yield and excellent diastereo- and enantioselectivity (99:1 dr, 99% ee). Reduction of the ester group with $LiBH_4$ gave the phosphonocyclopropanyl alcohol **244** in 86% yield with maintained excellent ee value. Compound **244** is a key intermediate towards PCG as demonstrated in Pellicciari's method.[171]

4.3.2. Trisubstituted Phosphonocyclopropyl-α-Amino Acids

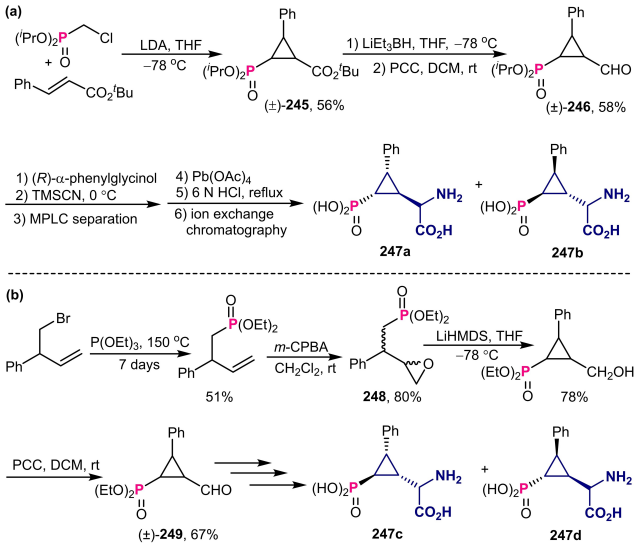
To evaluate the steric accessibility of the binding pocket of group III mGluRs, Pellicciari *et al.* introduced the hydrophobic phenyl group onto the cyclopropanyl ring of PCG, thus affording four new trisubstituted phosphono-phenylcyclopropyl-α-amino acids PPCG (Scheme 86).[175] For this purpose, the cyclopropane skeleton was constructed in the early stage of the synthetic plan via the addition of diisopropyl α-chloromethylphosphonate anion to *E*-*tert*-butyl cinnamate. The resulting major diastereoisomer **245** was then subjected to reduction and oxidation conditions to produce the phosphono-phenylcyclo-propanyl aldehyde **246**. Then, chiral phenylglycinol auxiliary and the Strecker reaction were used again as the key steps to give the final trisubstituted phosphono-phenylcyclopropyl-α-amino acids **247 a** and **247 b**, respectively (Scheme 86a). The synthesis of two other diastereoisomers started with an Arbuzov reaction to create the C–P bond followed by epoxidation by means of *m*-CPBA to give the epoxide **248** (Scheme 86b). Next, LiHMDS-triggered transannulation and PCC oxidation provided the trisubstituted



Scheme 84. Diastereoselective synthesis of phosphono-cyclopropyl glycine (PCG) derivatives.



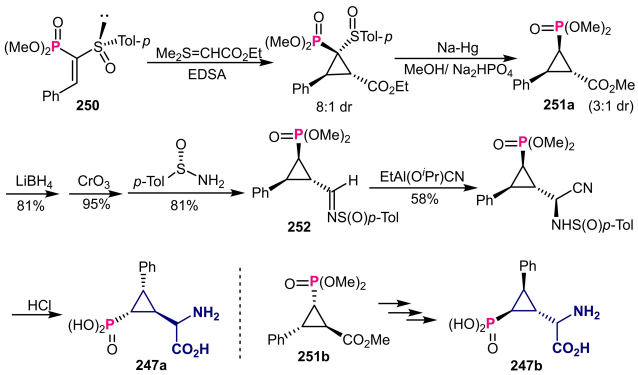
Scheme 85. Catalytic asymmetric synthesis of chiral phosphonocyclopropyl glycine precursor.



Scheme 86. Chiral auxiliary-induced asymmetric construction of phosphono-phenylcyclopropyl glycine (PPCG) derivatives.

cyclopropane intermediate as a single stereoisomer **249**. Finally, analogous procedure was performed to access the phosphono-phenylcyclopropyl glycines **247 c** and **247 d**.

The chiral sulfinyl moiety was also used as an effective directing group for the asymmetric synthesis of chiral phosphono-phenylcyclopropyl glycines. As illustrated in Scheme 87, starting from the trisubstituted vinyl sulfoxide **250**, Midura *et al.* prepared the phosphono-phenylcyclopropanyl ester **251** via a cyclopropanation/desulfurization sequence.[173] Then, the chiral *p*-toluenesulfinyl group was introduced to form the chiral Schiff base **252**, followed by a diastereoselective Strecker reaction and acid hydrolysis. This protocol allowed the preparation of conformationally constrained PPCGs (**247 a** and **247 b**).

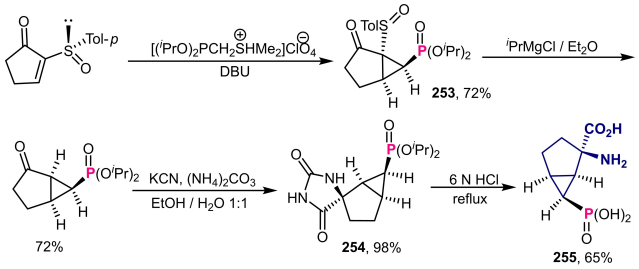


Scheme 87. Chiral sulfinyl-induced asymmetric construction of chiral phosphono-phenylcyclopropyl glycines.

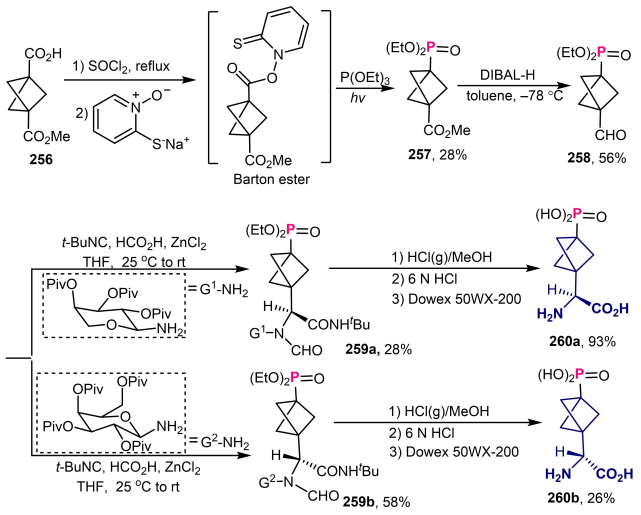
4.4. Bicyclo-[x.y.z]-Alkane Amino Acid Phosphonate Derivatives

As a constrained cycloalkyl analogue of glutamic acid, 2-amino-6-phosphonobicyclo-[3.0.1]-hexane-2-carboxylic acid **255** was synthesized by Mikołajczyk *et al.* in 2010 by using a chiral auxiliary approach (Scheme 88).[176] Cyclopropanation reaction of 2-(*p*-tolylsulfinyl)cyclopent-2-enone with a phosphoryl sulfonium ylide generated the bicyclic ketophosphonate **253** with moderate diastereoselectivity (3:1). After chiral *p*-tolylsulfinyl auxiliary elimination with *iso*-propylmagnesium chloride, a stereoselective Bucherer–Bergs reaction formed a single spirohydantoin **254** in almost quantitative yield. Ultimately, hydrolysis with 6 *N* HCl completed the synthesis of enantiopure bicyclic aminophosphonic acid **255** in 65% yield.

Bicyclo-[1.1.1]-pentane (BCP) motif exhibits special conformational rigidity and could mimic as bioisostere of benzene ring in drug discovery.[177] In this context, the chiral phosphonobicyclo-[1.1.1]-pentyl glycines **260** have been synthesized via a stereoselective Ugi condensation and evaluated as mGluRs ligands by Pellicciari *et al.* (Scheme 89).[178] Commercially available monoacid **256** was initially treated with $SOCl_2$, followed by the esterification with sodium salt of 2-mercapto-pyridine *N*-oxide to provide Barton's ester intermediate. Radical phosphorylation under photo-irradiation conditions gave the phosphonate ester **257** in 28% yield,[179] which was further reduced with DIBAL–H to form the aldehyde **258** in 56% yield. Subsequently, a diastereoselective Ugi reaction with chiral carbohydrate-derived amine, *tert*-butyl isocyanide, and formic acid led to the formation of the corresponding amide in 85:15 dr. After chromatographic separation, the major diastereoisomer **259 a** was obtained in 28% yield. The *N*-CHO group and the chiral auxiliary were cleaved at the meantime under HCl/methanol conditions. Further acid hydrolysis and ion exchange chromatography purification afforded the final free phosphonobicyclo-[1.1.1]-pentylglycine (PBPG) **260 a** in 93% yield. For the synthesis of the enantiomer **260 b**, a similar procedure was undertaken using galactose-derived amine as the chiral



Scheme 88. Asymmetric synthesis of chiral (+)-2-amino-6-phosphono-bicyclo-[3.0.1]-hexane-2-carboxylic acid.



Scheme 89. Asymmetric synthesis of chiral phosphonobicyclo-[1.1.1]-pentyl amino acid derivatives.

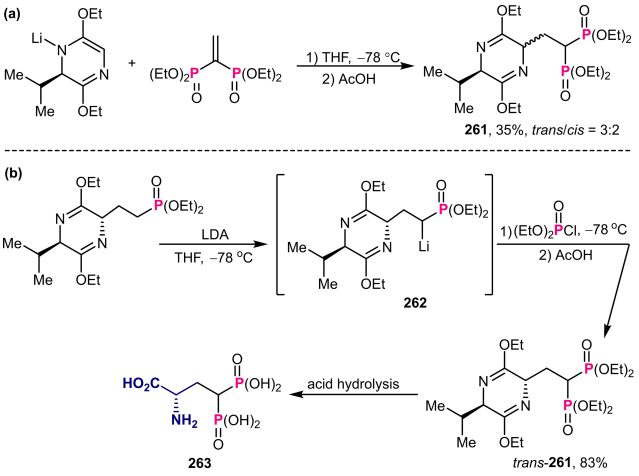
auxiliary.[180] The Ugi reaction proceeded with 90:10 diastereoisomeric ratio, thus giving the major isomer **259 b** in an improved 58% yield. Subsequent same acid hydrolysis conditions as described above yielded the final (*R*)-PBPG **260 b.**

5. Asymmetric Construction of Miscellaneous Derivatives

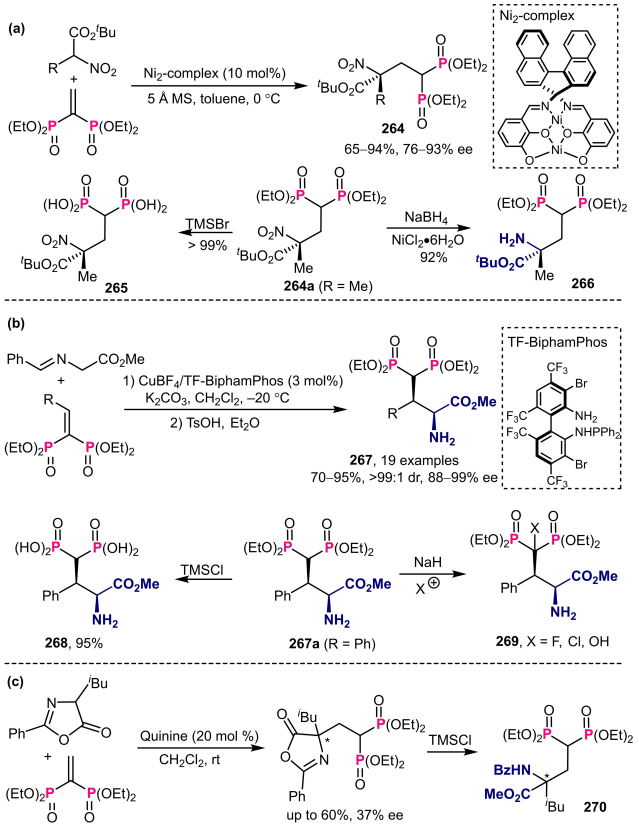
5.1. Bisphosphono-α-Amino Acids

Bisphosphonates represent a unique class of phosphorus compounds, which have found significant implications in bone-related diseases.[181–183] In particular, nitrogen-containing bisphosphonates have emerged as effective small molecular candidates in anti-osteoporosis and anti-cancer drugs.[184–188] However, amino acid-containing bisphosphonates, especially the chiral ones, still remain largely underexplored. In 2002, Ruiz, Ojea *et al.* documented an example of asymmetric synthesis of chiral bisphosphono-α-amino acids.[68] The authors initially used lithiated bis-lactim ethers to undergo the conjugate addition with vinyl bisphosphonate to afford the adduct **261**, albeit in low yield with poor diastereoselectivity (Scheme 90a). Switching the reaction route to electrophilic substitution of bis-lactim phosphonate carbanion **262** with phosphorochloridate selectively liberated *trans*-adduct **261** in high yield. Subsequent acid hydrolysis gave the free amino carboxylic phosphonic acid **263** in enantiomerically pure form (Scheme 90b).

An interesting catalytic enantioselective protocol to chiral amino carboxylic bisphosphonates was reported by Shibasaki *et al.* in 2009 (Scheme 91a).[189] This procedure consisted in a conjugate addition reaction that employed nitroacetates as nucleophiles to couple



Scheme 90. Chiral auxiliary-induced diastereoselective synthesis of enantiopure bisphosphono-α-amino acids.



Scheme 91. Catalytic enantioselective syntheses of chiral bisphosphono-α-amino acid derivatives.

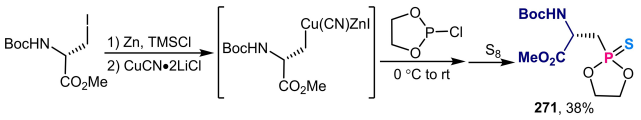
with vinyl bisphosphonates under the catalysis of a dinuclear Ni_2-Schiff base complex. Simple deprotection transformation of the adduct **264** to free bisphosphonic acid **265**, and direct reduction of the nitro moiety to bisphosphono-α-amino ester **266** were also presented with good results. Another breakthrough in

the catalytic enantioselective preparation of chiral bisphosphono-α-amino acids was implemented by Wang *et al.* in 2011.[190] The authors took advantage of azomethine ylides to undergo the Michael addition reaction with β-substituted vinyl bisphosphonates catalyzed by a Cu(I)/TF-BiphamPhos system (Scheme 91b). This platform built two adjacent stereocenters of the adducts **267** with high efficiency (70–95% yields in 30 minutes) and high enantioselectivities (88–99% ee) in a broad scope. Removal of the ethoxy groups in the Michael adduct **267 a** to free bisphosphonic acid **268** was realized with full retention of ee values. In addition, subsequent halogenation or oxidation transformations provided several potentially bioactive unnatural bisphosphono-α-amino acids **269**. In 2014, Albrecht *et al.* described an organocatalytic Michael reaction of azlactones with vinyl bisphosphonates, which provided facile access to bisphosphono tetrasubstituted amino acids **270** after azlactone ring-opening, but the utility is largely hampered because of the low enantioselectivity (Scheme 91c).[191]

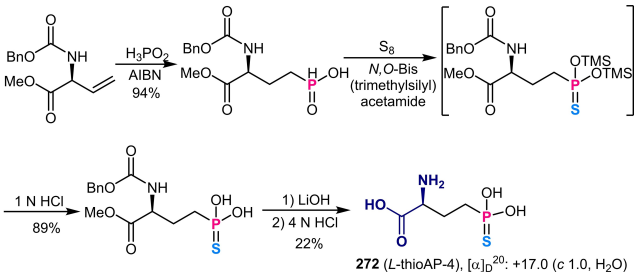
5.2. Thio-Phosphono-α-Amino Acids

The incorporation of sulfur atom(s) into phosphonic acids could dramatically modify their metabolic stability and cellular uptake known as the thio effect.[192] In this context, Gilbertson *et al.* developed a synthetic protocol by employing an easily available amino acid derivative accessible from the chiral pool (Scheme 92).[193] This C–P cross-coupling approach enabled access to thio-phosphono-α-amino acid **271**, albeit in low yield with undefined enantiopurity.

As mentioned in part 2.3, L-2-amino-4-phosphonobutyric acid (L-AP-4) is the most widely investigated agonist selective for group III metabotropic glutamate (mGlu) receptors. In this realm, Acher *et al.* further developed a new thiophosphonate analogue: L-thioAP-4, which displayed a two-fold higher potency compared with L-AP-4.[45] The improved potency of L-thioAP-4 was attributed to the increased distal acidity of the thiophosphonate moiety. The reported synthetic procedure to L-thioAP-4 entailed enantiomerically pure vinylglycine as the starting chiral material, and involved radical condensation, oxidation, deprotection, and hydrolysis steps, finally to furnish L-thioAP-4 **272** without any loss of enantiomeric purity (Scheme 93).



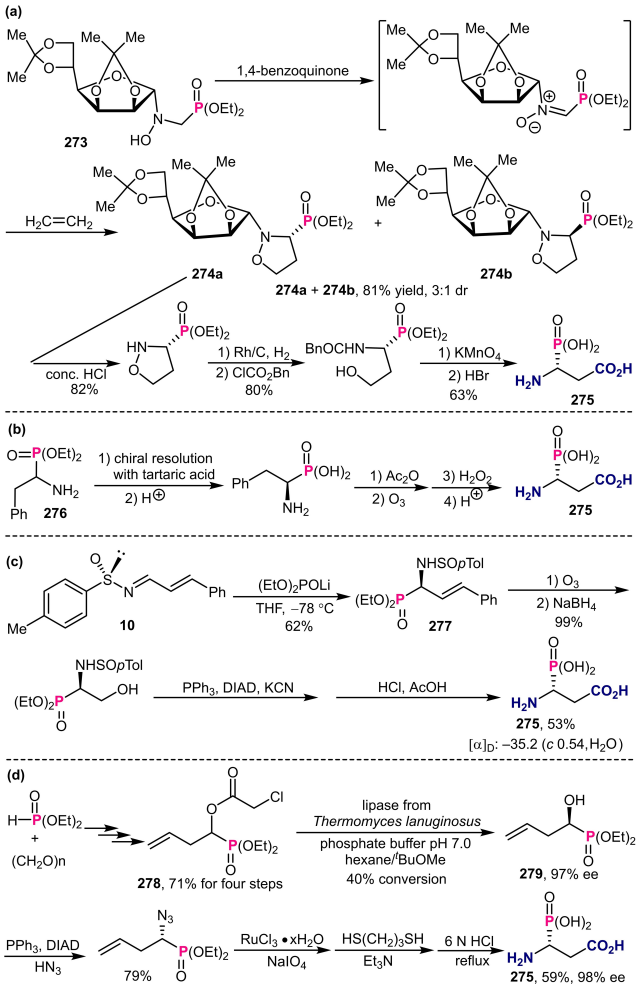
Scheme 92. Synthesis of chiral thio-phosphino-α-amino acid **271**.



Scheme 93. Asymmetric transformation of chiral substrate into 2-amino-4-thiophosphonobutyric acid L-thioAP-4.

5.3. Phosphono-β-Amino Acids

β-Amino acids play a prominent role in the construction of antibiotic β-lactams, peptidomimetics, β-peptides, and numerous bioactive small molecules.[194–196] Therefore, embedding the unique phosphonate motif into β-amino acids would be of high interest while remaining much less explored in comparison with the phosphono-α-amino acids.[197–199] In fact, as early as in 1982, Voeffray and Vasella described the synthetic example of chiral phosphono-β-amino acids exploiting the chirality of D-mannose (Scheme 94a).[200] *N*-Glycosyl-*C*-dialkoxy-phosphonoyl-nitrone, in-situ generated from the corresponding hydroxylamine **273** with the aid of *p*-benzoquinone, underwent the cycloaddition reaction with ethylene to give α-amino-phosphonate **274** with moderate diastereoselectivity. The cleavage of the glycoside moiety in the cycloadduct **274 a** produced simple cyclic aminophosphonate, which was then hydrogenolyzed, oxidized, and deprotected to yield the final phosphono-aspartic acid (AspP) **275** in a good overall yield. While inspiring, the lengthy procedure limits the practical utility of this method. Alternatively, Mastalerz *et al.* prepared compound **275** from α-amino-phosphonate **276** via chiral resolution with tartaric acid, followed by ozonolysis and oxidation as the key steps (Scheme 94b).[201] In 2013, this important phosphono-aspartic acid **275** was also synthesized via a chiral sulfinimine methodology by Łyżwa *et al.* (Scheme. 94c).[26] The key chiral precursor **277** was obtained upon *p*-tolylsulfinyl-directed diastereoselective addition of phosphite anion to cinnamaldimine **10** at cryogenic temperature. The cinnamylidene moiety was smoothly converted to the hydroxyl group through ozonolysis/reduction sequence in almost quantitative yield. Subsequent Mitsunobu cyanation and acid hydrolysis delivered the final chiral AspP **275** in 53% total yield. In 2017, the Hammerschmidt's group leveraged a chemoenzymatic resolution process en route to the asymmetric preparation of AspP **275** (Scheme 94d).[202] The synthetic manipulations starting from diisopropyl phosphite and paraformaldehyde produced 1-chloroacetoxy-3-butenyl-phosphonate **278** in high yield. Resolution of

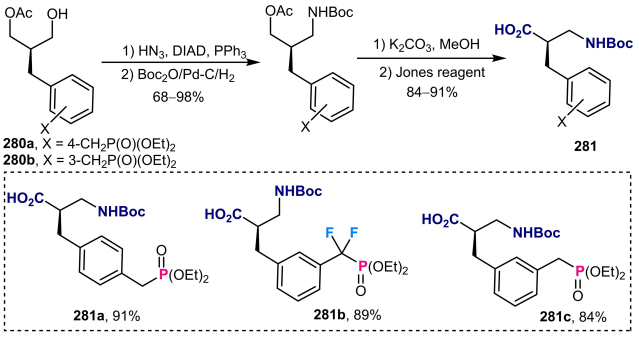


Scheme 94. Asymmetric construction of chiral β-phosphono-β-amino acid **275**.

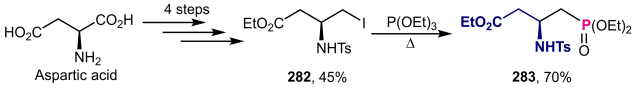
chloroacetate **278** was achieved by employing the lipase from *Thermomyces lanuginosus*, thus providing α-hydroxy-phosphonate **279** with 97% ee. Then, Mitsunobu azidation, oxidation, hydrogenation, and acid hydrolysis afforded the desired **275** with more than 98% ee.

As previously discussed in parts 2.6.4 and 3.2.2, enantiomerically enriched phosphonate 1,3-diol derivatives **280** are accessible via a lipase-catalyzed desymmetrization protocol.[96] In an extension of this work, Shibuya *et al.* performed a sequence of Mitsunobu azidation, hydrogenation, deacetylation, and Jones oxidation with **280** to construct the β-amino acid skeleton (Scheme 95). These functional group interconversions offered three types of phosphotyrosine analogues **281** including a phosphonodifluoromethyl-substituted product in good yields (see also 3.2.2).

In 2010, Teng devised a facile approach to a chiral γ-phosphono-β-amino acid from aspartic acid (Scheme 96).[203] The key Arbuzov reaction step proved to be sensitive to the amino protecting group, as *N*-Ts-



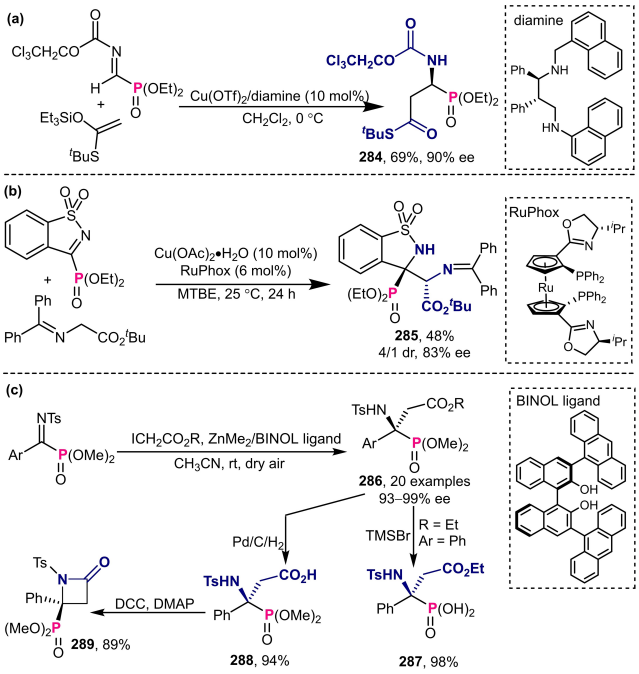
Scheme 95. Asymmetric transformation of chiral substrates into enantiomerically pure phosphonophenyl-β-amino acids.



Scheme 96. Asymmetric construction of chiral γ-phosphono-β-amino acid.

protected iodide **282** proceeded the phosphorylation smoothly to afford the desired chiral β-amino phosphonate **283** in 70% yield, whereas *N*-Boc-protected analogue underwent unexpected intramolecular cyclization to give 2-oxazolidinone as the major product.

The use of α-iminophosphonates as electrophilic substrates has gained increasing interest in the preparation of chiral α-amino phosphonic acid derivatives.[204] Among the productive efforts, the preparation of some chiral β-carboxylic α-amino phosphonic acids have been documented. For example, the Kobayashi's group reported a copper/diamine-catalyzed enantioselective Mannich reaction of iminophosphonate with silyl enol ethers (Scheme 97a).[205] As a special example, thioester-derived silyl ether underwent the C–C bond formation with high enantioselectivity, thus delivering the corresponding β-carboxylic α-amino phosphonate **284**. Xie *et al.* described a single example of copper/RuPhox-catalyzed Mannich reaction of cyclic phosphonate ketimine with glycine ester (Scheme 97b).[206] In spite of the low yield and moderate stereoselectivity, this study described the catalytic asymmetric preparation of the chiral quaternary β-phosphono β-amino acid derivative **285**. In 2019, Vicario *et al.* developed an enantioselective aza-Reformatsky reaction of α-phosphonated ketimines that allowed access to a broad scope of enantiopure β-phosphono β-amino esters **286** (Scheme 97c).[207] Operating the reaction under air atmosphere is critical for inhibiting side reactions, as only methyl addition by-product was observed under N_2 atmosphere. The enantioselectivity was controlled by using chiral anthracenyl-substituted BINOL ligand. Both the free phosphonic acid **287** and free carboxylic acid **288** could be easily accessed by treating with

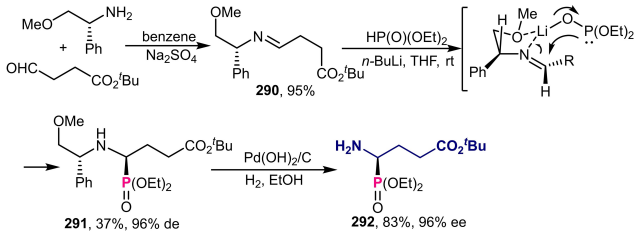


Scheme 97. Catalytic asymmetric construction of chiral β-phosphono-β-amino acid derivatives from iminophosphonates.

trimethylsilyl bromide and Pd–C/H_2, respectively. Interestingly, the intramolecular amidation of **288** also proved to be viable and delivered valuable chiral phosphonated β-lactam **289** in good yield.

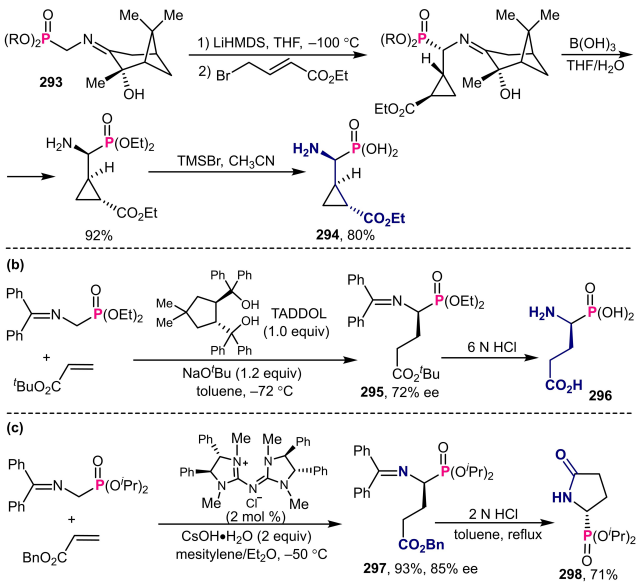
5.4. Phosphono-γ-Amino Acids

γ-Amino acids hold increasing promise for potential applications in therapeutics γ-peptides and foldamers.[208–210] One example of chiral phosphono-γ-amino acid was presented by Smith *et al.* (Scheme 98).[211,212] In an effort to synthesize versatile chiral α-amino-phosphonates, ester-remote-functionalized chiral chelating imine **290** was evaluated as one of the examples to expand the scope. Directed by the chiral auxiliary, the addition of lithium phosphite to **290** resulted in the diastereoselective formation of **291** with excellent diastereoselectivity, albeit in moderate yield. Unmasking the directing group was achieved by palladium hydroxide-catalyzed hydrogenolysis, thereby giving phosphono γ-amino ester **292** in good yield with 96% ee.



Scheme 98. Catalytic asymmetric synthesis of a chiral γ-phosphono-γ-amino acid.

Iminophosphoglycinates possess both amino and phosphonate moieties and have been frequently employed as effective nucleophiles to produce phosphono-amino acid building-blocks. Towards these targets, Roumestant *et al.* described a diastereoselective cyclopropanation of chiral auxiliary-tethered Schiff base **293** with 4-bromo crotonate (Scheme 99a).[213] Removal of the chiral directing group with boric acid and deprotection with TMSBr led to the enantiomerically pure cyclopropanyl α-aminophosphonate **294** without erosion of the chiral information. Subsequently, Jászay *et al.* investigated the catalytic enantioselective Michael reactions of phosphoglycine synthon with *tert*-butyl acrylate (Scheme 99b).[214–216] In the presence of a chiral diol (TADDOL) and a strong base (^{t}BuONa), the chiral γ-carboxylic amino phosphonate **295** was obtained in up to 72% ee. The final free γ-carboxylic amino phosphonic acid **296** could also be generated under simple hydrolysis conditions. In 2011, the Tan's group reinvestigated the Michael reaction of phosphoglycine synthon with benzyl acrylate by the use of the unique C2-symmetric chiral pentanidium as phase-transfer catalyst (Scheme 99c).[217] The resulting chiral γ-carboxylic amino phosphonate **297** was obtained in high yield with 85% ee. Under acid conditions, this adduct further underwent intramolecular amidation to give phosphonate γ-lactam **298** in good yield.



Scheme 99. Asymmetric construction of chiral γ-phosphono-γ-amino acid derivatives from iminophosphoglycinate derivatives.

6. Conclusions and Perspectives

Amino carboxylic-phosphonic acids participate actively in a wide variety of biochemical pathways in living cells. These non-hydrolyzable phosphate mimics have aroused a huge interest in the scientific community concerned with the role of transient protein phosphorylation in many diseases. This in turn is providing opportunity to understand the nuanced mechanism of signal transduction and to design molecules for the development of new therapeutic agents and strategies. Because most of the new drugs reaching the market today are single enantiomers, the class of amino carboxylic-phosphonic acids does not escape the tendency. This review has covered the methodologies related to the construction of chiral non-racemic amino carboxylic-phosphonic acids. First, the chiral pool was solicited, in particular natural amino acids, to further conduct chemical transformations distant to the stereogenic center. The intrinsic chirality of amino acids was also exploited to control adjacent or nearby centers in a diastereoselective manner. Along a similar vein, the use of a chiral auxiliary that is temporarily attached to the substrate was often applied as it is a powerful technique for intramolecular control of the stereoselectivity. More recently, modern approaches in asymmetric synthesis have widened the synthetic offer for amino carboxylic-phosphonic acids. Indeed, achiral substrates were converted into chiral products with concomitant formation of a stereogenic center with the aid of a chiral stoichiometric reagent or a chiral catalyst. Early reported synthetic routes to chiral amino carboxylic-phosphonic acids were embedded within a global therapeutic project for the rational design of enzyme inhibitors while, nowadays, the same molecules are often mentioned as synthetic application in papers reporting some novel methodologies. This trend demonstrates the continued concern and abundant research work on this family of therapeutic agents. Despite the many advances made, important synthetic challenges still need to be addressed toward sustainable and practical protocols. Also, the low diversity of the natural amino acids so far engaged in the installation of a phosphonic moiety is a limitation in the quest for the discovery of new drugs and the radiolabeling of amino carboxylic-phosphonic acids remains in its infancy. We anticipate that the scientific knowledge in synthesis and applications of chiral amino carboxylic-phosphonic acids will become more responsive to contemporary concerns as well as future challenges, and will continue to evolve and play a part in the provision of highly potent future drugs. We can rely on the vitality of the asymmetric synthesis field and the development of useful synthetic tools to supply the pipeline of existing and new chiral molecules. We believe that the chemistry discussed in this review could serve as a practical user guide to chemists and biochemists and a source of inspiration for future innovation.

Acknowledgements

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